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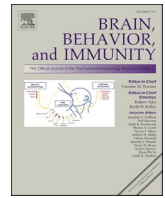
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Full-length Article

B Cell-activating factor (BAFF): A promising *trans*-nosographic biomarker of inflammation and autoimmunity in bipolar disorder and schizophrenia

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ABSTRACT

Immune dysregulation is an important aspect of schizophrenia (SZ) and bipolar disorders (BD) pathophysiology, including not only inflammatory but also autoimmune process reflective of abnormal humoral immune responses. Given that B cell-activating factor (BAFF) is an integral aspect of B lymphocyte regulation, the current study investigated BAFF in SZ and BD. 255 SZ patients, 407 BD patients and 185 healthy controls (HC) were investigated across three aspects of soluble BAFF (sBAFF) by (i) comparing sBAFF circulatory levels across SZ, BD and HC, (ii) determining potential correlations between the circulating levels of sBAFF and the genotype distribution of a functionally relevant polymorphism, namely the *TNFSF13B* 3'UTR insertion-deletion polymorphism (GCTGT>A), (iii) analyzing relationships between both sBAFF levels and 3'UTR insertion-deletion genotypes and disease risk, patients clinical characteristics and circulating levels of potent inflammatory molecules. In addition, in subsets of patients, we also searched for possible correlations between sBAFF levels and stigma of past infectious events as well as positivity for circulating systemic autoantibodies or those directed against central nervous system (CNS) structures. Studying blood derived serum and DNA, we observed that circulating sBAFF levels were significantly higher in SZ and BD patients, versus HC ($p = 5.3 \times 10^{-10}$ and $p = 4.4 \times 10^{-09}$). Patients experiencing acute episodes, versus stable patients, in between acute episodes, exhibited higher sBAFF levels ($p = 0.017$). In SZ patients, positive correlations were observed between elevated sBAFF levels and: (i) elevated positive psychotic symptoms (PANSS pos), (ii) history of childhood trauma (physical abuse), and (iii) low scores on global functioning (GAF) ($p = 0.024$, $p = 0.024$, and $p = 0.041$). We also found that the distribution of the BAFF Ins/Del genotypes was significantly correlated with circulating sBAFF levels in SZ and BD patients ($p = 0.0004$). Elevated sBAFF levels were also correlated with increased levels of pro-inflammatory markers in both SZ and BD cohorts ($p < 0.001$). Regarding infectious stigma, only patients seropositive, versus seronegative, for herpes simplex virus (HSV)1 immunoglobulin (Ig)G antibodies exhibited a significant association with high sBAFF levels ($p = 0.013$). In contrast, positivity for systemic or CNS autoantibodies was significantly associated with reduced sBAFF levels, compared to patients without autoantibodies ($p = 0.0017$). Overall, our findings indicate that BAFF may be a promising *trans*-nosographic biomarker of inflammation that is likely to offer predictive, diagnostic, and prognostic tools for the management of SZ and BD. The results therefore have practicable clinical utility given the availability of immunotherapeutic treatment options including targeted monoclonal antibodies against BAFF.

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1. Introduction

Innate and adaptive immune dysfunction in individuals with schizophrenia (SZ) and bipolar disorders (BD) have been extensively described (Khandaker et al., 2015; Simon et al., 2021) as likely stemming from complex interactions between specific interindividual immunogenetic backgrounds (Leboyer et al., 2016) and a variety of environmental stressors (Schumann, 2023). Among such processes, chronic inflammation, and auto-immunity driven by dysregulated immune cell subsets are core features of SZ and BD pathophysiology. In particular, a breakdown of the self-tolerance under the pressure of repeated environmental/antigenic stimulations with consequent chronic inflammation may underpin autoimmune processes. This is reminiscent of the non-efficient anti-infectious response/chronic low-grade inflammation/autoimmunity triptic that are commonly observed in psychiatric settings (Leboyer et al., 2016). An increased frequency of systemic auto-immune disorders is evident in SZ and BD (Benros et al., 2013), and an elevated production of autoantibodies directed against brain receptors such as the N-methyl-D-aspartate receptor (NMDA-R) highlight the clinical relevance of auto-immune processes in major mood and psychotic disorders (Jézéquel et al., 2017; Pollak et al., 2020).

Autoimmunity results from abnormal B- and T-cell recognition of self-antigens leading to B-cell autoantibody production (Yanaba et al., 2008) following B-cell differentiation. Autoantibodies can be specific to a given organ such as thyroid or pancreas or systemic having many organs as targets as exemplified by the prototypic autoimmune condition systemic lupus erythematosus (SLE) (Pisetsky, 2020). The B cell subset is therefore crucial to induce an adaptive humoral immune response along the development of inflammatory processes underpinning autoimmune processes. Notably, B lymphocyte subsets show alterations in mood disorders and schizophrenia (Bogerts et al., 2017).

Deciphering inflammatory and autoimmune processes require a focus on appropriate biomarker(s) reflective of the interactions among inflammation, immune cell subset dysfunction and environmental stressor(s)/challenges. The B-cell activating factor (BAFF) is one such important biomarker. BAFF is a cytokine belonging to the tumor necrosis factor (TNF) ligand superfamily. BAFF is a ligand for a number of receptors expressed on B-cells, including the BAFF-R (BR3), the transmembrane activator and calcium modulator to cyclophilin ligand interactor (TACI), and the B-cell maturation antigen (BCMA) receptors. These B-cell receptors interact with BAFF with different binding affinities. BAFF exists as a cell surface membrane bound molecule expressed by various immune cell subsets and as soluble circulating isoforms. Upon interaction with BAFF, the BAFF-R is involved in the triggering of naïve B cell survival and maturation, BCMA supports the survival of plasma cells in the bone marrow (Schneider et al., 1999, 2001; Vincent et al., 2014) while TACI exhibits a more complex biology (Mackay et al., 2003). Produced by monocytes, macrophages, neutrophils, and dendritic cells, BAFF is pivotal for differentiation, survival, and activation of the B lymphocytes but is also involved in monocyte, natural killer (NK) and T lymphocyte activating processes (Chang et al., 2006; Huard et al., 2001; Zhang et al., 2008). Several inflammatory models have shown that BAFF induces the secretion of pro-inflammatory molecules such as interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , IL-6, and IL-8, and its blockade inhibits the expression of their encoding genes (Chang et al., 2006; Lowin et al., 2020; Quan et al., 2020). In humans, numerous studies have shown that elevated BAFF circulating levels are associated with various inflammatory, autoimmune, and infectious disorders highlighting a role of BAFF as a master modulator of innate/adaptive immune responses that sustain inflammation and the likelihood of antibody production (Cheema et al., 2001; Kathamuthu et al., 2018; Zhang et al., 2022). Following extensive investigation in SLE, the first BAFF inhibitor, a selective anti-BAFF antibody (Belimumab), was approved for treatment (Miyazaki et al., 2022; Navarra et al., 2011).

BAFF is encoded by the *TNFSF13* gene, which is located on the

chromosome 13 (Mackay et al., 2003). The *TNFSF13* gene is polymorphic (Gottenberg et al., 2006; Kawasaki et al., 2002; Nezos et al., 2014), with the *TNFSF13B* 3'UTR insertion-deletion polymorphism (GCTGT>A) emerging from genome-wide association studies (GWAS) in the context of immune disorders (Steri et al., 2017). The uncovered at-risk A variant allele results in a shorter transcript that prevents microRNA-based inhibition with consequent increased production of the soluble BAFF isoform (sBAFF). Such functional relevance has prompted the analysis of its impacts in the context of immune-related disorders especially those underpinned by a dysregulated humoral immune processes (Steri et al., 2017).

The pivotal role of BAFF in inflammation maintenance and B lymphocyte activation have led to its extensive investigation, both at mRNA and protein levels, across diverse immune-linked conditions, including infections, inflammation, and autoimmunity but with very few investigations in psychiatric settings (Duan et al., 2022; Engh et al., 2022; Ermakov et al., 2023). While in 2022, Engh et al investigating BAFF levels in patients with major mood and psychotic disorders, observed increased BAFF level in bipolar disorders (BD) patients, versus controls, Ermakov et al, observed an increase of BAFF circulating levels in schizophrenia and Duan et al, both in SZ and BD altogether in agreement, although partially for the Engh's study, with our observations. Only one study of a small sample size of SZ patients found BAFF to be decreased possibly in relation with the studied low sample size (El Kissi et al., 2015).

In order to better clarify BAFF changes in BD and SZ, we performed a large case control study involving a sample of 662 participants consisting of 255 patients with SZ, 407 patients with BD and 185 healthy controls (HC) aiming at: (i) comparing the circulating levels of sBAFF molecules across groups, (ii) determining potential correlations between the circulating levels of sBAFF and the genotype distribution of a functionally relevant polymorphism namely the *TNFSF13B* 3'UTR insertion-deletion polymorphism (GCTGT>A), (iii) analyzing relationships between both sBAFF levels and 3'UTR insertion-deletion genotypes and disease risk, patients clinical characteristics and circulating levels of inflammatory factors. In addition, in subsets of patients, we also searched for possible correlations between sBAFF levels and stigma of past infectious events as well as positivity for systemic and CNS autoantibodies.

2. Material and methods

2.1. Study sample

A total of 662 patients (255 with SZ, and 407 with BD) were recruited during or after hospitalization in a French university affiliated psychiatric department, namely the department of psychiatry of the Henri Mondor Hospital, Créteil, France. 185 healthy controls (HC) were enrolled in the clinical investigation center of the same hospital. Patients and controls were included under the framework of a French National granted project termed I-GIVE (Immuno-Genetics, Inflammation, retroVirus, Environment).

Inclusion criteria were as follow: (i) current diagnosis of SZ or BD according to DSM-IV-TR criteria (Diagnostic and statistical manual of mental disorders, 4th ed, 1994) for patients and no personal or family history of any psychiatric illness for HC. The French version of the diagnostic Interview for Genetic Studies (DIGS) was used for both patient's diagnosis and HC assessments (Nurnberger et al., 1994); (ii) age between 18 and 65 years; (iii) absence of recent vaccination or infectious events; (iv) absence of any ongoing comorbid inflammatory or neurological disorder and (v) absence of any ongoing immunomodulatory treatment. The study was approved by the French local Ethic Committee (Henri Mondor Hospital, Créteil, France) (CPP Ile de France IX, number 08-046) and written informed consent was obtained from each study participant.

2.2. Clinical assessments

Clinical characteristics of patients including substance abuse or dependence (alcohol, cannabis, tobacco), history of suicide attempt, number of episodes and of hospitalizations, age at onset and current treatments were recorded when information was available.

For BD patients, manic symptomatology was assessed using the Young Mania Rating Scale (YMRS) (Young et al., 1978) while depressive symptoms were evaluated using the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The Calgary Depression Scale (CDSS) (Bernard et al., 1998) was used to measure depression in patients with SZ. For all patients, psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

The following cutoff scores were used to define acute ongoing depression (MADRS \geq 15 or CDSS \geq 6), mania (YMRS \geq 12) or psychosis (PANSS \geq 60). Patients with clinical scale scores below these cut-offs were considered stable and without acute symptomatology.

As mentioned above, healthy controls (HC) were enrolled in the clinical investigation center of the Henry Mondor hospital where the patients were included. This center, alongside other missions, is totally dedicated to thorough selection and recruitment of healthy individuals according to the guidelines of given research protocols. In our case, the selection was based on somatic examination and then interview with the DIGS to assess personal and familial history of psychiatric disorders using the National Institute for Mental Health Family Interview for Genetic Studies. Only those, with neither personal nor family history (first degree) of psychiatric disorders, affective disorders or suicidal behavior were included. HC were, as possible as, matched with patients in terms of age and gender. No clinical assessments were done for healthy controls given the exclusion of individuals with relationship with mental disorders. All patients and controls were of French descent from mainland France.

All participants were carefully interviewed by trained psychiatrists or psychologists.

2.3. Assessment of childhood maltreatment

A history of childhood maltreatment (CM) was recorded using the Childhood Trauma Questionnaire (CTQ) that retrospectively investigates five subtypes of CM, namely: physical (AP), emotional (AE) and sexual (AS) abuse; physical neglect (NP) and emotional neglect (NE) (Bernstein et al., 2003). The reliability and validity of the questionnaire have been previously demonstrated (Paivio and Cramer, 2004). In this study, the short French version (28 items) of the CTQ was used (Paquette et al., 2004). A subject was considered as having undergone maltreatment when indicating experience of at least one type of maltreatment in a “moderate” to “severe” manner according to the cut-offs of the CTQ subscales. Supplementary Table 1 describes the scores of each CM subtype.

2.4. Blood sampling

Venous blood was obtained from patients and controls without requiring fasting between 7:00 am and 9:00 am on weekdays. Five milliliters of peripheral blood were drawn by venipuncture and allowed to clot for 1 h before centrifugation. Serum samples were stored in 0.5 ml aliquots at -80°C and thawed on ice at the time of analysis. The experiments were carried out when a batch of patients or HC samples reach 30. As the recruitment of patients was more important in terms of number, HC characteristics were established towards sex and age matching.

2.5. Determination of the circulating levels of sBAFF and of the BAFF 3'UTR insertion/deletion genetic variation

Circulating serum levels of sBAFF were determined using commercially available ELISA kits (Bio-technie, Minneapolis, USA) according to the manufacturer's instructions. All samples were tested in duplicates.

For further analysis of the BAFF Insertion/Deletion genetic variation, genomic DNA was extracted from EDTA-treated peripheral blood samples using the automated Maxwell DNA purification system (Promega, USA) and quantified by the Quant-iT™ PicoGreen® dsDNA Assay Kit (Thermo Fisher Scientific, USA). The genotyping assay was performed using a TaqMan® 5'-nuclease assay (Applied Biosystems, Foster city, CA, USA) with allele-specific fluorogenic oligonucleotide probes for BAFF alleles i.e., Insertion or Deletion polymorphism (GCTGT>A) allowing the discrimination of the genotypes of each studied pair of alleles. The primer and probe sequences were designed by assay on demand (Applied Biosystems, Foster city, CA, USA).

2.6. Measurement of circulating levels of inflammatory molecules

The circulating serum/plasma levels of a panel of pro- and anti-inflammatory molecules reflecting the main inflammatory pathways were determined for the whole study sample. Serum concentrations of cytokines namely interleukin (IL)-2, IL-4, IL-6, IL-10, IL-12/IL-23p40, interferon gamma (IFN γ), and tumor necrosis (TNF) α as well as the acute phase molecule, C-reactive protein (CRP), which were measured using MesoScale Discovery (MSD) human V-Plex electro-chemiluminescence assay (MSD, Rockville, Maryland, USA). Plasma levels of the soluble isoforms of beta 2-microglobulin (s β 2M) were evaluated using a commercially available ELISA kit (BioVendor, Brno, Czech Republic). Both methods were performed according to manufacturer's recommendations. Inflammatory markers with more than 15 % of missing data and those with more than 50 % of concentrations outside the limit of detection (LLOD) were excluded from the analysis.

2.7. Anti-infectious antibody measurements

In order to uncover any potential infectious trigger of subsequently observed inflammatory processes, we screened a subsample of 387 patients for the presence of circulating anti-pathogen antibodies known to be associated with psychiatric disorders namely anti-Toxoplasma gondii, anti-cytomegalovirus (CMV) and anti-herpes simplex virus (HSV). Testing for IgM and IgG types of antibodies was performed as previously described using solid-phase enzyme immunoassays (Angrand et al., 2021; Dickerson et al., 2003, 2007). The participants were rated seropositive if the optimal density value was above or at the infection point in the sample distribution. For all antibodies, sero-intensity, defined as the quantitative level of antibody in terms of standardized units, was used as a continuous variable.

2.8. Autoantibodies profiling

In a subset of 118 patients with BD and 68 patients with SZ, we tested the presence of the following systemic autoantibodies: anti-thyroid peroxidase (TPO), anti-thyroglobulin TG), anti-tissue transglutaminase (TTG), anti-deamidated gliadin protein (DGP), anti-gliadin, anti-saccharomyces (ASCA) and anti-glutamic acid decarboxylase (anti-GAD). Using qualitative ELISA (Aesku Lab, Wendelsheim, Germany), all patients results were recorded, and patients informed as to whether positive or negative for the tested auto-Abs.

Similarly, 148 patients with BD and 89 patients with SZ were tested for the presence of autoantibodies directed against synaptic receptors, namely anti-N-methyl-D-aspartate (NMDA) receptor (NMDA-R) antibodies and anti-nicotinic acetylcholine-receptor $\alpha 7$ ($\alpha 7$ AChR) antibodies. Both types of antibodies were detected as previously described, namely using cell-based assays (Jézéquel et al., 2017) or ELISA (Darrau

et al, in press).

2.9. Statistical analysis

Demographic characteristics of the BD, SZ and HC groups were compared using chi squared (χ^2) test for categorical variables and Wilcoxon signed rank or Student's *t*-test for continuous variables. As the soluble BAFF (sBAFF) scores did not follow a normal distribution (as shown by Shapiro tests using $p < 0.05$, and graph), the correlations between sBAFF with the clinical scores were first assessed using Spearman's correlation coefficient followed by a suitable significance test. Subsequently, the Wilcoxon signed-rank and Kruskal-Wallis rank sum tests were performed to assess the associations between sBAFF and the categorical variables (diagnosis/category, namely BD, SZ, HC) and disease phase (acute and stabilized). A linear regression model was used to evaluate relationships between age and gender as independent variables and sBAFF level as a continuous dependent variable. The validity of the linear regression analysis was tested by checking the Studentized residual. P-values were two-tailed, and significance was defined as $P < 0.05$ for all statistical tests, which were performed using R software, version 4.0.3 (<https://www.r-project.org/>) and Graphpad PRISM 9 to generate graphs. P-values were corrected using the Bonferroni method when needed and then were designated as a corrected *p* value (pc).

3. Results

Demographic, clinical and immuno-inflammatory characteristics of the study participants are depicted in [Table 1](#).

The total sample included 255 patients with SZ, 407 patients with BD and 185 healthy controls (HC). The mean ages at inclusion of patients were 37.0 (± 11.6) years and 40.7 (± 13.9) years for SZ and BD patients, 31 % and 54.5 % females respectively. The HC group was comprised of 54.6 % females, with a mean age of 35.7 (± 13.3) years. The age of onset of SZ was 22.8 (± 6.5) years and of BD 24.9 (± 9.3) years, of whom 25.7 % and 45.2 % presented an early onset of their psychiatric illness (≤ 18 years and ≤ 22 years for SZ and BD respectively).

The analysis of the distribution of circulating sBAFF levels among the whole sample of patients (SZ and BD) revealed a statistically significant increase in patients, versus HC (mean sBAFF: 905.6 vs. 760.0, $p < 0.0001$, respectively) ([Fig. 1A](#)). Comparison of sBAFF levels with SZ and BD separately also showed significant differences, versus HC, (mean sBAFF: 905.2 vs. 760.0, $p = 5.3 \times 10^{-10}$ and 905.5 vs. 760.0, $p = 4.4 \times 10^{-09}$ in SZ and BD patients respectively, versus HC) ([Fig. 1B](#)). Further multivariate analysis adjusted for sex and age confirm the statistically significant increase of sBAFF levels in SZ and BD as compared to HC ($p < 0.001$ and $p < 0.001$ respectively). This significant difference was most strongly evident in female, versus male, patients ($P < 0.001$).

We then examined if the observed difference was driven by disease status and found that the mean sBAFF was significantly higher in the acutely ill, versus stabilized, SZ and BD subgroups combined, (mean: 919.1 vs 884.0; $p = 0.017$) ([Fig. 2](#)). After adjusting for sex and age, elevated sBAFF level was still associated with acute, versus stabilized, status in patients' group ($p = 0.042$) as was the case when age ($p = 0.042$), with female, versus male, patients again being even more significant ($P < 0.001$). After stratifying patients according to their diagnosis of SZ or BD, the mean sBAFF was no longer significantly increased in the acute, versus stable, phase. However, both SZ and BD groups showed a trend for raised sBAFF in the acute phase (mean: 925.6 \pm 249.7 vs 869.2 \pm 252.1, $p = 0.08$ and 914.5 \pm 277.4 vs 892.4 \pm 346.0, $p = 0.09$, in SZ and BD respectively) (data not shown). Euthymic/stabilized patients, versus HC, showed higher sBAFF levels (884.2 vs. 760.0, $p < 0.0001$). Such results suggest sBAFF may be a state biomarker.

Analyzing the potential correlations between circulating sBAFF levels and symptom characteristics, high levels of sBAFF in SZ were positively correlated with high scores of positive psychotic symptoms

Table 1

Demographic and clinical characteristics of the study subjects.

Variable	Missing value (%)	BD (n = 407)	SZ (n = 255)	HC (n = 185)	Overall p-value
Age (mean \pm SD)	0	40.7 \pm 13.9	37.0 \pm 11.6	35.7 \pm 13.3	< 0.001
Sex: F (%)	0	54.5	31.0	54.6	< 0.001
Acute status (%)	0	62.2	65.5	–	0.387
Early onset (%)	21.6	45.2	25.7	–	< 0.001
Age of first episode	21.6	25.0 \pm 9.3	22.8 \pm 6.5	–	0.163
Clinical variable (mean \pm SD)					
PANSS Positive	30.8	14.9 \pm 7.7	18.5 \pm 6.9	–	< 0.001
PANSS Negative	31.3	11.6 \pm 4.4	19.3 \pm 7.3	–	< 0.001
PANSS Global	30.8	28.7 \pm 8.0	34.8 \pm 8.9	–	< 0.001
PANSS Total	30.5	55.4 \pm 16.1	73.0 \pm 19.0	–	< 0.001
MADRS Total	28.4	13.7 \pm 10.4	13.0 \pm 8.5	–	0.939
YMRS Total	21.8	12.1 \pm 11.2	9.3 \pm 9.0	–	0.014
CGI	24.8	4.2 \pm 1.4	4.7 \pm 1.4	–	< 0.001
GAF-SYMP	26.0	47.5 \pm 19.6	39.5 \pm 18.5	–	< 0.001
GAF-HANDICAP	39.6	48.0 \pm 15.7	37.5 \pm 12.8	–	< 0.001
TCDSS	39.3	5.5 \pm 9.4	3.8 \pm 4.5	–	0.522
CTQ Total	42.9	42.3 \pm 14.3	45.5 \pm 16.1	33.7 \pm 8.4	< 0.001
CTQ – Physical Neglect	39.0	7.4 \pm 2.8	8.4 \pm 3.7	6.5 \pm 2.0	< 0.001
CTQ – Emotional Neglect	39.3	11.6 \pm 5.1	12.0 \pm 5.0	9.4 \pm 3.9	< 0.001
CTQ – Emotional Abuse	38.1	10.0 \pm 5.1	10.9 \pm 5.4	6.6 \pm 2.9	< 0.001
CTQ – Physical Abuse	37.5	6.9 \pm 3.3	7.7 \pm 4.2	6.0 \pm 2.1	< 0.001
CTQ – Sexual Abuse	38.7	6.2 \pm 2.4	7.3 \pm 4.9	5.3 \pm 1.3	< 0.001
CTQ – Denial	31.3	0.6 \pm 0.9	0.5 \pm 0.9	0.8 \pm 1.0	0.030

Abbreviations: BD: bipolar disorder; SZ: schizophrenia; HC: healthy control; PANSS: positive and negative syndrome scale; YMRS: Young Mania Rating Scale; CDSS: Calgary Depression Scale; MADRS: Montgomery-Asberg Depression Rating Scale; GAF: Global Assessment of Functioning scale; GAF-SYMP: GAF symptom score; GAF-HANDICAP: GAF Handicap score; CGI: clinical global impression; CTQ: childhood trauma questionnaire. Overall p-values: p-value after adjustment for multiple testing.

(Pos-PANSS), history of childhood trauma (physical abuse, CTQ scale), and low scores of global functioning (GAF scale) ($p = 0.024$, $p = 0.024$ and $p = 0.041$ respectively) ([Table 4](#)). Overall, such data indicates that more severe clinical presentations are associated with elevated sBAFF levels in schizophrenia. No significant correlation was noted between sBAFF levels and any of the assessed mood symptoms in BD patients.

To explore if high sBAFF production is determined by genetic factors, we analyzed the potential associations between the genotypes of the functionally relevant BAFF 3'UTR insertion-deletion (Ins/Del) polymorphism (GCTGT>A) and sBAFF circulating levels. In the whole cohort of patients, we found that the mean sBAFF increases in a linear manner along the BAFF Ins/Del genotypes (Ins/Ins = 862.4, Ins/Del = 1026.7, Del/Del = 1248.1 Overall $p = 0.0004$ and Ins/Ins vs Ins/Del + Del/Del = 862.4 vs 1038.3; $p = 0.0001$) ([Fig. 3A](#) and [B](#)). Such data indicates that elevated sBAFF in the group of combined patients is strongly determined by the Del allele in a dominant manner. This significant association still

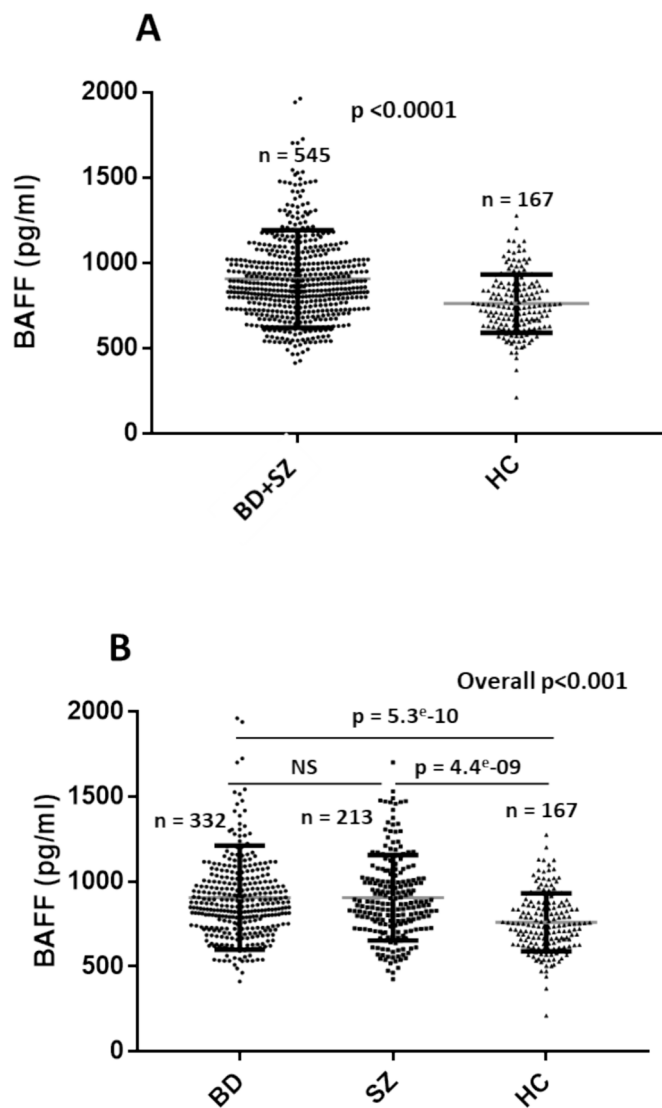


Fig. 1. Analysis of the distribution of circulating sBAFF levels among the whole sample of patients, and separately in SZ and BD patients and healthy controls. (A) Statistically significant increase in patients (SZ+BD) as compared to HC (mean sBAFF: 905.6 vs. 760.0. $p < 0.0001$ respectively in patients and HC). (B) Statistically significant increase in SZ and BD patients as compared to HC (mean sBAFF: 905.2 vs. 760.0. $p = 4.4 \times 10^{-09}$ in SZ vs. HC and 905.5 vs. 760.0. $p = 5.3 \times 10^{-10}$ in BD vs. HC).

held after adjusting for sex and age, with the high sBAFF levels being associated with the deletion alleles of the BAFF Ins/Del variants ($P < 0.002$) (Table 2). sBAFF levels according to BAFF Ins/Del genotypes was observed when SZ and BD patients were analyzed separately (Ins/Ins = 863.8, Ins/Del + Del/Del = 1055.8; $p = 0.017$ and Ins/Ins = 861.4, Ins/Del + Del/Del = 1014.0; $p = 0.0043$ for SZ and BD patients respectively) (Fig. 3C and D). The association of sBAFF levels with BAFF Ins/Del genotypes were also evident when patients and HC were pooled (overall $p < 0.0001$) (data not shown).

To determine the immunoinflammatory background either overall or in correlation with sBAFF, we analyzed the distribution of selected inflammatory molecules in SZ and BD, versus HC. We observed that the circulating level of IL-6, IL-10, TNF- α , CRP and $\beta 2M$ were significantly higher in patients than in controls, with results shown as SZ vs BD vs HC [mean \pm SD $^\circ$, IL-6: 1.4 ± 3.2 vs 1.5 ± 8.1 vs 0.4 ± 0.4 , adj $P < 0.001$; IL-10: 0.4 ± 0.4 vs 0.5 ± 1.5 vs 0.2 ± 0.2 , adj $P < 0.001$; TNF- α : 5.3 ± 9.1 vs 4.5 ± 12.8 vs 1.7 ± 0.7 , adj $P < 0.001$; CRP: 5.4 ± 13.5 vs 5.1 ± 14.3 vs 2.8 ± 5.9 , adj $P = 0.009$ and $\beta 2M$: 1.6 ± 0.5 vs 1.7 ± 0.6 vs 1.5 ± 0.4 , adj

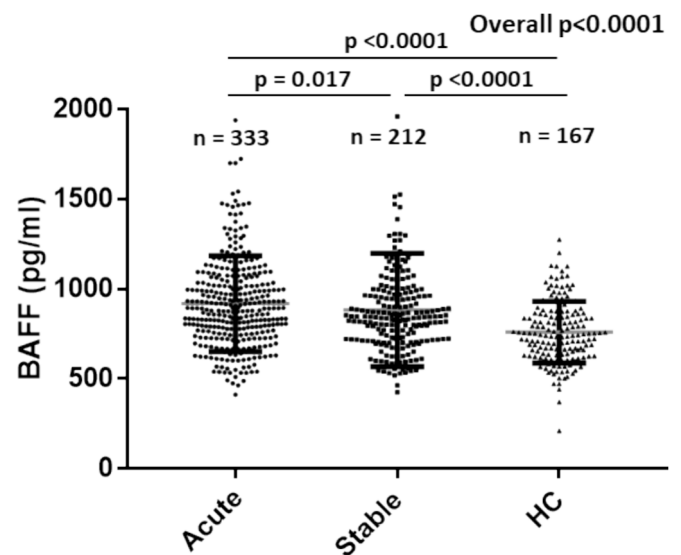


Fig. 2. Analysis of sBAFF distribution according to acute and stable phase as compared to HC (mean; 919.1 vs. 884.2 vs. 760.0. Overall $p < 0.0001$ in acute, stable phase and HC respectively). Acute vs HC (Kruskal-wallis test; 919.1 vs. 760.0. $p < 0.0001$; Stable phase vs HC (Kruskal-wallis test; 884.2 vs. 760.0. $p < 0.0001$; and Acute vs Stable phase (Wilcoxon test; 919.1 vs. 884.2. $p = 0.017$).

$P < 0.001$) (Table 1). In the SZ cohort, high circulating sBAFF levels were significantly associated with increased levels of IL-12/IL-23p40, CRP and $\beta 2M$ ($p = 0.002$, 0.017 and 0.002 respectively) and low levels of IL-2 ($p = 0.036$) (Table 3A). In the BD cohort, high levels of sBAFF were significantly associated with high levels of TNF- α , IL-6, IL-12/IL-23p40, IFN- γ , IL-10, CRP and $\beta 2M$ ($p < 0.001$) (Table 3B).

Analysis of sBAFF levels according to infectious serological status, showed that only patients seropositive, versus seronegative, for HSV1 IgG antibodies exhibited a significant association with a high sBAFF levels (898.3 vs 837.4; $p = 0.013$) (Fig. 4). No association was observed between sBAFF levels and IgG antibodies directed against Toxoplasma or CMV (data not shown).

Finally, we evaluated the potential associations between circulating levels of sBAFF and the positivity for selected systemic/peripheral (anti-TPO, anti-TTG, anti-gliadin, anti-deaminated gliadin peptide and anti-saccharomyces) or CNS (anti-NMDA-R and anti- $\alpha 7AChR$) autoantibodies. Such antibodies reflect underlying autoimmune processes and intriguingly revealed that positivity for one or more autoantibodies was significantly associated with reduced sBAFF level, versus patients without any autoantibodies (mean: 827.6 vs 902.8; $p = 0.056$ or 763.3 vs 865.0; $p = 0.0017$, respectively) (Fig. 5). We also evaluated the possible additive effect of the studied autoantibodies and failed to uncover any change when considering one versus multiple autoantibodies (data not shown).

4. Discussion

In the era of precision medicine in psychiatry, uncovering and validating accurate biomarkers for a given disorder is a pivotal step not only for the understanding of the underlying pathophysiological processes but also, and above all, to allow selection of homogeneous subgroups of patients eligible for innovative targeted therapeutic strategies. The ever-growing area of immune dysregulation in psychiatric disorders offers an important direction, although considerably complicated by the vast array of diverse immune-linked processes. Given the frequently observed conjunction of pro-inflammatory and dysfunctional humoral immune processes either at cellular or organ levels, the current study explored the potential involvement of the B cell activating factor (BAFF) in SZ and BD. We strived to examine the association of sBAFF with some

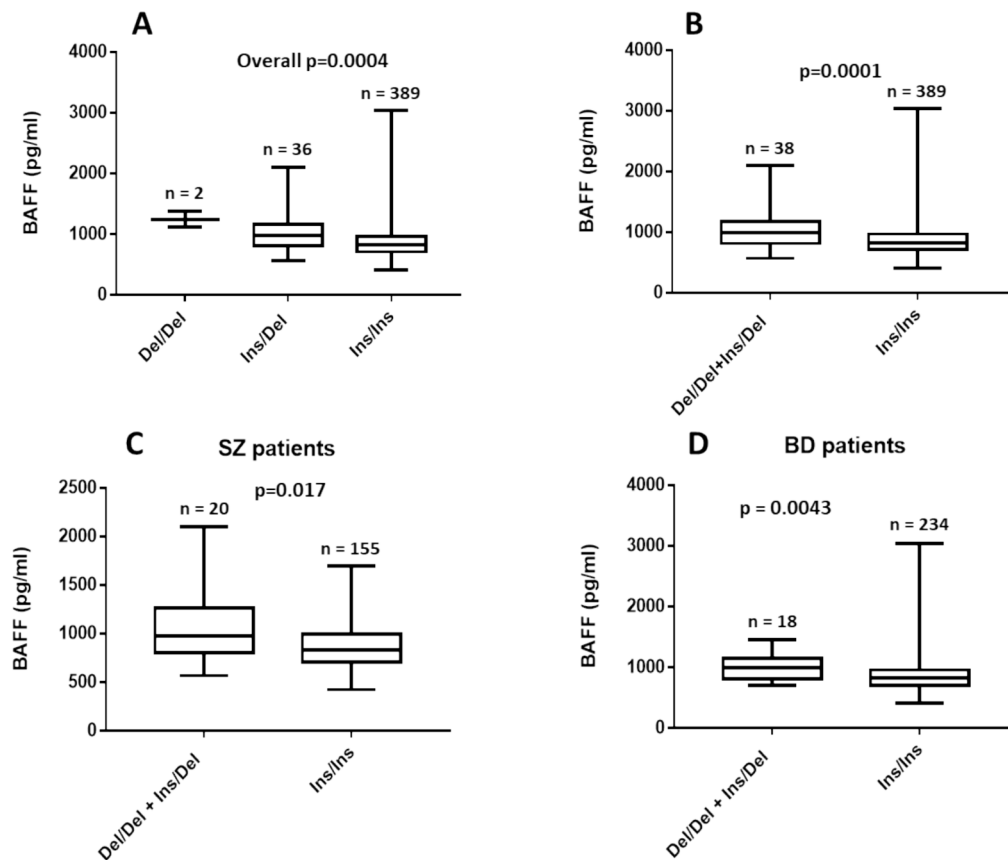


Fig. 3. Analysis of sBAFF levels according to the genetic distribution of the BAFF Ins/Ins, Ins/Del and Del/Del genotypes in the whole cohort of patients and in the samples of SZ and BD patients. (A and B) In the whole cohort of patients BAFF genotypes (Ins/Ins = 862.4, Ins/Del = 1026.7, Del/Del = 1248.1 Overall p = 0.0004 (Ins/Ins vs Ins/Del + Del/Del = 862.4 vs 1038.3; p = 0.0001). (C) In SZ patients BAFF genotypes (Ins/Ins = 863.8, Ins/Del + Del/Del = 1055.8p = 0.017). (D) In patients with BD BAFF genotypes (Ins/Ins = 861.4, Ins/Del + Del/Del = 1014.0p = 0.0043).

Table 2

Multivariate linear regression analysis adjusted for sex and age.

sBAFF			
Predictors	Estimates	CI	p
(Intercept)	2.228	2.219 – 2.237	<0.001
Age at inclusion	0.000	0.000 – 0.000	0.027
SEX [M]	-0.005	-0.007 --	0.002
BAFF Ins/Del [Ins/Ins vs Ins/Del + Del/Del]	-0.011	-0.019 --	0.002
Disease status [Acute vs Stable]	0.003	0.000 – 0.006	0.044
Observations	426		
R ² / R ² adjusted	0.081 /	0.070	

of the many factors implicated in the development of psychotic disorders, including: trigger and maintenance of inflammatory processes, interplay with other inflammatory molecules, induction of autoimmunity and history of possible involvement of stressor events including past infections and/or childhood maltreatment (see Table 5).

Analysis of the distribution of circulating sBAFF levels in SZ, BD and HC samples showed that SZ and BD, versus HC, either separately or combined had higher sBAFF levels. Moreover, sBAFF levels were higher in patients in an acute, versus stabilized, phase. Elevations in circulating sBAFF were especially high in female patients. Although to a smaller degree than for patients in an acute episode, stabilized SZ and euthymic BD patients also exhibited high sBAFF levels, versus HC.

sBAFF levels are known to be increased in a large spectrum of immune-related pathological conditions, including inflammatory and autoimmune disorders as well as severe infections (Cheema et al., 2001;

Table 3

Correlations between sBAFF and circulating levels of inflammatory markers in SZ (A) and BD (B) patients.

A		
Variable	Correlation	p-value
sβ2M	0.21	0.002
IFN-γ	0.12	0.073
IL-2	-0.14	0.036
IL-4	-0.08	0.27
IL-6	0.1	0.13
IL-10	0.03	0.632
IL-12/IL-23p40	0.21	0.002
TNF-α	0.11	0.107
CRP	0.19	0.017
B		
Variable	Correlation	p-value
sβ2M	0.23	<0.001
IFN-γ	0.2	<0.001
IL-2	-0.06	0.269
IL-4	-0.05	0.357
IL-6	0.18	<0.001
IL-10	0.18	<0.001
IL-12/IL-23p40	0.2	<0.001
TNF-α	0.22	<0.001
CRP	0.2	<0.001

Kathamuthu et al., 2018; Teixeira et al., 2017; Zhang et al., 2022). Increased sBAFF expression is evident in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), chronic inflammatory bowel diseases (IBD), Sjogren’s syndrome (SD), systemic sclerosis (SS) and a variety of

Table 4

Immunological, immunogenetic, infectious and autoimmune characteristics of the study subjects.

Variable	Missing value (%)	BD (n = 407)	SZ (n = 255)	HC (n = 185)	Overall p-value
Biomarkers		(mean ± SD)			
BAFF	15.9	905.5 ± 306.8	905.2 ± 251.4	760.0 ± 171.1	< 0.001
sβ2M	8.5	1.7 ± 0.6	1.6 ± 0.5	1.5 ± 0.4	< 0.001
IFN-γ	10.3	6.5 ± 12.3	6.0 ± 10.4	7.0 ± 14.5	0.384
IL-2	10.3	0.1 ± 0.4	0.1 ± 0.5	0.1 ± 0.2	0.975
IL-4	10.3	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.783
IL-6	10.3	1.5 ± 8.1	1.4 ± 3.2	0.4 ± 0.4	< 0.001
IL-10	10.3	0.5 ± 1.5	0.4 ± 0.4	0.2 ± 0.2	< 0.001
IL-12/IL-23p40	10.3	108.5 ± 77.1	101.8 ± 61.6	96.2 ± 51.3	0.487
TNF-α	10.3	4.5 ± 12.8	5.3 ± 9.1	1.7 ± 0.7	< 0.001
CRP	23.3	5.1 ± 14.37	5.4 ± 13.5	2.8 ± 5.9	0.009
BAFF Ins/Del polymorphism		n (%)			
Ins/Ins genotype	23.3	261 (92.9)	167 (89.3)	168 (92.3)	0.366
Ins/Del + Del/Del genotypes		20 (7.1)	20 (10.7)	14 (7.7)	
infectious serology		n (%)			
serology Pos: TOXO	38.8	172 (62.5)	97 (64.2)	–	0.729
serology Pos: HSV-1	38.8	165 (60)	83 (55)	–	0.314
serology Pos: CMV	38.8	161 (58.5)	87 (57.6)	–	0.852
Autoantibodies profiling		n (%)			
Systemic autoantibodies Pos	71.9	54 (45.6)	37 (55.2)	–	0.256
Central autoantibodies Pos	64.2	28 (18.9)	10 (11.2)	–	0.119

Abbreviations/symbols: BD: bipolar disorder; SZ: schizophrenia; HC: healthy control; sβ2M: soluble Beta 2 microglobuline; IFN-γ: interferon gamma; IL: interleukin; CRP: C-reactive protein; TNF-α: tumor necrosis factor; Ins/Del: Insertion/Deletion;; TOXO: Toxoplasma; HSV-1: herpes simplex virus; CMV: cytomegalovirus; Pos: Positive; Overall p-values: p-value after adjustment for multiple testing.

infectious conditions including septicemia, tuberculosis, malaria and *Helicobacter pylori* infection (Munari et al., 2014). These conditions are intimately associated with inflammation and/or autoimmunity, with some being comorbid with psychotic disorders as evidenced in large nation-wide studies (Benros et al., 2013; Eaton et al., 2006; Wang et al., 2018). Such data adds support to the inclusion of SZ and BD as immune-related disorders, with the data in the current study supporting sBAFF as a promising candidate biomarker in immune-psychiatric disorders. Only two studies explored the potential influence of circulating sBAFF levels on the development of psychiatric disorders (Duan et al., 2022; Engh et al., 2022). The study by the Andreassen's group on large samples of SZ, BD and MDD patients showed circulating sBAFF levels to be increased only in BD patients, versus healthy controls (Engh et al.,

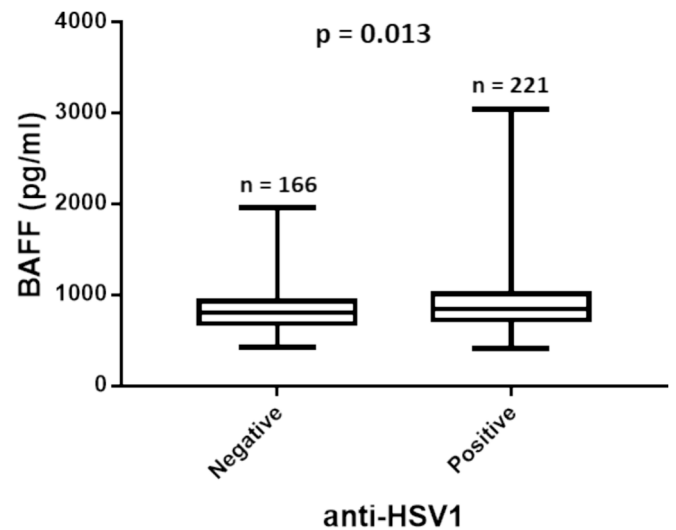


Fig. 4. Analysis of the distribution of circulating sBAFF levels according to the HSV1 serology status revealed that the patients with seropositivity for HSV1 IgG antibodies exhibited a significant association with a high level of BAFF as compared to those with seronegative status (898.3 vs 837.4; $p = 0.013$).

2022). In contrast, a very small sample study of drug free acutely ill SZ patients reported an intriguing and contra-intuitive lower level of sBAFF and IL-17 molecules (El Kissi et al., 2015). More recently, another very small sample study of acutely ill SZ and BD patients after monotherapy indicated that increased sBAFF levels at remission could potentially be a state marker of treatment response (Duan et al., 2022). Similarly, sBAFF levels in patients with recurrent depression were found to be initially low at presentation but to gradually increase over the course of treatment (Schmidt et al., 2019).

The most important observation in the current study pertains to the increased circulating sBAFF levels being isoform-determined regardless of diagnosis (SZ or BD) or state (acute or non-acute). Variation of sBAFF levels can therefore constitute either a trait or a state marker or both in case of disease follow up. This is unusual in psychiatry, whilst indicating the relevance of sBAFF as a potential marker of inflammation in both SZ and BD, as well as an enrichment marker and endpoint to be used in future clinical trials of immune-modulatory treatment. Using sBAFF as a blood-based biomarker may help to refine the nature of inflammatory processes, thereby better clarifying patient subgroups in clinical trials of immunomodulatory compounds. Another important finding in the current study is the raised sBAFF levels in females, parsimonious with the heightened levels of auto-immune disorders in females (Angum et al., 2020), which may be attributed to hormonal pathways (Desai & Brinton, 2019) and perhaps ultimately to processes underpinning hormonal dysregulation.

To clarify how out data linked to inflammation, correlations between sBAFF levels and inflammatory molecules were analyzed, using inflammatory factors reflecting the main immune pathways namely T helper 1 (Th1) (IL-1, IL-2, IL-6, IL-12, IL-17, IL-18, INFγ, TNFβ, and TNFα), Th2 (IL-4, IL-5, IL-6, IL-9, IL-13, and IL-17E) and Th17 (TGF-β, IL-6, IL-23). A diverse array of pro-inflammatory cytokines and counter-regulatory cytokines can be expressed in SZ and BD, generally attributable to dynamic dysregulation in patterned immune system responses (Khandaker et al., 2015; Leboyer et al., 2016; Leboyer et al., 2021; Tamouza et al., 2021). The current study showed significant correlations between sBAFF levels and IL-12/IL-23p40, CRP and sβ2M in the SZ cohort and TNF-α, IL-6, IL-12/IL-23p40, IFN-γ, IL-10, CRP and sβ2M in BD patients. Such data reinforce the relevance of BAFF interactions with the main immune pathways (Lyakh et al., 2008) including for example the heightened Th1 and Th17 responses that are often characteristic of SZ (Debnath & Berk, 2014) and which may be induced/amplified by IL-

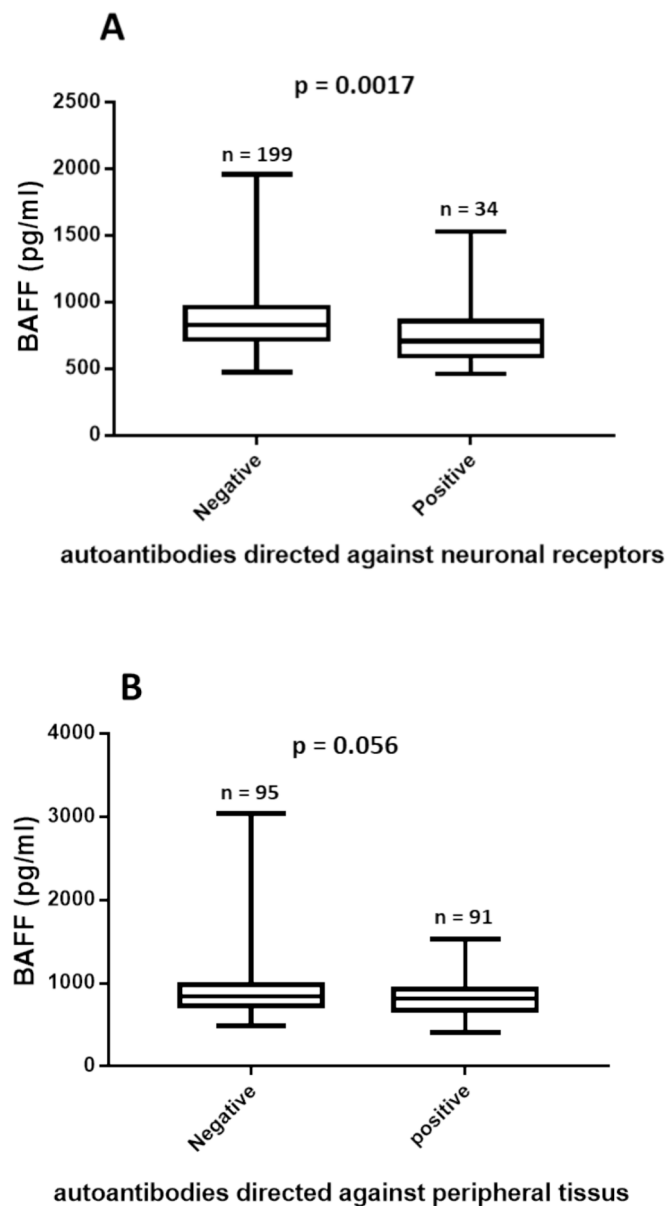


Fig. 5. Analysis of the distribution of circulating sBAFF levels according to the autoantibodies status showed that the positivity for the central (A) and peripheral (B) autoantibodies was significantly associated with reduced level of sBAFF as compared to that of patients without any autoantibodies (mean: 827.6 vs 902.8; $p = 0.056$ or 763.3 vs 865.0; $p = 0.0017$, respectively).

12 effects on Th1 responses and IL-23 on Th17 responses (Happel et al., 2005). Notably, stimulation of IL-23 by bacterial components at toll-like receptor 2 and the cytoplasmic receptor nucleotide oligomerization domain-containing protein 2 (NOD2) link the IL-23 increase to the two pivotal sensors previously implicated in BD pathophysiology (Oliveira et al., 2014a; Oliveira et al., 2014b). Hence, the observed disease associated correlations between sBAFF and inflammatory markers showed that some of them are shared between the two conditions likely reflecting a transversal role for sBAFF in generating inflammation rather than specific signatures. Clearly, this will have to be clarified in future studies. However, it is equally clear that sBAFF is significantly associated to inflammatory processes, including both innate and adaptive immune responses (Moisini and Davidson, 2009).

We then looked for a potential genetic control of circulating sBAFF levels by analyzing the distribution of a functionally relevant mutational event namely the 3'UTR insertion-deletion polymorphism (GCTGT>A),

Table 5

Correlation matrix between sBAFF and clinical variables in SZ.

Variable	Correlation	p-value
Age at inclusion	0.1	0.14
Age of the first episode	-0.12	0.114
MADRS Total	0.02	0.821
CDSS Total	-0.04	0.553
YMRS Total	0.13	0.08
PANSS Total	0.01	0.854
PANSS Positive	0.17	0.024
PANSS Negative	-0.04	0.548
PANSS Global	-0.04	0.592
GAF-SYMP	-0.17	0.024
GAF-HANDICAP	-0.02	0.791
CGI	0.11	0.157
CTQ Total	0.14	0.131
CTQ – Physical Neglect	0.04	0.652
CTQ – Emotional Neglect	0.03	0.736
CTQ – Emotional Abuse	0.12	0.17
CTQ – Physical Abuse	0.18	0.041
CTQ – Sexual Abuse	0.11	0.224
CTQ – Denial	-0.04	0.615

Abbreviations: PANSS: positive and negative syndrome scale; YMRS: Young Mania Rating Scale; CDSS: Calgary Depression Scale; MADRS: Montgomery-Asberg Depression Rating Scale; GAF: Global Assessment of Functioning Scale; GAF-SYMP: GAF symptom score; GAF-HANDICAP: GAF Handicap score; CGI: clinical global impression; CTQ: childhood trauma questionnaire.

known to abolish a fixation site for a microRNA with consequent over-expression of sBAFF molecules. Accordingly, we found that the mean sBAFF increase in a linear manner along the BAFF Ins/Del genotypes with the Del allele exerting its effect in a dominant manner. Such genetic effect was observed across the three studied cohorts as well as across clinical status, indicating that this polymorphism is a significant determinant of sBAFF expression. As well as contributing to the understanding of processes significantly contributing to variations in sBAFF production, the sBAFF polymorphism may provide an additional biomarker which could be useful to predict the development of inflammatory/autoimmune processes in at risk individuals or in patients with first episode psychosis.

Given the pivotal role of BAFF in B lymphocyte development and consequently in the development of autoimmunity, we screened subsamples of the studied cohorts for the presence of common systemic autoantibodies previously demonstrated to be comorbid of SZ or BD or both. These latter target organs/pathways including the thyroid gland (anti-TPO and anti-TG, which characterize auto-immune thyroiditis), the GI-tract either at a malabsorption or at chronic inflammatory levels namely anti-TTG, anti-gliadin and anti-deaminated gliadin peptide that sign celiac disease or anti-saccharomyces, which often characterize inflammatory bowel disorders including Crohn disease or ulcerative colitis. We intriguingly observed that the positivity for systemic autoantibodies, whatever their number, is significantly associated with lower levels of sBAFF, versus patients without autoimmunity. We also compared circulating sBAFF levels in patients with and without two CNS autoantibodies, namely anti-NMDA-R and anti- α 7AChR, similarly observing that autoantibody positive patients show lower sBAFF levels. Future research will be required to clarify the nature of this association, including as to whether it arises due to BAFF not being required for the survival or reactivation of memory B-cells (Moisini and Davidson, 2009). It cannot be excluded that there is a negative feedback loop due to an excess of sBAFF levels in such autoimmune situation where B-cells are activated or an as yet to be determined autoimmune process specific for psychiatric conditions.

We also tested for the presence of stigma of past infectious events by analyzing the correlations between biological history of infections *vis* antibodies directed against toxoplasma, HSV and EBV pathogens and sBAFF levels and observed that only positivity to HSV is correlated with high levels of sBAFF. Of interest, HSV1 is not an unknown pathogen in

psychiatric and autoimmune patients, with HSV1 serological positivity having negative impacts on cognitive performance in SZ, BD and healthy individuals thus reflecting a possible involvement in the development of psychiatric disorders, if in a latent state. Moreover and importantly, while it has been showed in murine models that asymptomatic HSV1 infection may be associated with severe autoimmune encephalomyelitis establishing hence a link between HSV1 and autoimmune processes (Duarte et al., 2021), in humans, HSV1 IgG seropositivity increases the likelihood of developing anti-NMDA-R encephalitis likely through molecular mimicry, (Dale and Nosadini, 2018; Salovin et al., 2018). This could suggest that the observed association with BAFF may reflect underlying autoimmune processes, which requires clarification in future research.

Beside such observation which likely relate to chronic/latent influence of the HSV1 pathogen, we cannot exclude, in terms of potential triggering event, the implication of another and yet to be determined pathogenic agent or the possibility of a non-infectious trigger such as mitochondrial byproducts known to be able to initiate inflammatory events or merely another environmental trigger such as childhood maltreatment which is also thought to initiate inflammation (Coelho et al., 2014). Notably, in the present study high circulating levels of sBAFF were associated with a history of childhood physical abuse.

The sBAFF data collected in this study has potential consequences for the various states of major mood and psychotic disorders and may provide the foundations for development of a biomarker for targeted immune-focused treatment of subgroups of inflamed SZ and BD. Nevertheless, the study has a number of limitations that must be acknowledged: (i) the absence of a dynamic follow-up evaluating in a longitudinal manner sBAFF involvement in the above-mentioned associations, which requires future prospective studies; (ii) psychotropic treatments were not incorporated for their impact on the levels inflammatory molecules, (iii) the relatively low sample sizes of the analyzed subsamples for autoimmunity and history of past infections and (iv) the non-availability of data concerning BMI and smoking status which could constitute confounding factors.

Overall, our findings and observations identify BAFF as a central player of inflammatory processes in SZ and BD, although requiring future longitudinal investigation, especially as to the relevance of the 3'UTR insertion-deletion polymorphism (GCTGT>A) that powerfully determines sBAFF levels. This will be important to carry out as biotherapeutic treatments targeting BAFF exist and are already used in autoimmune settings. The strong association of sBAFF with inflammation may also allow sBAFF to be utilized as an accurate inflammation marker in acute and stable phases of psychiatric disorders.

CRediT authorship contribution statement

Wahid Boukouaci: Writing – original draft, Investigation, Conceptualization. **Mohamed Lajnef:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Ching-Lien Wu:** Writing – review & editing, Methodology, Investigation. **Jihène Bouassida:** Writing – review & editing, Methodology, Investigation. **Kaori Saitoh:** Writing – review & editing, Methodology, Investigation. **Sobika Sugunasabesan:** Writing – review & editing, Methodology, Investigation. **Jean-Romain Richard:** Writing – review & editing, Project administration, Data curation. **Maud Apavou:** Writing – review & editing, Methodology, Formal analysis. **Anais Lamy:** Writing – review & editing, Methodology, Formal analysis. **Adèle Henensal:** Writing – review & editing, Resources. **Irène Nkam:** Writing – review & editing, Validation, Resources. **Lauren Hasty:** Writing – review & editing, Resources, Investigation. **Romain Sayous:** Writing – review & editing, Resources, Investigation. **Djaouida Bengoufa:** Writing – review & editing, Resources, Methodology, Investigation. **Caroline Barau:** Writing – review & editing, Resources. **Philippe Le Corvoisier:** Writing – review & editing, Resources. **Jérôme Honnorat:** Writing – review & editing, Methodology, Investigation. **Uwe Maskos:** Writing – review & editing, Methodology,

Investigation. **Robert Yolken:** Writing – review & editing, Methodology, Investigation. **Marion Leboyer:** Writing – original draft, Supervision, Funding acquisition, Formal analysis, Conceptualization. **Ryad Tamouza:** Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Author contributions

WB took the primary responsibility of the study, participating in data analysis and manuscript redaction. ML performed the entire statistical analysis. CLW, JB, KS, SS, MA and AL were involved in the experimental procedures. JRR was the data manager of the study. AH, IN, LH and RS recruited patients and controls and carried out the clinical assessments. DB performed the evaluation of circulating systemic autoantibodies. JH and UM were respectively in charge of the identification of the anti-NMDA and anti- α 7-nicotinic autoantibodies. PLC and CB oversaw the biobank. ML and RT designed and supervised the whole project, as well as writing the manuscript. All authors have carefully read and approved the manuscript.

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