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REVIEW ARTICLE

The association of blood biomarkers with cerebral white matter and myelin content in bipolar disorder: a systematic review

Mohammad **Ali**,[1,2] Renata **Husnudinov**,[3] Bianca **Wollenhaupt-Aguiar**,[2,4] Benicio N. **Frey**[4,5]

[1]*Neuroscience Graduate Program, McMaster University, Hamilton, ON, Canada.* [2]*Centre for Clinical Neurosciences, McMaster University, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada.* [3]*Department of Psychiatry, University of Toronto, Toronto, ON, Canada.* [4]*Mood Disorders Program, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada.* [5]*Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada.*

Objectives: Evidence from diffusion tensor imaging (DTI) and postmortem studies has demonstrated white-matter (WM) deficits in bipolar disorder (BD). Changes in peripheral blood biomarkers have also been observed; however, studies evaluating the potential relationship between brain alterations and the periphery are scarce. The objective of this systematic review is to investigate the relationship between blood-based biomarkers and WM in BD.
Methods: PubMed, Embase, and PsycINFO were used to conduct literature searches. Cross-sectional or longitudinal studies reporting original data which investigated both a blood-based biomarker and WM (by neuroimaging) in BD were included.
Results: Of 3,750 studies retrieved, 23 were included. Several classes of biomarkers were found to have a significant relationship with WM in BD. These included cytokines and growth factors (interleukin-8 [IL-8], tumor necrosis factor alpha [TNF-α], and insulin-like growth factor binding protein 3 [IGFBP-3]), innate immune system (natural killer cells [NK]), metabolic markers (lipid hydroperoxidase, cholesterol, triglycerides), the kynurenine (Kyn) pathway (5-hydroxyindoleacetic acid, kynurenic acid [Kyna]), and various gene polymorphisms (serotonin-transporter-linked promoter region).
Conclusion: This systematic review revealed that blood-based biomarkers are associated with markers of WM deficits observed in BD. Longitudinal studies investigating the potential clinical utility of these specific biomarkers are encouraged.
Systematic review registration: PROSPERO CRD42021279246.

Keywords: Cytokines; innate immune system; kynurenine; myelin; genetics

Introduction

Bipolar disorder (BD) is a lifelong illness characterized by episodes of mania or hypomania that alternate with episodes of depression,[1] with a peak age at onset of 15-24 years.[2] BD affects about 3% of the world's population and ranks among the top 20 leading disease causes of disability worldwide.[3,4] As the first episode of BD is often depressive and subsequent depressive episodes typically last longer than manic or hypomanic episodes, BD is commonly misdiagnosed as major depressive disorder.[5]

BD is known to be comorbid with several chronic medical conditions, such as metabolic syndrome, obesity, type 2 diabetes, and migraines.[5,6] Furthermore, psychiatric conditions such as substance use, anxiety, attention deficit-hyperactivity disorder, and personality disorders have been found to be associated with BD, all of which may increase the burden of illness and worsen prognosis.[5]

Individuals with BD have been found to experience difficulties in cognitive functioning and emotional processing – observations that suggest underlying abnormalities in brain anatomy, structure, and function.[7] While the precise etiologies of BD are not known, evidence from numerous functional magnetic resonance imaging (fMRI) studies have shown that functional connectivity is impaired in BD,[7] and postmortem and diffusion tensor imaging (DTI) studies have demonstrated microstructural abnormalities in white matter (WM).[7-10] Interestingly, deficits in WM microstructure have been found to correlate with poorer performance in attention, working memory, information processing, psychomotor coordination, and executive function, suggesting a possible mechanism through which cognitive deficits may occur.[8,11]

Correspondence: Benicio N. Frey, 100 West 5th Street, Suite C124, Hamilton, ON L8N 3K7, Canada.
E-mail: freybn@mcmaster.ca
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While neuroimaging studies have provided critical information on underlying pathophysiologic processes in BD, this technology is relatively expensive and is not readily accessible in most clinical settings. Blood-based biomarkers – which includes different classes of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), oxidative stress markers, and innate immune system markers – have also been of interest in understanding the physiological basis and consequences of BD.[12-14] However, whether blood-based biomarkers are a reliable source to assess changes within the brain is an ongoing debate. Several studies have demonstrated some correlation between biomarkers in blood and cerebrospinal fluid (CSF) in mood disorders, providing some validity for the use of peripheral markers. For example, significant associations between blood and CSF markers have been observed for brain-derived neurotrophic factor and metabolites within the kynurenine (Kyn) pathway.[15,16] In addition, the blood–brain barrier, a system of endothelial cells that regulates the passage of substances into and out of the brain and spinal cord, may have abnormally high permeability in individuals with BD, which would allow small molecules from the periphery to enter the brain.[17] Furthermore, peripheral blood is more accessible than CSF, and the fact that specific blood markers are associated with their CSF levels suggests there may be an association between blood-based biomarkers and WM. Unfortunately, there is still limited research on the relationship between the brain and the periphery. Investigating this relationship further can help to improve our knowledge of BD, since biochemical compounds within the body may serve as the basis for the morphological changes observed in the brain.[18] Thus, the objective of this systematic review is to investigate the association between blood-based biomarkers and WM abnormalities in BD, setting the stage for future studies to test the clinical utility of peripheral markers (e.g., prediction of treatment response, risk stratification, etc.).

Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and is registered with the International Prospective Register of Systematic Reviews (PROSPERO) under ID CRD42021279246.

Search strategy

The PubMed, Embase, and PsycINFO databases were searched without date, language, or geographical restrictions. The search was conducted on August 1, 2023, using the following syntax: (neuroinflammation OR pro-inflammatory OR inflammation OR microglia activation OR cytokines OR microgl* OR astrocyt* OR astrogli* OR chemokine* OR interleukin OR kynurenin* OR oxidative stress OR biological markers OR biological marker OR biomarker OR blood biomarker) AND (bipolar disorder OR bipolar disorders OR affective disorder OR affective disorders OR manic OR mania OR cyclothymic OR manic-depressive disorder OR hypomanic OR hypomania OR depression OR depress*) AND (white matter OR myelin OR oligodendro* OR axon*).

Eligibility criteria

In this systematic review, cross-sectional or longitudinal studies reporting original data which investigated both a blood-based biomarker and WM neuroimaging in BD samples were included. Reviews, randomized and non-randomized controlled trials, case reports, abstracts, conference presentations, and editorials were excluded.

The studies retrieved in the literature search were evaluated independently by two blinded reviewers (MA and RH) using Rayyan software[19] to determine if they met the predefined inclusion criteria. Any conflicts between the reviewers were resolved by a third-party reviewer (BWA). The reference lists of the included studies were also assessed.

Data extraction

The following data were extracted from each paper by two researchers (MA and RH): name, country, year, aim of the study, participant information (e.g., sample size, control vs. BD), blood biomarker assessed, and main result regarding the relationship between the blood marker and brain WM and/or myelin content in BD.

Results

Selection of studies

The literature search yielded 3,746 studies, of which 1,009 were duplicates. Hand searches were also conducted (n=4). Ultimately, 2,741 articles were screened, of which 2,713 were excluded based on publication type, study outcome, and/or design. Twenty-eight potentially eligible studies were reviewed in full; five of these were deemed ineligible as they did not include both a blood-based biomarker and WM neuroimaging. Thus, 23 studies were included in the current systematic review. The PRISMA flow diagram is shown in Figure 1.

Study characteristics

Among the 23 studies included, publication dates ranged from 2008 to 2023. Sixteen studies were conducted in Italy, three in the United States or Canada, and one each in Spain, the Republic of Korea, China, and Brazil. Total sample sizes ranged from 31 to 200 participants. All studies assessed the association between blood-based biomarkers and a neuroimaging technique measuring WM and myelin content in BD. The characteristics of the included studies are described in Table 1. Quality assessment of the included studies was conducted using the Newcastle-Ottawa Scale (NOS), as shown in Table 2.

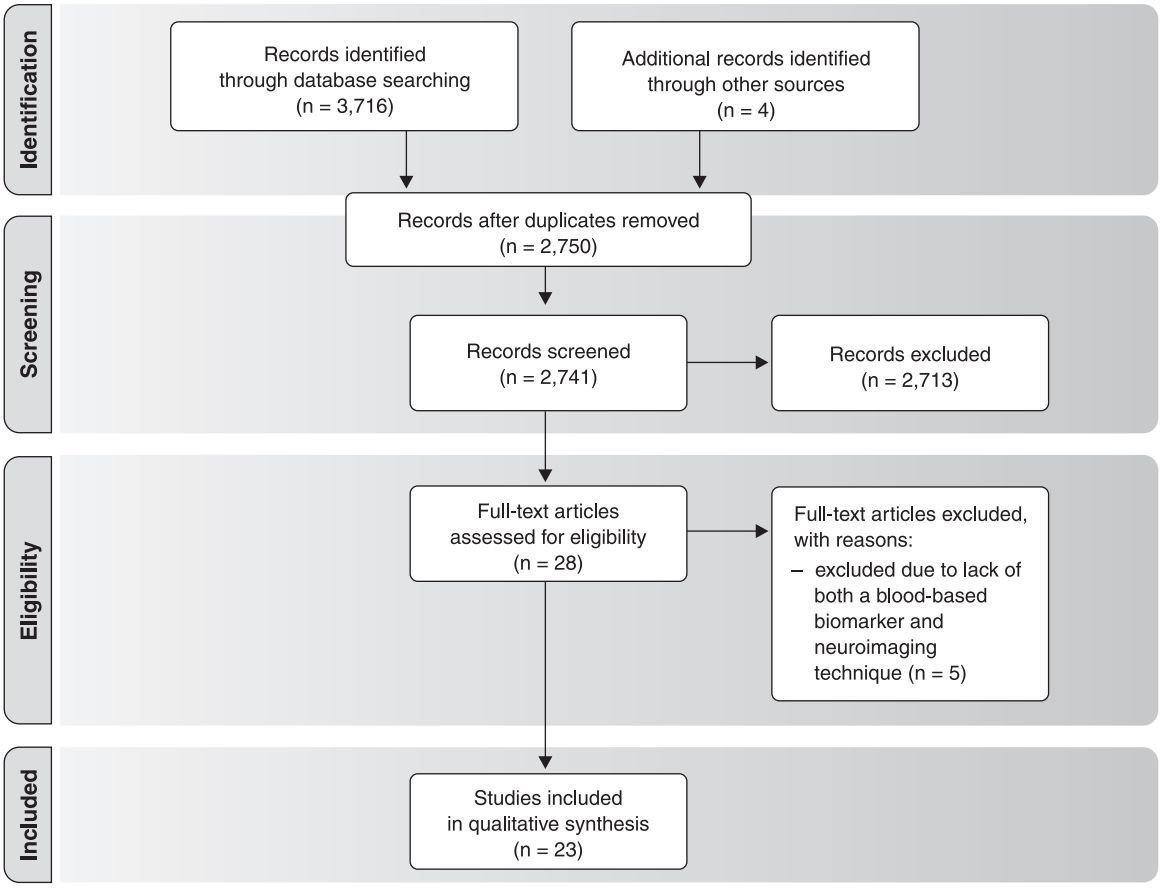

Figure 1 Adapted Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram summarizing the findings of each of the individual stages of the literature search and excluded and included studies.[20]

White matter and blood-based biomarkers in bipolar disorder

Tryptophan breakdown

Three studies investigated the relationship between tryptophan (Trp) breakdown and WM dysfunction in BD.[22,24,39] All three investigated measures of WM, using either magnetic resonance imaging (MRI) or DTI, focusing on axial, mean, and radial diffusivity (RD) and fractional anisotropy (FA).

Poletti et al.[24] analyzed peripheral levels of Trp, Kyn, and Trp-to-Kyn ratios in relation to gray-matter and WM volume in BD and healthy controls. The samples included 72 participants with BD and 33 healthy controls, who were imaged using a 3T Philips scanner to determine gray- and WM volume. MRI analysis demonstrated significant negative associations between Kyn/Trp ratio and the volume of multiple brain regions including the amygdala, corpus callosum, and cortical thickness in frontoparietal regions. An earlier study conducted by Poletti et al.[22] investigated peripheral levels of Trp and several catabolites including Kyn, kynurenic acid (Kyna), 3-hydroxykynurenine (3-HK), and 5-hydroxyindoleacetic acid (5-HIAA) in 22 participants with BD and 15 healthy controls. WM integrity was assessed using DTI and tract-based spatial statistics with threshold-free cluster enhancement. Their analysis found reduced levels of Kyna and 5-HIAA in BD, which demonstrated a significant association with multiple WM regions including the cingulum bundle, inferior and superior longitudinal fasciculus, corpus callosum, uncus, anterior thalamic radiation, and corona radiata. Lastly, Comai et al.[39] investigated the relationship between the Kyn pathway, cytokines, and WM in BD and unipolar depression. Their sample included 100 participants with unipolar depression and 66 with BD. To assess WM integrity, the investigators used DT-MRI and analyzed 27 different markers (Table 1). A negative association was found between Kyn/Trp ratio and the corpus callosum, body of the corpus callosum, inferior fronto-occipital fasciculus, corticospinal tract, and external capsule. In addition, Trp was found to have a negative association with FA in the external capsule, corpus callosum, and body of the corpus callosum. Regarding the cytokines of interest, only IL-1β was found to be negatively associated with WM tracts, which included the corpus callosum and inferior fronto-occipital fasciculus.

Polymorphisms

Four studies investigated the relationship between genetic polymorphisms and WM microstructure in BD.[25,27,35,36]

Table 1 Characteristics of included studies evaluating blood-based biomarkers and white-matter integrity by neuroimaging

First author	Study title (country)	Sample information (sample size, control vs. BD)	Neuroimaging	Peripheral marker(s)	WM association	Were participants medicated?
Furlan[21]	Natural killer cells protect white matter integrity in bipolar disorder (Italy)	BD: 30 HC: 36	DTI, fMRI	NK cells	↑ FA	Yes
				CD56+,TNF-α+, IFN-g+, GMCSF+	↑ FA ↓ RD and MD	
Poletti[22]	Kynurenine pathway and white matter microstructure in bipolar disorder (Italy)	BD: 22 HC: 15	DTI	Kyna	↓ RD, MD	Yes
				5-HIAA	↑ AD, RD, and MD	
				Trp, Kyn, 3-HK	No association	
Benedetti[23]	Inflammatory cytokines influence measures of white matter integrity in bipolar disorder (Italy)	BD: 31 HC: 0	DTI	TNF-α, IL-8, IFN-g, IL-10 (cytokines), IGFBP-2 and PDGF-BB (growth factors)	↓ FA ↑ MD and RD	Yes
				IL-5, IL-6, IL-7, IL-8, MCP-1, CXCL10, PTX3, G-CSF, VCAM-1, ICAM-1, IL-1RA, IL-2RA, BDNF, S100B, SCF, EGF, VEGF	No association	
Poletti[24]	Grey and white matter structure associates with the activation of the tryptophan to kynurenine pathway in bipolar disorder (Italy)	BD: 72 HC: 36	DTI	Kyn/Trp-ratio	↓ FA (in depressed group)	Yes
				Kyn	↑ FA (in manic group)	
				Trp	No association	
Poletti[25]	SREBF-2 polymorphism influences white matter microstructure in bipolar disorder (Italy)	BD: 93 HC: 0	DTI	SREBF-2 A homozygotes	↓ FA (compared to G carriers) ↑ RD (compared to G homozygotes)	Yes
				SREBF-1 polymorphism	No association	
Han[26]	Whole-exome sequencing identifies variants associated with structural MRI markers in patients with bipolar disorders (Korea)	BD: 53 HC: 82	DTI and T1-weighted	T allele homozygote of KMT2C rs4639425	↓ FA ↑ MD and RD	Yes
Bollettini[27]	Clock genes associated with white matter integrity in depressed bipolar patients (Italy)	BD: 140 HC: 0	DTI	CLOCK rs1801260*C carriers	↑ MD (compared to T/T homozygotes)	Yes
				PER3-4/4 homozygotes	↑ RD (compared to PER3-5/5 homozygotes) ↓ FA (compared to PER3-5/5 homozygotes)	
Papiol[28]	Gray matter deficits in bipolar disorder are associated with genetic variability at interleukin-1 beta gene (2q13) (Spain)	BD: 20 HC: 45	DTI	IL-1 cluster genetic variability	No association	Yes
Lotrich[29]	The relationship between interleukin-1 receptor antagonist and cognitive function in older adults with bipolar disorder (United States)	BD: 21 HC: 26	DTI	IL-1RA	No association	N/A

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Table 1 (*continued*)

First author	Study title (country)	Sample information (sample size, control vs. BD)	Neuroimaging	Peripheral marker(s)	WM association	Were participants medicated?
Magioncalda[30]	White matter microstructure alterations correlate with terminally differentiated CD8+ effector T cell depletion in the peripheral blood in mania: combined DTI and immunological investigation in the different phases of bipolar disorder (Italy)	BD: 60 HC: 20	DTI	CD8+ terminally differentiated effector memory and CD8+ IFN-g+ T cells	↑ FA (in mania) ↓ RD (in mania)	Yes
				CD4+ T cells and subpopulations CD8+ effector memory T cells	No association	
Poletti[31]	Th17 cells correlate positively to the structural and functional integrity of the brain in bipolar depression and healthy controls (Italy)	BD: 25 HC: 21	DTI and fMRI	CD4+CCR6+CXCR3CCR4+CCR10CD161+ (Th17) cells	↑ FA	Yes
				CD4+CD25+FoxP3 (Treg) cells	↑ RD and MD	
				Th1, Th2, Th22 cells	No association	
Reckziegel[32]	Bipolar disorder: an association of body mass index and cingulate gyrus fractional anisotropy not mediated by systemic inflammation (Brazil)	BD: 35 HC: 66	DTI	CRP	No association	Yes
Mazza[33]	Body mass index associates with white matter microstructure in bipolar depression (Italy)	BD: 164 HC: 0	DTI	Serum triglycerides	↓ FA ↑ AD, RD, and MD	Yes
				Serum glucose	↓ FA ↑ RD and MD	
				Serum cholesterol	↓ FA	
Benedetti[34]	Homer 1 gene variant influences brain structure and function, lithium effects on white matter, and antidepressant response in bipolar disorder: A multimodal genetic imaging study (Italy)	BD: 199 HC: 0	Structural MRI of grey and WM, and 50 with BOLD functional MRI of emotional processing, and DTI	Rs7713917 AA homozygotes	↓ FA (compared to rs7713917*G carriers)	Yes
Versace[18]	Elevated serum measures of lipid peroxidation and abnormal prefrontal white matter in euthymic bipolar adults: toward peripheral biomarkers of bipolar disorder (United States + Canada)	BD: 43 HC: 19	DTI	LPH	↓ FA ↑ RD	Yes
				4-HNE	No association	
Benedetti[35]	Lithium and GSK3-β Promoter Gene Variants Influence White Matter Microstructure in Bipolar Disorder (Italy)	BD: 70 HC: 0	DTI	GSK3 rs334558*C variant	↑ AD and MD (compared to T/T homozygotes)	Yes
Benedetti[36]	White matter microstructure in bipolar disorder is influenced by the serotonin transporter gene polymorphism 5-HTTLPR (Italy)	BD: 140 HC: 0	DTI	5-HTTLPR*s carriers	↑ RD and MD (compared to l/l homozygotes)	Yes

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Table 1 (*continued*)

First author	Study title (country)	Sample information (sample size, control vs. BD)	Neuroimaging	Peripheral marker(s)	WM association	Were participants medicated?
Mazza[37]	Insulin resistance disrupts white matter microstructure and amplitude of functional spontaneous activity in bipolar disorder (Italy)	BD: 92 HC: 0	DTI and fMRI	Insulin	↓FA ↑ RD and MD	Yes
				Glucagon	No association	
Aggio[38]	Neurofilaments light: Possible biomarker of brain modifications in bipolar disorder (Italy)	BD: 45 HC: 29	DTI	NfL	↑ AD	Yes
Comai[39]	Selective association of cytokine levels and kynurenine/tryptophan ratio with alterations in white matter microstructure in bipolar but not in unipolar depression (Italy)	MDD: 100 BD: 66	DT-MRI	IL-1β, Trp, Kyn,	↓ FA	Yes
				IL-1rα, IL-2, IL-4, IL-6, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, IFN-γ , TNF-α, CCL2, CCL3, CCL4, CCL5, CCL11, C-X-C motif chemokine CXCL10, FGF, G-CSF, GM-CSF, PDGF-B, VEGF	No association	
Poletti[40]	Long-term effect of childhood trauma: Role of inflammation and white matter in mood disorders (Italy)	MDD: 100 BD: 100	DT-MRI	IL-2, CCL3	↓ FA	Yes
				IL-1β, IL-1rα, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, IFN-γ, TNF-α, CCL3, CCL4, CCL5, CCL11, CXCL10, FGF basic, G-CSF, GM-CSF, PDGF-B, VEGF	No association	
Bond[41]	Association of total peripheral inflammation with lower frontal and temporal lobe volumes in early-stage bipolar disorder: A proof-of-concept study (Canada)	BD: 25 HC: 14	3T-MRI	TNF-α, IFN-γ, MCP-1, IL-1α, IL-2, IL-6, IL-8, IL-4, IL-10	↓ WM	Yes
Jiang[42]	Altered levels of plasma inflammatory cytokines and white matter integrity in bipolar disorder patients with suicide attempts (China)	BD: 38 HC: 26	DTI	IL-1b, IL-6, TNF-α	No association	Yes

3-HK = 3-hydroxykynurenine; 4-HNE = 4-hydroxy-2-nonenal; 5-HIAA = 5-hydroxyindoleacetic acid; 5-HTTLPR = serotonin-transporter-linked promoter region; AD = axial diffusivity; BD = bipolar disorder; BDNF = brain-derived neurotrophic factor; BOLD = blood oxygenation level dependent; CCL = C-C motif ligand; CD = neural cell adhesion molecule; CLOCK = circadian locomotor output cycles kaput; CRP = C-reactive protein; CXCL10 = C-X-C motif chemokine 10; DTI = diffusion tensor imaging; EGF = epidermal growth factor; FA = fractional anisotropy; FGF = fibroblast growth factor; fMRI = functional magnetic resonance imaging; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; GSK3-β = glycogen synthase kinase-3 beta; HC = healthy control; ICAM = intercellular adhesion molecule; IGFBP-2 = insulin-like growth factor-binding protein 2; IL = interleukin; INF = interferon; KMT2C = lysine methyltransferase 2C; Kyn = kynurenine; Kyna = kynurenic acid; LPH = lipid hydroperoxides; MCP-1 = monocyte chemoattractant protein-1; MD = mean diffusivity; MRI = magnetic resonance imaging; N/A = not available; NfL = neurofilament light chain; NK = natural killer; PDGF-B = platelet-derived growth factor beta; PDGF-BB = platelet derived growth factor; PER3 = Period3; PTX = pentraxin-related protein; RA = receptor antagonist; RD = radial diffusivity; S100B = S100 calcium binding protein B; SCF = stem cell factor; SREBF = sterol regulatory element binding transcription factor; T cells = thymus-derived cells; Th = T helper; TNF-α = tumor necrosis factor alpha; Trp = tryptophan; VCAM-1 = vascular cell adhesion protein 1; VEGF = vascular endothelial growth factor; WM = white matter.

Table 2 Quality assessment of included studies using the Newcastle-Ottawa scale

First author	Manuscript title	Representativeness	Selected group	Sample size	Diagnosis	Groups	Measurement method	Statistical test	Total
Furlan[21]	Natural killer cells protect white matter integrity in bipolar disorder	1	1	0	1	2	2	1	8
Poletti[22]	Kynurenine pathway and white matter microstructure in bipolar disorder	1	1	0	2	2	2	1	9
Benedetti[23]	Inflammatory cytokines influence measures of white matter integrity in bipolar disorder	1	1	0	1	2	2	1	8
Poletti[24]	Grey and white matter structure associates with the activation of the tryptophan to kynurenine pathway in bipolar disorder	1	1	0	2	2	2	1	9
Poletti[25]	SREBF-2 polymorphism influences white matter microstructure in bipolar disorder	1	1	0	2	2	2	1	9
Han[26]	Whole-exome sequencing identifies variants associated with structural MRI markers in patients with bipolar disorders	1	1	0	2	2	2	1	9
Bollettini[27]	Clock genes associated with white matter integrity in depressed bipolar patients	1	1	0	2	2	2	1	9
Papiol[28]	Gray matter deficits in bipolar disorder are associated with genetic variability at interleukin-1 beta gene (2q13)	0	1	0	2	2	2	1	8
Lotrich[29]	The relationship between interleukin-1 receptor antagonist and cognitive function in older adults with bipolar disorder	1	1	1	2	2	2	1	10
Magioncalda[30]	White matter microstructure alterations correlate with terminally differentiated CD8+ effector T cell depletion in the peripheral blood in mania: combined DTI and immunological investigation in the different phases of bipolar disorder	1	1	0	2	2	2	1	9
Poletti[31]	Th17 cells correlate positively to the structural and functional integrity of the brain in bipolar depression and healthy controls	1	1	0	2	2	2	1	9
Reckziegel[32]	Bipolar disorder: an association of body mass index and cingulate gyrus fractional anisotropy not mediated by systemic inflammation	1	1	0	2	2	2	1	9

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Table 2 (*continued*)

First author	Manuscript title	Representativeness	Selected group	Sample size	Diagnosis	Groups	Measurement method	Statistical test	Total
Mazza[33]	Body mass index associates with white matter microstructure in bipolar depression	1	1	0	2	2	0	1	7
Benedetti[34]	Homer 1 gene variant influences brain structure and function, lithium effects on white matter, and antidepressant response in bipolar disorder: A multimodal genetic imaging study	1	1	0	2	2	2	1	9
Versace[18]	Elevated serum measures of lipid peroxidation and abnormal prefrontal white matter in euthymic bipolar adults: toward peripheral biomarkers of bipolar disorder	1	1	0	2	2	2	1	9
Benedetti[35]	Lithium and GSK3-β promoter gene variants influence white matter microstructure in bipolar disorder	1	1	1	2	2	2	1	10
Benedetti[36]	White matter microstructure in bipolar disorder is influenced by the serotonin transporter gene polymorphism 5-HTTLPR	1	1	0	2	2	2	1	9
Mazza[37]	Insulin resistance disrupts white matter microstructure and amplitude of functional spontaneous activity in bipolar disorder	1	1	0	2	2	2	1	9
Aggio[38]	Neurofilaments light: Possible biomarker of brain modifications in bipolar disorder	1	1	0	2	2	2	1	9
Comai[39]	Selective association of cytokine levels and kynurenine/tryptophan ratio with alterations in white matter microstructure in bipolar but not in unipolar depression	1	1	0	2	2	2	1	9
Poletti[40]	Long-term effect of childhood trauma: Role of inflammation and white matter in mood disorders	1	1	0	1	2	2	1	8
Bond[41]	Association of total peripheral inflammation with lower frontal and temporal lobe volumes in early-stage bipolar disorder: A proof-of-concept study	1	1	0	2	2	2	1	9
Jiang[42]	Altered levels of plasma inflammatory cytokines and white matter integrity in bipolar disorder patients with suicide attempt	1	1	0	2	2	2	1	9

Scale range: 0-10 (0 = lowest quality, 10 = highest quality). Adapted from Modesti et al.[43]

Benedetti et al.[36] investigated the effects of the serotonin-transporter-linked promoter region polymorphism (5-HTTLPR) on WM microstructure in BD. The sample included 140 inpatients during a depressive episode. Participants who carried the short allele of the 5-HTTLPR polymorphism demonstrated significantly higher RD and mean diffusivity (MD) in comparison to homozygotes of the long allele for the serotonin transporter gene, which is more common. Higher RD and MD that is perpendicular to the main axis of a WM tract is believed to represent increased space between WM fibers, which may be due to demyelination. Poletti et al.[25] investigated gene polymorphisms in sterol regulatory element binding protein transcriptional factors 1 and 2 (SREBF-1 and SREBF-2), which regulate cholesterol and lipid metabolism. The study sample included 93 participants with BD who were imaged using DTI. In several brain regions, including the cingulum, corpus callosum, superior and inferior longitudinal fasciculi, and anterior thalamic radiation, the rs1052717 A/A genotype was associated with increased RD and reduced FA, which demonstrate a potential role of the SREB pathway in the demyelination process in BD. FA represents the degree of anisotropic diffusion, which is hypothesized to reflects the degree of myelination and the integrity of WM tracts. Thus, lower FA values are believed to reflect lower levels of myelin.[44] Bollettini et al.[27] investigated *CLOCK* 3111 T/C and Period3 (*PER3*) polymorphisms and DTI measures of WM microstructure in 140 participants with BD type 1. They performed tract-based spatial statistics analysis on DTI measures of WM for each of the polymorphisms of interest. Their results demonstrated that individuals with the *CLOCK* C variant, in comparison to *CLOCK* T homozygotes, displayed a widespread increase of MD in multiple WM tracts. In addition, participants who were $PER3^{4/4}$ homozygotes in comparison to those who were $PER3^{5/5}$ homozygotes had significantly increased RD and decreased FA in multiple WM tracts, which represents lower levels of myelination.

Lastly, Benedetti et al.[35] investigated the relationship between long-term lithium use and the GSK3-β promoter rs334558 polymorphism on WM microstructure in BD. Their sample included 70 participants with BD in a current depressive episode, who were imaged using DTI. Their results demonstrated that the GSK3-β rs334558*C gene-promoter variants and long-term lithium use increased axial diffusivity (AD) in many WM tracts such as the corpus callosum, forceps major, anterior and posterior cingulum bundle bilaterally including its hippocampal part, left superior and inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, bilateral corticospinal tract, left posterior thalamic radiation, and bilateral superior and posterior corona radiata. AD value represents the integrity of axons and the myelin sheath; lower values are thought to reflect axonal loss and/or loss of bundle coherence. These results suggest that the presence of the polymorphism in conjunction with lithium use reduces the activity of GSK3-β, which has been observed to negatively impact imaging markers of WM integrity.

Gene expression

Two studies investigated the association between WM structure and several genes, including Homer1 and IL-1 cluster genes. Benedetti et al.[34] investigated the AA risk genotype of the Homer rs7713917 A > G SNP in 199 inpatients during a major depressive episode. Of the 199, 147 were imaged using structural MRI, 50 with blood oxygenation level dependent (BOLD) functional MRI, and 122 with DTI to measure FA, RD, and MD. Patients who had the AA genotype displayed lower FA in bilateral frontal WM tracts including the body of the corpus callosum, superior longitudinal fasciculus, forceps minor, right cingulum (including hippocampal regions), and in the left hemisphere, the uncinate fasciculus, anterior thalamic radiation, inferior fronto-occipital fasciculus, and anterior and superior corona radiata. Papiol et al.[28] examined the relationship between IL-1 cluster (chromosome 2q13) genetic variability, specifically IL-1B and IL-1RN genes, and brain morphology in 20 participants with BD. The participants were imaged using structural MRI to obtain data for whole brain gray matter and WM. There were no significant associations between the cluster of genes and brain WM.

Innate immune system

Three studies investigated the relationship between the innate immune system and WM integrity in BD.[21,30,31] All three of these found significant relationships between circulating levels of cells involved in the innate immune system and WM integrity. Furlan et al.[21] explored the relationship between levels of circulating natural killer (NK) cells and WM microstructure in patients with BD. The study included 30 patients with BD and 36 healthy controls. Researchers conducted multiparameter cytofluorometry analysis of NK (CD56+) subpopulations, as well as DTI and tract-based spatial statistics. Circulating NK cells had a positive association with DTI measures of FA; specifically, CD56+TNFa+, CD56+INFg+, and CD56+GMCSF+ cells correlated positively with FA measures, and inversely with RD and MD measures.

Magioncalda et al.[30] investigated the relationship between peripheral blood levels of CD4+ and CD+ T cells (and their subpopulations and cytokines) and WM structure. These factors were further investigated across each mood state of BD. The study sample consisted of 60 patients with BD, of which 20 were in mania, 20 in depression, and 20 euthymic. The study also included 20 healthy controls. There was a significant direct relationship between decreased FA values and reduced frequencies of circulating CD8+ terminal effector memory and CD8 + interferon gamma (IFNγ) + T cells. Further, there was an inverse relationship between increased RD values and reduced frequencies of these same cell subpopulations. Finally, there was a specific correlation between FA-RD abnormalities in the body of the corpus callosum and left superior corona radiata with reduced circulating CD8+ terminal effector memory and CD8 + IFNγ + T cells in the manic phase. These relationships were not found in patients who were in the depressed or euthymic phases.

Poletti et al.[31] studied the relationship between T helper cells and WM structure in 25 depressed individuals with BD and 21 healthy participants. The study used flow cytometric analyses to determine percentages of T helper cells and their subpopulations, and DTI with tract-based spatial statistics to analyze WM structure. A positive correlation between the frequency of circulating pro-inflammatory Th17 cells and FA was observed in patients and healthy controls alike, while the frequency of circulating anti-inflammatory T regulatory cells correlated positively with higher RD and MD in patients.

Metabolic markers

Three studies investigated the relationship between body mass index (BMI) and indexes of WM integrity. Mazza et al.[33] investigated the relationship between BMI and WM abnormalities in 164 depressed participants with BD. The authors calculated the participants' BMI, measured serum triglycerides, glucose, and cholesterol, and performed DTI. BMI was found to correlate negatively with WM. Specifically, BMI correlated negatively with FA in several WM tracts in the brain such as the bilateral anterior thalamic radiation, bilateral anterior corona radiata, and right inferior fronto-occipital fasciculus, and positively with RD and MD in the corpus callosum. A positive correlation was also found between BMI and AD in the left superior corona radiata and the left anterior thalamic radiation. Versace et al.[18] investigated the relationship between peripheral measures of lipid peroxidation (serum measures of lipid damage) and WM integrity. The study sample consisted of 24 patients with BD and 19 healthy controls. Researchers conducted DTI and probabilistic tractography to compare FA, RD, and longitudinal diffusivity (L1), and examined serum lipid peroxidation via levels of lipid hydroperoxides (LPH, an early-stage biomarker of lipid peroxidation) and 4-hydroxy-2-nonenal (4-HNE, a late-stage biomarker of lipid peroxidation). Analysis revealed that patients with BD showed significantly greater RD and reduced RA overall compared to controls. LPH variance was found to explain 59% of the variance in FA, and 51% of the variance in RD in WM tracts. There were no differences between groups in 4-HNE levels.

Lastly, Reckziegel et al.[32] investigated BMI and C-reactive protein (CRP) and its association with WM in 35 participants with BD and 66 healthy controls. They measured WM integrity using DTI, focusing on FA. BMI was able to predict FA in several brain regions in the BD group, but when CRP was added to the analysis, it did not mediate the association between BMI and FA.

Cytokines and growth factors

Five studies investigated the relationship between cytokines and WM in BD. Across the five studies, certain cytokines were found to be associated with WM, while others were not. Specifically, Benedetti et al.[23] investigated 22 different analytes in the serum of 31 participants with BD who had experienced a major depressive episode. The authors used DTI and whole brain tract-based spatial statistics with threshold-free cluster enhancement to measure WM integrity, focusing on AD, RD, MD, and FA. Their results found IL-8, TNF-α, IFN-γ and IL-10, and the growth factors insulin-like growth factor-binding protein 2 (IGFBP-2) and platelet-derived growth factor-BB (PDGF-BB) were significantly correlated with higher RD, MD, and lower FA in many WM tracts within the brain. These regions included the superior and inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, cingulum, uncinate, forceps, thalamic radiation, corona radiata, corpus callosum, and internal capsule. Poletti et al.[40] investigated the association between adverse childhood experiences, inflammatory markers, and WM integrity using DT-MRI. The sample included 200 participants (100 MDD and 100 BD) and several classes of markers were investigated (Table 1). The authors analysis found that CCL3 was correlated with lower FA in the anterior corona radiata, anterior thalamic radiation, uncinate fasciculus, interior fronto-occipital fasciculus, and forceps minor. In addition, IL-2 was also found to be associated with reduced FA in the corpus callosum, corona radiata, forceps minor, corticospinal tract, and superior longitudinal fasciculus. Bond et al.[41] investigated total peripheral inflammation and WM in 25 BD participants and 14 healthy controls using 3T-MRI. They assessed seven proinflammatory cytokines (TNF-α, IFN-γ, monocyte chemoattractant protein-1, IL-1α, IL-2, IL-6, and IL-8) and two anti-inflammatory cytokines (IL-4 and IL-10) in serum. In the BD sample, increased total inflammation predicted lower left frontal lobe and bilateral temporal lobe WM volume. Lotrich et al.[29] investigated the relationship between WM and serum IL-1 receptor antagonist (IL-1RA) in 21 euthymic BD participants and 26 control participants. The researchers used DTI to obtain data regarding myelin integrity with a focus on FA. Their results demonstrated no correlation between FA and IL-1RA. Lastly, Jiang et al.[42] investigated inflammatory cytokines and WM integrity in BD participants who had attempted suicide. The sample included 36 BD participants and 26 healthy controls. The authors used DTI to measure WM integrity and assessed plasma levels of TNF-α, IL-β, and IL-6; they found no significant association with plasma inflammatory markers and WM integrity in BD.

Other markers

Three studies investigated the relationship between WM structure and other peripheral biomarkers that do not fit into one of the previously discussed categories. Han et al.[26] examined the relationship between single nucleotide variants (SNVs) from whole-exome sequencing (WES) and WM tract integrity in patients with BD. The study sample consisted of 53 patients with BD and 82 healthy controls. The researchers performed WES for genomic DNA obtained from peripheral blood samples, and DTI to obtain WM integrity measures (FA, MD, RD, and AD). This study found that one SNP in the lysine methyltransferase 2C gene (*KMT2C*) was significantly associated with DTI parameters of WM tracts. This gene regulates histone H2 lysine 4 methylation involved in

chromatin remodeling. Specifically, T-allele homozygosity of *KMT2C* rs4639425 was associated with widespread impairment of WM integrity as assessed by RD, MD, and FA. Mazza et al.[37] examined insulin resistance and WM microstructure in 92 BD participants using DTI and fMRI, where they focused on FA, RD, and MD. The study examined serum insulin and glucagon levels and found that insulin was negatively associated with FA and positively correlated with MD and RD. The brain regions found to be associated with insulin included the superior longitudinal fasciculus, superior and inferior fronto-occipital fasciculus, corpus callosum, corticospinal tract, corona radiata, and uncinate fasciculus. Finally, Aggio et al.[41] examined the relationship between neurofilament light chain (NfL) and WM in BD. The study included 45 depressed individuals with BD and 29 healthy controls. The authors used DTI to measure WM microstructure and tract-based spatial statistics to analyze the diffusion data. Their analysis demonstrated a significant positive association between NfL and AD in several tracts within a large cluster, including the superior and inferior longitudinal fasciculus, thalamic radiation, cingulum, corpus callosum, forceps major and minor, corona radiata, and internal and external capsule.

Discussion

This systematic review included 23 studies that covered a wide range of blood-based biomarkers and their association with WM in BD. To our knowledge, this is the first systematic review to combine all data in the published literature to further understand the relationship between WM deficits and blood-based biomarkers in BD. In summary, several peripheral biomarkers have been found to be associated with WM integrity in BD (Table 3).

Tryptophan breakdown

The studies that investigated Trp breakdown found an association between several catabolites and WM integrity in BD participants, suggesting a possible route for WM deficits to develop over time. The primary catabolic route for Trp is the Kyn pathway, with $>$ 95% of Trp being converted into Kyn. The pathway begins with Trp, which is either converted into 5-HT or Kyn; Kyn is then converted either down the neurotoxic arm or the neuroprotective arm of the pathway. The neuroprotective arm includes Kyna, while the neurotoxic arm includes 3-HK and quinolinic acid (QA). Kyna acts as an antagonist of NMDA receptors, which allows for the normal release of glutamate. However, 3-HK and QA have been linked to increased levels of oxidative stress and QA serves as an agonist for NMDA receptors, which promotes over-release of glutamate.[45] Several studies that have investigated the Kyn pathway in BD have found altered levels of its catabolites in comparison to controls.[45,46] Catabolites within the neurotoxic arm are found at higher levels than those of the neuroprotective arm, suggesting a possible neurotoxic effect in the brain.[45] Given the reduced levels of Kyna and the higher conversion of Trp to Kyn, damage to WM is expected in individuals with BD. This may be due to increased oxidative stress and an overabundance of glutamate caused by the imbalance of neurotoxic/neuroprotective catabolites, which leads to excitotoxicity and WM injury.

Table 3 Summary of associations found between blood-based markers and WM in each category discussed

Biomarker group	Correlation with WM
Tryptophan breakdown	Trp, Kyn, 3-HK, 5-HIAA[†] and Kyna,[†] Kyn/Trp[†]
Polymorphisms	5-HTTLPR,[†] SREBF-2 - rs1052717 A/A,[†] CLOCK 3111 C variant,[†] PER3-4/4,[†] GSK3-β rs334558[†] C,[†] Clock T variant, PER3-5/5
Metabolic markers	Serum triglycerides,[†] glucose,[†] cholesterol,[†] CRP, LPH[†]
Innate immune system	NK cells[†]: CD56 + TNF-α, +, CD56 + INFg +, and CD56 + GMCSF +, CD8 + terminal effector memory and CD8 + IFNg + T cells,[†] Th17 cells[†]
Cytokines and growth factors	IL-8,[†] TNF-α,[†] IFN-γ,[†] IL-10,[†] IGFBP-2,[†] PDGF-BB,[†] IL-5, IL-6, IL-7, IL-8, MCP-1, CXCL10, PTX3, G-CSF, VCAM-1, ICAM-1, IL-1RA, IL-2RA, BDNF, S100B, SCF, EGF, VEGF, IL-1RA, IL-1β,[†] IL-1rα, IL-2,[†] IL-4, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, CCL2, CCL3,[†] CCL4, CCL5, CCL11, FGF, G-CSF, GM-CSF, PDGF-B
Gene expression	Homer rs7713917 A $>$ G – AA risk genotype,[†] IL-1 cluster (chromosome 2q13)
Other	4-HNE, KMT2C,[†] NfL,[†] insulin,[†] glucagon

3-HK = 3-hydroxykynurenine; 4-HNE = 4-hydroxy-2-nonenal; 5-HIAA = 5-hydroxyindoleacetic acid; 5-HTTLPR = serotonin-transporter-linked promoter region; BDNF = brain-derived neurotrophic factor; CCL = C-C motif ligand; CD = neural cell adhesion molecule; CLOCK = circadian locomotor output cycles kaput; CRP = C-reactive protein; CXCL10 = C-X-C motif chemokine 10; EGF = epidermal growth factor; FGF = fibroblast growth factor; G-CSF = granulocyte colony stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; GSK3-β = glycogen synthase kinase-3 beta; ICAM = intercellular adhesion molecule; IGFBP-2 = insulin-like growth factor-binding protein 2; IL = interleukin; IFN = interferon; KMT2C = lysine methyltransferase 2C; Kyn = kynurenine; Kyna = kynurenic acid; LPH = lipid hydroperoxides; MCP-1 = monocyte chemoattractant protein-1; NfL = neurofilament light chain; NK = natural killer; PDGF-B = platelet-derived growth factor beta; PDGF-BB = platelet derived growth factor; PER3 = Period3; PTX = pentraxin-related protein; RA = receptor antagonist; S100B = S100 calcium binding protein B; SCF = stem cell factor; SREBF-2 = sterol regulatory element binding transcription factor 2; T cells = thymus-derived cells; Th = T helper; TNF-α = tumor necrosis factor alpha; Trp = tryptophan; VCAM-1 = vascular cell adhesion protein 1; VEGF = vascular endothelial growth factor; WM = white matter.
[†] Significant association with neuroimaging markers of WM.

Polymorphisms and gene expression

While each of the studies that investigated polymorphisms focused on different ones, significant correlations were found between the polymorphisms addressed and WM in BD, which suggests that polymorphism likely has a role in WM microstructure in BD. 5-HTTLPR is a polymorphism within the promotor region of the serotonin transporter encoding gene which has two different variants, long and short. Whether an individual has the long variant or short variant has an impact on the efficacy of serotonin transporters. For example, the short variant results in significantly less serotonin being transported back to the presynaptic neuron in comparison to the long variant, which results in excess serotonin being left in the synaptic cleft to interact with serotonin receptors.[47] As a result, individuals carrying the short variant have been found to display more anxiety-related traits, increased chances of developing suicidal ideation and attempts, and depression.[48,49] This imbalance of serotonin in the synaptic cleft may also explain the correlation found in the study by Benedetti et al.[36]

The Homer family proteins are primarily located in the postsynaptic density (PSD) at glutamatergic excitatory synapses and are coded by three different genes. Homer variants such as homer1 are involved in serotonin-glutamate cross talk.[50] Various studies, such as Benedetti et al.,[36] have shown that genes affecting serotonin affect WM; thus, it is possible that Homer variants such as homer1 might affect WM through this interaction.

Poletti et al.[25] investigated the relationship between the SREBP pathway and myelin in BD. Lipids are essential for the synthesis and maintenance of myelin, as it is primarily composed of lipids and proteins. Cholesterol, one of the primary lipids required to produce myelin, is regulated by SREBP2, while SREBP1 regulates the expression of triglycerides, fatty acids, and phospholipids.[51] With synthesis of myelin being heavily dependent on lipids such as cholesterol and the SREBP pathway regulating the production of lipids, this may explain why Polleti et al.[25] found a correlation between SREBP and WM in BD.

Bollettini et al.[27] found a significant relationship between DTI measures of WM and clock gene polymorphisms in *CLOCK* 3111 T/C and *PER3* in BD. These clock genes have been found to affect sleep; specifically, individuals who are homozygotes of $PER3^{4/4}$ have been shown to sleep later in the evening and have a diminished sleep pressure.[52] In addition, individuals with BD who are carriers of the *CLOCK* rs1801260*C allele have also been shown to have late sleep onset and insomnia.[53] With sleep having a critical role in promoting myelination and oligodendrocyte precursor cell proliferation,[54] polymorphisms in genes that regulate sleep quality may potentially harm WM through disrupted sleep patterns.

Benedetti et al.[35] investigated the GSK3-β promoter rs334558 polymorphism and WM in BD. GSK3-β has multiple roles in cell function, which include cell growth, differentiation, motility, and apoptosis. Increasing the activity of GSK3-β has been shown to increase neuronal apoptosis, while decreasing its function has been found to be neuroprotective.[35] The GSK3-β promoter rs334558 polymorphism and long-term lithium use were found to be associated with lower expression of GSK3-β, which provides a potential mechanism through which the polymorphism and lithium use, combined, increased AD through inhibition of GSK3-β.

Cytokines and growth factors

Several cytokines and growth factors – namely, IL-1β, IL-2, IL-8, TNF-α, IFN-γ, IL-10, C-C motif ligand 3 (CCL3), IGFBP-2, and PDGF-BB – were found to be associated with WM, which suggests that these classes of molecules likely have a role in WM integrity in BD.[23] Cytokines and growth factors have critical roles in cellular communication, growth, and maintenance. Specifically, certain cytokines can affect oligodendrocyte biology. For example, oligodendrocyte progenitor differentiation and survival can be inhibited by pro-inflammatory cytokines such as TNF-α, which can exert cytotoxic effects.[55,56] IFN-γ can also have a detrimental impact on WM by altering metabolic function in oligodendrocytes and reducing the expression of myelin proteins, leading to cell death.[57]

Metabolic markers

Mazza et al.[33] found a relationship between serum triglycerides, glucose, and cholesterol and WM integrity in BD, specifically in patients currently in a depressive episode. These findings support a relationship between BMI and WM integrity in BD, as BMI correlates directly with markers of metabolism such as serum glucose, triglyceride, and cholesterol levels. Thus, the relationship between serum markers and WM integrity in BD may suggest that the underlying processes regulating peripheral levels of these substances may also contribute to the relationship between BMI and WM changes in BD. Obesity overall is known to be a pro-inflammatory state. One mechanism linking obesity with WM changes in BD may be the direct effect of inflammation on WM integrity, as seen by Benedetti et al.,[23] who found a correlation between inflammatory cytokines and WM alterations in BD. Adipose tissue has been found to function as an endocrine organ by secreting pro-inflammatory factors,[58] possibly contributing to the relationship between obesity and WM abnormalities in BD.

Another underlying process may be attributed to insulin resistance seen in diabetes mellitus, a common comorbidity associated with BD. Insulin resistance leads to impaired glucose metabolism and thus elevated peripheral levels of glucose. Insulin receptors are found throughout the brain and are known to play a role in synaptic plasticity and cognitive functions,[33] suggesting that their dysregulation may contribute to WM changes seen in BD.

Furthermore, the CNS is high in cholesterol, especially within WM. Unlike regular plasma cholesterol, oxysterols, which are end products of cholesterol oxidation, have been found to cross the blood-brain barrier and disrupt the balance of normal cholesterol in the brain, and have been suggested to play a role in numerous neurologic

diseases, such as Alzheimer's dementia.[59,60] Thus, cholesterol oxidation may directly contribute to the relationship between elevated BMI and WM changes in BD, since elevated BMI has been linked to increased oxidative stress early in life.[61] This further coincides with the findings of Versace et al.,[18] who looked at markers of lipid peroxidation and found they can explain variance in markers of WM integrity.

On the other hand, Reckziegel et al.[32] found no association between CRP, a marker of peripheral inflammation directly related to BMI, and WM microstructure in BD. However, this study looked at BD patients in a euthymic state, rather than in a manic or depressed state. It is possible that inflammation is increased in manic or depressed states, but not in euthymic states, which may have contributed to the lack of association.[62]

Innate immune system

The immune system and its constituent immune cells are central in organizing the inflammatory response. T cells are also known to have brain-supporting functions as well as putatively play a role in various neurodegenerative disorders.[63] As BD has been consistently associated with increased levels of inflammation, the assumption follows that immune cells very likely play a role in mediating this inflammation and, in turn, altering WM structure in BD. Poletti et al.[31] found that proinflammatory Th17 cells (subset of CD4+ T cells) correlated with higher FA in patients currently in a depressive episode (as well as in controls), suggesting increased WM coherence. They further found anti-inflammatory Treg cells (subset of CD4+ T cells) to correlate with reduced WM integrity in BD patients in a depressive episode. These findings appear counterintuitive, as it was expected that WM abnormalities in BD would be associated with the pro-inflammatory markers. Thus, this may suggest that Th17 cells are not purely brain-destructive, but instead may play a beneficial role in maintaining structural and functional brain integrity.[31]

Furlan et al.[21] chose instead to look at NK cells, a subset of the innate immune system that have been found to be affected by stress and depression, as well as play a role in both neurotoxicity and neuroprotection via cytokine production. This study found that multiple cytokine-producing NK cell subpopulations correlated positively with WM integrity in patients with BD. This suggests that NK cells and their cytokines play a protective role in BD. Interestingly, this study further found that duration of lithium treatment correlated with increased levels of cytokine-producing NK cells, suggesting these cells may play a role in mediating the beneficial effects of lithium on FA and, thus, on WM integrity in BD.

Magioncalda et al.[30] found that, in patients in a current manic episode, increased CD4+, and decreased CD8+ terminal effector cells correlated with WM abnormalities. CD4+ cells are able to activate CD8+ T cell subpopulations, while CD8+ terminal effector memory cells are prone to migration in peripheral tissues. Thus, these findings suggest early CD4+ cell activation leads to activation of CD8+ cells, which then accumulate in CNS tissue and damage WM. This accumulation within the CNS might account for the decreased peripheral levels of these cells noted in patients with BD, suggesting that CD8+ terminal effector cells contribute to WM abnormalities in BD.[64]

While many of the studies reviewed in this paper found a significant relationship between blood-based biomarkers and WM in BD, it is important to understand that these biomarkers were measured in the periphery. This limits our understanding of how they may act in the brain. In addition, few investigated the same biomarker in relation to WM in BD, which precluded a meta-analysis. The studies included in this review found significant correlations between blood-based biomarkers and WM in BD; however, causality cannot be inferred, since they were correlational studies. In addition, most included studies ($\sim$ 70%) were conducted in Italy, which limits the generalizability of their findings to the rest of the world. While these limitations do exist, this paper reviews clear correlations that have been found between WM and blood-based biomarkers, which should further our understanding of the pathophysiological process underlying WM deficits in BD.

Medication use

Many participants with BD in the included studies were on a variety of medications, which included antidepressants, antipsychotics, and mood stabilizers. Lithium has been shown to have neuroprotective properties, with positive effects on brain morphology (such as reducing the risk of dementia and attenuating cognitive decline).[65] A recent systematic review investigating lithium and WM integrity further demonstrated that long-term use of lithium helped maintain and improve WM integrity in BD.[66] Thus, it is conceivable that medication use may influence the relationship between blood-based biomarkers and WM in BD. It is important to note that, although the majority of studies included medicated participants, many of the studies controlled for medication status in their analyses.

This review summarized the wide range of blood-based biomarkers that have been investigated as possible proxies of WM damage in BD. During periods of inflammation, there is often an increase in pro-inflammatory cytokines such TNF-α, which has cytotoxic effects on oligodendrocytes, neurons, and glial cells. The increase in certain cytokines may also cause a cascade of events that include increased oxidative stress mediated by free radicals and an overactivated immune response by activation of T cells and monocytes. Changes in these markers can also affect the expression of certain genes that are required for the maintenance of myelin content and cause mutations within these genes. Through this potential pathway involving different classes of biomarkers, WM deficits may occur in BD. By improving our understanding of the many blood-based biomarkers and their relationship to WM, current treatment paradigms can be improved, and blood testing may become an easy, accessible method to potentially track changes in WM.

Disclosure

The authors report no conflicts of interest.

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