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Biomarkers of neuroprogression and late staging in bipolar disorder: A systematic review

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Abstract

Background: Bipolar disorder may undertake a progressive course in a subset of patients, and research efforts have been made to understand the biological basis underlying this process. This systematic review examined the literature available on biological markers associated with illness progression in bipolar disorder.

Methods: Peer-reviewed articles were assessed using Embase, PsycINFO and PubMed, as well as from external sources. After initial screening, a total of 871 citations from databases and other sources were identified. Participants with a diagnosis of bipolar disorder were included in our systematic review; however, studies with participants younger than 15 or older than 65 were excluded. All studies were assessed using the Newcastle-Ottawa Scale assessment tool, and data pertaining to the results were extracted into tabular form using Google Sheets and Google Documents. The systematic review was registered on PROSPERO international prospective register of systematic reviews (ID Number: CRD42020154305).

Results: A total of 35 studies were included in the systematic review. Increased ventricular size and reduction of grey matter volume were the most common brain changes associated with illness progression in bipolar disorder. Among the several biomarkers evaluated in this systematic review, findings also indicate a role of peripheral inflammatory markers in this process.

Discussion: The studies evaluating the biological basis of the illness progression in bipolar disorder are still scarce and heterogeneous. However, current evidence supports the notion of neuroprogression, the pathophysiological process related to progressive brain changes associated with clinical progression in patients with bipolar disorder. The increase in peripheral inflammatory biomarkers and the neuroanatomical changes in bipolar disorder suggest progressive systemic and structural brain alterations, respectively.

Keywords

Bipolar disorder, staging, biomarkers, neuroprogression, illness progression

Introduction

Bipolar disorder (BD) is a chronic and highly debilitating mental disorder that affects approximately 1% of the population worldwide (Merikangas et al., 2011). The recurrence of mood episodes is often associated with unfavourable clinical outcomes, including functional and cognitive impairments, higher rates of medical and psychiatric comorbidities and a lower response to treatment (Rosa et al., 2012; Van Rheenen et al., 2019; Wingo et al., 2009). A substantial proportion of patients with BD shows cognitive impairments that persist even following remission of mood symptoms (Bortolato et al., 2016), particularly in patients who experience multiple

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episodes (Van Rheenen et al., 2019). In addition, a recent study showed that functional deterioration may be progressive in nearly half of patients, characterized mainly by a higher number of relapses, greater neurocognitive impairment and greater severity of depressive symptoms (López-Villarreal et al., 2020).

BD is known to have a heterogeneous course of illness, where a subgroup of patients may present with progressive biological alterations in the brain and the periphery, including changes to neuroanatomical structure, neurotrophic factors, inflammatory markers and oxidative stress markers (Kapczinski et al., 2019; Kauer-Sant'Anna et al., 2009; Strakowski et al., 2002). Taking into consideration the hypothesis of neuroprogression, the pathological rewiring of the brain that takes place in parallel with clinical deterioration (Berk et al., 2011; Kupka et al., 2021; Rosa et al., 2014; Tatay-Manteiga et al., 2018), major efforts have been made to understand BD through clinical staging models (Berk et al., 2017; Cosci and Fava, 2013; Duffy, 2014; Kapczinski et al., 2014; McGorry et al., 2010; Reinares et al., 2013; Rosa et al., 2014). Furthermore, systemic biological changes observed in this illness may play a critical role in the neuroprogression of BD (Andreazza et al., 2009; Fries et al., 2012; Kapczinski et al., 2009; Tatay-Manteiga et al., 2017).

Although there has been a substantial increase in the understanding of illness progression, the pathophysiology of BD is highly complex, and its underlying neurobiological mechanisms remain largely unclear. Therefore, it is crucial to study the course of this illness further to identify potential biological pathways that may be involved in illness progression and provide insight on new approaches to diagnosis, prognosis and treatment.

The goal of this systematic review, therefore, was to synthesize the current research on biological markers (biomarkers) associated with illness progression in BD in (1) studies that assessed the levels of biomarkers in patients with BD according to illness progression and (2) studies that correlated biomarkers with relevant variables for illness progression.

Methods

In this study, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015; Page et al., 2021). This study was registered on the PROSPERO international prospective register of systematic reviews (ID Number: CRD42020154305). A literature search was conducted using three databases (Embase, PsycINFO and PubMed) and included studies published until October 22, 2019.

Selection criteria

In this systematic review, cross-sectional studies, longitudinal studies, prospective studies, retrospective studies, non-randomized trials and case-control studies were included; the reference lists of the eligible studies were also assessed. Reviews, editorials, case reports, meta-analyses, randomized clinical trials and re-reports of raw data from a secondary source were excluded from this systematic review. No publication period, language or geographical restrictions were imposed in the current review. The inclusion criteria were participants between the ages of 15–65, with a diagnosis of BD. Studies consisting of paediatric populations were excluded from the systematic review. Geriatric populations were also excluded from the systematic review as older populations are considered more prone to medical comorbidities and neurodegenerative diseases, which may confound the data set (Lala and Sajatovic, 2012).

The following keywords were used in the systematic search strategy: (bipolar disorder OR bipolar disorders OR mania OR hypomania OR manic OR hypomanic OR manic-depressive disorder OR manic depressive disorder OR bipolar affective disorder) AND (neuroprogression OR illness progression OR early stage OR late stage OR early stage OR late stage OR staging OR progression) AND (biomarkers OR biological markers OR oxidative stress OR telomere length OR inflammation OR inflammatory markers OR cytokines OR neurotrophins OR neurotrophic factors OR imaging OR neuroimaging OR brain changes OR cellular changes OR cellular resilience OR blood biomarkers OR hormone changes OR protein changes).

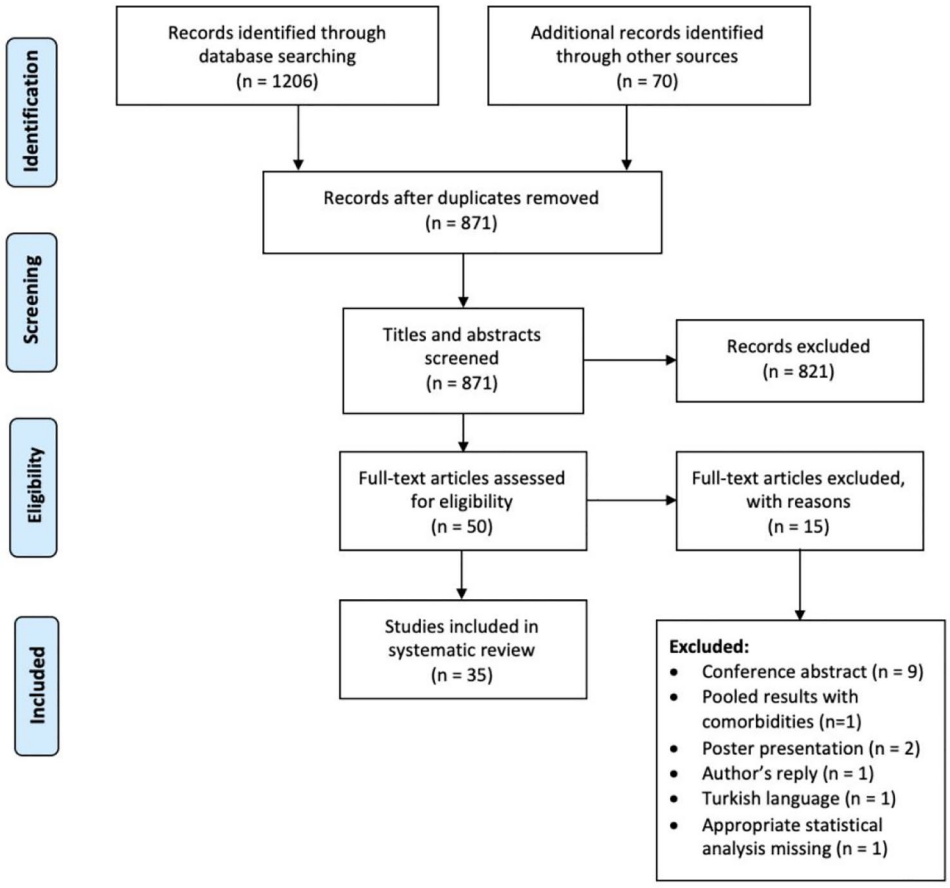
Selection of eligible studies

The titles and abstracts were screened using Rayyan – a screening software for systematic reviews (Ouzzani et al., 2016). Duplicates were removed by the software and studies not fulfilling the inclusion criteria were excluded upon title/abstract screening. The full texts of the articles were then retrieved and assessed for eligibility. All of the review processes were performed independently by S.M. and S.G., and consensus regarding discrepancies between reviewers was achieved with other members of the review team, B.W.A. and B.P. The PRISMA flow diagram is shown in Figure 1.

Data extraction

Data from eligible studies were extracted and reported independently by two authors (S.M. and S.G.) using Google Sheets. Discrepancies were resolved through discussion with B.W.A. and B.P. The following information was retrieved: (1) population (sample size, sex and age of each group); (2) staging model (when applicable); (3) clinical variables used for staging (when applicable); (4) type of biological sample; and (5) biomarkers assessed regarding staging or associated with illness progression.

Figure 1. PRISMA Flow Diagram (Moher et al., 2015) of the literature search and selection.



The title and abstract screening of the initial 871 studies was conducted on Rayyan web application, following the removal of duplicates. 50 full-text articles were assessed for eligibility, and 35 studies were selected for inclusion in the systematic review.

Quality assessment

A quality assessment using the Newcastle-Ottawa Quality Assessment Scale (Modesti et al., 2016) was also performed by S.M. and S.G., independently through a blind review. Conflicts were resolved with support from B.W.A. and B.P.

Results

Study characteristics

A total of 1206 studies were retrieved from three databases (581 from Embase, 211 from PsycINFO and 414 from PubMed), and 70 additional records were identified through other sources. Title/abstract screening was performed for 871 records, and 50 studies underwent full-text screening, for a total of 35 studies included in our systematic review.

Our systematic review included (1) studies that assessed biomarkers in patients with BD using staging models to classify patients into early and late stages, and (2) studies that presented correlations between biomarkers and clinical variables potentially associated with illness progression (such as duration of illness, number of hospitalizations, number of episodes, symptom severity and age at onset). The most common staging models for BD used in the publications were Kapczinski et al. (2009) and Rosa et al. (2014). The 35 studies included in our review reported changes in several peripheral biomarkers, including neurotrophic factors, inflammatory and oxidative stress markers, as well as brain changes. Data from the staging studies are in Table 1, and data from the studies investigating correlations between biomarkers and clinical variables associated with illness progression are in Table 2. An overview of the categorized peripheral biomarkers observed in more than one staging study is in Supplementary Table 1. The scoring for the Newcastle-Ottawa Quality Assessment is in Supplementary Tables 2 and 3.

Table 1. Clinical and biological characteristics of the included staging studies.

First author, year	Population	Sex and age (average age, SD)	Staging model	Clinical assessments used for staging	Type of sample or analysis	Biomarkers or brain regions analysed regarding staging	Significant Findings: Late vs. Early	Significant Findings: Early vs. Controls	Significant Findings: Late vs. Controls
Strakowski et al. (1999)	First episode: ($n = 12$) Multiple episode ($n = 12$) Controls: ($n = 22$)	Bipolar disorder: 70.8% male (27, 6) Controls: 59.1% male (28, 6)	Not specified; first episode and multiple episode distinction used	Duration of illness, number of previous hospital admissions, number of episodes	Brain imaging	Prefrontal, thalamic, hippocampal, amygdala, pallidal, striatal volumetric measurements	No significant changes	No significant changes	No significant changes
Strakowski et al. (2002)	First episode: ($n = 18$) Multiple episode: ($n = 17$) Controls: ($n = 32$)	First episode: 61.1% male (22, 6) Multiple episode: 35.3% male (25, 6) Controls: 50% male (24, 6)	Not specified; first episode and multiple episode distinction used	Number of mania episodes	Brain imaging	Cerebrum, lateral ventricles, 3rd ventricle, striatum (caudate and putamen), thalamus, and hippocampus	↑Lateral ventricles	↑Putamen	↑Lateral ventricles, ↓Total cerebral volume
Javadapour et al. (2007)	Bipolar disorder: ($n = 24$) Controls: ($n = 24$)	Bipolar disorder: 25% male (38.2, 11.0) Controls: 25% male (38.0, 11.1)	Not specified; first episode and multiple episode distinction used	Number of episodes, length of illness	Brain imaging	ACC	Not specified	↑ACC	No significant changes
Kauer-Sant'Anna et al. (2009)	Early stage: ($n = 30$) Late stage: ($n = 30$) Controls: ($n = 30$ early, $n = 30$ late)	Early stage: 43.3% male (22.4, 3.9) Late stage: 30% male (41.4, 8.4) Controls: early 33.3% male (22.1, 3.6), late 36.7% male (43.2, 6.4)	Not specified	Length of illness	Serum	TNF-α, IL-6, IL-10, BDNF	↓BDNF, ↓IL-6, ↑TNF-α	↑IL-6, ↑IL-10, ↑TNF-α	↑IL-6, ↑TNF-α, ↓BDNF
Andreazza et al. (2009)	Early stage: ($n = 30$) Late stage: ($n = 30$) Controls: ($n = 30$ early, $n = 30$ late)	Early stage: 43.3% male (22.4, 3.9) Late stage: 30% male (41.1, 8.4) Controls: early 33.3% male (22.1, 3.6), late 36.7% male (43.2, 6.4)	Not specified	Length of illness	Serum	Glutathione peroxidase, glutathione reductase, glutathione S-transferase, carbonyl levels, 3-nitrotyrosine	No significant changes	↑3-nitrotyrosine	↑glutathione reductase, ↑glutathione S-transferase, ↑3-nitrotyrosine
Grande et al. (2014)	Patients with BD: ($n = 115$) First-degree relatives: ($n = 25$)	Not specified	Not specified	Number of episodes, age of onset, time elapsed since first episode, functioning	Serum	IL-6, BDNF, TBARS	↑IL-6	Not applicable	Not applicable
Pfaffenseller et al. (2014)	Early stage: ($n = 10$) Late stage: ($n = 10$) Controls: ($n = 32$)	Early stage: 20% male (43.4, 9.3) Late stage: 60% male (52.6, 14.1) Controls: 37.5% male (42.94, 12.17)	Kapczinski et al. (2009)	Mood symptoms, functional decline, cognitive decline, patterns of recurrence	PBMCs (cell culture)	Protein levels of GRP78, eIF2α-P, and CHOP, ER stress-induced cell death	No significant changes	↑ER stress-induced cell death, ↓GRP78 and ↓eIF2α-P expression after in vitro induced ER stress for 24 hours	↑ER stress- induced cell death, ↓GRP78 and ↓eIF2α-P expression after in vitro induced ER stress for 12 and 24 hours

(Continued)

Table 1. (Continued)

First author, year	Population	Sex and age (average age, SD)	Staging model	Clinical assessments used for staging	Type of sample or analysis	Biomarkers or brain regions analysed regarding staging	Significant Findings: Late vs. Early	Significant Findings: Early vs. Controls	Significant Findings: Late vs. Controls
Fries et al. (2014)	Early stage: ($n = 10$) Late stage: ($n = 14$) Controls: ($n = 26$)	Early stage: 30% male (44.4, 7.38) Late stage: 28.6% male (48.79, 6.51) Controls: 30.8% male (46.9, 7.08)	Kapczinski et al. (2009)	Clinical parameters, including data on course of illness, functioning, and comorbidities	PBMCs (cell culture) and DNA	Salivary post-dexamethasone cortisol levels, ex vivo Glucocorticoid receptor responsiveness to dexamethasone, basal protein levels of FKBP51, FKBP5 DNA Methylation, basal FKBP5 mRNA	No significant changes	↑Methylation at intron 7 of the FKBP5 gene	↑Salivary post-dexamethasone cortisol levels, ↓ex vivo glucocorticoid receptor responsiveness to dexamethasone
Lavagnino et al. (2015)	Early stage: ($n = 20$) Late stage: ($n = 21$) Controls: ($n = 25$)	Early stage: 0% male (39, 11) Late stage: 0% male (39, 11) Controls: 0% male (40, 13)	Staging Systems Task Force Report of the International Society for Bipolar Disorders	Number of episodes, incomplete remission, hospitalization	Brain imaging	Anterior CC, Mid-anterior CC, Central CC, Mid-posterior CC, Posterior CC	↓Posterior CC	No significant changes	↓Posterior CC
Panizzutti et al. (2015)	Early stage: ($n = 17$) Late stage: ($n = 14$) Controls: ($n = 14$ early, $n = 13$ late)	Early stage: 23.5% male (40.65, 14.03) Late stage: 28.6% male (52.07, 11.64) Controls: early 28.6% male (39.64, 1.88), late 30.8% male (52.15, 11.08)	Kapczinski et al. (2009)	Number of episodes, functioning, comorbidity, cognitive parameters	Serum	IL-2, IL-4, IL-6, IL-10, IL-17, TNF-α, IFNγ, eotaxin/CCL11 and eotaxin-2/CCL24, BDNF, TBARS, carbonyl content, glutathione-peroxidase activity	No significant changes	No significant changes	↑Eotaxin/CCL11 serum levels
Barbé-Tuana et al. (2016)	Early stage: ($n = 14$) Late stage: ($n = 12$) Controls: ($n = 15$ early, $n = 19$ late)	Early stage: 21.4% male (40.71, 11.77) Late stage: 33.3% male (53.83, 11.44) Controls: early 40% male (38.13, 11.44), late 36.8% male (50.26, 9.48)	Kapczinski et al. (2009)	Not specified	DNA	Telomere length	Not applicable	↓Telomere length	↓Telomere length
Cao et al. (2016)	Early stage: ($n = 15$) Late stage: ($n = 16$) Controls: ($n = 112$)	Early stage: 26.7% male (40.47, 12.83) Late stage: 25% male (39.56, 10.65) Controls: 41.1% male (33.75, 11.99)	Not specified	Number of episodes, hospitalizations	Brain imaging	Hippocampal volume	No significant changes	No significant changes	↓Hippocampal volume, ↓verbal memory performance
Reininghaus et al. (2016)	Early stage: ($n = 65$) Late stage: ($n = 41$) Controls: ($n = 80$)	Early stage: Not specified Late Stage: Not specified Controls: 37.5% male (41.1, 17.1)	Kapczinski et al. (2009)	Subjective and objective estimate of cognitive or functional impairment	Serum	MMP9, sICAM-1	↑MMP9, ↑sICAM-1	Not applicable	Not applicable

(Continued)

Table 1. (Continued)

First author, year	Population	Sex and age (average age, SD)	Staging model	Clinical assessments used for staging	Type of sample or analysis	Biomarkers or brain regions analysed regarding staging	Significant Findings: Late vs. Early	Significant Findings: Early vs. Controls	Significant Findings: Late vs. Controls
Siwek et al. (2016a)	Early stage:, ($n=53$), divided in mania ($n=7$), depression ($n=21$) and remission ($n=25$) Late stage:, ($n=76$), divided in mania ($n=16$), depression ($n=37$) and remission ($n=23$) Controls: ($n=50$)	Early stage: Not specified Late Stage: Not specified Controls: 28% male (45.8, 12.4)	Kapczinski et al. (2009)	Not specified	Serum	Zinc	No significant changes	No significant changes	↓Zinc (in BD type I individuals in depressive phase)
Siwek et al. (2016b)	Early stage:, ($n=53$), divided in mania ($n=7$), depression ($n=21$) and remission ($n=25$) Late stage:, ($n=76$), divided in mania ($n=16$), depression ($n=37$) and remission ($n=23$) Controls: ($n=50$)	Early stage: Not specified Late Stage: Not specified Controls: 28% male (46, 12)	Kapczinski et al. (2009)	Not specified	Serum	TBARS	Not applicable	↑TBARS (only in the depressive phase)	↑TBARS (in the depressive phase and remission)
Wollenhaupt-Aguiar et al. (2016)	Early stage: ($n=6$) Late stage: ($n=6$) Controls: ($n=6$)	Early stage: 33.3% male (48.2, 4.7) Late stage: 33.3% male (49.0, 5.0) Controls: 33.3% male (48.8, 5.1)	Kapczinski et al. (2009)	Functional impairment, patterns of episode recurrences, severity of clinical features	SH-SY5Y human neuroblastoma cell line	Cell viability and neurite density	↓Cell viability	No significant changes	↓Cell viability, ↓neurite density
Cao et al. (2017a)	Early stage: ($n=16$) Late stage: ($n=15$) Controls: ($n=80$)	Not specified	Not specified	Number of manic episodes, hospitalizations	Brain imaging	Cortical gyrification	Negative local GI changes	No significant changes	↓GI
Tatay-Manteiga et al. (2017)	Early stage: ($n=25$) Late stage: ($n=23$) Controls: ($n=21$)	Early stage: 48% male (43.4, 10.3) Late stage: 47.8% male (45.1, 9.8) Controls: 33.3% male (36.7, 10.9)	Rosa et al. (2014)	Functioning	Serum and plasma	IL-6, IL-10, TNF-α, leukocyte blood count, fibrinogen, ESR, NT-3, BDNF	↓IL-10	↑IL-10	↑TNF-α, ↑leukocytes, ↑neutrophils, ↑monocytes
Çinar (2018)	Early stage: ($n=9$) Late stage: ($n=12$) Controls: ($n=20$)	Bipolar disorder: 100% male (30.64, 8.07) Controls: 100% male (32.30, 7.54)	Not specified	Number of episodes	Serum and DNA	LTL, hTERT, BDNF	↓LTL	Not applicable	↓LTL

(Continued)

Table 1. (Continued)

First author, year	Population	Sex and age (average age, SD)	Staging model	Clinical assessments used for staging	Type of sample or analysis	Biomarkers or brain regions analysed regarding staging	Significant Findings: Late vs. Early	Significant Findings: Early vs. Controls	Significant Findings: Late vs. Controls
Duarte et al. (2018)	Early stage: (n = 14) Late stage: (n = 15) Controls: (n = 14 early, n = 12 late)	Early stage: 28.6% male (40.79, 14.22) Late stage: 53.3% male (52.07, 11.08) Controls: early 42.9% male (39.93, 10.03), late 33.3% male (52.15, 11.08)	Rosa et al. (2014)	Functioning	Brain imaging	CC, total WM volume, total GM volume	Not applicable	↓CC, ↓total WM volume	↓CC, ↓total WM volume, ↓total GM volume
Ascoli et al. (2019)	Early stage: (n = 9) Late stage: (n = 9) Controls: (n = 10)	Early stage: 11.1% male (56.89, 12.23) Late stage: 33.3% male (50.22, 14.25) Controls: 30% male (48, 14.34)	Rosa et al. (2014)	Functioning	Macrophages (cell culture)	IL-1β, IL-6, IL-10, TNF-α	↓IL-6 (M0), ↓TNF-α (M0); ↓IL-1β (M1), ↓IL-6 (M1), ↓TNF-α (M1), ↓IL-10 (M1); ↓IL-10 (M2)	No significant changes	↓IL-1β (M0), ↓IL-10 (M0); ↓TNF-α (M1), ↓IL-6 (M1), ↓IL-1β (M1), ↓IL-10 (M1); ↓IL-10 (M2)
Borgelt et al. (2019)	First episode (fMRI): (n = 57) First episode (MRS): (n = 52) Multiple episode (fMRI): (n = 50) Multiple episode (MRS): (n = 54)	First episode (fMRI): 47.4% male (19, 5) First episode (MRS): 46.2% male (19, 5) Multiple episode (fMRI): 46% male (32, 11) Multiple episode (MRS): 44.4% male (32, 11)	Not specified; first episode and multiple episode distinction used	Number of mania episodes	Brain imaging	Brain activation in the following areas: amygdala, orbitofrontal cortex, VLPFC, ACC, caudate, putamen, and thalamus; glutamate, N-acetylaspartate	↓Regional activation in: VLPFC, orbitofrontal cortex, ACC, putamen, caudate, amygdala, thalamus; ↓N-acetylaspartate	Not applicable	Not applicable

$: 'Not specified' means the author did not clearly report the variables assessed or staging model used; %: 'Not applicable' means the authors did not report any findings between the groups being compared; §: ACC: anterior cingulate cortex; BDNF: brain-derived neurotrophic factor; CC: corpus callosum; CHOP: C/EBP homologous protein; eIF2α-P: Eukaryotic initiation factor 2-alpha; Eotaxin/CCL11: eosinophil chemotactic protein/C-C motif chemokine 11; ER: endoplasmic reticulum; ESR: erythrocyte sedimentation rate; FKBP51: FK506 binding protein 51; fMRI: functional magnetic resonance imaging; GI: gyrification index; GM: grey matter; GRP78: glucose-regulated protein 78; hTERT: human telomerase reverse transcriptase; IFNγ: interferon-gamma; IL: interleukin; LTL: leukocyte telomere length; MMP9: Matrix metallopeptidase 9; M0: non-stimulated macrophages; M1: macrophages with mainly pro-inflammatory profile; M2: macrophages with mainly anti-inflammatory profile; MRS: Magnetic resonance spectroscopy; NT-3: neurotrophin-3; PBMCs: peripheral blood mononuclear cells; sICAM-1: soluble intercellular adhesion molecule-1; TBARS: thiobarbituric acid reactive substances; TNF-α: tumour necrosis factor-alpha; VLPFC: ventrolateral prefrontal cortex; WM: white matter.

Table 2. Clinical and biological characteristics of the included studies correlating biomarkers to clinical variables.

First author, year	Population	Sex and age (average age, SD)	Staging model	Clinical assessments used for illness progression	Type of sample or analysis	Biomarkers or brain regions analysed regarding staging	Significant findings
Woods et al. (1990)	Bipolar disorder: (*n* = 9)	Bipolar disorder: 66.6% male (31.00, 15.72)	Not specified	Duration of illness	Brain imaging	Ventricular volume	No significant progression of ventricular size between first and final brain scan; no significant correlation between ventricular volume and duration of illness
Strakowski et al. (1999)	First episode: (*n* = 12) Multiple episode: (*n* = 12) Controls: (*n* = 22)	Bipolar disorder: 70.8% male (27, 6) Controls: 59.1% male (28, 6)	Not specified	Duration of illness, number of previous hospital admissions, number of episodes	Brain imaging	Prefrontal, thalamic, hippocampal, amygdala, pallidal, striatal volumetric measurements	No significant correlation between the brain regions and any of the staging assessments used (illness duration, number of hospitalizations, number of episodes)
Brambilla et al. (2001)	Bipolar disorder: (*n* = 22) Controls: (*n* = 22)	Bipolar disorder: 59.1% male (36, 10) Controls: 63.6% male (38, 10)	Not specified	Number of episodes	Brain imaging	Cerebellum, vermis, brainstem and its subregions (midbrain, pons, and medulla oblongata), 3rd ventricle, and lateral ventricles	Number of episodes directly correlated with right lateral ventricle volumes; no other significant correlation with number of episodes was found for the remaining brain structures
Strakowski et al. (2002)	First episode: (*n* = 18) Multiple episode: (*n* = 17) Controls: (*n* = 32)	First episode: 61.1% male (22, 6) Multiple episode: 35.3% male (25, 6) Controls: 50% male (24, 6)	Not specified	Number of mania episodes	Brain imaging	Cerebrum, lateral ventricles, 3rd ventricle, striatum (caudate and putamen), thalamus, and hippocampus	Larger ventricles were associated with a higher number of mania episodes
Deicken et al. (2003)	Bipolar disorder: (*n* = 15) Controls: (*n* = 20)	Bipolar disorder: 100% male (39.3, 10.3) Controls: 100% male (36.0, 10.3)	Not specified	Years of illness	Brain imaging	*N*-acetylaspartate, choline, and creatine concentrations in the hippocampus	Illness duration correlated with a reduction in *N*-acetylaspartate concentrations in the right hippocampus
Savas et al. (2006)	Bipolar disorder: (*n* = 27) Controls: (*n* = 20)	Bipolar disorder: 51.8% male (34.93, 14.78) Controls: 50.0% male (32.01, 9.92)	Not specified	Number of mania episodes	Serum	NO level, SOD activity	Number of mania episodes and other mood episodes was correlated with NO levels, but not SOD activity; no correlation found between NO levels and SOD activity
Javadapour et al. (2007)	Bipolar disorder: (*n* = 24) Controls: (*n* = 24)	Bipolar disorder: 25% male (38.2, 11.0) Controls: 25% male (38.0, 11.1)	Not specified	Number of episodes, length of illness	Brain imaging	Anterior cingulate cortex	Number of episodes correlated with right anterior cingulate cortex volume, patients with BD with equal to or less than 10 episodes had larger right anterior cingulate cortex compared to controls, which was not observed between patients with greater than 10 episodes and controls; no correlation between length of illness and right anterior cingulate cortex volume, a trend of increased anterior cingulate cortex volumes in patients with shorter illness duration reported
Moorhead et al. (2007)	Bipolar disorder: (*n* = 20) Controls: (*n* = 21)	Bipolar disorder: 50% male (41.5, 8.9) Controls: 47.6% male (38.5, 12.6)	Not specified	Number of episodes	Brain imaging	GM and WM density	Number of mania/hypomania episodes and the number of depressive episodes correlated with GM loss in the cerebellar and temporal lobe clusters

(Continued)

Table 2. (Continued)

First author, year	Population	Sex and age (average age, SD)	Staging model	Clinical assessments used for illness progression	Type of sample or analysis	Biomarkers or brain regions analysed regarding staging	Significant findings
Frey et al. (2008)	Bipolar disorder: (n = 36) Controls: (n = 55)	Bipolar disorder: 38.9% male (35.4, 10.8) Controls: 49.1% male (34.2, 11.6)	Not specified	Length of illness, age, age of onset, number of episodes	Brain imaging	Total brain matter volume, total GM volume, total WM volume	Length of illness correlated with a reduction in total GM volume in patients with BD (patients had illness for an average of 15 years); GM volume was not significantly correlated with age at illness onset and number of episodes
Nery et al. (2009)	Bipolar disorder: (n = 28) Controls: (n = 28)	Bipolar disorder: 42.9% male (34.0, 11.9) Controls: 42.9% male (32.5, 8.5)	Not specified	Symptom intensity, age of onset, number of episodes	Brain imaging	Orbitofrontal cortex GM volume	Orbitofrontal cortex GM volume was not correlated with age of onset, length of illness, or number of episodes
Ekman et al. (2010)	Bipolar disorder: (n = 55)	Bipolar disorder: 40% male (37, 12)	Not specified	Number of affective episodes, illness duration	Brain imaging	Local GM volume	Number of mania episodes correlated with a reduction of GM volume in the left and right inferior frontal gyri of the DLPFC; no association between GM volume and number of depressive episodes or illness duration
Elvsåshagen et al. (2011)	Bipolar disorder: (n = 28) Controls: (n = 28)	Bipolar disorder: 32.1% male (34.8, 7.7) Controls: 32.1% male (34.8, 9.2)	Not specified	Duration of illness, number of depressive episodes	DNA	Telomere length	Number of depressive episodes positively correlated with the load of short telomeres and negatively correlated with mean telomere length; no association between illness duration and the load of short telomeres and mean telomere length
Lisy et al. (2011)	Bipolar disorder: (n = 58) Controls: (n = 48)	Bipolar disorder: 44.8% male (27, 10) Controls: 43.8% male (27, 10)	Not specified	Illness duration (time between brain scans), number of episodes	Brain imaging	GM volume	Illness duration correlated with an increase in GM volume of portions of the prefrontal cortex; illness duration and number of depressive episodes correlated with an increase in GM volume in subcortical and limbic structures
Soeiro-de-Souza et al. (2013)	Bipolar disorder: (n = 50) Controls: (n = 50)	Bipolar disorder: 34% male (26.8, 4.5) Controls: 50% male (26.0, 4.00)	Not specified	Number of affective episodes, disease duration, psychotic symptoms	DNA	DNA levels of 8-OHdG, 5-HMec, and 5-Mec	Number of mania episodes correlated with an increase in 8-OHdG; level of 5-HMec was not correlated with number of episodes
Abé et al. (2015)	Mania group: (n = 13) No-Mania group: (n = 18)	Mania group: 69.2% male (41, 15) No-Mania group: 38.9% male (38, 9)	Not specified	Mania episodes	Brain imaging	Volume in the frontal cortex: DLPFC, inferior frontal cortex	Significantly decreased frontal cortical volume (DLPFC, inferior frontal cortex) in Mania group, compared to No-Mania group
Cao et al. (2017b)	Bipolar disorder: (n = 133) Controls: (n = 152)	Bipolar disorder: 31.6% male (38.8, 12.0) Controls: 36.8% male (35.4, 12.43)	Not specified	Illness duration, number of mood episodes	Brain imaging	Volume of 8 hippocampal subfields (cornu ammonis subfields 1-4, granule cell layer, molecular layer, presubiculum, and subiculum)	Illness duration in patients with BD-I correlated with a reduction in right cornu ammonis 1, molecular layer and subiculum; number of mania episodes in BD-I correlated with a reduction in volumes of both sides of the cornu ammonis 2/3, 4 and hippocampal tail; number of hypomania episodes in patients with BD-II had a positive correlation with left hippocampal tail volume

$: 'Not specified' means the author did not clearly report the variables assessed or staging model used; %: 'Not applicable' means the authors did not report any findings between the groups being compared; §: 5-HMec: 5-hydroxymethylcytosine; 5-Mec: 5-methylcytosine; 8-OHdG: 8-hydroxy-2k-deoxyguanosine; DLPFC: dorsolateral prefrontal cortex; GM: grey matter; NO: nitric oxide; SOD: superoxide dismutase; WM: white matter.

Neurotrophic factors

Five studies that investigated neurotrophic factors in regard to illness progression in BD were included in our review, all of which evaluated brain-derived neurotrophic factor (BDNF) peripheral levels. Çinar (2018), Tatay-Manteiga et al. (2017), Panizzutti et al. (2015) and Grande et al. (2014) found no statistically significant changes in BDNF levels between patients at the early and late stages of this illness. One study in particular, conducted by Kauer-Sant'Anna et al. (2009), found similar BDNF levels in patients with BD at the early stage compared with the control group; however, there was a decrease in BDNF levels in patients at the late stage of this illness when compared with controls and individuals at the early stage. Overall, the authors also found a negative correlation of length of illness with BDNF levels (Kauer-Sant'Anna et al., 2009).

Inflammatory markers

Interleukin-6. There were five studies that analysed inflammatory markers included in our review, all of which measured interleukin-6 (IL-6) levels. Although Tatay-Manteiga et al. (2017) and Panizzutti et al. (2015) found no significant changes in peripheral IL-6 levels between groups, Kauer-Sant'Anna et al. (2009) found an increase in IL-6 levels in patients at the late stage and at the early stage of the illness when compared to their respective control groups. However, these levels were lower in patients at the late stage when compared to patients at the early stage. Also, the authors found a negative correlation between length of illness and IL-6 levels (Kauer-Sant'Anna et al., 2009). However, Grande et al. (2014) identified an increase in IL-6 in patients at the late stage as compared to patients at the early stage. Another interesting study conducted by Ascoli et al. (2019) investigated the inflammatory response of monocyte-derived macrophages from patients with BD in regard to illness progression. In this study, M0 referred to non-stimulated macrophages, and M1 and M2 referred to macrophages polarized towards the mainly pro-inflammatory and mainly anti-inflammatory profiles, respectively. A decrease in the secretion of IL-6 was found in M0 and M1 from patients at the late stage compared to those at the early stage, and in M1 from patients at the late stage as compared to controls. No significant changes were found for any macrophage phenotype when comparing early stage patients to the control group.

Interleukin-10. The levels of interleukin-10 (IL-10), an anti-inflammatory cytokine, were examined in regard to staging for four of the five studies investigating inflammatory markers. Panizzutti et al. (2015) found no significant changes in serum IL-10 levels between groups. Although Kauer-Sant'Anna et al. (2009) and Tatay-Manteiga et al. (2017) found no differences in IL-10 levels between late stage patients and the control group, both studies noted a significant increase in IL-10 levels in patients at an early stage compared to controls. In addition, Kauer-Sant'Anna et al. (2009) found no change in serum IL-10 levels when comparing the early and late stage groups, and Tatay-Manteiga et al. (2017) noted a significant decrease in IL-10 levels in patients at the late stage compared to patients at the early stage. Furthermore, although Ascoli et al. (2019) did not find any changes in IL-10 when comparing early stage patients and the control group, there was a significant decrease in the secretion of IL-10 by all macrophage phenotypes from patients at the late stage compared to controls. There was also a decrease in IL-10 secretion by M1 and M2 in patients at the late stage as compared to patients in the early stage.

Tumour necrosis factor-α. While Panizzutti et al. (2015) found no significant changes in serum tumour necrosis factor-α (TNF-α) levels between groups, Tatay-Manteiga et al. (2017) found increased levels in patients at the late stage compared to controls, and Kauer-Sant'Anna et al. (2009) found an increase in TNF-α levels at the late stage group compared to the control group and also to the early stage, as well as an increase in patients at an early stage compared to controls. Ascoli et al. (2019) found a significant decrease in secretion of TNF-α in M0 and M1 from late stage patients compared to early stage patients. Furthermore, there were no significant changes in TNF-α levels in patients at the early stage compared to controls, but there was a significant decrease in TNF-α secretion in M1 from patients at the late stage compared to controls (Ascoli et al., 2019).

Other inflammatory markers. Other inflammatory markers have been explored in single studies. Panizzutti et al. (2015) found a notable increase in eosinophil chemotactic protein/C-C motif chemokine 11 (eotaxin/CCL11) serum levels in late stage patients compared to controls. In addition, Tatay-Manteiga et al. (2017) found a significant increase in leukocytes, neutrophils and monocytes count in patients at late stage compared to the control group. Furthermore, Ascoli et al. (2019) found that IL-1β secretion was decreased in M0 and M1 in patients at the late stage compared to controls, as well as compared to patients at the early stage in the M1 phenotype.

Oxidative stress

Our review included four studies that analysed oxidative stress in patients at early and late stages of BD. Thiobarbituric acid reactive substances (TBARS) levels were measured in three studies; two of them did not find differences between patients at early and late stages (Grande et al., 2014; Panizzutti et al., 2015), while one study conducted by Siwek et al. (2016b) found an increase in TBARS levels in patients at the early stage (in the depressive phase)

and in patients at the late stage of BD (in the depressive phase and remission) compared to the control group. Carbonyl content and glutathione peroxidase levels were also analysed by Andreazza et al. (2009) and Panizzutti et al. (2015); however, no significant changes were found between groups.

Andreazza et al. (2009) also found increased levels of glutathione reductase, glutathione S-transferase and 3-nitrotyrosine in patients at late stage BD compared to controls. In addition, 3-nitrotyrosine levels were found to be increased in early stage patients when compared to the control group.

Furthermore, the number of manic episodes was positively correlated with nitric oxide levels (Savas et al., 2006) and 8-hydroxy-2′-deoxyguanosine levels (Soeiro-de-Souza et al., 2013), but was not correlated with superoxide dismutase activity (Savas et al., 2006) and 5-hydroxymethylcytosine levels (Soeiro-de-Souza et al., 2013).

Brain changes

Our review included 18 studies analysing brain changes and illness progression in BD. Lavagnino et al. (2015) identified significant decreases in the volume of the posterior corpus callosum in late stage patients compared to individuals in the early stage and the control group. In Duarte et al. (2018), the authors found a decrease in corpus callosum volume in early and late stage patients relative to the control group.

Duarte et al. (2018) also found a significant decrease in total white matter (WM) volume and total grey matter (GM) volume in late stage patients compared to the control group. While the authors identified a decrease in total WM volume in patients at early stages compared to the control group, no significant change in total GM volume between early stage patients and the control group were detected.

Cao et al. (2016) found a significant decrease in hippocampal volume as well as a decrease in verbal memory performance in patients at the late stage compared to the control group. Using the average of local gyrification index (GI) at each surface vertex on the cortex, Cao et al. (2017a) identified a significant association between BD staging and the GI. While there were no significant changes between early stage patients and the control group in GI, late stage patients did demonstrate an overall decrease in GI compared to the control group.

In a former study, no significant differences were found in specific brain structures (prefrontal, thalamic, hippocampal, amygdala, pallidal, striatal) between patients experiencing a single episode as compared to patients experiencing multiple episodes (Strakowski et al., 1999). In a subsequent study, Strakowski et al. (2002) found that multiple episode patients with BD presented larger lateral ventricles compared to first episode patients and controls, and a smaller total cerebral volume compared to controls, while the putamen was found to be significantly larger in first episode patients compared to the control group. Strakowski et al. (2002) also found a positive correlation between the number of manic episodes and ventricle size, while Brambilla et al. (2001) found a positive correlation between the total number of episodes and right lateral ventricle volume, and Woods et al. (1990) found no significant correlation between ventricular volume and illness duration.

Borgelt et al. (2019) found decreased regional activation in the bilateral ventrolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex (ACC), putamen, caudate, amygdala and thalamus in multiple episode patients compared to first episode patients. Furthermore, they identified a lower level of glutamate and N-acetylaspartate in the ACC of multiple episode patients (Borgelt et al., 2019), while Deicken et al. (2003) found a negative correlation between illness duration and N-acetylaspartate concentrations in the right hippocampus. In addition, Javadapour et al. (2007) found that individuals who experienced equal to or less than 10 previous mood episodes presented significantly larger right ACC compared to the control group, and a positive correlation was found between the number of episodes and right ACC volume.

Although a negative correlation was found between illness duration and total GM volume, number of episodes and age at illness onset was not found to be associated with total GM volume (Frey et al., 2008). Moreover, Nery et al. (2009) found no significant correlation between orbitofrontal cortex GM volume and illness duration, number of episodes and age at illness onset. A decrease in GM volume in the left and right inferior frontal gyri of the dorsolateral prefrontal cortex (DLPFC) was also found to be associated with the number of manic episodes, but not the number of depressive episodes or illness duration (Ekman et al., 2010). Although Lisy et al. (2011) found a positive correlation between GM volume in subcortical and limbic structures and illness duration and number of depressive episodes, Moorhead et al. (2007) found a negative correlation between GM volume in cerebellar and temporal lobe clusters and number of manic and depressive episodes. Lisy et al. (2011) also found that illness duration correlated with an increase in GM volume in portions of the prefrontal cortex, while Abé et al. (2015) found significantly decreased frontal cortical volume (DLPFC and inferior frontal cortex) in individuals who experienced manic episodes within a 6-year period compared to those who did not.

Finally, Cao et al. (2017b) found that the number of manic episodes in patients with BD-I was negatively associated with the size of cornu ammonis (CA) subfields 2/3, and 4, as well as the hippocampal tail. The number of hypomanic episodes in populations with BD-II was also linked with an increase in left hippocampal tail volume, while illness duration correlated with reductions in hippocampal subfields CA1, the molecular layer and the subiculum (Cao et al., 2017b).

Telomere length

Three studies investigating the telomere length according to illness progression of BD were included. Çinar (2018) and Barbé-Tuana et al. (2016) both found a significant decrease in telomere length in patients at a late stage of BD compared to the control group. Furthermore, a decrease in telomere length in late stage patients compared to patients at the early stage was shown in Çinar (2018), while Barbé-Tuana et al. (2016) showed a decrease in telomere length in patients at the early stage compared to the control group. In addition, the number of depressive episodes, but not the illness duration, was found to be correlated with the load of short telomeres and mean telomere length, in a positive and negative direction, respectively (Elvsåshagen et al., 2011).

Other biomarkers

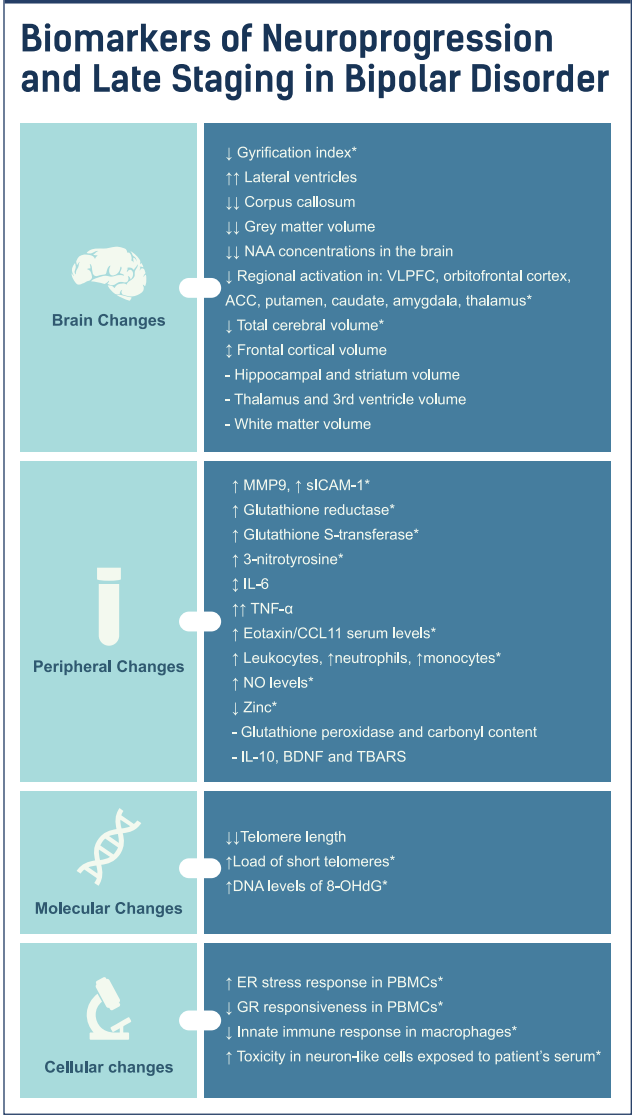
Several biomarkers were investigated in regard to illness progression in only one study. Notably, Siwek et al. (2016a) found a decrease in serum zinc concentration in depressive patients at the late stage of BD compared to the control group or patients in remission; Reininghaus et al. (2016) found a significant increase in matrix metallopeptidase 9 and soluble intercellular adhesion molecule-1 (sICAM-1) in patients at the late stage compared to patients at the early stage of the illness; and Fries et al. (2014) noted patients at the late stage of BD showed increased salivary post-dexamethasone cortisol levels compared to the control group. Furthermore, two in vitro studies were included in this systematic review: Pfaffenseller et al. (2014) found an impaired endoplasmic reticulum (ER) stress response in late stage patients and increased ER stress-induced cell death in early and late stage patients compared to controls (where cell death was more pronounced in late stage patients with BD), and Wollenhaupt-Aguiar et al. (2016) found a significant decrease in cell viability and neurite density in cells treated with serum from late stage patients compared to the control group.

Discussion

In this systematic review, we found that increase in ventricular size and reduction of GM volume were the most pronounced brain changes associated with illness progression in BD. Overall, a decrease in GM volume in various regions of the brain was also found to be correlated to relevant variables of illness progression, further supporting the notion of neuroprogression, the pathophysiological process related to progressive structural, functional and neurochemical brain changes associated with clinical progression in BD (Ekman et al., 2010; Frey et al., 2008; Moorhead et al., 2007; Nery et al., 2009). A comprehensive summary of the findings is shown in Figure 2.

It is known that inflammation may play a critical role in the pathophysiology of BD, potentially underlying the biological basis of neuroprogression. Among the several biomarkers evaluated in this systematic review, the inflammatory markers were the most assessed among the included studies. Although there are conflicting findings, it seems some inflammatory markers have been altered since the early stages which would suggest that inflammation may be a trait marker of BD. Noteworthy, studies showed increased levels of the pro-inflammatory cytokine TNF-α at late stages of BD compared to their respective control groups (Kauer-Sant'Anna et al., 2009; Tatay-Manteiga et al., 2017). This indicates that inflammation may worsen in the later stages of the illness and that the cumulative effects of inflammation over time may contribute to the progressive biological alterations such as the brain changes and an impaired immune system response. It is possible that this may be due to the cumulative effects of mood episodes over time (Kapczinski et al., 2008) since previous research has reported an increase in pro-inflammatory cytokines during the mood episodes of BD (Brietzke et al., 2009; Kim et al., 2007). In addition, previous research has suggested that patients with BD may have increased permeability of the blood–brain barrier, which may facilitate increased migration of inflammatory markers into the brain (Patel and Frey, 2015). Reininghaus et al. (2016) found that patients at the later stages of BD had higher circulating levels of sICAM-1, which has been implicated in inflammation. The serum level of sICAM-1 acts as a proxy for the immune system, and it is hypothesized that they increase the permeability of the blood–brain barrier, allowing cytokines and immune cells from the periphery to enter the central nervous system (CNS) to a greater degree (Muller, 2019). It is also known that cytokines such as IL-6, IL-10, TNF-α, IFNγ and chemokines can activate microglia in the brain which participate in inflammatory processes in response to damage to the CNS (Stertz et al., 2013). These cells help manage neuronal injury in the acute phase. However, their chronic activation can cause an imbalance in homeostasis and induce a constant inflammatory environment which can lead to pruning and remodelling synaptic plasticity, causing damage to neurons; this could be the case in patients with BD due to the recurrence of mood episodes (Watkins et al., 2014), which may contribute to the aforementioned neuroanatomical changes that have been associated with illness progression, and ultimately, the cognitive and functional impairment outcomes seen in BD (Brietzke et al., 2011). In a recent meta-analysis by Velosa et al. (2020), BD was found to be a significant risk factor for the development of dementia, and the number of mood episodes was found to be a relevant predictor for this process. In conjunction with our findings, these results suggest that progressive inflammatory processes and brain changes associated with the number of mood episodes may be positively associated with cognitive impairment, and ultimately, increased risk of dementia in patients with BD. Overall, our findings support the hypothesis that BD may follow a progressive course,

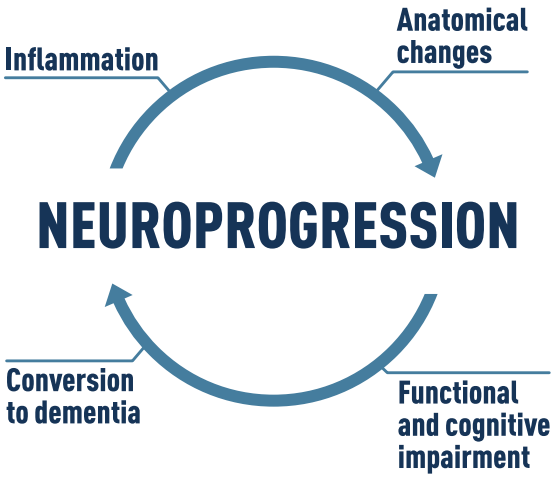
Figure 2. Summary of findings in the late stage patients with BD.



Findings from the staging studies and the studies which correlated biomarkers to clinical variables associated with illness progression (specifically, illness duration and number of episodes). If any conflicts arose between significant findings, we kept the most consistent result across the included studies, unless no consistent result could be determined. Results that showed no significant findings across more than one study were also included. 8-OHdG: 8-hydroxy-2′-deoxyguanosine; ACC: anterior cingulate cortex; BDNF: brain-derived neurotrophic factor; Eotaxin/CCL11: eosinophil chemotactic protein/C-C motif chemokine 11; ER: endoplasmic reticulum; GR: glucocorticoid receptor; IL: interleukin, MMP9: matrix metallopeptidase 9; NAA: N-acetylaspartate; NO: nitric oxide; PBMCs: peripheral blood mononuclear cells; sICAM-1: soluble intercellular adhesion molecule-1; TBARS: thiobarbituric acid reactive substances; TNF-α: tumour necrosis factor-alpha; VLPFC: ventrolateral prefrontal cortex. Conflicting findings: ↕; Results from a single study: single arrow (↑ or ↓) and marked by *. More than one study found these results: double arrow (↑↑ or ↓↓); no significant changes: -.

which may ultimately lead to deteriorating cognitive and functional performance (Figure 3).

Figure 3. Positive feedback-loop hypothesis for neuroprogression in BD.



According to our systematic review, our findings suggest that chronic inflammation in patients with BD may be correlated with progressive anatomical changes. Functional and cognitive impairment as a result of the anatomical changes may then precede the development of dementia in patients with BD, which is suspected to further increase the levels of inflammatory markers in the recurrent cycle of neuroprogression.

It is important to mention that although our focus has been on biomarkers, comorbidities may also be associated with illness progression. It is known that that the incidence of cardiovascular disease, diabetes, anxiety disorders and other comorbidities are high in BD (Aguglia et al., 2022; Krishnan, 2005; McIntyre et al., 2005; Spoorthy et al., 2019), and that these comorbidities have been associated with inflammation (Golia et al., 2014; Salim et al., 2012; Tsalamandris et al., 2019; Van Rheenen et al., 2019). In this sense, a potential relationship between inflammatory processes and comorbidities could contribute to the illness progression in BD. In a recent study by Aguglia et al. (2022), for instance, researchers reported a positive association between number of mood episodes and length of illness in patients with BD-I, and prospective cardiovascular complications. Therefore, future investigation should consider the influence of comorbidities in illness progression in patients with BD.

Although previous meta-analyses have indicated that oxidative stress markers (Brown et al., 2014; Rowland et al., 2018) and BDNF levels (Fernandes et al., 2015; Frey et al., 2013; Munkholm et al., 2016) are altered in patients with BD, more research is required to determine whether alterations also undertake a progressive course.

Another important biomarker that was evaluated in the included studies was the length of telomeres, repetitive sequences at the end of chromosomes that shorten naturally during cellular division. It has been suggested that BD may accelerate the body's natural aging process, and the role of telomeres has been investigated (Fries et al., 2020; Powell

et al., 2018; Squassina et al., 2019). Previous studies have suggested that, whenever the body experiences chronic stress, telomere shortening may be induced and even accelerated, resulting in apoptosis and genome instability (Muneer and Minhas, 2019; Simon et al., 2006). This process has therefore been proposed to be a potential biomarker in BD, alongside other markers such as inflammation and oxidative stress (Barbé-Tuana et al., 2016). However, more studies evaluating telomere shortening in patients at different stages of the illness are needed to clarify the potential association of illness progression and telomere shortening.

Noteworthy, across the included studies in this systematic review, contradictory results were shown and there were a few biomarkers that were not investigated by more than one study. It is also important to mention the heterogeneity of patients with BD, the small sample sizes in a few of the included studies, and the use of medications, which may have potentially confounded the findings. In addition, the majority of the included studies had a cross-sectional design; in a recent report by Vieta and Angst (2021), longitudinal cohort studies were proposed to help clarify the biological underpinnings of BD and inform prevention through timely therapeutic intervention. Through the implementation of a global BD cohort, the authors suggest long-term studies that better investigate progressive changes in biomarkers associated with illness progression will be possible.

The present systematic review also highlights the need for more consistency in the use of staging models in BD research to standardize the results and understand the variability of biomarkers across different studies. In this context, an updated task force was recently published proposing a standardized nomenclature about the clinical stages of BD (Kupka et al., 2021). This effort would be crucial for the consistency in future studies and will assist in the further understanding of the biological basis of illness progression in BD.

Staging models can be useful clinical tools, and therefore have also been proposed as a measure of illness progression in other psychiatric disorders, including schizophrenia and major depressive disorder (MDD) (Agius et al., 2010; Fuente-Tomas et al., 2019; Meisenzahl et al., 2008; Moylan et al., 2013; Pantelis et al., 2005). Progressive changes in biomarkers have also been identified in schizophrenia and MDD, indicating that the progressive course observed in a subset of patients with BD may not be unique to this illness. Future research into biomarkers and progression is encouraged to translate staging models for psychiatric disorders into practice.

In conclusion, the findings of this systematic review support the notion of neuroprogression in patients with BD, particularly changes in brain structures such as the ventricles and GM. The present systematic review further solidifies the importance of investigating biomarkers and their role in illness progression to obtain consistent findings that could highlight potential treatment targets and inform future clinical care.

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Supplemental Material

Supplemental material for this article is available online.

References

Abé C, Ekman CJ, Sellgren C, et al. (2015) Manic episodes are related to changes in frontal cortex: A longitudinal neuroimaging study of bipolar disorder 1. *Brain* 138: 3440–3448.

Agius M, Goh C, Ulhaq S, et al. (2010) The staging model in schizophrenia, and its clinical implications. *Psychiatria Danubina* 22: 211–220.

Aguglia A, Salvi V, Amerio A, et al. (2022) Number of episodes and duration of illness associated with hypertension and 10-year cardiovascular risk in patients with bipolar disorder type I. *Psychiatry Research* 308: 114344.

Andreazza AC, Kapczinski F, Kauer-Sant'Anna M, et al. (2009) 3-Nitrotyrosine and glutathione antioxidant system in patients in the early and late stages of bipolar disorder. *Journal of Psychiatry and Neuroscience* 34: 263–271.

Ascoli BM, Parisi MM, Bristot G, et al. (2019) Attenuated inflammatory response of monocyte-derived macrophage from patients with BD: A preliminary report. *International Journal of Bipolar Disorders* 7: 1–11.

Barbé-Tuana F, Parisi M, Panizzutti B, et al. (2016) Shortened telomere length in bipolar disorder: A comparison of the early and late stages of disease. *Brazilian Journal of Psychiatry* 38: 281–286.

Berk M, Kapczinski F, Andreazza AC, et al. (2011) Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. *Neuroscience and Biobehavioral Reviews* 35: 804–817.

Berk M, Post R, Ratheesh A, et al. (2017) Staging in bipolar disorder: From theoretical framework to clinical utility. *World Psychiatry* 16: 236–244.

Borgelt L, Strakowski SM, DelBello MP, et al. (2019) Neurophysiological effects of multiple mood episodes in bipolar disorder. *Bipolar Disorders* 21: 503–513.

Bortolato B, Miskowiak KW, Köhler CA, et al. (2016) Cognitive remission: A novel objective for the treatment of major depression? *BMC Medicine* 14: 9.

Brambilla P, Harenski K, Nicoletti M, et al. (2001) MRI study of posterior fossa structures and brain ventricles in bipolar patients. *Journal of Psychiatric Research* 35: 313–322.

Brietzke E, Stabellini R, Grassi -Oliveira R, et al. (2011) Cytokines in bipolar disorder: Recent findings, deleterious effects but promise for future therapeutics. *CNS Spectrums* 16: 157–168.

Brietzke E, Stertz L, Fernandes BS, et al. (2009) Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. *Journal of Affective Disorders* 116: 214–217.

Brown NC, Andreazza AC and Young LT (2014) An updated meta-analysis of oxidative stress markers in bipolar disorder. *Psychiatry Research* 218: 61–68.

Cao B, Passos IC, Mwangi B, et al. (2016) Hippocampal volume and verbal memory performance in late-stage bipolar disorder. *Journal of Psychiatric Research* 73: 102–107.

Cao B, Passos IC, Mwangi B, et al. (2017b) Hippocampal subfield volumes in mood disorders. *Molecular Psychiatry* 22: 1352–1358.

Cao B, Passos IC, Wu MJ, et al. (2017a) Brain gyrification and neuroprogression in bipolar disorder. *Acta Psychiatrica Scandinavica* 135: 612–613.

Çinar K (2018) Telomere length and hTERT in mania and subsequent remission. *Brazilian Journal of Psychiatry* 40: 19–25.

Cosci F and Fava GA (2013) Staging of mental disorders: Systematic review. *Psychotherapy and Psychosomatics* 82: 20–34.

Deicken RF, Pegues MP, Anzalone S, et al. (2003) Lower concentration of hippocampal N-acetylaspartate in familial bipolar I disorder. *American Journal of Psychiatry* 160: 873–882.

Duarte J, Massuda R, Goi PD, et al. (2018) White matter volume is decreased in bipolar disorder at early and late stages. *Trends in Psychiatry and Psychotherapy* 40: 277–284.

Duffy A (2014) Toward a comprehensive clinical staging model for bipolar disorder: Integrating the evidence. *Canadian Journal of Psychiatry* 59: 659–666.

Ekman CJ, Lind J, Ryden E, et al. (2010) Manic episodes are associated with grey matter volume reduction: A voxel-based morphometry brain analysis. *Acta Psychiatrica Scandinavica* 122: 507–515.

Elvsåshagen T, Vera E, Bøen E, et al. (2011) The load of short telomeres is increased and associated with lifetime number of depressive episodes in bipolar II disorder. *Journal of Affective Disorders* 135: 43–50.

Fernandes BS, Molendijk ML, Köhler CA, et al. (2015) Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: A meta-analysis of 52 studies. *BMC Medicine* 13: 289.

Frey BN, Andreazza AC, Houenou J, et al. (2013) Biomarkers in bipolar disorder: A positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. *Australian and New Zealand Journal of Psychiatry* 47: 321–332.

Frey BN, Zunta-Soares GB, Caetano SC, et al. (2008) Illness duration and total brain gray matter in bipolar disorder: Evidence for neurodegeneration? *European Neuropsychopharmacology* 18: 717–722.

Fries GR, Pfaffenseller B, Stertz L, et al. (2012) Staging and neuroprogression in bipolar disorder. *Current Psychiatry Reports* 14: 667–675.

Fries GR, Vasconcelos -Moreno MP, Gubert C, et al. (2014) Hypothalamic-pituitary-adrenal axis dysfunction and illness progression in bipolar disorder. *International Journal of Neuropsychopharmacology* 18: 1–10.

Fries GR, Zamzow MJ, Andrews T, et al. (2020) Accelerated aging in bipolar disorder: A comprehensive review of molecular findings and their clinical implications. *Neuroscience and Biobehavioral Reviews* 112: 107–116.

Fuente-Tomas L, Sanchez-Autet M, Garcia-Alvarez L, et al. (2019) Clinical staging in severe mental disorders: Bipolar disorder, depression and schizophrenia. *Revista de Psiquiatría y Salud Mental* 12: 106–115.

Golia E, Limongelli G, Natale F, et al. (2014) Inflammation and cardiovascular disease: From pathogenesis to therapeutic target. *Current Atherosclerosis Reports* 16: 1–7.

Grande I, Magalhães PV, Chendo I, et al. (2014) Staging bipolar disorder: Clinical, biochemical, and functional correlates. *Acta Psychiatrica Scandinavica* 129: 437–444.

Javadapour A, Malhi GS, Ivanovski B, et al. (2007) Increased anterior cingulate cortex volume in bipolar I disorder. *Australian and New Zealand Journal of Psychiatry* 41: 910–916.

Kapczinski F, Berk M and Magalhães PV (2019) *Neuroprogression in Psychiatry*. Oxford: Oxford University Press.

Kapczinski F, Dias VV, Kauer-Sant'Anna M, et al. (2009) The potential use of biomarkers as an adjunctive tool for staging bipolar disorder. *Progress in Neuro-psychopharmacology and Biological Psychiatry* 33: 1366–1371.

Kapczinski F, Magalhães PVS, Balanzá -Martinez V, et al. (2014) Staging systems in bipolar disorder: An International Society for Bipolar Disorders Task Force Report. *Acta Psychiatrica Scandinavica* 130: 354–363.

Kapczinski F, Vieta E, Andreazza AC, et al. (2008) Allostatic load in bipolar disorder: Implications for pathophysiology and treatment. *Neuroscience and Biobehavioral Reviews* 32: 675–692.

Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, et al. (2009) Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. *International Journal of Neuropsychopharmacology* 12: 447–458.

Kim YK, Jung HG, Myint AM, et al. (2007) Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. *Journal of Affective Disorders* 104: 91–95.

Krishnan KRR (2005) Psychiatric and medical comorbidities of bipolar disorder. *Psychosomatic Medicine* 67: 1–8.

Kupka R, Duffy A, Scott J, et al. (2021) Consensus on nomenclature for clinical staging models in bipolar disorder: A narrative review from the International Society for Bipolar Disorders (ISBD) Staging Task Force. *Bipolar Disorders* 23: 659–678.

Lala SV and Sajatovic M (2012) Medical and psychiatric comorbidities among elderly individuals with bipolar disorder: A literature review. *Journal of Geriatric Psychiatry and Neurology* 25: 20–25.

Lavagnino L, Cao B, Mwangi B, et al. (2015) Changes in the corpus callosum in women with late-stage bipolar disorder. *Acta Psychiatrica Scandinavica* 131: 458–464.

Lisy ME, Jarvis KB, DelBello MP, et al. (2011) Progressive neurostructural changes in adolescent and adult patients with bipolar disorder. *Bipolar Disorders* 13: 396–405.

López-Villarreal A, Sánchez-Morla EM, Jiménez-López E, et al. (2019) Progression of the functional deficit in a group of patients with bipolar disorder: A cluster analysis based on longitudinal data. *European Archives of Psychiatry and Clinical Neuroscience* 270: 947–957.

McGorry PD, Nelson B, Goldstone S, et al. (2010) Clinical staging: A heuristic and practical strategy for new research and better health and social outcomes for psychotic and related mood disorders. *The Canadian Journal of Psychiatry* 55: 486–497.

McIntyre RS, Konarski JZ, Misener VL, et al. (2005) Bipolar disorder and diabetes mellitus: Epidemiology, etiology, and treatment implications. *Annals of Clinical Psychiatry* 17: 83–93.

Meisenzahl E, Koutsouleris N, Gaser C, et al. (2008) Structural brain alterations in subjects at high-risk of psychosis: A voxel-based morphometric study. *Schizophrenia Research* 102: 150–162.

Merikangas K, Jin R, He J, et al. (2011) Prevalence and correlations of bipolar spectrum disorder in the world mental health survey initiative. *Archives of General Psychiatry* 68: 241–251.

Modesti PA, Reboldi G, Cappuccio FP, et al. (2016) Panethnic differences in blood pressure in Europe: A systematic review and meta-analysis. *PLoS ONE* 11: e0147601.

Moher D, Shamseer L, Clarke M, et al. (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 4: 1–9.

Moorhead TWJ, McKirdy J, Sussmann JE, et al. (2007) Progressive gray matter loss in patients with bipolar disorder. *Biological Psychiatry* 62: 894–900.

Moylan S, Maes M, Wray N, et al. (2013) The neuroprogressive nature of major depressive disorder: Pathways to disease evolution and

resistance, and therapeutic implications. *Molecular Psychiatry* 18: 595–606.
Muller N (2019) The role of intercellular adhesion molecule-1 in the pathogenesis of psychiatric disorders. *Frontiers in Pharmacology* 10: 1251.
Muneer A and Minhas FA (2019) Telomere biology in mood disorders: An updated, comprehensive review of the literature. *Clinical Psychopharmacology and Neuroscience* 17: 343.
Munkholm K, Vinberg M and Kessing LV (2016) Peripheral blood brain-derived neurotrophic factor in bipolar disorder: A comprehensive systematic review and meta-analysis. *Molecular Psychiatry* 21: 216–228.
Nery FG, Chen HH, Hatch JP, et al. (2009) Orbitofrontal cortex gray matter volumes in bipolar disorder patients: A region-of-interest MRI study. *Bipolar Disorders* 11: 145–153.
Ouzzani M, Hammady H, Fedorowicz Z, et al. (2016) Rayyan: A Web and Mobile App for systematic reviews. *Systematic Reviews* 5: 210.
Page MJ, McKenzie JE, Bossuyt PM, et al. (2021) The PRISMA 2020 Statement: an updated guidelines for reporting systematic reviews. *BMJ* 372: n160.
Panizzutti B, Gubert C, Schuh AL, et al. (2015) Increased serum levels of eotaxin/CCL11 in late-stage patients with bipolar disorder: An accelerated aging biomarker? *Journal of Affective Disorders* 182: 64–69.
Pantelis C, Yucel M, Wood S, et al. (2005) Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophrenia Bulletin* 31: 672–696.
Patel JP and Frey BN (2015) Disruption in the blood-brain barrier: The missing link between brain and body inflammation in bipolar disorder? *Neural Plasticity* 2015: 1–12.
Pfaffenseller B, Wollenhaupt-Aguiar B, Fries GR, et al. (2014) Impaired endoplasmic reticulum stress response in bipolar disorder: Cellular evidence of illness progression. *International Journal of Neuropsychopharmacology* 17: 1453–1463.
Powell T, Dima D, Frangou S, et al. (2018) Telomere length and bipolar disorder. *Neuropsychopharmacology* 43: 445–453.
Reinares M, Papachristou E, Harvey P, et al. (2013) Towards a clinical staging for bipolar disorder: Defining patient subtypes based on functional outcome. *Journal of Affective Disorders* 144: 65–71.
Reininghaus EZ, Lackner N, Birner A, et al. (2016) Extracellular matrix proteins matrix metallopeptidase 9 (MMP9) and soluble intercellular adhesion molecule 1 (sICAM-1) and correlations with clinical staging in euthymic bipolar disorder. *Bipolar Disorders* 18: 155–163.
Rosa AR, Gonzalez-Ortega I, Gonzalez-Pinto A, et al. (2012) One-year psychosocial functioning in patients in the early vs. late stage of bipolar disorder. *Acta Psychiatrica Scandinavica* 125: 335–341.
Rosa AR, Magalhães PV, Czepielewski L, et al. (2014) Clinical staging in bipolar disorder: Focus on cognition and functioning. *The Journal of Clinical Psychiatry* 75: e450–e456.
Rowland T, Perry BI, Upthegrove R, et al. (2018) Neurotrophins, cytokines, oxidative stress mediators and mood state in bipolar disorder: Systematic review and meta-analyses. *The British Journal of Psychiatry* 213: 514–525.
Salim S, Chugh G and Asghar M (2012) Inflammation in anxiety. *Advances in Protein Chemistry and Structural Biology* 88: 1–25.
Savas HA, Gergerlioglu HS, Armutcu F, et al. (2006) Elevated serum nitric oxide and superoxide dismutase in euthymic bipolar patients: Impact of past episodes. *The World Journal of Biological Psychiatry* 7: 51–55.
Simon NM, Smoller JW, McNamara KL, et al. (2006) Telomere shortening and mood disorders: Preliminary support for a chronic stress model of accelerated aging. *Biological Psychiatry* 60: 432–435.
Siwek M, Sowa-Kucma M, Styczen K, et al. (2016a) Decreased serum zinc concentration during depressive episode in patients with bipolar disorder. *Journal of Affective Disorders* 190: 272–277.
Siwek M, Sowa-Kucma M, Styczen K, et al. (2016b) Thiobarbituric acid-reactive substances: markers of an acute episode and a late stage of bipolar disorder. *Neuropsychobiology* 73: 116–122.
Soeiro-de-Souza MG, Andreazza AC, Carvalho AF, et al. (2013) Number of manic episodes is associated with elevated DNA oxidation in bipolar I disorder. *International Journal of Neuropsychopharmacology* 16: 1505–1512.
Spoorthy MS, Chakrabarti S and Grover S (2019) Comorbidity of bipolar and anxiety disorders: An overview of trends in research. *World Journal of Psychiatry* 9: 7.
Squassina A, Pisanu C and Vanni R (2019) Mood disorders, accelerated aging, and inflammation: Is the link hidden in telomeres? *Cells* 8: 52.
Stertz L, Magalhães PV and Kapczinski F (2013) Is bipolar disorder an inflammatory condition? The relevance of microglial activation. *Current Opinion in Psychiatry* 26: 19–26.
Strakowski SM, DelBello MP, Sax KW, et al. (1999) Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. *Archives of General Psychiatry* 56: 254–260.
Strakowski SM, DelBello MP, Zimmerman ME, et al. (2002) Ventricular and periventricular structural volumes in first-versus multiple-episode bipolar disorder. *American Journal of Psychiatry* 159: 1841–1847.
Tatay-Manteiga A, Balanza -Martinez V, Bristot G, et al. (2017) Clinical staging and serum cytokines in bipolar patients during euthymia. *Progress in Neuro-psychopharmacology and Biological Psychiatry* 77: 194–201.
Tatay-Manteiga A, Correa-Ghisays P, Cauli O, et al. (2018) Staging, neurocognition and social functioning in bipolar disorder. *Frontiers in Psychiatry* 9: 709.
Tsalamandris S, Antonopoulos AS, Oikonomou E, et al. (2019) The role of inflammation in diabetes: Current concepts and future perspectives. *European Cardiology Review* 14: 50.
Van Rheenen TE, Lewandowski KE, Bauer IE, et al. (2019) Current understandings of the trajectory and emerging correlates of cognitive impairment in bipolar disorder: An overview of evidence. *Bipolar Disorders* 22: 13–27.
Velosa J, Delgado A, Finger E, et al. (2020) Risk of dementia in bipolar disorder and the interplay of lithium: A systematic review and meta-analyses. *Acta Psychiatrica Scandinavica* 141: 510–521.
Vieta E and Angst J (2021) Bipolar disorder cohort studies: Crucial, but underfunded. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* 47: 31–33.
Watkins CC, Sawa A and Pomper MG (2014) Glia and immune cell signaling in bipolar disorder: Insights from neuropharmacology and molecular imaging to clinical application. *Translational Psychiatry* 4: 350.
Wingo AP, Harvey PD and Baldessarini RJ (2009) Neurocognitive impairments in bipolar disorder patients: Functional implications. *Bipolar Disorders* 11: 113–125.
Wollenhaupt-Aguiar B, Pfaffenseller B, Chagas V, et al. (2016) Reduced neurite density in neuronal cell cultures exposed to serum of patients with bipolar disorder. *International Journal of Neuropsychopharmacology* 19: 1–5.
Woods BT, Yurgelun-Todd D, Benes FM, et al. (1990) Progressive ventricular enlargement in schizophrenia: Comparison to bipolar affective disorder and correlation with clinical course. *Biological Psychiatry* 27: 341–352.