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Full Length Article

Blood-brain barrier pathology in patients with severe mental disorders: a systematic review and meta-analysis of biomarkers in case-control studies

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ABSTRACT

Background: Blood-brain barrier (BBB) pathology may be associated with mental disorders. The aim of this systematic review and meta-analysis is to identify, evaluate and summarize available evidence on whether potential biomarkers of BBB pathology are altered in patients with schizophrenia spectrum disorders, major depression and bipolar disorder compared to healthy controls.

Methods: The primary outcome is blood S100B, while secondary outcomes include biomarkers in blood and/or cerebrospinal fluid, i.e. albumin ratio, fibrinogen, immunoglobulin G, glial fibrillary acidic protein, amyloid beta (Aβ), matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases, endothelial glycocalyx constituents, and cell adhesion molecules (CAMs). A systematic search in PubMed, Embase and PsycINFO resulted in 131 eligible studies, of which 93 were included in the meta-analysis. Meta- and subgroup analyses were undertaken using random-effects modelling. The protocol was a priori registered on PROSPERO (CRD42020152721).

Results: S100B was increased in schizophrenia spectrum disorders (24 studies; 1107 patients; standardized mean difference (SMD) = 0.82; 95% confidence interval (CI) = 0.51 to 1.13; $I^2 = 90\%$), major depression (13 studies; 584 patients; SMD = 0.57; 95% CI = 0.31 to 0.83; $I^2 = 73\%$) and bipolar disorder (4 studies; 142 patients; SMD = 0.55; 95% CI = 0.16 to 0.94; $I^2 = 48\%$). Similarly, numerous secondary outcomes, including albumin ratio, fibrinogen, Aβ, MMPs and CAMs, were altered. Results of the included studies varied considerably, and important confounders were often not accounted for.

Conclusions: The findings implicate occurrence of BBB pathology in patients with schizophrenia spectrum disorders, major depression and bipolar disorder compared to healthy controls. However, definite conclusions cannot be drawn, mainly because the investigated biomarkers are indirect measures of BBB pathology.

1. Introduction

Severe mental disorders, i.e. schizophrenia spectrum disorders, major depression and bipolar disorder, account for a significant proportion of the global burden of disease (Murray et al., 2012) and, to varying degrees, share characteristic traits and specific genetic risk factors (Martin et al., 2018). Although traditionally considered to be disorders purely of the brain, abnormalities outside the central nervous system (CNS) are commonly seen (Benros et al., 2012; Correll et al., 2017; Krogh et al., 2014). In line with this, a growing body of research suggests that the blood-brain barrier (BBB), which separates the CNS from peripheral tissues, may be involved in the pathogenesis of severe mental disorders (Pollak et al., 2018). However, while it is well established that BBB pathology, which is defined as changes in the structural integrity and function of the BBB, is present in several neurological disorders (Larochelle et al., 2011; Marchi et al., 2012; Sweeney et al., 2018; Yang and Rosenberg, 2011), the evidence for BBB pathology in mental disorders has not yet been systematically reviewed and quantified.

Through complex structural and functional mechanisms, the BBB plays an important role in brain protection and homeostasis (Abbott

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et al., 2010). Consequences of BBB pathology comprise brain entry of toxins and pathogens that can injure neuronal tissue directly or indirectly, e.g. by causing oedema, which can induce hypoperfusion and hypoxia, or by activating microglia and astrocytes, which can lead to reactive gliosis and neuroinflammation (Zlokovic, 2011). Our primary outcome, S100B, is a calcium-binding protein abundant in glial cells of the CNS, predominantly in astrocytes. Under normal conditions, levels of S100B are low in blood and high in brain tissue (Fig. 1). During BBB disruption, S100B is released into blood in significant amounts and has thus been suggested to be a good biomarker of BBB disruption as well as brain injury in general (Marchi et al., 2003). Our secondary outcomes include compounds in blood and/or cerebrospinal fluid (CSF) that might otherwise be implicated in BBB pathology (Pollak et al., 2018; Sweeney et al., 2018), i.e. albumin ratio, albumin, fibrinogen, immunoglobulin G (IgG), glial fibrillary acidic protein (GFAP), amyloid beta (Aβ), matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), endothelial glycocalyx constituents, and cell adhesion molecules (CAMs) (Fig. 1).

In this comprehensive systematic review and meta-analysis, we aim to identify, evaluate and summarize available evidence on whether biomarkers of BBB pathology are altered in patients with schizophrenia spectrum disorders, major depression and bipolar disorder compared to healthy controls.

2. Methods

Our review follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the study protocol was a priori registered on PROSPERO (CRD42020152721).

2.1. Inclusion and exclusion criteria

We included studies fulfilling the following criteria: 1) Case-control study. 2) Investigation of markers of BBB pathology, as defined in section 2.2. 3) Inclusion of patients diagnosed with schizophrenia spectrum disorders, major depression or bipolar disorder versus healthy controls. Patients must have been diagnosed according to Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013), International Classification of Disease (ICD) (World Health Organization, 1992) or similar classifications that might have been used before implementation of DSM and ICD. 4) In case of a mixed patient population (e.g. inclusion of both patients with schizophrenia spectrum disorders and bipolar disorder), we only included the study if results for patient groups were available separately. 5) Published in a peer-reviewed journal. Studies written in other languages than English were excluded. No restrictions were imposed on publication period, age, gender or ethnicity of study participants.

2.2. Outcomes

2.2.1. Primary outcome

1. S100b in blood

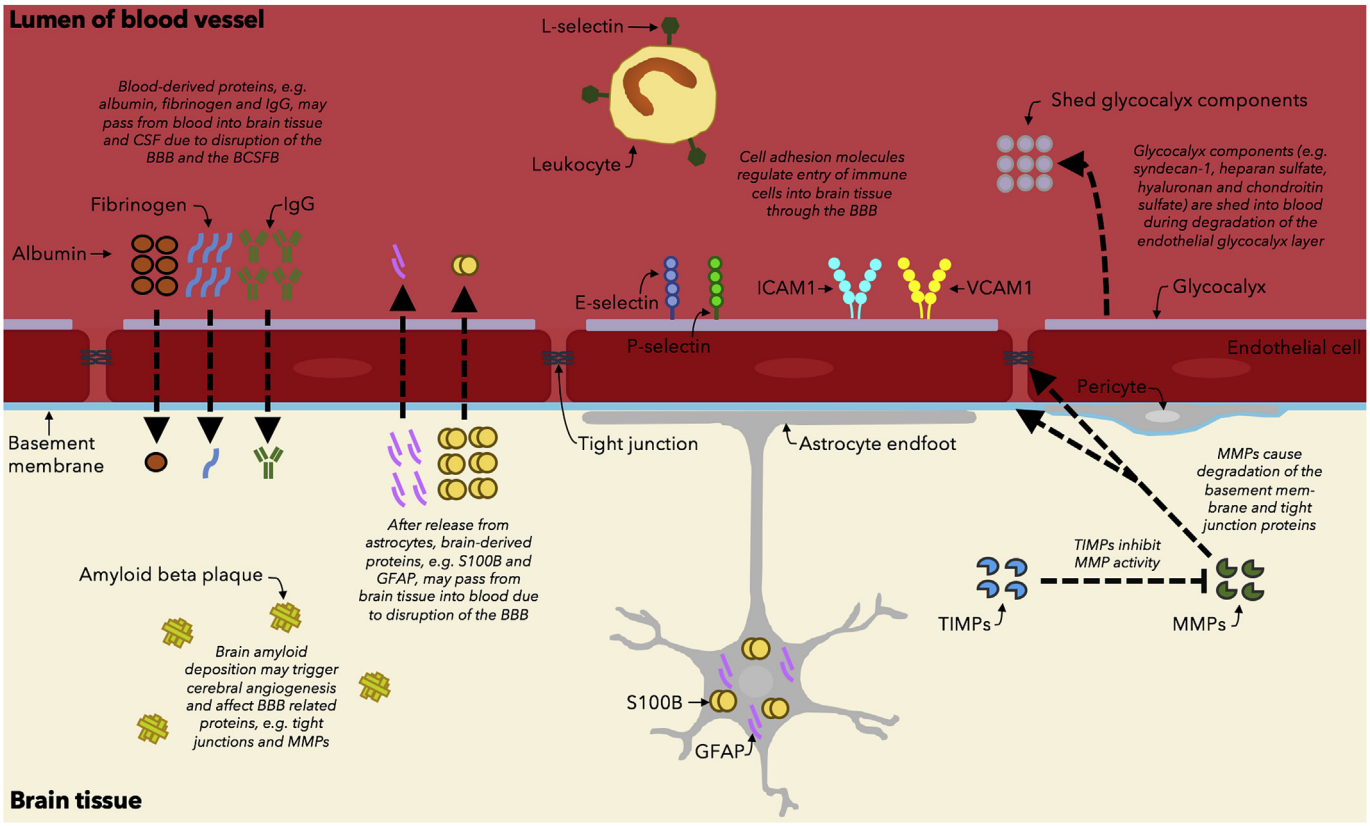


Fig. 1. Overview of the blood-brain barrier and the investigated biomarkers.
Figure information: The BBB separates brain tissue from blood and is composed of brain microvascular endothelial cells, pericytes and astrocyte endfeet. Tight junctional complexes restrict paracellular diffusion between the brain microvascular endothelial cells, while the luminal and abluminal surfaces are coated by the glycoprotein-rich glycocalyx layer and the basement membrane, respectively (Abbott et al., 2010; Kutuzov et al., 2018). In a similar, but not identical way, the BCSFB separates CSF from blood and is formed by the epithelial cells of the choroid plexus. Associations between study outcomes and BBB pathology are explained in the figure. Abbreviations: BBB = blood-brain barrier; BCSFB = blood-cerebrospinal fluid barrier; CSF = cerebrospinal fluid; GFAP = glial fibrillary acidic protein; ICAM1 = intercellular adhesion molecule 1; IgG = immunoglobulin G; MMPs = matrix metalloproteinases; TIMPs = tissue inhibitor of metalloproteinases; VCAM1 = vascular cell adhesion molecule 1.

2.2.2. Secondary outcomes

1. Markers exclusively in blood: GFAP.
2. Markers exclusively in CSF: Albumin, fibrinogen, plasminogen, Aβ and IgG.
3. Markers in both blood and CSF: Albumin ratio, MMPs, TIMPs, CAMs (i.e. soluble intercellular adhesion molecule 1 (sICAM1), soluble vascular cell adhesion molecule 1 (sVCAM1) and sE-, sL- and sP-selectin) and endothelial glycocalyx constituents (i.e. syndecan 1, heparan sulfate, hyaluronan and chondroitin sulfate).

2.3. Search strategy

References were identified through searches of PubMed, Embase and PsycINFO for articles published from inception to September 27, 2019, by the use of text words and, when appropriate, MeSH terms or similar, as described in detail in the search protocol (Table S1). Furthermore, reference lists of relevant reviews were carefully searched for additional studies. One investigator (JF) examined titles and abstracts and subsequently reviewed full-text articles for eligibility. If there were any doubts about a particular study, it was included for further assessment by a senior investigator (JK). Any disagreements were solved by discussion between investigators.

2.4. Data extraction and bias assessment

Two authors (JF and RM) independently extracted data using a prepiloted form. In case of missing or unclear data, authors were contacted by email. If no response was received, a follow-up email was sent. Similarly, two authors (JF and RM) independently assessed the risk of bias in each study using a modified version of the Newcastle-Ottawa Scale (NOS) for case-control studies (Table S5).

2.5. Statistical analysis

Meta-analyses were conducted using RevMan (v5.0) and Comprehensive Meta-Analysis (v2) and performed separately for patients with schizophrenia spectrum disorders, bipolar disorder and major depression. Since we expected differences in techniques, e.g. assays, we estimated differences between patients and controls using the random-effects approach and reported the results as standardized mean difference (SMD). The SMD is the mean difference between cases and controls divided by the pooled standard deviation (SD). The result is a unit free effect size and, by convention, SMDs of 0.2, 0.5 and 0.8 are considered small, medium and large effect sizes, respectively. The degree of heterogeneity was quantified using the I^2-statistic, which can be interpreted as the percentage of variation observed between the studies attributable to between study differences rather than stochastic variation. If SDs were not reported, we calculated SDs based on median and range as described by Hozo et al. (2005).

For the primary outcome, S100B, trial sequential analysis was applied to calculate the diversity-adjusted required information size and trial sequential monitoring boundaries for benefit and futility (Wetterslev et al., 2009). This approach allows to differentiate significant results into 'spuriously significant' (type I error) caused by sparse data or repetitive testing and 'truly significant' results, as well as neutral results into 'spuriously insignificant' (type II error) caused by lack of power and 'truly neutral' results. Based on 1545 healthy controls from 41 studies, the mean S100B was estimated to 104.4 (SD = 283) based on a random-effects analysis. A priori, we set the least significant change to 0.2 SD, which in this dataset corresponded to a difference of S100B of 57 ng/L, the two-sided alpha-values was set to 5%, and beta to 10%. Variance and heterogeneity correction were derived from each meta-analysis.

Furthermore, to determine whether heterogeneity of effect estimates was explained by population characteristics, we conducted meta-regression analyses of the following factors, when reported in ≥3 studies: 1) BMI (mean), 2) illness duration (mean), 3) age (mean), 4) psychotropic medications (% treated), 5) gender (% of males), and 6) cigarette smoking (% of smokers) (Table S6). In addition, we conducted subgroup analyses based on whether S100B was measured in serum or plasma. P-values of 0.05, or below, were considered significant for the primary outcome. Due to multiplicity, for the secondary outcomes and the meta-regression and subgroup analyses, p-values between 0.05 and 0.01 were considered 'potentially significant', while p-values below 0.01 were considered significant.

We also conducted stratified analyses and meta-regression in an attempt to determine whether particular clinical or study-design characteristic s influence the relationship bet ween tight glycemic control and patient outcomes.

3. Results

3.1. Search results and study characteristics

As outlined in the PRISMA flow diagram (Fig. 2), we identified 23,132 citations through the database search and two studies through other sources. A total of 131 studies were eligible for inclusion, and 93 of these reported data necessary for conducting the meta-analysis, while 38 studies were only included for qualitative synthesis either due to missing data (Table S3) or due to study participants overlapping with studies already included in the meta-analysis (Table S4). Of the 93 studies included in the meta-analysis (Table S2), 45 included patients with schizophrenia spectrum disorders, 36 included patients with major depression and 15 included patients with bipolar disorder. The median study sample size was 74 (range = 20–728), mean age ranged from 15 to 76 years, mean illness duration ranged from less than one to 35 years, and use of psychotropic medications varied regarding status, type and duration. Furthermore, studies varied regarding gender distribution.

3.2. Bias assessment

All studies were biased regarding at least one of the three assessed domains (i.e. selection, comparability and outcome) (Table S5). 15/93 (16%) studies stated that patients were consecutively enrolled, 88/93 (95%) studies included both males and females, 46/93 (49%) studies matched cases and controls on (or adjusted the results for) at least two relevant factors, 19/93 (20%) studies assessed outcomes blindly and 17/93 (18%) studies had more than 5% missing data (e.g. due to patient drop-out or assay issues).

3.3. Primary outcome

S100B was increased in patients with schizophrenia (24 studies; 1107 patients; SMD = 0.82; 95% CI = 0.51 to 1.13; I^2 = 90%), major depression (13 studies; 584 patients; SMD = 0.57; 95% CI = 0.31 to 0.83; I^2 = 73%) and bipolar disorder (4 studies; 142 patients; SMD = 0.55; 95% CI = 0.16 to 0.94; I^2 = 48%) compared to controls (Fig. 3). Due to missing data, six S100B studies could be included in the qualitative synthesis only. Five of these reported increased levels of S100B in patients compared to controls (Arostegui et al., 2016; Deng et al., 2017; Haenisch et al., 2014; Schroeter et al., 2002; Xiong et al., 2014), while one reported no difference between groups (Haenisch et al., 2015).

3.3.1. Trial sequential analysis

The required information size was reached for S100B in schizophrenia spectrum disorders, major depression and bipolar disorder (Figure S1), suggesting that the observed results are not due to random error.

3.3.2. Meta-regression and subgroup analyses

Increased duration of illness potentially predicted increased SMDs of S100B levels in patients with schizophrenia spectrum disorders (17

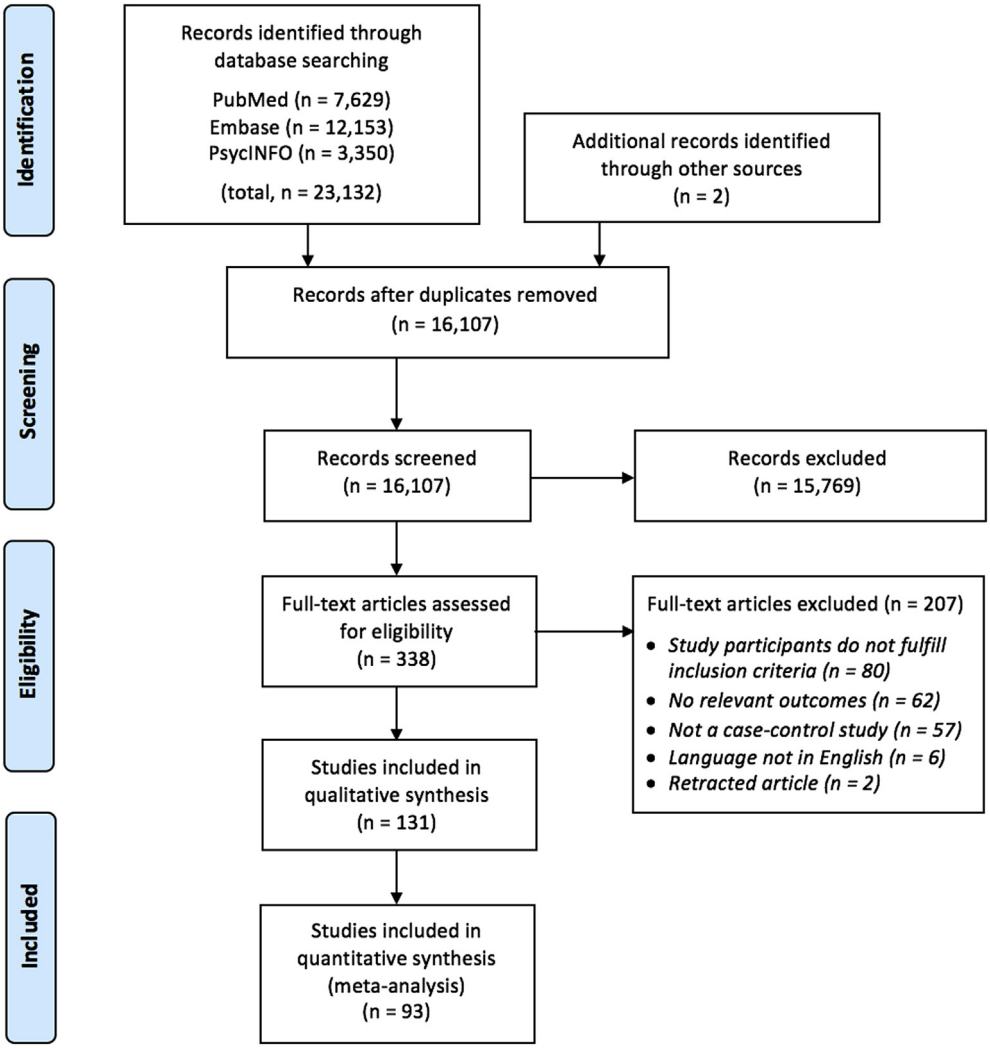


Fig. 2. PRISMA flow diagram of literature search and study selection.

studies; patients; SMD = 0.05, 95% CI 0.00 to 0.10, p = 0.03) and major depression (3 studies; 106 patients; SMD = 0.21, 95% CI 0.00 to 0.43, p = 0.05), while illness duration was only reported in two studies including patients with bipolar disorder (Table S6). Differences in mean age, mean BMI, percentages of males, percentages of smokers and percentages of patients receiving psychotropic medications did not explain heterogeneity of effect estimates. Furthermore, subgroup analyses revealed that the effect estimates did not depend on whether S100B was measured in plasma or serum. In a post-hoc analysis, we pooled results from the three patient groups (i.e. schizophrenia, major depression and bipolar disorder) to investigate if heterogeneity was explained by disease category. The result (p = 0.45) suggests that levels of S100B were independent of disease category.

3.4. Secondary outcomes

3.4.1. Schizophrenia spectrum disorders

The albumin ratio (2 studies; 69 patients; SMD = 0.71; 95% CI = 0.37 to 1.05; $I^2 = 0\%$) and blood levels of MMP9 (7 studies; 533 patients; SMD = 0.71; 95% CI = 0.34 to 1.08, $I^2 = 85\%$) and sP-selectin (3 studies; 98 patients; SMD = 4.45; 95% CI = 1.17 to 7.73, $I^2 = 98\%$) were increased in patients compared to controls. Levels of the following Aβ isoforms: Aβ1-17, −18, −19, −33, −34, −35, −36, −37, −38, −39, −40, −42 and Aβ11-40 were decreased, while blood levels of MMP2 (2 studies; 300 patients, SMD = −0.67; 95% CI = −0.49 to −0.09; $I^2 = 31\%$) were potentially decreased in patients compared to controls. Levels of Aβ10-40, Aβ11-42, albumin, fibrinogen, IgG, MMP3, TIMP1, sICAM1, sVCAM1, sE-, and sL-selectin did not differ between patients and controls (Table 1 and Figure S2). For the secondary outcomes, findings of studies included for the qualitative synthesis are presented in Table S3 exclusively.

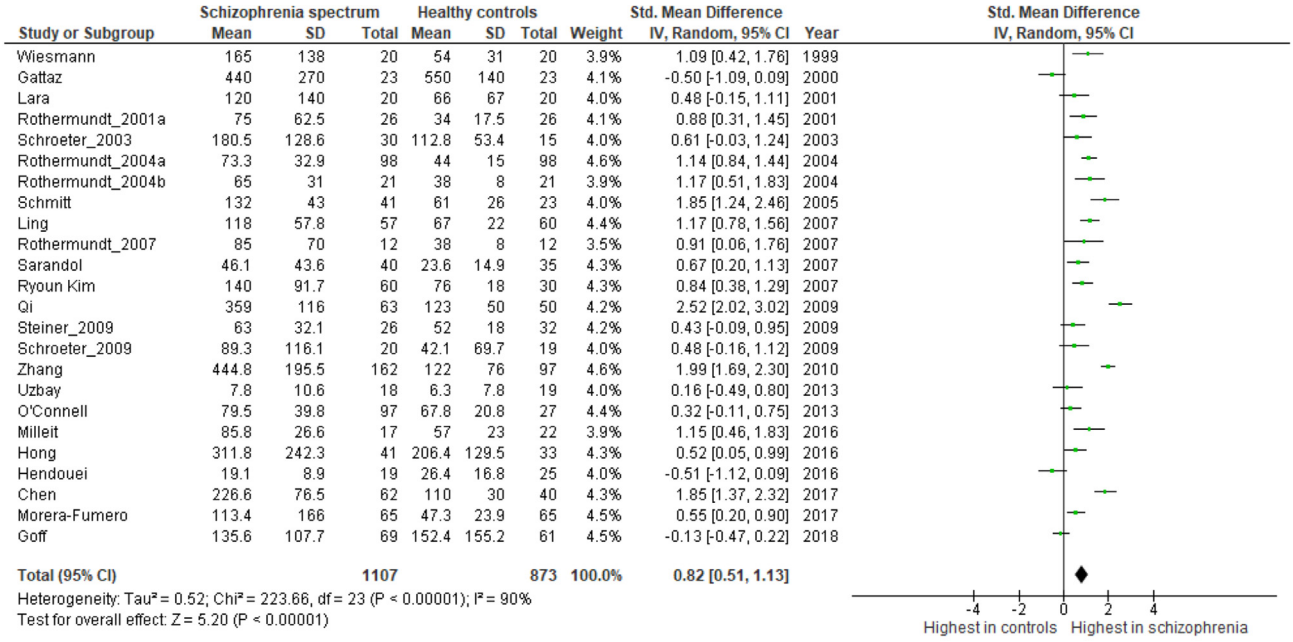
3.4.2. Major depression

Levels of fibrinogen (1 study; 66 patients; SMD = 0.56; 95% CI = 0.20 to 0.91) were increased, while blood levels of sICAM1 (5 studies; 338 patients; SMD = 0.73; 95% CI = 0.14 to 1.31; $I^2 = 86\%$) and sE-selectin (2 studies; 32 patients; SMD = 0.54; 95% CI = 0.08 to 1.00; $I^2 = 0\%$) were potentially increased in patients compared to controls. In contrast, levels of Aβ1-38 (1 study; 28 patients; SMD = −0.86; 95% CI = −1.37 to −0.35) and Aβ1-40 (3 studies; 71 patients; SMD = −0.8; 95% CI = −1.14 to −0.46; $I^2 = 0\%$) were decreased in patients compared to controls. The albumin ratio, Aβ1-42, albumin, IgG, MMP2, -3, -9, TIMP1, sVCAM1, sP- and sL-selectin did not differ between groups (Table 1 and Figure S2).

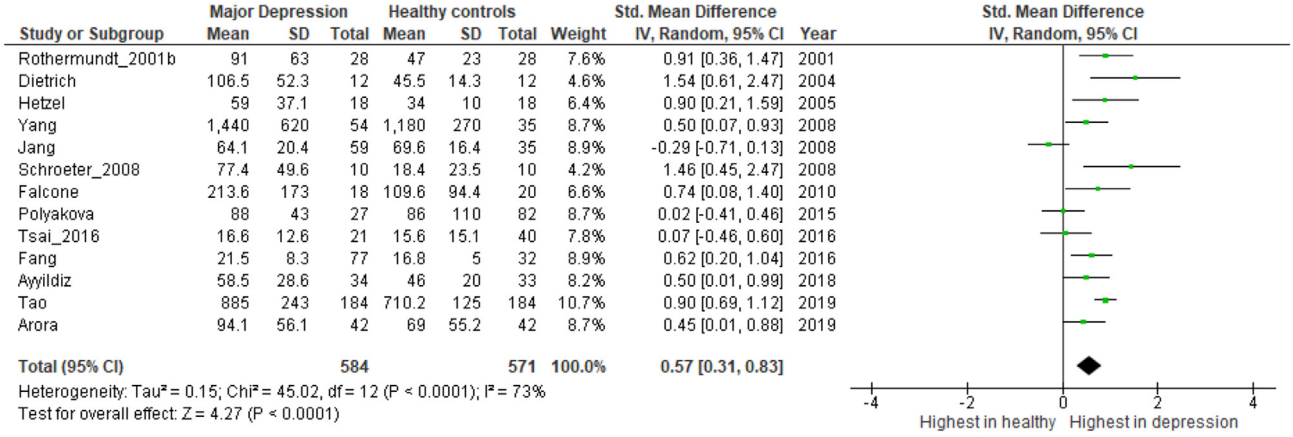
3.4.3. Bipolar disorder

The albumin ratio (1 study; 134 patients; SMD = 0.42; 95% CI = 0.15 to 0.70) and blood levels of sICAM1 (3 studies; 157 patients; SMD = 0.41; 95% CI = 0.18 to 0.64; $I^2 = 0\%$), sP-selectin (1 study; 130 patients; SMD = 0.33; 95% CI = 0.09 to 0.58) and MMP7 (2 studies; 119 patients; SMD = 0.80; 95% CI = 0.55 to 1.05; $I^2 = 0\%$) were increased in patients

Schizophrenia spectrum disorders vs. healthy controls:



Major depression vs. healthy controls:



Bipolar disorder vs. healthy controls:

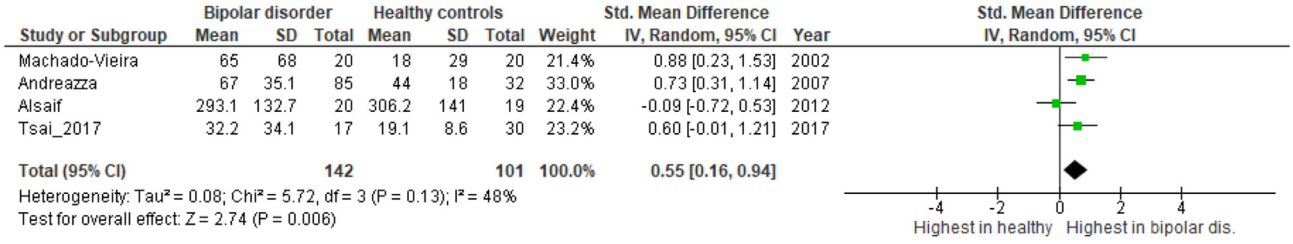


Table information: *Abbreviations: CI = confidence interval; SD = standard deviation.*

Fig. 3. Forest plots on the primary outcome, S100B.

compared to controls. Meanwhile, serum levels of MMP2 (1 study; 12 patients; SMD = −0.82; 95% CI = −1.49 to −0.16) were potentially decreased in patients compared to controls, and levels of Aβ1-38, −40, −42, MMP1, -3, -9, -10, TIMP1, -2, sVCAM1 and sE-selectin did not differ between groups (Table 1 and Figure S2).

4. Discussion

This is the first systematic review and meta-analysis gathering current evidence on whether biomarkers of BBB pathology are altered in patients with severe mental disorders, i.e. schizophrenia spectrum disorders,

Table 1
Markers of BBB pathology in patients compared to healthy controls.

Schizophrenia spectrum disorders vs. healthy controls							
Marker	Studies	Cases	Controls	SMD	95% CI	*p*-value	I^2
Serum/plasma S100B	24	1107	873	**0.82**	0.51 to 1.13	**<0.001**	90%
Albumin ratio	2	69	72	**0.71**	0.37 to 1.05	**<0.001**	0%
CSF albumin	3	101	103	0.30	−0.10 to 0.70	0.14	44%
CSF fibrinogen	1	46	35	−0.15	−0.59 to 0.29	0.51	NA
CSF Aβ1-38	1	11	20	**−1.22**	−2.03 to −0.42	**0.003**	NA
CSF Aβ1-40	1	11	20	**−1.47**	−2.31 to −0.64	**<0.001**	NA
CSF Aβ1-42	1	11	20	**−1.57**	−2.42 to −0.73	**<0.001**	NA
CSF IgG	3	101	103	0.14	−0.56 to 0.84	0.70	81%
CSF sICAM1	2	56	47	−0.19	−0.81 to 0.44	0.56	48%
CSF sVCAM1	2	61	50	−0.17	−1.13 to 0.79	0.73	80%
CSF TIMP1	1	46	35	0.36	−0.09 to 0.80	0.12	NA
CSF MMP3	1	46	35	0.16	−0.28 to 0.60	0.47	NA
Serum/plasma sICAM1	12	833	941	0.20	−0.07 to 0.47	0.15	83%
Serum/plasma sVCAM1	5	529	542	−0.44	−1.15 to 0.27	0.23	97%
Serum/plasma TIMP1	2	300	313	0.54	−0.25 to 1.33	0.18	94%
Serum/plasma MMP2	2	300	313	**−0.67**	−0.49 to −0.09	**0.02**	31%
Serum/plasma MMP3	2	300	313	−0.01	−0.17 to 0.15	0.91	0%
Serum/plasma MMP9	7	533	509	**0.71**	0.34 to 1.08	**<0.001**	85%
Serum/plasma sP-selectin	3	98	92	**4.45**	1.17 to 7.73	**0.008**	98%
Serum/plasma sE-selectin	3	112	105	0.79	−0.32 to 1.90	0.16	93%
Serum/plasma sL-selectin	2	62	55	−134.33	−401.9 to 133.3	0.33	99%

Major depression vs. healthy controls							
Marker	**Studies**	**Cases**	**Controls**	**SMD**	**95% CI**	***p*-value**	**I^2**
Serum/plasma S100B	13	584	571	**0.57**	0.31 to 0.83	**<0.001**	73%
Albumin ratio	4	82	124	0.13	−0.29 to 0.55	0.55	43%
CSF albumin	2	36	42	0.02	−0.51 to 0.55	0.94	0%
CSF fibrinogen	2	66	60	**0.56**	0.20 to 0.91	**0.002**	0%
CSF Aβ1-38	1	28	38	**−0.86**	−1.37 to −0.35	**0.001**	NA
CSF Aβ1-40	3	71	81	**−0.80**	−1.14 to −0.46	**<0.001**	0%
CSF Aβ1-42	9	205	297	0.13	−0.32 to 0.59	0.57	81%
CSF IgG	2	36	42	−0.22	−0.75 to 0.31	0.41	0%
CSF MMP9	1	22	13	−0.20	−0.89 to 0.49	0.57	NA
Serum/plasma sICAM1	5	338	345	**0.73**	0.14 to 1.31	**0.014**	86.1%
Serum/plasma sVCAM1	5	336	340	0.28	−0.03 to 0.59	0.08	52%
Plasma TIMP1	1	245	254	0.08	−0.09 to 0.26	0.36	NA
Serum/plasma MMP2	2	261	294	−0.56	−1.35 to 0.23	0.16	84%
Plasma MMP3	1	245	254	−0.01	−0.18 to 0.17	0.95	NA
Serum/plasma MMP9	3	330	372	0.19	−0.12 to 0.50	0.24	64%
Serum sP-selectin	2	166	166	0.20	−0.22 to 0.62	0.36	52%
Serum sE-selectin	2	32	51	**0.54**	0.08 to 1.00	**0.02**	0%
Serum sL-selectin	1	17	36	−0.01	−0.59 to 0.56	0.97	NA

Bipolar disorder vs. healthy controls							
Marker	**Studies**	**Cases**	**Controls**	**SMD**	**95% CI**	***p*-value**	**I^2**
Serum/plasma S100B	4	142	101	**0.55**	0.16 to 0.94	**0.006**	48%
Albumin ratio	1	134	85	**0.42**	0.15 to 0.70	**0.003**	NA
CSF Aβ1-38	1	139	71	−0.11	−0.39 to 0.18	0.47	NA
CSF Aβ1-40	1	139	71	−0.18	−0.46 to 0.11	0.23	NA
CSF Aβ1-42	2	155	96	−0.17	−0.70 to 0.37	0.54	60%
CSF TIMP1	1	125	87	0.18	−0.10 to 0.45	0.21	NA
CSF TIMP2	1	125	87	0.23	−0.04 to 0.51	0.10	NA
Serum/plasma sICAM1	3	157	144	**0.41**	0.18 to 0.64	**<0.001**	0%
Serum/plasma sVCAM1	3	157	144	0.37	−2.08 to 2.82	0.77	99%
Serum MMP1	1	24	21	0.39	−0.20 to 0.98	0.20	NA
Serum MMP2	1	12	40	**−0.82**	−1.49 to −0.16	**0.02**	NA
Serum MMP3	1	24	21	−0.16	−0.74 to 0.43	0.60	NA
Serum MMP7	2	119	162	**0.80**	0.55 to 1.05	**<0.001**	0%
Serum MMP9	3	328	224	0.11	−0.06 to 0.29	0.20	0%
Serum MMP10	1	24	21	0.16	−0.42 to 0.75	0.59	NA
Serum TIMP1	2	245	133	0.16	−0.09 to 0.42	0.21	12%
Serum TIMP2	1	221	112	0.05	−0.18 to 0.27	0.70	NA
Serum E-selectin	2	74	71	−0.18	−0.51 to 0.16	0.31	4%
Serum P-selectin	1	130	130	**0.33**	0.09 to 0.58	**0.008**	NA

Table information: *For space-saving purposes, results on CSF Aβ isoforms other than Aβ1-38, -40 and -42 are illustrated in Figure S2 exclusively. Abbreviations: Aβ = amyloid beta; CI = confidence interval; CSF = cerebrospinal fluid; IgG = immunoglobulin G; NA = not available; MMP = matrix metalloproteinase; sICAM1 = soluble intercellular adhesion molecule 1; SMD = standardized mean difference; sVCAM1 = soluble vascular cell adhesion molecule 1; TIMP = tissue inhibitor of metalloproteinases.*

major depression and bipolar disorder, compared to healthy controls. A subset of the included data is previously unpublished and was kindly provided to us by study authors (Bruno et al., 2017; Cai et al., 2018; Coughlin et al., 2013; Graham et al., 2008; Hayes et al., 2014; Pomara et al., 2014; Yamamori et al., 2013). The primary outcome, S100B, was increased in all patient groups. Similarly, numerous secondary outcomes, including the albumin ratio, fibrinogen, Aβ, MMPs and CAMs, were altered. Meta-regression and subgroup analyses revealed that heterogeneity of effect estimates was not explained by population characteristics. Together, the findings of the present study implicate occurrence of BBB pathology in patients with severe mental disorders compared to healthy controls.

The uncertainty regarding the extent to which the investigated biomarkers are associated with BBB pathology denotes the first and foremost limitation of the present study. Nonetheless, the investigated biomarkers all provide insights into the BBB, and more superior blood and CSF biomarkers have not been discovered yet. Secondly, important information (e.g. regarding use of psychotropic medications, illness duration, recent head trauma, BMI and smoking status) was not consistently reported in the included studies (Table S2 and -S3). Thirdly, 47/93 (51%) studies neither matched cases and controls, nor adjusted the results, for relevant confounding factors. Fourthly, publication bias, either due to non-publication of studies with non-significant results, or to inadequate reporting within the included studies, may pose a threat to the validity of the current review. To minimize publication bias, we systematically contacted study authors to request unreported results. Fifthly, the techniques used to analyse biomarkers varied across studies (Table S2 and -S3). Sixthly, considerable between-study heterogeneity of effect estimates was evident (Table 1). Finally, the investigated biomarkers were analysed separately, and uncertainty exists regarding the extent to which the biomarkers are interdependent.

Our meta-analysis includes ten studies on S100B (Arora et al., 2019; Ayyildiz et al., 2018; Chen et al., 2017; Falcone et al., 2010; Goff et al., 2018; Hendouei et al., 2016; Hong et al., 2016; Milleit et al., 2016; Morera-Fumero et al., 2017; Tao et al., 2019) that were neither included in previous meta-analyses on S100B in schizophrenia (Aleksovska et al., 2014; Schroeter et al., 2009; Schumberg et al., 2016) or affective disorders (da Rosa et al., 2016; Kroksmark and Vinberg, 2018; Schroeter et al., 2011). Nonetheless, our findings of increased blood levels of S100B are congruous with the previous meta-analyses. Since S100B is also secreted by adipose tissue, one may hypothesize that increased levels of S100B can be explained by the increased prevalence of obesity in severe mental disorders (Steiner et al., 2010). However, our meta regression analysis revealed that BMI did not predict the between-study heterogeneity in S100B effects estimates (Table S6). Yet, only 13 of the included studies reported BMI, and the lack of clarity on this matter gives evidence of the importance of considering confounding factors when investigating S100B in future studies. Similar to S100B, GFAP is almost exclusively expressed by astrocytes, and BBB disruption is a prerequisite for entry of GFAP into blood (Marchi et al., 2003). However, evidence to support the validity of GFAP as a biomarker of BBB disruption is limited compared to S100B. Only one study investigating GFAP was eligible for inclusion, but found decreased serum GFAP and increased serum S100B in patients with schizophrenia compared to controls (Xiong et al., 2014). These contrasting results as well as the limited amount of available evidence confirms that uncertainty remains associated with GFAP regarding its potential as a biomarker of BBB disruption.

A few more eligible studies have investigated the albumin ratio, which is widely considered to be a valid measure of BBB disruption. The albumin ratio was increased in patients with schizophrenia spectrum disorders and bipolar disorder, while it did not differ significantly between patients with major depression and controls. The latter finding may be due to fewer eligible cases with major depression. A previous meta-analysis, which gathered affective disorders into one group, found an increased albumin ratio in patients with affective disorders compared to healthy controls (Orlovska-Waast et al., 2019). In addition, the above mentioned previous meta-analysis investigated CSF albumin and IgG and made the same findings as the current study (Orlovska-Waast et al., 2019).

Our meta-analysis revealed that multiple CSF Aβ isoforms were decreased in patients with schizophrenia spectrum disorders and major depression. In Alzheimer's disease and other conditions, brain amyloid deposition, which is inversely related to CSF Aβ, has been identified as a potential contributor to BBB pathology (Biron et al., 2011; Gosselet et al., 2013; Hartz et al., 2012). Specifically, Aβ may trigger cerebral angiogenesis and affect the expression of tight junctions and MMPs, thereby causing BBB disruption (Biron et al., 2011; Gosselet et al., 2013; Hartz et al., 2012). No previous meta-analyses have examined MMPs and TIMPs in severe mental disorders, and the finding of increased levels of certain MMPs in patients with schizophrenia spectrum disorders and bipolar disorder may prove important, since MMPs contribute to BBB pathology and neuroinflammation (Rempe et al., 2016). As part of a complex system of regulation, TIMPs inhibit MMP activity and prevent excessive tissue degradation. The current study revealed that levels of TIMPs did not differ between patients and controls. The fact that the increases in levels of certain MMPs are not accompanied by increases in TIMPs suggests that MMP activity, and not just levels of MMPs, are increased. Similarly, this is the first meta-analysis examining CAMs in severe mental disorders. We found increased blood levels of sP-selectin in patients with schizophrenia spectrum disorders, increased blood levels of sICAM1 and sP-selectin in patients with bipolar disorder and potentially increased blood levels of sICAM1 and sE-selectin in patients with major depression. Although CAMs are not specific for the endothelial cells of the BBB, they reflect migration of immune cells across the BBB and serve as markers of both peripheral and central inflammation (Muller, 2019; Pollak et al., 2018).

Interestingly, the endothelial glycocalyx layer, which mainly consists of glycoproteins and proteoglycans, exerts an important role in maintaining BBB integrity (Ando et al., 2018; Kutuzov et al., 2018). However, we did not find any eligible studies investigating biomarkers of degradation of the endothelial glycocalyx layer. Considering the potential role of inflammation in the pathogenesis of severe mental disorders, it is notable that inflammatory conditions have been associated with degradation of the endothelial glycocalyx layer (Kolarova et al., 2014).

4.1. Conclusion and perspectives

The current systematic review and meta-analysis implicates occurrence of BBB pathology in patients with severe mental disorders compared to healthy controls. Dysfunctional brain function and structure have previously been identified as substrate for severe mental disorders (Drevets et al., 2008). Accordingly, considering the functions of the BBB in maintaining CNS homeostasis and protecting the brain from toxins and pathogens, BBB pathology is expected to contribute to the pathogenesis of severe mental disorders. However, definite conclusions cannot be drawn since findings of the included studies varied considerably and since important confounders were often not accounted for. Furthermore, the investigated biomarkers are indirect measures of BBB pathology and therefore have a degree of uncertainty. This uncertainty may be reduced in future studies thanks to technological progress in neuroimaging techniques (Veksler et al., 2014), which can now be used in combination with blood and CSF biomarkers to improve the understanding of the role of the BBB in severe mental disorders.

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Declaration of competing interests

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2020.100102.

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