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Glial Cell Abnormalities in Major Psychiatric Diseases: A Systematic Review of Postmortem Brain Studies

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Abstract

There have been a large number of reports about glial cell dysfunction being related to major psychiatric diseases such as schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD). In this review, we provide an overview of postmortem studies analyzing the structural changes of glial cells in these three major psychiatric diseases, including the density, number and size of glial cells, and the expression of related markers. Up to May 1, 2021, 108 articles that met the inclusion criteria were identified by searching PubMed and Web of Science. Although most studies evaluating total glial cells did not show abnormalities in the brains of postmortem patients, astrocytes, microglial cells, and oligodendrocytes seem to have specific patterns of changes in each disease. For example, out of 20 studies that evaluated astrocyte markers in MDD, 11 studies found decreased astrocyte marker expression in MDD patients. Similarly, out of 25 studies evaluating oligodendrocyte markers in SCZ, 15 studies showed decreased expression of oligodendrocyte markers in different brain regions of SCZ patients. In addition, activated microglial cells were observed in patients with SCZ, BD, and MDD, but suicide may be a confounding factor for the observed effects. Although the data from the included studies were heterogeneous and this cannot be fully explained at present, it is likely that there are a variety of contributing factors, including the measured brain regions, methods of measurement, gender, age at time of death, and medications.

Keywords Schizophrenia · Bipolar disorder · Major depressive disorder · Postmortem · Astrocytes · Microglia · Oligodendrocytes

Introduction

George Somjen was prescient in his comments about glial cells in 1988 [1]. Indeed, the crucial role of glia in psychiatric diseases has been neglected over the past two decades [2, 3]. Glial cells are involved in every major aspect of brain development, function, and disease by communicating with neurons and releasing neurotransmitters and other signals [4]. In the central nervous system (CNS), astrocytes, oligodendrocytes, and microglia are the three main types of glial cells, which play an important role in synaptic function, neuronal metabolism and migration [3]. Over the years, there has been a shift in our understanding of the relative number of glial cells, and detailed studies suggest that the proportions vary greatly by brain region [5]. Schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD) are three major psychiatric diseases, with some similarities in their occurrence and symptoms, at least in the early stages [6–8]. A growing body of research is attempting to clarify the pathogenesis associated with these mental disorders. Genetic studies have shown a high correlation between multiple genes involved in the regulation of the immune system and SCZ, BD, and MDD [9]. Postmortem evidence supports the role of cerebral inflammation in the etiological pathways of these mental disorders [10–12]. Nevertheless, the neurobiological mechanisms underlying these diseases are still not fully understood.

In the literature related to major psychiatric diseases such as SCZ, BD, and MDD, there have been a large number of reports on glial cell dysfunction, which undoubtedly provides evidence of a relationship between psychiatric disease

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and glial pathology [13–15]. However, there are problems in these studies, such as the diversity of results due to differences in the studied brain regions and research methods. It is difficult to draw straightforward conclusions based on these results. To help improve our understanding of the pathogenesis and pathophysiology of psychiatric diseases, we systematically reviewed postmortem studies on the structure of brain cells in patients with SCZ, BD, and MDD. The density, number, and size of the astrocytes, microglia, and oligodendrocytes, as well as the expression of cell type-specific markers in postmortem brain samples, were evaluated. By emphasizing the importance of glial cells in these mental diseases, we have provided a preliminary conclusion on the changes of glial cells in the postmortem brain and a guideline for future studies to improve our understanding of the mechanism of mental diseases and to identify new therapeutic targets.

Methods

We performed a literature search for records indexed within PubMed and Web of Science up to May 1, 2021. The search strategy was '(glia or microglia or astrocytes or oligodendrocytes) and (schizophrenia or bipolar disorder or major depressive disorder or depression) and (postmortem or brain sample)'.

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 in SCZ, BD, or MDD; (2) measured glial cells, including microglia, astrocytes, or oligodendrocytes, as well as several related markers; and (3) matched psychiatric-disease-free controls. Studies with matched samples (by age, sex, race, brain pH or postmortem interval, etc.) [16–109] or studies that statistically adjusted for these specific variables (age and sex primarily) [110–116] were included. Duplicates and studies that did not meet the above criteria were excluded. In addition, review articles, in vitro studies, and animal studies were excluded.

Eligible studies were assessed and 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 glial cell 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.

Results

Our search strategy resulted in the identification of 1070 unique studies from the initial search. After screening of the titles and abstracts for relevance, 175 articles were full-text screened against the inclusion criteria. Out of the 175 articles, 69 articles were excluded because they did not measure glial cells (50 studies); data not separable from other diagnostic groups (9 studies); did not include any psychopaths (6 studies) and healthy controls (2 studies); and incorrect measurement methods, such as single-cell sequencing (2 studies). Two more articles were found in the reference section of papers identified in the database search. Thus, a total of 108 studies were ultimately included in this review, including 31 studies on total glial cells that did not differentiate between glial cell types, 41 studies on astrocytes, 24 studies on microglia, and 30 studies on oligodendrocytes (Fig. 1).

The regions of the brain studied among our reviewed papers mainly included the anterior cingulate cortex (ACC), anterior cingulate gyrus (ACG), anterior midcingulate cortex (AMC), anteroventral nucleus (AVN), corpus callosum (CC), caudate nucleus (CN), dorsolateral prefrontal cortex (DLPFC), dorsal raphe nucleus (DRN), entorhinal cortex (EC), frontal cortex (FC), hippocampus, locus coeruleus (LC), medial frontal gyrus (MFG), occipital cortex (OC), orbitofrontal cortex (OFC), prefrontal cortex (PFC), superior frontal gyrus (SFG), superior temporal gyrus (STG), temporal cortex (TC), amygdala, cerebellum, putamen, subiculum, and thalamus (Table 1; Figs. 2 and 3).

Total Glia

In our review, a total of 31 studies evaluated total glial cells (astrocytes, microglia, oligodendrocytes) in postmortem brain samples without the use of cell type-specific markers.

Several studies looking at total glia found that decreased cell density was associated with SCZ. Cotter et al. [37] published their first study in 2001, with glial cell density measured by cresyl violet staining, and observed a decrease in layer VI of the ACC in SCZ and MDD compared to healthy controls, whereas no change was observed in BD. In their second year of study [35], comparable effects were observed again in layer V of the DLPFC. However, in their two subsequent studies, neither Heschl's gyrus [36] nor OFC [34] observed evidence for changes in glial cell size or density between the three groups of mental diseases and healthy controls. Beasley et al. [18] published a study on the effects on glial cells in 2009. In

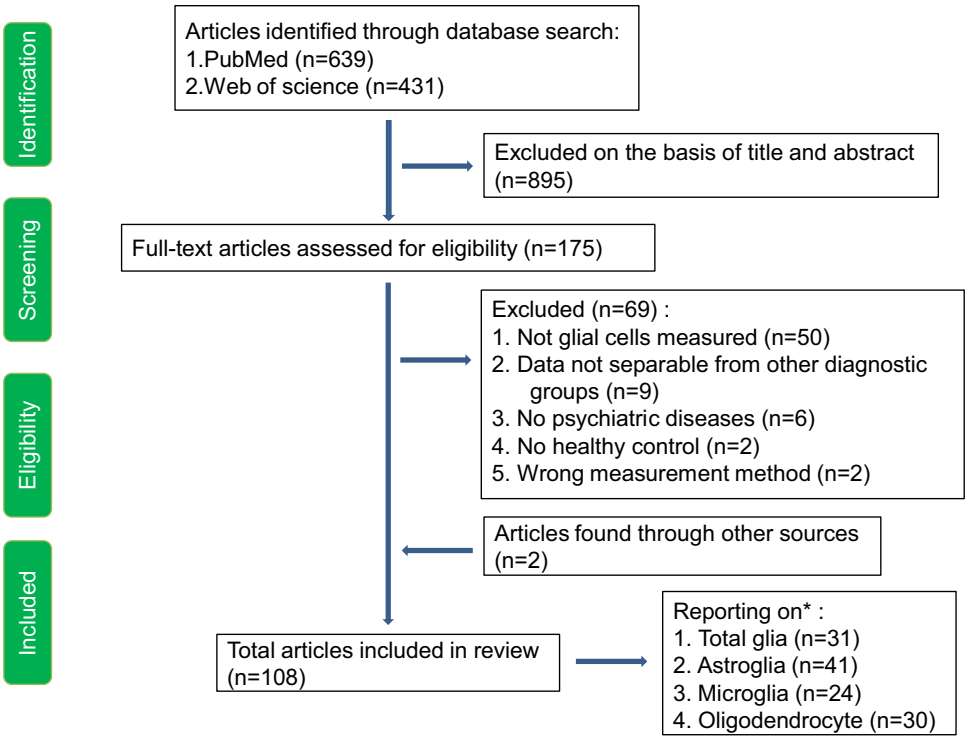

Fig. 1 Flow chart of the systematic search. Asterisk indicates that various studies report on more than one cell type

the white matter near the temporal plane of 15 patients in each group, they found that only schizophrenic patients, not the BD or MDD patients, had a lower glial cell density than the control subjects. Similar decreases in glial cell density were observed in the CA3 and CA4 regions of the hippocampus [41] and layer III of the primary motor cortex [19] of patients with SCZ.

In fact, changes in glial cells were also observed in postmortem brains from BD and MDD patients. For example, Rajkowska et al. [73] found that the density of glial cells decreased in sublayer IIIc of the DLPFC in patients with BD, coupled with enlargement and changes in the shape of the glial nuclei. Brauch et al. [24] also found that the area occupied by the glial cells was reduced in the TC of bipolar patients compared with that of healthy controls. In a study on the amygdala, Nissl staining showed that the density of glial cells decreased only in the MDD group, while there was no significant difference between the BD and control groups [50]. In contrast, glial cell density in the hippocampus was significantly increased in 19 major depressive patients compared with healthy controls [91].

Twenty-two studies evaluating glial cells did not detect any changes associated with SCZ, BD, and MDD. In a cohort of 18 schizophrenic patients [29], there was no difference in the numbers of glial cells in the PFC and ACC, regardless of whether the patients had superimposed mood disturbances. In another cohort of 18 schizophrenic patients, quantified analysis after hematoxylin and eosin staining showed no difference in glial cell density in the CC compared to healthy controls. However, it is worth mentioning they found gliosis in the CC in patients with late-onset SCZ compared with early-onset SCZ and controls [68]. In a study of postmortem brain samples from the Stanley Foundation Neuropathology Consortium, for SCZ, BD, and MDD, Nissl staining revealed no differences in the glial cell density or size in the amygdala [22] and no changes in glial number in the TC [24]. Similarly, whether from the EC [42], PFC [113], OC [113], dentate gyrus [23], fusiform gyrus [78], FC [82], DLPFC [82], lateral geniculate nucleus [83], and primary auditory cortex [87] of SCZ or the OC [75], basolateral amygdala [78, 114], and auditory cortex [87] of MDD, Nissl staining failed to detect any changes in the density or number of glial cells. Cresyl violet staining revealed no changes in glial cell density in the ACC [20, 30] and PFC [117] from SCZ or BD. Gallocyanin, another staining technique, also did not detect an effect of SCZ on glial cell density in the dorsal ACC [53]. Moreover, in Khundakar's four studies of the MDD postmortem brain, no changes in glial cell density were obtained in the DLPFC [56], OFC [57], CN [58], and ACG [59] compared with healthy controls.

Astroglia

Our search strategy yielded a total of 41 studies assessing astrocytes in postmortem brain samples from patients with major psychiatric diseases.

Glial fibrillary acidic protein (GFAP) is often used as an astrocyte-specific marker in postmortem studies [118].

Table 1 Summary information of the included studies

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Altshuler et al. 2010	Stanley Medical Research Center	SCZ 9 BD 10 MDD 11 HC 14	SCZ 5/4 BD 6/4 MDD 7/4 HC 8/6	SCZ 45 BD 45 MDD 46 HC 47	SCZ 3 BD 7 MDD 5	Basolateral nucleus of the amygdala	IHC	GFAP	Decrease in GFAP immunoreactive astrocyte density was observed in the amygdala of subjects with MDD (43.54 ± 71.75, $p = 0.018$) compared to the SCZ (47.88 ± 22.08), BD (58.00 ± 47.97), and normal controls (63.42 ± 36.15)
Barley et al. 2009	Stanley Foundation Neuropathology Consortium	Varies across brain regions	Varies across brain regions	Varies across brain regions	Varies across brain regions	AVN, PU, IC, MTN	PCR	GFAP, ALDH1L1, CNPase, MAG, MOG	(1) GFAP and ALDH1L1 had higher mean expression levels across regions in SCZ and MDD relative to HCs, but no significant differences were found in BD. (2) CNPase, MAG, MOG exhibited decreased expression levels in SCZ across all regions
Bayer et al. 1999	Institute of Neuropathology, University of Bonn Medical Center	SCZ 14 HC 13	SCZ 3/11 HC 8/5	SCZ 64 HC 58	NA	FC, HPC	IHC	HLA-DR	HLA-DR positive (activated) microglia cells were present in 3/14 of patients with SCZ (late onset) in both gray and white matter
Beasley et al. 2009	Stanley Medical Research Institute's brain collection	SCZ 15 BD 15 MDD 15 HC 15	SCZ 9/6 BD 9/6 MDD 9/6 HC 9/6	SCZ 44 BD 42 MDD 47 HC 48	SCZ 2 BD 1	PT	Cresyl violet	Glia	Glial density was only lower in the SCZ groups (894.01 ± 198.88, $p = 0.013$), compared to BD (980.65 ± 229.93), MDD (1038.68 ± 167.79) and control group (1072.15 ± 155.94)
Benes et al. 1986	Harvard Brain Tissue Resource Center	SCZ 10 HC 10	NA	SCZ 60 HC 66	SCZ 1	PFC (BA10), PMC (BA4), ACC (BA24)	Cresyl violet	Glia	Glial density tended to be lower throughout most layers of all three cortical regions; however, the differences noted between the two groups were significant only in layer III of motor cortex ($p = 0.015$)
Benes et al. 1991	Harvard Brain Tissue Resource Center	SCZ 9 SCZ (mood disturbances) 9 HC 12	NA	SCZ 53 SCZ (mood disturbances) 49 HC 59	NA	PFC (BA10), ACC (BA24)	Cresyl violet	Glia	Glial numbers did not differ between SCZ and control groups
Benes et al. 2001	Harvard Brain Tissue Resource Center	SCZ 11 BD 10 HC 12	SCZ 7/4 BD 9/1 HC 7/5	SCZ 52 BD 60 HC 58	SCZ 5 BD 1	ACC (BA24)	Cresyl violet	Glia	The density of glial cells was similar across the SCZ, BD, and control groups
Bernard et al. 2011	Brain Donor Program at the University of California	BD 6 MDD 12 HC 9	BD 5/1 MDD 11/1 HC 8/1	BD 43 MDD 50 HC 51	BD 4 MDD 6	locus coeruleus	PCR	GFAP, S100b	GFAP (1.83 fold, $p = 0.034$) and S100b (1.62 fold, $p = 0.014$) mRNA expression were reduced only in MDD
Bezchlibnyk et al. 2007	Stanley Foundation Neuropathology Consortium	SCZ 13 BD 11 MDD 14 HC 15	SCZ 8/5 BD 7/4 MDD 8/6 HC 9/6	SCZ 47 BD 44 MDD 47 HC 48	NA	AG	Nissl	Glia	Glial density and size did not differ among groups

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Boldrini et al. 2019	New York State Psychiatric Institute Brain Collection	MDD 26 HC 26	MDD 18/8 HC 18/8	MDD 39 HC 38	MDD 26	DG	IHC	Glia	There was a trend ($p=0.016$) association of early life adversity with more glia in whole DG in MDD suicide and control subjects
Brauch et al. 2006	Stanley Foundation Neuropathology Consortium	SCZ 13 BD 14 MDD 12 HC 14	NA	SCZ 46 BD 43 MDD 46 HC 47	NA	TC	Nissl	Glia	There was no critical difference in glia number across the four diagnostic groups; however, the areas occupied by glia was reduced in BD (39.29 ± 11.069, $p=0.018$) compared with normal controls (50.36 ± 12.444)
Brisch et al. 2017	Magdeburg brain bank	SCZ (p) 9 SCZ (r) 9 BD 12 MDD 15 HC 22	SCZ (p) 4/5 SCZ (r) 7/2 BD 8/4 MDD 4/11 HC 7/15	SCZ (p) 45 SCZ (r) 64 BD 55 MDD 49 HC 52	SCZ 8 BD 7 MDD 9	DRN	IHC	HLA-DR	The density of HLA-DR positive microglia decreased only in non-suicidal MDD subjects, and the microglia response decreased significantly
Busse et al. 2012	Magdeburg brain bank	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 (p) 5	HPC	IHC	HLA-DR	HLA-DR positive microglia were increased in paranoid SCZ vs. residual SCZ (left: $p=0.030$, right: $p=0.012$)
Byne et al. 2006	Mount Sinai/Bronx VA Brain Bank	SCZ 23 HC 12	SCZ 14/9 HC 8/4	SCZ 68 HC 74	NA	anterior principal thalamic nucleus	IHC	Oligodendrocytes	The number of oligodendrocytes was significantly reduced in male SCZ ($p<0.001$) relative to normal controls
Byne et al. 2008	Mount Sinai/Bronx VA Brain Bank	SCZ 14 HC 16	SCZ 10/4 HC 9/7	SCZ 79 HC 77	NA	TH	PCR	MAG, CNPase, MBP	There were no significant differences in all gene expressions of SCZ compared to the control group, but the expression levels of MAG and CNPase were much more highly expressed in females than in males
Catts et al. 2013	New South Wales Tissue Resource Center	SCZ 37 HC 37	SCZ 24/13 HC 30/7	SCZ 51 HC 51	SCZ 8	DLPFC (BA46)	PCR, IHC, WB	GFAP	(1) GFAP (mRNA and protein) levels and astrocyte morphology were not significantly different between patients with SCZ and controls (2) SCZ with neuroinflammation had increased expression of GFAP mRNA ($p=0.005$)
Chana et al. 2003	Stanley Foundation Neuropathology Consortium	SCZ 15 BD 15 MDD 15 HC 15	SCZ 9/6 BD 9/6 MDD 9/6 HC 9/6	SCZ 45 BD 42 MDD 47 HC 48	SCZ 7 BD 9 MDD 4	ACC (BA24)	Cresyl violet	Glia	No significant differences in glial cell density among each group

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Chandley et al. 2013	Cuyahoga County Coroner's Office, Quebec Suicide Brain Bank	MDD 18 HC 20	MDD 18/0 HC 20/0	MDD 43 HC 42	NA	locus coeruleus	PCR, IHC, WB	GFAP	GFAP immunoreactivity levels and the density of GFAP labeled astrocytes were significantly lower in MDD than in matched control samples
Clark et al. 2016	Maryland Neuropathology Clinical Brain Disorders Branch	MDD 45 HC 36	MDD 30/15 HC 27/9	MDD 43 HC 42	MDD 25	VLPFC	IHC	IBA-1	Scattered and very low numbers of IBA-1 positive amoeboid microglial cells were found in both controls and MDD individuals
Cobb et al. 2016	Cuyahoga County Medical Examiner's Office	MDD 17 HC 17	MDD 12/5 HC 13/4	MDD 52 HC 52	MDD 10	CA1, CA2/3, DG hilus	IHC	GFAP	(1) The density of astrocytes in the DG hilus, but not CA1 or CA2/3, was significantly decreased only in depressed subjects not taking an antidepressant drug, but not for depressed subjects taking an antidepressant drug (2) The area fraction of GFAP immunoreactivity was significantly decreased in the DG in women but not men with depression
Cotter et al. 2001	Stanley Foundation Neuropathology Consortium	SCZ 15 BD 15 MDD 15 HC 15	SCZ 9/6 BD 9/6 MDD 9/6 HC 9/6	SCZ 45 BD 42 MDD 47 HC 48	SCZ 4 BD 9 MDD 7	ACC (BA24)	Cresyl violet	Glia	(1) Glial cell density was reduced in layer VI in MDD (22%; $p=0.004$) compared with controls (2) No evidence for differences in glial density in BD, but there was some evidence for reduced glial density in layer VI in SCZ (20%; $p=0.02$) compared with controls
Cotter et al. 2002	Stanley Foundation Neuropathology Consortium	SCZ 15 BD 15 MDD 15 HC 15	SCZ 9/6 BD 9/6 MDD 9/6 HC 9/6	SCZ 45 BD 42 MDD 47 HC 48	SCZ 7 BD 9 MDD 4	DLPFC (BA9, 46)	Cresyl violet	Glia	The density of glial cells in layer V decreased only in SCZ (34%; $p=0.003$) and MDD (30%; $p=0.007$)
Cotter et al. 2004	Stanley Foundation Neuropathology Consortium	SCZ 15 BD 15 MDD 15 HC 15	SCZ 9/6 BD 9/6 MDD 9/6 HC 9/6	SCZ 45 BD 42 MDD 47 HC 48	SCZ 4 BD 9 MDD 7	Heschl's gyrus (BA41)	Optical disector	Glia	There is no significant difference glial cell density between each group and the control group
Cotter et al. 2005	Stanley Foundation Neuropathology Consortium	SCZ 15 BD 15 MDD 15 HC 15	SCZ 9/6 BD 9/6 MDD 9/6 HC 9/6	SCZ 45 BD 42 MDD 47 HC 48	SCZ 4 BD 9 MDD 7	OFC (BA24)	Cresyl violet	Glia	No evidence for group differences in glial cell size nor for differences in glial density
Cullen et al. 2006	NA	SCZ 10 HC 10	SCZ 6/4 HC 6/4	SCZ 60 HC 60	NA	PFC (BA9)	Cresyl violet	Glia	There was no change in glial cell density

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Damadzic et al. 2001	(1) Clinical Brain Disorder Branch at the National Institute of Mental Health, (2) Stanley Foundation Neuropathology Consortium	(1) SCZ 7 HC 8 (2) SCZ 14 BD 13 MDD 14 HC 15	(1) SCZ 3/4 HC 3/5 (2) SCZ 9/5 BD 7/6 MDD 8/6 HC 9/6	(1) SCZ 49 HC 47 (2) SCZ 46 BD 44 MDD 46 HC 48	(1) SCZ 3 HC 1 (2) SCZ 2 BD 7 MDD 7 HC 3	EC	IHC	GFAP	There was no significant difference in the density of GFAP positive astrocytes between the psychiatric group and the control group
Davis et al. 2002	Neuropathology Department Brain Tissue Bank	MDD 20 HC 20	MDD 7/13 HC 7/13	MDD 75 HC 74	MDD 0	DLPFC (BA9, 46), ACC (BA24)	IHC	GFAP	(1) GFAP immunoreactivity was significantly higher in layer I of the DLPFC in MDD subjects than in controls ($p=0.04$) (2) The immunoreactivity of GFAP in gray matter was lower than that in white matter in MDD subjects
Durrenberger et al. 2014	Brain Bank for Psychiatric Diseases at the Gottingen University	SCZ 10 HC 10	SCZ 5/5 HC 5/5	SCZ 66 HC 61	NA	Temporal lobe (BA22)	qPCR	HLA-DRA, HLA-DRB4	Both the genes were significantly downregulated in SCZ
Falkai et al. 1986	Vogt Institute of Brain Research	SCZ 13 HC 11	SCZ 2/11 HC 7/4	SCZ 43 HC 43	SCZ 1	CA1/2,3,4, PSC, SC	Nissl	Glia	The number of glial cells in CA3 (48%; $p=0.03$), CA4 (28%; $p=0.05$) and PSC (51%; $p=0.03$) regions of schizophrenic patients was significantly lower than that of normal controls
Falkai et al. 1988	Vogt Institute of Brain Research	SCZ 13 HC 11	SCZ 11/2 HC 7/4	SCZ 43 HC 43	NA	EC	Nissl	Glia	There were no changes in absolute glial cell numbers
Falkai et al. 1999	Dusseldorf Brain Collection	SCZ 33 HC 26	SCZ 14/19 HC 13/13	SCZ 54 HC 53	SCZ 4	EC, SC, PMC, SVZ	IHC	GFAP	No evidence for increased astrogliosis in brains of schizophrenic patients compared with healthy controls
Falkai et al. 2016	Düsseldorf Brain Collection	SCZ 10 HC 10	SCZ 5/5 HC 5/5	SCZ 55 HC 50	SCZ 2	DG, CA1,2/3,4, SC	Nissl	Oligodendrocytes	It showed a decreased number of oligodendrocytes in the left CA4 in patients with SCZ
Farkas et al. 2010	Magdeburg brain bank	SCZ 9 HC 7	SCZ 5/4 HC 4/3	SCZ 52 HC 56	SCZ 2	ACC	Nissl	ADAM12	A significantly reduced numerical density of ADAM12 immunoreactive oligodendrocytes was found in the white matter of the ACC of SCZ patients
Farnsworth et al. 2017	Maudsley brain bank, Harvard brain bank, Stanley brain bank	SCZ 55 HC 55	SCZ 32/23 HC 32/23	SCZ 55 HC 59	NA	PFC, SFG (BA6, 8, 9)	PCR	GFAP	Gene expression of GFAP is upregulated in the PFC of brain samples of SCZ individuals ($p<0.001$)
Fatemi et al. 2003	Stanley Foundation Brain Collection	SCZ 15 BD 15 MDD 15 HC 15	SCZ 9/6 BD 9/6 MDD 9/6 HC 9/6	SCZ 44 BD 42 MDD 47 HC 48	NA	lateral CB	WB	GFAP	GFAP protein levels were reduced by 32%, 17%, and 14.5% in SCZ, BD, and MDD, respectively, vs. controls, but only the MDD value was significantly different ($p=0.015$)

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Feresten et al. 2013	Stanley Medical Research Institute;	SCZ 35 BD 34 HC 35	SCZ 26/9 BD 16/18 HC 26/9	SCZ 43 BD 45 HC 44	SCZ 7 BD 15	DLPFC (BA9)	WB	GFAP, ALDH1L1	Increased levels of GFAP were observed in SCZ and BD compared to controls, whereas ALDH1L1 levels did not differ between groups
Gos et al. 2013	Magdeburg Brain Bank	BD 6 MDD 9 HC 13	BD 3/3 MDD 2/7 HC 7/5	BD 56 MDD 50 HC 55	MDD 7	HPC	IHC	GFAP, S100b	The numerical density of S100b-immunopositive astrocytes was decreased in the CA1 pyramidal layer of MDD (left: $p=0.004$; right: $p=0.01$) and BD (left: $p=0.049$; right: $p=0.042$) patients compared to controls, whereas only the BD showed a decreased density of S100b-immunopositive oligodendrocytes in the left alveus ($p=0.028$)
Gos et al. 2014	Magdeburg Brain Bank	SCZ 13 HC 12	SCZ 7/6 HC 6/6	SCZ 51 HC 49	SCZ 2	CA1,2,3, DG	IHC	HLA-DR	No diagnosis-related differences were observed for the overall density of microglial cells (HLA-DR expression)
Hamidi et al. 2003	Harvard Brain Tissue Resource Centre;	BD 9 MDD 8 HC 10	BD 6/3 MDD 5/3 HC 9/1	BD 53 MDD 78 HC 65	BD 3 MDD 2	AG	Nissl, IHC	S100b, HLA-DR	(1) The density of total glia and oligodendrocytes in the amygdala was significantly lower in MDD, but not in BD, than in control subjects (2) There was no significant decrease in astrocyte or microglia density in BD or MDD subjects

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Hercher et al. 2014	Stanley Medical Research Institute Array Collectio	SCZ 20 BD 20 HC 20	SCZ 13/7 BD 8/12 HC 14/6	SCZ 45 BD 47 HC 45	NA	DLPFC (BA9) white matter	IHC	GFAP, IBA-1, CNPase	(1) Oligodendrocyte density ($p=0.012$)) and CNPase protein levels ($p=0.038$) differed between groups, being increased in BD compared with control samples. (2) The GFAP area fraction ($p=0.05$) and astrocyte spatial distribution ($p=0.040$) also differed between groups, reflecting decreased area fraction and increased cell clustering in both SCZ and BD samples (3) The density of IBA1-stained microglia did not differ among the groups, but observed numerous activated microglial cells in 3 SCZ, not in BD or controls
Hof et al. 2003	NA	SCZ 7 HC 7	SCZ 3/4 HC 4/3	SCZ 77 HC 79	NA	SFG (BA9)	Nissl, IHC	CNPse	A decrease in total numbers (or densities) of cortical layer III (28.3%; $p<0.01$) oligodendrocytes and a decrease in the white matter (27.3%; $p<0.01$) were detected in SCZ compared with control cases
Hoistad et al. 2013	NA	SCZ 13 HC 13	SCZ 13/0 HC 13/0	SCZ 52 HC 52	SCZ 3	ACC (BA24)	Gallocyanin	Glia	No changes were observed in glial densities
Karson et al. 1993	District of Columbia Medical Examiner's Office	SCZ 25 HC 28	SCZ 22/3 HC 22/6	SCZ 34 HC 35	SCZ 16 HC 8	FC, STG, OC, CB, TH, pons	WB	GFAP	GFAP levels did not differ between schizophrenic and comparison subjects in any brain region
Kerns et al. 2010	Stanley Foundation Neuropathology Consortium	SCZ 14 HC 14	SCZ 9/5 HC 8/6	SCZ 49 HC 44	NA	TH	Nissl	Oligodendrocytes	Oligodendrocytes densities were significantly decreased in SCZ. ($p=0.017$)
Khundakar et al. 2009	Newcastle Brain Tissue Resource	MDD 17 HC 10	MDD 5/12 HC 4/6	MDD 76 HC 77	MDD 1	DLPFC (BA9, 46)	Nissl	Glia	There were no changes in glial density of cells
Khundakar et al. 2011	Newcastle Brain Tissue Resource	MDD 13 HC 11	MDD 5/8 HC 4/7	MDD 74 HC 73	NA	OFC	Optical disector	Glia	No changes were found in mean density of glial cell
Khundakar et al. 2011	Newcastle Brain Tissue Resource	MDD 13 HC 9	MDD 7/6 HC 3/6	MDD 73 HC 75	MDD 2	CN	Optical disector	Glia	There were no significant changes in glial density in either area
Khundakar et al. 2011	Newcastle Brain Tissue Resource	MDD 9 HC 11	MDD 6/3 HC 8/3	MDD 76 HC 75	MDD 1	ACG (BA24)	Nissl	Glia	No changes were found in glial cell density

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Kolomeets et al. 2018	Moscow Psychiatric Hospitals, Moscow Higher Medical School	SCZ 17 HC 22	SCZ 8/9 HC 13/9	SCZ 58 HC 55	NA	PFC (BA10)	Nissl	Oligodendrocytes	(1) The numerical density of oligodendrocytes in layer V of BA10 was significantly lower (32%, $p < 0.001$) in the SCZ group as compared to the control group (2) Young (age < 50 years old) and elderly (age > 50 years old) SCZ subgroups did not differ significantly
Kolomeets et al. 2020	SMRI Neuropathology Consortium Collection	SCZ 15 BD 15 MDD 15 HC 15	SCZ 9/6 BD 9/6 MDD 9/6 HC 9/6	SCZ 45 BD 42 MDD 47 HC 48	NA	Anterior putamen	Optical disector	Oligodendrocytes	It found a significant reduction in both the numerical density of oligodendrocytes (34%; $p < 0.01$) and the numerical density of oligodendrocyte clusters (41%; $p < 0.05$) was found in the SCZ group but not in the BD and MDD groups as compared to the control group
López-González et al. 2019	Parc Sanitari Sant Joan de Déu, Institute of Neuropathology Brain Bank	SCZ 14 HC 14	SCZ 14/0 HC 14/0	SCZ 76 HC 71	NA	DLPFC	PCR	CD68, GFAP	(1) It reported that the CD68 levels was down-regulated in elderly SCZ subjects, and the expression levels of all inflammatory genes in SCZ were correlated with microglia marker CD68 (2) No associations were found with the astroglial marker GFAP
Malchow et al. 2014	Dusseldorf Brain Collection	BD 8 MDD 8 HC 10	BD 4/4 MDD 3/5 HC 5/5	BD 56 MDD 42 HC 50	BD 3 MDD 7	SC, CA1,2/3,4	Nissl	Astrocytes	Neither the mean number/density of astrocytes showed statistically significant differences between patients with BD, MDD and HCs in any of the investigated subregions
Martins-de-Souza et al. 2009	Brain Bank of the Central Institute of Mental Health	SCZ 9 HC 7	SCZ 4/5 HC 5/2	SCZ 71 HC 63	SCZ 0	DLPFC (BA46)	Two-dimensional gel electrophoresis	MBP	The protein levels of MBP were downregulated in SCZ
Marui et al. 2018	Tokyo Metropolitan Matsuzawa Hospital	SCZ 10 HC 9	SCZ 8/2 HC 6/3	SCZ 59 HC 56	NA	STG, HPC	IHC	MOG	The expression of MOG was significantly lower in the middle layer of the neocortex of the STG ($p = 0.03$) and stratum lucidum of CA3 in the HPC ($p = 0.03$) in the SCZ brains than in matched controls

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Mauney et al. 2015	Harvard Brain Tissue Resource Center	SCZ 9 HC 9	SCZ 5/4 HC 5/4	SCZ 65 HC 65	NA	PFC (BA9)	IHC, PCR	NG2, Olig2	It found that the density of NG2-immunoreactive cells was unaltered, but the density of Olig2-immunoreactive cells was significantly decreased in subjects with schizophrenia (21.3%; $p=0.032$)
Miguel-Hidalgo et al. 2000	Cuyahoga County Coroner's Office	MDD 14 HC 15	MDD 7/7 HC 10/5	MDD 53 HC 45	MDD 9	DLPFC (BA9)	IHC	GFAP	The mean areal fraction and packing density of GFAP-immunoreactive astrocytes in the DLPFC of MDD subjects were not significantly different from those in control subjects; however, in MDD, there was a significant strong positive correlation between age and GFAP immunoreactivity
Miguel-Hidalgo et al. 2010	Cuyahoga County Coroner's Office	MDD 23 HC 13	MDD 13/10 HC 6/7	MDD 50 HC 51	MDD 15	OFC	IHC, WB	GFAP	The area fraction of GFAP was lower in MDD than in controls ($p=0.040$)
Miguel-Hidalgo et al. 2000	Cuyahoga County Coroner's Office	MDD 14 HC 15	MDD 7/7 HC 10/5	MDD 53 HC 45	MDD 9	DLPFC (BA9)	IHC	GFAP	The mean areal fraction and packing density of GFAP-immunoreactive astrocytes in the DLPFC of MDD subjects were not significantly different from those in control subjects
Müller et al. 2001	Netherlands Brain Bank	BD 2 MDD 13 HC 16	BD 2/0 MDD 9/4 HC 10/6	BD 51 MDD 63 HC 65	BD 1 MDD 3	HPC	IHC	GFAP	No differences in the distribution of GFAP-immunoreactivity could be observed in the BD and MDD patients compared to the controls
Nagy et al. 2015	Douglas-Bell Canada Brain Bank;	MDD 76 HC 45	MDD 76 HC 45	NA	MDD 76	PFC (BA10) gray matter	PCR	GFAP, ALDH1L1	Both astrocyte gene showing significantly decreased expression in cases compared with controls ($p<0.001$)
Nasralla et al. 1983	National Insititute of Mental Health	SCZ (early onset) 11 SCZ (late onset) 7 HC 11	NA	SCZ (early onset) 66 SCZ (late onset) 73 HC 64	NA	CO	Hematoxylin–eosin stain	Glia	No difference between groups in glial cells
Nishioka et al. 2004	Pennsylvania State hospitals, University of Pennsylvania's Center for Neurodegenerative Disease Resear	SCZ 10 HC 13	SCZ 3/7 HC 4/9	SCZ 75 HC 76	NA	DG granule cell layer, DG hilus, SC, EC, CA1,2,3	IHC	GFAP	There were no significant correlations in GFAP astrocytes for the either group
O'Leary et al. 2021	NA	MDD 10 HC 10	MDD 10/0 HC 10/0	MDD 39 HC 41	MDD 10	DLPFC, dorsal CN, MTN	Optical disector	GFAP, VIM	Density of GFAP–immunoreactivity astrocyte and VIM–immunoreactivity astrocyte were both reduced in suicidal depression

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Pantazopoulos et al. 2010	Harvard Brain Tissue Resource Center	SCZ 11 BD 11 HC 15	SCZ 4/7 BD 7/4 HC 10/5	SCZ 62 BD 67 HC 66	SCZ 1	AG, EC	IHC	GFAP	No significant changes were detected GFAP-positive glial cells in the SCZ and BD compared with controls in any of the subdivisions and layers examined
Petrasch-Parwez et al. 2020	Stanley Foundation Neuropathology Consortium	SCZ 17 BD 13 HC 17	SCZ 11/6 BD 4/9 HC 13/4	SCZ 45 BD 46 HC 45	SCZ 4 BD 5	AMC	IHC	IBA-1	The microglial densities did not differ significantly between individuals with SCZ, BD and control subjects, whereas microglial density was significantly lower in BD individuals who did not commit suicide compared with BD individuals who died from suicide ($p=0.002$)
Qi et al. 2019	Netherlands Brain Bank	(1) BD 9 MDD 5 HC 14 (2) BD 7 MDD 5 HC 12	NA	(1) BD 75 MDD 69 HC 75 (2) BD 79 MDD 69 HC 80	NA	Study (1) DLPFC, study (2) ACC	PCR, IHC	GFAP	(1) It found that GFAP mRNA levels were significantly increased in the ACC of BD patients ($p=0.018$) (2) GFAP IHC showed that the area fraction of GFAP immunoreactive astrocytes was decreased in the ACC of BD patients ($p=0.035$)
Radewicz et al. 2000	Charing Cross Hospital, State Psychiatric Hospital	SCZ 12 HC 11	NA	SCZ 80 HC 72	NA	DLPFC (BA9), STG (BA22), ACG (BA24)	IHC	HLA-DR, GFAP	(1) Significant increased were found in HLA-DR microglial numerical density in BA9 (28%; $p<0.05$) and 22 (57%; $p<0.01$) (2) For all areas, numerical density of astroglia showed no significant differences between SCZ and controls
Rajkowska et al. 1998	NA	SCZ 9 HC 10	SCZ 7/2 HC 6/4	SCZ 41 HC 44	SCZ 5	PFC (BA9), OC (BA17)	Nissl	Glia	The size of glial cells in PFC and OC did not decrease in schizophrenia
Rajkowska et al. 2001	Harvard Brain Tissue Resource Centre, Case Western Reserve University	BD 10 HC 11	BD 7/3 HC 8/3	BD 47 HC 52	BD 5	DLPFC (BA9)	Nissl	Glia	It found a reduction in glial density (19%; $p=0.017$) was found in sublayer IIIc coupled with enlargement and changes in shape of glial nuclei spanning multiple layers

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Rajkowska et al. 2002	Cuyahoga County Coroner's Office	SCZ 9 HC 15	SCZ 2/7 HC 10/5	SCZ 47 HC 47	SCZ 3	DLPFC (BA9)	IHC	GFAP	(1) In layer V of the DLPFC, there was a significant reduction in the GFAP-area fraction (32%; $p=0.006$) (2) An increase in the density of the GFAP-positive cell bodies (81%; $p=0.003$) and a decrease (14%; $p=0.025$) in the width of the cortical layer V, as compared to the control subjects
Rajkowska et al. 2005	Cuyahoga County Coroner's Office	MDD 15 HC 11	MDD 8/7 HC 7/4	MDD 75 HC 72	MDD 8	OC	Optical disector	Glia	There were no differences in the density of glia between depressed and control subjects
Rao et al. 2010	Harvard Brain Tissue Resource Center	BD 10 HC 10	NA	BD 49 HC 43	NA	FC	WB, PCR, IHC	GFAP, CD11b, HLA-DR	(1) There was significantly higher protein and mRNA levels of astroglial and microglial markers (GFAP and CD11b) in the FC from BD compared with control subjects (2) The elevation in astrocyte and microglia markers was also supported by immunohistochemical staining for both GFAP and HLA-DR
Rosa et al. 2009	NA	SCZ 11 HC 13	SCZ 6/5 HC 7/6	SCZ 66 HC 68	SCZ 1	Fusiform gyrus	Nissl	Glia	Glial cell density was unaltered
Rubinow et al. 2014	Cuyahoga County Medical Examiner's Office	MDD 13 HC 10	MDD 7/6 HC 6/4	MDD 49 HC 47	MDD 7	basolateral amygdala	Nissl	Glia	There were no differences in the number or density of glia between depressed and control subjects
Schmitt et al. 2009	Düsseldorf Brain Collection	SCZ 10 HC 10	SCZ 5/5 HC 5/5	SCZ 55 HC 50	SCZ 1	CA1,2/3,4, SC	Nissl	Astrocytes	Neither the mean number/density of astrocytes was significantly different between the patients with SCZ and the controls
Schmitt et al. 2011	Brain Bank for Psychiatric Diseases at the Gottingen University	SCZ 10 HC 10	SCZ 5/5 HC 8/2	SCZ 66 HC 61	NA	STC (BA22)	PCR	HLA-DPA1, HLA-DRB3	It reported that HLA-DPA1, and HLA-DRB3 mRNA were not different significantly
Segal et al. 2009	Mount Sinai School of Medicine Brain Bank	SCZ 13 HC 13	SCZ 5/8 HC 8/5	SCZ 74 HC 75	SCZ 0	anterior cingulum bundle	Nissl	Oligodendrocytes	It found that no significant differences in the oligodendrocyte distribution or density in the cingulum bundle between the two groups
Selemon et al. 2003	Harvard Brain Tissue Resource Center	SCZ 9 HC 14	SCZ 6/3 HC 10/4	SCZ 56 HC 54	SCZ 3	FC (BA44), DLPFC (BA9)	Nissl	Glia	There were no differences in the density of glia between schizophrenic patients and control subjects

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Selemon et al. 2007	Stanley Foundation Consortium Collection	SCZ 15 HC 15	SCZ 9/6 HC 9/6	SCZ 45 HC 48	SCZ 4	Lateral geniculate nucleus	Nissl	Glia	No changes were found in glial cell density
Seredenina et al. 2017	Stanley Medical Research Institute	SCZ 15 BD 15 HC 15	SCZ 9/6 BD 9/6 HC 9/6	SCZ 44 BD 42 HC 48	NA	ACC	IHC	CD68, CD11b, IBA-1	The analysis of microglial markers showed that the expression of CD11b and CD68 was significantly decreased in BD group as compared with control; however, there were no significant differences for IBA-1
Shimamoto-Mitsuyama et al. 2021	Victorian Brain Bank	SCZ 95 HC 91	SCZ 70/25 HC 71/20	SCZ 46 HC 48	SCZ 44 HC 1	CC	PCR	IBA-1, CD68, GFAP, Olig2, MBP, MAG	Only the expression levels of microglial markers (IBA-1 and CD68) was found reduced in the CC of SCZ compared to controls ($p < 0.0001$)
Si et al. 2004	Cuyahoga County Coroner's Office	MDD 15 HC 15	MDD 8/7 HC 8/7	MDD 55 HC 54	MDD 9	DLPFC (BA9)	WB	GFAP	The mean level of GFAP were significantly lower in subjects with MDD (0.57 ± 0.55, $p = 0.011$) as compared to controls (1.05 ± 0.86), and this decrease was most prominent in subjects less than 60 years old at the time of death ($p = 0.005$)
Smiley et al. 2015	Skopje Macedonia Institute for Forensic Medicine	SCZ 14 MDD 17 HC 20	SCZ 7/7 MDD 9/8 HC 14/6	SCZ 51 MDD 53 HC 50	SCZ 8 MDD 17	AC	Nissl	Glia	No significant differences in glial cell density
Sneeboer et al. 2019	Netherlands Brain Bank	(1) BD 16 HC 12 (2) BD 15 HC 16	(1) BD 12/4 HC 7/5 (2) BD 12/3 HC 5/11	(1) BD 72 HC 76 (2) BD 75 HC 75	NA	MFG	IHC, PCR	IBA-1, HLA-DRA, CD68	No differences in microglial density and mRNA expression of microglial markers in the medial frontal gyrus of patients with BD
Sneeboer et al. 2020	Netherlands Brain Bank	SCZ 5 HC 7	(2) SCZ 3/2 HC 5/2	SCZ 69 HC 70	NA	MFG, CC	IHC	GFAP, IBA-1	No significant differences both in the staining pattern between patients and controls
Snijders et al. 2021	Netherlands and Edinburgh Brain Banks	(1) SCZ 18 HC 19 (2) SCZ 9 HC 14	(1) SCZ 6/12 HC 6/13 (2) SCZ 4/5 HC 8/6	(1) SCZ 67 HC 69 (2) SCZ 61 HC 73	HC 1	STG	IHC, PCR	IBA-1, HLA-DR	(1) No differences in IBA-1-IR microglial density and area (2) Decreased in HLA-DR mRNA in patients with MDD

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Steiner et al. 2006	Magdeburg Brain Collection	SCZ 16 HC 16	SCZ 8/8 HC 8/8	SCZ 55 HC 58	SCZ 2	DLPFC, ACC, HPC, MTN	IHC	HLA-DR	(1) Region-specific HLA-DR-positive cell density was not significantly different between cases with SCZ and controls (2) Two patients with SCZ who committed suicide during acute psychosis, ACC and MTN microglia cell numbers were significantly increased
Steiner et al. 2008	Magdeburg Brain Collection	SCZ 16 BD 5 MDD 14 HC 10	SCZ 7/9 BD 3/2 MDD 6/8 HC 5/5	SCZ 53 BD 49 MDD 49 HC 54	SCZ 6 MDD 7	HPC, DLPFC, ACC, MTN	IHC	HLA-DR	Microglia cell density was not affected in each group, however, significant microgliosis was observed in the DLPFC, ACC and MTD of suicide patients
Stockmeier et al. 2004	Cuyahoga County Coroner's Office	MDD 19 HC 21	MDD 12/7 HC 12/9	MDD 57 HC 58	MDD 13	HPC	Optical disector	Glia	The density of granule cells and glia in the DG, and glia in all CA/ hippocampal subfields is significantly increased (30%~35%) in MDD
Tanti et al. 2017	Douglas-Bell Canada Brain Bank	MDD 18 HC 18	MDD 18/0 HC 18/0	MDD 46 HC 38	MDD 18	VMPFC	IHC, WB	Olig2, MBP, MOG, MAG, CNPase, PLP1	(1) Olig2-oligodendrocytes density was decreased in the VMPFC white matter depressed suicide with a history of child abuse as compared to controls and non-abused depressed suicides (2) Only the expression of MBP protein was decreased in the VMPFC white matter of depressed suicides
Tkachev et al. 2003	Stanley Medical Research Institute	SCZ 15 BD 15 HC 15	NA	NA	NA	PFC (BA9)	qPCR	GFAP	No changes were observed in SCZ and BD cases compared to control group
Torii et al. 2020	NA	SCZ 5 HC 5	SCZ 3/2 HC 3/2	SCZ 60 59	NA	STG	IHC	MOG	The thickness of the MOG-positive fiber-like structures was significantly smaller in the SCZ patients without 22q11DS than in the normal controls ($p=0.028$)
Toro et al. 2006	NA	SCZ 15 BD 15 MDD 15 HC 15	SCZ 9/6 BD 9/6 MDD 10/5 HC 9/6	SCZ 45 BD 42 MDD 47 HC 48	SCZ 4 BD 9 MDD 7 HC 0	PFC (BA9,11/47)	Optical disector	GFAP	GFAP immunoreactivity was increased in BA9 in patients with SCZ, whereas decreased in BA11/47 in patients with SCZ and BD

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Torres-Platas et al. 2011	Quebec Suicide Brain Bank	MDD 10 HC 10	MDD 7/3 HC 8/2	MDD 49 HC 48	MDD 10	ACC (BA24) white matter	Golgi-impregnated	Astrocytes	In BA24 white matter, fibrous astrocytes in depressed suicides showed significant morphological changes, such as larger cell bodies as well as longer and more ramified processes
Torres-Platas et al. 2014	Douglas-Bell Canada Brain Bank	MDD 24 HC 17	MDD 18/6 HC 16/1	MDD 46 HC 39	MDD 24	dorsal ACC	PCR, IHC	IBA-1, CD68	(1) Total densities of IBA1-IR microglia did not differ between depressed suicides and controls, whereas the ratio of primed over ramified ("resting") microglia was significantly increased in depressed suicides (2) IBA-1 gene expression was significantly upregulated in depressed suicides
Torres-Platas et al. 2015	Douglas-Bell Canada Brain Bank	MDD 22 HC 22	MDD 22/0 HC 22/0	MDD 40 HC 42	MDD 22	PMC (BA4), PVC (BA17), CB, MTN, CN	qPCR, WB, IHC	GFAP	(1) Downregulation of GFAP mRNA and protein in the MTN and CN of depressed suicides compared with controls, whereas GFAP expression in other brain regions was similar between groups (2) IHC showed that astrocytes in both MTH and CN displayed larger cell bodies and extended more ramified processes across larger domains
Tzioras et al. 2021	Corsellis Collection	SCZ 10 HC 10	NA	NA	NA	PFC	IHC	IBA-1, CD68	There was no difference in the co-localization between CD68 and IBA-1 in controls and schizophrenia brains
Uranova et al. 2020	Anatomical Department of Moscow Psychiatric Hospitals	SCZ 21 HC 20	SCZ 11/10 HC 12/8	SCZ 56 HC 58	NA	PFC (BA10) gray matter layer 5	Electron microscopy	Glia	It showed microglial activation and dystrophic alterations of microglia and oligodendrocytes adjacent to each other in SCZ as compared to controls
Uranova et al. 2004	Stanley Foundation Neuropathology Consortium	SCZ 15 BD 15 MDD 15 HC 15	SCZ 9/6 BD 9/6 MDD 9/6 HC 9/6	SCZ 45 BD 42 MDD 47 HC 48	NA	PFC (BA9)	Nissl	Oligodendrocytes	A significant reduction in numerical density of oligodendroglial cells was found in layer VI of subjects with SCZ (25%; $p=0.04$), BD (29%; $p=0.03$) and MDD (19%; $p=0.04$) as compared to controls
Uranova et al. 2018	Moscow Psychiatric Hospitals, Moscow Higher Medical School	SCZ 21 HC 20	SCZ 10/11 HC 11/9	SCZ 56 HC 56	NA	PFC (BA10)	Electron microscope	Oligodendrocytes	Oligodendrocytes density was not changed in the SCZ group as compared to controls

Table 1 (continued)

Author/year	*Brain bank*	*Sample size (patients and controls)*	*Sex(m/f)*	*Age*	*Death from suicide*	*Brain region*	*Technique*	*Glial cells markers*	*Main findings*
Uranova et al. 2020	Anatomical Department of Moscow Psychiatric Hospitals	SCZ 21 HC 20	SCZ 11/10 HC 12/8	SCZ 56 HC 58	NA	PFC (BA10) gray matter	Electron microscopy	Microglia	(1) There was no differ in cell density between the SCZ and control groups (2) Dystrophy changes in microglia and adjacent oligodendrocytes
Vikhreva et al. 2016	Moscow Psychiatric Hospitals, Moscow Higher Medical School	SCZ 21 HC 20	SCZ 10/11 HC 12/8	SCZ 56 HC 56	NA	layer IV of BA10	Electron microscope	Oligodendrocytes	The area of oligodendrocyte was no changes in SCZ groups compared with control groups. However, in patients with SCZ, there are ultrastructural changes in the oligodendrocytes, such as swelling, vacuolated ribosomes and mitochondria deficiency, and the accumulation of lipofuscin granules
Vostrikov et al. 2008	Mental Health Research Center	SCZ 12 HC 12	SCZ 7/5 HC 7/5	SCZ 56 HC 56	NA	PC (BA10)	Electron microscope	Oligodendrocytes	Subjects with schizophrenia had a significantly lower (23%; $p < 0.005$) number of pericapillary oligodendrocytes compared to controls
Walker et al. 2017	Maryland and Alabama Brain Collections	SCZ 14 HC 9	SCZ 9/5 HC 5/4	SCZ 48 HC 43	NA	substantia nigra	Electron microscope	Oligodendrocytes	No significant differences were detected between SCZ and normal controls for areas of oligodendrocyte
Webster et al. 2005	Stanley Foundation Neuropathology Consortium	SCZ 15 BD 15 MDD 15 HC 15	SCZ 9/6 BD 9/6 MDD 9/6 HC 9/6	SCZ 45 BD 42 MDD 47 HC 48	SCZ 4 BD 9 MDD 7	ACC (BA24)	Riboprobe and in situ hybridization	GFAP	(1) It found higher levels of GFAP mRNA in white matter and at the pial surface as compared with gray matter levels in all cases (2) In the gray matter there was a significant effect of layer with the highest levels of GFAP mRNA in layer VI in all groups (3) In the white matter, the mean GFAP mRNA levels were decreased in individuals with SCZ and BD as compared with controls, but the difference was not statistically significant
Wesseling et al. 2014	Stanley Medical Research Institute	SCZ 22# BD 23* MDD 22# HC 22	SCZ 14/8 BD 13/10 MDD 13/9 HC 8/14	SCZ 41 BD 42 MDD 42 HC 42	NA	PFC (BA10)	Multiplexed selected reaction monitoring assay	MOG, MBP, MYPR, CNPase	It shown a decrease of all 4 tested oligodendrocyte specific proteins in BD
Williams et al. 2014	Corsellis Brain Collection	SCZ 12 MDD 13 HC 13	SCZ 7/5 MDD 4/9 HC 9/4	SCZ 60 MDD 57 HC 52	SCZ 2 MDD 9	Substantia nigra	IHC	GFAP	(1) Astrocyte density was decreased in SCZ compared to controls (2) No changes were observed in depression cases compared to control group

Table 1 (continued)

Author/year	Brain bank	Sample size (patients and controls)	Sex(m/f)	Age	Death from suicide	Brain region	Technique	Glial cells markers	Main findings
Zhang et al. 2020	Stanley Medical Research Institute Array Collection	BD 44 HC 45	BD 15/15 HC 25/9	BD 19–64 HC 31–60	BD 13	DLPFC (BA46), ACC (BA24)	qPCR	ALDH1L1, GFAP, S100b, CD68, HLA-DR, IBA-1	It found no evidence of immune activation in BD, however, CD68 mRNA levels to be downregulated in the DLPFC of non-suicidal individuals with BD

Abbreviations: ACC, anterior cingulate cortex; ACG, anterior cingulate gyrus; ADAM, a disintegrin and metalloprotease; AG, amygdala; ALDH, aldehyde dehydrogenase; AMC, anterior midcingulate cortex; AVN, anteroventral nucleus; BA, Brodmann area; BD, bipolar disorder; CA, cornu ammonis; CB, cerebellum; CC, corpus callosum; CD, cluster of differentiation; CN, caudate nucleus; CNPase, 2',3'-cyclic-nucleotide 3'-phosphodiesterase; CO, corpus callosum; DG, dentate gyrus; DLPFC, dorsolateral prefrontal cortex; DRN, dorsal raphe nucleus; EC, entorhinal cortex; FC, frontal cortex; GFAP, glial fibrillary acidic protein; HC, healthy control; HLA, human leukocyte antigen; HPC, hippocampus; IBA, ionized calcium-binding adaptor molecule; IC, internal capsule; IHC, immunohistochemistry; LC, locus coeruleus; MAG, myelin-associated glycoprotein; MBP, myelin basic protein; MDD, major depressive disorder; MFG, medial frontal gyrus; MOG, myelin oligodendrocyte glycoprotein; MTN, mediodorsal thalamus; NA, not available; NG, neural/glial antigen; OC, occipital cortex; OFC, orbitofrontal cortex; Olig, oligodendrocyte lineage genes; PAC, primary auditory cortex; PFC, prefrontal cortex; PLP, myelin proteolipid protein; PU, putamen; PMC, primary motor cortex; PVC, primary visual cortex; PCR, polymerase chain reaction; PT, planum temporale; SC, subiculum; SCZ, schizophrenia; SCZ (p), schizophrenia paranoid; SCZ (r), schizophrenia residual; SFG, superior frontal gyrus; STG, superior temporal gyrus; SVZ, subventricular zone; TH, thalamus; TC, temporal cortex; VIM, vimentin; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; WB, western blot

Among 41 studies, 34 studies evaluated differences in astrocytes by measuring the expression of GFAP or the distribution of immunoreactivity.

The first study to evaluate GFAP was published in 1993. Karson et al. [54] measured the protein level of GFAP in the brains of 25 patients with SCZ by western blot and found no differences in multiple brain regions, including the FC, STG, OC, cerebellum, thalamus, and pons relative to healthy controls. Fatemi et al. [46] later published a study of lateral cerebellum samples from the Stanley Foundation Brain Collection, in which they found that GFAP protein levels were reduced to different degrees in SCZ, BD and MDD. However, only the MDD value remained statistically significant following correction. This is in agreement with several subsequent studies, where reduced GFAP protein levels were observed in the DLPFC [86], LC [119], and OFC [66] of MDD. However, different from the result observed in MDD, two studies detected increased protein levels of GFAP in the DLPFC [47, 63] in SCZ patients compared to healthy controls. Similar increases were also observed in the DLPFC [47] and FC [77] in BD patients.

Similar to the research on GFAP mentioned above, several studies have reported increased GFAP mRNA expression in the brain from SCZ and BD. For example, Farnsworth et al. [110] found that schizophrenic patients had increased GFAP mRNA levels in the PFC and SFG. Qi et al. [72] investigated the expression of GFAP mRNA in the gray matter isolated from the ACC and DLPFC samples from patients with BD and MDD and found that only BD patients had significantly higher levels of GFAP in the ACC than control subjects. The authors did note, however, a lower area fraction of GFAP immunoreactive astrocytes in the ACC of BD. Although GFAP mRNA, as measured by a riboprobe, was decreased in the white matter of the ACC in SCZ and BD [106], Barley et al. [17] again observed that the levels of GFAP mRNA were increased in several brain regions including AVN, putamen, internal capsule, and mediodorsal thalamic nuclei, in patients with SCZ and MDD. In contrast, most studies evaluating GFAP mRNA expression of various brain regions of MDD, including the LC [21], gray matter of the PFC [67], mediodorsal thalamus [97], and CN [97], detected a reduced GFAP mRNA expression in MDD. Not all studies, however, have detected differences in GFAP mRNA expression. For example, no changes were detected between SCZ patients and healthy controls in several brain regions, including the PFC [93], MFG [115], CC [85], and DLPFC [62]. Similarly, no changes in GFAP mRNA were observed in the DLPFC and ACC in patients with BD compared with healthy controls [109].

Other studies have assessed GFAP expression by immunohistochemical analysis. Rajkowska et al. [74] published a study in 2002 of a cohort of 9 schizophrenic brains and found that GFAP-positive astrocyte density in layer V of the

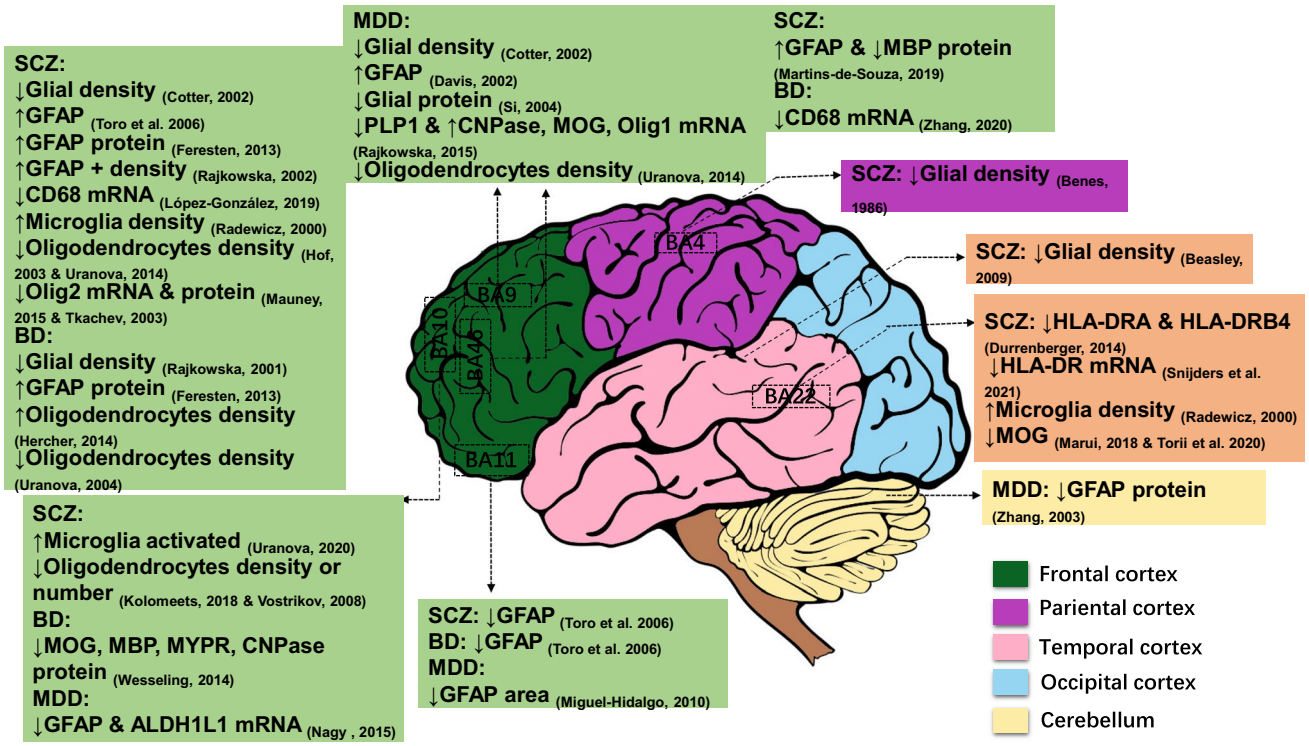

Fig. 2 Postmortem evidence of glial abnormalities in different brain regions in SCZ, BD, and MDD

DLPFC increased by 81%, whereas the GFAP labeling area was reduced by 32%. These changes were layer-specific, as no difference was detected between layers III and IV. This is slightly different from what two subsequent studies both observed that there were no differences in the density of GFAP cells in the DLPFC [43, 51] of patients with SCZ,

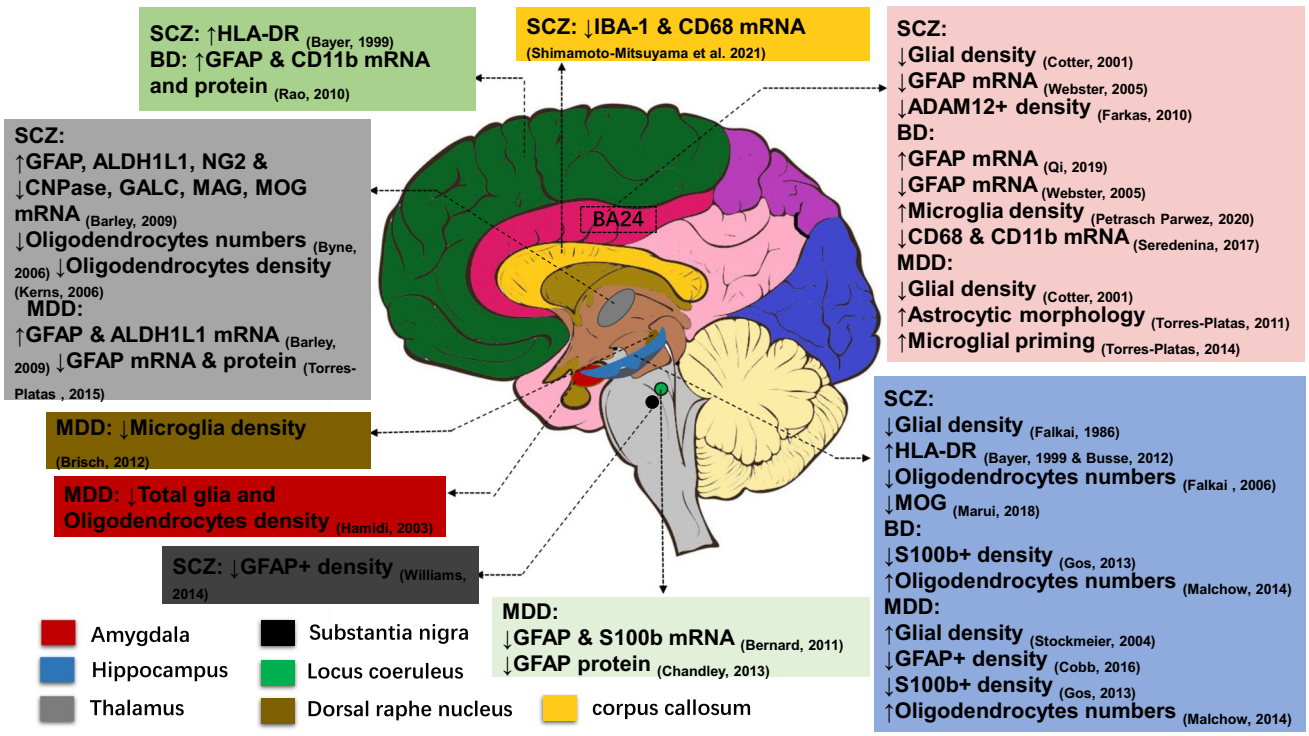

Fig. 3 Postmortem evidence of glial abnormalities in different brain regions in SCZ, BD, and MDD

although Hercher et al. [51] did find a decreased GFAP fraction area and increased cell clustering in the DLPFC in their study. Similarly, many quantitative studies found no differences in the density of GFAP cells in multiple other brain regions in patients with SCZ, including the hippocampus [69], EC [39, 69, 120, 121], amygdala [39], ACG [43], subiculum [69, 120], STG [43], primary motor cortex [120], DLPFC [28, 43], and subventricular zone [120]. Although Williams [108] and his colleagues examined the cellular structure of the substantia nigra in the postmortem brain with schizophrenia and MDD and found a decrease in astrocyte density in SCZ patients relative to healthy controls, this effect was not detected in patients with MDD.

However, many quantitative immunohistochemical studies have detected a decrease in the density of cells expressing GFAP in the brains of patients with MDD. For instance, Altshuler et al. [16] found a decrease in the density of GFAP-immunoreactive astrocytes in the amygdala of subjects with MDD compared to SCZ, BD, and healthy control postmortem samples. Similarly, in the study of Cobb et al. [33], the authors found that the density of GFAP-immunoreactive astrocytes in the dentate gyrus of MDD patients who did not take antidepressants was significantly lower than that in controls, whereas no change was found in CA1 or CA2/3. Other studies have also found that MDD patients had a lower GFAP-immunoreactive astrocyte density in the LC [119], DLPFC, dorsal CN, and MTN [70]. Nevertheless, not all immunohistochemical studies have detected this effect in MDD. No changes in GFAP cell density in several brain regions, including the ACC [38], hippocampus [48, 112], DLPFC [65], and substantia nigra [108], were observed in other studies.

Other astrocytic markers have also been measured in postmortem brain specimen from psychosis. With the increase in GFAP, aldehyde dehydrogenase (ALDH)1 mRNA in the SCZ and MDD was increased in several brain regions, including the putamen, AVN, internal capsule, and mediodorsal thalamic nucleus [17]. In contrast, two studies found no change in ALDH1 L1 mRNA in the DLPFC of patients with SCZ and BD [47, 109], whereas one other study detected a decrease in the PFC gray matter of MDD [67].

Hamidi and his colleagues examined the astrocyte marker S100b [50]. They did not observe changes in astrocyte density in the amygdala of patients with BD and MDD. Gos et al. [48], however, did find that the numerical density of S100b-immunopositive astrocytes was significantly decreased in the CA1 pyramidal layer in patients with BD and MDD compared to healthy controls. S100b has been measured by qPCR in a few other studies with mixed results. One study found a decrease in S100b mRNA in the LC of patients with MDD [21], and another found no change in the ACC and DLPFC in either BD or MDD [109].

Astrocytes have also been identified in postmortem brain by microscopic analysis with other staining techniques. In a cohort of 10 depressed suicides from the Quebec Suicide Brain Bank, Golgi-impregnated fibrous astrocytes had significantly larger cell bodies and longer, more ramified processes in depressed suicides [96]. This is consistent with another study, where examining astrocyte morphology by immunohistochemistry showed that astrocytes in both the thalamus and CN displayed larger cell bodies and extended more ramified processes across larger domains than cortical astrocytes [97]. However, two stereological counting studies on Nissl-stained astrocytes showed no differences in the number of hippocampal astrocytes, whether in SCZ, BD or MDD [63, 79, 122].

Microglia

From our search, a total of 24 studies assessed microglial marker in postmortem brain samples. Out of these 24 studies, 11 studies reported increased microglial markers in the postmortem brain, whereas 6 studies reported a decrease, and 7 studies found no change.

Cluster of differentiation (CD) is a microglial marker, and multiple studies have found lower CD gene expression in postmortem brains associated with SCZ. For example, in one study, downregulation of CD68 mRNA levels in the DLPFC was detected by qPCR in SCZ patients compared with healthy controls [62]. This is similar to the results of a recent study [85] in which CD68 mRNA levels were also decreased in the CC of SCZ. Similar decreases in the expression of CD68 and CD11b mRNA were observed in the ACC of BD patients [84], despite the expression of CD11b mRNA and protein in the FC was increased [77]. Moreover, Zhang et al. [109] reported a decrease in CD68 mRNA in the DLPFC of BD patients without suicide compared to BD patients with suicide and controls. This effect, however, was not seen in the ACC. Similarly, no difference in CD68 mRNA was detected in the dorsal ACC in MDD [95].

HLA antigen D-related (DR) is an immunohistochemical marker that specifically reacts with activated microglial cells. Bayer et al. [120] found that 3 of 14 schizophrenic patients had positive HLA-DR staining in the hippocampus and FC. This is in agreement with a study conducted the following year, where HLA-DR was increased in the DLPFC and STG [43], and although a similar increase was observed in the ACG, the results were not significant [43]. This increase in the HLA-DR marker appears to be more pronounced in the hippocampus of patients with paranoid SCZ, as HLA-DR was increased in this group compared with the residual SCZ group, but it was not significant compared to the control group [26].

In a microarray analysis, decreases in HLA-DRA and HLA-DRB4, subunits of HLA-DR, and mRNA expression

were observed in the temporal lobe of SCZ patients compared to healthy controls [40]. Similar decreases in HLA-DRA1 and HLA-DPB3 mRNA expression were detected in the superior TC of SCZ [80]. The decreases, however, were not statistically significant when mRNA expression was confirmed by qPCR [80].

Other immunohistochemical studies have assessed microglial activation by measuring ionized calcium-binding adapter molecule (IBA)1. In a cohort of 24 patients with MDD, a significant increase in the density of IBA1-immunoreactive amoeboid-like cells was found in the surrounding blood vessels in depression suicide, accompanied by an increase in IBA1 gene expression, although the total microglial densities in the dorsal ACC did not change [95]. This was confirmed in a subsequent study with a larger cohort, in which amoeboid microglial cells were increased in the ventrolateral PFC in depressed patients compared to healthy controls, but the overall density was very low [32]. However, IBA1 as measured by immunohistochemistry, showed no differences in microglial density in several brain regions of SCZ, such as the DLPFC [51], AMC [71], ACC [84], MFG [115], CC [115], PFC [98], and STG [88], as well as the DLPFC [51, 109], ACC [84, 109], and MFG [116] in BD.

Several anatomical studies have also examined microglial density in postmortem brain samples. In the two studies by Steiner et al. [89, 90], there were no changes in microglial density in various brain regions between the psychiatric group and the control group, but it was noted that suicide was accompanied by higher microgliosis. This effect is similar to a recently published study, where there was no significant difference in microglial density among individuals with SCZ, BD and control subjects. However, there was significantly higher microglial density in suicidal BD individuals than in nonsuicidal BD individuals [71]. Similarly, Brisch et al. [25] evaluated HLA-DR-positive microglial cell density in the DRN and found that nonsuicidal depressed patients revealed significantly lower microglial reactions than controls. In addition, two other studies reported no changes in microglial density in the hippocampus [48] of SCZ and the amygdala [50] of BD and MDD.

Changes in microglial cells have also been investigated by electron microscopy. In a cohort of 21 schizophrenic patients, patients with positive and negative symptoms of SCZ both showed significant microglial activation and dystrophic alterations in layer V of the gray matter in the PFC, although the microglial density did not differ from the control group [101].

Oligodendrocytes

Oligodendrocytes have been measured in postmortem brain samples from patients with major psychiatric diseases in 30 studies. Of the 30 studies, 20 studies reported decreased oligodendrocyte-related markers in the postmortem brain, whereas 2 studies reported an increase, and 8 studies found no change.

Several studies assessed differences in the expression of oligodendrocyte-related or myelin-related genes in postmortem brain samples. Tkachev et al. [93] reported a reduction in key oligodendrocyte- and myelin- related genes, such as oligodendrocyte lineage genes (Olig)2, myelin oligodendrocyte glycoprotein (MOG), and coding region of proteolipid protein (PLP)1, in SCZ and BD, and these gene expression changes in the PFC for both disorders showed a high degree of overlap. Wesseling et al. [107] used a labeled multiplexed selected reaction monitoring assay and found that in the PFC of patients with BD, four oligodendrocyte-specific proteins, 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNPase), MOG, myelin basic protein (MBP), and myelin proteolipid protein (MYPR), showed a decrease, whereas this decrease was less pronounced in SCZ and MDD. However, in other brain regions, such as the AVN, putamen, internal capsule, and mediodorsal thalamic nuclei, the mRNA expression levels of oligodendrocyte-associated genes, such as CNPase, MOG, galactosyl ceramidase (GALC), and myelin-associated glycoprotein (MAG), were only low in SCZ, whereas no significant difference in BD and MDD [17]. The downregulation of MOG [111] and MBP [63] expression seems to be closely related to SCZ. In a cohort of 10 long-term schizophrenic brains, in the middle layer of the STG and stratum lucidum of CA3 in the hippocampus, the thickness of the MOG-positive fiber-like structures decreased significantly along with reduced MOG expression [111]. In a recent study [94], the thickness of MOG-positive fibrous structures also decreased in the middle layer of the STG, regardless of the presence of 22q11DS in patients with SCZ compared to controls. MBP protein expression was decreased in the DLPFC of patients with SCZ in a proteomic analysis [63]. Furthermore, two studies on the expression of oligodendrocyte-related genes in the brains of patients with MDD have yielded conflicting results [76, 92]. Rajkowska et al. [76] detected oligodendrocyte-related mRNA expression of CNPase, PLP1, MBP, MOG, MOBP, oligodendrocyte transcription factor (OLIG) 1, and OLIG2 in the PFC by qPCR and found that PLP1 mRNA levels were significantly reduced in MDD, whereas there was increased mRNA expression of CNPase, OLIG1, and MOG. No changes in protein expression for CNPase, PLP1, MOG, and MAG were detected in the ventromedial prefrontal white matter of suicidal patients with MDD, but there was decreased Olig2 and MBP protein expression [92].

The majority of studies have reported that changes in the number or density of oligodendrocytes are associated with SCZ. Byne et al. [27] reported a decrease in oligodendrocyte number in the anterior principal thalamic nucleus in men

with SCZ; although women had a similar trend, the differences were not significant. In one of his subsequent studies [31], however, there were no changes in oligodendrocyte-specific genes in the thalamus of schizophrenic patients, including MAG, CNPase, and MBP. In fact, CNPase is a marker of oligodendrocyte progenitor cells in addition to differentiating and myelinating oligodendrocytes. Hof et al. [52] reported a decrease in oligodendrocyte total number in layer III of the SFG in 7 schizophrenic brains compared with healthy controls, which was measured by CNPase staining and confirmed by Nissl counts. Another study evaluated oligodendrocyte numbers in the entire hippocampus of 10 schizophrenic patients and found a significant decrease in CA4 in the hippocampus [44]. No effect of SCZ was observed in the dentate gyrus, CA1,2/3, and subiculum [44]. Mauney et al. [64] quantified cells that were immunoreactive for neural/glial antigen (NG)2, a selective marker for oligodendrocyte progenitor cells (OPCs), and those that were immunoreactive for OLIG2, an oligodendrocyte lineage marker of mature oligodendrocytes, and found that there was no significant change in the density of NG2-immunoreactive cells in the PFC of patients with SCZ, but the OLIG2-immunoreactive cell density was decreased significantly. The authors suggest that impaired OPC differentiation and myelin sheath lesions appear to be involved in the pathogenesis of SCZ [64]. A disintegrin and metalloprotease (ADAM)12, a member of the family of multidomain metalloprotease-disintegrins that possess cell-binding, cell-signaling and proteolytic properties [45], might also be involved in the pathophysiology of SCZ since the author found that the density of ADAM12-immunoreactive oligodendrocytes in the white matter of the ACC was significantly decreased in schizophrenic patients [45]. Kolomeets et al. [60] found that the density of oligodendrocytes was reduced in layer V of the PFC in patients with SCZ. In their next study with a large sample size, they also found that the numerical density of oligodendrocytes and oligodendrocyte clusters was reduced in the anterior putamen in SCZ [61]. Although this effect was not observed in BD and MDD, the density of oligodendrocyte clusters was significantly reduced in all male clinical cases compared to male controls [61]. Reductions in oligodendrocyte density were also observed in other brain regions of schizophrenic patients, such as the thalamus and [55] layer VI of the PF [102]. This effect, however, was not seen in the anterior cingulum bundle [81] or substantia nigra [81].

A few studies have also detected differences in the density of oligodendrocytes in the postmortem brains of patients with BD and MDD. For example, Gos et al. [48] reported a decreased density of S100B-immunopositive oligodendrocytes in the left alveus of the hippocampus in a cohort of 6 BD patients compared to the MDD and control groups. In contrast, in another stereological study of the posterior hippocampus [122], Nissl staining revealed that BD patients had significantly more oligodendrocytes in the CA1 region of the hippocampus than healthy controls. Similarly, in patients with MDD, the density of oligodendrocytes was higher in the CA2/3 region, CA4 region, and subiculum of the hippocampus. The authors also noted that antidepressant doses correlated with the density and number of oligodendrocytes in CA2/3 [122]. Although one study reported an increase in oligodendrocyte density in the DLPFC of patients with BD [123], in the other two studies, varying degrees of decrease in oligodendrocyte density were observed in the amygdala [50] and layer VI of the PFC [102] in MDD.

The morphological changes in oligodendrocytes have also been investigated by electron microscopy. Vostrikov et al. [104] reported that SCZ patients had a significantly lower number of pericapillary oligodendrocytes than controls. The author also noted obvious ultrastructural dystrophic and degenerative alterations of pericapillary oligodendrocytes in the PFC of schizophrenic brains. In two studies by Uranova et al. [99, 100], significant ultrastructural changes in oligodendrocytes were observed in the PFC [99, 100] and CN [99] of SCZ and BD, despite no changes in the density of oligodendrocytes. This is consistent with what Vikhreva et al. [103] observed, where the ultrastructure of the oligodendrocytes was changed, which was observed in layer IV of the PFC white matter in SCZ. These pathological changes in oligodendrocytes are aggravated when antipsychotic drugs are administered [105].

Discussion

Although the pathogenesis of SCZ, BD and MDD is largely unclear, accumulating postmortem brain sample studies allow for the study of the pathological mechanism of these psychiatric diseases at the cellular level. Therefore, we systematically reviewed the literature reporting glial cell number, density and cell type-specific markers in the postmortem brains of patients with SCZ, BD and MDD.

We tried to elucidate a trend for each cell type in the different diseases, although most of the study designs and results were heterogeneous. Astrocyte dysfunction appears to be a unique pathology in MDD, as multiple autopsy studies have reported a decrease in the number/density of GFAP-reactive astrocytes in several brain regions of patients with MDD, including the LC [119], OFC [66], amygdala [16], and hippocampus [33]. Similarly, decreases in GFAP gene and protein levels were also observed in other brain regions, including the cerebellum [46], DLPFC [86], PFC [67], thalamus, and CN [97] in patients with MDD. However, not all MDD studies have detected this effect. One plausible explanation is that GFAP immunoreactivity varies with the duration of depression because the GFAP protein levels [86]

and the packing density of GFAP-immunoreactive astrocytes [65] are positively correlated with the age of death, which may reflect a compensatory response to neuronal injury in elderly patients with MDD [75]. This may also partly explain why Davis and his colleagues [38] observed an increase in the density of GFAP-immunoreactive astrocytes in MDD brains with an average age of 75. Thus, the pattern of astrocyte pathology in the cerebral cortex in younger patients with MDD appears to be different from that in older patients.

Antidepressants are also most likely a confounding factor for this heterogeneous result, as antidepressants have been found to alter the expression pattern of glia-specific genes, including genes encoding GFAP, vimentin, and aquaporin, and affect glial cell numbers [124]. In this respect, it is important to know that a study using the chronic social defeat stress paradigm as an animal model for depression demonstrated that chronic exposure to antidepressant medications (fluoxetine) can counteract the significant reduction in the number of astrocytes induced by stress, resulting in hippocampal astrocyte numbers in the control range [125]. In our systematic review, supporting evidence from Cobb and his colleagues indicated that depressed people who were taking antidepressants (including fluoxetine) had more GFAP-immunoreactive astrocytes in the dentate gyrus [33]. One possible explanation for such findings is that antidepressant treatment may influence glial cell numbers by affecting glial cell proliferation, although the evidence thus far has shown only that fluoxetine-treated experimental animals have an increase in gliogenesis in the prefrontal cortex [126, 127]. Together, although controversial and somewhat inconsistent, the current evidence from postmortem MDD brain studies tends to support the hypothesis that astrocytic pathology represents a prominent feature of MDD and participates in the pathogenesis of MDD.

Astrogliosis was previously considered to be the basis of the changes in the morphology and number of astrocytes in SCZ. However, consistent evidence for astrocytic pathology in postmortem brains from patients with SCZ has proven elusive, in part due to some conflicting findings in the included studies. Investigations of astrogliosis include studies measuring not only GFAP mRNA and GFAP protein but also glial morphology and size. From our search, multiple studies on GFAP expression of genes/proteins have reported increased levels of GFAP gene and protein in different brain regions of SCZ [47, 63, 74, 110]. However, few immunochemical studies have detected an increased number/density of GFAP astrocytes [39, 43, 48, 51, 66, 120, 121]. Antipsychotic medications appear to be an important factor, which was supported by studies in which increased GFAP mRNA levels [17], GFAP protein levels [28], and GFAP immunoreactivity [128] were significantly correlated with lifetime antipsychotic treatment. Therefore, whether astrogliosis is a pathological feature of SCZ and the influence of antipsychotic treatment on glial pathology of SCZ needs further study.

Similarly, our data show that conflicting findings have also been found in studies evaluating microglia in the brains of SCZ patients postmortem. In support of the fact that most studies have not observed a difference in microglial density, several studies have observed changes in gene expression between controls and SCZ patients. One possible explanation is that microglia are known to be highly reactive and can show changes in a host of genes or proteins, which may or may not reflect changes in their morphology or quantity. Our results show that a reduction in CD68 mRNA levels was found in the DLPFC [62] and CC [85] of SCZ patients, which partly reflects that microglial activation was decreased in these brain regions of SCZ patients, as CD68 is generally thought to be highly expressed in round/activated microglia [129]. In two studies, however, more activated microglia were observed in the cortical areas of postmortem brains of several individuals with SCZ [51, 120]. The confounding factor may be that psychiatric patients include some suicide victims, since studies have shown that the suicidal brain may have high levels of pro-inflammatory cytokines [130]. This is consistent with the findings of two studies by Steiner et al. [89, 90] where patients with any psychiatric condition who committed suicide had the highest number of HLA-DR-positive cells. However, when suicide victims were considered, there were no differences in the same groups between diagnostic groups. The same effect was also observed for BD and MDD, and patients who committed suicide tended to have a higher microglial density [25, 71]. Furthermore, the cohort of healthy controls also included suicide victims, which may potentially confound the results.

In postmortem brain studies of oligodendrocytes, oligodendrocyte density and the expression levels of myelin-related genes, such as MAG, Olig2, and CNPase, were decreased in SCZ. A genetic study has shown that variations in oligodendrocyte-related genes affect the microstructural integrity of white matter bundles and cognitive performance in SCZ [131]. Repeated findings of the downregulation of these genes in the brains of postmortem patients with SCZ provides supporting evidence, although the hypothetical function of oligodendrocyte-related genes and white matter structural integrity is currently unclear. Oligodendrocyte dysfunction leads to changes in synaptic formation and function, which in turn leads to cognitive dysfunction, which is considered to be one of the core symptoms of SCZ [132, 133].

However, not all studies have detected this effect, and a plausible explanation is that there may be sex differences in gene expression, since Byne et al. [31] found higher expression of CNPase and MAG in females compared to males in the thalamic regions of SCZ. In addition, multiple studies have detected an effect of a decreased number/density of

oligodendrocytes in several brain regions in SCZ patients by immunohistochemistry and Nissl staining, and it is very likely that this effect is due to the loss of mature oligodendrocytes rather than oligodendrocyte precursor cells. A quantitative study detected a significant loss of Olig2-immunoreactive cells in the PFC of patients with SCZ but not NG2-immunoreactive cells [64]. This suggests that in future studies, the use of stage-specific markers to describe the specific stages of differentiation and maturation of oligodendrocytes in patients with SCZ may be more helpful to understand the pathology of oligodendrocytes related to SCZ.

However, there were still several limitations to this study that merit emphasis. Firstly, considering the relatively small number of BD studies that met the inclusion criteria for this review, we cannot draw a definite conclusion, which limited our ability to explain similar and different trends at the cellular level across diseases. Second, anxiety disorders are highly comorbid with MDD. However, the reviewed studies did not report anything with regard to comorbidities with anxiety; therefore, the presence of an anxiety disorder in MDD patients could be an important confounder for the observed between-study heterogeneities [134]. A third limitation is the high level of heterogeneity across studies derived from the research design, measurement methods, and sample selection. For example, some studies have found layer-specific effects in areas of the brain that evaluate glial cells [20, 35, 37, 73]. However, not all studies have measured the cortical layer of glial cells. Although a few studies have considered the impact of suicide on their measurements, many studies have not included it in their statistical analysis, which makes this another limitation. In addition, postmortem histopathological studies often include psychiatric patients with a history of use of various antidepressants and/or antipsychotic medications, so medication therapy itself may also lead to changes in glial morphology and number. Finally, since we did not consider non-English articles and unpublished data, there is a possibility of publication bias. Thus, our findings should be interpreted with caution.

In conclusion, although most studies evaluating total glial cells in postmortem brain samples from patients with psychiatric disease reported no difference, multiple other studies evaluating glial cell subtypes found evidence of glial cell abnormalities (see Supplementary Table S1). For example, although 19 studies did not find any effect of psychiatric disease on astrocyte markers, 22 studies presented both increased and decreased astrocyte markers. In particular, 11 studies found that astrocyte number/density and GFAP expression were decreased in various brain regions in MDD. Similarly, 15 studies reported a decrease in the density and related gene expression of oligodendrocytes in multiple brain regions of SCZ. These findings suggest that glial subtypes seem to have specific patterns of change in each disease, which is of great significance for us to understand the pathophysiology of glial cells in major psychiatric diseases and to provide new directions for disease treatment.

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Author Contribution All authors have read and agree with the published version of the manuscript. Yong Cheng conceived and designed this study; Shu-Han Liu and Yang Du searched database and identified eligible studies; Shu-Han Liu and Lei Chen extracted the data; all authors critically reviewed the manuscript; Shu-Han Liu drafted the manuscript with critical revisions from Yong Cheng.

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Data Availability All data are contained within the manuscript.

Declarations

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Consent to Participate Not applicable.

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