Psychiatry Research 348 (2025) 116492

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

How variants in inflammatory mediator genes influence symptom severity of psychiatric disorders: Findings from the PsyCourse study

Mojtaba Oraki Kohshour [a,b], Kristina Adorjan [a,c], Monika Budde [a], Maria Heilbronner [a], Janos L. Kalman [a,d], Alba Navarro-Flores [a,e], Daniela Reich-Erkelenz [a,d], Eva C. Schulte [a,d,f,g,h], Fanny Senner [a,d,i], Thomas Vogl [a], Ion-George Anghelescu [j], Volker Arolt [k], Bernhardt T. Baune [l,m,n], Udo Dannlowski [k], Detlef E. Dietrich [o,p,q], Andreas J. Fallgatter [r,s], Christian Figge [t], Fabian U. Lang [u], Georg Juckel [v], Carsten Konrad [w], Jens Reimer [x,y], Eva Z. Reininghaus [z], Max Schmauß [aa], Andrea Schmitt [d,ab], Carsten Spitzer [ac], Jens Wiltfang [ad,ae,af], Jörg Zimmermann [ag], Peter Falkai [d,h,ah], Urs Heilbronner [a,*], Sergi Papiol [a,ah], Thomas G. Schulze [a,h,ai,aj]

[a] Institute of Psychiatric Phenomics and Genomics (IPPG), LMU University Hospital, LMU Munich, Munich, 80336, Germany
[b] Department of Immunology, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[c] University Hospital of Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland
[d] Department of Psychiatry and Psychotherapy, LMU University Hospital, LMU Munich, Munich, 80336, Germany
[e] International Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany
[f] Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital Bonn, University of Bonn, Bonn, 53127, Germany
[g] Institute of Human Genetics, University Hospital, Faculty of Medicine, University of Bonn, Bonn, Germany
[h] DZPG (German Center for Mental Health), partner site Munich/Augsburg, Germany
[i] Centres for Psychiatry Suedwuerttemberg, Ravensburg, 88214, Germany
[j] Department of Psychiatry and Psychotherapy, Mental Health Institute Berlin, Berlin, 14050, Germany
[k] Institute for Translational Psychiatry, University of Münster, Münster, 48149, Germany
[l] Department of Psychiatry, University of Münster, Münster, 48149, Germany
[m] Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Melbourne, Australia
[n] The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia
[o] AMEOS Clinical Center Hildesheim, Hildesheim, 31135, Germany
[p] Center for Systems Neuroscience (ZSN), Hannover, 30559, Germany
[q] Department of Psychiatry, Medical School of Hannover, Hannover, 30625, Germany
[r] Department of Psychiatry and Psychotherapy, Tübingen Center for Mental Health (TüCMH), University of Tübingen, Tübingen, 72076, Germany
[s] German Center for Mental Health (DZPG), partner site Tübingen, Tübingen, 72076, Germany
[t] Karl-Jaspers Clinic, European Medical School Oldenburg-Groningen, Oldenburg, 26160, Germany
[u] Department of Psychiatry II, Ulm University, Bezirkskrankenhaus Günzburg, Günzburg, 89312, Germany
[v] Department of Psychiatry, Ruhr University Bochum, LWL University Hospital, Bochum, 44791, Germany
[w] Department of Psychiatry and Psychotherapy, Agaplesion Diakonieklinikum, Rotenburg, 27356, Germany
[x] Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, 20246, Germany
[y] Center for Psychosocial Medicine, Academic Teaching Hospital Itzehoe, Itzehoe, Germany
[z] Division of Psychiatry and Psychotherapeutic Medicine, Research Unit for Bipolar Affective Disorder, Medical University of Graz, Graz, 8036, Austria
[aa] Clinic for Psychiatry, Psychotherapy and Psychosomatics, Augsburg University, Medical Faculty, Bezirkskrankenhaus Augsburg, Augsburg, 86156, Germany
[ab] Laboratory of Neuroscience (LIM27), Institute of Psychiatry, University of Sao Paulo, 05453-010 São Paulo - SP - Brazil
[ac] Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Rostock, Rostock, 18147, Germany
[ad] Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, 37075, Germany
[ae] German Center for Neurodegenerative Diseases (DZNE), Göttingen, 37075, Germany
[af] Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal
[ag] Psychiatrieverbund Oldenburger Land gGmbH, Karl-Jaspers-Klinik, Bad Zwischenahn, 26160, Germany
[ah] Max Planck Institute of Psychiatry, Munich, 80804, Germany
[ai] Department of Psychiatry and Behavioral Sciences, Norton College of Medicine, SUNY Upstate Medical University, Syracuse, NY, USA
[aj] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

* Corresponding author at: Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, 80336, Munich, Germany.
E-mail address: Urs.Heilbronner@med.uni-muenchen.de (U. Heilbronner).

https://doi.org/10.1016/j.psychres.2025.116492
Received 4 March 2025; Received in revised form 8 April 2025; Accepted 10 April 2025
Available online 11 April 2025

ARTICLE INFO

Keywords:
Neuroinflammation
Mania
IL-1/IL-1R1 signaling

ABSTRACT

Alterations in glial cell function and cytokine levels in the central nervous system may be influenced by neuroinflammatory processes, which have a pathogenic role in psychiatric disorders. Variability in genes that encode inflammatory mediators is associated with risk of developing mental disorders. Therefore, by analyzing data from the transdiagnostic PsyCourse Study, we aimed to investigate whether variations in inflammatory mediator genes are associated with current symptom severity.

We used cross-sectional data from 1320 individuals with a psychiatric disorder and 466 neurotypical individuals. Outcome variables were the psychopathological data from various rating scales and questionnaires that measured depressive, psychotic, and manic symptoms. Furthermore, from a whole-genome SNP array dataset, we extracted single nucleotide polymorphisms (SNPs) in the loci of genes related to inflammatory mediators, and we performed an association analysis by considering covariates. False discovery rate (FDR) was used to adjust the results for multiple comparisons.

A total of 1594 individuals and 1336 SNPs were included in the analyses. The results of regression analysis showed a significant positive association of six SNPs located on the interleukin (IL)-1 receptor type 1 (*IL-1R1*) gene locus with Altman Self-Rating Mania Scale scores (FDR-adjusted p value < 0.05).

Our findings show that genetic variations in *IL-1R1* may influence the pathophysiology of psychiatric disorders by affecting brain cytokine profiles associated with manic episodes. *IL-1R1* encodes a membrane-bound receptor for IL-1. Several physiological functions, including inflammation, are linked to the IL-1/IL-1R1 signaling pathway. Replication of our findings is warranted.

1. Introduction

As psychoneuroimmunology has evolved in the past decades, the involvement of the immune system in brain function and the interplay between neuroendocrine-immune regulatory mechanisms and psychiatric disorders have been increasingly studied (Bennett and Molofsky, 2019; Mihailova et al., 2016). Interactions of the brain's multicellular immune system with peripheral immunity may play a role in regulating mood and behavior (Mihailova et al., 2016). Accordingly, neuroinflammation, i.e., immune system reactions to stressors in the central nervous system (CNS), which affects the type and level of cytokines in the CNS and may result in modifications to glial cell function, could be an important pathogenic factor in mental disorders such as schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD) (Messina et al., 2023; Mikhalitskaya et al., 2023; Scangos et al., 2023). Some evidence suggests the interaction of neuroinflammation with glutamatergic, dopaminergic, and serotonergic systems, resulting in malfunctioning of the CNS and development of psychiatric disorders (Mihailova et al., 2016; Mikhalitskaya et al., 2023). Moreover, previous research has shown an association and unifying link between inflammatory cytokines and the various severe mental disorders, such as SCZ, BD, and MDD (Lesh et al., 2018; Mikhalitskaya et al., 2023; Momtazmanesh et al., 2019; Rodrigues-Amorim et al., 2018). To this end, it has long been known that disorders from the affective-to-psychotics spectrum overlap considerably (transdiagnostic approach) (Budde et al., 2019).

More than 300 cytokines are involved in controlling immunological responses, and different cytokines can promote similar immune functions (Mikhalitskaya et al., 2023; Zhang and An, 2007). Cytokines can also behave in a cascade mode, with one cytokine promoting the production of others (Zhang and An, 2007). Pro-inflammatory cytokines (e.g., interleukin [IL]-1β, IL-6, and tumor necrosis factor [TNF]-α) are involved in the upregulation of inflammatory responses, and such pro-inflammatory cytokine responses are modulated by anti-inflammatory cytokines (e.g., IL-1 receptor antagonist [IL-1RN], IL-4, and IL-10) (Zhang and An, 2007). In addition, some cytokines (e.g., IL-6 and transforming growth factor [TGF]-β) can either promote or inhibit inflammation depending on the situation (Zhang and An, 2007).

There is a body of evidence linking immune-related gene variants, including those pertaining to inflammatory cytokines, to the etiology, development, and severity of psychiatric disorders (Bull et al., 2009; Felger and Lotrich, 2013; Kalmady et al., 2014; Khandaker et al., 2018; Mikhalitskaya et al., 2023; Momtazmanesh et al., 2019; Rodrigues-Amorim et al., 2018). For example, certain polymorphisms in distinct regions of inflammatory genes (e.g., the promoter/enhancer regions) are linked to modified secretion of inflammatory cytokines; consequently, the existence of the corresponding haplotype may confer increased susceptibility or resistance to the impact of risk factors for psychiatric disorders (Kudinova et al., 2016). For instance, Frydecka et al. reported that *IL-6* gene polymorphism (rs1800795) is associated with the severity of positive symptoms in individuals with SCZ (Frydecka et al., 2015). In addition, the researchers suggested that in individuals with SCZ, the severity of clinical symptoms is strongly positively associated with an insertion/deletion polymorphism in the *Nuclear factor kappa B* gene (rs28362691) (Swain et al., 2022). Research has also shown that *IL-10* gene polymorphisms have a significant impact on a subdomain of SCZ negative symptoms (avolition and apathy) (Golimbet et al., 2022). One study in a population-based birth cohort found an association of a functional variation (rs2228145) in the *IL-6 receptor (IL-6R)* gene with a lower risk of severe depression or psychosis or both (Khandaker et al., 2018). Furthermore, rs1800795 in *IL-6* and rs16944 in *IL-1β* were shown to affect depression severity after chronic exposure to interpersonal stress (i.e., romantic relationships, relationship with a best friend, family relationships, and social life) (Tartter et al., 2015).

Accordingly, in this study we investigated the association of genetic variations in some of the replicated and well-known inflammatory mediator loci with symptom severity of the major psychiatric disorders SCZ, BD and MDD. The aim of the study was to find single nucleotide polymorphisms (SNPs) in inflammatory mediator genes that explain differences in psychopathological characteristics in the transdiagnostic PsyCourse Study.

2. Method

2.1. Participants

We used cross-sectional data from the baseline assessment of the PsyCourse Study, a longitudinal naturalistic multicenter study being conducted in Germany and Austria (www.psycourse.de) (Budde et al., 2019). The PsyCourse Study's participants are mostly of European genetic ancestry (Budde et al., 2019). Data were available from 1320 individuals with a diagnosis from the affective-to-psychotic spectrum and 466 control individuals. The current analyses were based on version 6.0 of the PsyCourse dataset (Heilbronner et al., 2023). Written informed consent was acquired from every participant. The study was performed in compliance with the Declaration of Helsinki and was authorized by the ethics committees of the University Medical Center Göttingen, the University Hospital Munich (Project number: 17-13) and all other study

sites (Budde et al., 2019).

2.2. Clinical symptomatology assessment

Outcome variables were the psychopathological data from various rating scales and questionnaires that measure positive and negative, depressive, and manic symptoms at the time of the study participation, as follows: Positive and Negative Syndrome Scale (PANSS; positive [POS], negative [NEG] and general [GEN] scores) (Kay et al., 1987), Inventory of Depressive Symptomatology (IDS-C_{30}) (Rush et al., 2000), Beck Depression Inventory (BDI-II) (Hautzinger et al., 2006), Young Mania Rating Scale (YMRS) (Young et al., 1978), Altman Self-Rating Mania Scale (ASRM) (Altman et al., 1997), and the Self-Report Manic Inventory (MSS) (Krüger et al., 1997). The psychopathological tests are briefly described in Table 1; detailed additional information on them is available elsewhere (Budde et al., 2019; Heilbronner et al., 2023).

2.3. Genotyping and quality control

Individuals were genotyped with the Illumina Infinium Global Screening Array-24 Kit (GSA Array, version 1 and 3; Illumina, San Diego, CA, USA). The final imputed dataset (post-quality control [QC]) contained 1600 individuals and 7712,287 SNPs (the good quality best-guess format included 5764,189 SNPs). Details on QC and imputation, which also included the calculation of ancestry multi-dimensional scaling (MDS) components and exclusion of population outliers, can be found in the *Supplementary Material*. As the post-imputation reference genome, we used the Haplotype Reference Consortium (version r1.1 2016) (hg19) (McCarthy et al., 2016).

2.4. SNPs related to inflammatory mediator genes

Inflammatory mediator genes, including *IL-1α, IL-1β, IL-1RN, IL-1 receptor type 1 (IL-1R1), IL-1R2, IL-4, IL-6, IL-6R, IL-8, IL-10, IL-11, IL-13, IL-17, IL-18, IL-33, TNF-α, TGF-β,* and *interferon-gamma*, were selected based on the literature (Mikhalitskaya et al., 2023). SNPs within the above-mentioned gene loci (reference genome: GRCh37/hg19) (https://genome.ucsc.edu) and within 10-kb flanking sequences on either side of the target gene locus (to cover the upstream and downstream regions of the genes) were extracted from the whole genome SNP array dataset (the best-guess format).

2.5. Statistical analysis

For normalization of the psychopathology tests sum scores in R version 4.3.0 (https://www.R-project.org/), log2-transformation was used for PANSS-POS, YMRS, and ASRM and inverse transformation for PANSS-NEG, PANSS-GEN, IDS-C_{30}, BDI-II, and MSS. A linear regression model was used in PLINK 1.9 to run association analyses between the extracted inflammatory mediator-related best-guess imputed SNPs and the normalized test scores. Analyses were adjusted for sex, age, diagnosis, duration of illness, medications (i.e., number of antipsychotics, antidepressants, mood stabilizers, and tranquilizers taken at the time of the PsyCourse interview), and the first two ancestry principal components as covariates. The results were adjusted for multiple comparisons by using the False Discovery Rate (FDR), and a p value of <0.05 was considered statistically significant.

3. Results

After quality control, a total of 1594 individuals, including 1190 cases and 404 controls (768 women, 826 men; mean age, 41.4 ± 13.9 years), and 1336 SNPs located in the inflammatory mediator genes loci (± 10 kb) were included in the genetic association analysis. Table 2 and *supplementary figure S1* present the demographic and psychopathological data of the study participants and cross-diagnostic differences. The results of the linear regression analyses showed significant positive associations of the following six SNPs with the ASRM scores: rs3917285 (FDR-adjusted p value = 0.024, β = 0.44), rs10194716 (FDR-adjusted p value = 0.043, β = 0.28), rs3755292 (FDR-adjusted p value = 0.043, β = 0.28), rs949963 (FDR-adjusted p value = 0.043, β = 0.27), rs871656 (FDR-adjusted p value = 0.043, β = 0.27), and rs871657 (FDR-adjusted p value = 0.043, β = 0.27) (Fig. 1; *Supplementary Figure S2 and Table S1*). All of these SNPs mapped to the intronic region of the *IL-1R1* gene locus on chromosome 2, and none of them has a described clinical significance in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar). We performed separate analyses for ASRM for the cases and controls, but as expected (given the decline in statistical power); neither of them yielded any significant results (*Supplementary Tables S2-S3*).

To perform association analyses with a common design and sufficient power, we incorporated control samples into our analyses. These samples often have very low psychopathology test scores. The six SNPs that were significantly associated with ASRM scores in the analysis of all samples were among the top seven SNPs that were significantly associated with ASRM scores in the analysis with only the case samples (*Supplementary Table S2*), indicating the significance of the clinical group's impact in our investigation. In addition, all six of the SNPs that were significantly associated with ASRM scores showed nominal positive significance for scores on the MSS, which also measures manic symptoms in a self-rating mode.

4. Discussion

In this data analysis of the PsyCourse Study, we found a significant association between the *IL-1R1* gene locus and ASRM scores. The ASRM is a reliable and valid self-rating mania scale that contains five items to evaluate manic symptoms such as elevated/euphoric mood, increased self-esteem, decreased need for sleep, pressured speech, and psychomotor agitation in the week before filling out the questionnaire (Altman et al., 1997; Heilbronner et al., 2023). Even though the ASRM, the MSS, and the YMRS all assess manic symptoms, they are not perfectly correlated. The ASRM and the MSS are self-rating scales, while the YMRS is interviewer-rated (Table 1). As we expected, the highest correlation between two sum scores can therefore be found between the two self-rating scales. While the scoring of the YMRS is in large parts dependent on information given by the study participant, it also involves behavioural observations (e.g., regarding speech rate, irritability, aggressive behaviour, and thought disorder) by the interviewer. The ASRM does also not include any items on irritability/aggression or psychotic symptoms, which are covered by the YMRS and by the MSS. In addition, another important difference between the scales is the assessed time period. The YMRS covers symptoms during the last 48 h before the interview, the ASRM the last seven days, and the MSS the past month.

The IL-1R1 gene, which has 115,331 base pairs and is located on chromosome 2, encodes an active 80 kDa transmembrane protein, the cytokine receptor IL-1R1, a member of the IL-1 receptor family that serves as the "epicenter" of inflammatory signaling networks (https://www.genecards.org, 2024; Luís et al., 2022). Cytokines in the IL-1 family play a crucial role in microglia activation and neuroinflammatory processes (Basu et al., 2004). In homeostasis and disease conditions, IL-1α and IL-1β have biological effects (e.g., long-lasting effects on neuroplasticity and behavior) that are mediated through binding to IL-1R1 (on various glial cells), which could regulate neuroinflammatory processes, including the cytokine network (Luís et al., 2022; Nemeth and Quan, 2021).

IL-1R1 is widely expressed throughout the brain, and its activation by binding of IL-1 causes a rapid increase in neuronal excitability (Thome et al., 2019). During neuroinflammation, elevated levels of IL-1 are a well-known feature of the immune response, and several physiological functions, including mood and sleep regulation and memory consolidation in the CNS, are linked to IL-1/IL-1R1 signaling pathways (Liu et al., 2019; Luís et al., 2022). The results of other studies on

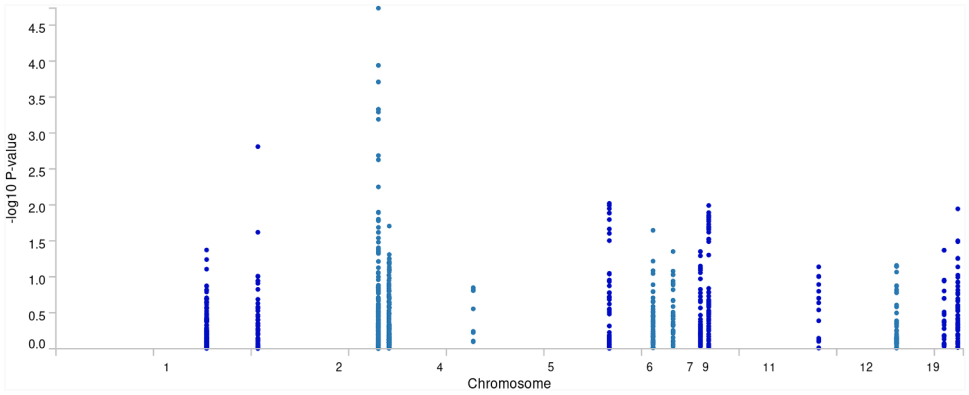

Fig. 1. Manhattan plot of variants in the investigated inflammatory mediator genes and Altman Self-Rating Mania Scale scores.

Table 1
Description of the tests used to assess psychopathological symptom severity in the PsyCourse Study.

Name	Description
PANSS-POS	To assess the severity of positive symptoms in schizophrenia
PANSS-NEG	To assess the severity of negative symptoms in schizophrenia
PANSS-GEN	To assess the severity of general psychopathology symptoms in schizophrenia
IDS-C30	Observer-rating scale to assess the severity of depressive symptoms
BDI-II	Self-report questionnaire to assess the severity of depressive symptoms
YMRS	Observer-rating scale to assess the severity of manic symptoms
ASRM	Self-report questionnaire to assess the severity of manic symptoms
MSS	Self-report questionnaire to assess the severity of manic symptoms

Note: In all tests, higher scores indicate more severe symptoms.
ASRM, Altman Self-Rating Mania Scale; BDI-II, Beck Depression Inventory; IDS-C30, Inventory of Depressive Symptomatology; MSS, Self-Report Manic Inventory (German: Manie-Selbstbeurteilungsskala); PANSS-GEN, Positive and Negative Syndrome Scale - General; PANSS-NEG, Positive and Negative Syndrome Scale - Negative; PANSS-POS, Positive and Negative Syndrome Scale - Positive; YMRS, Young Mania Rating Scale.

individuals with BD and mania indicate that patients with higher levels of chronic inflammation have more manic symptoms (Dickerson et al., 2013; Queissner et al., 2024). For example, one study found increased levels of IL-1β in the cerebrospinal fluid of individuals with BD (Söderlund et al., 2011), and the release of this pro-inflammatory cytokine has also been linked to manic episodes (Abé et al., 2023). In addition, inhibition of IL-1R1 signaling was shown to reduce neuroinflammation and delay the onset of CNS diseases (Luís et al., 2022). Also, levels of IL-1R1 mRNA in blood lymphocytes were higher in individuals with SCZ (Pandey et al., 2015a), BD (Pandey et al., 2015b), and MDD (Rizavi et al., 2016) than in control individuals. Furthermore, by mediating neuroinflammatory signaling, IL-1R1 is involved in the stress response and neuronal viability (DiSabato et al., 2021; Nemeth and Quan, 2021). Research in mice without IL-1R1 (i.e., *IL-1R1* knockout mice), which serve as a model for impaired memory performance and synaptic plasticity, demonstrated that the transplantation of wild-type neural precursor cells—which express *IL-1R1*—restored all of the impaired memory functioning and some of the long-term potentiation (Ben Menachem-Zidon et al., 2011).

Although several studies found that polymorphisms in the *IL-1* gene cluster are linked to major psychiatric disorders (Kapelski et al., 2015; Katila et al., 1999; Kim et al., 2004; Papiol et al., 2008; Sasayama et al., 2011), to the best of our knowledge, no evidence has been found for an association of *IL-1R1* gene polymorphisms with symptom severity in a transdiagnostic sample of individuals with psychiatric disorders. Thus, our study appears to be the first to show such an association. Regarding transdiagnostic perspective, traditional categorical nosological systems have recently been challenged by hierarchically and dimensionally measured concepts such as the Hierarchical Taxonomy of Psychopathology (HiTOP) (Kotov et al., 2017), and the NIMH Research Domain Criteria (RDoC) (Cuthbert and Insel, 2010; Insel et al., 2010). The latter concept emphasizes shared biology underlying similar symptoms, a view that comprises multiple levels of analysis (see also (Alameda et al., 2022), and in which inflammatory cytokines appear to play an important role (McQuaid, 2021).

While no inference of causality can be drawn from our findings, our results suggest that IL-1R1 gene polymorphisms may influence brain cytokine profiling associated with manic episodes, a finding that generally supports the mounting body of evidence highlighting the significance of the IL-1/IL-1R1 signaling pathways in the pathophysiology of psychiatric disorders. In this vein, genetic variability in *IL-1R1* might modulate total expression of the wild type form, or putatively play a role in balancing between the canonical and alternative forms of this receptor by binding to distinct accessory proteins that may determine whether IL-1 has a neurotoxic or neuroprotective effect (Nemeth and Quan, 2021), thus potentially affecting mood states. According to several in vivo and in vitro studies (Akkouh et al., 2020; Liu et al., 2011; Osete et al., 2023; Petersein et al., 2015), lithium (Li)—the first-line treatment for BD—increases the expression of some proinflammatory cytokines, such as IL-1β. It is likely that Li therapeutic effect in mood regulation and the treatment of manic episodes comes from its influence on cytokine signaling, particularly the activation of proinflammatory cytokines (Petersein et al., 2015). In light of these findings, our study's results can also be viewed as showing that genetic variations of the *IL-1R1*, which encodes the IL-1β receptor, may be involved in action mechanisms of Li by controlling IL-1/IL-1R1 signaling and, consequently, the intensity of manic episodes.

Despite the available literature about other inflammatory mediators (e.g., IL-6 and IL-8, which have been reported as biomarkers for manic episodes in individuals with BD (Munkholm et al., 2015)), we did not find a significant association between SNPs in other inflammatory mediator genes and the symptoms under consideration. Moreover, no significant associations were found between inflammatory mediator gene polymorphisms and SCZ symptomatology rating scores. This lack of associations might stem from the several limitations of our investigation, including the relatively small sample size, which may have led to insufficient statistical power, and the small effect size of the discovered associations between inflammatory mediator gene polymorphisms and the severity of the symptoms being studied. Additionally, it could result from potential symptom heterogeneity and inconsistency across different disorders as well as a bias in the way these symptoms are measured using various scales. Another limitation of our study is the limited number of inflammatory mediator genes studied. Independent replication with larger cohorts is required to confirm the findings.

Table 2
Demographic and psychopathological data of the study participants.

	SCZ	BD	MDD	HC	Group differences			
					Groups	Test result		
						χ-squared	F value	P value
Participants, n	572	524	94	404	–			
Sex, % female	38	49	59	59	SCZ vs BD	**12.87**		**0.0003**
					SCZ vs MDD	**14.48**		**0.0001**
					BD vs MDD	3.13		0.077
					SCZ vs HC	**39.36**		**3.51×10^{-10}**
					BD vs HC	**8.09**		**0.004**
					MDD vs HC	0.002		0.963
Age, mean ± SD, y	40.52 ± 12.19	45.41 ± 13.14	43.77 ± 15.23	36.8 ± 15.08	SCZ vs BD		**40.85**	**2.43×10^{-10}**
					SCZ vs MDD		**5.32**	**0.021**
					BD vs MDD		1.18	0.278
					SCZ vs HC		**18.1**	**2.3×10^{-5}**
					BD vs HC		**86.13**	**$<2 \times 10^{-16}$**
					MDD vs HC		**16.25**	**6.44×10^{-5}**
Duration of illness, mean ± SD, y	13.18 ± 10.57	12.58 ± 11.26	8.64 ± 9.74	–	SCZ vs BD		0.78	0.37
					SCZ vs MDD		**14.79**	**0.0001**
					BD vs MDD		**9.74**	**0.002**
Patient status, % inpatient	52	29	50	–	SCZ vs BD	**57.95**		**2.68×10^{-14}**
					SCZ vs MDD	0.065		0.797
					BD vs MDD	**14.39**		**0.0001**
PANSS - positive sum score, mean ± SD	13.8 ± 5.73	9.27 ± 3.31	7.85 ± 1.77	7.06 ± 0.28	SCZ vs BD		**244.3**	**$<2 \times 10^{-16}$**
					SCZ vs MDD		**98.53**	**$<2 \times 10^{-16}$**
					BD vs MDD		**16.33**	**6.02×10^{-5}**
PANSS - negative sum score, mean ± SD	15.75 ± 6.57	10.19 ± 4.03	12.89 ± 5.42	7.18 ± 0.64	SCZ vs BD		**269.7**	**$<2 \times 10^{-16}$**
					SCZ vs MDD		**15.25**	**0.0001**
					BD vs MDD		**30.23**	**5.71×10^{-8}**
PANSS - general sum score, mean ± SD	29.72 ± 9.85	23.38 ± 6.7	27.53 ± 7.85	16.43 ± 1.02	SCZ vs BD		**147**	**$<2 \times 10^{-16}$**
					SCZ vs MDD		**3.957**	**0.047**
					BD vs MDD		**27.57**	**2.12×10^{-7}**
IDS-C_{30} sum score, mean ± SD	13.02 ± 10.43	13.41 ± 11.23	24.07 ± 16.18	2.62 ± 2.91	SCZ vs BD		0.313	0.576
					SCZ vs MDD		**67.74**	**1.18×10^{-15}**
					BD vs MDD		**55.33**	**3.9×10^{-13}**
BDI-II sum score, mean ± SD	12.66 ± 10.73	13.61 ± 11.9	20.94 ± 13.3	2.72 ± 3.7	SCZ vs BD		1.635	0.201
					SCZ vs MDD		**38.51**	**1.07×10^{-9}**
					BD vs MDD		**25.35**	**6.54×10^{-7}**
YMRS sum score, mean ± SD	2.48 ± 4.23	3.82 ± 5.93	1.49 ± 2.02	0.5 ± 1.04	SCZ vs BD		**17.11**	**3.81×10^{-5}**
					SCZ vs MDD		**4.747**	**0.029**
					BD vs MDD		**13.76**	**0.0002**
ASRM sum score, mean ± SD	2.22 ± 3.06	2.74 ± 3.57	2.08 ± 2.38	1.49 ± 2.2	SCZ vs BD		**5.741**	**0.016**
					SCZ vs MDD		0.157	0.692
					BD vs MDD		2.681	0.102
MSS sum score, mean ± SD	7.17 ± 7.17	6.89 ± 7.88	5.53 ± 5.08	3.13 ± 3.93	SCZ vs BD		0.243	0.622
					SCZ vs MDD		3.244	0.072
					BD vs MDD		1.89	0.17

ASRM, Altman Self-Rating Mania Scale; BD, bipolar disorder patients; BDI-II, Beck Depression Inventory scale; HC, healthy controls; IDS-C30, Inventory of Depressive Symptomatology scale; MDD, major depressive disorder patients; MSS, Self-Report Manic Inventory (German: Manie-Selbstbeurteilungsskala); PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenia patients; YMRS, Young Mania Rating Scale.

5. Conclusion

Overall, although there is still much to learn about the precise roles of IL-1, IL-1R1, and IL-1/IL-1R1 signaling pathways in neurophysiology and neuropathology inside the brain, our study—along with others—may pave the way for more extensive research and new perspectives on the significance of neuroinflammatory processes in the pathophysiology of psychiatric disorders. In this sense, in the future it may be beneficial to use genomic and proteomic panels of inflammatory mediators to better define diagnostic strategies (e.g., to prove the presence of inflammation-related states by considering the pro- to anti-inflammatory ratio of inflammatory mediators) and therapeutic plans (e.g., by targeting pivotal inflammatory mediators with anti-inflammatory agents).

CRediT authorship contribution statement

Mojtaba Oraki Kohshour: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Kristina Adorjan:** Data curation. **Monika Budde:** Data curation. **Maria Heilbronner:** Data curation. **Janos L. Kalman:** Data curation. **Alba Navarro-Flores:** Data curation. **Daniela Reich-Erkelenz:** Data curation. **Eva C. Schulte:** Data curation. **Fanny Senner:** Data curation. **Thomas Vogl:** Data curation. **Ion-George Anghelescu:** Data curation. **Volker Arolt:** Data curation. **Bernhardt T. Baune:** Data curation. **Udo Dannlowski:** Data curation. **Detlef E. Dietrich:** Data curation. **Andreas J. Fallgatter:** Data curation. **Christian Figge:** Data curation. **Fabian U. Lang:** Data curation. **Georg Juckel:** Data curation. **Carsten Konrad:** Data curation. **Jens Reimer:** Data curation. **Eva Z. Reininghaus:** Data curation. **Max Schmauß:** Data curation. **Andrea Schmitt:** Data curation. **Carsten Spitzer:** Data curation. **Jens Wiltfang:** Data curation. **Jörg Zimmermann:** Data curation. **Peter Falkai:** Data curation. **Urs Heilbronner:** Writing – original draft, Methodology, Data curation, Conceptualization. **Sergi Papiol:** Methodology, Data curation, Conceptualization. **Thomas G. Schulze:** Supervision, Project administration, Data curation.

Declaration of competing interest

Carsten Konrad received fees for an educational program from Aristo

Pharma, Janssen-Cilag, Lilly, MagVenture, Servier, and Trommsdorff as well as travel support and speakers honoraria from Aristo Pharma, Janssen-Cilag, Lundbeck, Neuraxpharm and Servier. None of the other authors reported conflict of interest.

Data availability statement

A unique feature of the PsyCourse Study is that it has been conceptualized as a continuously growing data resource available to the scientific community. Data sharing will be based on mutually agreed research proposals and within the Open Science framework of the PsyCourse Study (Please see psycourse.de/openscience-en.html).

Acknowledgements

The authors thank Jacquie Klesing, Board-certified Editor in the Life Sciences (ELS), for editing assistance with the manuscript.

Funding

Thomas G. Schulze is supported by the German Research Foundation (Deutsche Forschungsgemeinschaft [DFG]) within the framework of the projects www.kfo241.de and www.PsyCourse.de (SCHU 1603/4-1, 5-1, 7-1; FA241/16-1) and by the Dr. Lisa Oehler Foundation (Kassel, Germany). Thomas G. Schulze and Peter Falkai received support via the German Center for Mental Health (BMBF 01EE2303F). Eva C. Schulte was supported by the Munich Clinician Scientist Program. Udo Dannlowski is supported by DFG (grant FOR2107 DA1151/5-1, DA1151/5-2, DA1151/9-1, DA1151/10-1, DA1151/11-1; SFB-TRR393, Projects S02 and A02) and by the Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster (grant Dan3/022/22). Urs Heilbronner was supported by the European Union's Horizon 2020 Research and Innovation Program (PSY-PGx, grant agreement No 945151) and DFG (project number 514201724).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2025.116492.

References

Abé, C., Liberg, B., Klahn, A.L., Petrovic, P., Landén, M., 2023. Mania-related effects on structural brain changes in bipolar disorder - a narrative review of the evidence. Mol. Psychiatry 28, 2674–2682. https://doi.org/10.1038/s41380-023-02073-4.

Akkouh, I.A., Skrede, S., Holmgren, A., Ersland, K.M., Hansson, L., Bahrami, S., Andreassen, O.A., Steen, V.M., Djurovic, S., Hughes, T., 2020. Exploring lithium's transcriptional mechanisms of action in bipolar disorder: a multi-step study. Neuropsychopharmacology 45, 947–955. https://doi.org/10.1038/s41386-019-0556-8.

Alameda, L., Trotta, G., Quigley, H., Rodriguez, V., Gadelrab, R., Dwir, D., Dempster, E., Wong, C.C.Y., Forti, M.D., 2022. Can epigenetics shine a light on the biological pathways underlying major mental disorders? Psychol. Med. 52, 1645–1665. https://doi.org/10.1017/S0033291721005559.

Altman, E.G., Hedeker, D., Peterson, J.L., Davis, J.M., 1997. The Altman self-rating mania scale. Biol. Psychiatry 42, 948–955. https://doi.org/10.1016/S0006-3223(96)00548-3.

Basu, A., Krady, J.K., Levison, S.W., 2004. Interleukin-1: a master regulator of neuroinflammation. J. Neurosci. Res. 78, 151–156. https://doi.org/10.1002/jnr.20266.

Ben Menachem-Zidon, O., Avital, A., Ben-Menahem, Y., Goshen, I., Kreisel, T., Shmueli, E.M., Segal, M., Ben Hur, T., Yirmiya, R., 2011. Astrocytes support hippocampal-dependent memory and long-term potentiation via interleukin-1 signaling. Brain Behav. Immun. 25, 1008–1016. https://doi.org/10.1016/j.bbi.2010.11.007.

Bennett, F.C., Molofsky, A.V., 2019. The immune system and psychiatric disease: a basic science perspective. Clin. Exp. Immunol. 197, 294–307. https://doi.org/10.1111/cei.13334.

Budde, M., Anderson-Schmidt, H., Gade, K., Reich-Erkelenz, D., Adorjan, K., Kalman, J. L., Senner, F., Papiol, S., Andlauer, T.F.M., Comes, A.L., Schulte, E.C., Klöhn-Saghatolislam, F., Gryaznova, A., Hake, M., Bartholdi, K., Flatau, L., Reitt, M., Quast, S., Stegmaier, S., Meyers, M., Emons, B., Haußleiter, I.S., Juckel, G., Nieratschker, V., Dannlowski, U., Schaupp, S.K., Schmauß, M., Zimmermann, J., Reimer, J., Schulz, S., Wiltfang, J., Reininghaus, E., Anghelescu, I.-G., Arolt, V., Baune, B.T., Konrad, C., Thiel, A., Fallgatter, A.J., Figge, C., von Hagen, M., Koller, M., Lang, F.U., Wigand, M.E., Becker, T., Jäger, M., Dietrich, D.E., Stierl, S., Scherk, H., Spitzer, C., Folkerts, H., Witt, S.H., Degenhardt, F., Forstner, A.J., Rietschel, M., Nöthen, M.M., Falkai, P., Schulze, T.G., Heilbronner, U., 2019. A longitudinal approach to biological psychiatric research: the PsyCourse study. Am. J. Med. Genet. B Neuropsychiatr. Genet. 180, 89–102. https://doi.org/10.1002/ajmg.b.32639.

Bull, S.J., Huezo-Diaz, P., Binder, E.B., Cubells, J.F., Ranjith, G., Maddock, C., Miyazaki, C., Alexander, N., Hotopf, M., Cleare, A.J., Norris, S., Cassidy, E., Aitchison, K.J., Miller, A.H., Pariante, C.M., 2009. Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon-alpha and ribavirin treatment. Mol. Psychiatry 14, 1095–1104. https://doi.org/10.1038/mp.2008.48.

Cuthbert, B.N., Insel, T.R., 2010. Toward new approaches to psychotic disorders: the NIMH Research Domain Criteria project. Schizophr. Bull. 36, 1061–1062. https://doi.org/10.1093/schbul/sbq108.

Dickerson, F., Stallings, C., Origoni, A., Vaughan, C., Katsafanas, E., Khushalani, S., Yolken, R., 2013. A combined marker of inflammation in individuals with mania. PLoS One 8, e73520. https://doi.org/10.1371/journal.pone.0073520.

DiSabato, D.J., Nemeth, D.P., Liu, X., Witcher, K.G., O'Neil, S.M., Oliver, B., Bray, C.E., Sheridan, J.F., Godbout, J.P., Quan, N., 2021. Interleukin-1 receptor on hippocampal neurons drives social withdrawal and cognitive deficits after chronic social stress. Mol. Psychiatry 26, 4770–4782. https://doi.org/10.1038/s41380-020-0788-3.

Felger, J.C., Lotrich, F.E., 2013. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience 246, 199–229. https://doi.org/10.1016/j.neuroscience.2013.04.060.

Frydecka, D., Misiak, B., Pawlak-Adamska, E., Karabon, L., Tomkiewicz, A., Sedlaczek, P., Kiejna, A., Beszłej, J.A., 2015. interleukin-6: the missing element of the neurocognitive deterioration in schizophrenia? The focus on genetic underpinnings, cognitive impairment and clinical manifestation. Eur. Arch. Psychiatry Clin. Neurosci. 265, 449–459. https://doi.org/10.1007/s00406-014-0533-5.

Golimbet, V., Lezheiko, T., Mikhailova, V., Korovaitseva, G., Kolesina, N., Plakunova, V., Kostyuk, G., 2022. A study of the association between polymorphisms in the genes for interleukins IL-6 and IL-10 and negative symptoms subdomains in schizophrenia. Indian J. Psychiatry 64, 484–488. https://doi.org/10.4103/indianjpsychiatry.indianjpsychiatry_212_22.

Hautzinger, M., Keller, F., Kühner, C., 2006. Beck Depressions-Inventar Revision (BDI II). Harcourt Test services Frankfurt, Frankfurt, Germany.

Heilbronner U, A. Kristina, A.-S. Heike, et al., 2023. The PsyCourse Codebook, Version 6.0.

https://www.genecards.org, 2024. IL1R1 [WWW Document]. URL. https://www.genecards.org/cgi-bin/carddisp.pl?gene=IL1R1&keywords=il1r1.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am. J. Psychiatry 167, 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379.

Kalmady, S.V., Venkatasubramanian, G., Shivakumar, V., Gautham, S., Subramaniam, A., Jose, D.A., Maitra, A., Ravi, V., Gangadhar, B.N., 2014. Relationship between interleukin-6 gene polymorphism and hippocampal volume in antipsychotic-naïve schizophrenia: evidence for differential susceptibility? PLoS One 9, e96021. https://doi.org/10.1371/journal.pone.0096021.

Kapelski, P., Skibinska, M., Maciukiewicz, M., Wilkosc, M., Frydecka, D., Groszewska, A., Narozna, B., Dmitrzak-Weglarz, M., Czerski, P., Pawlak, J., Rajewska-Rager, A., Leszczynska-Rodziewicz, A., Slopien, A., Zaremba, D., Twarowska-Hauser, J., 2015. Association study of functional polymorphisms in interleukins and interleukin receptors genes: IL1A, IL1B, IL1RN, IL6, IL6R, IL10, IL10RA and TGFB1 in schizophrenia in Polish population. Schizophr. Res. 169, 1–9. https://doi.org/10.1016/j.schres.2015.10.008.

Katila, H., Hänninen, K., Hurme, M., 1999. Polymorphisms of the interleukin-1 gene complex in schizophrenia. Mol. Psychiatry 4, 179–181. https://doi.org/10.1038/sj.mp.4000483.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/schbul/13.2.261.

Khandaker, G.M., Zammit, S., Burgess, S., Lewis, G., Jones, P.B., 2018. Association between a functional interleukin 6 receptor genetic variant and risk of depression and psychosis in a population-based birth cohort. Brain Behav. Immun. 69, 264–272. https://doi.org/10.1016/j.bbi.2017.11.020.

Kim, S.J., Lee, H.J., Koo, H.G., Kim, J.W., Song, J.Y., Kim, M.K., Shin, D.H., Jin, S.Y., Hong, M.S., Park, H.J., Yoon, S.H., Park, H.K., Chung, J.-H., 2004. Impact of IL-1 receptor antagonist gene polymorphism on schizophrenia and bipolar disorder. Psychiatr. Genet. 14, 165–167. https://doi.org/10.1097/00041444-200409000-00009.

Kotov, R., Krueger, R.F., Watson, D., Achenbach, T.M., Althoff, R.R., Bagby, R.M., Brown, T.A., Carpenter, W.T., Caspi, A., Clark, L.A., Eaton, N.R., Forbes, M.K., Forbush, K.T., Goldberg, D., Hasin, D., Hyman, S.E., Ivanova, M.Y., Lynam, D.R., Markon, K., Miller, J.D., Moffitt, T.E., Morey, L.C., Mullins-Sweatt, S.N., Ormel, J., Patrick, C.J., Regier, D.A., Rescorla, L., Ruggero, C.J., Samuel, D.B., Sellbom, M., Simms, L.J., Skodol, A.E., Slade, T., South, S.C., Tackett, J.L., Waldman, I.D., Waszczuk, M.A., Widiger, T.A., Wright, A.G.C., Zimmerman, M., 2017. The Hierarchical Taxonomy of Psychopathology (HiTOP): a dimensional alternative to traditional nosologies. J. Abnorm. Psychol. 126, 454–477. https://doi.org/10.1037/abn0000258.

Krüger, S., Bräunig, P., Shugar, G., 1997. Manie-Selbstbeurteilungsskala: MSS: deutsche Bearbeitung des Self-Report manic inventory (SRMI). Beltz Test.

Kudinova, A.Y., Deak, T., Hueston, C.M., McGeary, J.E., Knopik, V.S., Palmer, R.H.C., Gibb, B.E., 2016. Cross-species evidence for the role of interleukin-33 in depression risk. J. Abnorm. Psychol. 125, 482–494. https://doi.org/10.1037/abn0000158.

Lesh, T.A., Careaga, M., Rose, D.R., McAllister, A.K., Van de Water, J., Carter, C.S., Ashwood, P., 2018. Cytokine alterations in first-episode schizophrenia and bipolar disorder: relationships to brain structure and symptoms. J. Neuroinflammation 15, 165. https://doi.org/10.1186/s12974-018-1197-2.

Liu, K.-J., Lee, Y.-L., Yang, Y.-Y., Shih, N.-Y., Ho, C.-C., Wu, Y.-C., Huang, T.-S., Huang, M.-C., Liu, H.-C., Shen, W.W., Leu, S.-J., 2011. Modulation of the development of human monocyte-derived dendritic cells by lithium chloride. J. Cell. Physiol. 226, 424–433. https://doi.org/10.1002/jcp.22348.

Liu, X., Nemeth, D.P., McKim, D.B., Zhu, L., DiSabato, D.J., Berdysz, O., Gorantla, G., Oliver, B., Witcher, K.G., Wang, Y., Negray, C.E., Vegesna, R.S., Sheridan, J.F., Godbout, J.P., Robson, M.J., Blakely, R.D., Popovich, P.G., Bilbo, S.D., Quan, N., 2019. Cell-type-specific interleukin 1 receptor 1 signaling in the brain regulates distinct neuroimmune activities. Immunity 50, 317–333. https://doi.org/10.1016/j.immuni.2018.12.012 e6.

Luís, J.P., Simões, C.J.V., Brito, R.M.M., 2022. The therapeutic prospects of targeting IL-1R1 for the modulation of neuroinflammation in Central nervous system disorders. Int. J. Mol. Sci. 23. https://doi.org/10.3390/ijms23031731.

McCarthy, S., Das, S., Kretzschmar, W., Delaneau, O., Wood, A.R., Teumer, A., Kang, H. M., Fuchsberger, C., Danecek, P., Sharp, K., Luo, Y., Sidore, C., Kwong, A., Timpson, N., Koskinen, S., Vrieze, S., Scott, L.J., Zhang, H., Mahajan, A., Veldink, J., Peters, U., Pato, C., van Duijn, C.M., Gillies, C.E., Gandin, I., Mezzavilla, M., Gilly, A., Cocca, M., Traglia, M., Angius, A., Barrett, J.C., Boomsma, D., Branham, K., Breen, G., Brummett, C.M., Busonero, F., Campbell, H., Chan, A., Chen, S., Chew, E., Collins, F.S., Corbin, L.J., Smith, G.D., Dedoussis, G., Dorr, M., Farmaki, A.-E., Ferrucci, L., Forer, L., Fraser, R.M., Gabriel, S., Levy, S., Groop, L., Harrison, T., Hattersley, A., Holmen, O.L., Hveem, K., Kretzler, M., Lee, J.C., McGue, M., Meitinger, T., Melzer, D., Min, J.L., Mohlke, K.L., Vincent, J.B., Nauck, M., Nickerson, D., Palotie, A., Pato, M., Pirastu, N., McInnis, M., Richards, J.B., Sala, C., Salomaa, V., Schlessinger, D., Schoenherr, S., Slagboom, P.E., Small, K., Spector, T., Stambolian, D., Tuke, M., Tuomilehto, J., Van den Berg, L.H., Van Rheenen, W., Volker, U., Wijmenga, C., Toniolo, D., Zeggini, E., Gasparini, P., Sampson, M.G., Wilson, J.F., Frayling, T., de Bakker, P.I.W., Swertz, M.A., McCarroll, S., Kooperberg, C., Dekker, A., Altshuler, D., Willer, C., Iacono, W., Ripatti, S., Soranzo, N., Walter, K., Swaroop, A., Cucca, F., Anderson, C.A., Myers, R.M., Boehnke, M., McCarthy, M.I., Durbin, R., 2016. A reference panel of 64,976 haplotypes for genotype imputation. Nat. Genet. 48, 1279–1283. https://doi.org/10.1038/ng.3643.

McQuaid, R.J., 2021. Transdiagnostic biomarker approaches to mental health disorders: consideration of symptom complexity, comorbidity and context. Brain Behav. Immun. Health 16, 100303. https://doi.org/10.1016/j.bbih.2021.100303.

Messina, A., Concerto, C., Rodolico, A., Petralia, A., Caraci, F., Signorelli, M.S., 2023. Is it time for a paradigm shift in the treatment of schizophrenia? The use of inflammation-reducing and neuroprotective drugs-a review. Brain Sci. 13. https://doi.org/10.3390/brainsci13060957.

Mihailova, S., Ivanova-Genova, E., Lukanov, T., Stoyanova, V., Milanova, V., Naumova, E., 2016. A study of TNF-α, TGF-β, IL-10, IL-6, and IFN-γ gene polymorphisms in patients with depression. J. Neuroimmunol. 293, 123–128. https://doi.org/10.1016/j.jneuroim.2016.03.005.

Mikhalitskaya, E.V., Vyalova, N.M., Ermakov, E.A., Levchuk, L.A., Simutkin, G.G., Bokhan, N.A., Ivanova, S.A., 2023. Association of single nucleotide polymorphisms of cytokine genes with depression, schizophrenia and bipolar disorder. Genes 14. https://doi.org/10.3390/genes14071460.

Momtazmanesh, S., Zare-Shahabadi, A., Rezaei, N., 2019. Cytokine alterations in Schizophrenia: an updated review. Front. Psychiatry 10, 892. https://doi.org/10.3389/fpsyt.2019.00892.

Munkholm, K., Weikop, P., Kessing, L.V., Vinberg, M., 2015. Elevated levels of IL-6 and IL-18 in manic and hypomanic states in rapid cycling bipolar disorder patients. Brain Behav. Immun. 43, 205–213. https://doi.org/10.1016/j.bbi.2014.09.021.

Nemeth, D.P., Quan, N., 2021. Modulation of neural networks by interleukin-1. Brain Plast. 7, 17–32. https://doi.org/10.3233/BPL-200109.

Osete, J.R., Akkouh, I.A., Ievglevskyi, O., Vandenberghe, M., de Assis, D.R., Ueland, T., Kondratskaya, E., Holen, B., Szabo, A., Hughes, T., Smeland, O.B., Steen, V.M., Andreassen, O.A., Djurovic, S., 2023. Transcriptional and functional effects of lithium in bipolar disorder iPSC-derived cortical spheroids. Mol. Psychiatry 28, 3033–3043. https://doi.org/10.1038/s41380-023-01944-0.

Pandey, G.N., Ren, X., Rizavi, H.S., Zhang, H., 2015a. Proinflammatory cytokines and their membrane-bound receptors are altered in the lymphocytes of schizophrenia patients. Schizophr. Res. 164, 193–198. https://doi.org/10.1016/j.schres.2015.02.004.

Pandey, G.N., Ren, X., Rizavi, H.S., Zhang, H., 2015b. Abnormal gene expression of proinflammatory cytokines and their receptors in the lymphocytes of patients with bipolar disorder. Bipolar Disord. 17, 636–644. https://doi.org/10.1111/bdi.12320.

Papiol, S., Molina, V., Desco, M., Rosa, A., Reig, S., Sanz, J., Palomo, T., Fañanás, L., 2008. Gray matter deficits in bipolar disorder are associated with genetic variability at interleukin-1 beta gene (2q13). Genes Brain Behav. 7, 796–801. https://doi.org/10.1111/j.1601-183X.2008.00421.x.

Petersein, C., Sack, U., Mergl, R., Schönherr, J., Schmidt, F.M., Lichtblau, N., Kirkby, K. C., Bauer, K., Himmerich, H., 2015. Impact of lithium alone and in combination with antidepressants on cytokine production in vitro. J. Neural Transm. 122, 109–122. https://doi.org/10.1007/s00702-014-1328-6.

Queissner, R., Fellendorf, F.T., Dalkner, N., Bengesser, S.A., Maget, A., Birner, A., Platzer, M., Reininghaus, B., Häussl, A., Schönthaler, E., Tmava-Berisha, A., Lenger, M., Reininghaus, E.Z., 2024. The influence of chronic inflammation on the illnesscourse of bipolar disorder: a longitudinal study. J. Psychiatr. Res. 174, 258–262. https://doi.org/10.1016/j.jpsychires.2024.04.024.

Rizavi, H.S., Ren, X., Zhang, H., Bhaumik, R., Pandey, G.N., 2016. Abnormal gene expression of proinflammatory cytokines and their membrane-bound receptors in the lymphocytes of depressed patients. Psychiatry Res. 240, 314–320. https://doi.org/10.1016/j.psychres.2016.04.049.

Rodrigues-Amorim, D., Rivera-Baltanás, T., Spuch, C., Caruncho, H.J., González-Fernandez, Á., Olivares, J.M., Agís-Balboa, R.C., 2018. Cytokines dysregulation in schizophrenia: a systematic review of psychoneuroimmune relationship. Schizophr. Res. 197, 19–33. https://doi.org/10.1016/j.schres.2017.11.023.

Rush, A.J., Carmody, T., Reimitz, P.-E., 2000. The inventory of depressive symptomatology (IDS): clinician (IDS-C) and self-report (IDS-SR) ratings of depressive symptoms. Int. J. Methods Psychiatr. Res. 9, 45–59. https://doi.org/10.1002/mpr.79.

Sasayama, D., Hori, H., Teraishi, T., Hattori, K., Ota, M., Iijima, Y., Tatsumi, M., Higuchi, T., Amano, N., Kunugi, H., 2011. Possible association between interleukin-1β gene and schizophrenia in a Japanese population. Behav. Brain Funct. 7, 35. https://doi.org/10.1186/1744-9081-7-35.

Scangos, K.W., State, M.W., Miller, A.H., Baker, J.T., Williams, L.M., 2023. New and emerging approaches to treat psychiatric disorders. Nat. Med. 29, 317–333. https://doi.org/10.1038/s41591-022-02197-0.

Söderlund, J., Olsson, S.K., Samuelsson, M., Walther-Jallow, L., Johansson, C., Erhardt, S., Landén, M., Engberg, G., 2011. Elevation of cerebrospinal fluid interleukin-1ß in bipolar disorder. J. Psychiatry Neurosci. 36, 114–118. https://doi.org/10.1503/jpn.100080.

Swain, S.A., Sarangi, P., Rattan, R., Sahu, P.K., Lamare, A.A., 2022. A study of nuclear factor-kappa B1 gene polymorphism types in schizophrenia patients and their correlation with disease severity. Cureus 14, e24401. https://doi.org/10.7759/cureus.24401.

Tartter, M., Hammen, C., Bower, J.E., Brennan, P.A., Cole, S., 2015. Effects of chronic interpersonal stress exposure on depressive symptoms are moderated by genetic variation at IL6 and IL1β in youth. Brain Behav. Immun. 46, 104–111. https://doi.org/10.1016/j.bbi.2015.01.003.

Thome, J.G., Reeder, E.L., Collins, S.M., Gopalan, P., Robson, M.J., 2019. Contributions of interleukin-1 receptor signaling in traumatic brain injury. Front. Behav. Neurosci. 13, 287. https://doi.org/10.3389/fnbeh.2019.00287.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435. https://doi.org/10.1192/bjp.133.5.429.

Zhang, J.-M., An, J., 2007. Cytokines, inflammation, and pain. Int. Anesthesiol. Clin. 45, 27–37. https://doi.org/10.1097/AIA.0b013e318034194e.