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Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder

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ABSTRACT

Background: Previous studies suggest elevated inflammation in schizophrenia and bipolar disorder, with increased activity of the Interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor (TNF)-alpha, von Willebrand factor (vWf) and osteoprotegerin (OPG). It is unclear how immune activation is involved in the psychopathology. We investigated if elevated inflammation was associated with disease severity (trait) or current symptom level (state), comparing psychotic with general characteristics.
Methods: Plasma levels of sTNF receptor 1 (sTNF-R1), IL-1 receptor antagonist (IL-1Ra), IL-6, vWf and OPG were measured with ELISA techniques in 322 patients with schizophrenia spectrum and bipolar disorder. Current symptom level (state) was measured with Global Assessment of Functioning (GAF) and Positive and Negative Syndrome Scale (PANSS). Disease severity (trait) was measured with premorbid adjustment scale (PAS), age at onset, number of psychotic episodes and number and length of hospitalizations.
Results: After controlling for confounders, IL-1Ra and TNF-R1 were independently associated with GAF, and significantly correlated with PANSS negative and positive, respectively. In addition, Il-1Ra was associated with PAS, and sTNF-R1 with number of hospitalizations and psychotic episodes. VWf was significantly correlated with psychotic episodes, OPG with hospitalizations and IL-6 with history of psychosis. Linear regression analysis showed that GAF remained associated with sTNF-R1 and IL-1Ra with PANSS, after controlling for the other clinical measures.
Conclusions: This supports that inflammatory markers, particularly IL-1Ra and sTNF-R1 are associated with both general disease severity and psychotic features. This supports a role of immune activation in the core pathological mechanisms of severe mental disorders.

1. Introduction

The underlying pathological mechanisms of severe mental disorders are still largely unknown. The disorders are highly heritable (Harrison and Weinberger, 2005) with complex genetic and environmental interactions involved (Burmeister et al., 2008). However, the specific mechanisms involved remain elusive. Several lines of evidence have implicated the immune system in the development of severe psychiatric disorders (Watanabe et al., 2010) and inflammatory mediators are involved in neurotransmission and cognition (McAfoose, 2009).

Psychotic features are common to both schizophrenia and bipolar disorder, although not all bipolar disorder patients have psychotic episodes (Jabben et al., 2009). Schizophrenia and bipolar disorder also have similarities in genetic risk factors, which support the hypotheses of a continuum (Williams et al., 2011). Several studies have reported signs of systemic inflammatory activation in both schizophrenia and bipolar disorder (Drexhage et al., 2011), although there has been many inconsistent results(Schmitt et al., 2005; Freudenreich et al., 2010; Kunz et al., 2011; Miller et al., 2011). According to a meta-analysis there is fairly consistent evidence of raised activity in three inflammatory pathways, the tumor necrosis factor (TNF), interleukin 1 (IL-1), and IL-6 (Drexhage et al., 2010). We previously reported a significant increase in sTNF receptor type 1 (sTNF-R1) and von Willebrand factor (vWf) (Hope et al., 2009). The patients also had

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increased levels of osteoprotegerin (OPG), a soluble decoy receptor in the TNF receptor superfamily related to calcium metabolism (Hope et al., 2010). There was no significant elevation of IL-6 or IL-1Ra, but these markers were associated with affective state and severity of depression in bipolar disorder (Hope et al., 2011).

Research into the relationship between immune factors and disorder characteristics in psychotic patient populations is sparse (Goldstein et al., 2009; Miller et al., 2011). To the best of our knowledge, there is no adequately powered study of associations between inflammatory markers and disorder severity across schizophrenia and bipolar disorder groups. Based on raised serum levels of sTNF, IL-β and IL-6 in previous meta-analysis, and our findings of elevated OPG and vWf in schizophrenia and bipolar disorders, we examined if activities in these pathways were associated with severity of the mental disorders. High cytokine levels may be a trait influenced by genetic factors (Rafiq et al., 2007; Clerici et al., 2009; Vistoropsky et al., 2010), and thus influence stable disease characteristics. In addition, cytokine levels may be affected by acute physical and mental challenges, and thus fluctuate in relation to stressors (Kop et al., 2008; Brydon et al., 2009). A cross-sectional study with no direct follow-up of disease characteristics related to fluctuations of immune markers in the individual has clear limitations concerning inferences about causality or direction of effect, but can provide valuable descriptive information. We investigated if inflammatory markers are associated with severity of psychotic disorders in an adequately powered study across both schizophrenia and bipolar disorder groups in the same sample of patients as in our previous studies (Hope et al., 2009, 2010). The hypothesis was that high levels of inflammation would be associated with more severe clinical symptom levels (*state*) and with a more severe disease history (*traits*).

2. Methods

2.1. Participants

The study population has previously been reported in detail (Hope et al., 2009). Briefly, patients were included through referrals to the ongoing Thematically Organized Psychosis (TOP) Study in Oslo, Norway (for details, see Birkenaes et al., 2007).

Inclusion criteria: being registered in the psychiatric services of any one of the four University Hospitals in Oslo; age 18 to 65 years; meeting DSM-IV criteria for schizophrenia or bipolar spectrum disorders.

Exclusion criteria: history of moderate or severe head injury, neurological disorder, mental retardation, malignancies and acute or chronic infectious disorders. The patients were included between 2003 and 2008. We do not have a precise number of all eligible patients, but the fraction of eligible patients that declined to participate or were not included for other reasons was 13%. Due to IRB regulations we could not collect information from the patients who declined to participate. However, previous analysis based on hospital charts from all treated psychotic patients found no significant difference between the study sample and the clinical hospital sample regarding illness severity and sociodemographic variables and substance abuse (Ringen et al., 2008). Included in the current analyses were consecutive referred patients with valid measurements of inflammatory markers, without any use of immunomodulating drugs including non-steroid anti-inflammatory drugs or statins, consisting of a total of 322 patients (192 had a DSM-IV non affective psychotic disorder, comprising schizophrenia [n = 147], schizophreniform [n = 11] and schizoaffective disorder [n = 34], 130 had a bipolar spectrum disorder (Bipolar I disorder [n = 77], Bipolar II disorder [n = 45] and Bipolar not otherwise specified [n = 8]). One patient had missing data regarding IL-1Ra and OPG. All participants gave written informed consent to participation including the permission to re-use the data for further analysis, and the study has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

2.2. Study design

We explored if markers of inflammation were associated with the current *clinical* severity (*state*) or history of disease severity (*trait*) of both *general* and *psychotic* characteristics in a cross-sectional study. We used Global Assessment of Functioning; (GAF) (Greenberg and Rosenheck, 2005; Aas, 2010) as measure of *general state*, and Positive and Negative Syndrome Scale; (PANSS) (Santor et al., 2007) as measure of *psychotic state*. *General traits* was measured with premorbid adjustment scale (PAS) (Brill et al., 2008), age at onset of first episode and number and length of hospitalizations and *psychotic traits* with history of psychosis, age at first psychotic episode and number of psychotic episodes.

2.2.1. Confounding factors

We included age, gender, ethnicity, smoking, alcohol intake, kidney and liver function, having a diagnosis of autoimmune disorder, hypertension, high-sensitivity C-reactive protein (hsCRP), medication with antipsychotics, mood stabilizers and antidepressants as confounders.

2.3. Assessments

All patients were assessed by trained clinical research personnel (psychiatrists and clinical psychologists). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used for diagnostic purposes, and global symptomatology and functioning was measured by the GAF Scale (split version). Inter-rater reliability was good, with an overall kappa score of 0.77 (95% confidence interval: 0.60–0.94) for diagnoses and an ICC (1.1) of 0.86 for both symptom and function GAF scores, and 0.73, 0.73 and 0.71 for PANSS positive, negative and general subscales respectively. PANSS is a commonly used scale to measure symptoms in psychotic disorders (Kay et al., 1987). For all participants, daily smoking, the use of alcohol and drugs during the last 2 weeks prior to assessment was recorded.

2.4. Biochemical and Immunological measures

Blood sampling was performed between 8 am and 14 pm. The analysis of clinical chemistry parameters was performed at Department of Clinical Chemistry, Oslo University Hospital, Oslo, Norway on an Integra 800 from Roche Diagnostics (Basel, Switzerland) using standard methods. For immunological analysis, blood was drawn on EDTA vials, and plasma was extracted the next workday and stored at −80 °C. The methods for the measurements of plasma levels of sTNF-R1, IL-1Ra, OPG, vWf and hsCRP as well as the results from these measurements in the present study population have previously been reported (Hope et al., 2009, 2010), using enzyme immunoassays (EIA) obtained from R&D Systems, Minneapolis, MN (sTNFR1, IL-1Ra, OPG) or an EIA using antibodies from DakoCytomation (Oslo, Norway; vWf) (Bollerslev et al., 2006). In the vWf analyses, levels are given in plasma concentration percent (%) and the standard curve is based on samples from a plasma pool of healthy individuals, where the normal range is set to 70–130%. All intra- and inter-assay coefficients of variance were <10%.

2.5. Statistical procedures

All statistical analyses were done using the SPSS software package for Windows version 15.0 (SPSS, Chicago, IL). Bipolar disorder and schizophrenia were merged for the main analysis, and sub analyses were done for schizophrenia spectrum and bipolar disorder independently. All tests were two-sided with a preset level of significance of 0.05. Correlation tests were done by both Spearman's Rho and Pearson's dependent on the distribution of data. Regarding IL-1Ra, there were significant associations with both methods, and we reported the Pearson correlations, as these associations tended to be

stronger. Regarding IL-6, Spearman's Rho was reported, as there were no linear correlations, only non-parametrical.

2.5.1. Multiple testing

We did 13 tests for each of the 5 inflammatory markers. To reduce the probability of chance findings, we did a family-wise error rate Bonferroni correction, with a significance threshold at $p = 0.00038$. In addition we calculated the cumulative probability of that a number of significant associations would occur by chance.

2.5.2. Confounding factors

Inflammatory marker levels could be influenced by confounders and we analyzed the following factors: age, gender, ethnicity, smoking, alcohol intake, kidney and liver function, having a diagnosis of autoimmune disorder, hypertension, high-sensitivity C-reactive protein (hsCRP), time of blood sampling, medication with antipsychotics, mood stabilizers and antidepressants. Control for confounders was done by first analyzing which of the possible confounders were correlated with the immune markers, i.e. Pearson correlation coefficient $r > 0.05$ and $p < 0.1$. The factors that correlated with immune markers were controlled for by doing linear regression analysis. In a final model, we controlled for all the possible confounding factors, regardless if the factors were correlated with immune markers or not, including control for medication with antipsychotics, mood stabilizers and antidepressants.

2.6. Regression analysis regarding correlations between variables

Although general symptoms and psychotic symptoms are regarded different clinical characteristics, they may overlap to some extent. Thus, we analyzed the Pearson correlation coefficient between *state* and *trait* measures. Regression analysis with co-linearity analysis was done to find out whether clinical severity measures were independently associated with inflammatory markers. We also analysed the correlation between the inflammatory markers, and regression analysis was done if two or more inflammatory markers were correlated with the same clinical severity measure. Only patients with psychotic episodes were included in the analyses of age at onset of psychosis and number of psychotic episodes.

3. Results

3.1. Patient characteristics are listed in Table 1

3.1.1. Correlations with possible confounding factors

Bivariate analysis showed that sTNF-R1 was correlated with age, smoking, having a diagnosis of diabetes or hypertension, autoimmune disorder, kidney function (creatinine) and with hsCRP. IL-1Ra was correlated with age, gender, time of blood sampling, smoking and having a diagnosis of diabetes or hypertension. VWf was correlated with age, gender, European ethnicity, autoimmune disorder and creatinine.

High-sensitivity C-reactive protein (hsCRP) was included as a possible confounder of peripheral infection, although hsCRP was not significantly correlated with any of the disease characteristics.

Clinical state measures were correlated with each other, and the highest Pearson coefficient was between GAF-f and GAF-s ($r = 0.83$). Both GAF-s and GAF-f correlated with PANSS positive ($r = -0.71$ and $r = -0.55$) and PANSS negative ($r = -0.52$ and $r = -0.53$). The strongest correlation between clinical *trait* measures was between number of psychotic episodes and number of hospital admissions ($r = 0.64$), $p < 0.001$ for all.

3.1.2. Whole sample correlations between inflammatory markers and general disease severity measures

3.1.2.1. General state (Table 2). sTNF-R1 and IL-1Ra was associated with poorer function (GAF-f) ($p = 0.001$ and $p = 0.003$ respectively).

Table 1
Demographics.

	All Patients n = 322	Schizophrenia n = 192	Bipolar disorder n = 130
Age (years)	34 (11)	33.6 (12)	35.5 (12)
Gender (female)	51%	43%	63%*
European (white)	82%	77%	90%*
Years of education	13 (3)	12 (3)	14 (3)*
Creatinine (μmol/l) n = 307	71 (15)	71 (13)	71(17)
ALAT (U/l) (n = 311)	29 (20)	30 (19)	27 (21)
Diabetes/hypertension	5%	5%	5%
Alcohol use (units) (n = 310)	9 (20)	7 (17)	13 (23)*
Smoking (n = 315)	56%	58%	53%
GAF-Symptoms	48 (14)	41 (11)	59 (11)*
GAF-Function	48 (13)	42 (10)	57 (12)*
PANSS positive	13 (6)	15 (6)	10 (3)*
PANSS negative	13 (6)	16 (6)	10 (4)*
PANSS general	29 (8)	63 (16)	45 (10)*
Current psychosis	39%	60%	8.4%*
History of psychosis	83%	100%	57%
No of psychotic episodes (n = 242)	3.0 (4)	3.2 (4.6)	2.3 (2.2)*
Hospital admissions (n = 238)	4.0 (4.7)	4.5(5.1)	2.9 (3.6)*
Age of onset	24 (9)	25 (9)	23 (10)
Duration of disorder	9	10	9
Antipsychotic medication	71%	88%	45%*
Mood stabilizer	35%	21%	57%*
Antidepressants	38%	35%	40%
Medication free	9%	7%	11%

Mean (Standard deviation) or percent is presented. ALAT; alanine aminotransferase, Alcohol use: number of alcohol units (10 ml alcohol) during the last 2 weeks. GAF; General Assessment of Functioning, split version, PANSS; Positive and Negative Syndrome Scale; Current psychosis; A score on PANSS items P1,P3, P5, P6 or G9 ≥4 Age at onset; age at the first episode of depression, mania or psychosis according to criteria in DSM-IV.* = significant difference between bipolar and schizophrenia group, $p < 0.05$.

The associations remained significant after controlling for possible confounders (see Methods) ($p = 0.002$ for sTNF-R1 and $p = 0.03$ for IL-1Ra). A common regression analysis for predicting GAF-f showed that both sTNF-R1 and IL-1Ra were independent predictors ($p = 0.005$ and $p = 0.02$). As for the other markers (OPG, vWf and IL-6) no associations were found with any of state variables (Table 2).

3.1.2.2. General trait (Table 2). IL-1Ra was associated with PAS late adolescence and PAS adulthood ($p = 0.009$ and 0.007 respectively), which was significant also after controlling for confounders ($p = 0.048$ for both). In those who had been admitted to hospital, sTNF-R1 was associated with number and length of hospitalizations ($p = 0.001$ for both) which was significant after controlling for confounders ($p = 0.02$). As for the other inflammatory markers (OPG, vWf and IL-6), the only significant correlation with trait markers was a weak but significant correlation of OPG with number of hospitalizations (Table 2).

3.1.3. Whole sample correlations between inflammatory markers and psychotic measures

3.1.3.1. Psychotic state (Table 3). The associations between sTNF-R1 and currently being in a psychotic state and the level of PANSS positive symptoms were still significant after controlling for confounders ($p = 0.012$ and $p = 0.03$, respectively).These correlations did not remain statistically significant when patients without psychosis were excluded ($n = 265$, $r = 0.11$, $p = 0.09$ for PANSS positive, and $r = 0.10$, $p = 0.13$ for present psychosis). IL-1Ra was associated with severity of PANSS negative symptoms which remained significant after controlling for confounders ($p = 0.001$, $n = 314$) and when patients without previous psychosis were excluded ($r = 0.18$, $p = 0.006$, $n = 257$). OPG, vWf and IL-6, were not correlated with any of the psychotic state markers (Table 3).

Table 2
Pearson correlation coefficients between general disease severity measures and immune markers.

	sTNF-R1	IL-1Ra	OPG	vWf	IL-6
State					
GAF-function (n = 322)	−0.18**[a]	−0.16**[a]	0.06	−0.07	−0.05
GAF-symptoms (n = 322)	−0.11*[a]	−0.10	0.06	−0.03	−0.01
PANSS general (n = 321)	−0.01	0.13*	−0.08	0.02	−0.03
Trait					
Age at onset	0.07	−0.09	0.05	0.08	0.02
PAS late adulthood (n = 276)	−0.02	0.16**[a]	−0.03	0.08	−0.003
Number of hospitalizations (n = 238)	0.22**[a]	0.04	0.14*	0.10	0.13[b]
Duration of hospitalizations (n = 232)	0.23**[a,b]	0.10	0.09	0.11	0.09[b]

Pierson correlation coefficients are given for all parameters except IL-6, were Spearman Rho is reported. GAF; General Assessment of Functioning, split version (F; function, S; symptoms), PANSS; Positive and negative syndrome scale, PAS; total score on Premorbid Assessment of Functioning. sTNF-R1; soluble Tumor Necrosis Factor – R1, IL-1Ra, Interleukin 1 receptor antagonist; OPG, osteoprotegerin; vWf: von Willebrand factor.
* p<0.05.
** p<0.01.
[a] Significant correlation in the schizophrenia subsample.
[b] Significant correlation in the bipolar subsample.

3.1.3.2. Psychotic trait (Table 3). IL-1Ra, sTNF-R1, vWf and IL-6 were associated with having a lifetime psychotic episode (Table 3) also after controlling for confounders (p = 0.03, p = 0.02, p = 0.02, p = 0.02, respectively), while the association of IL-1Ra with age at onset of psychosis lost its significance after controlling for confounders (p = 0.11).

3.1.4. Multiple testing

There were 16 significant associations out of the 13 × 5 = 65 tests performed. The cumulative probability of finding this by chance is $p = 1 \times 10^{-8}$. For TNF-R1, 8 out of 13 tests were significant, and the likelihood of this being a chance finding is $p = 1 \times 10^{-9}$. For IL-1Ra, 6 out of 13 tests were significant, with $p = 1 \times 10^{-6}$ for being chance finding. The significance threshold after family-wise error rate Bonferroni correction was p = 0.004. After correction sTNF-R1 remained significantly associated with GAF-f (p = 0.001), number of hospital admissions (p = 0.001) and with length of hospital stays (p = 0.001), and IL-1Ra remained significantly associated with PANSS negative symptoms (p = 0.00009).

Table 3
Correlation coefficients between immune markers and clinical severity measures of psychosis.

	TNF-R1	IL-1Ra	OPG	vWf	IL-6
State					
Current psychosis (n = 322)	0.13*[a]	0.03	−0.003	−0.001	0.06
PANSS Positive (n = 322)	0.13*	0.08	0.05	0.005	0.04
PANSS Negative (n = 322)	0.02	0.22**	−0.09	0.10[b]	−0.05
Trait					
Psychosis life time (n = 321)	0.13*[,b]	0.15**[b]	−0.02	0.11*	0.12*[,b]
Age at onset of psychosis[y] (n = 256)	0.06	−0.14*	0.11	0.03	0.04
Number of psychotic episodes[y] (n = 242)	0.19**[a,b]	0.02	0.09	0.17**	0.07

Pierson correlation coefficients are given for all parameters except IL-6, were Spearman Rho is reported. One patient is missing regarding IL-1Ra and OPG. PANSS: Positive and negative syndrome scale, Current psychosis: PANSS items P1, P3, P5, P6 or G9.≥4, TNF-R1: soluble Tumor Necrosis Factor-R1, IL-1Ra: Interleukin 1 receptor antagonist, OPG: osteoprotegerin; vWf: von Willebrand factor; IL-6: interleukin 6.
[b]Significant correlation in the bipolar subsample [y] = only patients with a history of psychosis were included.
* p<0.05.
** p<0.01.
[a] Significant correlation in the schizophrenia subsample.

3.1.5. Regression analysis regarding clinical measures and sTNF-R1 and IL-1Ra

Linear regression analysis showed that GAF-f was the clinical severity measure with the highest independent association with TNF-R1 in the whole sample, and TNF-R1 was significantly predictive of GAF-f also when 17 possible confounding factors were controlled for (Table 4). PANSS negative symptoms was the clinical severity measure that showed the highest independent association with IL-1Ra and IL1-Ra was predictive of PANSS negative symptoms when 18 possible confounding factors were controlled for (Table 5).

3.1.6. Correlations within the schizophrenia and bipolar disorders diagnostic groups

We examined if our correlations were significant also in the two diagnostic subgroups separately (Tables 2 and 3).

3.1.6.1. Schizophrenia. The following correlations were significant also after controlling for confounders sTNF-R1 with GAF-f (p = 0.007), GAF-s (p = 0.04) and currently being psychotic (p = 0.004). IL1Ra was correlated with GAF-f (p = 0.04) and PANSS negative symptoms (p = 0.02). VWf was significantly associated with PANSS negative symptoms (p = 0.03).

3.1.6.2. Bipolar disorder. There were no significant correlations between clinical state variables and inflammatory markers but there was a non-significant trend similar to that seen in schizophrenia of a correlation between sTNF-R1 and GAF-function (r = -0.13, p = 0.16), and between IL-1Ra with negative symptoms (r = 0.13, p = 0.15). The following correlations were significant also after controlling for confounders. STNF-R1 was correlated with length of hospital stays (p = 0.04). IL-6 was correlated with length of hospitalization (p = 0.04) and with history of psychosis (p = 0.02). Il-1Ra was correlated with history of psychosis (p = 0.03). VWf was correlated with number of psychotic episodes in patients with a previous psychotic episode (p = 0.02). OPG showed no significant correlations with these trait variables after controlling for confounders (data not shown).

Table 4
Regression model for prediction of GAF functioning.

	B	t	Significance
Constant	30.25	4.28	<0.01**
Age	−0.03	−0.35	0.73
Gender	3.44	2.05	0.04*
Ethnic White	4.75	2.58	0.01*
Smoking	−1.92	−1.31	0.19
Alcohol	0.01	0.13	0.89
Drug abuse	0.12	0.22	0.82
Diabetes/CVD	1.28	0.39	0.69
Autoimmune disease	0.08	0.06	0.95
HsCRP	−0.12	−0.33	0.74
Creatinine	0.05	0.89	0.38
ALAT	0.02	0.41	0.68
Cholesterol	−1.10	−1.58	0.12
Glucose	0.74	1.35	0.18
Antipsychotics	−2.02	−1.19	0.23
Mood stabilizing	0.56	0.35	0.73
Antidepressive	−1.19	−0.84	0.40
Diagnostic category	11.82	6.98	<0.01**
TNF-R1	−5.55	−2.31	0.02*

Diabetes/CVD = Diabetes or cardiovascular disease; Alcohol: No of units drunk last two weeks; Substance abuse = use of illegal drugs last 2 weeks. ALAT = alanine aminotransferase; hsCRP = high sensitivity C - reactive protein; Antipsychotic = medicated with antipsychotics or not; Mood stabilizing = medicated with mood stabilizing agent; Antidepressive = medicated with antidepressive agent; sTNF-R1; soluble tumor necrosis factor receptor 1.
* p<0.05.
** p<0.01.

Table 5
Regression model for prediction of PANSS negative symptoms.

	B	T	Sig
Constant	20.97	4.76	<0.01
Age	−0.03	−0.93	0.35
Gender	−2.02	−2.93	<0.01*
Ethnic White	0–.46	0–.57	0.57
Smoking	0.70	1.11	0.27
Alcohol	−0.02	−1.53	0.13
Drug abuse	−0.20	−0.78	0.43
Diabetes/CVD	−1.61	−1.10	0.27
Autoimmune disease	0.02	0.04	0.97
hsCRP	−0.14	−0.88	0.38
Creatinine	−0.01	−0.48	0.63
ALAT	0.00	−0.60	0.55
Cholesterol	0.33	1.07	0.29
Glucose	−0.05	−0.21	0.83
Antipsychotics	0.86	1.19	0.24
Mood stabilizing	0.11	0.17	0.87
Antidepressive	1.54	2.51	<0.01*
Diagnostic category	−4.13	−5.80	<0.01*
Time of blood sampling	0.06	0.19	0.85
IL-1Ra	0.83	2.85	0.005*

Diabetes/CVD = Diabetes or cardiovascular disease; Alcohol: No of units drunk last two weeks; Substance abuse = use of illegal drugs last 2 weeks. ALAT = alanine aminotransferase; hsCRP = high sensitivity C-reactive protein; Antipsychotic = medicated with antipsychotics or not; Mood stabilizing = medicated with mood stabilizing agent; Antidepressive = medicated with antidepressive agent; IL-1Ra = soluble Interleukin 1 receptor antagonist.
* $p<0.05$.
** $p<0.01$.

4. Discussion

The main finding of the present study was a significant association between clinical severity and levels of sTNF-R1 and IL-1Ra in psychotic disorders, including both state and trait characteristics of a general and specific (psychotic) nature. After Bonferroni correction for multiple testing, and control for interaction and confounders, TNF-R1 remained significantly correlated with general function and IL-1Ra remained significantly correlated with PANSS negative symptoms. The results were consistent in that high levels of these two markers were correlated with more severe characteristics as indicated by lower general function scores, age at onset, and premorbid adjustment measures, and by higher number and durations of disorder episodes, and higher current symptom levels. This may indicate a role of inflammation and in particular the TNF and IL-1 pathways in psychotic disorders and suggests their involvement in both development aspects and in ongoing fluctuations in psychopathology.

CRP is a reliable marker of inflammation, but it is unlikely that it reflects all pathways in this complex process. One reason is that hsCRP is made by the liver and is too large to pass the BBB (Hsuchou et al., 2012), while TNF-R1 and IL-1Ra is expressed by neurons in the brain (Tchelingerian et al., 1993). Our findings showing that sTNF-R1 and IL-1Ra were correlated with disease characteristics also after correcting for hsCRP further support such a notion.

Several studies and meta-analyses have found evidence of elevated levels of TNF-α in schizophrenia, bipolar disorder and major depression (Dowlati et al., 2010; Drexhage et al., 2010), and a previous smaller study also reported that TNF-α was correlated with positive psychotic symptoms (Erbaægci et al., 2001). In our sample, TNF-R1 is the only inflammatory marker that was both highly significantly elevated compared to controls, as well as associated with several clinical severity measures. This supports that TNF-R1 is a central inflammatory marker in severe mental disorders.

As for IL-1Ra, no previous studies have investigated if serum levels of this marker are associated with negative symptoms (Drexhage et al., 2010), but an association between negative symptoms and IL-1Ra (Sirota et al., 2005) and between the polymorphisms in the IL-Ra gene and negative symptoms (Mata et al., 2006) have been reported, which seem to support the current results.

However, it is puzzling that IL-1Ra is associated with symptom severity, as the average IL-Ra levels in these patients are not different from controls (Hope et al., 2009). This may indicate some disease-specific effects related to pathological regulation of mood and reality monitoring. There are several lines of evidence supporting disease specific effects on biological processes in severe mental disorders (Prata et al., 2009; Wirgenes et al., 2010). Further, our finding may also indicate a subgroup of patients being strongly affected, and others well within the range of healthy controls.

One explanation for the lack of association between TNF and IL-1 to trait markers in previous studies (Drexhage et al., 2010) could be low statistical power, as our study included a larger number of patients. Another explanation might be that Il-1Ra and sTNF-R1 are more stable markers than IL-1β and TNF-α themselves (Gu et al., 2009). Both TNF-α and in particular IL-1β circulate at very low levels, just above the detection limit of the various EIAs. And although TNF-R1 and IL-1Ra can antagonize IL-1 and TNF activity, circulating levels of Il-1Ra and sTNF-R1 are regarded as stable and reliable markers of the activity in the IL-1 and TNF system (Diez-Ruiz et al., 1995; Spulber et al., 2009). Moreover, it has been suggested that IL-1Ra itself should be regarded as an acute phase response as both IL-1β and IL-6, both inducers of CRP, are strong inducers of IL-1Ra in humans (Gabay et al., 1997).

The current findings show similar immune profile in bipolar disorder and schizophrenia and seem to support the view that these disorders have some common pathological mechanisms. However, our findings also show some differences as sTNF-R1 and IL-1Ra were independently associated with clinical state measures in patients with schizophrenia; this was not significant in bipolar disorders. In both bipolar disorder and schizophrenia, the inflammatory markers were independently associated with trait measures. Thus, we could speculate that the inflammatory factors are associated with trait related measures in both disorders due to some shared genetic susceptibility, and that they may be associated with affective state in bipolar disorder, and with psychotic state in schizophrenia. The reason for the different pattern in schizophrenia and bipolar disorders is not clear, but might partly be explained by the lower level of psychotic symptoms in bipolar disorder. In the current study, 57% of the bipolar disorder patients have experienced a psychotic episode, which is equal to the frequency (58%) reported in a meta-analysis (Goodwin and Jamison, 1990). However, 8.4% of those who had been psychotic were currently in a psychotic state, which is somewhat lower than the 14% found in the meta-analysis (Goodwin and Jamison, 1990). The prevalence of current psychosis in the schizophrenia patients was much higher (60%), and equal to a previous study (Eberhard et al., 2009). The relatively low percentage of psychotic bipolar disorder patients may have reduced the statistical power to find associations, and thus the difference between schizophrenia and bipolar disorder should be interpreted with caution.

The biological mechanisms responsible for the associations between disease severity and sTNF-R1 and IL-1Ra are not known. However, animal studies have found that IL-1Ra increases as a response to social withdrawal (Bluthâe et al., 1997; Rohleder et al., 2006; Arakawa et al., 2009; Norman et al., 2010), which is a core item of PANSS negative symptoms. Furthermore, both animal and human studies have found that elevated TNF induces cognitive disturbances (Jiang et al., 2011; Yirmiya and Goshen, 2011; Belarbi et al., 2012), and cognitive disorganization is an item of PANSS positive scale. Both sTNF-R1 and IL-1Ra are also affected by dopamine (Gomez-Santos et al., 2007; Koprich et al., 2008), and it is possible that inflammatory interactions with dopamine neurotransmission is an underlying mechanism of the present findings.

At present, there are no direct clinical implications of the current results, mainly because we do not know the cause of the elevated

inflammation. Patients have elevated frequency of both autoimmune diseases and neurotropic infections (Eaton et al., 2010; Chen et al., 2012a), and both anti-inflammatory and anti-infective drugs have been reported to be beneficial as adjunctive medication (Chaudhry et al., 2012; Prasad et al., 2012; Sommer et al., 2012). It has also been reported that antipsychotic and mood stabilizing medications have immunomodulating properties (Drzyzga et al., 2006; Chen et al., 2012b; Nahman et al., 2012), and further research is needed to elucidate if these drugs may influence IL-1, TNF and other inflammatory pathways.

The major limitation of the current study is the cross-sectional nature with no possibility to investigate disease characteristics related to fluctuations of inflammatory markers in the individual. This makes it impossible to draw conclusions about causal relationships. The correlation coefficients between inflammation and disease characteristics were in the 0.1–0.26 range, explaining only around 1–7% of the variance in severity. However, the current correlation range is similar to results in previous studies of inflammation and psychiatric symptoms (Chadwick et al., 2008; Zhang et al., 2008; Orre et al., 2009). Furthermore, the patients in the current sample are young and well functioning, and it is possible that investigations of samples with a larger variation in severity could lead to higher correlation coefficients.

Our study shows that serum levels of sTNF-RI and IL-1Ra were correlated to more severe symptom states and disorder traits, both general and psychotic, in patients with schizophrenia and bipolar disorders. This extends previous reports of inflammatory markers in severe mental disorder, and may suggest an involvement of inflammation in both state and trait related pathophysiological mechanisms. Further studies are needed to replicate the current findings and such studies should include a longitudinal design.

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Contributors

Drs. Hope and Andreassen conceived the study and its design and acquired and analysed the data. Drs. Aukrust and Ueland contributed to the study conception and the analysis and interpretation of data. Drs. Hope, Dieset, Berg,Steen, Lorentzen, and Agartzcontributed to data acquisition. Drs. Hope and Andreassen wrote the manuscript, which was reviewed by all other authors. All authors approved the final version submitted forpublication.

Conflict of interest

No authors reported any biomedical financial interests or potential conflicts of interest relevant to the subject matter of the manuscript.

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