Review

Infectious and immunogenetic factors in bipolar disorder

Oliveira J, Oliveira-Maia AJ, Tamouza R, Brown AS, Leboyer M.

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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.

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.
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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, centered 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
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
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 2.67 hazard ratio (HR) (95% CI: 1.92–3.716) 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

### 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 | United States | Serum antibody to the 38/40 kDa and 24 kDa antigen | Fu et al., 1993 [115]^†   |
|             | ↑     | 2.94 (1.07–9.19) – 24 kDa antigen | 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| Antibodies to BDV/BDV nucleic acids                  | Na et al., 2008 [118]      |
|             | ↑     | 1.98 (1.10–3.53) | United States | Increased circulating immune complexes                | Mazeri-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 | United States | Serum antibody titres.                                | Okusaga et al., 2011 [122]|
|             | ↑     | 7.86 (2.51–26.49) – Influenza B | United States | Influenza A, Influenza B and coronavirus              |                           |
|             | ↑     | 6.95 (3.04–15.88) – Coronavirus | United States | associated with history of mood disorders but not with the specific diagnosis of unipolar or bipolar depression |                           |
| HSV-1       | ↔     | Not reported | Germany     | Influenza B virus was associated with age at onset of BD | Gerber et al., 2012 [123] |
| HSV-2       | ↔     | Not reported | United States | IgG antibodies                                       | Avramopoulos et al., 2015 [89]|
|             | ↔     | Not reported | United States | IgG antibodies                                       | Prossin et al., 2015 [125]|
|             | ↔     | Not reported | Germany     | Association with decreased cognitive functioning     | Gerber et al., 2012 [123] |
| CMV         | ↔     | 0.00 (0.00–1.11) | Ethiopia    | IgG antibodies                                       | Tedla et al., 2011 [124]  |
|             | ↔     | Not reported | Germany     | IgG antibodies                                       | Gerber et al., 2012 [123] |
| HHV-6       | ↔     | Not reported | United States | IgG antibodies                                       | Avramopoulos et al., 2015 [89]|
|             | ↔     | Not reported | Germany     | IgG antibodies                                       | Prossin et al., 2015 [125]|
|             | ↔     | No adequate number of positive individuals for calculation | Iran       | Detection of HHV-6 DNA. HHV-6A detected in 1 BD patients and none of the controls. | Yavarian et al., 2015 [126]|
| Toxoplasma  | ↑     | 2.96 (1.06–8.28) | Germany     | IgG antibodies                                       | Hinze-Selch et al., 2010 [127]|
|             | ↑     | Unadjusted values not reported | Germany    | IgG antibodies                                       | Tedla et al., 2011 [124]  |
|             | ↑     | Unadjusted values not reported | United States | IgG antibodies                                       | Gerber et al., 2012 [123] |
|             | ↑     | 3.58 (1.93–6.75) | France      | IgG antibodies                                       | Peace et al., 2012 [128]  |
|             | ↑     | 1.28 (0.77–2.12) | Iran        | IgG and IgM antibodies                                | Hamdani et al., 2013 [129]|
|             | ↑     | 1.77 (0.64–4.94) | Germany     | IgG antibodies                                       | Avramopoulos et al., 2015 [89]|

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.
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 6587036 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).
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 rs1927914 A and rs11536891 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 rs2066842 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 rs2066842 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 rs1800629 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

Fig. 2. Article selection process of studies on the association between immunogenetic markers and bipolar disorder.
Table 2. Genetic association studies between non-HLA immunogenetic markers and bipolar disorder

| Gene          | Polymorphism | OR (CI 95%)* | Population      | Comments                                                                 | Reference                                      |
|---------------|--------------|--------------|-----------------|--------------------------------------------------------------------------|-----------------------------------------------|
| CCL2          | rs1024611 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 (0.90–1.03) | 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)                    |
| CCR2          | rs1799864 G/A| G = 0.86 (0.58–1.28) | Turkish         | No association                                                          | Tokac et al., 2016 (72)                       |
|               | rs172633 C/T | G allele and GG genotype are associated with BD | Turkish         | No association                                                          | Tokac et al., 2016 (72)                       |
| CCR5          | rs333 In/Del | Del = 0.38 (0.16–0.85) | Turkish         | No association                                                          | Tokac et al., 2016 (72)                       |
|               | rs308229 A/G | G = 0.94 (0.71–1.25) | Turkish         | No association                                                          | Tokac et al., 2016 (72)                       |
| CSF2RB        | rs4821565 C/T | Not reported | Chinese         | No association                                                          | Chen et al., 2011 (70)                        |
| 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)                       |
| IFNγ          | rs2430561 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., 2008 (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 rs16944 T/C and IL1RN intron 2 86 bp VNTR | A2 = 1.43 (0.95–2.12) | Spanish | The IL1B C allele -- IL1RN allele*2 (2 tandem repeats) is associated with BD | Papiol et al., 2004 (76)                       |
|               | IL1RN 86 bp  intron 2 VNTR | Not reported | Korean         | No association with BD                                                   | Kim et al., 2004 (78)                         |
|               | IL1B rs16944 T/C | T = 2.06 (1.15–3.60) | Iranian        | IL1RN allele*2 (2 tandem repeats) carriage is associated with later onset of BD | Rafiei et al., 2013 (79)                      |
|               | IL1A rs1800687 C/T | T = 0.81 (0.40–1.62) | Iranian        | No association                                                          | Talaee et al., 2016 (71)                      |
|               | IL6            | rs1800679 G/C | Not reported | No association                                                          | Talaee et al., 2016 (71)                      |
|               | IL10           | rs1800896 A/G | G = 1.03 (0.67–1.58) | Reduced percentage of GA genotype in BD type I when compared to controls in BD type II | Clerici et al., 2009 (62)                      |
| IL1B          | rs2229084 T/C | Not reported | United States | Not reported                                                             | Dickerson et al., 2007 (131)                  |
| MASP2         | rs17550870 A/G | Not reported | Danish         | No association                                                          | Feldager et al., 2014 (44)                    |
| MBL2          | rs11003125 G/C | C = 0.85 (0.61–1.18) | Danish         | No association                                                          | Feldager et al., 2014 (44)                    |
|               | rs7096206 G/C | C = 1.64 (1.14–2.34) | No association | No association                                                          |                                                |
|               | rs7096981 G/A | A = 0.91 (0.61–1.34) | No association | No association                                                          |                                                |
|               | rs6030737 C/T | T = 0.96 (0.50–1.73) | No association | No association                                                          |                                                |
|               | rs1800450 A/G | A = 0.78 (0.47–1.25) | No association | No association                                                          |                                                |
|               | rs1800451 G/A | A = 1.17 (0.25–4.17) | No association | No association                                                          |                                                |
| NOD2          | rs2066842 C/T | T = 0.67 (0.52–0.88) | French         | T allele carrier state is less prevalent in BD                           | Oliveira et al., 2014a (58)                   |
|               | rs2066843 C/T | T = 0.65 (0.42–1.02) | No association | No association                                                          |                                                |
|               | rs2066845 G/C | C = 0.83 (0.36–2.08) | No association | No association                                                          |                                                |
|               | rs2066847 C/CinsC | CinsC = 0.73 (0.34–1.68) | No association | No association                                                          |                                                |
| PTGS2         | rs685466 G/C | C = 0.96 (0.67–1.38) | Turkish         | No association                                                          | Ozdemir et al., 2015 (69)                     |
| TLR2          | rs20417 A/G | G = 0.47 (0.31–0.70) | No association | AA genotype more prevalent in BD patients                                | Oliveira et al., 2014b (74)                   |
|               | -196 to -174 ins/del | Del = 0.87 (0.63–1.21) | French         | No association                                                          |                                                |
|               | rs804098 T/C | T = 1.17 (0.93–1.47) | No association | No association                                                          |                                                |
|               | rs804100 T/C | T = 1.02 (0.81–1.29) | TT genotype more prevalent in early-onset than in late-onset BD patients | Oliveira et al., 2014b (74)                   |
| TLR4          | rs1927914 A/G | A = 1.29 (0.10–2.63) | French         | AA genotype more prevalent in early-onset BD than in controls            | Oliveira et al., 2014c (57)                   |
|               | rs1075932 T/C | C = 0.95 (0.68–1.34) | No association | No association                                                          |                                                |
|               | rs866790 A/G | G = 0.89 (0.56–1.45) | G allele carrier state was associated with thyroid disorders among BD patients | Oliveira et al., 2014b (74)                   |
|               | rs986791 C/T | T = 0.87 (0.55–1.41) | T allele carrier state was associated with thyroid disorders among BD patients | Oliveira et al., 2014c (57)                   |
|               | rs11536889 G/C | C = 1.14 (0.83–1.59) | No association | No association                                                          |                                                |
implicated in BD. A study reported a lower percentage of the TT high producer genotype of the *INFG* T + 874A (rs2430561) in BD patients in Italy (62). Once again, contradictory results were also described with T allele carrier status 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 G allele of the G-174C 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 rs20417 promoter polymorphism, known to decrease transcripational 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*, *SF2RB*, *CXCL12*, *CXC4* and *IL1A* genes have also been explored, but no associations were found (70–72).

**Table 2. (Continued)**

| Gene     | Polymorphism | OR (CI 95%)* | Population | Comments                          | Reference               |
|----------|--------------|--------------|------------|-----------------------------------|-------------------------|
| *TNF*    | rs1800629 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; DLPC: dorsolateral prefrontal cortex; GM: grey matter; *CL2*: 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; *CXC4*: 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*: lymphotxin alpha; *MASP2*: mannan-binding lectin serine peptidase 2; *MBL2*: mannos 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.

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* rs3804099 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-714C polymorphism of the *IL6* gene (rs1800795) 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 (rs16944) 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 rs1024611 (~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 genomewide 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 rs2794520 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 (rs3804099) 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 rs3804099 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 (rs3804099) 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).

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 rs4986790 G and rs4986791 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.](https://wileyonlinelibrary.com)

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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.

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Declaration of interest

The authors declare that there is no conflict of interest.

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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.