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Plasma Levels of the Cytokines B Cell-Activating Factor (BAFF) and A Proliferation-Inducing Ligand (APRIL) in Schizophrenia, Bipolar, and Major Depressive Disorder: A Cross Sectional, Multisite Study

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Background: **Immune dysfunction has been implicated in the pathogenesis of schizophrenia and other nonaffective psychosis (SCZ), bipolar spectrum disorder (BIP) and major depressive disorder (MDD). The cytokines B cell-activating factor (BAFF) and A proliferation-inducing ligand (APRIL) belong to the tumor necrosis factor (TNF) super family and are essential in orchestrating immune responses. Abnormal levels of BAFF and APRIL have been found in autoimmune diseases with CNS affection.** ***Methods:*** **We investigated if plasma levels of BAFF and APRIL differed between patients with SCZ, BIP, and MDD with psychotic symptoms (n = 2009) and healthy control subjects (HC, n = 1212), and tested for associations with psychotic symptom load, controlling for sociodemographic status, antipsychotic and other psychotropic medication, smoking, body-mass-index, and high sensitivity CRP.** ***Results:*** **Plasma APRIL level was significantly lower across all patient groups compared to HC (P < .001; Cohen's d = 0.33), and in SCZ compared to HC (P < .001; d = 0.28) and in BIP compared to HC (P < .001; d = 0.37). Lower plasma APRIL was associated with higher psychotic symptom load with nominal significance (P = .017), but not with any other clinical characteristics. Plasma BAFF was not significantly different across patient groups vs HC, but significantly higher in BIP compared to HC (P = .040; d = 0.12) and SCZ (P = .027; d = 0.10).** ***Conclusions:*** **These results show aberrant levels of BAFF and APRIL and association with psychotic symptoms in patients with SCZ and BIP. This suggest that dysregulation of the TNF system, mediated by BAFF and APRIL, is involved in the pathophysiology of psychotic disorders.**

Key words: severe mental disorder/immune/cytokine/TNF/neuropsychiatric/autoimmune disease

Introduction

Several lines of evidence implicate immune dysfunction in people with schizophrenia and other nonaffective psychotic disorders (SCZ),[1–3] bipolar spectrum disorder (BIP)[4,5] and major depressive disorder (MDD).[6–8] SCZ, BIP and MDD are defined as separate diagnostic entities, yet, they are genetically related disorders[9–11] associated with abnormalities in immune-inflammatory pathways.[12] These disorders also share some clinical features with systemic autoimmune diseases such as systemic lupus erythematosus (SLE).[13–17] Nearly a third of patients with SLE experience neuropsychiatric symptoms, including psychotic symptoms,[18–20] which may be due to abnormal activation of the adaptive immune system producing autoantibodies directed against neurons or other central nervous system (CNS) components.[21–23] Moreover, recent studies indicate a moderate genetic correlation between SCZ and SLE.[24–26]

Cytokines are signaling molecules produced by both immune and nonimmune cells[27] acting as key regulators of inflammation and coordinating the innate and the adaptive immune system.[28] These mediators facilitate neurotransmission, neurogenesis, synaptic plasticity, and inflammatory responses,[29] thus, playing a pivotal role in the cross-talk between the immune system and the brain.[30,31] Several studies have identified a positive correlation of serum levels of cytokines (eg, interleukins 6 and 1β, tumor necrosis factor α) with disease severity.[32–34] Members of the tumor necrosis factor (TNF) superfamily (TNFSF) are cytokines involved in infection, inflammation, and tissue homeostasis,[35,36] as well as autoimmune diseases.[37] The two related cytokines B cell-activating factor (*BAFF*/*TNFSF13B*) and A proliferation-inducing ligand (*APRIL*/*TNFSF13*) [38] are transmembrane proteins mainly produced by hematopoetic cells.[39,40] BAFF is a crucial factor for B cell maturation[41] and essential for the humoral immune response.[42] The BAFF protein is expressed by monocytes, macrophages, dendritic cells, and neutrophils, as well as subpopulations of B and T cells.[43,44] APRIL is involved at later stages of the immune response, acting as costimulator for B and T cell proliferation. Both cytokines are essential for class-switching of B cells, permitting the synthesis of immunoglobulins to alter from one type to another.[45,46] They interact with transmembrane activator and Ca^{2+} modulator (CAML) interactor (TACI, TNF receptor (R) SF13B), B cell maturation antigen (BCMA/TNFRSF17), and BAFF receptor (BAFF-R/ TNFRSF13C) with BAFF having the highest affinity for TACI and APRIL for BCMA.

Circulating BAFF and APRIL are increased in patients with SLE,[40] and the capacity of the innate immune system to regulate B cell activation is reflected in an altered BAFF/APRIL ratio. Individuals with SLE and concurrent CNS pathology seemed to have higher serum BAFF and lower serum APRIL (ie, increased BAFF/APRIL ratio) compared to individuals with SLE without CNS pathology,[47] potentially reflecting that APRIL, but not BAFF, may have a protective role in the CNS by acting on astrocytes.[48]

Previous smaller studies (<100 patients) have indicated reduced serum BAFF levels in both individuals with SCZ[49] and MDD.[50] A study of people with autism, however, showed an association between serum BAFF levels and autistic traits when adjusting for confounders. The authors also compared BAFF levels in serum and cerebrospinal fluid and found no association.[51] BAFF and APRIL have not been investigated in well powered samples comprised by individuals with severe mental disorders, controlling for potential confounders. In light of previous research on immunocompetent cells we anticipated inverse aberrancies encompassing elevated plasma BAFF and decreased plasma APRIL levels in individuals with severe mental disorders compared to HC subjects. In the current study we therefore investigate if plasma levels of BAFF and APRIL are dysregulated in people with severe mental disorders, applying a well-powered sample (n = 3221) controlling for many confounders that may influence cytokines levels.[52] Further, we investigate if plasma levels of BAFF and APRIL are associated with psychotic features and pharmacological treatment.

Materials and Methods

Study Design and Participant Recruitment

The current study is a naturalistic, cross-sectional study which is part of the ongoing Thematically Organized Psychosis (TOP) Study at the NORMENT Centre. The clinical participants were referred from primary care to treatment in psychiatric units at South-Eastern regional hospitals, in addition to hospitals in Inland, Arendal, Stavanger, Bergen, Kristiansund, and Trondheim, Norway.[53,54] The psychiatric units in Norway are catchment area based and publicly funded. The clinical participants were recruited to the current study consecutively from 2003 through 2018 mainly from outpatient clinics, but also from intermediate and long term units. Inclusion of patients admitted to acute treatment units was awaited until they were stabilized and able to consent and participate in interviews and assessments. Main criterion of inclusion in the TOP Study is a diagnosis of SCZ, BIP or MDD with one or more psychotic episodes according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or International Statistical Classification of Diseases and Related Health Problems (ICD-10) (WHO, 1994). Eligible for the study were patients fulfilling these diagnostic criteria aged between 18 and 65 years with ability to give informed consent. Exclusion criteria were

history of moderate or severe head injury, severe somatic illness including neurological disorders and IQ below 70. All patients underwent the same investigation protocol, which includes assessment of psychiatric symptoms, diagnosis, physical examination, neuropsychological testing and collection of blood samples.

All participants gave written informed consent and the study was approved by the Regional Committees for Medical and Health Research Ethics (REC) and the Norwegian Data Protection Agency. The authors assert that all procedures contributing to this work comply with the ethical standards for medical research involving human subjects as stated in the Helsinki Declaration. The participants including HC were interviewed with description of ethnicity, somatic and psychiatric history taking, smoking habits, alcohol consumption, and use of illicit drugs in the two weeks period prior to physical examination and blood sampling. Additionally, body-mass-index (BMI) was assessed.

Healthy control (*HC*) *participants* of the same age range were recruited in the period between 2004 and 2019 by randomly selecting individuals from the same catchment area as the clinical participants in the Oslo region using national population records (http://www.ssb.no). HC participants were without any history of SCZ, BIP or MDD, severe head injury, neurological disorders or other severe somatic illness, illicit drug abuse or dependency, or close relatives with severe mental disorder.[55] To exclude current or previous history of mental disorders among HC or in their family, the HC were interviewed with a screening questionnaire for mental disorders based on main items from the SCID-I and assessed with Primary Care Evaluation of Mental Disorders.[56] Individuals with severe mental disorders in need of treatment or exhibiting substantial vocational or social incapacities such as schizophrenia, bipolar disorder or severe recurrent depression were not included in the study. Hospitalization or treatment with psychotropic medications (eg, treatment with central stimulants in individuals diagnosed with ADHD) implied study exclusion. Persons with one or more first degree relatives (parent/sibling) with severe mental disorders were not included in the study. HC participants were contacted by letter inviting them to participate.

Patients: All patients were interviewed recording psychiatric symptoms, medication and potential side effects. Diagnostic interviews based on Structured Clinical Interview in DSM-IV axis I Disorders (SCID-I)[57] were performed by trained psychologists and psychiatrists, all of whom participated regularly in diagnostic meetings supervised by professors in psychiatry with expertise in diagnostics. The reliability of diagnostic and symptom assessments was very good. The overall agreement for the DSM-IV diagnostic categories tested was 82% and the overall κ 0.77 (95% confidence interval 0.60–0.94).[58] Severity of psychotic symptoms was assessed by Positive and Negative Syndrome Scale (PANSS).[59]

Protocol and Samples

We included variables in the study protocol considered to potentially modulate the cytokines BAFF and APRIL. These variables were ethnicity (European/non-European), smoking status, BMI, hsCRP, PANSS positive and negative subscale, and treatment with antipsychotic medication. In the current study we utilized a full sample comprised of all patients and all HC participants, a case-control subsample, as well as a patient subsample with a series of clinical variables and a subsample containing patients prescribed antipsychotics. The full patient sample (n = 2009) and the full HC participant sample (n = 1212) contained data on the sociodemographic variables age, sex and ethnicity. A subsample of data from patients (n = 981) and HC participants (n = 571) containing the additional variables BMI and smoking status were utilized as case-control. A well-characterized extensive subsample of participants with the diagnoses SCZ, BIP and MDD derived from the case-control patient sample and encompassing all variables of the protocol (n = 668) was also applied. Finally, we used a subsample of patients based on prescription of psychotropic medication (antipsychotics/antidepressants/anticonvulsants/lithium DDD) and assessed serum levels of the antipsychotic agents (aripiprazole n = 80; quetiapine n = 145; risperidone n = 56; olanzapine n = 182).

Psychotropic Medications

Information on patients' medications including antipsychotics, antidepressants, anticonvulsants and lithium were obtained by clinical interview and from medical records. Blood samples was taken detecting serum levels of psychotropic medication. Patients' use of antipsychotic medication, anticonvulsants, lithium and antidepressants was also calculated as defined daily doses (DDD) in accordance with guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (http://www.whocc.no/atcdd). The DDD is the assumed standard maintenance dose per day for a drug used for its main indication on adults (ie, antipsychotics in patients with schizophrenia) providing a rough estimate of pharmaceutical drugs consumption. Participants' psychotropic drugs prescription was presented as the number of DDD based on approved dose recommendations. We calculated the total number of DDD for antipsychotic medication (antipsychotic DDD) for each participant accounting for treatment with different antipsychotic agents. For example, the DDDs for oral olanzapine and oral risperidone are 10 mg and 5 mg, respectively, and for the participant prescribed both antipsychotic drugs the total antipsychotic DDD equals two.

Blood Sampling and Immune Measures

Blood was drawn by venipuncture within two weeks of symptom assessments and plasma was stored in the biobank. Serum concentrations of antipsychotic compounds was assessed in a subset of patients. Plasma levels of BAFF, APRIL and high sensitivity C-reactive protein (hsCRP) were analyzed in duplicate using commercially available antibodies in a 384 format using a combination of a SELMA (Jena, Germany) pipetting robot and a BioTek dispenser/washer. Absorption was read at 450 nm with wavelength correction set to 540 nm using an ELISA plate reader. Intra/inter-assay coefficients of variation were <10%. Effects of diurnal and postprandial variation on plasma BAFF and APRIL levels were evaluated in six different individuals who had blood draws at different times of the day, and no significant effects were detected.

Statistical Methods

All statistical analyses were performed using IBM SPSS (Statistical Package for the Social Sciences for Windows, version 26, IBM, Inc., Chicago, IL, USA). The dependent variables *BAFF* and *APRIL* did not follow a normal distribution (inspection of QQ-plots of dependent variables and standardized residuals), and BAFF was thus subject to reciprocal transformation, whereas log transformation was applied to APRIL. Log transformation enabled presentation of back transformed means with confidence intervals of APRIL, while BAFF was displayed with medians and estimated confidence intervals based on method of empirical centiles (ie, approximate calculation of the probability that observations are under the 0.025 and above the 0.975 percentile). Standardized residuals of the two dependent variables were inspected and extreme parts of the distribution were removed (>3 times the interquartile range, 2.4% of the total sample) to comply with the normality assumption. Correlations between BAFF and APRIL were tested in the whole sample and within the diagnostic groups and HC by using Pearson r method. Analysis of covariance (ANCOVA) was employed to investigate differences of BAFF and APRIL between all patients vs all HC. In order to examine differences between diagnostic groups vs all HC, whilst adjusting for age and sex, ANCOVA with post hoc group comparisons was conducted. A Bonferroni adjustment for multiple comparisons was applied. ANCOVA was also employed to investigate the differences in plasma BAFF and APRIL when additionally adjusting for BMI and smoking status in a case-control subsample of patients (n = 981) and HC participants (n = 571). Further, we conducted a post-hoc stepwise regression analysis in a reduced well characterized subsample of patients with SCZ, BIP and MDD with psychotic symptoms (n = 668). The regression analysis was employed to determine the strongest predictors of APRIL using age, sex, ethnicity, BMI, hsCRP, antipsychotic medication (DDD), smoking status, and psychotic symptom level as explanatory variables. There were no violations of multiple linear regression assumptions. Residuals were normally distributed, homoscedasticity was confirmed and relations among variables were linear and additive. Interaction terms were tested within the regression model, and the outcomes were unaltered. Pearson r method and stepwise regression analysis were utilized for investigation of the relationship between BAFF and APRIL and aripiprazole DDD, quetiapine DDD, risperidone DDD, and olanzapine DDD, respectively, when controlling for age and sex. To estimate effect sizes of the group differences Cohen's d (d) was applied building on pooled standard deviation.

Results

Sample Characteristics

We included n = 2009 patients and n = 1212 HC in the current study. All patients underwent a thorough diagnostic evaluation including personal interview and review of medical records and were classified in diagnostic groups according to the DSM-IV (American Psychiatric Association, 1995) or ICD-10 (WHO, 1994) and divided into three main groups as follows: (i) SCZ (n = 1123) including schizophrenia (n = 640), schizoaffective disorder (n = 161), schizophreniform disorder (n = 55), delusional disorder (n = 48), brief psychotic disorder (n = 12) and psychotic disorder not otherwise specified (n = 207)), (ii) BIP (n = 846) including bipolar I disorder (n = 514), bipolar II disorder (n = 283) and bipolar disorder not otherwise specified (n = 49)), and (iii) MDD (n = 40). All patients with diagnoses of MDD had current or previous psychotic episodes.

Data was complete in the sample of all patients and all HC participant (n = 3221) and in the case–control subsample (n = 1552). In the subsample derived from the case-control subsample (extensive subsample, n = 668) there was missing data on hsCRP for 18 patients (1.8% of the patients), on antipsychotics DDD for 300 patients (30.6% of patients), on PANSS positive subscale for six patients (0.6% of patients), and on PANSS negative subscale for six patients (0.5% of patients).

As shown in table 1, the patients with SCZ were younger (M = 31.4, SD = 12.5), more frequently male (58.4% male) and less frequently of European ethnicity (81.1%) compared to both HC subjects (M = 36.8, SD = 15.1; 51.2% male sex; 98.4% European ethnicity) and patients with BIP (M = 38.3, SD = 13.9; 40.4% male sex; 93.0% European ethnicity). Patients with BIP (M = 38.3, SD = 13.9) were older than patients with MDD (M_{age} = 31.0, SD = 13.3). There were more men among individuals with SCZ (58.4%) than among BIP (40.4%) and HC subjects (51.2%) and fewer men among persons with BIP than HC participants. There was 50.3%

men among the patients and 55.3% among the HC participants in the case-control subsample. The patients (M = 31.0, SD = 10.6) were significantly younger than the HC subjects (M = 33.1, SD = 9.4), and the number of smokers (39.8%) and BMI (M_{BMI} = 26.1, SD_{BMI} = 5.2) were significantly higher in patients than in HC (19.4% smokers; M_{BMI} = 24.7, SD_{BMI} = 3.8).

Comparing All Patients and Healthy Controls on Plasma BAFF and APRIL

Mean plasma APRIL was significantly lower in all patients (270 pg/ml) than in all HC (335 pg/ml) [$F(3,3220) = 39.3$, $P < .001$; $d = 0.33$] in age and sex-adjusted analysis. In contrast, the plasma level of BAFF in all patients (234 pg/ml) was not different from all HC (228 pg/ml) [$F(3,3220) = 2.0$, $P = .16$; $d = 0.01$]. In a subsample of patients and HC (patients n = 981, HC n = 571) adjusting for age, sex, ethnicity, BMI, and smoking status we found that plasma APRIL was significantly lower in the patients (254 pg/ml) than in HC (325 pg/ml) [$F(6,1551) = 36.0$, $P < .001$; $d = 0.35$]. Plasma BAFF was 236 pg/ml in the patients and 227 pg/ml in HC, and no significant differences were found between the groups.

Comparing Diagnostic Groups and Healthy Controls on Plasma BAFF and APRIL

Plasma level of APRIL was significantly lower in SCZ than in HC ($P < .001$, $d = 0.28$), and significantly lower in

Table 1. Demographic and Clinical Characteristics of Participants

	Full Sample (n = 3221)				Subsample (n = 1552)		Extensive Subsample
Group (*n*)	SCZ (1123)	BIP (846)	MDD (40)	HC (1212)	Patients (981)	HC (571)	Patients (668)
Male (%)	58.4*#	40.4#	55.0	51.2	50.3*	55.3	53.3
Age, years (mean, SD)	31.4*# (12.5)	38.3· (13.9)	31.0 (13.3)	36.8 (15.1)	31.0# (10.6)	33.1 (9.4)	30.7 (10.3)
Ethnicity (% European)	81.1*#	93.0#	72.5	98.4	82.5#	97.9	81.0
BMI (mean, SD)	N/A	N/A	N/A	N/A	26.1# (5.2)	24.7 (3.8)	26.1 (5.2)
Smoking (%)	N/A	N/A	N/A	N/A	39.8#	19.4	43.2
hsCRP (mean, SD)	N/A	N/A	N/A	N/A	N/A	N/A	3.3 (5.0)
PANSS pos (mean, SD)	N/A	N/A	N/A	N/A	N/A	N/A	13.1 (5.2)
PANSS neg (mean, SD)	N/A	N/A	N/A	N/A	N/A	N/A	13.6 (6.0)
Antipsychotics DDD (mean, SD)	N/A	N/A	N/A	N/A	N/A	N/A	1.2 (0.9)

SCZ, schizophrenia and other nonaffective psychotic disorders; BIP, bipolar spectrum disorder; MDD, major depressive disorder; HC, healthy control participants. Full sample (SCZ, BIP, MDD, HC), n = 3380. Subsample (case−control), n = 1552. Extensive patient subsample derived from subsample, n = 668. Age (years) and body-mass-index (BMI) in mean and standard deviation. Male, ethnicity (% European ethnicity), and smoking status presented in percent. hsCRP, PANSS positive subscale, PANSS negative subscale and antipschotics DDD presented in mean and standard deviation. ANOVA post hoc group comparisons conducted. Group comparisons on demographic and clinical variables were adjusted for multiple comparison. Missing data on hsCRP for 18 patients (1.8% of the patients in extensive subsample), on antipsychotics DDD for 300 patients (30.6% of patients in extensive subsample), on PANSS positive subscale for six patients (0.6% of patients in extensive subsample), and on PANSS negative subscale for six patients (0.5% of patients in extensive subsample). SD, standard deviation; N/A, not applicable. * vs BIP, · vs MDD, # vs HC.

Table 2. Plasma BAFF and APRIL in the Full Sample Comprised by Diagnostic Groups and Healthy Controls Adjusting for Age and Sex

Cytokines	SCZ (n = 1123)	BIP (n = 846)	MDD (n = 40)	HC (n = 1212)	Group Comparison
BAFF, median (CI)	234 [228;241]	241 [233;249]	240 [227; 283]	235 [227;240]	BIP>SCZ,BIP>HC
APRIL, mean (CI)	281 [269;292]	259 [247;270]	260 [203;332]	335 [323;347]	HC>ALL,HC>SCZ,HC>BIP

SCZ, schizophrenia and other nonaffective psychotic disorders; BIP, bipolar spectrum disorder; MDD, major depressive disorder; HC, healthy control participants; ALL, all diagnostic groups; Plasma BAFF, B cell activating factor belonging to the TNF Family', presented with the units pg/ml; CI, confidence interval. Data analysis based on transformed data (reciprocal transformation). BAFF is presented using back-transformed median with estimated confidence intervals based on empirical centiles in parenthesis. Plasma APRIL, a proliferation-inducing ligand, presented with the units pg/ml. Data analysis based on log-transformed data. Back-transformed mean presented with 95% confidence interval in parenthesis. ANCOVA with post hoc tests were applied for pairwise group comparison on BAFF and APRIL. All analyses were adjusted for age and sex. Alpha level was adjusted due to multiple comparisons (Bonferroni).

BIP than in HC ($P < .001$, $d = 0.37$) (table 2). The plasma level of BAFF was higher in BIP both vs SCZ ($P = .027$, $d = 0.10$) and vs HC ($P = .040$, $d = 0.12$). No significant differences were found between SCZ subgroups. All analyses were adjusted for age and sex.

The BAFF/APRIL Ratio

The BAFF/APRIL plasma level ratio was compared between diagnostic groups and healthy control subjects. We found no significant group differences.

BAFF and APRIL and Psychotropic Medication

The analysis revealed no significant associations between BAFF and APRIL and antipsychotic medication DDD, antidepressive medication DDD, anticonvulsants DDD and lithium DDD in a subsample of patients when adjusting for age and sex. We found no significant associations between BAFF and APRIL and serum levels of the specific antipsychotic agents aripiprazole, quetiapine, risperidone, and olanzapine when controlling for age and sex and adjusting for multiple group comparisons.

BAFF and APRIL and Psychotic Symptom Load

As shown in table 3, stepwise regressions were conducted in a subsample of patients (extensive subsample, $n = 668$) to identify clinical characteristics associated with APRIL. The regression model was statistically significant ($F(1,667) = 5.8$, $P = .017$). PANSS positive subscale was significantly associated to APRIL ($t = -2.40$, $P = .017$, beta $= -0.09$) when controlling for age, sex, ethnicity, BMI, CRP, antipsychotic medication, smoking, and PANSS negative subscale. None of the other explanatory variables were significantly related to APRIL. We found no predictors with significant associations to BAFF in the regression model.

Table 3. Clinical and Demographic Predictors of Plasma APRIL in a Subsample of Patients with SCZ, BIP, and MDD ($n = 668$)

Covariates	Standardized Coefficients (Beta)	t	P-value	Adjusted R^2
Age	−0.04	−0.90	.37	0.007
Sex	0.03	1.65	.10	
Ethnicity	0.05	1.39	.17	
BMI	0.04	1.05	.29	
hsCRP	−0.01	−0.35	.73	
Smoking status	−0.02	−0.46	.65	
PANSS positive	−0.09	−2.40	.017*	
PANSS negative	−0.01	−0.30	.77	
Anti-psychotics (DDD)	0.06	1.51	.13	

SCZ, schizophrenia and other nonaffective psychotic disorders; BIP, bipolar spectrum disorder; MDD, major depressive disorder. *$P < .05$. Stepwise regression analysis was employed; Plasma APRIL, a prroliferation-inducing ligand; Ethnicity, European ethnicity in percent; BMI, body-mass-index, weight/(height)^2, (kg/m^2); Plasma hsCRP, high sensitivity C-reactive protein; antipsychotics (DDD), prescribed antipsychotics, number of defined daily doses. Smoking status (yes/no), PANSS positive, Positive and Negative Syndrome Scale, positive subscale. PANSS negative, Positive and Negative Syndrome Scale, negative subscale.

Relations Between BAFF and APRIL

There was no significant correlation between plasma level of BAFF and APRIL in the sample consisting of all patients and all HC (Pearson's $r = 0.03$, $P = .060$, ($n = 3221$)). When separating all patients ($n = 2009$) and all HC ($n = 1212$) we found a weak significant correlation between plasma BAFF and APRIL across all patients ($r = 0.05$, $P = .029$), but not in all HC ($r = -0.01$, $P = .855$). Subdivision of patients into SCZ ($r = 0.05$, $P = .127$), BIP ($r = 0.05$, $P = .138$), and MDD ($r = -0.003$, $P = .984$) showed no significant correlations between plasma levels of BAFF and APRIL.

Discussion

This is the first study of BAFF and APRIL in a well-powered sample of persons with psychosis controlling for confounders. Our main findings were: (i) lower plasma levels of APRIL in patients as a whole compared to HC; (ii) lower plasma APRIL was associated with higher positive psychotic symptom load in BIP, SCZ, and MDD, and (iii) plasma BAFF was significantly higher in BIP compared to HC and SCZ, with low effect size. The present study showing dysregulated plasma levels of BAFF and APRIL supports modulation of the TNF system in psychotic disorders.

A major finding of the current study was that APRIL levels were reduced in persons with SCZ and BIP and associated with symptom severity. We and others have previously demonstrated dysregulation of TNF pathways in people with severe mental disorders based on soluble receptors suggesting enhanced TNF activity.[60–62] The present study extends these findings suggesting that APRIL, a potential neuroprotective cytokine, is dysregulated in individuals with severe mental disorders. Studies investigating the relationship between APRIL levels and disease activity in people with autoimmune disease associated with occurrence of concurrent psychiatric symptoms, such as SLE, have showed mixed results. Some investigators have noted a weak correlation between elevated APRIL levels and disease activity,[63] while others have reported an inverse correlation between the two consistent with the findings in the current study.[64,65] In multiple sclerosis (MS), APRIL has been shown to have a protective role

in the CNS by inducing astrocytes to produce anti-inflammatory IL-10 and dampening T cell proliferation and inflammatory cytokine production.[48] Furthermore, neuronal connectivity is attenuated in SCZ and experimental studies suggest axonal growth is impaired due to glycogen synthase kinase-3 (GSK-3) dysregulation.[66] Thus, APRIL has been shown to promote axon elongation by inactivation of the isoform GSK-3β in developing hippocampal neurons.[67] Our findings involving APRIL showed low to moderate effect sizes, whereas the plasma levels of BAFF, a pivotal factor for B cell maturation and the humoral immune response, was only elevated in individuals with BIP, with low effect size, but not associated with symptom severity. BAFF is produced by CNS astrocytes and up-regulated in MS plaques as a response to inflammation.[68,69] In general, astrocytes exert a neuroprotective function.[70] However, the extent and implications of astrogliosis in individuals with severe mental disorders,[71–74] and whether dysregulation of the TNF ligands BAFF and APRIL could contribute to neuroinflammation, and unfold their effects in the CNS by crossing the blood-brain-barrier or migration of immune cells should be clarified in experimental studies. As we found no association between peripheral BAFF and APRIL and the use of antipsychotics or serum levels of antipsychotic agents, other treatment modalities would be needed to modify levels of these proteins in individuals with psychosis. While it is tempting to hypothesize a direct link between systemic levels of BAFF and APRIL, neuroinflammation and CNS pathology, these factors primarily play important roles in the regulation of B and T cell immunity. Indeed, dysregulated B and T cell function has been demonstrated in both SCZ and BIP.[75–78] The few studies conducted in patients with BIP indicate a lack of regulatory T cells,[78–80] leading to dysregulated trafficking of immune cells into the CNS, potentially enhancing demyelination, axonal loss[81] and cognitive disturbance in humans.[82] Furthermore, as BAFF and APRIL are potent growth factors for B cells and B cell-driven autoimmunity, our findings support a role for altered B cell activation in these disorders. In turn gonadal steroids are possible endogenous regulators of both BAFF and the number of B cells. Estradiol has been shown to increase BAFF mRNA levels and the relative number of mature B cells in the spleen,[83] whereas testosterone suppresses BAFF. These findings are in accordance with lower prevalence of autoimmune diseases in men than in women.[84]

There are some limitations in the current study. Circulating BAFF and APRIL are not necessarily active molecules due to soluble decoy forms of the receptors BCMA and TACI blocking the cytokines and affecting their quantification.[85,86] In the current study we have not assessed whether the measured plasma levels of BAFF and APRIL represent active or inactive forms, the relative fractions of BAFF/APRIL homotrimers and heterotrimers are unknown, and the proportion of these cytokines bound by the receptors BCMA, TACI, BAFF-R or heparan sulfate proteoglycans (HSPGs) outside the circulation was not determined. Moreover, plasma levels of these molecules may not necessarily reflect their expression in the brain. Finally, some of the associations were nominally significant, and these findings should be replicated in independent samples. Although a large number of patients was examined, association does not imply causal relationship.

To conclude, the present findings of dysregulated APRIL, and to a lesser degree BAFF levels in individuals with severe mental disorders further support the involvement of immune dysregulations in the pathophysiology. Further studies are warranted to clarify the mechanisms of this aberrant modulation of the TNF system leading to development of severe mental disorders and relationship to psychotic symptoms.

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Conflicts of Interest

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

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