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Brain Inflammatory Marker Abnormalities in Major Psychiatric Diseases: a Systematic Review of Postmortem Brain Studies

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Abstract

Schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD) are common neuropsychiatric disorders that lead to neuroinflammation in the pathogenesis. It is possible to further explore the connection between inflammation in the brain and SCZ, BD, and MDD. Therefore, we systematically reviewed PubMed and Web of Science on brain inflammatory markers measured in SCZ, BD, and MDD postmortem brains. Out of 2166 studies yielded by the search, 46 studies met the inclusion criteria in SCZ, BD, and MDD postmortem brains. The results were variable across inflammatory markers. For example, 26 studies were included to measure the differential expression between SCZ and control subjects. Similarly, seven of the included studies measured the differential expression of inflammatory markers in patients with BD. The heterogeneity from the included studies is not clear at present, which may be caused by several factors, including the measured brain region, disease stage, brain source, medication, and other factors.

Keywords Schizophrenia · Major depressive disorder · Bipolar disorder · Inflammatory markers · Postmortem

Introduction

Schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD) are three types of common neuropsychiatric disorders that are characterized by severity and recurrence and are among the leading causes of serious self-harm or even suicidal behavior in young people [1–3]. In the early stages of the disease, they are usually difficult to distinguish by clinical diagnosis with symptoms overlapping across diagnoses, and shared phenotypes [4]. Although the etiology of these psychiatric disorders is still unknown and there are no effective drugs for treatment, several neuropathology [5], oligodendrocyte abnormalities [6], and metabolic disturbances [7] have been proposed. Among these underlying biological factors, several studies support the role of neuroinflammation in the pathogenesis of these mental disorders [8–10].

Neuroinflammation is an inflammatory response within the central nervous system (CNS) characterized by the proliferation and activation of glial cells (e.g., microglia and astrocytes) [11, 12]. Microglia are macrophages in the central nervous system that mediate innate and adaptive immune responses in the brain [13]. Under abnormal conditions such as brain infection, injury, or disease, microglia change from ramified ("resting") state to an "activated" state, releasing proinflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, or several chemokines [14]. Proinflammatory cytokines released from microglia can activate astrocytes, which are generally manifested by increased glial fibrillary acidic protein (GFAP) expression [8].

Given the pathology of inflammation in the brain, most studies have attempted to elucidate the link between inflammation and psychiatric disorders during the past 20 years. For example, advances in molecular biology and genetics have shown that genes involved in regulating the immune system are highly associated with the risk of SCZ, BD, and MDD [15]. Inflammatory biomarkers derived from peripheral blood of major psychiatric diseases have been

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investigated by several studies, which is due to the easy accessibility of the "blood and periphery as a window to the brain" hypothesis [16]. Elevated serum and plasma levels of proinflammatory cytokines, such as IL-1β and TNF-α, have been found in SCZ and BD [17, 18]. In addition, a recent meta-analysis focused on cerebrospinal fluid (CSF) cytokines in patients with SCZ, BD, and MDD and found that CSF levels of IL-6 and IL-8 were similarly elevated in these patients [19].

Although the above studies have suggested overall similarities in the pattern of blood cytokine alterations in patients with SCZ, BD, and MDD and raise the possibility that inflammation is involved in a potential brain pathologic pathway for these mental disorders, peripheral inflammatory markers are not representative of cerebral inflammatory markers since the CNS is the ultimate site of disease. However, in the literature related to major psychiatric disorders such as SCZ, BD, and MDD, there have been a large number of reports evaluating markers related to inflammation in the brain. This makes it possible to further explore the connection between inflammation in the brain and disease. Therefore, we systematically reviewed the literature on brain inflammatory markers measured in SCZ, BD, and MDD postmortem brains to identify more elevated inflammatory markers in the postmortem brain of these patients, and to provide a preliminary conclusion on the inflammatory pathways by which postmortem brain samples of these diseases are affected.

Methods

We performed this systematic review as stated in a prospective protocol following guidelines that are recommended by the PRISMA Statement (Preferred Reporting Items for Systematic reviews) [20].

Literature Search Strategy

We performed a literature search for records indexed within PubMed (1974 to 8th May 2022) and Web of Science (1985 to 8th May 2022) using the following search terms: "(schizophrenia or bipolar disorder or major depressive disorder or depression) and (inflammation or cytokine or chemokine or interleukin or interferon or tumor necrosis factor or colony-stimulating factor) and (postmortem or brain sample)."

Eligibility Criteria

Studies were screened for relevance based on their title and abstract by two researchers independently. The full text of potentially relevant articles was retrieved and screened against the following inclusion criteria: (1) studies that focused on postmortem brain samples, including SCZ, BD, and MDD; (2) measurement of inflammation-related markers, including any kind of inflammatory cytokine/chemokines, and other related markers were considered if the authors mentioned their role in neuroinflammation; and (3) matched healthy controls were included. Duplicates and articles that did not meet the above criteria were excluded. In addition, review articles, in vitro studies, and animal studies were excluded. Finally, conference abstracts and non-English papers were also excluded.

Data Extraction

Eligible studies were assessed, the data were extracted into an Excel spreadsheet by the researcher, and any disagreements were resolved by discussion. For the eligible studies, the first author's name, publication year, brain bank, sample size, sex, age, and death from suicide were extracted as background information. In addition to inflammatory markers measured, measuring techniques and in which brain regions the measurements were made were all extracted, along with comparative results between the patient subjects and the healthy controls. Graphical data were extracted using a Web plotter (https://apps.automeris.io/wpd/).

Given the differences in the brain regions measured, we decided that if studies measured the same parameters in the cortical (or subcortical) layer and at least two sets of data were available, we performed a systematic review of these studies. The effective size (ES) was used except where stated. ES was produced by sample size, mean concentration, and standard deviation (SD), or by sample size and *P* value if the data of mean concentration were not available [21]. This excluded several studies (e.g., which used medians and interquartile ranges).

Results

Our search strategy resulted in the identification of 2166 unique studies from the initial search. After screening the titles and abstracts for relevance, 77 articles were full-text screened against the inclusion criteria. Out of the 77 articles, 31 articles were excluded because they did not measure inflammation-related markers (12 studies); data was not separable from other diagnostic groups (8 studies); postmortem brain from the dataset (2 studies); and incorrect measurement methods, such as cDNA microarray experiments, and gene network analysis (9 studies). Thus, a total of 46 studies were ultimately included in this review (Fig. 1).

Characteristics of the Included Studies

Table 1 summarizes the basic demographics of these included studies. The incorporated studies contained relatively small numbers of subjects with BD, which may be due to the BD postmortem brain samples being scarce. Most

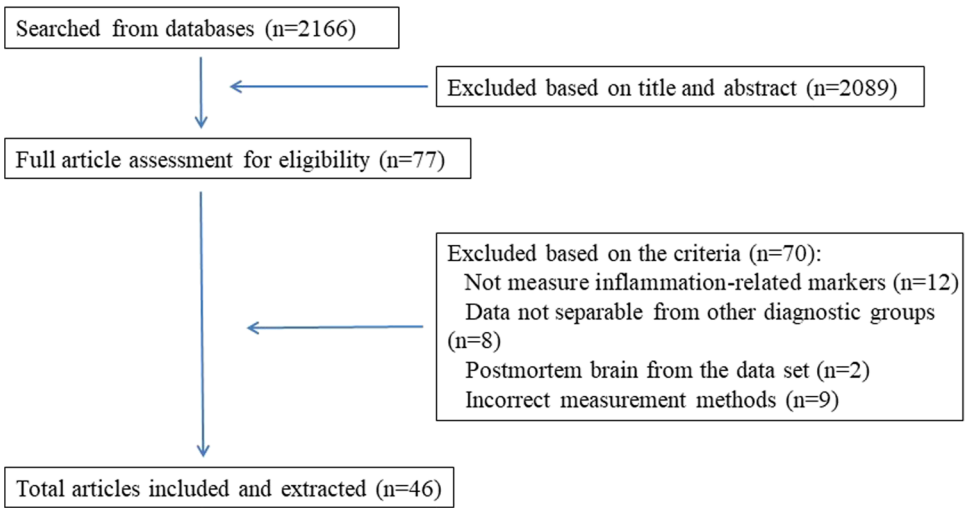

Fig. 1 Flow chart of the systematic search

Table 1 Demographic characteristics of the studies included in the systematic review

	SCZ[a]	BD	MDD	HC
Patients per study (n)				
Mean ± SD	32.52 ± 22.01	19 ± 11.93	23.78 ± 9.41	27.25 ± 18.12
Range	8–82	9–44	6–45	5–88
Males per study (*n*)[b]				
Mean ± SD	21.79 ± 15.83	9.91 ± 6.20	15 ± 7.81	21.10 ± 16.30
Range	4–54	4–23	3–30	4–69
Age (years)[c]				
Mean ± SD	52.76 ± 11.74	50.25 ± 10.58	50.50 ± 11.48	52.70 ± 11.89
Range	41–81	42–76	40–75	33–80

[a]Excluding Purves-Tyson et al. 2020; see Table 2

[b]Studies with known sex-specific information did not include Rao et al. (2010) and Wang et al. (2018); see Tables 3 and 4

[c]Studies with known age-specific information did not include Mahajan et al. (2017) and Wang et al. (2018); see Table 4

studies involving donor subjects were defined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III or DSM-IV, but the remaining studies used other criteria or were not specified and were therefore not included in the statistics. Although several studies included one or more diagnostic groups, our results were still discussed by disease classification and summarized in Tables 2, 3 and 4, highlighting the main results the authors reported as being statistically significant in their study.

Studied Brain Areas

The regions of the brain studied in the included studies mainly included the anterior cingulate cortex (ACC; Brodmann area (BA)24), dorsolateral prefrontal cortex (DLPFC; BA46), frontal cortex (FC), hippocampus, orbitofrontal cortex (OFC; BA11), prefrontal cortex (PFC; BA9), medial frontal gyrus (MFG), superior frontal gyrus (SFG), and superior temporal gyrus (STG).

Immune/Inflammation Response, Cell Regulatory Proteins, Glia/Macrophage Proliferation, Metabolic Pathway, and Chemokines in Postmortem Studies of SCZ

A total of 39 studies were included to measure the difference between SCZ and control subjects. In detail, immune/inflammation response (Arion et al. [22], Dean et al. [23], Durrenberger et al. [24], Fillman et al. [25], Fillman et al. [26], Foster et al. [27], Harris et al. [28], Hoseth et al. [29], Hwang et al. [30], Iwamoto et al. [31], Izumi et al. [32], Kim et al. [33], Kindler et al. [34], Lanz et al. [35], López-González et al. [36], Maida et al. [37], Murphy et al. [38], Murphy et al. [39], Pandey et al. [40], Saetre et al. [41], Schmitt et al. [42], Toyooka et al. [43], Volk et al. [44], Volk et al. [45], Yokota et al. [46], Zhang et al. [47]), cell regulatory proteins (Abdolmaleky et al. [48], Catts et al. [49], Gibbons et al. [50]), glia/macrophage proliferation (Busse et al. [51], Purves-Tyson et al. [52], Sneeboer et al. [53], Zhang et al. [54], Zhang et al. [55]), metabolic pathway (Afia et al. [56], Tang et al. [57]), and chemokines (Hill et al. [58], Nakatani et al. [59], Volk et al. [60]) were measured in postmortem brains of SCZ. The characteristics of included studies are summarized in Table 2.

As shown in Table 2, the main regions of the postmortem brains of patients with SCZ consisted of the DLPFC, PFC, CB, HPC, temporal lobe, cortical gray, STG, etc. The different regions of brain were analyzed using polymerase chain reaction (PCR) , Western blot (WB), enzyme linked immunosorbent assay (ELISA), and immunohistochemical (IHC)

Table 2 Inflammatory markers of the included studies in postmortem schizophrenia brain

Author/year	Brain bank	Sample size (patients and controls)	Sex (m/f)	Age	Death from suicide	Brain region	Technique	Inflammatory markers	Main results	
Abdolmaleky et al. 2019	SMRIAC	SCZ 35 HC 35	SCZ 26/9 HC 26/9	SCZ 43 HC 44	SCZ 7	DLPFC (BA46)	PCR	NR2E1 (1.3-fold, p=0.038), TGF-β2 (1.26-fold, p=0.019)	↑	Stanley Medical Research Institute Array Collection
Afia et al. 2021	Neuro-logical Tissue of Sant Joan de Déu, Hospital Universitari de Bellvitge	(1) SCZ 15 HC 14 (2) SCZ 15 HC 13	(1) SCZ 15/0 HC 14/0 (2) SCZ 15/0 HC 13/0	(1) SCZ 74 HC 74 (2) SCZ 75 HC 74	NA	(1) PFC* (2) CB#	WB, ELISA	IL-1β, IL-4, IL-10*,IDO1*, IDO2*, TDO*, KMO*, KATII*	↓*↔#	
Arion et al. 2006	UPCNMDBBU	SCZ 14 HC 14	SCZ 12/2 HC 12/2	SCZ 43 HC 42	SCZ 3	PFC (BA9)	PCR	SERPINA3*, IFITM2*, IFITM3*, CHI3L1*, MT2A*, HSPB1*,DIRAS2#, CRYM#, TF#, MOG#, MAPK1#, RGS4#	↑ ↔#	University of Pittsburgh's Center for the Neuroscience of Mental Disorders Brain Bank, mu-crystallin (CRYM), transferrin (TF), mitogen-activated protein kinase 1 (MAPK1), regulator of G-protein signaling 4 (RGS4)
Busse et al. 2012	MBB	SCZ (p) 10* SCZ (r) 7 HC 11	SCZ (p) 5/5 SCZ (r) 4/3 HC 6/5	SCZ (p) 50 SCZ (r) 56 HC 56	SCZ 5#	HPC	IHC	CD3, CD20, HLA-DR	↑*#	Magdeburg brain bank
Catts et al. 2012	SMRIAC, NSWTRC	SCZ 72 HC 71	SCZ 50/22 HC 55/16	SCZ 47 HC 48	SCZ 15	DLPFC*#, OFC	PCR	TNFSF13*, FASR, CLFAR, BID#	↑* ↓#	FASR, Tumor Necrosis Factor Superfamily member 6 receptor, BH3 interacting domain death agonist (BID)
Dean et al. 2013	VBBN, MHRI	SCZ 19 HC 20	SCZ 15/4 HC 16/4	SCZ 41 HC 47	SCZ 8	DLPFC (BA46), ACC (BA24)*	WB, PCR	sTNF-α#, tmTNF-α#, TNF-α#, TNFR1*, TNFR2#	↑* ↔#	Victorian Brain Bank Network, Mental Health Research Institute
Durrenberger et al. 2014	BBPDGU	SCZ 10 HC 10	SCZ 5/5 HC 5/5	SCZ 66 HC 61	NA	Temporal lobe (BA22)	PCR	HLA-DRA, HLA-DRB4, L-13RA1, ALOX5AP, TIMP1, TNFRSF1A, TYROBP	↓	Brain Bank for Psychiatric Diseases at the Gottingen University
Fillman et al. 2013	NSWTRC	SCZ 37 HC 37	SCZ 24/13 HC 30/7	SCZ 51 HC 51	NA	DLPFC (BA46)	PCR	IL-8*, IL-6*, IL-1β, PTGS2 (COX-2)#, NF-κB, SERPINA3*, IL6ST	↑* ↓#	New South Wales Tissue Resource Centre
Fillman et al. 2014	SMRIAC	SCZ 35 HC 35	SCZ 26/9 HC 26/9	SCZ 43 HC 44	SCZ 7	MFG	PCR	SERPINA3*, IL-1RL1, PTGS2, IL-1β, IL-18, IL-6, IL-8#, TNF-α	↑* ↓#	Stanley Medical Research Institute Array Collection
Foster et al. 2006	SFBC	SCZ 15 HC 15	SCZ 9/6 HC 9/6	SCZ 44 HC 48	SCZ 4	DLPFC (BA9)	ELISA	Calprotectin	↑	Stanley Foundation Brain Collection

Table 2 (continued)

Author/year	Brain bank	Sample size (patients and controls)	Sex (m/f)	Age	Death from suicide	Brain region	Technique	Inflammatory markers	Main results	
Gibbons et al. 2020	VBBN	SCZ 20 HC 20	SCZ 16/4 HC 16/4	SCZ 48 HC 49	SCZ 8	BA24,46	WB	SMAD2*, SMADA4#	↓* ↔#	
Harris et al. 2012	SMRIAC	SCZ 35 HC 33	SCZ 26/9 HC 25/8	SCZ 43 HC 45	NA	BA10	ELISA	IFN-γ*, TIMP1#	↑* ↔#	
Hill et al. 2020	SMRIAC	SCZ 35 HC 35	SCZ 26/9 HC 26/9	SCZ 43 HC 44	SCZ 7	DLPFC	WB*, PCR, ELISA	Fractalkine (CX3CL1)*, CX3CR1#, ADAM10#	↓* ↔#	
Hoseth et al. 2017	NA	SCZ 80 HC 88	SCZ 54/26 HC 69/19	SCZ 47 HC 45	NA	DLPFC (BA9/46) gray matter	PCR, ELISA	TNF-α, TNFR1, TNFR2, ADAM17	↔	
Hwang et al. 2013	SNC, SMRIAC	SCZ 33 HC 34	SCZ 23/10 HC 23/11	SCZ 44 HC 46	NA	HPC	PCR	ADRORA2A*, APOL1*, CD163#, IGFBP4*, IFITM1*, IFITM2*, IFITM3*	↑* ↔#	Stanley Neuropathology Consortium, Stanley Medical Research Institute Array Collection
Iwamoto et al. 2004	SFNC	SCZ 13 HC 15	SCZ 8/5 HC 9/6	SCZ 44 HC 48	SCZ 4	PFC (BA10)	PCR	IFITM3	↑	
Izumi et al. 2021	FBBDN, FMU, BRINU	SCZ 24 HC 26	SCZ 15/9 HC 15/11	SCZ 68 HC 62	NA	STG	Bradford protein assay kit	EGF, G-CSF, GM-CSF, INF-α*, IL-10, IL-12P, IL-13, IL-15, IL-1RA, IL-1α#, IL-1β, IL-6, IL-7, IL-8, IP-10#, MCP-1, MIP-1a, MIP-1b, TNF-α, VEGF	↑* ↓#	Fukushima Brain Bank at the Department of Neuropsychiatry, Fukushima Medical University, and Brain Research Institute at Niigata University
Kim et al. 2016	HBTRC	SCZ 10 HC 9	SCZ 4/6 HC 4/5	SCZ 77 HC 79	NA	FC (BA9, 10, 24)	WB, ELISA, Luminex	NLRP3#, ASC#, caspase-1*, IL-1β*, IFN-γ#, IL-10*, IL-6*, TNF-α*	↑* ↔#	Harvard Brain Tissue Resource Centre
Kindler et al. 2019	(1) NSWTRC (2) SMRI	(1) SCZ 37 HC 37 (2) SCZ 34 HC 35	(1) SCZ 24/13 HC 30/7 (2) SCZ 25/9 HC 26/9	(1) SCZ 51 HC 51 (2) SCZ 43 HC 44	(1) SZC 8 (2) SZC 7	DLPFC	PCR	TDO*, KATI*, KATII*, KMO#	↑* ↔#	New South Wales Tissue Resource Center
Lanz et al. 2019	PU	SCZ 19 HC 19	SCZ 10/9 HC 10/9	SCZ 45HC 48	NA	HPC	(1) PCR (2) ELISA	(1) S100A9*, S100A8*, IL-6*, MAFF*, APOLD1*, IFITM3*, BAG3*, HSPB1#, CEBPD#, IL-2#, IL-12A#, IL-12B# (2) IL-2*, IL-12p70*, IL-8#, IL-6#, IL-1β#, IL-13#, IL-4#, IL-10#, TNF-α#	(1) ↑* ↔# (2) ↑* ↔#	Pittsburgh University

Table 2 (continued)

Author/year	Brain bank	Sample size (patients and controls)	Sex (m/f)	Age	Death from suicide	Brain region	Technique	Inflammatory markers	Main results	
López-González et al. 2019	NBBI	SCZ 14 HC 14	SCZ 14/0 HC 14/0	SCZ 76 HC 71	NA	DLPFC	PCR	C1QL1#,C1QTNF7#, C3AR1#, CSF1R*, CSF3R#, TLR4*, TLR7#, IL-1β#, IL-8#, IL-6*, IL-6ST#, TNF-α#, TNFRSF1A#, IL-10*, IL-10RA*, IL-10RB*, TGF-β1#, TGF-β2#	↓* ↔#	Neuropathology Brain Bank Institute
Maida et al. 2006	SFNC	SCZ 15 HC 15	SCZ 9/6 HC 9/6	SCZ 45 HC 48	SCZ 4	PFC (BA8)*, TC (BA21, 22)#, OC (BA18)#	WB, IHC	COX-1#, COX-2 #, cPGE2*	↓*↔#	
Murphy et al. 2020	NSWTRC	SCZ 37 HC 37	SCZ 24/13 HC 30/7	SCZ 53 HC 51	NA	DLPFC	PCR, in situ hybridisation, IHC	HIVEP2, SERPINA3*	↑*	New South Wales Tissue Resource Centre
Murphy et al. 2020	NSWTRC, SMRI	SCZ 72 HC 69	SCZ 50/22 HC 53/16	SCZ 47 HC 48	NA	DLPFC (BA46)	PCR	TNFR1*, IL-1R1, TLR4#, CD40, LTβR, TNFR2, IKKα#, IKKβ#, NIK, IκBα#, IκBβ#, IκBε#, HIVEP2#, RelA#, cRel#, NFκB1#, RelB, NFκB2	↑* ↓#	New South Wales Tissue Resource Centre, Stanley Medical Research Institute
Nakatani et al. 2006	VIFM	SCZ 7 HC 7	SCZ 3/4 HC 3/4	SCZ 61 HC 61	SCZ 1	DLPFC (BA46), PC (BA40)	PCR	CCL3	↓	Victorian Institute of Forensic Medicine
Pandey et al. 2017	MBB	SCZ 31 HC 24	SCZ 23/8 HC 17/7	SCZ 43 HC 38	SCZ 16	PFC (BA9)	(1) PCR, (2) ELISA, (3) WB	(1) TNF-α*, IL-1β, IL-2, IL-6*, IL-8, IL-10#, IL-13, LTA, IL-1RA, (2) TNF-α*, IL-1β#, IL-6*, (3) IL-8#, IL-10#, IL-13, LTA*, IL-1RA	(1) ↑* ↓#; (2) ↑* ↔#; (3) ↑* ↓#	Magdeburg Brain Bank
Purves-Tyson et al. 2020	NSWBTRC	(1) SCZ (h) 13 SCZ (l) 15 HC 28 (2) SCZ (h)* 12 SCZ (l)# 13 HC 26	(1) SCZ (h) 8/5 SCZ (l) 11/4 HC 20/8 (2) SCZ (h) 7/5 SCZ (l) 9/4 HC 19/4	(1) SCZ (h) 55 SCZ (l) 48 HC 51 (2) SCZ (h) 56 SCZ (l) 49 HC 51	NA	Midbrain	(1) PCR (2) WB	(1) ICAM1*, CD163*, FN1*, HEXB#, CD64,* MRC1#, C1qA*, C3*, C4*, CD55 (DAF)#, CD59 (MAC-IP)# (2) CD163*, C3, C4#	(1) ↑* ↔# (2) ↑*#	New South Wales Brain Tissue Resource Center
Saetre et al. 2017	SFBC, MBB, HBTRC	SCZ 55 HC 55	NA	SCZ 55 HC 59	NA	SFG, FC, BA8,9	PCR	SERPINA3*, IFITM2*, IFITM3*, GBP1*, HLA-A#	↑* ↔#	Stanley Foundation Brain Consortium Maudsley Brain Bank Harvard Brain Tissue Resource Centre

Table 2 (continued)

Author/year	Brain bank	Sample size (patients and controls)	Sex (m/f)	Age	Death from suicide	Brain region	Technique	Inflammatory markers	Main results	
Schmitt et al. 2011	BBPDGU	SCZ 10 HC 10	SCZ 5/5 HC 8/2	SCZ 66 HC 61	NA	STC (BA22)	PCR	PTGER4*, EDG3*, LPL*, CFD*, IL-8*, IL-1α*, IL-1β*, CCL2*, GPX#, IL1RAP#, IFNAR2#, SOD2#, CD84#, LTC4S#, MTHFD2#, IFI16#, LCP1#, ITGA1#	↓* ↔#	Brain Bank for Psychiatric Diseases at the Gottingen University
Sneeboer et al. 2019	NBB	SCZ 8 HC 10	SCZ 5/3 HC 6/4	SCZ 81 HC 64	NA	MFG	PCR	TSPO	↔	Netherlands Brain Bank
Tang et al. 2012	VBBN	SCZ 38 HC 38	NA	SCZ 43 HC 44	NA	DLPFC (BA46)	PCR	PTGS1, PTGS2, PTGER3, CYP4Z1	↔	
Toyooka et al. 2003	NA	SCZ 22 HC 23	SCZ 16/6 HC 14/9	SCZ 59 HC 66	NA	PFC (BA46)*, HT, PC (BA1-3), PU	PCR, ELISA	IL-1β#, IL-1RA*	↓* ↔#	
Volk et al. 2014	ACOME	SCZ 62 HC 62	SCZ 47/15 HC 47/15	SCZ 48 HC 49	NA	PFC	PCR	CXCR4, CXCR7	↑	Allegheny County Office of the Medical Examiner
Volk et al. 2015	ACOME	SCZ 62 HC 62	SCZ 47/15 HC 47/15	SCZ 48 HC 49	SCZ 16	PFC (BA9)	PCR	IL-1β*, IL-6*, IL-8, IFN-β*, NFκB1*, NFκB2*, Shn-2#	↑*↓#	Allegheny County Office of the Medical Examiner
Volk et al. 2018	ACOME	SCZ 62 HC 62	SCZ 47/15 HC 47/15	SCZ 48 HC 49	NA	PFC (BA9) gray matter	PCR	IL-1R*, TLR4*, TNFR1*, TNFR2*, CD40*, LTβR*, IKKα*, IKKβ*, IkBα*, IkBβ#, IkBε#, NIK*, RelA*, RelB#, cRel*	↑* ↔#	
Yokota et al. 2004	NA	SCZ 17 HC 22	SCZ 12/5 HC 13/9	SCZ 69 HC 71	SCZ 0	HPC	IHC	COX-2	↔	
Zhang et al. 2016	NSWBTRC	SCZ 31 HC 31	SCZ 15/16 HC 17/14	SCZ 52 HC 53	NA	OFC	PCR	IL-6*, IL-1β*, IL-8#, SERPINA3*	↑* ↔#	New South Wales Brain Tissue Resource Centre
Zhang et al. 2020a	SFBC	SCZ 15 HC 15	SCZ 9/6 HC 9/6	SCZ 45 HC 48	NA	PC (BA7), CB*	WB	CSF1R#, SPI1*	↑* ↔#	Stanley Foundation Brain Collection
Zhang et al. 2020b	SMRI	SCZ 35* HC 34	SCZ 26/9 HC 25/9	SCZ 43 HC 45	SCZ 7#	DLPFC (BA46)#, ACC (BA24)*		CX3CR1	↑* ↔#	Stanley Medical Research Institute

↑ represents up-regulation, ↓ represents down-regulation, ↔ represents no change

Table 3 Inflammatory markers of the included studies in postmortem bipolar disorder brain

Author/year	Brain bank	Sample size (patients and controls)	Sex (m/f)	Age	Death from suicide	Brain region	Technique	Inflammatory markers	Main results	
Abdolmaleky et al. 2019	SMRIAC	BD 35 HC 35	BD 17/18 HC 26/9	BD 45 HC 44	BD 15	DLPFC (BA46)	PCR	NR2E1*, TGF-β2#	↑* ↔#	
Bezchlibnyk et al. 2001	SFNC	BD 10 HC 10	BD 4/6 HC 4/6	BD 45 HC 48	NA	FC	PCR	TGF-β1*, Casp-8*, Tob*, ERK-5#, PLC#	↑* ↔#	Casp-8, caspase-8 precursor, ERK-5, extracellular signal-regulated kinase-5, PLC, phospholipase C (epsilon subunit), Tob, transducer of erbB2
Catts et al. 2012	SMRIAC, NSWTRC	BD 31 HC 34	NA	NA	NA	DLPFC*, OFC	PCR	TNFSF13, FASR, CLFAR, BID*	↓*	
Dean et al. 2013	VBBN, MHRI	BD 10 HC 10	BD 6/4 HC 7/3	BD 31 HC 63	BD 4	DLPFC (BA46)#, ACC (BA24)*	WB, PCR	sTNF-α, tmTNF-α*, TNFR1, TNFR2#, Pro-IL-1β	↑* ↓#	Victorian Brain Bank Network, Mental Health Research Institute
Fillman et al. 2014	SMRIAC	BD 34 HC 35	BD 16/18 HC 26/9	BD 45 HC 44	BD 15	MFG	PCR	SERPINA3, IL-1RL1, PTGS2, IL-1β, IL-18*, IL-6, IL-8, TNF-α	↓*	
Foster et al. 2016	SFBC	BD 15 HC 15	BD 9/6 HC 9/6	BD 42 HC 48	BD 9	DLPFC (BA9)	ELISA	Calprotectin	↔	Stanley Foundation Brain Collection
Hill et al. 2020	SMRIAC	BD 34 HC 35	BD 16/18 HC 26/9	BD 45 HC 44	BD 15	DLPFC	WB, PCR, ELISA	fractalkine, CX3CR1, ADAM10	↔	
Hoseth et al. 2017	NA	BD 44 HC 88	BD 23/21 HC 69/19	BD 47 HC 45	NA	DLPFC (BA9/46)	ELISA	TNF-α, TNFR1, TNFR2, ADAM17	↔ ()	
Iwamoto et al. 2004	SFNC	BD 11 HC 15	BD 8/3 HC 9/6	BD 39 HC 48	BD 8	PFC (BA10)	PCR	IFITM3	↑	

Table 3 (continued)

Author/year	Brain bank	Sample size (patients and controls)	Sex (m/f)	Age	Death from suicide	Brain region	Technique	Inflammatory markers	Main results
Kim et al. 2010	HBTRC	BD 10 HC 10	BD 6/4 HC 9/1	BD 49 HC 43	BD 5	FC (BA9)	PCR, WB, ELISA, IHC	BAX*, BAD*, caspase-9*, caspase-3*, BDNF#, Bcl-2#	↑* ↓#
Kim et al. 2011	HBTRC	BD 10 HC 10	BD 6/4 HC 9/1	BD 49 HC 43	BD 5	FC	PCR, WB	cPLA2*, sPLA2*, iPLA2, COX-2*, COX-1#, mPGES*, cPGES#, 5-LOX, 5-LOX, 12-LOX, 15-LOX, TXS,	↑* ↓#
Kim et al. 2016	HBTRC	BD 9 HC 9	BD 4/5 HC 4/5	BD 76 HC 79	NA	FC (BA9, 10, 24)	WB, ELISA, Luminex	NLRP3*, ASC*, caspase-1*, IL-1β*, IFN-γ#, IL-10*, IL-6*, TNF-α*	↑* ↔#
Lanz et al. 2019	PU	BD 19 HC 19	BD 10/9 HC 10/9	BD 46 HC 48	NA	HPC	(1) PCR, (2) ELISA	(1) S100A9*, S100A8*, IL-6*, MAFF#, APOLD1#, IFITM3#, BAG3#, HSPB1#, CEBPD#, IL-2*, IL-12A*, IL-12B#; (2) IL-2, IL-12p70, IL-8, IL-6, IL-1β, IL-13, IL-4, IL-10, TNF-α	(1) ↑* ↔# (2) ↔

Table 3 (continued)

Author/year	Brain bank	Sample size (patients and controls)	Sex (m/f)	Age	Death from suicide	Brain region	Technique	Inflammatory markers	Main results	
Maida et al. 2006	SFNC	BD 15 BD 15	BD 9/6 HC 9/6	BD 42 HC 48	BD 8	PFC (BA8)*, TC (BA21, 22)*, OC (BA18)#	WB, IHC	COX-1#, COX-2#, cPGE2*	↓* ↔#	
Nakatani et al. 2006	VIFM	BD 7 HC 7	BD 3/4 HC 3/4	BD 62 HC 61	NA	DLPFC (BA46), PC (BA40)	PCR	CCL3	↓	
Nascimento et al. 2020	BAS	(1) BD 17 HC 17 (2) BD 14 HC 14	(1) BD 5/12 HC 5/12 (2) BD 3/11 HC 3/11	(1) BD 68 HC 66 (2) BD 66 HC 65	(1) BD 1 (2) BD 2	(1) HPC (2) ACC	ELISA	(1) Cortisol*, CRP#, IL-1β*, IL-6*, IL-10*, IL-17A*, TNF-α* (2) Cortisol*, CRP#, IL-1β#, IL-6#, IL-10#, IL-17A*, TNF-α#	(1) ↑* ↔# (2) ↑* ↔#	Biobank for Aging Studies
Rao et al. 2010	HBTRC	BD 10 HC 10	NA	BD 49 HC 43		FC	WB, PCR	IL-1*, IL-1R*, MyD88*, NF-κB p50*, NF-κB p65*, iNOS*, nNOS#, c-fos*, TNF-α#, CD11b*	↑* ↔#	
Zhang et al. 2020	SFBC	BD 15 HC 15	BD 9/6 HC 9/6	BD 42 HC 48	NA	PC (BA7), CB*	WB	CSF1R#, SPI1*	↑* ↔#	

↑ represents up-regulation, ↓ represents down-regulation, ↔ represents no change

Table 4 Inflammatory markers of the included studies in postmortem major depressive disorder brain

Author/year	Brain bank	Sample size (patients and controls)	Sex (m/f)	Age	Death from suicied	Brain region	Technique	Inflammatory markers	Main results	
Böttcher et al. 2020	PDPNDD	MDD 6 HC 5	MDD 3/3 HC 4/1	MDD 60 HC 80	NA	Frontal lobe, temporal lobe, thalamus, subventricular zone	CyTOF measurements	CD11b#, CD45#, HLA-DR#, CD68#, P2Y12*, TMEM119*, CCL2#, IL-1β#, IL-6#, TNF-α#, MIP-1β (CCL4)#, IL-10#	↑* ↔#	Psychiatric Donor Program of the Netherlands Brain Bank single-cell high-dimensional mass cytometry
Clark et al. 2016	MNCBDB	MDD 45 HC 36	MDD 30/15 HC 27/9	MDD 43 HC 42	MDD 25	VLPFC	(1) GC/MS (2) PCR	(1) TRP#, Kynurenine#, KYNA#, 3-HK#, QUIN*, IDO1*, IDO2*, TDO2*, KATII#, KMO#; (2) IL-1β#, IL-2*, IL-4#, IL-5#, IL-6#, IL-13*, IL-33*, IFN-γ*, TNF-α*, CCL2*	↓* ↔#	Maryland Neuropathology Clinical Brain Disorders Branch
Dean et al. 2010	NA	MDD 10 HC 10	MDD 6/4 HC 7/3	MDD 62 HC 62	NA	BA24, 46*	WB	tmTNF-α*, sTNF-α#	↑* ↔#	
Dean et al. 2013	VBBN, MHRI	MDD 10 HC 10	MDD 6/4 HC 6/4	MDD 39 HC 63	MDD 8	DLPFC (BA46)*, ACC (BA24)	WB, PCR	TNF-α, TNFR1#, TNFR2*, Pro-IL-1β#	↓* ↔#	Victorian Brain Bank Network, Mental Health Research Institute
Foster et al. 2016	SFBC	MDD 15 HC 15	MDD 9/6 HC 9/6	MDD 46 HC 48	MDD 7	DLPFC (BA9)	ELISA	Calprotectin	↔	Stanley Foundation Brain Collection
Khundakar et al. 2011	NA	MDD 20 HC 20	MDD 7/13 HC 7/13	MDD 75 HC 74	NA	OC (BA11,12)	IHC	TGF-β1	↔	

Table 4 (continued)

Author/year	Brain bank	Sample size (patients and controls)	Sex (m/f)	Age	Death from suicied	Brain region	Technique	Inflammatory markers	Main results	
Lanz et al. 2019	PU	MDD 19 HC 19	MDD 10/9 HC 10/9	MDD 45 HC 48	NA	DLPFC (BA46), DST, HPC	(1) PCR (2) ELISA	(1) S100A9, S100A8, IL-6, MAFF, APOLD1, IFITM3, BAG3, HSPB1, CEBPD, IL-2, IL-12A, IL-12B, (2) IL-2, IL-12p70, IL-8, IL-6, IL-1β, IL-13, IL-4, IL-10, TNF-α	↔	University of Mississippi Medical Center
Mahajan et al. 2017	UMMC	MDD 23 HC 23	MDD 14/9 HC 14/9	NA	MDD 17	DG	PCR	ISG15, IFI44L, IFI6, NR4A1/Nur-77, CCL2/MCP-1	↑	Basque Institute of Legal Medicine
Maida et al. 2006	SFNC	MDD 15 MDD 15	MDD 9/6 HC 9/6	MDD 47 HC 48	BD 7	PFC (BA8)*, TC (BA21, 22)#, OC (BA18)#	WB, IHC	COX-1#, COX-2#, cPGE2*	↓* ↔#	Lieber Institute for Brain Development
Martín-Hernández et al. 2018	BILM	MDD 30 HC 30	MDD 22/8 HC 22/8	MDD 46 HC 46	MDD 26	DLPFC (BA9)	WB	TLR4, Hsp60, Hsp70*, p-ERK1/2*, p-JNK*, p-p38*, DUSP2#, PI3K, Keap-1, Nrf-2#, S100A10, NF-κB (p65)#	↑* ↓#	Maryland Brain Collection at the Maryland Psychiatric Research Center
Morrison et al. 2019	LIBD	MDD 25 HC 13	MDD 22/3 HC 11/2	MDD 43 HC 50	MDD 6	DLPFC	PCR	IL-1A	↓*	Maryland Psychiatric Research Center

Table 4 (continued)

Author/year	Brain bank	Sample size (patients and controls)	Sex (m/f)	Age	Death from suicied	Brain region	Technique	Inflammatory markers	Main results	
Pandey et al. 2014	MBCMPRC	MDD 34# HC 20	MDD 19/15 HC 16/4	MDD 42 HC 37	MDD 22*	DLPFC	PCR*, WB*#	TLR3, TLR4	↑* ↔#	New York State Psychiatric Institute and Columbia University
Pandey et al. 2018	MPRC	MDD 36 HC 24	MDD 21/15 HC 20/4	MDD 42 HC 42	MDD 24*	PFC (BA9)	PCR, WB*	TLR1#, TLR2*, TLR5#, TLR6*, TLR7#, TLR8#, TLR9#, TLR10*	↑* ↔#	Douglas-Bell Canada Brain Bank
Pandey et al. 2021	Maryland Brain Collection at the Maryland Psychiatric Research Center	MDD 24 HC 24	NA	NA	MDD 24	PFC (BA9)	PCR, WB	NLRP1*, NLRP3*, NLRP6*, ASC*, Caspase-1#, Caspase-3*, IL-18#, TNF-α*, IL-1β*, IL-6*	↑* ↔#	
Pantazatos et al. 2016	NYSPICU	MDD 30 HC 29	MDD 19/11 HC 23/6	MDD (ns) 58 MDD (s) 52 HC 44	MDD 21	BA9	PCR	MTRNR2L8#, SERPINH1*, IL-8*, CCL4*, MRPS6*	↓* ↔#	
Tanti et al. 2019	DBCBB	MDD 26 HC 13	MDD 26/0 HC 13/0	MDD 40 HC 33	MDD 26*	ACC	PCR	GJB6/CX30#, GJA1/CX43#, GJB1/CX32*, GJC2/CX47*, CAV1*, CAV2*, OCLN*, DBN1#	↓* ↔#	Maryland Brain Collection
Thomas et al. 2000	NA	MDD 20 HC 20	MDD 7/13 HC 7/13	MDD 75 HC 74	MDD 2	DLPFC (BA9,19,46), OC (BA19,39)	IHC	ICAM-1	↑	

Table 4 (continued)

Author/year	Brain bank	Sample size (patients and controls)	Sex (m/f)	Age	Death from suicied	Brain region	Technique	Inflammatory markers	Main results	
Torres-Platas et al. 2014	DBCBB	MDD 24 HC 17	MDD 18/6 HC 16/1	MDD 46 HC 39	MDD 24	dorsal ACC	IHC, PCR	MCP-1*, IL-1β#, TNF-α#, IL-1RA#, IL-10#	↑* ↔# ()	Stanley Medical Research Institute Array Collection
Wang et al. 2018	(1) QSBC (2) MBC	(1) MDD 21 HC 16 (2) MDD 26 HC 12	NA	NA	(1) MDD 21 (2) MDD 14*	DLPFC	PCR	TNF-α	↑*	
Zhang et al. 2020	SFBC	MDD 15 HC 15	MDD 9/6 HC 9/6	MDD 47 HC 48	NA	PC (BA7), CB*	WB	CSF1R#, SPI1*	↑* ↔#	
Zhao et al. 2015	SMRIAC	MDD 24 HC 12	MDD 13/11 HC 8/4	MDD (ns) 46 MDD (s) 40 HC 47	MDD 17	ACC (BA24), DLPFC (BA46)	PCR	TNF-α, IL-1β	↔	

↑ represents up-regulation , ↓ represents down-regulation, ↔ represents no change

methods. Therefore, the analysis of different regions of the brain showed differential expression of inflammatory factors. For example, 8 studies reported the expression of TNF-α protein levels; 3 studies on DLPFC and one for cortical gay and STG respectively found no difference in expression; one study on PFC, STG, and FC respectively found an increase. Furthermore, other inflammatory factors including IL-1β, IL-4, and IL-10 had similar results.

Immune/Inflammation Response, Cell Regulatory Proteins, Glia/Macrophage Proliferation, and Chemokines in Postmortem Studies of BD

Regarding BD, 18 studies were included. The immune/inflammation response (Bezchlibnyk et al. [61], Dean et al. [23], Fillman et al. [26], Foster et al. [27], Hoseth et al. [29], Iwamoto et al. [31], Kim et al. [62], Kim et al. [63], Kim et al. [33], Lanz et al. [35], Maida et al. [37], Nascimento et al. [64], Rao et al. [65]), cell regulatory proteins (Abdolmaleky et al. [48], Catts et al. [49]), glia/macrophage proliferation (Zhang et al. [55]), and chemokines (Hill et al. [58], Nakatani et al. [59]) were measured in postmortem brains of BD (Table 3).

Table 3 shows that the main regions of the postmortem brains of patients with BD consisted of DLPFC, FC, OFC, ACC, MFG, CB, etc. The different regions of brain were analyzed using PCR, WB, ELISA, and IHC methods. Few studies were included in the analyses of postmortem brains of BD. Therefore, the analysis of inflammatory factors was less than that of SCZ. Unlike SCZ, the postmortem brains of BD showed different expressions in the same regions of the brain in different studies. For example, two studies analyzed the expression of TNF-α protein levels in DLPFC, one study an increase, and one study no difference. This may be due to the number of deaths from suicide, technique, and/or other factors affecting the heterogeneity of the study.

Immune/Inflammation Response, Cell Regulatory Proteins, Glia/Macrophage Proliferation, and Metabolic Pathways in Postmortem Studies of MDD

As shown in Table 4, there were 21 studies included for MDD, immune/inflammation response (Böttcher et al. [66], Dean et al. [67], Dean et al. [23], Foster et al. [27], Khundakar et al. [68], Lanz et al. [35], Maida et al. [37], Martín-Hernández et al. [69], Morrison et al. [70], Pandey et al. [71], Pandey et al. [72], Pandey et al. [73], Pantazatos et al. [74], Thomas et al. [75], Torres-Platas et al. [76], Wang et al. [77], Zhao et al. [78]), cell regulatory proteins (Tanti et al. [79]), glia/macrophage proliferation (Zhang et al. [55]), and metabolic pathway (Clark et al. [80]) were measured in postmortem brains of MDD.

The main regions of the postmortem brains of patients with MDD consisted of frontal the lobe, temporal lobe, thalamus, subventricular zone, DLPFC, BA, and OC. The methodological approaches mainly used CyTOF measurements, GC/MS, PCR, WB, and IHC. Similar to SCZ, the analysis of different regions of the brain showed different expressions of inflammatory factors. For example, 10 studies reported the expression of TNF-α protein levels; four studies on the DLPFC and one for the frontal lobe, ACC, and PC respectively found no difference in expression; one study on the ACC, VLPFC, and PFC respectively found an increase, and one study for the VLPFC found a decrease. Moreover, other inflammatory factors included HLA-DR, TNFR1, and NF-κB, but only one study reported it, and therefore, it cannot be summarized effectively.

Discussion

SCZ, BD, and MDD have been linked to neuroinflammation and metabolic disorders [81], which have been shown to have aberrant blood cytokines in blood [15, 82]. This study systematically reviewed the literature reporting brain inflammatory markers in the postmortem brains of SCZ, BD, and MDD patients.

Multiple studies have evaluated neuroinflammation markers, chemokines, and microglial activation in postmortem brain samples of SCZ [8, 83, 84]. However, it is impossible to determine whether there are the abovementioned facts in postmortem brain samples of SCZ due to a large number of null studies. For example, 39 studies were included to measure the differential expression between SCZ and control subjects. Out of 26 studies that evaluated inflammatory markers, 12 examined IL-1β. Therefore, whereas eight studies found no differences, three found a decrease, and one had elevated IL-1β expression. Similarly, six studies evaluated the anti-inflammatory cytokine IL-10, three found no effect of SCZ, two studies found a decrease, and one study found an increase. Previous studies have implicated proinflammatory profiles in psychiatric disorders, where the most consistent findings were alterations in TNF-α and related pathways [85–87], which have been reported in peripheral blood. Thus, the researchers set out to examine TNF pathway-related molecules at the protein and mRNA levels in the postmortem brain of SCZ patients in search of a larger association. TNF-α protein levels or mRNA expression were determined in eight studies, six had no effect, and two studies found an increase. Cytokine modulators (Toll-like receptors, colony-stimulating factors, and members of the complement system) have been evaluated in several studies. Three studies reported TLR4 in the postmortem brains of SCZ patients; one study found an increase and two studies found a decrease. The analysis of different regions of the brain is one of the heterogeneous variables in studies. For example, studies evaluating IL-1β expression have analyzed nine brain regions, including the PFC, DLPFC, cortical gray, STG, FC, HPC, STC, and CFC. Therefore, eight of them with no differences included the PFC, DLPFC, cortical gray, STG, and HPC. For the PFC analysis, four studies found no differences and one found a decrease. Nevertheless, although more studies have indicated no difference in IL-1β expression in the PFC, not all studies.

SCZ is a common mental illness associated with suicide [88]. A previous study found that there was a trend in microglial density and elevated proinflammatory cytokines in SCZ [89, 90]. In this study, fewer included studies analyzed the differential expression of inflammatory factors between suicide and nonsuicide. However, there is evidence that there is a difference in the expression of inflammatory factors between suicide and nonsuicide SZ patients [40]. Previous studies have shown an effect of SCZ on neurokinin receptors compared to suicide victims, which may confound the results [91]. Although some studies have considered the impact of suicide on the measurements of inflammatory factors, many studies have not reported these data or included it in statistical analysis, which makes it a limitation. Treatment for SCZ might reduce proinflammatory markers [92]. These findings may be associated with potential effects on neuroinflammatory markers in SCZ in postmortem brains. This is noteworthy because not all studies measured antipsychotic levels at death or corrected for this potential confounding factor. Furthermore, the separation of antipsychotics was not considered in the statistical analysis. In addition, subjects in the control group were not exposed to antipsychotics, which may cause confusion between the HC group and the SCZ group.

The same effect was also observed for BD and MDD, and it is impossible to determine whether inflammatory factors were significantly expressed in postmortem brain samples of BD and MDD. For example, seven of the included studies that measured the differential expression of inflammatory markers between the BD and control groups examined TNF-α. Therefore, six studies found no differences, and one had elevated TNF-α expression. Similar to BD, the MDD results found that six studies found no effect, one decreased, and three studies found an increase. Previous studies have indicated that inflammation is documented extensively in BD and MDD [93, 94]. The heterogeneity of our systematic review may be explained by these results. One of the heterogeneous variables may be the brain region. Significant functional and structural alterations in the neural circuits of emotion or reward processing may explain the heterogeneity. During emotional, reward, and/or cognitive related tasks, different activation patterns occur in the neural network including the amygdala, ACC, PFC, and striatum [95]. In addition, different stages of BD and MDD have distinct

neurobiological changes in the related brain regions [96, 97]. Similar to SCZ, the treatments for inflammation also influence the expression of neuroinflammation markers. Aspirin has beneficial effects in clinical trials of mood disorders; it inhibits the inflammatory response and reduces the levels of inflammatory biomarkers, including C-reactive protein, TNF-α, and IL-6 [98]. These missing treatment statistics may influence the effects on neuroinflammatory markers in BD and MDD in postmortem brains. Another variable may be the differences in the methodological approaches. Although most techniques of the included studies were PCR and WB, other detection methods such as CyTOF measurements may contribute to the heterogeneous results. A previous study showed that the kynurenine pathway in the CNS of suicide attempts is chronically dysregulated, and an increase in inflammatory cytokines is associated with more severe symptoms [99]. In addition, a similar study also reported on BD, which is related to baseline biomarkers of suicide attempts with clinical outcomes [100]. Therefore, it is important to consider elevated proinflammatory cytokines in postmortem brains of suicide victims, which may confound the results. Several other confounding factors, such as age, lifestyle choices, and brain banks (diagnostic methods, storage, inclusion and exclusion criteria, and many other variables), may also need consideration.

These findings indicate that inflammatory markers appear to have different expression patterns in each psychiatric disease, which is of great significance for us to realize the pathophysiology of inflammatory markers in major psychiatric diseases and provide new directions for therapy. However, because the samples all came from postmortem brains, there was no record of the use of antipsychotic drugs before death. It is a limitation of this paper that the influence of antipsychotic drugs on the expression of the protein and molecules in the samples cannot be taken into account in statistics.

In conclusion, although numerous included studies have noted a lack of changes in neuroinflammatory markers in postmortem brain samples of SCZ, BD, and MDD, there are still multiple studies that have indicated an increase or decrease in neuroinflammatory markers. The heterogeneity is not clear at present, and may be caused by several factors, including the measured brain region, disease stage, brain source, medication, and other factors. The expression of neuroinflammatory markers was different, which means that inflammation was accompanied by the occurrence of neuropsychiatric disorders. Whether the inflammation in the brain is the pathogeny of schizophrenia, bipolar disorder, and major depressive disorder or the pathological manifestations of these diseases. According to some preclinical studies [101, 102], after some anti-inflammatory treatment, the neuropsychiatric disorder symptoms have improved significantly. This finding revealed that inflammation in the brain may be the pathogenesis of schizophrenia, bipolar disorder, and major depressive disorder.

In the future, these potential sources of heterogeneity should be considered to measure neuroinflammatory markers in postmortem brain samples for patients with SCZ, BD, and MDD, which will contribute to the successful construction of a similar study.

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Declarations

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