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REVIEW ARTICLE

Postmortem evidence of brain inflammatory markers in bipolar disorder: a systematic review

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Abstract

Bipolar disorder (BD) is a chronic affective disorder with extreme mood swings that include mania or hypomania and depression. Though the exact mechanism of BD is unknown, neuroinflammation is one of the numerous investigated etiopathophysiological causes of BD. This article presents a systematic review of the data regarding brain inflammation evaluating microglia, astrocytes, cytokines, chemokines, adhesion molecules, and other inflammatory markers in postmortem BD brain samples. This systematic review was performed according to PRISMA recommendations, and relevant studies were identified by searching the PubMed/MEDLINE, PsycINFO, EMBASE, LILACS, IBECS, and Web of Science databases for peer-reviewed journal articles published by March 2019. Quality of included studies appraised using the QUADAS-2 tool. Among the 1814 articles included in the primary screening, 51 articles measured inflammatory markers in postmortem BD brain samples. A number of studies have shown evidence of inflammation in BD postmortem brain samples. However, an absolute statement cannot be concluded whether neuroinflammation is present in BD due to the large number of studies did not evaluate the presence of infiltrating peripheral immune cells in the central nervous system (CNS) parenchyma, cytokines levels, and microglia activation in the same postmortem brain sample. For example, out of 15 studies that evaluated microglia cells markers, 8 studies found no effect of BD on these cells. Similarly, 17 out of 51 studies evaluating astrocytes markers, 9 studies did not find any effect of BD on astrocyte cells, whereas 8 studies found a decrease and 2 studies presented both increase and decrease in different brain regions. In addition, multiple factors account for the variability across the studies, including postmortem interval, brain area studied, age at diagnosis, undergoing treatment, and others. Future analyses should rectify these potential sources of heterogeneity and reach a consensus regarding the inflammatory markers in postmortem BD brain samples.

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Introduction

Bipolar disorder (BD) is a neuropsychiatric disorder that belongs to a group of severe, recurrent affective disorders that are among the leading cause of disability and death in young people [1]. Irrespective of nationality, ethnic or cultural origin, and socioeconomic status BD affects 2–3% of the world's population [2, 3]. The etiology of this psychiatric disorder is still unknown, however several morphological, metabolic, and signaling abnormalities have been proposed, including volume decrease in the hippocampus [4] and in the frontal cortical in the Mania group [5]. Among these potential-contributing factors, number of studies evidence the role of neuroinflammation in BD pathogenesis [6–8] and variation in microglia, astrocytes, and oligodendrocytes markers also have been found in postmortem studies in patients with BD [9–11]. However, the term neuroinflammation referred for conditions that

meet all the four signs including elevations in proinflammatory cytokines, microglial activation, infiltration of immune cells from the bloodstream and secondary degeneration in the brain [12, 13].

The brain has specific immunological and inflammatory adaptations, including a protective blood–brain barrier (BBB) and highly efficient glial cells [14]. The main innate immune cells that contribute to the immune response in central nervous system (CNS) includes microglia, astrocytes, macrophages, natural killer (NK) cells, mast cells as well as oligodendrocytes and neurons [15]. Microglia, the resident macrophages of the CNS, are activated after injury or stress, release of proinflammatory cytokines that generate reactive oxygen and nitrogen species and phagocytic activity [16]. Interleukin (IL)-1β released from microglia can activate astrocytes, another important cell type in the neuroimmune system, which in turn release additional cytokines and chemokines such as IL-1β, tumor necrosis factor (TNF)-α, and chemokine (c-c motif) ligand (CCL5) and express glial fibrillary acidic protein (GFAP) and S100 calcium-binding protein B (S100B) [17–20].

Evidence from preclinical and clinical studies, including neuroimaging and genetic studies, supports the role of inflammation in the etiological pathway of BD. A recent systematic review demonstrated the increased the levels of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, interferon (INF)-γ, and IL-18 in serum and plasma from acute phase of BD patients. On the other hand reduction in the levels of anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta 1 (TGF-β1) was observed during the manic phases of BD [21]. Another systematic review and meta-analysis revealed fluctuations in components of the TNF pathway, including soluble and membrane-bound TNF and its two receptors, in the peripheral blood of BD subjects [22]. Even genetic studies have indicated that a multitude of genes that partake in various neuroimmunological and inflammatory pathways are either up- or downregulated in BD [23–25]. A clear pictorial visualization of neuroinflammation in BD has been made possible through in vivo positron emission tomography (PET) imaging studies. The activation of microglia visualized in vivo using [(11)C]-(R)-PK11195 PET imaging demonstrates the focal neuroinflammation in BD [26]. Recently reported largest cohort of study from MRI findings revealed that cortical gray matter was thinner in frontal, temporal, and parietal regions of both brain hemispheres in BD patients [27]. The implications of results from previous findings it seems plausible that inflammation may have a role in BD. In this article, we systematically review the literature on brain inflammatory markers measured in BD postmortem brains to (i) identify the inflammatory markers that are elevated in the postmortem brain of BD patients, (ii) draw attention to immune cells and immunological and inflammatory pathways, and recognize neuroinflammation in postmortem brain samples of BD patients.

Methods

We performed this systematic review as stated in a prospective protocol following the PRISMA Statement guidelines [28]. The review protocol is registered at PROSPERO (registration number: CRD42017083459; http://www.crd.york.ac.uk/prospero).

Literature search strategy

This systematic review of clinical studies was conducted to evaluate inflammatory markers in postmortem BD brain studies. The studies were identified by searching the PubMed/MEDLINE (National Library of Medicine), PsycINFO, and EMBASE (Ovid) databases for peer-reviewed journal articles that were published by March 2019. To identify additional relevant citations, we conducted forward searches in the LILACS (Latin American and Caribbean Health Sciences Literature), IBECS (Bibliographical Index in Spanish in Health Sciences), and Web of Science databases. The abovementioned databases were searched with the following combinations of keywords: ("bipolar disorder" OR "bipolar patient" OR "bipolar depression" OR "manic depressive illness" OR "mania") AND ("postmortem" OR "post-mortem" OR "brain sample" OR "autopsy") AND ("inflammation" OR "neuroinflammation" OR "glia" OR "microglia" OR "astrocytes" OR "cytokines" OR "chemokines").

Review of patients, interventions, comparators, outcome measures, and study designs (PICO framework)

We posed the question "Do postmortem brain samples of BD patients' present inflammatory markers?"

Eligibility criteria

We included original peer-reviewed articles and abstracts with no language and year restriction to identify inflammatory markers in postmortem BD brains. We omitted review articles, in vitro studies, animal studies, and studies that did not present inflammatory markers in postmortem BD brain samples.

Screening

A total of 1814 articles were included in the primary screening. Reference management software (EndNote X7 for Windows from Thomson Reuters, 2013) was used for

screening purposes. After the omission of 455 duplicates, a total of 1359 articles were selected for the study. The retrieved studies were first screened based on their titles and abstracts, and 1286 articles were further omitted based on the exclusion criteria (reviews, in vitro studies, animal studies, no BD, no inflammatory markers). The remaining 73 full-text articles were obtained and thoroughly evaluated in a second screening. At the end of the second screening, 51 articles were ultimately included after 22 articles were discarded based on the exclusion criteria (Fig. 1).

Article selection

The authors (PS, OFP, NA, VVG, and TB) screened the titles and abstracts for eligibility. Any controversies regarding the studies were resolved through simultaneous evaluation by the three primary authors. Upon agreement from the three authors, references that were valid based on the selection criteria were selected for final inclusion, and full-text PDFs were obtained and analyzed. The two authors, TB and VVG, settled issues whenever a consensus could not be reached between the first three authors.

Data extraction

The data were extracted from the comprehensively reviewed journal articles in a methodical manner. The variables extracted for our review included the study design, sample size (*n*), and inflammatory biomarkers as well as the way in which the inflammatory marker profile was associated with BD.

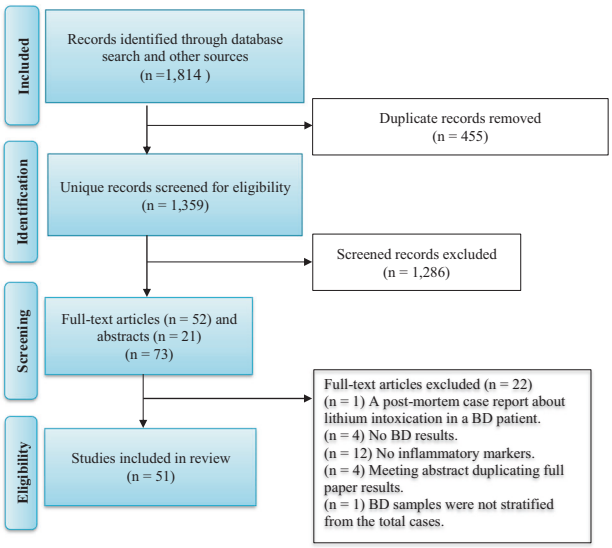

Fig. 1 Flowchart of study selection

Quality assessment of the included studies

Methodological quality assessment of studies was performed according to Quality Assessment of Diagnostic Accuracy Studies-2 checklist (QUADAS-2), that consists of four key domains: patient selection, index test, reference standard and flow and timing [29]. The quality assessment was performed using Review Manager® (RevMan) version 5.3.

Results

Areas of the brain studied

The areas of the brain studied among our reviewed papers include prefrontal cortex (PFC; Brodmann area (BA) 10), dorsolateral prefrontal cortex (DLPFC; BA 46), frontal cortex (FC), orbitofrontal cortex (OFC; BA 11), anterior cingulated cortex (ACC; BA 24), frontoparietal cortex (FPC), parietal cortex (PC; BA 40), temporal cortex (TC; BA 20), superior temporal gyrus (STG), inferior temporal cortex (ITC), entorhinal cortex (ECx), hippocampus, amygdala, thalamus, cerebellum, dorsal raphe nucleus (DRN), subventricular zone (SVZ), and caudate putamen (Tables 1 and 2; Figs. 2 and 3).

Cellular parameters

Astrocytes

Astrocytes provide structural and nutritional support to neurons and play a significant role in CNS immune responses, synaptic function, neuronal metabolism, and myelin sheath development and maintenance. Changes in the number, density, or function of astrocytes seriously influence the nervous system [30, 31]. Recently, two different subtypes of reactive astrocytes that were termed “A1” and “A2” in analogy to the “M1” and “M2” macrophage nomenclature have been reported. Microglia when activated induces A1 astrocytes by secreting IL-1α, TNF and C1q. The subtype A1 lose the ability to promote neuronal survival, outgrowth, synaptogenesis, and phagocytosis but gain neurotoxic function, rapidly killing neurons and oligodendrocytes [32]. Our database search revealed 21 studies that estimated astrocyte-related changes in postmortem BD brains including changes in astrocyte size, density, and areal fraction; astrocytic end feet; and the expression of markers such as GFAP, phosphorylated GFAP (pGFAP), and S100B (Table 1; Figs. 2 and 3).

Table 1 Cellular mechanisms in postmortem brain tissue of bipolar disorder patients

Author	Title	Study design	Brain bank, Country	Sample size (patients and controls/sex/age)	Death from suicides	Brain region studied	Technique	Tissue/ biochemical evaluation	Main findings
Glial density and cytoarchitecture									
Altshuler et al. [121]; USA	Amygdala astrocyte reduction in subjects with major depressive disorder but not bipolar disorder.	PMCCS	SFNC, SMRI, USA	Total cases = 24, BD = 10: 6 m, 4 f; normal control = 14, 8 m, 6 f.	BD = 7	Amygdala	IHC	Astrocyte density	There are no glial density changes in BD samples.
Brauch et al. [122]; USA	Glial cell number and neuron/ glial cell ratios in postmortem brains of bipolar individuals.	PMCCS	SFNC, USA	Total cases = 30, BD = 15; age: 43.2 ± 11.64, and normal control = 15; age: 46.6 ± 9.47.	NA	TC	Nissl staining	Glial area, number and density	The glial area is reduced in BD (39.29 ± 11.069, $p = 0.018$) compared to control (50.36 ± 12.444). The ratio of glial space to neuronal area is reduced in BD (0.88 ± 0.399, $p = 0.0278$) vs. normal control (1.36 ± 0.732).
Brisch et al. [70]; Germany	Microglia in the dorsal raphe nucleus plays a potential role in both suicide facilitation and prevention in affective disorders.	PMCCS & PMCCGS	MBB, Germany	Total cases = 34, BD = 12; 8 m, 4 f; age 39–69, mean age 54, and normal control = 22; 7 m, 15 f; age 24–48, mean age 52.	BD = 7	DRN	IHC	Density of HLA-DR positive microglia	Decreased density of HLA-DR positive microglial in non-suicidal depressed subjects when compared to depressed suicide victims and controls.
Comte et al. [41]; USA	The human subventricular zone in neuropsychiatric disease.	PMCCS & PMCCGS	SFNC, SMRI (ventral SVZ); HBTRC, MLH (dorsal SVZ), USA	NA	NA	Ventral and dorsal SVZ	NA	GFAP	No alteration in astrocytic width or density in ventral and dorsal SVZ. Normal levels of GFAP and in BD indicate absence of gliosis.
Cotter et al. [123]; UK	Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder.	PMCCS	SFNC, USA	Total cases = 30, BD = 15; 9 m, 6 f; age 42.3 ± 11.7, and normal control = 15; 9 m, 6 f; age 48.1 ± 10.7.	BD = 9	Area 24b of the supracallosal ACC	Nucleator and optical dissector	Glial cell density	BD samples showed no difference in glial density and density in ACC compared to control.
Cotter et al. [124]; Ireland	Cell density and cortical thickness in Heschl's gyrus in schizophrenia, major depression, and bipolar disorder.	PMCCS	SFNC, USA	Total cases = 30, BD = 15, and normal control = 15.	NA	Heschl's gyrus within the STG	Optical dissector	Glial cell density	There is no significant difference glial cell density in Heschl's gyrus in BD when compared to control.
Cotter et al. [125]; Ireland	Evidence for orbitofrontal pathology in bipolar disorder and major depression, but not in schizophrenia.	PMCCS	SFNC, USA	Total cases = 30, BD = 15; 9 m, 6 f; age 42.3 ± 11.7, and normal control = 15; 9 m, 6 f; age 48.1 ± 10.7.	BD = 9	cOFC	Nucleator and optical dissector	Glial size density	There are no glial size and density changes between groups.
Damadzic et al. [42]; USA	A quantitative immunohistochemical study of astrocytes in the entorhinal cortex in schizophrenia, bipolar disorder and major depression: Absence of significant astrocytosis.	PMCSS	SFNC	Total cases = 56, BD = 13; 7 m, 6 f; age 44 ± 12, and normal control = 15; 9 m, 6 f; age 48 ± 11.	BD = 7	ECx	IHC	GFAP number and density	No difference in GFAP number and density between BD and control samples.
Gilmore et al. [126]; USA	Analysis of ependymal abnormalities in subjects with schizophrenia, bipolar disorder, and depression.	PMCCS	SFNC, USA	Total cases = 30, BD = 15; 9 m, 6 f; age 42.3 ± 11.7, and normal control = 15; 9 m, 6 f; age 48.1 ± 10.7.	NA	Anterior hippocampus with ependyma of the temporal horn	HE staining	Ependymal discontinuities, subventricular rosettes, and nodular gliosis	In BD, there is no significant changes in ependymal discontinuities, subventricular rosettes, and nodular gliosis as compared to control.
Gos et al. [19]; Germany	S100B-immunopositive astrocytes and oligodendrocytes in the hippocampus are differentially afflicted in unipolar and bipolar depression: A postmortem study.	PMCCS	MBB, Germany	Total cases = 18, BD = 6; 3 m, 3 f; age 55.7 ± 13.3, and normal control = 12; 7 m, 5 f; age 55.3 ± 12.3.	NA	CA1 pyramidal layer and alveus of hippocampus	Optical dissector	S100B-immunopositive astrocytes	Right and left CA1 pyramidal layers showed a reduction in the numerical density of S100B-immunopositive astrocytes in BD (right: 107 ± 86, $p = 0.04$; left: 165 ± 210, $p = 0.049$) compared to control (right: 441 ± 392, left: 425 ± 268).
Hercher et al. [18]; Canada	Evidence for morphological alterations in prefrontal white matter glia in schizophrenia and bipolar disorder.	PMCCS	SFNC, SMRI, USA	Total cases = 40, BD = 20; 8 m: 12 f; age: 47.4 ± 0.7 and normal control = 20; 14 m: 6 f; age: 45.3 ± 6.5.	BD = 6	White matter adjacent to the DLPFC (BA 9)	Nissl staining ELISA, and WB	Density, areal fraction, and spatial distribution of GFAP and IBA-1- microglia	The GFAP area fraction ($p = 0.05$) and astrocyte spatial distribution ($p = 0.040$) also differed among groups, reflecting decreased GFAP area fraction (BD 27%, $p = 0.027$) and increased GFAP positive astrocyte cell clustering ($p = 0.025$) in BD samples. There is no difference in IBA-1 and microglial area fraction or space distribution.
Miller et al. [104]; USA	Upregulation of the initiating step of the kynurenine pathway in postmortem anterior cingulate cortex from individuals with schizophrenia and bipolar disorder.	PMCCS and PMCCGS	SFNC, USA	Total cases = 28, BD = 14; m: f = 1.5: 1; age 41.8 ± 3.2, BD with psychosis m:f = 1.8:1; age 43.2 ± 3.7, and normal control = 14; m:f = 1.33:1; age 48.6 ± 2.9.	NA	ACC	HPLC, RT-PCR, and IHC	The density of TDO2 positive white and gray matter glial cells	The density and intensity of glial cells in both gray and white matter stained for TDO2 increased in BD (6.71 ± 0.72) as compared to control (5.00 ± 0.55) ($p = 0.02$).
Pantazopoulos et al. [43]; USA	Extracellular matrix-glial abnormalities in the amygdala and entorhinal cortex of subjects diagnosed with schizophrenia.	PMCCS	HBTRC, MLH, USA	Total cases = 36, single cohort of BD = 11; 7 m, 4 f; age: 66.7 ± 17.3, and two separate cohorts of normal control = 15 and 10; 10 m, 5 f; age 65.9 ± 12.0.	NA	Amygdala and ECx	IHC and immune cyto chemistry	Numerical densities of CSPG-positive glial cells, PNNs, GFAP in the amygdalar nuclei and ECx	There is significant increase in CSPG positive glial cells in deep amygdala (lateral) and ECx (28.07 ± 37.52, $p = 0.04$, 112%) in BD as compared to control (13.22 ± 19.90). In addition, there is a decrease in

Table 1 (continued)

Author	Title	Study design	Brain bank, Country	Sample size (patients and controls/sex/age)	Death from suicides	Brain region studied	Technique	Tissue/ biochemical evaluation	Main findings
									layer III of the left ECx (6.50 ± 5.99, $p = 0.02$, −51%) in BD as compared to control (5.86 ± 1.81). No significant changes in GFAP expression between BD and control.
Rajkowska et al. [80]; USA	Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder.	PMCCS	HBTRC, MLH; courtesy of Craig Stockmeier, Ph.D., CWRU, USA	Total cases = 21, BD = 10; 7 m, 3 f; mean age 47.2 and normal control = 11; 8 m, 3 f; mean age 51.7.	BD = 5	DLPFC area 9	Three-dimensional morpho metric method	Glial density, shape of glial nuclei	A significant reduction in mean glial cell density in sublayer IIIc (19%, $p = 0.03$) in BD. The small glial cell density decreased 62% ($p = 0.04$) in layer I of BD (4.8 ± 4.5) compared to normal control (12.5 ± 10.4); Medium glial cell density decreased by 39% ($p = 0.02$) in layer III in BD (22.7 ± 10.6) compared to normal control (37.1 ± 8.0). In addition, there is an increase in mean glial cell body size in cortical layer I by 9% ($p = 0.02$) and sublayer IIIc by 7% ($p = 0.04$) which is coupled with glial nuclear shape. The reduction in density of glial cells with round nuclei by 26% ($p = 0.001$) and density of glial cell with less spherical nuclear shape by 77% ($p = 0.04$) is observed in BD.
Schmitt et al. [127]	Histological studies of oligodendrocytes in psychiatric diseases.	PMCCS	NA	Total cases = 18, BD = 8, and normal control = 10.	NA	Hippocampus	Nissl staining	Numbers and densities of astrocytes	BD cases presented with no change in glial cell number or density.
Schmitt et al. [25]	Histological and gene expression studies of the hippocampus in schizophrenia.	PMCCS and PMCCGS	NA	Total cases = 18, BD = 8, and normal control = 10.	NA	Anterior and posterior hippocampus subregions	Nissl staining, genome-wide cDNA microarray, and qRT-PCR	Numbers and densities of astrocytes	In BD, there is no associated changes in the number and densities of astrocytes.
Steiner et al. [74]; Germany	Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide.	PMCCS	MBB, Germany	Total cases = 15, BD = 5; 3 m, 2 f; mean age 49.2, and normal control = 10; 5 m, 5 f; mean age 54.	NA	DLPFC, ACC, mediodorsal thalamus, and hippocampus	IHC	Microglial density via HLA-DR expression	No significant difference in microglial density between BD and control.
Weis et al. [64]; USA	Reduced expression of human endogenous retrovirus (HERV)-W GAG protein in the cingulate gyrus and hippocampus in schizophrenia, bipolar disorder, and depression.	PMCCS	SFNC, USA	Total cases = 30, BD = 15, and normal control = 15.	NA	ACC and hippocampus	IHC and WB	HERV-W capsid (GAG) protein expression in the neurons and astroglial cells of cingulate gyrus and hippocampus	GAG protein expression is significantly reduced in BD hippocampus (glial cells, $p = 0.03$) as compared to control.
Glial protein expression									
Dean et al. [44]; Australia	Regionally specific changes in levels of cortical S100β in bipolar 1 disorder but not schizophrenia.	PMCCS	VIFM and NHPBPR	Total cases = 56, BD = 13; 7 m, 6 f; age 44 ± 12, and normal control = 15; 9 m, 6 f; age 48 ± 11.	NA	BA 9, BA 10, BA 46, and BA 40	WB and RT-PCR	S100B and GFAP	Levels of S100B decreased in BA 9 and increased in BA 40. No change in GFAP levels.
Fatemi et al. [47]; USA	Glial fibrillary acidic protein is reduced in cerebellum of subjects with major depression, but not schizophrenia.	PMCCS	SFNC, USA	Total cases = 30, BD = 15; 9 m, 6 f; age 42.3 (25–61), and normal control = 15; 9 m, 6 f; age 48.1 (29–68).	NA	Cerebellum (white matter and gray matter)	WB	GFAP levels	There is a reduction in GFAP levels by 17% (121.5 ± 48.2) in the cerebellum of BD subjects compared to normal control (146.0 ± 25.3) that did not reach statistical significance.
Feresten et al. [50]; Canada	Increased expression of glial fibrillary acidic protein in prefrontal cortex in psychotic illness.	PMCCS & PMCCGS	SMRI, USA	Total cases = 104, BD = 34; 16 m, 18 f; age 45.4 ± 10.7; and normal control = 35; 26 m, 9 f; age 44.2 ± 7.9.	BD = 15	DLPFC	WB	GFAP, ALDH1L1, and EAAT1	Increase in GFAP levels and no change in ALDH1L1 and EAAT1 levels.
Hamidi et al. [59]; USA	Glial reduction in amygdala in major depressive disorder is due to oligodendrocytes.	PMCCS	HBTRC, USA	Total cases = 27, BD = 9; 6 m, 3 f; age 15–80, and normal control = 10; 9 m, 1 f; age 33–88.	BD = 3	Amygdala	IHC	S100B and HLA	No significant changes in S100B and HLA in BD samples as compared to controls.
Johnston-Wilson et al. [20]; USA	Disease-specific alterations in frontal cortex brain proteins in schizophrenia, bipolar disorder, and major depressive disorder.	PMCCS	SFNC, USA	Total cases = 46, BD = 23, and normal control = 23.	NA	FC (BA 10) of the cerebral hemisphere	Two-dimensional gel electrophoresis	Protein sequences are determined and compared with the Swiss protein database for known matches	The protein spot, 500-GFAP ($p = 0.0042$) is decreased in BD samples.
Muller et al. [46]; Netherlands	Neither major depression nor glucocorticoid treatment affects the cellular integrity of the human hippocampus.	PMCCS	NBB, Netherlands	Total cases = 41, BD/MDD = 15; 11 m, 4 f; age 21–82; mean age 51.5, glucocorticoid treated subjects with no psychiatric disorder = 10; 4 m, 6 f; age 33–78; mean age 55.5 and normal control = 16; 10 m, 6 f; age 32–85; mean age 58.5.	BD/ MDD = 4	Hippocampus	HE, Nissl and Bodian staining, and IHC	GFAP	The GFAP positive astrocytes is decreased ($p < 0.05$) in CA1 and CA2 regions of BD samples (0.09 ± 0.09); steroid treated samples (0.13 ± 0.13) as compared to control (0.50 ± 0.15).

Table 1 (continued)

Author	Title	Study design	Brain bank, Country	Sample size (patients and controls/sex/age)	Death from suicides	Brain region studied	Technique	Tissue/ biochemical evaluation	Main findings
Toro et al. [48]; UK	Glial fibrillary acidic protein and glutamine synthetase in subregions of prefrontal cortex in schizophrenia and mood disorder.	PMCSS	Stanley Consortium	Total cases = 60, BD = 15; 9 m, 6 f; age 25–61; mean age 42.3, and normal control = 15; 9 m, 6 f; age 48.07.	BD = 9	PFC (BA 9, 32, and 46), OFC (BA 11, 12, 47, and 45)	Immuno auto radio graphy and IHC	GFAP	Decrease in GFAP immunoreactivity in area 11/ 47.
Webster et al. [45]; USA	Immunohistochemical localization of phosphorylated glial fibrillary acidic protein in the prefrontal cortex and hippocampus from patients with schizophrenia, bipolar disorder, and depression.	PMCCS	SFNC, USA	Total cases = 30, BD = 15; 9 m, 6 f; age 25–61; mean age 42.3, and normal control = 15; 9 m, 6 f; age 29–68; mean age 48.1.	BD = 9	DLPFC and hippocampus	IHC	pGFAP labeled astrocytes	There is no reduction of astrocytes in pGFAP labeled areas in BD as compared to control.
Weis et al. [73]; USA	Expression of cellular prion protein (PrP(c)) in schizophrenia, bipolar disorder, and depression.	PMCCS	SFNC, USA	Total cases = 30, BD = 15; 9 m, 6 f; age 42.3 (25–61), and normal control = 15; 9 m, 6 f; age 48.1 (29–68).	NA	ACC	IHC	Rating scores and numerical density of PrP(c) positive and negative glial cells	PrP(c)-positive glial cells are significantly reduced in the white matter of patients with BD ($p = 0.02$) compared to control.
Glial gene expression									
Barley et al. [9]; USA	Subcortical oligodendrocyte- and astrocyte-associated gene expression in subjects with schizophrenia, major depression, and bipolar disorder.	PMCCGS	SFNC, USA	Total cases = 120, BD = 60; 31 m, 20 f, and normal control = 60; 36 m, 23 f, (age 25–68; mean age 41.9–49).	NA	Four subcortical regions (AV and MDN of thalamus, and IC and putamen)	RT-PCR	mRNA expression of astrocytes genes	GFAP and ALDH1L1 had higher mean expression levels across regions in BD relative to normal controls.
Rao et al. [11]; USA	Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients.	PMCCS & PMCCGS	HBTRC, MLH, USA	Total cases = 30, BD = 10 and normal control = 20.	NA	FC	WB and RT-PCR	GFAP, cFos, and CD11B	Increased mRNA and protein levels of GFAP, cFos, and CD11B.
Seredenina et al. [71]; Switzerland	Decreased NOX2 expression in the brain of patients with bipolar disorder: association with valproic acid prescription and substance abuse.	PMCSS	SMRI, USA	mRNA analysis: Total cases = 60, BD = 15 and normal control = 15.	NA	ACC	RT-PCR and IHC	CD68 and CD11B	Decrease in microglial markers CD68 and CD11B in BD samples.
Webster et al. [49]; USA	Glial fibrillary acidic protein mRNA levels in the cingulate cortex of individuals with depression, bipolar disorder, and schizophrenia.	PMCCGS and PMCCGS	SFNC, USA	Total cases = 30, BD = 15; 9 m, 6 f; age 42.3 ± 11.7, and normal control = 15; 9 m, 6 f; age 48.1 ± 10.7.	BD = 9	ACC	In situ hybridi zation	GFAP mRNA levels	GFAP mRNA levels are more in white matter when compared with gray matter levels in all samples. Within the gray matter, the levels of GFAP are more in layer VI ($p < 0.01$). The GFAP mRNA levels are significantly decreased in the white matter ($p = 0.04$) of all areas and gray matter of ACC ($p < 0.008$) in BD as compared to control.

7-AAD 7-aminoactinomycin D, *ACC* anterior cingulate cortex, *AD* astrocyte density, *ALDH1L1* aldehyde dehydrogenase 1 family, member L1, *APN* anterior principal nucleus, *AV* anteroventral, *BA* Broadmann's area, *BD* bipolar disorder, *CA1* and 2 cornu ammonis1 and 2, *cDNA* complementary deoxyribonucleic acid, *cOFC* caudal orbitofrontal cortex, *CSPG* choindroitin sulfate proteoglycan, *CWRU* Case Western Reserve University, *DLPFC* dorsolateral prefrontal cortex, *DNA* deoxyribonucleic acid, *EAAT* Excitatory amino acid transporters, *ECx* entorhinal cortex, *ELISA* enzyme-Linked Immunosorbent Assay, *f* female, *FC* frontal cortex, *GFAP* glial fibrillary acidic protein, *HBTRC* Harvard's brain tissue resource center, *HE* hematoxylin and eosin, *HERV-W* human endogenous retrovirus-W, *HLA-DR* human leukocyte antigen-antigen D related, *HPLC* high performance liquid chromatography, *IBA-1* ionized calcium binding adaptor molecule -1, *IHC* Immunohistochemistry m male, *M* mean, *MBB* Magdeburg brain bank, *MD* mean difference, *MDD* major depressive disorder, *MDN* mediodorsal thalamic nucleus, *MLH* Mc Lean hospital, *mRNA* messenger ribonucleic acid, *NWMHPBPR* North Western Mental Health Program Behavioural and Psychiatric Research, *PFC* prefrontal cortex, *pGFAP* phosphorylated glial fibrillary acidic protein, *PM* postmortem, *PMI* postmortem interval, *PMCCS* postmortem case control study, *PMCCGS* postmortem case control genetic study, *PNN* perineuronal nets, *PrPc* cellular prion protein, *qRT-PCR* quantitative or qualitative real time polymerase chain reaction, *RNA* ribonucleic acid, *RT-PCR* real time polymerase chain reaction, *S100B* S 100 calcium binding protein B, *SD* standard deviation, *SFNC* Stanley Foundation Neuropathology Consortium, *SMRI* Stanley Medical Research Institute, *SNP* single nucleotide polymorphism, *STG* superior temporal gyrus, *SVZ* sub ventricular zone, *TC* temporal cortex, *TDO2* tryptophan 2,3-dioxygenase, *USA* United States of America, *VIFM* Victorian Institute of Forensic Medicine, *WB* western blot

Astrocyte markers (GFAP, pGFAP, S100B, HERV-W capsid (GAG) protein iNOS, and nNOS) Glial fibrillary acidic protein (GFAP)

GFAP is a protein in astrocyte intermediate filaments and is an important marker for astrocytes [33, 34]. Increases in GFAP may signify astrogliosis, reactive injury, or neurodegeneration, while decreased levels indicate reduced synaptic capabilities of neurons [35–38]. GFAP expression is regulated by several factors, such as cytokines, hormones, and growth factors [39, 40]. Twelve studies measured GFAP in the form of GFAP expression, GFAP-positive astrocyte number, GFAP area fraction, or GFAP mRNA expression. Among the 13 studies, five studies documented no BD-associated variations in GFAP levels [41–45]. Whereas three studies observed reduced GFAP expression [46–48], one study noted a decrease in the GFAP area

Table 2 Molecular mechanisms in postmortem brain tissue of bipolar disorder patients

Author	Title	Study design	Brain Bank, Country	Sample size (patients and controls/sex/age)	Death from suicides	Brain region studied	Technique	Tissue/ biochemical evaluation	Main findings
Inflammatory protein expression									
Abdolmaleky et al. [109]; USA	Aberrant transcriptomes and DNA methylomes define pathways that drive pathogenesis and loss of brain laterality/asymmetry in schizophrenia and bipolar disorder.	PMCSS	SMRC, USA	Total cases = 105, BD = 35; 17 m, 4 f; age 39–69, mean age 54, and normal control = 22; 7 m, 15 f; age 24–48, mean age 52.	NA	DLPFC (BA = 46)	GSEA, DNA microarray, qRT-PCR	NR2E1 and TGFB2	The key genes of the TGFβ-signaling pathway are upregulated in BD.
Bezchlibnyk et al. [110]; Canada	Gene expression differences in bipolar disorder revealed by cDNA array analysis of post-mortem frontal cortex.	PMCSS	SFNC	Total cases = 20, BD = 10; 4 m, 6 f; age 30–61, mean age 44.8, and normal control = 10; 4 m, 6 f; age 35–59, mean age 47.8.	NA	FC	WB, RT-PCR, cDNA array	TGF-β1 and erbB2	Decreased TGF-β1 and increased erbB2 observed in BD samples as compared to controls.
Busse et al. [72]; Germany	Decreased quinolinic acid in the hippocampus of depressive patients: Evidence for local anti-inflammatory and neuroprotective responses?	PMCCS	MBB, Germany	Total cases = 22, BD = 6; 5 m, 1 f; age 50 ± 7, and normal control = 10; 5 m, 5 f; age 56 ± 6.	BD = 6	CA 1 & CA 2/3 areas of hippocampus	IHC	Microglial QUIN expression	In BD, microglial QUIN expression is either similar (left CA 1, right CA 2/3) or reduced (right CA 1: $p = 0.004$, left CA 2/3: $p = 0.044$) compared to normal control. This QUIN reduction in the right CA 1 hippocampus is $p = 0.017$ (Kruskal–Wallis test) and $p = 0.031$ (post-hoc analysis).
Chen et al. [77]; USA	Altered MHC class I expression in dorsolateral prefrontal cortex of nonsmoker patients with schizophrenia.	PMCCS & PMCCGS	SFNC, SMRI, USA	Total cases = 70, BD = 35 (15 smokers, 6 nonsmokers and 14 unknown), and normal control = 35 (9 smokers, 9 nonsmokers and 17 unknown).	NA	DLPFC & OFC	WB and qRT-PCR	MHC class I protein	No difference between BD and control groups.
Foster et al. [83]; UK	Calprotectin in microglia from frontal cortex is up-regulated in schizophrenia: evidence for an inflammatory process?	PMCSS	SFNC, USA	Total cases = 60, BD = 15.	NA	DLPFC (BA 9)	ELISA and IHC	Calprotectin	No significant difference in calprotectin levels in BD as compared to control.
Kim et al. [92]; Canada	Nod-like receptor pyrin containing 3 (NLRP3) in the post-mortem frontal cortex from patients with bipolar disorder: A potential mediator between mitochondria and immune-activation.	PMCCS	HBTRC	Total cases = 28, BD = 9; 4 m, 5 f; age: 58–92; and normal control = 9; 4 m, 5 f; age: 65–91.	NA	FC (BA 9, 10, 24)	WB and ELISA	NLRP3, ASC, caspase-1, IL-1β, IFN-γ, IL-10 and IL-6 and TNF-α	The levels of NLRP3, ASC, caspase-1, IL-1β, IL-10 and IL-6 and TNF-α increased in BD.
Quinones et al. [98]; USA	Central and peripheral immune activation in bipolar illness: Possible role of the chemokine CXCL5 in disease pathogenesis.	PMCCS	HBSFRC PM sample trios (serum, cerebrospinal fluid—CSF and brain), USA	Total cases = 12, BD = 5 and normal control = 7.	NA	BA 46 (PFC)	Multiplex immunoassay	CCCL5	BD patients have higher levels of the CXCL5 in brain ($p = 0.02$) compared to normal control.
Quinones et al. [87]; USA	Upregulation of type I immune responses in the brain of individuals with bipolar disorder: Uncoupling of central and peripheral responses.	PMCCS	HBSFRC PM samples (serum and brain), USA	Total cases = 12, BD = 5 and normal control = 7.	NA	BA 46 (PFC)	Multiplex immunoassay	IL-12, IL-2, IL-4, IL-5, and IFN-γ	In BD, the levels of the type I cytokines IFN-γ ($p = 0.01$), IL-2 ($p = 0.01$) and IL-12 p40 ($p = 0.04$) are higher in PFC compared to normal control.
Rao et al. [11]; USA	Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients.	PMCCS & PMCCGS	HBTRC, MLH, USA	Total cases = 30, BD = 10; age: 49 ± 7.2 and normal control = 20; age: 43 ± 3.5.	NA	FC	RT-PCR	Protein levels of IL-1β, MyD88, iNOS, nNOS, nuclear NF-κB p50, and NF-κB p65	There is a significant increase in protein and mRNA levels of IL-1β (41%; $p < 0.05$; 2.2 fold; $p < 0.01$), IL-1R (41%; $p < 0.05$; 3.6 fold; $p < 0.001$), MyD88 (38%; $p < 0.05$; 3.6 fold; $p < 0.01$), NF-κB subunits p50 (45%, $p < 0.05$; 0.8 fold, $p < 0.05$) and p65 (62%, $p < 0.01$; 1.4 fold, $p < 0.001$), iNOS (37%; $p < 0.05$; 1.7 fold; $p < 0.01$) and c-fos in FC of BD compared with controls. However, mRNA levels of TNF-α or neuronal nNOS showed no significant difference.
Sawa et al. [78]; USA	Expression of immune molecules (MHC class I and complement C3) in postmortem brains of patients with schizophrenia.	PMCCS & PMCCGS	SFNC, SMRI, USA	Total cases = 70, BD = 35, and normal control = 35.	NA	FC	RT-PCR and WB	MHC class I expression	There is no significant difference in MHC class I expression between BD and normal controls.
Thomas et al. [101]; UK	Elevation of cell adhesion molecule immunoreactivity in the anterior cingulate cortex in bipolar disorder.	PMCCS	SFNC, USA	Total cases = 30, BD = 15; 9 m, 6 f; age 42.3 ± 11.7, and normal control = 15; 9 m, 6 f; 48.1 ± 10.7.	BD = 8	ACC & DLPFC	IHC and image analysis	ICAM-1 and VCAM-1 microvascular immuno-reactivity	Microvascular immunoreactivity of ICAM-1 is increased in the gray matter (12.3 ± 9.5 vs. 2.1 ± 3.4; $p = 0.001$) and white matter (18.1 ± 11.2 vs. 4.8 ± 7.7; $p < 0.001$) of the ACC in BD vs. controls. There is no significant difference in the DLPFC. The ICAM-1 immunoreactivity in ACC showed significantly higher levels in gray matter

Table 2 (continued)

Author	Title	Study design	Brain Bank, Country	Sample size (patients and controls/sex/age)	Death from suicides	Brain region studied	Technique	Tissue/ biochemical evaluation	Main findings
									($p = 0.009$) and white matter ($p < 0.001$) compared with DLPFC.
Webster et al. [99]; USA	Immunohistochemical localization of the cell adhesion molecules Thy-1 and L1 in the human prefrontal cortex: Patients with schizophrenia, bipolar disorder, and depression.	PMCCS	SFNC, USA	Total cases = 30, BD = 15; 9 m, 6 f; age 25–61; mean age 42.3, and normal control = 15; 9 m, 6 f; age 29–68; mean age 48.1.	NA	DLPFC	WB and IHC	L1 and Thy-1 members of the immunoglobulin superfamily of cell adhesion molecules	There is no significant difference in L1 ($p = 0.89$) and Thy-1 ($p = 0.43$) intensity in the PFC of BD compared to normal controls.
Weis et al. [73]; Austria	Expression of cellular prion protein (PrPc) in schizophrenia bipolar disorder, and depression.	PMCCS	SFNC, USA	Total cases = 60, BD = 15; 9 m, 6 f; mean age 42.3, and normal control = 15; 9 m, 6 f; mean age 48.1.	NA	ACG	IHC	PrPc	PrPc-positive glial cells were significantly reduced in the white matter of BD samples.
Inflammatory gene expression									
Dean et al. [51]; Australia	Different changes in cortical tumor necrosis factor-α-related pathways in schizophrenia and mood disorders.	PMCCS & PMCCGS	VBB, MHRI, Parkville, Australia	Total cases = 40, BD = 10; 6 m, 4 f; age 60 ± 4.0, normal control group A = 20; 16 m, 4 f; age 47 ± 4.1, normal control group B = 10; 7 m, 3 f; age 56 ± 4.8, and normal control group C = 10; 6 m, 4 f; age 63 ± 4.1.	BD = 6	DLPFC (BA 46) & ACC (BA 24)	WB and qRT-PCR	Levels of tmTNF-α and sTNF-α, IL-1β, pro IL-1β	Levels of tmTNF-α significantly increased (305%, $p < 0.05$) in BA 24, but not in BA 46, in BD samples. The sTNF-α, TNF mRNA and TNFR1 mRNA levels are unaltered in BD, whereas levels of TNFR2 mRNA decreased in BA 46, but not in BA 24 in BD (79%, $p < 0.001$). The level of IL-1β and pro-IL-1β remained the same in the cortex of BD compared to controls.
De Baumont [128]; Brazil	Innate immune response is differentially dysregulated between bipolar disease and schizophrenia.	PMCCGS	SFNC	Total cases = 88, BD = 29; 15 m, 14 f; age 44, 46 and normal control = 30; 23 m, 7 f; age 44, 43.	NA	FC	cDNA microarray	Inflammatory genes	The pairs of CCR1/SERPINA1, CCR5/HCST, C1QA/CD68, CCR5/S100A11, and SERPINA1/TLR1 presented increased expression in BD.
Fillman et al. [129]; Australia	Markers of inflammation and stress distinguish subsets of individuals with schizophrenia and bipolar disorder.	PMCCS	SMRI, USA	Total cases = 34, BD = 34; 16 m, 18 f; age 19–64, mean age 45.4, and normal control = 35; 26 m, 9 f; age 31–60, mean age 44.2.	BD = 15	PFC	qPCR and microarray analysis	Inflammatory genes	No significant difference in IL-8, IL-1β, IL-18, TNF, and SERPINA3 mRNA levels in BD as compared to controls.
Hoseth et al. [91]; Norway	A study of TNF pathway activation in schizophrenia and bipolar disorder in plasma and brain tissue.	Prospective AMCCS & PMCCS	NA	Total cases in plasma cohort = 871, BD = 247; 103 m, 144 f; age: 32 ± 18; and normal control = 624; 330 m, 294 f; age: 32 ± 13. Total cases in brain cohort = 132, BD = 44; 23 m, 21 f; age: 46.8 ± 2.1; and normal control = 88; 69 m, 19 f; age: 44.7 ± 1.7.	NA	DLPFC gray matter with BA 9/46 areas	ELISA	TNF, TNFR1, TNFR2, and mRNA levels DLPFC	No differences in mRNA levels of TNF, TNFR1, TNFR2, and ADAM17 between BD and controls.
Hu et al. [107]; China	Systematically characterizing dysfunctional long intergenic non-coding RNAs in multiple brain regions of major psychosis.	PMCCGS	SFNC, SMRI, USA	Total cases in BA 11, 24, and 9 areas = 54, BA 11 (BD = 16; 8 m, 8 f; age 47.7 ± 9.7, and normal control = 12; 9 m, 3 f; age 41.8 ± 6.3), BA 24 (BD = 7; 4 m, 3 f; age 46.6 ± 6.0, and normal control = 6; 5 m, 1 f; age 46.5 ± 16.0), BA 9 (BD = 7; 4 m, 3 f; age 46.6 ± 6.0, and normal control = 6; 5 m, 1 f; age 46.5 ± 16.0).	NA	OFC (BA 11), ACC (BA 24) & DLPFC (BA 9)	RNA sequencing	lincRNA and protein-coding gene (PCG)	The dysfunctional lincRNA modules (M3) in BD BA 11 brain region involved with oligodendrocyte differentiation and activation of innate immune response.
Kaminsky et al. [84]; Canada	A multi-tissue analysis identifies HLA complex group 9 gene methylation differences in bipolar disorder.	PMCCGS	SFNC, SMRI; HBTRC, MLH, USA	Total cases = 69, BD = 34; 16 m, 18 f; age 45.4 ± 10.7, and normal control = 35; 26 m, 9 f; age 44.2 ± 7.58. MLH—total cases = 84, BD = 34; 16 m, 20 f; age 61.4 ± 18.9, and normal control = 50; 30 m, 20 f; age 58.4 ± 15.6.	NA	PFC, PC, OC & corpus callosum	Sodium metabisulfite conversion along with pyro-sequencing	DNA methylation	The DNA methylation at the human leukocyte antigen (HLA) complex group 9 gene (HCG 9), decreased in SMRI (PFC, OC and corpus callosum) BD samples (BD 35.6 ± 5.22, normal control 50.4 ± 4.48, $p = 0.018$) and an increased in MLH (PFC) batch (BD 37.1 ± 1.36, normal control 31.2 ± 1.72, $p = 0.011$). However, both cohorts showed reduced DNA methylation at HCG9 ($p = 0.026$), on adjusting for age, medication as well as DNA sequence variation (SNP rs1128306).
Nakatani et al. [79]; Japan	Genome-wide expression analysis detects eight genes with robust alterations specific to bipolar I disorder: relevance to neuronal network perturbation.	PMCCGS	VIFM, Australia	Total cases = 21, BD = 7; 3 m, 4 f; age 61.9 ± 6.3 and normal control = 7; 3 m, 4 f; age 61.4 ± 12.0.	BD = 0	DLPFC (BA 46) and parietal cortex (BA 40)	Microarray and qRT-PCR	Inflammatory genes	In BD-1, BA 46 region, HLA-DRA decreased in both microarray and qRT-PCR. Chemokine CCL3 also downregulated in BD-1.
Pacifico et al. [108]; USA	Transcriptome sequencing implicates dorsal striatum specific gene network, immune response and energy metabolism pathways in bipolar disorder.	PMCCGS	HBTRC, MLH, USA	Total cases = 35, BD = 18 and normal control = 17.	NA	Dorsal striatum (CN & putamen)	Transcriptome sequencing	Gene network analysis	The immune and inflammatory related genes NLRC5 and S100A12 upregulated in striatum of BD samples.

Table 2 (continued)

Author	Title	Study design	Brain Bank, Country	Sample size (patients and controls/sex/age)	Death from suicides	Brain region studied	Technique	Tissue/ biochemical evaluation	Main findings
Rao et al. [10]; USA	Epigenetic modifications in frontal cortex from Alzheimer's disease and bipolar disorder patients.	PMCCGS	HBTRC, MLH, USA	Total cases = 20, BD = 10; age 49 ± 7.2 and normal control = 10; age 43 ± 3.5.	NA	FC (BA 9)	RT-PCR and ELISA	COX-2, 12-LOX, p450 epoxygenase, and drebrin-like genes	In FC, BD brains showed hypo- and hypermethylation of CpG islands in COX-2 ($p < 0.05$) promotor region. Also, increased global histone H3 acetylation and hypermethylation of the promotor region for the drebrin-like protein ($p < 0.05$) gene. There is no significant epigenetic modification for 12-LOX or p450 epoxygenase in BD. The mRNA and protein levels are inversely related to epigenetics with an increase in protein and mRNA levels of AA cascade markers (cPLA2-IVA, sPLA2-IIA and COX-2), neuroinflammatory markers (IL-1β and TNF-α) in BD brains.

ACC anterior cingulate cortex, *ACG* anterior cingulate gyrus, *ADAM17* a disintegrin and metalloprotease 17, *AMCCS* antemortem case control study, *ASC* apoptosis associated speck-like protein containing a CARD, *AV* anteroventral, *BA* Broadmann's area, *BD* bipolar disorder, *C3* complement 3, CA1, 2 & 3 cornu ammonis1, 2 & 3, *CC* cingulate cortex, *CD* cluster of differentiation, *cDNA* complementary deoxyribonucleic acid, *CI* confidence interval, *CN* caudate nucleus, *cPLA2* cytosolic phospholipase, *CSF* cerebrospinal fluid, *DE* differentially expressed, *DLPFC* dorsolateral prefrontal cortex, *DNA* deoxyribonucleic acid, *DRN* dorsal raphe nucleus, *EAAT* excitatory amino acid transporter, *ELISA* enzyme-linked immunosorbent assay, ErbB2 Receptor Tyrosine Kinase 2, *f* female, *FC* frontal cortex, *FCGBP* Fc fragment of IgG binding protein, *GSEA* gene set enrichment analysis, *HBSFRC* Human Brain and Spinal Fluid Resource Center, *HBTRC* Harvard's Brain Tissue Resource Center, *HCG9* human leukocyte antigen complex group 9 gene, *HE* hematoxylin and eosin, *HLA-DR* human leukocyte antigen-antigen D related, *IC* internal capsule, *ICAM-1* intercellular adhesion molecule-1, *IFN-γ* interferon gamma *IHC* immunohistochemistry, *IL* interleukin, *IL-1β* interleukin-1β, *IL-R* interleukin receptor, *IL-1R* interleukin-1 receptor, *iNOS* inducible nitric oxide synthase, *m* male, *12-LOX* 12-lipooxygenase, *MBB* Magdeburg Brain Bank, *MD* mean difference, *MDD* major depressive disorder, *MDN* mediodorsal thalamic nucleus, *MHC* Class major histocompatibility complex class I, *MHRI* Mental Health Research Institue, *MLH* Mc Lean Hospital, *MPRC* Maryland Psychiatry Research Center, *mRNA* messenger ribonucleic acid, MyD 88 myeloid differentiation factor 88, *NBB* Netherlands Brain Bank, *NF-κB* nuclear factor kappa B, *NF-L* neurofilament low molecular weight, *NLRC5* NLR family CARD domain containing 5, *NLRP3* Nod-like receptor pyrin containing 3, *nNOS* neuronal nitric oxide synthase, *OC* occipital cortex, *OFC* orbitofrontal cortex, *OL* oligodendrocytes, *OLP* oligodendrocyte precursors, *PC* parietal cortex, *PCR* polymerase chain reaction, *PFC* prefrontal cortex, *PGH* Psychiatry and Geriatric Hospital, *PM* postmortem, *PMCCS* postmortem case control study, *PMCCGS* postmortem case control genetic study, *QUIN* quinolinic acid, *qRT-PCR* quantitative or qualitative real time polymerase chain reaction, *RNA* ribonucleic acid, *RT-PCR* real time polymerase chain reaction, *S100A12* S 100 calcium binding protein A12, *SD* standard deviation, *SFNC* Stanley Foundation Neuropathology Consortium, *SMRC* Stanley Medical Research Center, *SMRI* Stanley Medical Research Institute, *SNP* single nucleotide polymorphisms, *sTNF-α* soluble tumor necrosis factor alpha, *sTNF-R1* soluble tumor necrosis factor receptor 1, *sTNF-R2* soluble tumor necrosis factor receptor 2, *Thy-1* thymus cell antigen 1, *TLRs* toll-Like receptors, *tmTNF-α* transmembrane tumor necrosis factor-alpha, *TNF-α* tumor necrosis factor-alpha, *TNF-R1* tumor necrosis factor-alpha receptor 1, *TNF-R2* tumor necrosis factor-alpha receptor 2, *UOGSM* University of Geneva School Medicine, *UD* unipolar depression, *USA* United States of America, *VBB* Victorian Brain Bank, *VCAM-1* vascular cell adhesion molecule-1, *VIFM* Victorian Institute of Forensic Medicine, *WB* western blot, *WGCNA* weighted gene co-expression network analysis

fraction [47], one study reported a decrease in GFAP messenger ribonucleic acid (mRNA) levels [49], one study reported an increase in GFAP mRNA levels [9]; and only three studies cited increased the expression of GFAP [11, 18, 50]. One study demonstrated a reduction in pGFAP protein in the FC [20], whereas another reported no reduction in pGFAP-labeled astrocytes [45]. One study demonstrated no difference in astrocyte density in amygdala [51] (Table 1). When cerebellar GFAP levels in BD brains were compared with those in normal control brains, there was a 17% reduction in GFAP levels in BD brains. These levels were influenced by treatment with antidepressants, but not with antipsychotics or mood stabilizers. However, these antidepressant-induced changes may hint towards the role of antidepressants in the synthesis or destruction of GFAP by astrocytes. In addition, as astrocytes constitute 25% of the gray matter volume and as they outnumber neurons in the brain by fivefold, they may be an important target for antidepressant action in the brain [47]. When the CA1 pyramidal layer and the alveus of the hippocampus were analyzed for presence of GFAP- and S100B-positive astrocytes, the CA1 pyramidal layers in BD brains showed an attenuation in the numerical density of S100B-positive astrocytes, with no variation in the density of GFAP-immunoreactive astrocytes, compared to those in control brains [19]. When GFAP43 and GFAP41 levels were measured alongside TNF parameters in BA 24 and BA 46 in the brain, the levels in BD samples were similar to those in controls [51]. A study conducted by Pantazopoulos and collaborators noted no difference in GFAP-positive

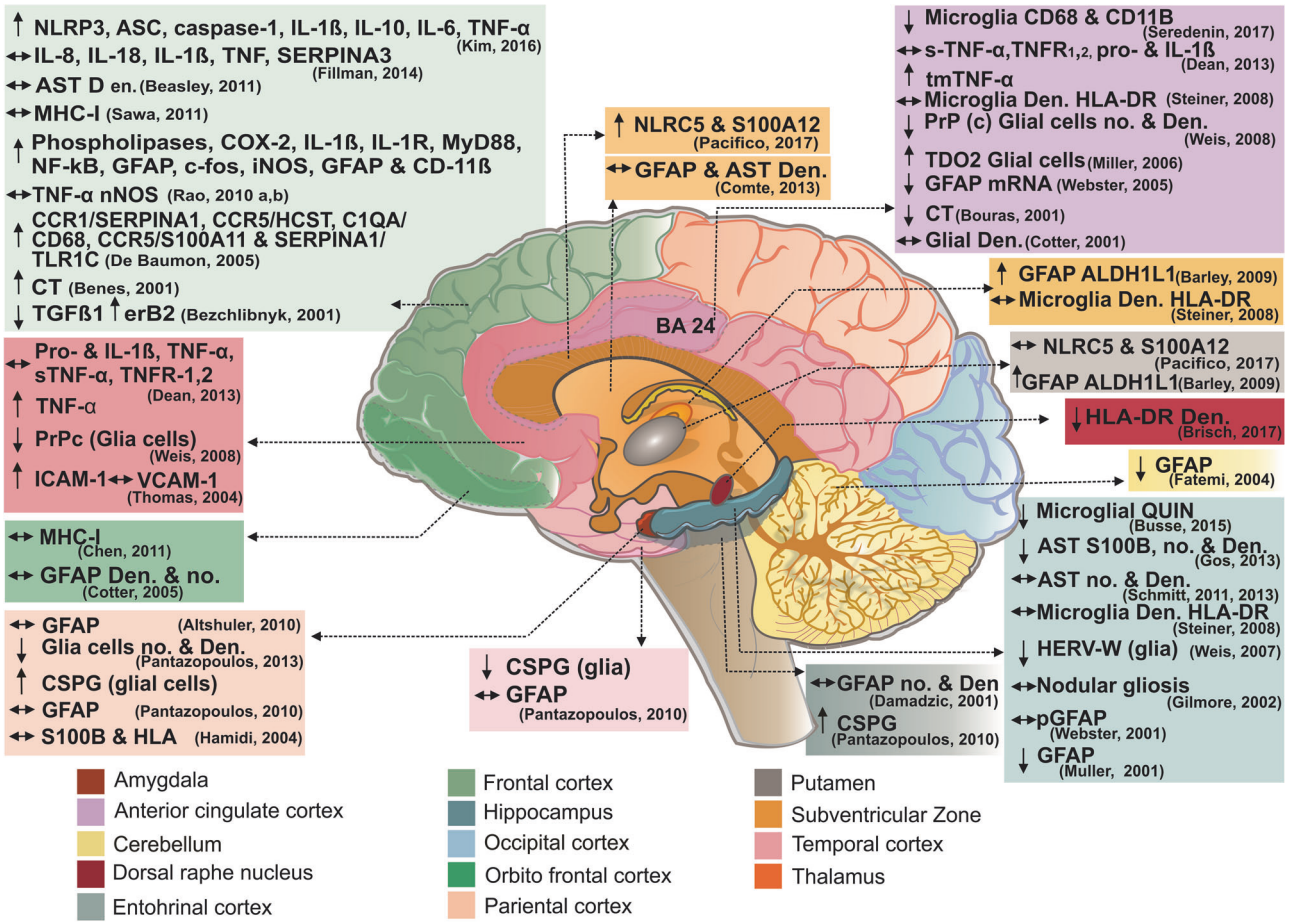

Fig. 2 Brain areas investigated in BD postmortem brain samples

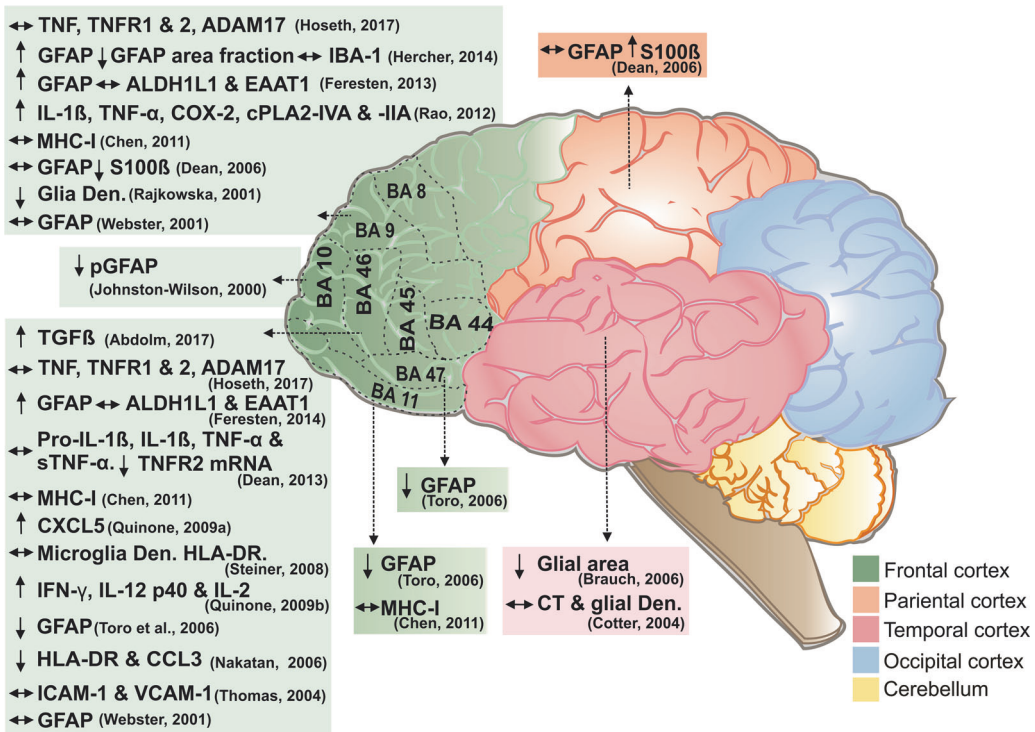

Fig. 3 Brain areas investigated in BD postmortem brain samples

astrocyte density in the amygdala and ECx [43]. Even ventral and dorsal SVZ analysis has not shown any astrocytic alteration or gliosis, as evidenced by normal levels of GFAP [41]. Analysis of reactive astrogliosis and GFAP levels in the hippocampus after glucocorticoid elevation in chronic (BD) and acute cases (steroid treatment) has revealed that the number of GFAP-positive astrocytes is decreased in the CA1 and CA2 regions of BD samples compared to controls [46]. The GFAP area fraction is reduced in BD, and there is a difference in astrocyte space distribution and an elevation in astrocyte clustering in PFC and DLPFC white matter [18]. In the FC of postmortem BD brain samples, IL-1R cascade activation and upregulation of nuclear factor kappa beta (NF-κβ) results in increased expression of GFAP and iNOS in BD subjects compared to the expression in controls. While GFAP-positive astrocytes display fine fibrous processes in control brains, they show hypertrophy in BD brains [11, 52]. Statistics on white and gray matter reveal that GFAP mRNA levels are significantly decreased in the white matter of all brain areas and in the gray matter of the ACC in BD brains compared to the levels in control brains. These data suggest that GFAP-positive astrocytes may contribute to the glial density reduction noted in other psychiatric disorders [49]. These disparities in the outcome may partly explained by the variations in the methodology, statistical analysis and/or samples across studies. Considering brain region is one such variable across the studies, the results from four studies showed decrease astrocyte expression in hippocampus, two studies showed increased astrocyte clustering in FC; another study showed no change in astrocyte markers in FC. The other variable to be considered is the treatment regimen, a report from Ferensztajn-Rochowiak et al., demonstrated that the mRNA expression GFAP (not reach the level of statistical significance) in peripheral blood, was higher in BD patients not taking lithium than in healthy controls [53]. Thus, the reduction in GFAP levels observed in most of the studies may partially explained by the treatment regimen.

pGFAP

Phosphorylation of GFAP occurs at 5 sites (Thr7, Ser8, Ser13, Ser17, and Ser38) [54]. One study reported a reduction in pGFAP protein in the FC [20], whereas another showed no reduction in pGFAP-labeled astrocytes [45]. Proteomic analysis of 89 frontal cortical areas has shown that there is a reduction in GFAP500 in BD brains compared to the level in controls [20]. There is no reduction in astrocytes labeled with pGFAP in BD brains compared to the number in control brains [45].

S100B

S100B is a calcium-binding protein secreted by astrocytes and oligodendrocytes [55, 56]. Increased S100B levels in serum and cerebrospinal fluid (CSF) represent a suitable marker of glial damage in mood disorders [57, 58]. When the CA1 pyramidal layer and the alveus of the hippocampus were examined for S100B positive astrocytes, the right and left CA1 pyramidal layers showed a reduction in the numerical density of S100B-positive astrocytes in BD brains compared to that in controls [19]. One study demonstrated that the levels of S100B decreased in BA 9 and increased in BA 49 [44]. In addition, no significant changes was found in S100B in amygdala of BD samples [59].

Human endogenous retrovirus (HERV)

HERV, the ancient acquired elements shown to modulate innate immune responses and has protective effect against exogenous infections [60]. On the one side, it regulates inflammatory and autoimmune disorders, while on the other side to the control of excessive immune activation through their immunosuppressive properties [61–63]. The expression of capsid (GAG) protein of HERV− detected in neurons as well as astroglial cells in normal brain both in the anterior cingulate cortex and in the hippocampal formation. In postmortem samples from BD patients, there was a reduction of this expression in neurons and astroglial cells. This downregulation may be a result of abnormal gene regulation, a disturbance of the normal gene expression profile, or impaired genetic mechanisms during HERV transcription at the ribonucleic acid (RNA) level [64].

Astrocyte gene expression The expression of GFAP mRNA significantly decreased in the white matter of all brain areas and in gray matter of the ACC in BD brains compared to the levels in control brains [49]. The astrocyte genes, 10-formyltetrahydrofolate dehydrogenase (ALDH1L1) and GFAP, shows increased expression in anteroventral (AV) and mediodorsal thalamic nuclei (MDN), internal capsule (IC), and putamen (Put) areas of BD brains compared to its expression in controls [9].

Microglia

Microglia, the brain sentinels, carryout the first line of defense against injury and infections [65]. Upon activation, they release proinflammatory cytokines, which exert negative effects on neuroprotective mechanisms and result in pathophysiological disturbances in BD [16, 66, 67]. In addition to causing proinflammatory cytokine release and neurotoxic effects, microglia negatively regulate anti-inflammatory and neuroprotective mechanisms. Microglia also possess phagocytic potential characterized by the surface expression of antigen-presenting markers such as MHC class II [68, 69].

Microglial markers (MHC I, MHC II, HLA-DR, IBA-1, CD11B, c-fos, QUIN, and PrP(c)) Out of 15 studies that analyzed microglial markers in BD postmortem brain, eight studies

were neutral; one study cited decreased microglial reaction due to a reduction in human leukocyte antigen-D related (HLA-DR) density in the DRN [70]; one study demonstrated decreased CD68 and CD11B in ACC [71]. One study demonstrated increased expression of c-fos and CD11B in the FC [11]; one study noted decreased QUIN in the hippocampus [72]; one study reported reduced cellular prion protein (PrP(c)) immunoreactivity in the ACC [73]; and one study reported no significant change in HLA-DR density in the DLPFC, ACC, mediodorsal thalamus and hippocampus in non-suicidal cases but reported microgliosis in BD-suicide victims [74] (Table 1). MHC induction via HLA-DR in microglia is a sensitive marker of neuroinflammation and neurodegenerative processes [75]. Examination of MHC class I protein in the DLPFC, OFC and FC has revealed that there is no difference in MHC class I levels in BD brains compared to the levels in control brains [76–78]. When HLA-DR positive microglia were analyzed in the DRN, a significant reduction in microglial reaction was evident from a decreased density of HLA-DR-positive microglial cells; this effect was seen only in non-suicidal depressed subjects and not in depressed suicide victims or controls. A strong correlation between antidepressant medication use and HLA-DR-positive microglial density has been noted in non-suicidal patients, supporting the protective role of the microglial reaction in these patients. A positive effect of microglia on ribosomal deoxyribonucleic acid (DNA) transcription in DRN neurons in non-suicidal depressed subjects has also been noted. DRN microglial and neuronal interactions in counteracting directions may facilitate or reduce suicidal ideation in depressed patients [70]. There are no significant differences in HLA-DR-positive microglial density between patients with BD and controls in the DLPFC, ACC, mediodorsal thalamus and hippocampus [74] and in amygdala of BD patients [59]. However, significant microgliosis has been noted in suicide patients, regardless of diagnosis, in the DLPFC, ACC and mediodorsal thalamus, and a trend towards microgliosis has been noted in the hippocampus, suggesting that increased microglial density in BD-depression is associated with suicide. In addition, in BD-1, BA 46 region, HLA-DRA decreased in both microarray and qRT-PCR [79]. Our search results showed total of 18 studies with BD suicide cases. Among these, one study reported suicide in 2 out of 7 cases due to over-dose of medication [70], one study reported suicide in 1 out of 6 cases due to intoxication [72], and one reported 3 cases out of 5 with alcohol or drug use [80]. Patients with bipolar disorder are at great risk for suicide, these findings raise the question of whether pre-suicidal stress leads to microglial activation or microglial activation triggers the release of neuroendocrine and inflammatory mediators that bring about an imbalance of noradrenergic or serotonergic neurotransmission that ultimately leads to suicidal ideation [74]. In the DLPFC, there are no significant differences in the density, area fraction or spatial distribution of ionized calcium binding adaptor molecule-1 (IBA-1)-immunoreactive microglia in BD patients compared to the corresponding parameters of controls [18]. In an analysis of microglial markers in the FC, c-fos and CD11B protein and mRNA were found to be significantly elevated in the postmortem brains of BD subjects compared to the levels in control brains. In BD tissue, HLA-DR-stained microglia display thickened processes compared to the microglia in control tissue [11]. However, in another study, CD11B levels were found not to vary in the DLPFC and ACC of BD subjects compared to the levels in controls [51]. QUIN is produced by activated microglia cells and acts as an NMDA-receptor (NMDA-R) agonist in glutamatergic neurotransmission and as a proinflammatory mediator with neurotoxic properties. When hippocampal QUIN expression and volume was analyzed, microglial QUIN expression was found to be either similar to control expression in the left CA1 and right CA2/3 areas or decreased in the right CA1 and left CA2/3 areas of the hippocampus, with no volume changes [72]. PrP(c) is a copper-binding cell surface glycosyl phosphatidylinositol (GPI)-anchored glycoprotein expressed by neurons and microglia [81, 82]. PrP(c) protects against oxidative stress, promotes neuroprotection, acts as a laminin receptor (laminin and PrP(c) together help in the learning and memory pathway), and mediates neuronal survival and differentiation. When PrP(c)-positive neurons and glial cells in the ACC were examined, the number of PrP(c)-positive glial cells was found to be significantly reduced in the white matter of BD brains compared to the number in the white matter of control brains [73]. Confounding factors, especially drugs (antipsychotics, antidepressants, and mood stabilizers), had a significant impact on the reduced expression of PrP(c) by neurons and glial cells. Overall, there is a reduction in PrP(c) immunoreactivity in white matter glial cells that significantly influenced by drugs, and there are no associated signs of oxidative stress [73]. Calprotectin is a 36 kDa calcium-binding protein of the S100 family and this protein did not present significance in BA 9 of BD patient samples [83].

Microglial gene expression A study on DNA methylation in the HCG-9 region revealed that there is a decrease in DNA methylation in BD subjects compared to the that in controls after adjusting for the effects of discrepancies such as age, medication, and DNA sequence variation (single nucleotide polymorphism (SNP) rs1128306) [84].

Molecular parameters

Cytokines

Cytokines are a broad category of small secretory proteins that include interleukins, interferons and growth factors.

They are secreted by immune cells and regulate the body's immune responses to infection, inflammation and injury [85]. They affect neurotransmitter and neuropeptide pathways as well as the hypo-thalamic pituitary adrenal (HPA) axis. The immune system, serotonin pathway and HPA axis are all altered in BD, thus determining the roles of the cytokines that influence all these pathways in BD is crucial [86]. An assay of proinflammatory cytokines such as IL-12, IL-2, IL-4, IL-5, and IFN-γ in the PFC revealed that the levels of the type I cytokines, IFN-γ and IL-12p40, were higher in BD patients than in controls, with no differences in serum levels. However, type I cytokines showed a dissociative effect, type II cytokines exhibited no differences between central and peripheral levels. These data suggest that enhanced central, rather than peripheral, levels of type I cytokines might play a role in BD pathogenesis [87]. In another study, TNF-α, IL-1β, and IL-6 were found increased in the PFC (BA 10) of BD teenage suicide victims as compared to controls; the BD patients also had elevated levels of TNF-α and IL-1β in BA 8 of the PFC. In addition, there was an increase in the expression of toll-like receptor (TLR)-3 and TLR-4 in the PFC of depressed and non-depressed suicide victims [88]. Rao and collaborators showed elevations in the protein and mRNA levels of IL-1β, IL-1R, and MyD88 that led to IL-1R cascade activation, which in turn resulted in the upregulation of the transcription factor NF-κB and increased levels of NF-κβ subunits p50 and p65. Increases in NF-κβ levels stimulate expression of excitotoxicity markers (iNOS and c-fos) and astrocyte and microglial markers (GFAP and CD11B). The TNF family includes proinflammatory cytokines expressed by macrophages, endothelial cells, neurons, astrocytes and microglia. The family has two receptors, TNFR1 and TNFR2; TNFR2 is selectively expressed by immune cells, neurons and glial cells [89]. TNF helps to regulate synaptic transport, neurotransmission, homeostatic synaptic scaling, neurogenesis and long-term potentiation [90]. A study examining TNF parameters in BA 24 and BA 46 demonstrated that the levels of tmTNF-α are significantly increased in BA 24, but not in BA 46, in BD brain samples. sTNF-α, TNF and TNFR1 mRNA levels are unaltered in BD; in contrast, levels of TNFR2 mRNA are decreased in BA 46, but not in BA 24, in BD [51]. Levels of tmTNFα, rather than sTNFα (which is a form of TNF-α measured in blood) are altered in the cortex. The findings of that study suggest that TNF-related pathway changes in the cortex of patients with mood disorders may be a response to balance the pathophysiological processes associated with BD. As the DLPFC and the ACC are critical for cognitive processes and mood control, respectively, changes in TNF-α-related pathways in these areas could be involved in the changes in cognition and mood that occur in BD. As drugs that act on tmTNF-α have mild antidepressant activity, a better understanding of TNF pathways may even help in the development of novel drug therapies. Levels of most of the glial and inflammatory marker proteins, such as IL-1β, GFAP43, GFAP41, CD11B, and pro-IL1β, do not vary in the cortex of patients with these disorders, suggesting that these TNF-α-related changes may be different from the usual changes in the neuroinflammatory pathway [51]. A study on TNF mRNA found that there is no significant difference in the mRNA expression of the TNF pathway in the DLPFC of BD patients compared to the expression in the DLPFC of controls. However, there is an increase in plasma TNF markers, such as TNF, sTNFR1 and sTNFR2, an increased TNF/sTNFR ratio, and a reduced TNF mRNA level in plasma and whole blood without concomitant gene expression changes in PM tissue [91]. The levels of NLRP3, ASC, caspase-1, IL-1β, IL-10, and IL-6 and TNF-α increased in BA 9, 10, and 24 of BD patients' samples [92].

Chemokines

Chemokines are chemoattractive cytokines that recruit peripheral leukocytes to sites of inflammation. They are of importance in neuropsychiatric diseases such as BD as they play a role in neuronal and glial cell apoptosis, angiogenesis, and neurogenesis [93]. Abnormalities in immune mediators in the periphery may be associated with analogous immune abnormalities in the brain. Among different chemokine tested, decreased mRNA levels of CCR-5 reported in BD patients' serum [94]. MCP-1 also known as CCL-2 a chemokine produced by microglia, astrocytes and neurons found to be higher in CSF from euthymic patients with BD compared with controls [95]. Another study also reported the increased CSF levels of MCP-1 in euthymic patients with BD and these differences remained after controlling for confounding factors, such as age, sex, smoking, blood-CSF barrier function, acute-phase proteins and body mass index [96]. A study by Barbosa et al. reported that BD patients presented higher plasma levels of CCL11, CCL24, CXCL10 and decreased plasma levels of CXCL8 [97]. When chemotactic cytokine CXCL5 levels were measured in the PFC, BD patients were found to have higher CXCL5 levels in the serum and brain compared to controls. In addition, there was an association between serum, brain and CSF levels in BD patients, suggesting a role of CXCL5 in BD and a correlation between central brain-related and peripheral serological immune activation [98]. In addition, in BD-1, BA 46 region, CCL3 decreased in both microarray and qRT-PCR [79].

Cell adhesion molecules (ICAM-1, VCAM-1, L1, and Thy-1)

Cell adhesion molecules play a major role in brain development, and consequently, their imbalance may result in

psychiatric illness [99]. Intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 are expressed by endothelial cells, monocytes, and astrocytes and help in leukocyte-endothelial cell adhesion and other immune and inflammatory mechanisms [100]. Microvascular immunoreactivity of ICAM-1 is higher in the gray and white matter of the ACC in BD patients than in that of controls and schizophrenics and is higher in white matter of BD patients than in that of patients with unipolar depression (UD). There is no difference within the DLPFC. In BD, the gray and white matter of the ACC have significantly higher levels of ICAM-1 immunoreactivity than that of the DLPFC. VCAM-1 levels are too low for analysis. ICAM-1 is a marker of cerebral inflammation and ischemia. Ischemia is indicated by the presence of white matter hyperintensities in magnetic resonance imaging (MRI) in BD-associated depression [101]. The inflammatory response in the ACC and the elevation in ICAM-1 are parallel to each other and may be associated with the HPA axis [102].

Kynurenine pathway metabolites

Activation of the kynurenine pathway is a common feature of many psychiatric disorders. Linking glutamatergic neurotransmission and immune mononuclear phagocyte system (MPS) activation with the neurodegenerative hypothesis of depression in UD and BD, kynurenine metabolites generated through the indoleamine-2,3-dioxygenase (IDO) pathway are of special interest. IDO is expressed by activated microglia and induces the production of QUIN, an endogenous NMDA-R agonist with neurotoxic properties. The neurotoxicity of QUIN arises from several mechanisms, such as its agonizing effect on glutamate receptors sensitive to NMDA, its pro-oxidant properties, and its proinflammatory capacity, which results from its ability to increase the IFN-γ/IL-10 ratio as well as corticosterone and cytokine levels [72]. An increase in QUIN expression and QUIN-immunopositive microglia has been observed in the subgenual and supracallosal ACC in depressed patients [103]. However, when hippocampal QUIN expression and volume were analyzed, microglial QUIN expression in BD patients was found to be either similar to that of controls in the left CA1 and right CA2/3 areas or decreased in the right CA1 and left CA2/3 areas of the hippocampus, with no volume changes. This reduction in QUIN expression may have resulted from anti-inflammatory and neuroprotective compensatory mechanisms. Overall, the changes in QUIN levels signify the importance of NMDA-R signaling, glutamate transmission and MPS in BD-depression [72]. In the tryptophan 2,3-dioxygenase (TDO2) pathway of kynurenine, TDO2 catalyzes the first step. When the regulation of TDO2 activity was analyzed at the mRNA, protein and metabolic product levels in the ACC, an increase in kynurenine level was seen in the BD group, primarily in the BD group with psychosis, compared to the level in the control group. The ratio of KA to kynurenine was lower in the BD group than in the control group, as KA levels were unchanged. There was also an elevation in the density and intensity of both TDO2-positive white matter glia and TDO2-positive gray matter glia in the BD group [104].

AA cascade markers (cPLA2, sPLA2, COX-2, LOX-2, and cytochrome P (CYP) 450 epoxygenase)

In the CNS binding of microglial-derived cytokines to calcium channel coupled receptors on astrocytes results in activations of phospholipase enzymes that liberate AA from membrane lipoproteins. Thus, the mobilization of AA has been suggested to be a useful biomarker of neuroinflammation [105]. Results from multiple sclerosis postmortem brain samples and CSF demonstrated that arachidonic acid metabolism activated via cyclooxygenases (COXs) and lipoxygenases (LOXs). It has been postulated that motor dysfunction the hallmark of multiple sclerosis is triggered by arachidonic acid–mediated brain inflammation [106]. One study analyzed AA cascade markers in the FC and found an elevation in the mean protein and mRNA levels of phospholipases (cPLA2 type IVA, and sPLA2 type IIA) and COX-2 in BD brains compared to the levels in control brains [52]. BD brains show some epigenetic similarities to AD brains, such as global DNA methylation and histone H3 phosphorylation in the FC. Hypo- and hypermethylation of CpG islands in COX-2 and brain derived neurotrophic factor (BDNF) promoter regions, respectively, is proof of this. There is no significant epigenetic modification of 12-lipoxygenase (12-LOX) or p450 epoxygenase in AD or BD. Treatment of BD and AD with mood stabilizers and antipsychotics not targeting epigenetic regulation may not provide full recovery, as disease progression may reintroduce pathological changes due to epigenetic regulation [10].

Gene expression of inflammatory markers

When long intergenic non-coding RNAs (lincRNAs) were analyzed in the BA 11, 24, and 9 regions of BD brains, one billion reads were generated, among which 73.3% were known lincRNAs, 87.6% were novel lincRNAs and 95.7% were protein-coding genes (PCGs) expressed in all three brain regions. The lincRNAs have a significantly lower coding potential and ORF (open reading frame) ratio (ratio of ORF size to transcript length) and are relatively shorter and less conserved than the PCGs. There are many differentially expressed PCGs (DEPCGs) in BD; for example, the BD-related BDNF and gamma amino butyric acid type A

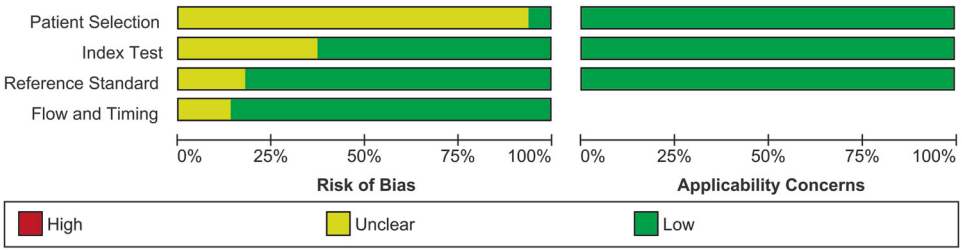

Fig. 4 Quality of included studies was appraised using the QUADAS-2 tool

receptor alpha 1 subunit (GABRA1) genes are dysregulated in BA 11. Additionally, these DEPCGs are involved in the pathology of certain functions such as synaptic transmission, CNS development and oligodendrocyte differentiation. There are 20 differentially expressed lincRNAs (DELincRNAs) in BA 11 that show brain region-specific patterns in BD. A weighted gene coexpression network analysis demonstrated that DELincRNAs, along with other genes, function as modulators of some functions, such as immune system development in BA 24 and oligodendrocyte differentiation in BA 9. Dysregulation of lincRNAs resulting from DNA methylation changes and other causes might lead to BD pathology. There is potential clinical value in investigating gene expression levels in peripheral blood samples of patients with major psychosis, so future studies should focus on investigating the dysfunctional lincRNAs in peripheral blood samples of patients with major psychosis to identify potential lincRNA biomarkers, which could help guide the diagnosis and treatment of major psychosis [107]. In a study involving the transcriptome sequencing of the dorsal striatum (caudate and putamen), 47,886 genes were studied, among which 1468 were DE genes of nominal significance; of those, 14 DE genes remained significant after multiple-testing correction at a 5% false discovery rate. These included a few immune response genes such as NLR family CARD domain containing 5 (NLRC5), S100 calcium binding protein A12 (S100A12), leukocyte immunoglobulin like receptor A4 (LILRA4) and Fc fragment of IgG binding protein (FCGBP). In a study involving gene set enrichment analysis of functional pathways, an enrichment of upregulated BD genes across immune/inflammation pathways was noted. Gene co-expression analysis by a weighted gene co-expression network analysis (WGCNA) method revealed 20 modules of highly interconnected genes for controls and BD patients, among which two modules (M11 and M13) were significantly enriched for BD susceptibility SNPs obtained from a large GWAS dataset. In addition, one of these two modules (M11) was also highly enriched in regional striatal markers and medium spiny neuronal (MSN) markers. On further analysis, it was determined that the genetic risk for BD associated with the M11 module was mainly distributed across MSN-specific genes. This revealed, to an extent, that BD etiology at the gene level is somehow linked to the striatal signaling pathway [108]. The key genes of the TGFβ-signaling pathway was upregulated in BA 46 of BD patient samples [109], however in another study TGF-β decreased in FC brain samples [110] (Table 2).

Quality assessment of the included studies

QUADAS-2 showed an unclear bias in patients selection presented in most studies, 18 studies were unclear in index test and 10 studies were unclear of information about reference standard selection. The "applicability concern" was low, showing a good quality of the included studies (Figs. 4 and 5).

Limitations

The discussed postmortem case-control studies are observational, and hence, causation cannot be established. The clinical articles presented a moderate amount of bias, which was expected given the designs of the included clinical studies. Most of the studies involved a relatively small number of subjects. Several studies examined only one section of the brain rather than the whole brain. The long-term influences of lithium, antidepressants, antipsychotics, and other mood stabilizers on the outcomes of the studies cannot be excluded. As the studies discussed were postmortem studies, it was also hard to track data on the history of inflammation, infections, or other chronic medical conditions across the patients' entire life span. Differences in age between diagnostic subgroups (controls and non-suicidal and suicidal patients) is a gross limitation, mainly because of the younger age of suicidal patients, and age could also influence the inflammatory profile. The duration since death is another major limitation, as prolonged PMI could influence the analyzed results. The polymerase chain reaction (PCR) analysis in most of the studies requires brain tissue with relatively short PMI and with high-quality RNA, which is not possible in most cases. Moreover, the RNA sequencing quantification and mapping methods used may lead to potential underestimation of mRNA levels. Immunohistochemical analyses used in many of the published articles often give variable results in postmortem tissue due to variations in agonal state, PMI, fixation, and storage.

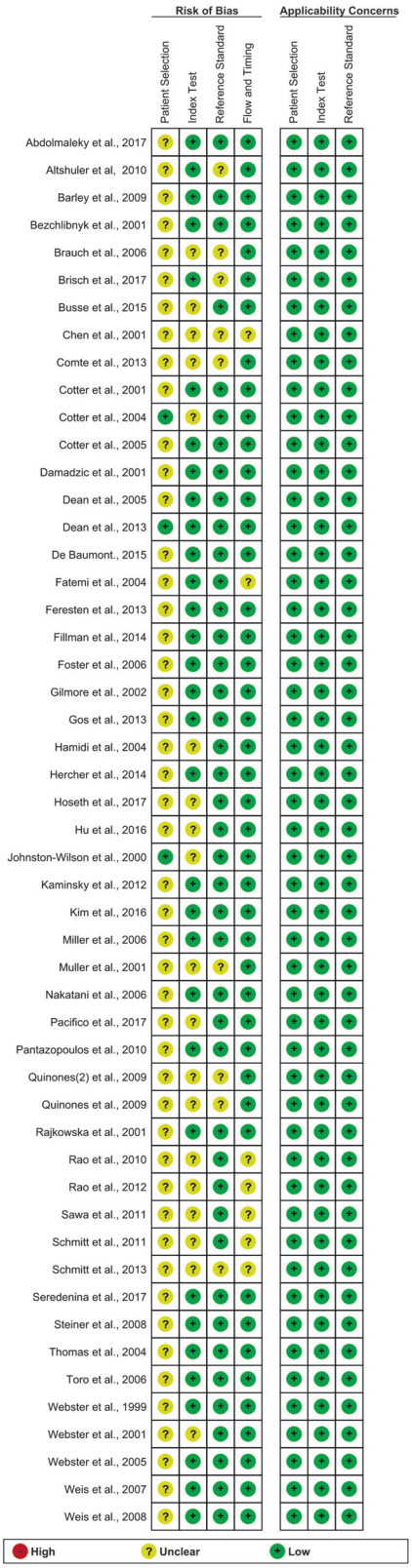

Fig. 5 Summary of methodological quality of studies according to QUADAS-2 tool regarding the risk of bias and applicability in review authors' judgments about each domain for each included study about each domain

Discussion and conclusion

BD has been associated with brain inflammation for the reason that several studies have been demonstrated elevated inflammatory cytokines in the bloodstream [111–113], and BD patients have been presented elevated microglia activation, in the brain as measured by translocator protein (TSPO), a marker of microglial activation, using PET imaging [114, 115]. In spite of that, TSPO/PET is not a consensus of in vivo microglia activation marker and TSPO polymorphism reduces binding affinity for all second-generation tracers tested in man hitherto, in mutants relative to wild type [116]. Several studies found evidence of inflammation in BD postmortem brain samples. However, an absolute statement cannot be concluded whether neuroinflammation is present in BD due to the large number of studies did not evaluate the presence of infiltrating peripheral immune cells in the CNS parenchyma, cytokines levels, and microglia activation in the same postmortem brain sample. In addition, several studies did not find any effect of BD on brain inflammatory markers. For example, out of 15 studies that evaluated microglia cells markers, 8 studies found no effect of BD on these cells, whereas 4 studies found a decrease of markers. Similarly, 17 out of 51 studies evaluating astrocytes markers, 9 studies did not find any effect of BD on astrocyte cells, whereas 8 studies found a decrease and 2 studies presented an increase and a decrease in different brain regions. As discussed above, microglia cells are the brain-resident macrophages and these cells are key players in neurodegenerative and neuroinflammatory diseases [117]. Despite that, activated microglia cells induce neurotoxic reactive astrocytes and these cells lose the ability to promote brain homeostasis, and induce the death of neurons and oligodendrocytes [32]. An additional aspect of this systematic review about BD and neuroinflammation is a non-consistent result from glial cell markers and inflammatory mediator levels in postmortem BD brain samples. Nonetheless, without a positive correlation between these two factors we cannot affirm that BD is associated with neuroinflammation. A few studies reported increase in pro-inflammatory cytokines in BD brain samples, for example, among 7 studies, 4 presented increased IL-1β and 3 increased the expression of TNF-α levels. However, it is not possible to conclude whether these cytokines were produced in the periphery and crossed the BBB or produced in the brain of BD patients. Blood-borne cytokines might affect the function of the CNS by crossing the BBB for direct interaction with CNS tissue [118]. Mechanisms by which this process is accomplished may involve the following: (i) saturable transport systems from blood to the CNS for example IL-1α, IL-1β, IL-6, and TNF-α; (ii) simple diffusion; and (iii) areas in the brain where the BBB is incomplete. In addition, cytokines may also damage the

BBB and increase its permeability without entering the brain, such as through activation and destruction of tight junctions of microvascular endothelial cells forming the BBB, for example TNF-α [118–120]. The diversity of studies and variations in results due to non-standardized confounding factors, whose impact may change the marker profiles, make it difficult to thoroughly compare the studies and come to an overall conclusion without discrepancies. Future analyses should rectify these potential sources of heterogeneity and reach a consensus regarding the inflammatory markers in postmortem brain samples to make them more promising for novel diagnostic and therapeutic purposes.

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Compliance with ethical standards

Conflict of interest JQ: Clinical Research Support: Allergan (Clinical Trial), Janssen Pharmaceuticals, Inc. (Clinical Trial). Advisory Boards, Speaker Bureaus, Expert Witness, or Consultant. Assurex Health, Inc. (Speaker Bureau), Daiichi Sankyo (Speaker Bureau), Janssen Pharmaceuticals, Inc. (Speaker Bureau). Patent, Equity, or Royalty: Instituto de Neurociencias. Dr. Joao Quevedo (Stockholder), Other Artmed Editora (Copyright), Artmed Panamericana (Copyright), Elsevier (Copyright). The other authors declare that they have no conflict of interest.

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