Archival Report

Biological Psychiatry

Systemic Cell Adhesion Molecules in Severe Mental Illness: Potential Role of Intercellular CAM-1 in Linking Peripheral and Neuroinflammation

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ABSTRACT

BACKGROUND: Cell adhesion molecules (CAMs) orchestrate leukocyte trafficking and could link peripheral and neuroinflammation in patients with severe mental illness (SMI), by promoting inflammatory and immune-mediated responses and mediating signals across blood-brain barrier. We hypothesized that CAMs would be dysregulated in SMI and evaluated plasma levels of different vascular and neural CAMs. Dysregulated CAMs in plasma were further evaluated in vivo in leukocytes and brain tissue and in vitro in induced pluripotent stem cells.

METHODS: We compared plasma soluble levels of different vascular (VCAM-1, ICAM-1, P-SEL) and neural (JAM-A, NCAD) CAMs in circulating leukocytes in a large SMI sample of schizophrenia (SCZ) spectrum disorder (n = 895) and affective disorder (n = 737) and healthy control participants (n = 1070) controlling for age, sex, body mass index, C-reactive protein, and freezer storage time. We also evaluated messenger RNA expression of *ICAM1* and related genes encoding ICAM-1 receptors in leukocytes using microarray (n = 842) and in available RNA sequencing data from the CommonMind Consortium (CMC) in postmortem samples from the dorsolateral prefrontal cortex (n = 474). The regulation of soluble ICAM-1 in induced pluripotent stem cell–derived neurons and astrocytes was assessed in patients with SCZ and healthy control participants (n = 8 of each).

RESULTS: Our major findings were 1) increased soluble ICAM-1 in patients with SMI compared with healthy control participants; 2) increased *ITGB2* messenger RNA, encoding the beta chain of the ICAM-1 receptor, in circulating leukocytes from patients with SMI and increased prefrontal cortex messenger RNA expression of *ICAM1* in SCZ; and 3) enhanced soluble ICAM-1 release in induced pluripotent stem cell–derived neurons from patients with SCZ.

CONCLUSIONS: Our results support a systemic and cerebral dysregulation of soluble ICAM-1 expression in SMI and especially in patients with SCZ.

https://doi.org/10.1016/j.biopsych.2022.06.029

Genetic and epidemiological studies support aberrant immune activation and inflammation as a pathogenic mechanism in severe mental illness (SMI) (1), including schizophrenia (SCZ) (2,3) and affective disorder (AFF) (4). Dysregulated activation of immune cells in the vasculature, including leukocyte subsets and endothelial cells, and their bidirectional interactions have been demonstrated as reflected by secreted activation markers preceding (5) and following diagnosis of SCZ and AFF (6–8). These processes could directly affect the brain and potentially lead to the progression of SMI involving both cell and soluble mediators (9). Indeed, molecular neuroscience studies suggest that inflammation and immune activation can influence neuronal functioning and plasticity and may predispose glial cells to a proinflammatory state associated with neurodegeneration.

These neuron-glia interactions include microglia, the primary immune cells of the central nervous system (CNS), and astroglia, both of which are critical in maintaining neurohomeostasis and are involved in inflammatory dysregulation in neuropsychiatric disorders (10,11). Furthermore, these interactions may be neurodevelopmentally dysregulated in SCZ (12). Maternal infections may skew the immune phenotype of

ISSN: 0006-3223

fetal microglia with potential negative long-term effects on microglia responsiveness during adulthood (13). Furthermore, transplantation of induced pluripotent stem cell (iPSC)–derived glial progenitor cells from patients with childhood-onset SCZ into chimeric mice revealed impaired astroglial maturation and a behavioral phenotype consistent with SCZ (14). Thus, early maternal immune activation may induce pathological interactions between neurons and glial cells, adversely affecting neurodevelopmental processes as outlined by Dietz *et al.* (15).

Although the blood-brain barrier (BBB) is not deteriorated in SMI as in neurologic diseases and neurodegenerative disorders, increased permeability in SCZ has been shown by postmortem transcriptomic studies showing dysregulated expression of tight junction–related genes in the prefrontal cortex (PFC) (16,17) and BBB transcripts enriched in brain endothelial cells such as *ICAM1* (18) as well as aberrant immunoreactivity of claudin-5 in brain sections from the parietal lobe (19). While there is less evidence in AFF, magnetic resonance imaging studies suggest subgroups of patients may have extensive and diffuse BBB dysfunction (20).

Cell adhesion molecules (CAMs) orchestrate leukocyte trafficking, and their dysregulation could influence BBB permeability, promoting inflammatory and immune-mediated trafficking to the CNS, linking peripheral and neuroinflammation in SMI (21–24). Activated endothelial cells initially upregulate selectins (e.g., P-selectin) to slow leukocytes on the endothelial surface before firm adhesion by integrins and Ig superfamily CAMs (e.g., intercellular adhesion molecule [ICAM], vascular CAM [VCAM]). The expression of integrin receptors on leukocytes, which may bind CAMs and facilitate transmigration across the BBB, has been shown to be increased in SCZ (21,25,26). Junctional adhesion molecules (e.g., JAM-A) and cadherins (CADs) maintain the structural integrity of cells and tissues with important roles during extravasation of leukocytes following firm adhesion (24,27,28). Neural CAD (NCAD) enables endothelial cell adhesion and communication with other cells, such as pericytes and astrocytes (29,30). These CAMs may shed from the cell surface by different mechanisms and their soluble (s) form releases into the circulation. As shown in Table S1, many previous studies have found evaluated circulating CAMs, showing quite consistent upregulation of proteins such as sICAM-1 in SMI (18,31–37), while inconsistent regulation was found for sVCAM-1 (31–34) and sP-SEL (38–42), possibly because of differences in sample material and controlling for different demographics. To our knowledge, systemic levels of sJAM-A and sNCAD have not been evaluated in SMI.

Based on the role of CAMs in promoting inflammatory and immune responses and mediating signals across BBB, we hypothesized that evaluation of a range of circulating CAMs, reflecting leukocyte/vascular interactions such as sICAM-1, sVCAM-1, and sP-SEL, as well as neural CAMs such as sJAM-A and sNCAD, could identify a novel pattern of dysregulation with clinical relevance for SMI. We focused on CAMs increased beyond the generalized systemic inflammation and metabolic distress in SMI as reflected by C-reactive protein (CRP) and body mass index (BMI), by controlling for these factors. To test this hypothesis, we adopted a multistep approach. Step 1: we evaluated plasma levels of different vascular and neural CAMs in patients with SMI (n = 1632) and healthy control participants (HCs) (n = 1070) and associations with symptom severity. Step 2: among the observed regulated CAMs in step 1, we assessed microarray messenger RNA (mRNA) expression of the CAM and relevant receptors in leukocytes in a subset including 579 patients with SMI and 263 HCs. Step 3: we assessed dysregulated CAMs and corresponding receptors by estimating cell type–specific gene expression through computational deconvolution in leukocytes and RNA sequencing (RNA-seq) data of postmortem dorsolateral PFC (DLPFC) samples from the CommonMind Consortium (CMC) (n = 474). Step 4: we studied the regulation of dysregulated CAMs and their receptors in human iPSC-derived neurons and astrocytes from SCZ and HC donors (n = 8).

METHODS AND MATERIALS

Setting and Participants

This study is part of the ongoing Thematically Organized Psychosis (TOP) Study including clinically stable patients 18 to 65 years of age, who were able to give a written informed consent, with a diagnosis of SCZ spectrum disorder (schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder, and psychosis not otherwise specified) included in the diagnostic group "schizophrenia" (SCZ), or affective disorder (bipolar I, bipolar II, bipolar not otherwise specified, and major depressive disorder with psychotic features) included in the diagnostic group "affective" (AFF) according to DSM-IV as described (4). See the Supplement for details. All participants gave written consent, and the study was approved by the Regional Committees for Medical and Health Research Ethics in Norway and the Norwegian Data Protection Agency. Participants with CRP >10 mg/L for any reason were excluded from the study.

Clinical Assessments and Medication

We evaluated patients using the Positive and Negative Syndrome Scale (PANSS) (43), Young Mania Rating Scale (44), and Global Assessment of Functioning scale (45). All participants including HCs were screened for medical history, and physical examination and routine blood tests were performed in addition to isolation of plasma for CAM analysis. Information regarding prescribed antipsychotics (APs) was obtained through clinical interviews and hospital records. We calculated defined daily dose of APs according to the World Health Organization (Geneva) principles, as described (46).

Analysis Plan

We first assessed plasma CAMs in 1632 patients with SMI (SCZ = 895, AFF = 737) and 1070 HCs, recruited between 2002 and 2017. As shown in Table 1, the groups were not well matched because patients with AFF were older than HCs and patients with SCZ, and BMI was higher in patients with AFF and SCZ than in HCs. The SCZ group had more males than AFF and HC groups, while the AFF group had more females than the HC group. In plasma with dysregulated CAMs, we proceeded with 1) microarray mRNA analysis in leukocytes, 2) cell type–specific gene expression imputation through computational deconvolution of microarray blood expression data and RNA-seq data of the DLPFC, and 3) analysis of

Table 1. Demographic and Clinical Information in Patients With Severe Mental Illness and Healthy Control Participants

Characteristics	SCZ		AFF		HC		ANOVA	SCZ vs. HC	AFF vs. HC	SCZ vs. AFF
	n	Mean ± SD or %	*n*	Mean ± SD or %	*n*	Mean ± SD or %	*p*	*p*	*p*	*p*
Age, Years	895	32.8 ± 13.3	737	38.6 ± 13.7	1070	32.5 ± 10	$<2 \times 10^{-16}$	.92	$<2 \times 10^{-16}$	$<2 \times 10^{-16}$
Sex, Male	425	57.7%	363	40.6%	559	52.2%	7.0×10^{-12}	.03	3.0×10^{-7}	8.3×10^{-12}
BMI, kg/m^2	455	26 ± 5.3	779	25.9 ± 4.8	849	24.7 ± 3.9	1.1×10^{-8}	5.1×10^{-6}	3.0×10^{-7}	.98
PANSS Total	555	63.6 ± 16.6	421	45.4 ± 10.2	–	–	–	–	–	$<2 \times 10^{-16}$
PANSS Neg	561	15.8 ± 6.2	421	10.0 ± 3.4	–	–	–	–	–	$<2 \times 10^{-16}$
PANSS Pos	559	15.3 ± 5.4	423	9.8 ± 3.4	–	–	–	–	–	$<2 \times 10^{-16}$
PANSS Gen	558	32.5 ± 8.4	422	25.6 ± 5.9	–	–	–	–	–	$<2 \times 10^{-16}$
YMRS	472	5.2 ± 5.1	416	3.1 ± 4.4	–	–	–	–	–	1.6×10^{-10}
GAF-S	602	42.7 ± 11.7	437	58.1 ± 11.6	–	–	–	–	–	$<2 \times 10^{-16}$
CRP, mg/L	509	3.5 ± 3.6	376	3.2 ± 3.4	968	2.3 ± 2.6	1.3×10^{-14}	$<2 \times 10^{-16}$	5.3×10^{-6}	.14
AP Use	525	71.2%	223	24.9%	0	0.0%	–	–	–	$<2 \times 10^{-16}$
Ddd APs	525	1.18 ± 0.82	223	0.87 ± 0.64	–	–	–	–	–	9.1×10^{-7}

Categorical data are given as percentage; continuous data are given as mean ± SD.

AFF, affective disorder; ANOVA, analysis of variance; AP, antipsychotic; BMI, body mass index; CRP, C-reactive protein; ddd, defined daily dose; GAF-S, Global Assessment of Functioning scale-Symptom scale; Gen, general; HC, healthy control participant; Neg, negative; PANSS, Positive and Negative Syndrome Scale; Pos, positive; SCZ, schizophrenia; YMRS, Young Mania Rating Scale.

regulation in human iPSC-derived neurons and astrocytes. Methods are detailed below.

Protein Measurements

Plasma levels of sICAM-1, sVCAM-1, sP-SEL, sJAM-A, and sNCAD were measured in duplicate through enzyme immunoassays using commercially available antibodies (R&D Systems) as described in detail in the Supplement. Intra- and interassay coefficients of variation were <10% for all enzyme immunoassays. For immunoassays, blood was collected using EDTA vials, and the plasma was isolated within the next working day and stored at −80 °C. Blood sampling was performed between 8 AM and 5 PM with some variation between patients and HCs. A validation of the immune assays with regard to performance, diurnal and postprandial variation, and effect bench/fridge time is presented in Table S2.

RNA Microarray Analysis and Gene Expression Imputation

Leukocyte mRNA expression was evaluated in 842 samples (SCZ = 338, AFF = 241, HC = 263), described in Table S3. Blood samples were collected in Tempus Blood RNA Tubes (Life Technologies Corp.) and processed as described previously (47). In brief, 200 ng of total RNA was biotin labeled and amplified using the Illumina TotalPrep-96 RNA Amplification Kit (Thermo Fisher Scientific), and global gene expression quantification was performed using Illumina HumanHT-12 version 4 Expression BeadChip (Illumina Inc.). Multidimensional scaling and hierarchical clustering were used for regular quality control and removal of multiple batch effects (RNA extraction batch, RNA extraction method, DNase treatment batch, complementary RNA labeling batch, and chip hybridization). The detectOutlier function in the R package lumi (https://rdrr.io/bioc/lumi/man/detectOutlier.html) identified 84 samples as outliers. Further details are provided in the Supplement.

The computational deconvolution tool CIBERSORTx (48) imputed cell type–specific gene expression for 10 major blood cell populations as defined by the LM22 reference dataset available through the web-based version of the tool (https://cibersortx.stanford.edu/). The Group Mode analysis type was used to impute cell type–specific expression, and differential expression analyses were carried out according to the guidelines recommended by the developers (49).

RNA-Seq of Brain Samples From the CMC

RNA-seq data of postmortem brain DLPFC samples were obtained from the CMC (50). A subset of 474 samples (SCZ = 214, AFF = 45, HC = 215) was used, including only donors of Caucasian ethnicity. Details on extraction procedures, yield, and quality control and details on the RNA-seq are given in the Supplement. All cases had a read count of >25 million reads (mean: 39.2 million). A prefiltering step excluded all lowly expressed and nonexpressed genes (<1 count per million in >50% of cases), retaining 16,895 genes for analysis. Differential expression analyses were carried out using the DESeq2 package (51), controlling for age, sex, postmortem interval, and biobank repository (laboratory batch effects). Associations with false discovery rates of < .05 were considered significant. For cell type–specific imputation of gene expression,

CIBERSORTx was used (49), selecting the High Resolution data analysis mode. Gene expression reference profiles for human neurons, astrocytes, and endothelial cells were obtained from the article by Zhang *et al.* (52) and used as input for imputation of cell type–specific expression.

Generation, Differentiation, and Stimulation of Astrocytes and Neurons From Donor iPSCs

For reprogramming and astrocyte and neuron iPSC differentiation, fibroblast/skin biopsies were isolated from 4 HCs (mean age 45.5 ± 13.9 years, 2 male) and 4 patients with SCZ (mean age 25.0 ± 3.6 years, 2 male). We differentiated and thoroughly characterized astrocytes and neurons from patient and control iPSCs following previously published glial and neuron differentiation and phenotyping protocols with small modifications (see the Supplement). Culture pellets and supernatants were collected after 0, 4, 7, 11, and 14 days of incubation for quantitative polymerase chain reaction (PCR) and enzyme immunoassay analysis as described above. Harvested samples were stored at −80 °C. Extraction procedure, reverse transcriptase-PCR, and quantitative PCR analysis are detailed in the Supplement.

Statistical Analyses

Statistical analyses were performed in R using the base statistical package. Associations between diagnosis (HC, SCZ, AFF, SCZ+AFF) and circulating levels of CAMs were assessed using linear regression, controlled for freezer storage time, age, sex, BMI, and circulating levels of CRP. Similarly, associations between diagnosis and bulk mRNA levels of ICAM-1 receptors were also assessed using linear regression with same covariates. Release of sICAM-1 from in vitro cultures was assessed using a univariate general linear model applying group (HC or SCZ) and time as fixed factors, ID number as random factor, and the interaction time × group.

RESULTS

Demographics and Clinical Characteristics

Patients with SCZ had more severe symptoms as reflected by PANSS and Young Mania Rating Scale scores and lower levels of functioning as reflected by the Global Assessment of Functioning scale score than patients with AFF. CRP levels were higher in patients with AFF and SCZ than in HCs. As expected, use of APs was more frequent in SCZ than in AFF, with a higher defined daily dose of APs.

Circulating sCAMs in Severe Mental Disorders

Differences in plasma sCAM levels between patients and HCs and within diagnostic subgroups, controlled for age, sex, BMI, and CRP, are shown in Figure 1, with coefficient estimates shown in Table S4. Patients with SMI were characterized by higher plasma sICAM-1 ($p = 3.0 \times 10^{-7}$) with the highest levels in SCZ ($p = 5.3 \times 10^{-8}$), although patients with AFF ($p = 6.7 \times 10^{-4}$) also had higher levels than HCs. Patients with SMI as a whole also displayed higher levels of sJAM-A ($p = 2.4 \times 10^{-4}$) with a comparable increase in SCZ ($p = 2.4 \times 10^{-4}$) and AFF ($p = .009$), while sVCAM-1, sP-SEL, and sNCAD showed no differences between diagnostic groups and HCs.

Associations Between sICAM-1, sJAM-A, Symptom Scores, and AP Treatment

sICAM-1 and sJAM-A levels were not associated with AP treatment ($p = .77$ and $p = .33$) or defined daily dose of APs ($p = .59$ and $p = .28$) and there were no strong associations between plasma sICAM-1 and symptom scores as reflected by PANSS, Young Mania Rating Scale, and Global Assessment of Functioning scale (Table S5) in SMI. A modest positive association was seen between PANSS negative scores ($p = .038$) in the SMI group, mainly driven by an association in SCZ ($p = .063$). In addition, sICAM-1 correlated with both BMI ($r = 0.14$, $p < .001$) and CRP ($r = 0.12$, $p < .001$), while no correlation was seen between sJAM-A and BMI or CRP ($p > .2$).

Evaluation of *ICAM1*, *F11R* (JAM-A Gene), and Receptor Genes in Leukocytes

As shown in Figure 2A, *ICAM1* and *F11R* mRNA expression in circulating leukocytes was similar between all diagnostic and control groups and did not correlate with corresponding plasma levels of sICAM-1 ($r = 0.03$, $p = .60$) or sJAM-A ($r = -0.01$, $p = .86$).

ICAM-1–mediated and JAM-A–mediated transmigration is facilitated by the β2 integrins, LFA-1 (CD11a/CD18 encoded by the *ITGAL*/*ITGB2* genes) and Mac-1 (CD11b/CD18 encoded by *ITGAM*/*ITGB2*). We evaluated mRNA expression of these integrins in circulating leukocytes. As shown in Table 2, *ITGB2* was increased in SMI as a whole and in SCZ and AFF subgroups, controlled for age, sex, and BMI. Further controlling for CRP attenuated these associations, suggesting that enhanced systemic inflammation could contribute to elevated *ITGB2* expression in SMI. Imputation of cell type–specific gene expression of the receptors through computational deconvolution (Figure 2B) revealed that *ITGB2* expression was higher in

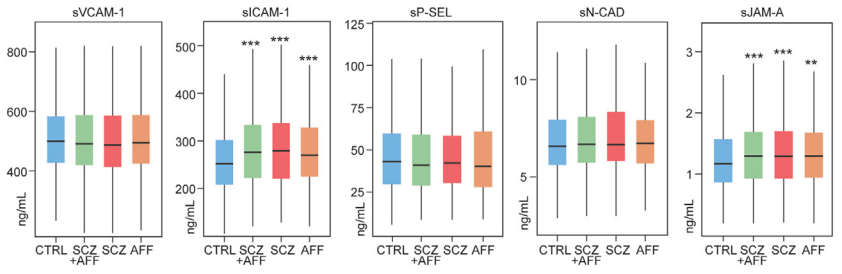

Figure 1. Circulating soluble CAMs in severe mental disorders. Evaluation of difference in soluble CAM levels between patients with severe mental illness ($n = 1632$) and healthy control participants ($n = 1070$) and within SCZ ($n = 895$) and AFF ($n = 737$) subgroups, controlled for age, sex, body mass index, and C-reactive protein. p Values from linear regression controlling for the mentioned covariates: $^{**}p < .01$, $^{***}p < .001$ vs. healthy control participants. AFF, affective disorder; CTRL, control; SCZ, schizophrenia; sICAM-1, soluble intercellular adhesion molecule 1; sJAM-A, soluble junctional adhesion molecule A; sNCAD, soluble neural cadherin; sP-SEL, soluble selectin P; sVCAM-1, soluble vascular cell adhesion molecule 1.

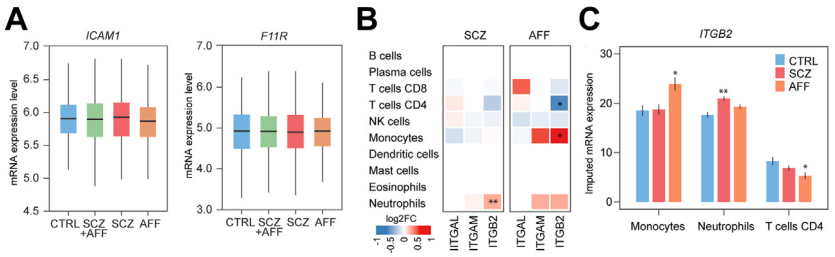

Figure 2. Expression of leukocyte ICAM-1, JAM-A, and integrin genes in severe mental illness. **(A)** Microarray mRNA expression of *ICAM1* and *F11R* (encoding JAM-A) in circulating leukocytes. **(B)** Data were deconvoluted using CIBERSORTx. Heatmap showing imputed expression of genes encoding β2 integrins, LFA-1 (CD11a/CD18 encoded by the *ITGAL*/*ITGB2* genes) and Mac-1 (CD11b/CD18 encoded by *ITGAM*/*ITGB2*) according to cell type. **(C)** Imputed mRNA expression of *ITGB2* across diagnostic groups. *$p < .05$, **$p < .001$ in false discovery rate–adjusted *t* tests. AFF, affective disorder; CTRL, control; FC, fold change; ICAM-1, intercellular adhesion molecule 1; mRNA, messenger RNA; NK, natural killer; SCZ, schizophrenia.

neutrophils and monocytes in SCZ and AFF, respectively, while it was decreased in $CD4^+$ T cells from AFF (Figure 2C).

Evaluation of *ICAM1*, *F11R*, and Its Receptors in the Brain

We next assessed RNA-seq data in a large sample ($n = 474$) of postmortem DLPFC tissues from the CMC (50). Differential expression analyses of the whole-brain regions (bulk RNA-seq) showed an elevated expression of *ICAM1* and *ITGAL*, but not *F11R* in patients with SCZ (Figure 3A) compared with HCs, and for *ITGAL* also compared with patients with AFF. *ITGAM* and *ITGB2* were not regulated. To investigate whether this association was driven by a specific cell population, we imputed cell type–specific expression in neurons, astrocytes (the 2 most abundant cell types in the brain), and endothelial cells. While gene expression in neurons and endothelial cells could not be reliably imputed, likely because of inadequate statistical power for these cell types, we found that *ICAM1* expression was significantly increased in the astrocyte subpopulation in SCZ (Figure 3B) while *ITGAL* was not regulated in subpopulations.

To further investigate the potential association between ICAM-1 in the brain and SCZ, we finally assessed whether iPSC-derived neurons and astrocytes generated from HCs and patients with SCZ released sICAM-1 during long-term culturing. As shown in Figure 3C, neurons derived from patients with SCZ released increased levels of sICAM-1 over time compared with HCs. Increasing sICAM-1 release was also observed in astrocytes during culture (Figure 3D), but with a similar temporal profile in SCZ and HCs. We were not able to detect *ICAM1* mRNA expression in pellets from these cultures owing to low expression (cycle threshold values >38).

DISCUSSION

This study evaluated previously investigated and novel sCAMs in a large sample of patients with SMI and HCs. We confirm enhanced plasma sICAM-1 in patients with SMI, increased mRNA levels of *ITGB2*, encoding the beta chain of the ICAM-1 receptor, in circulating leukocytes from patients with SMI, and elevated DLPFC mRNA expression of *ICAM1* in SCZ. Novel findings of our study are the dysregulation of *ITGB2* in leukocytes in AFF, increased *ITGAL* mRNA expression in DLPFC in SCZ, and enhanced release of sICAM-1 from neurons in SCZ. In addition, we report increased sJAM-A in SMI but found no regulation in DLPFC samples.

Plasma and serum levels of sICAM-1 have previously been evaluated in SMI [reviewed in (53) and summarized in Table S1]. Our finding of increased sICAM-1 supports most studies reporting higher levels in SCZ (18,32,34,35) and bipolar disorders (31,33,36,37), while some studies report lower levels in SCZ (54,55). In these studies, higher sICAM-1 levels were related to the stage of disease (31,33,34,36,37) and inflammatory and cardiometabolic burden (18,35), while lower levels were associated with ICAM-1 single nucleotide polymorphisms (54) and AP treatment (31). With some exceptions (34), and similar to our findings, these studies present only marginal or no correlation with symptom scores. Based on the widespread vascular expression of ICAM-1 (56) and role in

Table 2. Associations Between mRNA Expression of ICAM-1 Receptor Genes in Leukocytes and Diagnosis, Controlled for Age, Sex, BMI, and CRP

		SCZ+AFF		SCZ		AFF	
Model	Outcome	Coefficient ± SD	*p*	Coefficient ± SD	*p*	Coefficient ± SD	*p*
Age	*ITGAM*	0.042 ± 0.028	.134	0.056 ± 0.031	.070	0.014 ± 0.036	.698
	ITGB2	0.048 ± 0.012	6.4×10^{-5}	0.046 ± 0.013	.001	0.044 ± 0.015	8.3×10^{-4}
	ITGAL	−0.013 ± 0.001	.402	−0.011 ± 0.022	.605	−0.013 ± 0.025	.617
Age+Sex+BMI	*ITGAM*	−0.005 ± 0.027	.865	0.028 ± 0.030	.349	−0.058 ± 0.033	.075
	ITGB2	0.050 ± 0.013	1.1×10^{-4}	0.049 ± 0.015	.001	0.052 ± 0.017	.002
	ITGAL	0.022 ± 0.020	.277	0.013 ± 0.022	.573	0.041 ± 0.026	.119
Age+Sex+BMI+CRP	*ITGAM*	−0.011 ± 0.028	.706	0.013 ± 0.031	.677	−0.06 ± 0.034	.078
	ITGB2	0.038 ± 0.013	.005	0.031 ± 0.016	.052	0.047 ± 0.018	.009
	ITGAL	0.022 ± 0.021	.307	0.002 ± 0.023	.940	0.059 ± 0.028	.037

The table shows coefficients ± SD compared with healthy control participants.

AFF, affective disorder; BMI, body mass index; CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule 1; mRNA, messenger RNA; SCZ, schizophrenia.

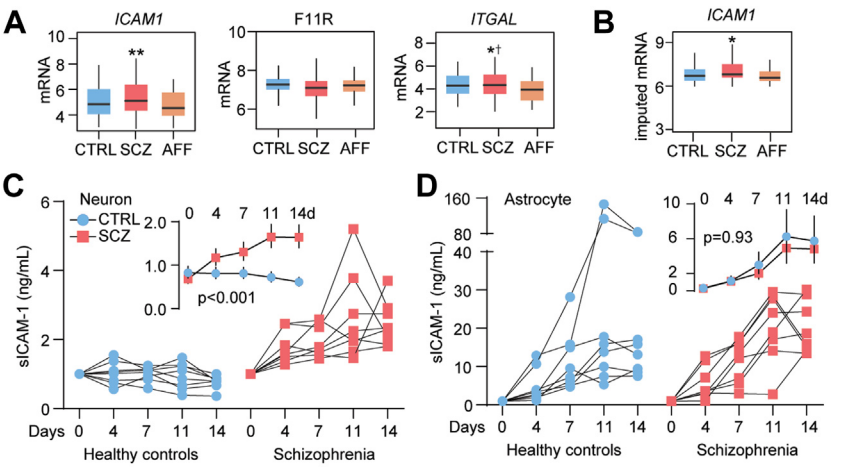

Figure 3. Regulation of ICAM-1, JAM-A, and integrins in brain tissue and brain cells in severe mental illness. **(A)** Expression of *ICAM1*, *F11R* (encoding JAM-A), and *ITGAL* in bulk RNA sequencing data from 474 dorsolateral prefrontal cortex donors (SCZ = 214, AFF = 45, HCs = 215). *t* Test FDR < .05 vs. HCs; **FDR < .001 vs. HCs; †FDR < .05 vs. AFF. **(B)** Imputed expression of *ICAM1* in astrocytes. *$p < .05$. Release of sICAM-1 at different time points from induced pluripotent stem cell–derived **(C)** neurons and **(D)** astrocytes from patients with SCZ and HCs ($n = 8$ in each group). The inset shows estimated marginal means and 95% confidence intervals from the mixed-model regression with p value reflecting the diagnostic group effect. AFF, affective disorder; CTRL, control; FDR, false discovery rate; HC, healthy control participant; JAM-A, junctional adhesion molecule A; mRNA, messenger RNA; SCZ, schizophrenia; sICAM-1, soluble intercellular adhesion molecule 1.

atherosclerosis and metabolic disease (57,58), increased levels driven by potential cardiometabolic risk could obscure associations with symptom severity in SMI. Indeed, increased BMI and CRP correlated with sICAM-1 levels in our patients, suggesting that enhanced subclinical inflammation could contribute to increased sICAM-1 in SMI, but in contrast to the above studies, we controlled for CRP and BMI in our analyses. Regardless of demographic or comorbid factors contributing to elevated systemic levels, sICAM-1 could link systemic inflammation and immune activation and neuroinflammation in SMI. Regarding potential effects of AP treatment, we found no significant associations, but this may be best assessed by a temporal design. Taken together, in by far the largest study of patients with SMI, we show elevated sICAM-1 levels in both SCZ and AFF, beyond the subclinical inflammation as assessed by CRP and metabolic risk as assessed by BMI.

Transmigration across the BBB is facilitated by the β2 integrins LFA-1 and Mac-1 (59), and our finding of increased *ITGB2* mRNA levels encoding the common beta chain protein for these integrins in SMI leukocytes, as shown previously for mRNA (25) and protein levels (26) in SCZ, further support that ICAM-1–mediated mechanisms could promote inflammatory cell trafficking across the BBB. Cai *et al.* (18) showed monocytes in the PFC and brain tissue macrophages in close proximity to neurons in patients with SCZ, and increased density of macrophages has been shown along the lateral ventricle (60,61) and in the midbrain (62). The imputed increased *ITGB2* in monocytes support infiltration of these cells also in AFF as suggested by deconvolution of RNA-seq data from postmortem samples of the dorsal striatum, estimating more monocytes in bipolar disorder than in HCs (63). The increased *ITGB2* on neutrophils in SCZ in our study may suggest a role these cells have in disruption of, or migration across, the BBB as seen in Alzheimer's disease (64). Neutrophil counts correlate with reductions in gray matter volume and enlarged ventricles in SCZ (65). Finally, the lower imputed *ITGB2* in $CD4^+$ T in AFF, suggests reduced migration of these cells following astrocyte-derived chemotaxis as shown in SCZ (66). Because $CD4^+$ T regulatory cells are important anti-inflammatory regulators, their reduced ingress into the brain in SMI may contribute to a more inflammatory environment. Taken together, we hypothesize that an inflammatory systemic environment could increase β2 integrins in leukocytes in SMI, and exposure to elevated ICAM-1 could potentiate leukocyte arrest along the BBB vasculature and eventual migration into the perivascular space, further promoting neuroinflammation through secretion of inflammatory signals.

Cai *et al.* (18) showed a 68% higher *ICAM1* mRNA expression in DLPFC in 37 patients with SCZ, in particular in a subgroup with high inflammation, with enrichment in the brain endothelium (18). Here, we extend these findings showing increased *ICAM1* mRNA expression in SCZ in a large postmortem DLPFC sample, with imputed expression primarily in astrocytes. Inflammatory challenge may induce *ICAM1* mRNA and cell surface expression on cultured astrocytes (67–69), and the higher levels in postmortem samples could reflect a higher inflammatory environment in vivo as found by Cai *et al.* (18). We were not able to detect any *ICAM1* mRNA using quantitative PCR from our iPSC-derived cells suggesting low levels. Still, spontaneous sICAM-1 correlates strongly with membrane-bound expression on astrocytes (70) and is detected in supernatants of resting cells (70,71). Thus, the lack of difference between SCZ and HCs in unstimulated cells supports that increased astrocyte-derived ICAM-1 in SCZ is due to a higher inflammatory environment. In contrast, the higher secretion of sICAM-1 from neurons in SCZ, without an inflammatory trigger, could point to some genotypic differences between patients with SCZ and HCs. Enhanced oxidative stress is a feature of iPSC-derived neurons in SCZ (72), and it is tempting to hypothesize that ICAM-1 may promote oxidative stress–induced neuronal loss (73). Astrocytes express low levels of LFA-1, which are enhanced by IFN-γ (74), and we speculate that the increased *ITGAV* imputed in SCZ astrocytes could promote inflammatory signaling involving glial cells, neurons, and infiltrating leukocytes. sICAM-1 may induce MIP-2 release in both mouse astrocytes and brain microvascular endothelial cells (70), which could advance

recruitment of leukocytes and inflammation in the brain (75). In addition to regulation of vascular permeability, ICAM-1–dependent adhesion to astrocytes induces tumor necrosis factor secretion, suggesting a direct role in inflammatory signal transduction (76). Similar effects of sICAM-1 have been shown in endothelial cells and macrophages, invoking a range of inflammatory responses (77,78). Thus, ICAM-1–related mechanisms in SMI may not be restricted to transmigration of leukocytes across the BBB, but could both enhance and be enhanced by inflammation within the CNS.

A novel finding in our study was the increased sJAM-A levels in SMI. JAM-A is expressed on endothelial cells, epithelial tight junctions, and leukocytes (79,80) and mediates transmigration of leukocytes across the BBB in an LFA-1–dependent manner (81). However, we observed no regulation of F11R in the DLPFC samples. A study evaluating sJAM-A as a BBB breakdown marker in human brain microvascular cells found no effects of inflammatory or hypoxic challenge and detected no upregulation in patients with clinically active multiple sclerosis (82). Because JAM-A is also expressed in atherosclerotic plaques (83) and increased soluble levels have been shown in patients with atherosclerotic disease (84), comorbid conditions could contribute to increased sJAM-A in SMI.

A strength of our study was the large number of patients and control participants. While previous studies on sICAM-1 have been relatively consistent, not requiring this statistical power, our study brings confidence to markers such as sP-SEL and sVCAM-1, for which previous studies are highly inconsistent. P-SEL is abundantly expressed in platelets (85) and serum and would therefore not reflect in vivo circulating levels but rather ex vivo release during platelet degranulation, which may be less relevant in SMI. Nonetheless, while we did not detect systemic dysregulation of P-SEL, VCAM-1, and NCAD, this does not necessarily imply that these proteins have no role in the progression of SMI, but merely that this was not reflected by circulating levels in our study.

Limitations to our study include the blood sampling protocol, which was not optimal with differences between patients and HCs in the time of day when samples were obtained and with isolation of plasma the next day. However, our validation experiments found no systematic effects on the measured CAMs. Samples were collected and stored at −80 °C over a period of 15 years; however, controlling for this had no major impact on the results. The lack of smoking status in our control population is a limitation of our study. RNA integrity number was only determined in a subsample of our leukocyte mRNA samples, and quality control to remove samples with lower numbers of detected transcripts and low signal-to-noise ratio was performed with an R algorithm, resulting in the removal of 84 samples. We were not able to impute gene expression for neurons or endothelial cell in the postmortem DLPFC samples, most probably because of low expression of the ICAM-related genes and low number of the cells compared with astrocytes in the cortex. In addition, to ensure a more homogeneous study population, we obtained a set of RNA-seq data from the CMC collection owing to technical differences with regard to strand specificity as described by the authors (50), as well as non-Caucasian samples. While these strict criteria negatively affected the sample size, our sample was still much larger than the sample size used in most similar studies. Patients had stable, chronic SMI, and results could be different in acute SMI.

Finally, the study had a cross-sectional design, making the causality described suggestive. We do not suggest that sICAM-1 represents a clinically useful biomarker in these patients because there was a large overlap in the sICAM-1 distributions in patients with SMI and control participants.

In conclusion, our results support a systemic and cerebral dysregulation of sICAM-1 signaling in SMI, especially in SCZ, potentially contributing to CNS pathology in this patient group.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the South-Eastern Norway Regional Health Authority (Grant Nos. 2018-089 and 2019-108) and The Research Council of Norway (Grant Nos. 223273 and 300309).

We thank the participants of the study. We also acknowledge the technical support and service from the Genomics Core Facility at the Department of Clinical Science, University of Bergen.

OAA is a consultant to HealthLytix and has received speaker's honorarium from Sunovion and Lundbeck. All other authors report no biomedical financial interests or potential conflicts of interest.

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Received Jan 10, 2022; revised and accepted Jun 14, 2022.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2022.06.029.

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