Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2017: 136: 409–423

DOI: 10.1111/acps.12791

Review

Infectious and immunogenetic factors in bipolar disorder

Oliveira J, Oliveira-Maia AJ, Tamouza R, Brown AS, Leboyer M. Infectious and immunogenetic factors in bipolar disorder.

Objective: Despite the evidence supporting the association between infection and bipolar disorder (BD), the genetic vulnerability that mediates its effects has yet to be clarified. A genetic origin for the immune imbalance observed in BD, possibly involved in the mechanisms of pathogen escape, has, however, been suggested in recent studies.
Method: Here, we present a critical review based on a systematic literature search of articles published until December 2016 on the association between BD and infectious/immunogenetic factors.
Results: We provide evidence suggesting that infectious insults could act as triggers of maladaptive immune responses in BD and that immunogenetic vulnerability may amplify the effects of such environmental risk factors, increasing susceptibility to subsequent environmental encounters. Quality of evidence was generally impaired by scarce attempt of replication, small sample sizes and lack of high-quality environmental measures.
Conclusion: Infection has emerged as a potential preventable cause of morbidity in BD, urging the need to better investigate components of the host–pathogen interaction in patients and at-risk subjects, and thus opening the way to novel therapeutic opportunities.

J. Oliveira[1,2], **A. J. Oliveira-Maia**[1,3,4,5], **R. Tamouza**[6,7], **A. S. Brown**[8], **M. Leboyer**[7,9,10]

[1]Champalimaud Clinical Centre, Champalimaud Centre for the Unknown, Lisboa, Portugal, [2]Centro Hospitalar Psiquiátrico de Lisboa, Lisboa, Portugal, [3]Department of Psychiatry and Mental Health, Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal, [4]Champalimaud Research, Champalimaud Centre for the Unknown, Lisboa, Portugal, [5]Faculdade de Ciências Médicas, NOVA Medical School, Universidade Nova de Lisboa, Lisboa, Portugal, [6]Hôpital Saint Louis, INSERM U1160, Université Paris Diderot, Paris, France, [7]Fondation Fondamental, Créteil, France, [8]Columbia University Medical Center, New York, NY, USA, [9]Department of Psychiatry, AP-HP, DHU PePSY, Hôpital Henri Mondor, Université Paris-Est-Créteil, Créteil, France and [10]Translational Psychiatry, INSERM U955, Créteil, France

Key words: bipolar disorder; infection; inflammation; immunogenetics

José Oliveira, Champalimaud Clinical Centre, Champalimaud Centre for the Unknown, Av. Brasília, 1400-038 Lisboa, Portugal.
E-mail: jose.oliveira@neuro.fchampalimaud.org

Accepted for publication July 25, 2017

Summations

- Immunogenetic variants associated with increased risk of BD are thought to lead to increased vulnerability to infection.
- Cumulative exposure to early-life infection and other environmental stressors causes persistent disruption of immune homeostasis, potentially increasing the risk of BD and comorbid general medical disorders.
- Chronic immune dysfunction emerging from early-life host–pathogen interactions may be a preventable cause of morbidity in BD.

Considerations

- Replication studies are needed to confirm the association between immunogenetic variants and BD.
- Collection of high-quality prospective environmental data, to address causal associations between infection and BD, is lacking.
- A model of the contribution of immune and infectious factors towards the pathogenesis of BD is needed to guide future research and potential interventions in this area.

Introduction

While the pathophysiology of bipolar disorder (BD) has not yet been precisely described, the life course of the disorder seems to originate in part from environmental insults acting on a background of vulnerability during specific developmental windows (1, 2). There are likely a multitude of pathways in which neurodevelopment can be disrupted, leading to inadequate mood regulation that characterizes BD (3). A multiple-hit model, centred in the perinatal period, has been proposed as a sequence of three events: genetic predisposition acts as 'hit 1' while perinatal environment acts as 'hit 2', giving rise to phenotypes of vulnerability to 'hit 3', that is later life-experiences and exposures (4). Although the mechanistic details are unclear, this sequence of events has been proposed to chronically dysregulate homeostasis, in a process that is thought to involve the immune system (5).

While not as thoroughly studied as in major depressive disorder (MDD) or schizophrenia (SZ), immune dysregulation in BD has, however, been consistently documented as a component of a broader range of biological findings such as changes in neurotrophin and neurotransmitter levels, increased oxidative stress and mitochondrial dysfunction (6, 7). This chronic immune dysfunction, including activation of cell-mediated immunity, development of autoimmune disorders and systemic inflammation, may be a primary consequence of inflammatory processes and/or result from altered central nervous system integrity, and thus be a reflection of neuroprogression (8, 9). Furthermore, it is expected that such chronic low-grade inflammation contributes to the development of comorbidities in BD, such as obesity, metabolic syndrome, cardiovascular disorders and autoimmune disorders as well as a more severe clinical presentation (5, 10–13).

The present critical review is based on a systematic search of the literature on infectious and immunogenetic factors in BD. We will discuss the evidence supporting the association between infections and BD and argue that immunogenetic vulnerability may amplify the effects of these environmental exposures, generating low-grade chronic inflammation, among other potential consequences of infection.

Epidemiologic evidence for the association between infection and bipolar disorder

Mood dysregulation may be directly linked to external stressors and such stressors may exacerbate an underlying genetic or biochemical predisposition in BD (1, 5). Well-known environmental influences, such as childhood trauma, seem to cluster early in life (14) as well as infectious events induced by neurotropic pathogens, thought to induce maladaptive biological responses if sufficiently intense and/or persistent (15–18). The infection hypothesis posits that neurodevelopmental disruption could result from pathogens acting on the central nervous system and in peripheral systems, during gestational and perinatal periods, when both the nervous and immune systems are highly permeable to environmental influences (19, 20).

The following critical review on the association between infection and BD is based on a systematic literature search of PubMed for peer-reviewed articles published until December 2016, performed using the following syntax: ('bipolar disorder' OR bipolar) AND (toxoplasma OR toxoplasmosis OR Borna OR influenza OR herpes OR cytomegalovirus OR infection). Only bipolar disorder type I, type II or not otherwise specified as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-III or later edition), or its equivalent in the International Classification of Diseases (ICD) was considered. Moreover, only studies that tested the prevalence of infectious agents (in serum or cerebrospinal fluid) based on antibody, antigen or genetic material detection were included. Articles were limited to the English language. Quality assessment was performed using the Newcastle–Ottawa scale for case–control studies (21). A flow chart of the selection process is represented in Fig. 1, and quality assessment of the included studies is displayed in Table S1. Case–control studies concerning the association between infectious events and BD are summarized in Table 1. Unadjusted odds ratios and 95% confidence intervals are reported when available. Further evidence on the association between infection and BD is reported in Table S2.

Interestingly, most BD-associated pathogens share, at least to some degree, two characteristics that may be important in chronic, deviant developmental processes: neurotropism and latency. Associations of BD with Borna disease virus, influenza virus, herpes simplex virus type 1, herpes simplex virus type 2, cytomegalovirus, human herpes virus 6 and *Toxoplasma gondii* suggest that these relationships may not be specific to any one pathogen but rather involve a common mechanism, possibly immune activation. Although it has been proposed that some infections act early in life on specific stages of neurodevelopment (22), most studies are still rather inconclusive in this regard. Most

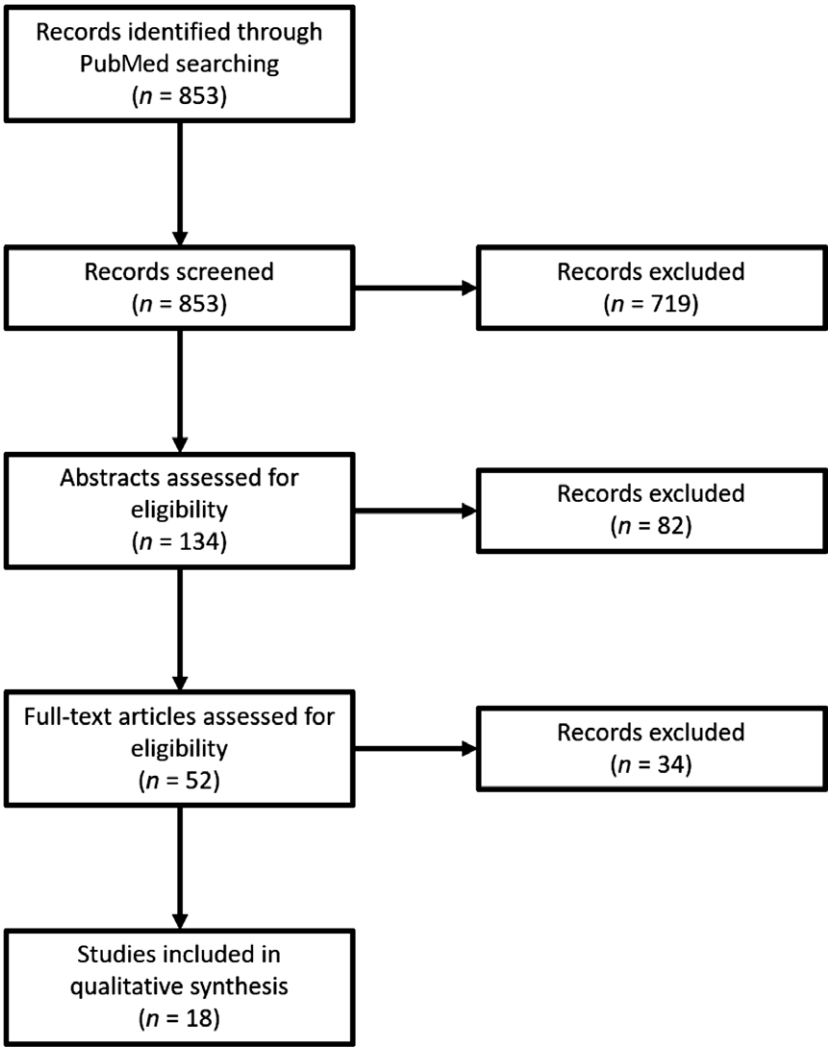

Fig. 1. Article selection process of studies on the association between infection and bipolar disorder.

research in BD has restricted the detection of infectious stigma to IgG antibodies, which are informative of a previous exposure but not able to identify the particular period of that exposure. These studies are thus insufficient to demonstrate that infections predate the diagnosis of BD, leaving open the possibility that they might even have occurred after onset. In that case, such infections would not be causal for BD, and their increased prevalence could reflect lifestyle-related factors, or even be an epiphenomenon of BD-related genetic backgrounds, that could independently increase liability to infection.

Nevertheless, some studies have provided clearer evidence of infections being associated with a higher risk of developing BD later in life. Parboosing et al (23), suggested that influenza during pregnancy increased the risk of BD in offspring by a factor of approximately 4 [OR: 3.82 (95% CI: 1.58–9.24)]. A key advantage of this study is that the infection was measured long prior to onset of BD, indicating that BD was not a consequence of influenza exposure. Moreover, Benros et al. (24), in a population-based analysis in Denmark, have shown that a previous hospitalization for an infectious disease was associated with an incidence rate ratio (IRR) of 1.61 (95% CI: 1.55–1.68) for a subsequent BD diagnosis. Additional evidence has similarly suggested that infections occurring during adult life may be associated with BD, probably triggering mood episodes or influencing clinical presentation. One such study demonstrated that anti-*Toxoplasma gondii* circulating IgM antibody levels were significantly higher in manic patients at hospital admission as compared to healthy controls [OR: 2.33 (95% CI: 1.08–5.03)], suggesting a recent infection, and the possibility that even a first contact with this parasite may trigger mood episodes in those susceptible (25). Similarly, another study showed a trend towards an increased prevalence of urinary tract infection in hospital-admitted patients, with approximately 21% of

Table 1. Studies exploring the association between infection and bipolar disorder

Agent	↑/↔/↓	OR (CI 95%)*	Country	Comments	Reference
BDV	↑	3.22 (1.77–5.94) – 38/40 kDa antigen 2.94 (1.07–9.19) – 24 kDa antigen	United States	Serum antibody to the 38/40 kDa and 24 kDa antigen	Fu et al., 1993 (115)†
	↑	OR 58.30 (15.36–367.13)	Germany	BDV antigens more prevalent in patients with a major depressive episode (MDD or BD)	Ferszt et al., 1999 (116)
	↔	2.00 (0.05–81.02)	Japan	Serum anti-p10-BDV antibodies in bipolar depression	Terayama et al., 2003 (117)
	↔	Antibodies were not detected.	South Korea	BDV antibody and p24, p40 RNA	Na et al., 2009 (118)
	↔	Antibodies were not detected	United States	Antibodies to BDV/BDV nucleic acids	Hornig et al., 2012 (119)
	↑	1.98 (1.10–3.53)	Iran	Increased circulating immune complexes	Mazaheri-Tehrani et al., 2014 (120)
EBV	↔	0.76 (0.02–10.48)	Germany	IgG antibodies	Stich et al., 2015 (121)
Influenza	↑	2.38 (1.03–5.39) – Influenza A 7.86 (2.51–26.49) – Influenza B 6.95 (3.04–15.80) – Coronavirus	United States	Serum antibody titres. Influenza A, Influenza B and coronavirus associated with history of mood disorders but not with the specific diagnosis of unipolar or bipolar depression	Okusaga et al., 2011 (122)
	↔	Not reported	Germany	Influenza B virus was associated with age at onset of BD	Gerber et al., 2012 (123)
HSV-1	↔	0.00 (0.00–1.11)	Ethiopia	IgG antibodies	Tedla et al., 2011 (124)
	↑	Not reported	Germany	IgG antibodies. Association with decreased cognitive functioning	Gerber et al., 2012 (123)
	↔	Not reported.	United States	IgG antibodies	Avramopoulos et al., 2015 (89)
	↔	Not reported	United States	IgG antibodies	Prossin et al., 2015 (125)
	↔	Not reported for HSV-1 separately	Germany	IgG antibodies	Stich et al., 2015 (121)
HSV-2	↔	1.60 (0.71–3.87)	Ethiopia	IgG antibodies	Tedla et al., 2011 (124)
	↔	Not reported	Germany	IgG antibodies	Gerber et al., 2012 (123)
	↔	Not reported	United States	IgG antibodies	Prossin et al., 2015 (125)
	↔	Not reported for HSV-2 separately	Germany	IgG antibodies	Stich et al., 2015 (121)
CMV	↔	0.00 (0.00–47.26)	Ethiopia	IgG antibodies	Tedla et al., 2011 (124)
	↔	Not reported	Germany	IgG antibodies	Gerber et al., 2012 (123)
	↔	Not reported	United States	IgG antibodies	Avramopoulos et al., 2015 (89)
	↑	1.83 (1.08–3.10)	United States	IgG antibodies	Prossin et al., 2015 (125)
	↔	0.53 (0.19–1.48)	Germany	IgG antibodies	Stich et al., 2015 (121)
HHV-6	↔	Not reported	Germany	IgG antibodies	Gerber et al., 2012 (123)
	↔	Not reported	United States	IgG antibodies	Avramopoulos et al., 2015 (89)
	↔	Insufficient number of positive individuals for calculation	Iran	Detection of HHV-6 DNA. HHV-6A detected in 1 BD patients and none of the controls. HHV-6B detected in none of the patients and in 2 controls	Yavarian et al., 2015 (126)
Toxoplasma gondii	↔	Not reported	Germany	IgG antibodies	Hinze-Selch et al., 2010 (127)
	↑	2.96 (1.06–8.28)	Ethiopia	IgG antibodies	Tedla et al., 2011 (124)
	↔	Unadjusted values not reported	Germany	IgG antibodies	Gerber et al., 2012 (123)
	↑	Unadjusted values not reported	United States	IgG antibodies	Pearce et al., 2012 (128)
	↑	3.58 (1.93–6.75)	France	IgG antibodies	Hamdani et al., 2013 (129)
	↔	1.28 (0.77–2.12)	Iran	IgG and IgM antibodies	Khademvatan et al., 2013 (130)
	↑	Unadjusted values not reported	United States	IgG and IgM antibodies. Increased IgM seropositivity in individuals with mania	Dickerson et al., 2014 (25)
	↔	Not reported	United States	IgG antibodies	Avramopoulos et al., 2015 (89)
	↔	1.77 (0.64–4.94)	Germany	IgG antibodies	Stich et al., 2015 (121)

BDV: Borna disease virus; EBV: Epstein–Barr virus; HSV-1: herpes simplex virus type 1; HSV-2: herpes simplex virus type 2; CMV: cytomegalovirus; HHV-6: human herpesvirus 6.
*Non-adjusted odds ratio (OR) and 95% confidence intervals (CI) for case–control comparisons.
†Mixed group of patients suffering from unipolar or bipolar depression. ↑/↔/↓ arrows indicate positive association, no association or negative association respectively.

those with BD affected, compared with only 3% of controls [OR: 8.1 (95% CI: 0.9–69.3] (26). A nationwide population-based retrospective cohort study in Taiwan found a 2.671 hazard ratio (HR) (95% CI: 1.921–3.716) of newly diagnosed BD in subjects with pelvic inflammatory disease, further suggesting that infection/inflammation is a risk factor (27).

The literature also suggests potential differences in how BD patients react to the presence of pathogens, a pathway that may underlie their vulnerability to the harmful consequences of infection. Seminog and Goldacre (28) observed that the risk of pneumococcal disease (lobar pneumonia and other pneumococcal diseases) in people hospitalized for BD is 2.3 times higher than in people without a record of hospitalization for a psychiatric disorder [RR: 2.3 (95% CI 2.2–2.3)] and that the risk remained high for years after discharge, suggesting an association with the psychiatric

disorder rather than with the event of hospitalization. Davydow et al. (29), in a Danish population-based cohort study, found that individuals with serious mental illness (in this study, SZ and BD) are at increased risk of hospitalization for pneumonia [IRR: 1.72 (95% CI: 1.66–1.79)] and urinary tract infection [IRR: 1.70 (95% CI: 1.62–1.78)] and rehospitalization for the same reason within 30 days. In Sweden, in a national cohort study involving 6 587 036 individuals, of which 6618 were diagnosed with BD, the mortality rate from influenza or pneumonia was found to be increased in BD patients when compared to the general population [adjusted hazard ratio (aHR) in women: 3.74 (95% CI: 2.39–5.88); aHR in men: 4.38 (95% CI: 2.76–6.96)] (30). Also, Ribe and collaborators (2015) observed that the 30-day mortality after any infection was 52% higher [mortality ratio = 1.52 (95% CI: 1.43–1.61)] for individuals with severe mental illness (BD and SZ) than for individuals without (31). Hayes et al. (32), in a recent review and meta-analysis, found that a standardized mortality ratio (SMR) of 2.25 (95% CI 1.70–3.00) can be attributed to infection in BD. These observations may partly explain the premature mortality in BD, with rates comparable to those of a heavy smoker (33), leaving aside other potential contributors namely risk behaviours, delays in seeking care and/or low adherence to treatment (34–37).

One mechanism currently proposed for how these infections can increase the risk of BD is the existence of a defective systemic immune/inflammatory response that interferes with the expression of proinflammatory cytokines in the peripheral immune system (20). Given that individual variation in immunogenetic background is an important determinant of postinfectious outcome (38), infectious agents may trigger the systemic and neuroinflammatory state observed in BD (39, 40).

Immunogenetic markers of susceptibility

Since the early years of the last century, there have been reports of dysfunction of the immune system in individuals with mental illness. Most of the early reports focused on immune hyporeactivity in SZ as demonstrated by a diminished cutaneous response to exogenous intradermal antigens such as guinea pig serum (41) and pertussis vaccine (42) or to histamine (43). Only recently has dysfunction of the immune system become a subject of interest in BD, with studies suggesting that this phenomenon may be under genetic control (5, 44, 45). Padmos and collaborators, when studying adolescent offspring of BD patients, observed a proinflammatory gene expression signature in monocytes of 85% of those who developed a mood disorder, and 45% of those who did not, compared to only 19% of control adolescents, suggesting that this immunopathology may be, at least in part, inherited (46). Additional evidence for genetic control of immune dysfunction has been collected in several different styles of experiments, as described below. A systematic literature search using PubMed for peer-reviewed articles published until December 2016 was performed using the following syntax: ('bipolar disorder' OR bipolar) AND (cytokine OR chemokine OR interleukin OR 'pattern recognition receptor' OR complement OR immunity OR immune OR inflammation OR leukotriene OR prostaglandins) AND (gene OR genetic OR polymorphism). Only bipolar disorder type I, type II or not otherwise specified as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-III or later edition), or its equivalent in the International Classification of Diseases (ICD) was considered. Moreover, genetic association studies with a case–control design analysing non-HLA genetic markers were included. Articles included in the critical review were limited to the English language. Quality assessment of the selected articles was performed using the Quality of Genetic Studies (Q-Genie) Tool (47). A flow chart of the selection process is represented in Fig. 2, and the quality assessment of the included studies is displayed in Table S3. Studies concerning the association between non-HLA immunogenetic markers and BD are summarized in Table 2.

Case–control associations

The highly polymorphic HLA region is probably the most associated genetic cluster to common diseases and its characterization allowed for major advances in transplantation medicine and genetics of susceptibility to autoimmune disorders and infectious diseases (48, 49). Genetic variations in the *HLA* locus have also been associated with BD, namely in HLA-B, HLA-C and HLA-DRA, but its potentiality as a genetic marker in BD remains controversial (50, 51). Nevertheless, these studies reinforce earlier findings that associated BD with the *HLA* region and also more recently with the non-classical HLA-G molecules (52–56). Potential susceptibility or protective *HLA* haplotypes in BD are still understudied. In the field of immunogenetics, only a few studies, often with discrepant results, have explored non-*HLA* loci, mainly focusing on polymorphisms of acute-phase and complement system proteins, cytokines, chemokines and pattern recognition receptors (PRRs).

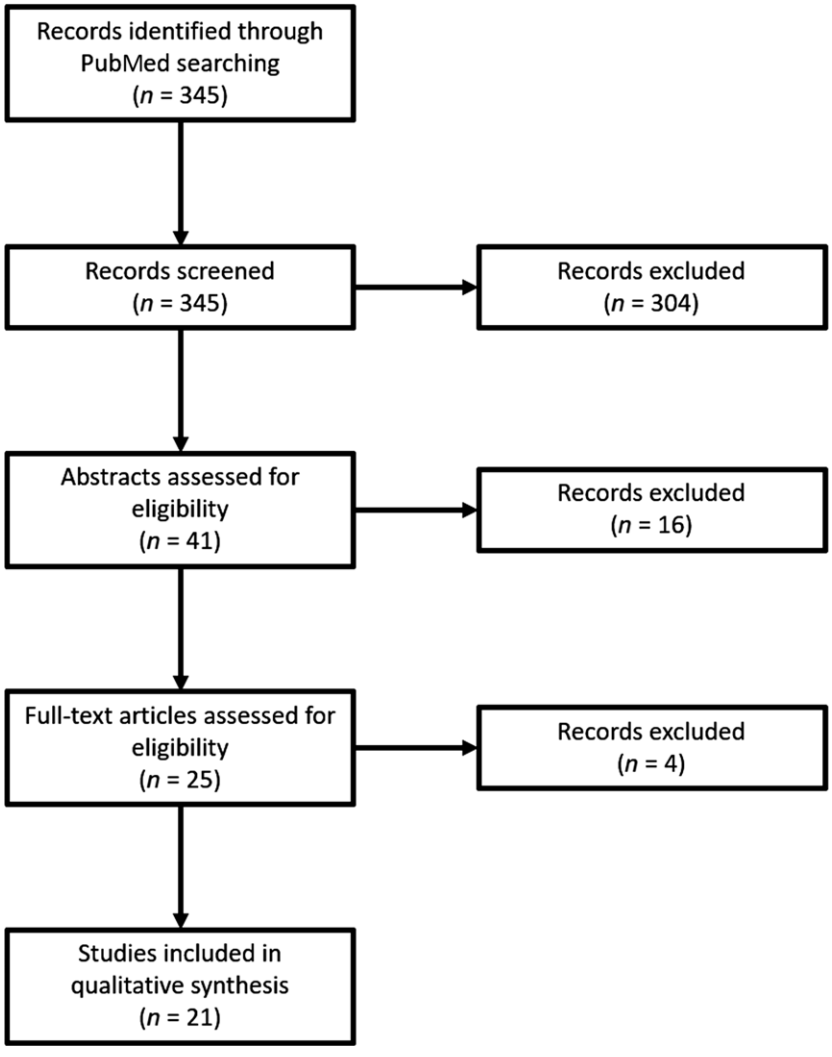

Fig. 2. Article selection process of studies on the association between immunogenetic markers and bipolar disorder.

The genetic diversity of Toll-like receptor 4, a major innate immune response molecule and pathogen receptor belonging to the TLR family, has been analysed in BD (57). The *TLR4* *rs*1927914 A and *rs*11536891 T alleles in homozygous states, suggested to be 'low expressor' genotypes, were associated with BD, specifically with the early-onset subgroup (57). Furthermore, by exploring genetic variants of the *NOD2* gene, an intracytoplasmic pathogen receptor particularly well described in intestinal inflammatory disorders, the same research group showed that the *NOD2* *rs*2066842 T allele is less prevalent in cases than in controls, seemingly conferring some 'protection' against BD (58). This allele has been described as a 'standing' common variant in Caucasians but rare in other ethnic groups (59). The maintenance of the *NOD2* *rs*2066842 polymorphism in Caucasians (in contrast to other population groups) is believed to be due to selection of heterozygotes by factors that are specific to the Caucasian environment, namely through increased resistance to bacterial infection (60, 61).

Further genetic association studies on cytokines, chemokines and other inflammatory markers are also evocative of a genetically determined weaker inflammatory/anti-infectious response. This is the case of the *TNF* gene, located in the class III region of the MHC on chromosome 6 (6p21.3), for which the *TNF* *rs*1800629 G allele, associated with lower production of TNF-α, was significantly more prevalent in BD patients than in healthy controls in the Polish and Italian populations (62–64). However, these findings have not been replicated in the Brazilian and the British populations (65, 66) and the inverse association, that is an increased frequency of the A allele among BD patients, has been described in a South Korean sample (67).

Interferon-γ (IFN-γ), an activator of macrophages and inducer of class II MHC expression, critical for innate and adaptive immunity against viral and protozoal infections, has also been

Table 2. Genetic association studies between non-HLA immunogenetic markers and bipolar disorder

Gene	Polymorphism	OR (CI 95%)*	Population	Comments	Reference
CCL2	*rs*1024611 A/G	G – 1.24 (0.81–1.89)	Korean	'A' allele more prevalent among manic than in depressed or mixed episode BD patients	Pae et al., 2004 (82)
		G – 0.79 (0.60–1.03)	Korean	No association with BD	Roh et al., 2007 (83)
		G – 1.32 (0.81–2.21)	Italian	Higher prevalence of A allele and AA genotype in BD when compared with MDD patients	Altamura et al., 2010 (81)
		G – 0.56 (0.40–0.79)	Turkish	G allele and GG genotype are associated with BD	Tokac et al., 2016 (72)
CCR2	*rs*1799864 G/A	G – 0.86 (0.58–1.28)	Turkish	No association	Tokac et al., 2016 (72)
CCR5	*rs*333 Ins/Del	Del – 0.38 (0.16–0.85)	Turkish	No association	Tokac et al., 2016 (72)
	A55029G A/G	G – 0.94 (0.71–1.25)	Turkish	No association	Tokac et al., 2016 (72)
CSF2RB	*rs*4821565 C/T	Not reported†	Chinese	No association	Chen et al., 2011 (70)
	*rs*2072707 G/T	Not reported†		No association	
	*rs*2284031 C/T	Not reported†		No association	
	*rs*909486 C/T	Not reported†		No association	
	*rs*11705394 C/T	Not reported†		No association	
	*rs*1801117 C/T	Not reported†		No association	
	*rs*738149 A/G	Not reported†		No association	
CXCL12	CXCL12 3′A	A – 0.94 (0.70–1.26)	Turkish	No association	Tokac et al., 2016 (72)
CXCR4	C138T	T – 0.60 (0.37–0.95)	Turkish	No association	Tokac et al., 2016 (72)
INFG	*rs*2430561 T/A	T – 1.18 (0.77–1.82)	Italian	Lower percentage of TT genotype in BD type II as compared to healthy controls	Clerici et al., 2009 (62)
		T – 2.08 (1.36–3.20)	Korean	T allele carrier state is associated with BD. T allele carriers had higher YMRS scores than patients with the AA genotype	Yoon and Kim, 2012 (68)
Interleukin-1 cluster	*IL1B rs*16944 T/C and *ILR1N* intron 2 86 bp VNTR	T – 0.79 (0.54–1.15) A2 – 1.43 (0.95–2.12)	Spanish	The *IL1B* C allele – *ILR1N* allele*2 (2 tandem repeats) is associated with BD	Papiol et al., 2004 (76)
	ILR1N 86 bp intron 2 VNTR	Not reported†	Korean	No association with BD	Kim et al., 2004 (78)
		A2 – 1.35 (0.99–1.85)	Iranian	*IL1RN* allele*2 (2 tandem repeats) carriage is associated with later onset of BD	Rafiei et al., 2013 (79)
		Not reported†	Iranian	No association	Talaei et al., 2016 (71)
	*IL1B rs*16944 T/C	T – 2.06 (1.15–3.69)	Iranian	C allele and C genotype more prevalent in controls than in patients	Talaei et al., 2016 (71)
	*IL1B rs*1143634 C/T	T – 0.81 (0.40–1.62)	Iranian	No association	Talaei et al., 2016 (71)
	*IL1A rs*1800587 C/T	T – 0.83 (0.45–1.56)	Iranian	No association	Talaei et al., 2016 (71)
IL6	*rs*1800795 G/C	Not reported†	Italian	G allele non-carriers had a lower mean BD age at onset	Clerici et al., 2009 (62)
IL10	*rs*1800896 A/G	G – 1.03 (0.67–1.58)	Italian	Reduced percentage of AA genotype in BD type I when compared to controls	Clerici et al., 2009 (62)
LTA	*rs*2229094 T/C	Not reported†	United States	Not reported	Dickerson et al., 2007 (131)
MASP2	*rs*72550870 A/G	Not reported†	Danish	No association	Foldager et al., 2014 (44)
MBL2	*rs*11003125 G/C	C – 0.85 (0.61–1.18)	Danish	No association	Foldager et al., 2014 (44)
	*rs*7096206 G/C	C – 1.64 (1.14–2.34)		No association	
	*rs*7095891 G/A	A – 0.91 (0.61–1.34)		No association	
	*rs*5030737 C/T	T – 0.95 (0.50–1.73)		No association	
	*rs*1800450 G/A	A – 0.78 (0.47–1.25)		No association	
	*rs*1800451 G/A	A – 1.17 (0.25–4.17)		No association	
NOD2	*rs*2066842 C/T	T – 0.67 (0.52–0.86)	French	T allele carrier state is less prevalent in BD	Oliveira et al., 2014a (58)
	*rs*2066844 C/T	T – 0.65 (0.42–1.02)		No association	
	*rs*2066845 G/C	C – 0.83 (0.36–2.08)		No association	
	*rs*2066847 C/C*ins*C	C*ins*C – 0.73 (0.34–1.68)		No association	
PTGS2	*rs*689466 G/C	C – 0.96 (0.67–1.38)	Turkish	No association	Ozdemircan et al., 2015 (69)
	*rs*20417 A/G	G – 0.47 (0.31–0.70)		AA genotype more prevalent in BD patients	
TLR2	−196 to −174 ins/del	Del – 0.87 (0.63–1.21)	French	No association	Oliveira et al., 2014b (74)
	*rs*4696480 T/A	T – 1.17 (0.93–1.47)		No association	
	*rs*3804099 T/C	T – 1.02 (0.81–1.29)		TT genotype more prevalent in early-onset than in late-onset BD patients	
	*rs*3804100 T/C	C – 0.95 (0.61–1.52)		No association	
TLR4	*rs*1927914 A/G	A – 1.29 (1.02–1.63)	French	AA genotype more prevalent in early-onset BD than in controls	Oliveira et al., 2014c (57)
	*rs*10759932 T/C	C – 0.95 (0.68 – 1.34)		No association	
	*rs*4986790 A/G	G – 0.89 (0.56 – 1.45)		G allele carrier state was associated with thyroid disorders among BD patients	
	*rs*4986791 C/T	T – 0.87 (0.55 – 1.41)		T allele carrier state was associated with thyroid disorders among BD patients	
	*rs*11536889 G/C	C – 1.14 (0.83 – 1.59)		No association	

Table 2. (Continued)

Gene	Polymorphism	OR (CI 95%)*	Population	Comments	Reference
	*rs*11536891 T/C	T – 1.38 (1.03 – 1.84)		TT genotype more prevalent in early-onset BD than in controls	
TNF	*rs*1800629 G/A	A – 0.83 (0.52–1.35)	British	No association with BD	Middle et al., 2000 (66)
		A – 0.92 (0.61–1.35)	Brazilian	No association with BD	Meira-Lima et al., 2003 (65)
		A – 3.50 (1.93–6.47)	Korean	'A' allele is associated with BD	Pae et al., 2004 (67)
		A – 0.73 (0.55–0.98)	Polish	'G' allele is associated with BD	Czerski et al., 2008 (63)
		Not reported†	Italian	'G' allele is associated with BD type II	Clerici et al., 2009 (62)

BD: bipolar disorder; MDD: major depressive disorder; *DLPFC*: dorsolateral prefrontal cortex; *GM*: grey matter; *CCL2*: chemokine (C-C motif) ligand 2; *CCR2*: C-C motif chemokine receptor 2; *CCR5*: C-C motif chemokine receptor 5; *CSF2RB*: colony-stimulating factor 2 receptor beta common subunit; *CXCR4*: C-X-C motif chemokine receptor 4; *CXCL12*: C-X-C motif chemokine ligand 12; *IL6*: interleukin-6; *IL10*: interleukin-10; *INFG*: interferon-γ; *LTA*: lymphotoxin alpha; *MASP2*: mannan-binding lectin serine peptidase 2; *MBL2*: mannose binding lectin 2; *NOD2* nucleotide binding oligomerization domain containing 2; *PTGS2*: prostaglandin endoperoxide synthase 2; *TNF*: tumour necrosis factor; *TLR2*: Toll-like receptor 2; *TLR4*: Toll-like receptor 4; *IL1RN*: interleukin-1 receptor antagonist; *IL1B*: interleukin-1β.

*Non-adjusted odds ratio and confidence intervals for the allelic model in case–control comparisons.

†Absolute counts not reported.

implicated in BD. A study reported a lower percentage of the TT high producer genotype of the *INFG* T + 874A (*rs*2430561) in BD patients in Italy (62). Once again, contradictory results were also described with T allele carrier state found to be more prevalent in a Korean sample (68). Regarding IL-10, an anti-inflammatory cytokine, in an Italian sample, a lower percentage of BD patients were homozygous for the low-producer *IL10* G1082A (*rs*1800896) polymorphism, further suggesting a genetic origin for an immune imbalance that could potentiate pathogen escape (62).

Two polymorphisms in the *PTGS2* gene, encoding the cyclooxygenase-2 enzyme, found that the G allele carriers of the *rs*20417 promoter polymorphism, known to decrease transcriptional activity and mRNA levels, are more prevalent in controls, in this case, rather suggesting a protective status against BD type I (69). The complement cascade has also been investigated. In one study, by Foldager et al., lower peripheral levels of MASP-2 (mannan-binding lectin serine protease 2), a protein involved in the activation of the complement cascade, were found in BD patients, but no statistically significant associations with two genes involved in the complement system, *MBL2* and *MASP2*, were found. Of note, however, is an association of nominal significance for the X/Y SNP of the *MBL2* gene, although this result did not withstand correction for multiple comparisons (44). Polymorphisms in the *CCR2*, *CCR5*, *CSF2RB*, *CXCL12*, *CXCR4* and *IL1A* genes have also been explored, but no associations were found (70–72).

Modulators of clinical presentation

By stratifying genetic data according to more homogeneous phenotypes based on clinical presentation, several studies revealed specific associations, namely with early-onset BD (73). Regarding immunogenetics, the genetic diversity of *TLR2*, considered to be the most pleiotropic TLR (sensing Gram-positive bacteria, viruses and *T. gondii* among others), has been explored (74). The *TLR2 rs*3804099 T allele in the homozygous state, potentially a low inducer of cytokine production (75), was found to be significantly more prevalent among early- than late-onset BD patients, although not when compared with controls (74). Another study found that BD patients not carrying the high producer G allele of the G-174C polymorphism of the *IL6* gene (*rs*1800795) had a lower mean age at onset (24.25 ± 5.71 vs. 34.87 ± 1.48; $P = 0.048$) (62). Additionally, regarding the IL-1 cluster locus, a study involving 88 patients with BD and 176 healthy individuals in Spain found a statistically significant excess of the −511 C allele/VNTR allele*2 (2 tandem repeats) haplotypic combination (76). In the same locus, another study in the Iranian population on the −511 C>T (*rs*16944) polymorphism found that the T allele carrier state is associated with BD (71), an allele previously linked with longer episodes and total brain and more specifically left dorsolateral prefrontal cortex grey matter deficits when compared to the non-T allele carrier counterparts (71, 77). Although two other studies regarding the same VNTR (variable number tandem repeat) of 86 bp in length in intron 2 of the *IL1RN* gene (interleukin-1 receptor antagonist) did not confirm this association in the Korean and Iranian populations, Rafiei et al., in a Iranian sample, after having stratified BD patients into two subgroups according to age at onset, found that presence of the allele containing two repeats was associated with later onset (71, 76, 78, 79). This allele is associated with more prolonged and severe proinflammatory immune responses (80). When considered jointly with the results

regarding the *TLR2*, *TLR4* and *IL6* genes, these findings, although conflicting, suggest that feeble proinflammatory responses, potentially associated with pathogen escape, may be linked to an earlier onset of BD.

The *CCL2*, also referred to as monocyte chemoattractant protein 1 (MCP1) and belonging to the CC chemokine family, has also been studied. The *CCL2 rs*1024611 (−2518 A>G) polymorphism, affecting the transcriptional activity of the distal regulatory region with functional impact on monocyte CCL2 production, has been analysed in four studies. In only one study, genotype and allelic distributions were found to be significantly heterogeneous, with a higher prevalence of the A allele and AA genotype when comparing BD patients with healthy controls in the Turkish population (72, 81–83). Interestingly, in another example of the value of stratification, the prevalence of the low-producer A allele was found to be higher in manic patients as compared with depressed or mixed episode bipolar patients (82, 84), and a higher frequency of the A allele and AA genotype was found in BD patients compared with patients diagnosed with major depressive disorder (81).

Among the inflammation markers, CRP is the most robustly associated with BD (85, 86). The genetics of CRP production has been recently explored in 32 complex somatic and psychiatric outcomes, including autism (n = 90 patients; n = 1476 controls), BD (n = 7481 patients; n = 9250 controls), major depressive disorder (n = 9240 patients; n = 9519 controls) and schizophrenia (n = 34241 patients; n = 45604 controls) (87). In this large-scale study, two genetic risk scores were used, one consisting of four SNPs in the *CRP* gene and the second consisting of 18 SNPs associated with CRP levels in a previously published genome-wide association study (88). A CRP polygenic risk score showed a statistically significant protective relationship with schizophrenia but not with BD, after correction for multiple comparisons (87). In another large-scale study, the *CRP rs*2794520 polymorphism was associated with CRP levels, but showed no association with BD or schizophrenia (89). While not associated with BD *per se*, we suggest that *CRP* genetic diversity should be investigated according to particular clinically defined BD subsets, for instance, in patients presenting with psychotic features, earlier onset or autoimmune and other comorbid disorders.

Gene–environment interactions

Despite being a logical source of candidate genes for the study of gene–environment interactions in BD, the field of immunogenetics in relation to BD has yet to be fully explored. To the best of our knowledge, only three studies examined potential interactions between immunogenetic markers and environmental insults (89–91). A recent study explored the interaction between immunogenetic variants and presence of early and severe stress in a sample of BD patients. The authors observed a cumulative effect of a genetic variant of *TLR2* (*rs*3804099) and self-reported childhood sexual abuse on the age at onset of BD (91). According to these results, a model was proposed whereby the *TLR2 rs*3804099 TT genotype carriers may be more susceptible to inflammation-mediated damage induced by early-life stress, with consequent younger age at onset of BD (91). A subsequent study from the same group, using an independent sample set of modest size, observed a nominal interaction between that *TLR2* polymorphism (*rs*3804099) and *Toxoplasma gondii* seropositivity (IgG), although the finding did not persist following correction for multiple comparisons (90). Nevertheless, and consistent with these findings, mechanisms of immune priming early in life have been related to the higher vulnerability to subsequent exposure to stress in animal models (92, 93). Avramopoulos et al. (89), using a genomewide approach, also explored potential interactions between infection, determined by plasma IgG antibody against *Toxoplasma gondii*, herpes simplex virus type 1, cytomegalovirus and human herpes virus 6, and the genetic background. In this study, no signal reached genomewide significance for BD.

Although these findings are not supportive of an interaction between immunogenetic background and environmental insults, it is important to keep in mind that the genetics are likely complex, with the potential for multiple gene–gene and gene–environment interactions in BD aetiopathogenesis. In addition to the limited sample sizes often used in these studies, reducing statistical power, this may be one of the reasons for not detecting significance in statistical interaction analyses, such as regression analysis. Moreover, these studies were limited to data on IgG antibodies, which is not informative of the 'time window' of exposure, possibly compromising the quality of the analysed environmental measure. Higher quality environmental data are needed in the future to assess interactions between immunogenetic background and infections in the occurrence of BD.

As discussed in greater detail below, we propose that, if infection is timely, frequent or intense enough, it may chronically disrupt immune function in those that are susceptible, eliciting the development of immune phenotypes of

susceptibility to BD (5). Specifically, infections could lead to (i) chronic low-grade inflammation; (ii) altered intestinal permeability and gut dysbiosis; (iii) development of auto-antibodies and autoimmune disorders; and (iv) reactivation of human endogenous retroviruses.

Chronic immune dysfunction in bipolar disorder

The necessary 'amount' of inflammation in response to stressors is not determined in BD; however, it seems logical that particular combinations between the individual's genetic makeup and the environment may polarize the spectrum of inflammatory reactions from protective to pathological, allowing for the development of disease. One of the proposed pathophysiological mechanisms in BD invoked to explain such immune abnormalities involves acute stressor-mediated events inducing persistent alterations in immune/inflammatory processes in genetically predisposed individuals.

Immune dysfunction seems to be an integral component of BD and to parallel the onset, progression and occurrence of the psychiatric and other medical comorbid disorders (39, 94). Recent meta-analyses reported increased circulating levels of CRP, IL-4, IL-6, IL-10, sIL-2R, sIL-6R, TNF-α, sTNFR1 and IL-1RA in BD patients when compared with healthy controls (85, 95, 96). Proinflammatory alterations also occur centrally, as IL-1β has been found to be increased in the cerebrospinal fluid of BD patients (97). Protein and mRNA levels of several inflammation markers, including not only IL-1β but also the IL-1 receptor, myeloid differentiation factor 88 (MyD88) and nuclear factor kappa B (NF-κB), were increased in the prefrontal cortex (98), with decreased levels of the inhibitory cytokine transforming growth factor beta 1 (TGF-β1) in the frontal cortex of BD patients (99). Of importance, only two studies explored the relationship between immunogenetic and serological levels of the respective encoded protein in BD, namely of MBL, MASP-2 and CRP but with negative results (44, 89).

Microbial influences have also been suggested to play a role in the development of autoimmunity, pointing to another infection-related pathway in BD. In a preliminary study, Parvovirus B19 was associated with comorbid bipolar and autoimmune thyroid disorders in women (100). Autoimmune thyroiditis has been suggested to be a condition comorbid with BD, emerging independently of lithium treatment, and inherited as a common trait in BD (101–103). In fact, a constitutional vulnerability to thyroiditis in BD patients has been linked to the TLR4 pathogen receptor as the exonic *rs*4986790 G and *rs*4986791 T alleles were associated with thyroiditis in bipolar patients (57).

Another suspected candidate responsible for chronic proinflammatory states is gut dysbiosis and increased intestinal permeability, but studies on this issue in BD are very scarce. Nor surprisingly, however, plasma levels of IgA and/or IgM directed against commensal bacteria lipopolysaccharide are increased in BD, suggestive of intestinal bacterial translocation (104). Besides the conceivable existence of a 'leaky gut' contribution to systemic inflammation in mood disorders, systemic inflammation has also been suggested to increase intestinal permeability, possibly through the facilitation of paracellular mechanisms (105).

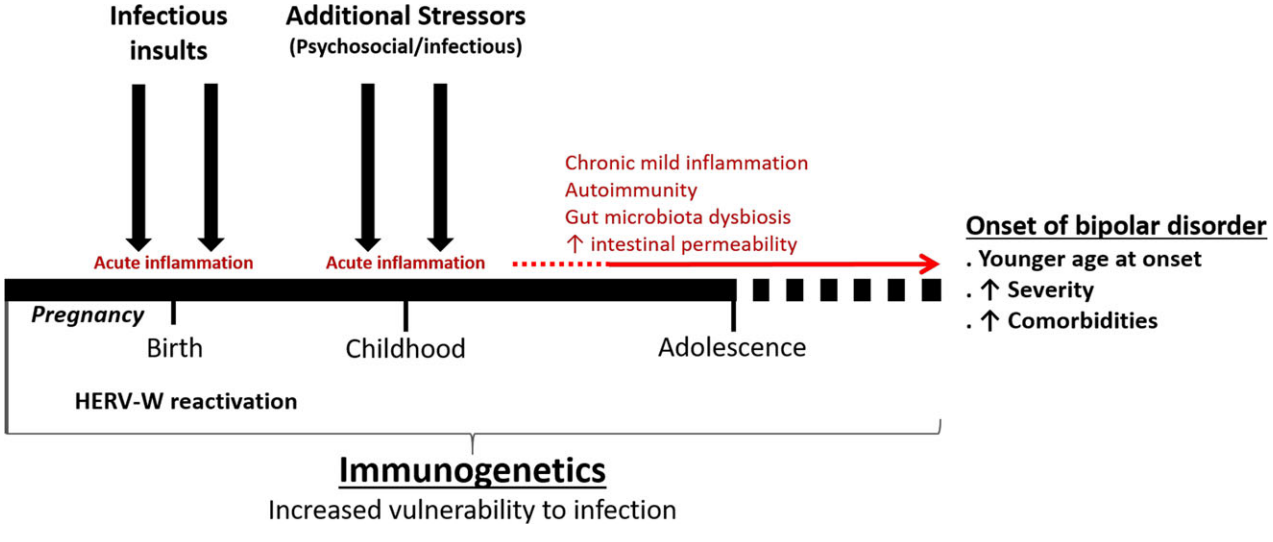

Fig. 3. Increased vulnerability to infection in bipolar disorder: a multiple-hit model. [Colour figure can be viewed at wileyonlinelibrary.com].

The pleiotropy and wide expression of innate immune receptors such as TLR4, present in brain structures rich in vasculature and lacking a normal blood–brain barrier like the circumventricular organs, place them as potential transducers of the gut–brain immune-inflammatory axis. TLR expression in other leaky structures such as choroid plexus and leptomeninges, in endothelial and perivascular cells of the BBB, has also been proposed as well as in neurons, astroglia and microglia (106). Work from Gárate et al. (107), in a murine model, using antibiotic intestinal decontamination, suggested a role for intestinal bacterial translocation in the upregulation of TLR4 expression in mice prefrontal cortex after stress exposure.

Human endogenous retroviruses (HERVs) are constituents of human genomic DNA and have been proposed to be a 'missing link' between infections, chronic immune dysfunction and risk of psychiatric disorders (108). HERVs belong to the superfamily of transposable elements, resulting from the integration of genetic elements from ancestral infectious retroviruses into human genomic DNA along evolution (109). Although epigenetic silencing mechanisms as well as the predominance of defective or inactive copies prevent the expression of HERVs, they may also be responsive to environmental stressors and thus be reactivated (108, 110). This has been shown for influenza and herpes simplex type 1 viruses, both acting as potent transactivators of HERV-W element expression (111, 112). Reactivation of HERV-W is not without consequences as production of Envelope (Env) protein, a TLR4 agonist, activates inflammation and neurotoxic effects through the activation of this pattern recognition receptor (111, 113). One study involving 45 patients diagnosed with schizophrenia, 91 patients diagnosed with BD and 73 healthy controls found HERV-W Env transcription to be increased in both psychiatric disorders, as compared with the control group, with higher values present in BD than in schizophrenia (114).

Here, we propose that immunopathological consequences of early-life infectious insults over BD may be modulated by the immunogenetic background of vulnerability. Further exposure to environmental stressors may persistently disrupt immune regulatory mechanisms increasing susceptibility to BD and its prominent burden of comorbidities. A simplified model is depicted in Fig. 3.

Limitations of our critical review should nevertheless be noted. In fact, our systematic literature searches were based only on PubMed, but not alternate databases, and there was no prior published protocol of the methods. Furthermore, the literature search on the association between infectious factors and BD was performed only on *Toxoplasma gondii*, Borna disease virus, influenza, herpes virus, cytomegalovirus and infection, while the literature search concerning the association between immunogenetic factors and BD was performed only on non-HLA genetic loci.

To conclude, in psychiatric disorders, as with any complex disorder, individual differences in vulnerability to environmental stressors may be genetically driven. However, characterization of genetic influences remains difficult as they may be dependent on epistatic and environmental interactions. Likewise, BD-associated immune dysfunction most likely has multiple origins and may reflect aberrant immune activation triggered by gene–environment interactions. Improvement in the quality of environmental measures is critical to move this area of research forward, as most studies rely on retrospective information with imprecise data on time of exposure. Collecting this information is essential because consequences of environmental insults, such as early-life infections, acting on a background of immunogenetic vulnerability may (i) increase susceptibility to subsequent environmental exposures; (ii) increase vulnerability to the development of chronic immune dysfunction with consequent low-grade inflammation, autoimmune and autoinflammatory phenomena, 'leaky gut'/altered microbiota and reactivation of human endogenous retroviruses; (iii) increase the risk of other general medical comorbid conditions. Infection and psychosocial stress may be major preventable causes of BD, opening new research possibilities for public health intervention in psychiatry. Understanding the immunologic component of the pathophysiology of BD may provide innovative therapeutic targets to alleviate psychological suffering, comorbidity burden and diversify interventions in treatment-resistant individuals.

Acknowledgements

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Declaration of interest

The authors declare that there is no conflict of interest.

References

1. Uher R. Gene-environment interactions in severe mental illness. Front Psychiatry 2014;**5**:48.
2. Marangoni C, Hernandez M, Faedda GL. The role of environmental exposures as risk factors for bipolar disorder: a systematic review of longitudinal studies. J Affect Disord 2016;**193**:165–174.

3. Harrison PJ. Molecular neurobiological clues to the pathogenesis of bipolar disorder. Curr Opin Neurobiol 2016;**36**:1–6.
4. Daskalakis NP, Bagot RC, Parker KJ, Vinkers CH, de Kloet ER. The three-hit concept of vulnerability and resilience: toward understanding adaptation to early-life adversity outcome. Psychoneuroendocrinology 2013;**38**: 1858–1873.
5. Leboyer M, Oliveira J, Tamouza R, Groc L. Is it time for immunopsychiatry in psychotic disorders? Psychopharmacology 2016;**233**:1651–1660.
6. Maletic V, Raison C. Integrated neurobiology of bipolar disorder. Front Psychiatry 2014;**5**:98.
7. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: a review of the interactions between inflammation and mood disorders. Prog Neuropsychopharmacol Biol Psychiatry 2014;**53**:23–34.
8. Berk M, Conus P, Kapczinski F et al. From neuroprogression to neuroprotection: implications for clinical care. Med J Aust 2010;**193**:S36–S40.
9. Altamura AC, Buoli M, Pozzoli S. Role of immunological factors in the pathophysiology and diagnosis of bipolar disorder: comparison with schizophrenia. Psychiatry Clin Neurosci 2014;**68**:21–36.
10. Buoli M, Dell'Osso B, Caldiroli A et al. Obesity and obstetric complications are associated with rapid-cycling in Italian patients with bipolar disorder. J Affect Disord 2017;**208**:278–283.
11. Buoli M, Caldiroli A, Cumerlato Melter C, Serati M, de Nijs J, Altamura AC. Biological aspects and candidate biomarkers for psychotic bipolar disorder: a systematic review. Psychiatry Clin Neurosci 2016;**70**:227–244.
12. Gigante AD, Barenboim IY, Dias R da S et al. Psychiatric and clinical correlates of rapid cycling bipolar disorder: a cross-sectional study. Rev Bras Psiquiatr 2016;**38**:270–274.
13. Oliveira J, Debnath M, Etain B, et al. Violent suicidal behaviour in bipolar disorder is associated with nitric oxide synthase 3 gene polymorphism. Acta Psychiatr Scand 2015;**132**:218–225.
14. Etain B, Mathieu F, Henry C, et al. Preferential association between childhood emotional abuse and bipolar disorder. J Trauma Stress 2010;**23**:376–383.
15. Machón RA, Mednick SA, Huttunen MO. Adult major affective disorder after prenatal exposure to an influenza epidemic. Arch Gen Psychiatry 1997;**54**:322–328.
16. Moore PB, El-Badri SM, Cousins D et al. White matter lesions and season of birth of patients with bipolar affective disorder. Am J Psychiatry 2001;**158**:1521–1524.
17. Dickerson FB, Boronow JJ, Stallings C et al. Infection with herpes simplex virus type 1 is associated with cognitive deficits in bipolar disorder. Biol Psychiatry 2004;**55**:588–593.
18. Sutterland AL, Fond G, Kuin A et al. Beyond the association. *Toxoplasma gondii* in schizophrenia, bipolar disorder, and addiction: systematic review and meta-analysis. Acta Psychiatr Scand 2015;**132**:161–179.
19. Brodin P, Jojic V, Gao T et al. Variation in the human immune system is largely driven by non-heritable influences. Cell 2015;**160**:37–47.
20. Meyer U. Prenatal poly(i:C) exposure and other developmental immune activation models in rodent systems. Biol Psychiatry 2014;**75**:307–315.
21. Wells G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. 2011. http://www.ohri.ca/program
22. Buoli M, Serati M, Caldiroli A, Cremaschi L, Altamura AC. Neurodevelopmental versus neurodegenerative model of schizophrenia and bipolar disorder: comparison with physiological brain development and aging. Psychiatr Danub 2017;**29**:24–27.
23. Parboosing R, Bao Y, Shen L, Schaefer CA, Brown AS. Gestational influenza and bipolar disorder in adult offspring. JAMA Psychiatry 2013;**70**:677–685.
24. Benros ME, Waltoft BL, Nordentoft M et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. JAMA Psychiatry 2013;**70**:812–820.
25. Dickerson F, Stallings C, Origoni A et al. Antibodies to *Toxoplasma gondii* in individuals with mania. Bipolar Disord 2014;**16**:129–136.
26. Graham KL, Carson CM, Ezeoke A, Buckley PF, Miller BJ. Urinary tract infections in acute psychosis. J Clin Psychiatry 2014;**75**:379–385.
27. Shen C-C, Yang AC, Hung J-H, Hu L-Y, Chiang Y-Y, Tsai S-J. Risk of psychiatric disorders following pelvic inflammatory disease: a nationwide population-based retrospective cohort study. J Psychosom Obstet Gynaecol 2016; **37**:6–11.
28. Seminog OO, Goldacre MJ. Risk of pneumonia and pneumococcal disease in people with severe mental illness: English record linkage studies. Thorax 2013;**68**:171–176.
29. Davydow DS, Ribe AR, Pedersen HS et al. Serious mental illness and risk for hospitalizations and rehospitalizations for ambulatory care-sensitive conditions in Denmark: a nationwide population-based cohort study. Med Care 2016;**54**:90–97.
30. Crump C, Sundquist K, Winkleby MA, Sundquist J. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. JAMA Psychiatry 2013;**70**: 931–939.
31. Ribe AR, Vestergaard M, Katon W et al. Thirty-day mortality after infection among persons with severe mental illness: a population-based cohort study in Denmark. Am J Psychiatry 2015;**172**:776–783.
32. Hayes JF, Miles J, Walters K, King M, Osborn DPJ. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. Acta Psychiatr Scand 2015;**131**:417–425.
33. Latalova K, Kamaradova D, Prasko J. Suicide in bipolar disorder: a review. Psychiatr Danub 2014;**26**:108–114.
34. Wang PS, Angermeyer M, Borges G et al. Delay and failure in treatment seeking after first onset of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry 2007;**6**:177–185.
35. Reddy LF, Lee J, Davis MC et al. Impulsivity and risk taking in bipolar disorder and schizophrenia. Neuropsychopharmacology 2014;**39**:456–463.
36. Goi PD, Vianna-Sulzbach M, Silveira L et al. Treatment delay is associated with more episodes and more severe illness staging progression in patients with bipolar disorder. Psychiatry Res 2015;**227**:372–373.
37. Levin JB, Krivenko A, Howland M, Schlachet R, Sajatovic M. Medication adherence in patients with bipolar disorder: a comprehensive review. CNS Drugs 2016;**30**:819–835.
38. Kotb M, Norrby-Teglund A, McGeer A et al. An immunogenetic and molecular basis for differences in outcomes of invasive group A streptococcal infections. Nat Med 2002;**8**:1398–1404.
39. Berk M, Kapczinski F, Andreazza AC et al. Pathways underlying neuroprogression in bipolar disorder: focus

on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev 2011;**35**:804–817.
40. Hamdani N, Doukhan R, Kurtlucan O, Tamouza R, Leboyer M. Immunity, inflammation, and bipolar disorder: diagnostic and therapeutic implications. Curr Psychiatry Rep 2013;**15**:387.
41. Molholm HB. Hyposensitivity to foreign protein in schizophrenic patients. Psychiatr Q 1942;**16**:565–571.
42. Vaughan WT, Sullivan JC, Elmadjian F. Immunity and schizophrenia; a survey of the ability of schizophrenic patients to develop an active immunity following the injection of pertussis vaccine. Psychosom Med 1949;**11**: 327–333.
43. Ehmala P, Autio L. Iv, 6. on intradermal histamine tests in schizophrenia. Acta Psychiatr Scand 1950;**25**: 136–144.
44. Foldager L, Köhler O, Steffensen R et al. Bipolar and panic disorders may be associated with hereditary defects in the innate immune system. J Affect Disord 2014;**164**: 148–154.
45. Dickerson F, Stallings C, Origoni A et al. Pentraxin 3 is reduced in bipolar disorder. Bipolar Disord 2015;**17**:409–414.
46. Padmos RC, Hillegers MHJ, Knijff EM et al. A discriminating messenger RNA signature for bipolar disorder formed by an aberrant expression of inflammatory genes in monocytes. Arch Gen Psychiatry 2008;**65**:395–407.
47. Sohani ZN, Meyre D, de Souza RJ et al. Assessing the quality of published genetic association studies in meta-analyses: the quality of genetic studies (Q-Genie) tool. BMC Genet 2015;**16**:50.
48. Trowsdale J, Knight JC. Major histocompatibility complex genomics and human disease. Annu Rev Genomics Hum Genet 2013;**14**:301–323.
49. Picascia A, Grimaldi V, Napoli C. From HLA typing to anti-HLA antibody detection and beyond: the road ahead. Transplant Rev (Orlando) 2016;**30**:187–194.
50. Biederman J, Keller M, Lavori P et al. HLA haplotype A26-B38 in affective disorders: lack of association. Biol Psychiatry 1987;**22**:221–224.
51. Jun T, Pae C, Chae J, Pyo C, Han H. Human leukocyte antigen alleles in patients with bipolar disorder in the Korean population. Psychiatry Clin Neurosci 2002;**56**: 453–457.
52. Debnath M, Busson M, Jamain S et al. The HLA-G low expressor genotype is associated with protection against bipolar disorder. Hum Immunol 2013;**74**:593–597.
53. Johnson GF. HLA antigens and manic-depressive disorders. Biol Psychiatry 1978;**13**:409–412.
54. Shapiro RW, Ryder LP, Svejgaard A, Rafaelsen OJ. HLA antigens and manic-depressive disorders: further evidence of an association. Psychol Med 1977;**7**:387–396.
55. Shapiro RW, Bock E, Rafaelsen OJ, Ryder LP, Svejgaard A. Histocompatibility antigens and manic-depressive disorders. Arch Gen Psychiatry 1976;**33**:823–825.
56. Targum SD, Gershon ES, Van Eerdewegh M, Rogentine N. Human leukocyte antigen system not closely linked to or associated with bipolar manic-depressive illness. Biol Psychiatry 1979;**14**:615–636.
57. Oliveira J, Busson M, Etain B, et al. Polymorphism of Toll-like receptor 4 gene in bipolar disorder. J Affect Disord 2014;**152–154**:395–402.
58. Oliveira J, Hamdani N, Etain B, et al. Genetic association between a 'standing' variant of NOD2 and bipolar disorder. Immunobiology 2014;**219**:766–771.
59. Nakagome S, Mano S, Kozlowski L et al. Crohn's disease risk alleles on the NOD2 locus have been maintained by natural selection on standing variation. Mol Biol Evol 2012;**29**:1569–1585.
60. Ogura Y, Lala S, Xin W et al. Expression of NOD2 in Paneth cells: a possible link to Crohn's ileitis. Gut 2003;**52**:1591–1597.
61. Pugazhendhi S, Santhanam S, Venkataraman J, Creveaux I, Ramakrishna BS. NOD2 gene mutations associate weakly with ulcerative colitis but not with Crohn's disease in Indian patients with inflammatory bowel disease. Gene 2013;**512**:309–313.
62. Clerici M, Arosio B, Mundo E et al. Cytokine polymorphisms in the pathophysiology of mood disorders. CNS Spectr 2009;**14**:419–425.
63. Czerski PM, Rybakowski F, Kapelski P et al. Association of tumor necrosis factor -308G/A promoter polymorphism with schizophrenia and bipolar affective disorder in a Polish population. Neuropsychobiology 2008;**57**:88–94.
64. Wilson AG, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. Proc Natl Acad Sci U S A 1997;**94**:3195–3199.
65. Meira-Lima IV, Pereira AC, Mota GF et al. Analysis of a polymorphism in the promoter region of the tumor necrosis factor alpha gene in schizophrenia and bipolar disorder: further support for an association with schizophrenia. Mol Psychiatry 2003;**8**:718–720.
66. Middle F, Jones I, Robertson E, Lendon C, Craddock N. Tumour necrosis factor alpha and bipolar affective puerperal psychosis. Psychiatr Genet 2000;**10**:195–198.
67. Pae C-U, Lee K-U, Han H, Serretti A, Jun T-Y. Tumor necrosis factor alpha gene-G308A polymorphism associated with bipolar I disorder in the Korean population. Psychiatry Res 2004;**125**:65–68.
68. Yoon H-K, Kim Y-K. The T allele of the interferon-gamma +874A/T polymorphism is associated with bipolar disorder. Nord J Psychiatry 2012;**66**:14–18.
69. Ozdemircan A, Dasdemir S, Kucukali CI, Bireller ES, Ozturk H, Cakmakoglu B. COX-2 gene variants in bipolar disorder-I. Psychiatr Danub 2015;**27**:385–389.
70. Chen P, Huang K, Zhou G et al. Common SNPs in CSF2RB are associated with major depression and schizophrenia in the Chinese Han population. World J Biol Psychiatry 2011;**12**:233–238.
71. Talaei A, Tavakkol Afshari J, Fayyazi Bordbar MR et al. A study on the association of interleukin-1 cluster with genetic risk in bipolar I disorder in Iranian patients: a case-control study. Iran J Allergy Asthma Immunol 2016;**15**:466–475.
72. Tokac D, Tuzun E, Gulec H et al. Chemokine and chemokine receptor polymorphisms in bipolar disorder. Psychiatry Investig 2016;**13**:541–548.
73. Kennedy KP, Cullen KR, DeYoung CG, Klimes-Dougan B. The genetics of early-onset bipolar disorder: a systematic review. J Affect Disord 2015;**184**:1–12.
74. Oliveira J, Hamdani N, Busson M et al. Association between toll-like receptor 2 gene diversity and early-onset bipolar disorder. J Affect Disord 2014;**165**:135–141.
75. Chen K-H, Gu W, Zeng L et al. Identification of haplotype tag SNPs within the entire TLR2 gene and their clinical relevance in patients with major trauma. Shock 2011;**35**:35–41.
76. Papiol S, Rosa A, Gutiérrez B et al. Interleukin-1 cluster is associated with genetic risk for schizophrenia and bipolar disorder. J Med Genet 2004;**41**:219–223.

77. Papiol S, Molina V, Desco M et al. Gray matter deficits in bipolar disorder are associated with genetic variability at interleukin-1 beta gene (2q13). Genes Brain Behav 2008;**7**:796–801.
78. Kim SJ, Lee HJ, Koo HG et al. Impact of IL-1 receptor antagonist gene polymorphism on schizophrenia and bipolar disorder. Psychiatr Genet 2004;**14**:165–167.
79. Rafiei A, Hosseini SH, Taheri M, Hosseni-khah Z, Hajilooi M, Mazaheri Z. Influence of IL-1RN intron 2 variable number of tandem repeats (VNTR) polymorphism on bipolar disorder. Neuropsychobiology 2013;**67**:116–121.
80. Witkin SS, Gerber S, Ledger WJ. Influence of interleukin-1 receptor antagonist gene polymorphism on disease. Clin Infect Dis 2002;**34**:204–209.
81. Altamura AC, Mundo E, Cattaneo E et al. The MCP-1 gene (SCYA2) and mood disorders: preliminary results of a case-control association study. NeuroImmuno Modulation 2010;**17**:126–131.
82. Pae C-U, Kim J-J, Yu H-S et al. Monocyte chemoattractant protein-1 promoter -2518 polymorphism may have an influence on clinical heterogeneity of bipolar I disorder in the Korean population. Neuropsychobiology 2004;**49**:111–114.
83. Roh M-S, Lee KY, Joo E-J, Lee N, Kim YS. No association of the MCP-1 promoter A-2518G polymorphism with bipolar disorder in the Korean population. Neurosci Lett 2007;**427**:1–5.
84. Rovin BH, Lu L, Saxena R. A novel polymorphism in the MCP-1 gene regulatory region that influences MCP-1 expression. Biochem Biophys Res Commun 1999;**259**: 344–348.
85. Dargél AA, Godin O, Kapczinski F, Kupfer DJ, Leboyer M. C-reactive protein alterations in bipolar disorder: a meta-analysis. J Clin Psychiatry 2015;**76**:142–150.
86. Fernandes BS, Steiner J, Molendijk ML et al. C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry 2016;**3**:1147–1156.
87. Prins BP, Abbasi A, Wong A et al. Investigating the causal relationship of C-reactive protein with 32 complex somatic and psychiatric outcomes: a large-scale cross-consortium mendelian randomization study. PLoS Med 2016;**13**:e1001976.
88. Dehghan A, Dupuis J, Barbalic M et al. Meta-analysis of genome-wide association studies in >80 000 subjects identifies multiple loci for C-reactive protein levels. Circulation 2011;**123**:731–738.
89. Avramopoulos D, Pearce BD, McGrath J et al. Infection and inflammation in schizophrenia and bipolar disorder: a genome wide study for interactions with genetic variation. PLoS ONE 2015;**10**:e0116696.
90. Oliveira J, Kazma R, Le Floch E et al. *Toxoplasma gondii* exposure may modulate the influence of TLR2 genetic variation on bipolar disorder: a gene-environment interaction study. Int J Bipolar Disord 2016;**4**:11.
91. Oliveira J, Etain B, Lajnef M, et al. Combined effect of TLR2 gene polymorphism and early life stress on the age at onset of bipolar disorders. PLoS ONE 2015;**10**: e0119702.
92. Giovanoli S, Engler H, Engler A et al. Stress in puberty unmasks latent neuropathological consequences of prenatal immune activation in mice. Science 2013;**339**:1095–1099.
93. Giovanoli S, Engler H, Engler A et al. Preventive effects of minocycline in a neurodevelopmental two-hit model with relevance to schizophrenia. Transl Psychiatry 2016;**6**:e772.
94. Leboyer M, Soreca I, Scott J et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? J Affect Disord 2012;**141**:1–10.
95. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biol Psychiatry 2013;**74**:15–25.
96. Munkholm K, Braüner JV, Kessing LV, Vinberg M. Cytokines in bipolar disorder vs. healthy control subjects: a systematic review and meta-analysis. J Psychiatr Res 2013;**47**:1119–1133.
97. Söderlund J, Olsson SK, Samuelsson M et al. Elevation of cerebrospinal fluid interleukin-1ß in bipolar disorder. J Psychiatry Neurosci 2011;**36**:114–118.
98. Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. Mol Psychiatry 2010;**15**:384–392.
99. Bezchlibnyk YB, Wang JF, McQueen GM, Young LT. Gene expression differences in bipolar disorder revealed by cDNA array analysis of post-mortem frontal cortex. J Neurochem 2001;**79**:826–834.
100. Hammond CJ, Hobbs JA. Parvovirus B19 infection of brain: possible role of gender in determining mental illness and autoimmune thyroid disorders. Med Hypotheses 2007;**69**:113–116.
101. Kupka RW, Nolen WA, Post RM et al. High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. Biol Psychiatry 2002;**51**:305–311.
102. Padmos RC, Bekris L, Knijff EM et al. A high prevalence of organ-specific autoimmunity in patients with bipolar disorder. Biol Psychiatry 2004;**56**:476–482.
103. Hillegers MHJ, Reichart CG, Wals M et al. Signs of a higher prevalence of autoimmune thyroiditis in female offspring of bipolar parents. Eur Neuropsychopharmacol 2007;**17**:394–399.
104. Maes M, Kubera M, Leunis J-C, Berk M. Increased IgA and IgM responses against gut commensals in chronic depression: further evidence for increased bacterial translocation or leaky gut. J Affect Disord 2012;**141**:55–62.
105. Hietbrink F, Besselink MGH, Renooij W et al. Systemic inflammation increases intestinal permeability during experimental human endotoxemia. Shock 2009;**32**:374–378.
106. García Bueno B, Caso JR, Madrigal JLM, Leza JC. Innate immune receptor Toll-like receptor 4 signalling in neuropsychiatric diseases. Neurosci Biobehav Rev 2016;**64**:134–147.
107. Gárate I, Garcia-Bueno B, Madrigal JLM et al. Stress-induced neuroinflammation: role of the Toll-like receptor-4 pathway. Biol Psychiatry 2013;**73**:32–43.
108. Leboyer M, Tamouza R, Charron D, Faucard R, Perron H. Human endogenous retrovirus type W (HERV-W) in schizophrenia: a new avenue of research at the gene-environment interface. World J Biol Psychiatry 2013;**14**: 80–90.
109. Griffiths DJ. Endogenous retroviruses in the human genome sequence. Genome Biol 2001;**2**:REVIEWS1017.
110. Schulz WA, Steinhoff C, Florl AR. Methylation of endogenous human retroelements in health and disease. Curr Top Microbiol Immunol 2006;**310**:211–250.
111. Nellåker C, Yao Y, Jones-Brando L, Mallet F, Yolken RH, Karlsson H. Transactivation of elements in the human endogenous retrovirus W family by viral infection. Retrovirology 2006;**3**:44.
112. Perron H, Lang A. The human endogenous retrovirus link between genes and environment in multiple sclerosis

and in multifactorial diseases associating neuroinflammation. Clin Rev Allergy Immunol 2010;**39**:51–61.
113. Rolland A, Jouvin-Marche E, Viret C, Faure M, Perron H, Marche PN. The envelope protein of a human endogenous retrovirus-W family activates innate immunity through CD14/TLR4 and promotes Th1-like responses. J Immunol 2006;**176**:7636–7644.
114. Perron H, Hamdani N, Faucard R et al. Molecular characteristics of human endogenous retrovirus type-W in schizophrenia and bipolar disorder. Transl Psychiatry 2012;**2**:e201.
115. Fu ZF, Amsterdam JD, Kao M, Shankar V, Koprowski H, Dietzschold B. Detection of Borna disease virus-reactive antibodies from patients with affective disorders by western immunoblot technique. J Affect Disord 1993;**27**:61–68.
116. Ferszt R, Severus E, Bode L et al. Activated Borna disease virus in affective disorders. Pharmacopsychiatry 1999;**32**:93–98.
117. Terayama H, Nishino Y, Kishi M, Ikuta K, Itoh M, Iwahashi K. Detection of anti-Borna Disease Virus (BDV) antibodies from patients with schizophrenia and mood disorders in Japan. Psychiatry Res 2003;**120**:201–206.
118. Na K-S, Tae S-H, Song J-W, Kim Y-K. Failure to detect Borna disease virus antibody and RNA from peripheral blood mononuclear cells of psychiatric patients. Psychiatry Investig 2009;**6**:306–312.
119. Hornig M, Briese T, Licinio J et al. Absence of evidence for bornavirus infection in schizophrenia, bipolar disorder and major depressive disorder. Mol Psychiatry 2012;**17**:486–493.
120. Mazaheri-Tehrani E, Maghsoudi N, Shams J et al. Borna disease virus (BDV) infection in psychiatric patients and healthy controls in Iran. Virol J 2014;**11**:161.
121. Stich O, Andres TA, Gross CM, Gerber SI, Rauer S, Langosch JM. An observational study of inflammation in the central nervous system in patients with bipolar disorder. Bipolar Disord 2015;**17**:291–302.
122. Okusaga O, Yolken RH, Langenberg P et al. Association of seropositivity for influenza and coronaviruses with history of mood disorders and suicide attempts. J Affect Disord 2011;**130**:220–225.
123. Gerber SI, Krienke UJ, Biedermann N-C et al. Impaired functioning in euthymic patients with bipolar disorder–HSV-1 as a predictor. Prog Neuropsychopharmacol Biol Psychiatry 2012;**36**:110–116.
124. Tedla Y, Shibre T, Ali O et al. Serum antibodies to *Toxoplasma gondii* and Herpesvidae family viruses in individuals with schizophrenia and bipolar disorder: a case-control study. Ethiop Med J 2011;**49**:211–220.
125. Prossin AR, Yolken RH, Kamali M et al. Cytomegalovirus antibody elevation in bipolar disorder: relation to elevated mood states. Neural Plast 2015;**2015**:939780.
126. Yavarian J, Shatizadeh Malekshahi S, Yavarian R et al. Type specific real time PCR for detection of human herpes virus 6 in schizophrenia and bipolar patients: a case control study. BMC Psychiatry 2015;**15**:296.
127. Hinze-Selch D, Däubener W, Erdag S, Wilms S. The diagnosis of a personality disorder increases the likelihood for seropositivity to *Toxoplasma gondii* in psychiatric patients. Folia Parasitol (Praha) 2010;**57**:129–135.
128. Pearce BD, Kruszon-Moran D, Jones JL. The relationship between *Toxoplasma Gondii* infection and mood disorders in the Third National Health and Nutrition Survey. Biol Psychiatry 2012;**72**:290–295.
129. Hamdani N, Daban-Huard C, Lajnef M et al. Relationship between *Toxoplasma gondii* infection and bipolar disorder in a French sample. J Affect Disord 2013;**148**:444–448.
130. Khademvatan S, Khajeddin N, Izadi S, Saki J. Study of *Toxoplasma gondii* infection in patients with Bipolar disorder. J Med Sci 2013;**13**:215.
131. Dickerson F, Boronow J, Stallings C, Origoni A, Yolken R. The lymphotoxin Cys13Arg polymorphism and cognitive functioning in individuals with schizophrenia. Schizophr Res 2007;**89**:173–176.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary of critical appraisal of included studies using the Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies on the association between infectious agents and bipolar disorder.

Table S2. Further evidence on the association between infection and bipolar disorder.

Table S3. Summary of critical appraisal of included studies using the Q-Genie Tool on the association between immunogenetic markers and bipolar disorder.