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Abnormalities in chemokine levels in schizophrenia and their clinical correlates

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abstract

Chemokines are promising biomarkers of immune activation and inflammation, but evidence for chemokine abnormalities in schizophrenia and their relationship to clinical factors remains inconclusive. We aimed to understand chemokine-related diagnostic differences and clinical correlates using a comprehensive panel and studying a large, well-characterized sample of adults with and without schizophrenia. We studied 134 outpatients with schizophrenia or schizoaffective disorder and 112 healthy comparison (HC) individuals, 26 to 65 years of age. Clinical measures were obtained, and plasma levels of 11 chemokines were assessed using multiplex immunoassay. Schizophrenia vs. HC differences were tested for each chemokine, adjusting for age, gender, body mass index, and current smoking status. We also examined whether age and gender relationships differed between diagnostic groups. Using logistic regression, we created a Chemokine Index (CI) and explored its clinical correlates. Levels of monocyte chemoattractant protein-1 (MCP-1/CCL2), macrophage inflammatory protein-1β (MIP-1β/CCL4), Eotaxin-1 (CCL11), thymus and activation-regulated chemokine (TARC/CCL17), and macrophage-derived chemokine (MDC/CCL22) were significantly higher in persons with schizophrenia than HCs. Group differences in TARC were reduced after adjusting for covariates. The CI, a linear combination of Eotaxin-1 and MDC levels, was positively associated with age, duration of schizophrenia, and severity of negative symptoms. Levels of chemokines with neuroimmune regulatory effects were higher in individuals with schizophrenia, particularly in older and chronic patients. Treatments aimed at normalizing chemokine levels might improve mental and physical health among schizophrenia patients as they age.

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1. Introduction

Persons with schizophrenia have increased morbidity and mortality rates from medical illnesses, especially cardiovascular diseases (Brown, 1997; Inskip et al., 1998). Schizophrenia has been associated with immune dysfunction and inflammation (Dickerson et al., 2016), which may contribute to accelerated aging and greater comorbidity and mortality (Kirkpatrick et al., 2008). The large CATIE study reported higher levels of inflammatory markers (Meyer et al., 2009) and elevated coronary heart disease risk in people with schizophrenia, especially among women (Goff et al., 2005). Autoimmune diseases and chronic inflammatory conditions occur with higher frequency in persons with schizophrenia (Benros et al., 2014b). Individuals with schizophrenia reportedly have increased plasma concentrations of C-reactive protein, interleukin (IL)-6, IL-6 receptor, tumor necrosis factor-α, and soluble IL-2 receptor (Joseph et al., 2015; Lin et al., 1998; Maes et al., 1995; Mondelli et al., 2015; Naudin et al., 1996). Also, treatment with non-steroidal anti-inflammatory cyclooxygenase-2 inhibitors was shown to reduce psychotic symptoms in patients with recent-onset psychosis but not chronic psychosis (Nitta et al., 2013; Rapaport et al., 2005). Taken together, immune activation/inflammation is associated with schizophrenia, but more comprehensive investigations are necessary to specify the nature of immune alterations and their clinical correlates.

Chemokines constitute a family of small (7–12 kDA) cytokines and induce directed chemotaxis in nearby responsive cells. Chemokines

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play an integral role in immune function, mediating leukocyte migration and trafficking, and inflammatory responses (Foxman et al., 1997; Murphy et al., 2000b; Springer, 1994). Recent studies suggest direct roles of chemokines in the central nervous system (CNS), including neuroendocrine function, neurotransmission, and neurodegeneration (Reaux-Le Goazigo et al., 2013). Elevated levels of chemokines in the CNS and blood are observed in several neuroinflammatory disorders such as multiple sclerosis (Balashov et al., 1999; Sorensen et al., 1999), as well as psychiatric conditions including depression, bipolar disorder, and schizophrenia (Eyre et al., 2016; Panizzutti et al., 2015; Stuart and Baune, 2014).

The literature on chemokine levels in schizophrenia is informative but has limitations. Most studies examined a relatively small number of chemokines in male-dominant samples. These investigations vary widely in considering potential demographic and clinical correlates in analyzing schizophrenia-chemokine relationships (Beumer et al., 2012; Xu et al., 2015). Monocyte chemoattractant protein (MCP)-1 is the best-studied chemokine, but the findings are equivocal with nearly equal numbers of studies showing significantly higher (Beumer et al., 2012; Dimitrov et al., 2013; Domenici et al., 2010; Reale et al., 2011; Zakharyan et al., 2012) or similar (Asevedo et al., 2013; Brambilla et al., 2014; Di Nicola et al., 2013; Martinez-Cengotitabengoa et al., 2012; Schwarz et al., 2012; Teixeira et al., 2008) levels between schizophrenia patients and healthy comparison subjects (HCs). There are also inconsistent findings for IL-8 (Dennison et al., 2012; Di Nicola et al., 2013; Erbagci et al., 2001; Kaminska et al., 2001; Maes et al., 2002; O'Brien et al., 2008; Ramsey et al., 2013; Reale et al., 2011; Zhang et al., 2002), Eotaxin-1 (Asevedo et al., 2013; Domenici et al., 2010; Pedrini et al., 2014; Ramsey et al., 2013; Teixeira et al., 2008), and macrophage derived chemokine (MDC; Brambilla et al., 2014; Dimitrov et al., 2013; Domenici et al., 2010; Ramsey et al., 2013; Schwarz et al., 2012). Other chemokines, including macrophage inflammatory protein (MIP)-1α (Asevedo et al., 2013; Brambilla et al., 2014; Dimitrov et al., 2013; Domenici et al., 2010; Nikkila et al., 2002; Schwarz et al., 2012; Teixeira et al., 2008; Zakharyan et al., 2012), MIP-1β (Beumer et al., 2012; Brambilla et al., 2014; Dimitrov et al., 2013; Domenici et al., 2010; Schwarz et al., 2012), and interferon-induced protein-10 (IP-10; Asevedo et al., 2013; Brambilla et al., 2014; Dimitrov et al., 2013; Teixeira et al., 2008) have not been shown to differ between people with schizophrenia and HCs. Finally, MCP-4 (Teixeira et al., 2008), Eotaxin-3 (Schwarz et al., 2012), fractalkine (Dimitrov et al., 2013), and thymus and activation-regulated chemokine (TARC) have received little attention in schizophrenia. Men with schizophrenia have shown higher chemokine levels (e.g., IL-8, MCP-1, MDC, MIP-1α, and MIP-1β) than women with schizophrenia in some studies (Beumer et al., 2012; Domenici et al., 2010; Ramsey et al., 2013).

We assessed plasma levels of 11 chemokines in a well-characterized group of outpatients with schizophrenia and HCs. These chemokines included eight C\\C motif chemokine ligands: MCP-1 (CCL2), MIP-1α (CCL3), MIP-1β (CCL4), Eotaxin-1 (CCL11), MCP-4 (CCL13), TARC (CCL17), MDC (CCL22), Eotaxin-3 (CCL26); two C\\X\\C motif ligands: IL-8 (CXCL8) and IP-10 (CXCL10); and one C\\X3\\C motif ligand: fractalkine (CX3CL1). Our panel contained chemokines of both innate and adaptive immunity with inflammatory (MCP-1, MIP-1α, MIP-1β, MCP-4, Eotaxin-3, IL-8, IP-10), and dual (both inflammatory and homeostatic; Eotaxin-1, TARC, MDC, and fractalkine) functions (Zlotnik and Yoshie, 2012), and also includes chemokines with known roles in the CNS (MCP-1, MIP-1α, MIP-1β, Eotaxin-1, IL-8, IP-10, and fractalkine) (Stuart et al., 2015). We compared levels of each chemokine in our panel between people with schizophrenia and HCs. For those plasma chemokines that differed between the two groups, we examined whether the differences remained significant after adjusting for covariates. We also examined subgroups of patients who were more comparable to the HCs on body mass index (BMI) and smoking. The relationship of age and gender to the chemokines was examined separately in the persons with schizophrenia and HCs. Finally, we created a Chemokine Index (CI) based on a combination of markers that differed most between the two diagnostic groups, and explored clinical correlates of the Index in the two groups.

2. Experimental/materials and methods

2.1. Participants

The protocol was approved by the University of California, San Diego (UCSD) Human Research Protections Program. Participants provided written informed consent. These included 134 outpatients with schizophrenia or schizoaffective disorder (hereafter referred to collectively as schizophrenia) and 112 HCs with no history of major neuropsychiatric disorder, recruited from the greater San Diego community and enrolled in an ongoing study of aging in schizophrenia. Schizophrenia diagnosis was confirmed using the Structured Clinical Interview for the DSM-IV-TR (SCID; First et al., 2002). Participants were recruited using a structured multi-cohort design, with the two groups being age-matched by decade (26–35, 36–45, 46–55, and 56–65 years). Subject selection criteria have been previously described (Joseph et al., 2015).

2.2. Sociodemographic and clinical characteristics

Sociodemographic characteristics (i.e., age, education, gender, race/ethnicity, and smoking status) and illness-related variables (i.e., duration of schizophrenia and daily antipsychotic medication dosages (Sweileh et al., 2014) were ascertained through participant interviews and reviews of records (with HIPAA authorization). The Multisystem Disease Risk Score (Carroll et al., 2015) was calculated by summing the z-scores of high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, hemoglobin A1c, glucose, insulin, and C-reactive protein levels in blood. The Framingham 10-year Coronary Heart Disease Relative Risk Score (Wilson et al., 1998) was also computed (Jin et al., 2011).

2.3. Psychosocial and cognitive assessments

Psychotic symptoms were evaluated with interviewer-administered Scales for Assessment of Positive Symptoms and Negative Symptoms (SAPS and SANS, respectively) (Andreasen, 1983, 1984), depression with the Patient Health Questionnaire – 9-Item Version (PHQ-9; Kroenke and Spitzer, 2002), health-related quality of life and functioning with the physical and mental health composite scores from the Medical Outcomes Study 36-item Short Form (SF-36; Ware and Sherbourne, 1992), and medical comorbidity with the Cumulative Illness Rating Scale (CIRS; Parmelee et al., 1995). Current medications, including psychotropic and anti-inflammatory agents, were recorded for both groups. Assessment of cognitive deficits focused on executive functioning (Fucetola et al., 2000; Wobrock et al., 2008), based on three subtests from the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001).

2.4. Chemokine assays

Fasting blood was collected in EDTA-treated vacutainers between 7:00 am–12:00 pm through an intravenous catheter inserted into an antecubital vein using minimal tourniquet. White blood cell count and hematocrit were assessed by the UCSD Clinical Laboratory using standard procedures. Plasma was stored at − 80 °C until assays were performed. Plasma chemokine levels were quantified using Meso Scale Discovery (MSD) MULTI-SPOT® Assay System and analyzed on a SECTOR Imager 2400 instrument (Rockville, MD, USA). Using MSD Discovery Workbench® analysis software, standard curves were formed by fitting ECL signal from calibrators to a 4-parameter logistic model with a $1/y^2$ weighting. Samples were run in duplicates, using V-PLEX Human Biomarker panels (Catalog # K151A0H-2) to measure the

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chemokines. Human fractalkine/CX3CL1 kit (Catalog # K151MKD-2) was used to assay fractalkine levels. V-PLEX kits are fully validated according to fit-for-purpose principles and the FDA's analytical validation guidelines according to the manufacturer (MSD). The laboratory technician performing the assays was "blind" to the subject's diagnosis. Intra- and inter-assay variations for chemokines were b10%, except the intra-assay variation (19.4%) and inter-assay variation (19.5%) for Eotaxin-3, inter-assay variation for MCP-1 (16.5%), and intra-assay variation for MIP-1α (19.8%). The lowest detected level for each chemokine was as follows: 0.10 pg/mL (MCP-1), 1.62 pg/mL (MIP-1α), 0.86 pg/mL (MIP-1β), 2.94 pg/mL (Eotaxin-1), 1.24 pg/mL (MCP-4), 0.131 pg/mL (TARC), 4.22 pg/mL (MDC), 1.15 pg/mL (Eotaxin-3), 0.06 pg/mL (IL-8), 0.12 pg/mL (IP-10), and 9.58 pg/mL (fractalkine). No sample showed chemokine levels below the detection limits.

2.5. Statistical analysis

Values of all chemokines were $\log_{10}$ transformed to approximate a normal distribution. Independent samples t-tests and Chi-square analysis were used to compare continuous and discrete sample characteristics, respectively. Cohen's d effect sizes were calculated for group differences for continuous variables, and values N0.30 were interpreted as greater than a small effect. The Success Rate Difference (SRD) was calculated for categorical variables as the group difference between the percent of each reference category versus all others (Kraemer and Kupfer, 2006). The SRD ranges from − 1 to + 1 with zero as its null value, and values N0.17 were interpreted as greater than a small effect. Chemokine data for MCP-4, MIP-1α, and TARC were only available in a subgroup of 155 subjects (84 schizophrenia and 71 HC).

Based on the literature regarding factors that might impact chemokine levels or an inflammatory state in general or in schizophrenia specifically, we conducted a general linear model to examine the effect of group when age, gender, BMI, and current smoking status were entered as covariates. Additionally, because BMI and smoking status were markedly different between the groups, we tested whether smaller subgroups of patients who resembled HCs on BMI and smoking also differed from them in chemokine levels.

To create a single CI, we first conducted a forward stepwise logistic regression with group as the dependent variable. The CI was calculated for each participant as a linear combination of the intercept and the value of each significant chemokine weighted by its parameter estimate from the logistic regression model. We then explored potential associations between clinical variables and the CI by examining Pearson correlations in both persons with schizophrenia and HCs.

3. Results

There was, as expected, no significant difference in age or gender between the people with schizophrenia and HCs (Table 1). The people with schizophrenia had a slightly lower proportion of Caucasians, lower education level, greater cigarette smoking, higher BMI, greater medical comorbidity and disease risk, more severe depressive symptoms, and poorer executive functioning than HCs. Persons with schizophrenia were more likely to be taking psychotropic medications and anti-inflammatory agents. Both groups had normal hematological tests and did not have clinical evidence of fever or infection, although total white blood cell counts were somewhat higher in the persons with schizophrenia.

Levels of five CC chemokines (MCP-1, MIP-1β, Eotaxin-1, TARC, and MDC) were significantly higher in the people with schizophrenia than in the HCs with medium Cohen's d effect sizes (Table 2). Effect sizes for the group difference were not notably reduced after adjusting for covariates (Table 3), except in the case of TARC, where the effect size fell from d = − 0.38 to d = − 0.25. When subsets of non-smoking schizophrenia (n = 64) and HC participants (n = 105) were compared, there were still medium to large effect sizes for the group difference

Table 1
Demographic and clinical characteristics of healthy comparison vs. schizophrenia groups.

	Healthy comparison			Schizophrenia			Difference	
	N	Mean	SD	N	Mean	SD	t or χ^2	Cohen's d or SRD
Age (years)	112	48.4	12.0	134	48.1	10.1	0.19	0.03
Gender (N/%women)	64/57%			60/45%			3.7	0.12[a]
Race (N/%Caucasian)	68/61%			57/43%			8.1**	0.18[a]
Education (N/%high school and below)	16/14%			78/58%			8.0***	−0.44 [a]
Body mass index	109	27.9	7.2	132	32.2	7.4	−4.6***	−0.59
Current smoking status (N/%smokers)	7/6.2%			70/52%			60.0***	−0.46[a]
Illness duration (years)	–	–	–	133	25.1	11.2	–	–
SAPS total score	–	–	–	134	6.5	4.3	–	–
SANS total score	–	–	–	134	7.4	4.4	–	–
Antipsychotic daily dosage (total WHO DDD)	–	–	–	134	1.7	1.4	–	–
PHQ9 severity score	109	1.8	2.8	130	7.6	6.6	−9.0***	−1.1
Psychotropic medication (N/%on one or more)	7/6%			106/94%			130.4***	−0.88[a]
Anti-inflammatory medication (N/%on one or more)	18/16%			41/31%			7.1**	−0.15[a]
Multi-system disease risk score	87	−3.0	2.9	96	0.07	4.7	−5.3***	−0.77
SF-36 physical composite scale	109	52.2	8.2	132	43.2	10.1	7.7***	0.98
SF-36 mental composite scale	109	54.6	5.4	132	43.4	11.3	10.1***	1.3
CIRS - total score	93	3.0	3.2	116	6.8	4.9	−6.6***	−0.92
CIRS - severity index	93	1.0	0.7	116	1.5	0.6	−6.0***	−0.77
Executive functioning composite[b]	112	0.5	0.6	134	−0.5	0.7	11.8***	1.5
Framingham CHD risk score	103	1.0	0.6	115	1.4	0.8	−4.3***	−0.58
White blood cell count	108	5.5	1.6	118	6.9	2.1	−1.4***	−0.75
Hematocrit	108	41.1	3.7	118	41.2	3.7	−0.1	−0.03

t = Student's t, χ^2 = Pearson's chi-square, SRD = success rate difference, WHO DDD = World Health Organization defined daily dose, CHD = coronary heart disease, SF-36 = Medical Outcome Survey 36-item Short Form, CIRS = Cumulative Illness Rating Scale, SAPS = Scale for the Assessment of Positive Symptoms, SANS = Scale for the Assessment of Negative Symptoms, PHQ = Patient Health Questionnaire.

***, **, and * = significant group difference at ≤0.001, 0.01 and 0.05, respectively.

[a] For effect sizes Cohen's d and SRD were calculated for continuous and categorical variables, respectively. SRD ranges from − 1 to + 1.

[b] The Delis-Kaplan Executive Function System (D-KEFS), (62) raw scores were converted to z-scores and coded such that higher scores represented better performance; mean z-score across tasks was used as an executive functioning composite score.

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Table 2
Chemokine levels in healthy comparison vs. schizophrenia groups.

	Healthy comparison			Schizophrenia			Group comparison		
	N	Mean	SD	N	Mean	SD	t	p	d
MCP-1/CCL2 (pg/ml)#	112	89.5	56.5	134	97.8	36.8	−2.8	0.005	−0.36
MIP-1α/CCL3 (pg/ml)	70	18.6	44.1	83	19.8	36.6	−0.99	0.32	−0.16
MIP-1β/CCL4 (pg/ml)#	112	60.2	27.3	134	72.2	35.9	−2.8	0.006	−0.36
Eotaxin-1/CCL11 (pg/ml)#	112	115.0	53.9	134	151.6	99.4	−3.2	0.002	−0.41
MCP-4/CCL13 (pg/ml)	71	64.7	42.6	84	76.3	48.7	−1.7	0.09	−0.27
TARC/CCL17 (pg/ml)#	71	62.4	41.3	84	83.5	65.8	−2.4	0.02	−0.38
MDC/CCL22 (pg/ml)#	112	762.2	357.3	134	933.1	456.7	−3.5	0.001	−0.45
Eotaxin-3/CCL26 (pg/ml)	112	47.9	224.5	134	64.0	367.8	−0.15	0.88	−0.02
IL-8/CXCL8 (pg/ml)	112	4.2	5.4	133	4.2	3.6	−0.84	0.35	−0.12
IP-10/CXCL10 (pg/ml)	112	400.6	374.3	134	401.5	385.8	0.98	0.33	0.13
Fractalkine/CX3CL1 (pg/ml)	112	6192.6	1940.4	133	5957.8	2280.7	1.3	0.20	0.16

= chemokines that differed by group with small to medium effects, t = Student's t, d = Cohen's d, MCP = monocyte chemoattractant protein, CCL = C\\C motif chemokine ligand, MIP = macrophage inflammatory protein, TARC = thymus and activation-regulated chemokine, MDC = macrophage-derived chemokine, IL = interleukin, CXCL = C\\X\\C motif chemokine ligand, IP = interferon-inducible protein, CX3CL = C\\X3\\C motif chemokine ligands.

for all five chemokines (Cohen's ds from − 0.30 to − 0.50). Similarly, when subsets of non-obese patients (n = 60) were compared to non-obese HC participants (n = 84), there were medium to large group effect sizes for all chemokines, with some diagnostic effects slightly larger in this non-obese subsample than in the total sample that included the full range of BMIs (Cohen's ds from − 0.43 to − 0.77).

In the above general linear model (Table 3), we observed main effects of age on MCP-1 and Eotaxin-1 (higher values in older participants) and main effects of gender on TARC and MDC (women > men for TARC; men > women for MDC). In a separate model with age, gender, group, and all their interactions, no chemokine showed a group-specific gender association or any age relationships that depended on either group or gender.

To create the CI, we entered MCP-1, MIP-1β, Eotaxin-1, and MDC in a forward stepwise fashion into a logistic regression with group membership as the dependent variable; the final model was significant (χ^2 (2) = 20.7, p < 0.001, Nagelkerke R^2 = 0.11). MDC entered on the first step, and Eotaxin-1 entered on the second step. In the final model, which correctly identified individuals as members of the schizophrenia vs. HC groups 64% of the time, MDC (Wald test = 9.7, p = 0.002), and Eotaxin-1 (Wald test = 7.9, p = 0.005) levels both significantly distinguished patients from HCs, and so this model was used to calculate the CI. The equation used for the CI calculation was: $-10.612 + (0.762 \times \log_{10}(\text{Eotaxin-1})) + (1.08 \times \log_{10}(\text{MDC}))$. As expected, the CI was higher in persons with schizophrenia (− 5.84 ± − 0.27) than in HCs (− 5.99 ± − 0.23; t = − 5.26, p < 0.0001).

Schizophrenia patients with a higher CI were older, had longer durations of illness, and had more negative symptoms. Among the HCs, CI was higher in women, individuals with higher levels of subclinical depressive symptoms, worse self-rated mental well-being, and greater overall severity of generally mild medical illnesses (Table 4).

4. Discussion

Plasma levels of five CC chemokines were greater in schizophrenia compared to HC: MCP-1/CCL2, MIP-1β/CCL4, Eotaxin-1/CCL11, TARC/CCL17, and MDC/CCL22. Eotaxin-1 and MDC were particularly useful in distinguishing between the schizophrenia and HC groups, although they should not be regarded as diagnostic markers. The group difference in TARC levels decreased considerably after adjusting for age, gender, BMI, and smoking, suggesting that it was primarily related to demographic factors. Our findings add to studies of MCP-1 in schizophrenia that show significantly higher levels compared to HCs (Beumer et al., 2012; Dimitrov et al., 2013; Domenici et al., 2010; Reale et al., 2011; Zakharyan et al., 2012), in contrast to other reports of no group differences (Asevedo et al., 2013; Brambilla et al., 2014; Di Nicola et al., 2013; Martinez-Cengotitabengoa et al., 2012; Schwarz et al., 2012; Teixeira et al., 2008). The existing literature presents inconsistent findings for Eotaxin-1 (Asevedo et al., 2013; Brambilla et al., 2014; Dimitrov et al., 2013; Domenici et al., 2010; Ramsey et al., 2013; Schwarz et al., 2012; Teixeira et al., 2008) and MDC (Brambilla et al., 2014; Dimitrov et al., 2013; Domenici et al., 2010; Pedrini et al., 2014; Ramsey et al., 2013; Schwarz et al., 2012) and negative findings for MIP-1β in most reports (Beumer et al., 2012; Brambilla et al., 2014; Dimitrov et al., 2013; Domenici et al., 2010; Schwarz et al., 2012). In contrast to the C\\C chemokine family, all C\\X\\C and C\\X3\\C chemokines examined in our study did not differ between the two groups. Together, our findings suggest potential differences in neuroimmune regulatory chemokines in schizophrenia, although the link between structure and functions of chemokines in schizophrenia is unclear.

Two beta chemokines with dual homeostatic and inflammatory functions, MDC and Eotaxin-1, had particularly strong relationships to diagnosis even after accounting for interrelations among the chemokines. Eotaxin-1 acts primarily on eosinophils and is involved in

Table 3
General linear models testing group effect with age, gender, BMI, and smoking status as covariates.

	Full model		t-value and Cohen's d from general linear model									
			Group		Age		Gender		BMI		Smoking status	
	F	R^2	t	d	t	d	t	d	t	d	t	d
MCP-1/CCL2 (pg/ml)#	4.5***	0.09	−2.3*	−0.31	3.2**	0.42	−1.2	−0.15	1.3	0.17	−0.11	−0.00
MIP-1β/CCL4 (pg/ml)#	3.6**	0.07	−2.1*	−0.28	1.6	0.21	−0.51	−0.06	2.3*	0.31	−0.46	−0.06
Eotaxin-1/CCL11 (pg/ml)#	9.4***	0.17	−2.7**	−0.35	3.8**	0.50	0.54	0.06	−3.3***	−0.43	2.0*	0.26
TARC/CCL17 (pg/ml)	3.1*	0.10	−1.5	−0.25	1.9	0.33	2.1*	0.35	0.47	0.09	0.64	0.11
MDC/CCL22 (pg/ml)#	5.5***	0.10	−2.7**	−0.35	0.24	0.00	−3.5***	−0.45	1.2	0.15	0.56	0.06

= Chemokines that differed by group with small to medium effects in a multiple model; Age and BMI were centered (mean for the sample subtracted from each participant's value), and group, gender and smoking status were coded as − 0.5 (women, HC, non-smokers) and + 0.5 (men, schizophrenia, smokers). MCP = monocyte chemoattractant protein, CCL = cysteine-cysteine ligand, MIP = macrophage inflammatory protein, TARC = thymus and activation-regulated chemokine, MDC = macrophage-derived chemokine, IL = interleukin; for Group, negative t-values indicate levels higher in schizophrenia patients, for Gender, negative t-values indicate levels higher in men, for Smoking status, negative t-values indicate levels higher in smokers. ***, **, and * = significant difference at ≤0.001, 0.01 and 0.05, respectively.

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Table 4
Pearson correlations of demographic and clinical variables with chemokine index based on eotaxin-1 and MDC levels in schizophrenia and healthy comparison groups.

	Schizophrenia		Healthy comparison	
	r or t[a]	p	r or t[a]	p
Age (years)	0.23*	0.007	0.11	0.24
Gender	1.1[a]	0.26	2.1[a]*	0.04
Race	1.8[a]	0.07	0.23[a]	0.82
Education (years)	0.14[a]	0.89	−0.84[a]	0.40
Body mass index	−0.16	0.06	0.05	0.60
Current smoking status	−1.0[a]	0.32	−1.5[a]	0.14
Illness duration (years)	0.21*	0.02	–	–
SAPS-total	0.01	0.87	–	–
SANS-total	0.18*	0.04	–	–
Antipsychotic daily dosage (total WHO DDD)	−0.05	0.60	–	–
Depressive symptoms (PHQ-9 severity score)	0.01	0.95	0.28**	0.003
Psychotropic medication	−0.28[a]	0.78	0.1.3[a]	0.20
Anti-inflammatory medication	−0.03[a]	0.97	−0.66[a]	0.51
Multisystem disease risk score	0.04	0.70	0.21	0.05
SF-36, physical composite scale	0.01	0.90	−0.11	0.26
SF-36, mental composite scale	0.01	0.87	−0.20*	0.04
CIRS- total score	0.13	0.16	0.30**	0.003
CIRS- severity score	0.04	0.66	0.26*	0.01
Executive functioning composite	−0.11	0.20	−0.05	0.64
Framingham coronary heart disease risk score	0.04	0.68	0.16	0.10

r = Pearson's correlation, SAPS = Scale for the Assessment of Positive Symptoms, SANS = Scale for the Assessment of Negative Symptoms, WHO DDD = World Health Organization defined daily dose, PHQ = patient health questionnaire, SF-36 = Medical Outcome Survey 36-item Short Form, CIRS = Cumulative Illness Rating Scale; ** and * = significant difference at ≤0.01 and 0.05, respectively.
[a] t = Student's t.

aging-associated disruptions of memory and hippocampal neurogenesis (Villeda et al., 2011). MDC is secreted by dendritic cells and macrophages, and acts on T cells, NK cells, and monocytes. (Mantovani et al., 2000). The combination of MDC and Eotaxin-1 suggests possible dysregulation of both peripheral and neuroinflammatory activities.

While our findings do not directly address pathophysiology of schizophrenia, peripheral blood markers may aid in discovering reliable and practical biomarkers of immune dysregulation in schizophrenia. Growing evidence indicates that CNS immune surveillance is critical in maintaining optimal brain functioning (Kipnis et al., 2008). Disruption of 'patrolling' immune cells' entry into the brain leads to impaired learning and memory, and behavioral abnormalities (Schwartz and Shechter, 2010). Thus, dysregulation of the chemokine network may contribute to disease processes in schizophrenia, given the critical role of chemokines in initiating migration of immune cells to target tissues for maintenance and inflammatory functions (Foxman et al., 1997; Murphy et al., 2000a; Springer, 1994). Furthermore, human fetal astrocyte and microglial cells express chemokines and chemokine receptors (Rezaie et al., 2002), and maternal inflammation during gestation is linked to development of schizophrenia (Benros et al., 2014a; Krause et al., 2010). Recently, complement component 4 (C4) protein expression abnormalities were found in post-mortem brain tissue from patients with schizophrenia, consistent with excessive C4-mediated synaptic pruning during mice neurodevelopment (Sekar et al., 2016). Expression of chemokines can be activated by complement components (Selvan et al., 1998), so our findings may reflect long-standing dysregulation of complement function.

Given that the CI was associated with illness duration and severity of negative symptoms, a dysregulated chemokine "system" may be a feature of chronic schizophrenia with negative features. These associations need clarification in longitudinal studies. Nonetheless, it can be speculated that physical and mental health could be improved by treatments that regulate chemokine levels in schizophrenia patients (Keller et al., 2013). The associations of CI with levels of subclinical depressive symptoms and perception of mental and physical health that were seen only in HCs may suggest a statistical anomaly. Unlike some studies (Asevedo et al., 2013; Martinez-Cengotitabengoa et al., 2012) we did not observe associations of cognitive (executive) function performance with chemokine levels. Further work is needed to examine whether other aspects of cognition might be related to chemokine elevations in schizophrenia. A number of the chemokine levels were age- or gender-related. Identifying specific gender and/or age groups among schizophrenia patients that exhibit immune dysregulation may be clinically valuable.

Our study has several limitations. This cross-sectional investigation of chronic outpatients does not provide direct evidence for the chemokines' involvement in schizophrenia pathophysiology. Also, there is a possibility of type I errors as we did not correct for multiple comparisons in our univariate analyses. Although group effect sizes persisted after statistically adjusting for factors like BMI and smoking and examining non-smoking and non-obese subsamples, both these approaches have their limitations. Longitudinal studies would help in examining whether changes in BMI or physical health precede changes in chemokines or vice versa. Finally, our results may not apply to persons with acute or first-episode schizophrenia or antipsychotic-naive patients.

Longitudinal and functional investigations of chemokines and their receptors will advance the field in testing whether these biomarkers predict changes in clinical severity, and possibly contribute to pathophysiological processes in schizophrenia. Future research is needed to evaluate whether treatments that normalize chemokine dysregulation may ameliorate psychopathology among chronic schizophrenia patients.

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Conflict of interest
None of the authors had any financial conflict of interest with the subject matter of this study.

Contributors
Dr. Hong wrote the first draft of the manuscript, performed literature searches, and conducted analyses. Drs. Lee and Martin performed literature searches and conducted analyses. Dr. Benchawanna Soontornniyomkij performed the assays. Dr. Virawudh Soontornniyomkij and Dr. Achim contributed to manuscript preparation. Mr. Reuter performed all statistical analyses. Dr. Irwin wrote sections of the manuscript. Drs. Eyler and Jeste designed the study and wrote the protocol. All the authors contributed to and approved the submitted manuscript.

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