C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis

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Summary

Background Inflammatory processes and neural–immune interactions have been implicated in the pathogenesis of psychiatric conditions, but studies in bipolar disorder are inconclusive so far. We aimed to investigate whether peripheral concentrations of C-reactive protein (CRP), an acute-phase response protein of inflammatory activity, are increased in bipolar disorder across the mood spectrum.

Methods In this systematic review and meta-analysis, we searched MEDLINE, the Cochrane Library, Scopus, and Web of Knowledge from database inception to Aug 14, 2016, for studies that measured serum and plasma CRP concentrations in adult patients with bipolar disorder (as defined by DSM-IV-TR) and healthy controls. We extracted data from published reports. We did three between-group meta-analyses comparing CRP concentrations in patients in mania, depression, or euthymia, with those in healthy controls (cross-sectional studies), and two within-group meta-analyses comparing changes in CRP concentrations before and after treatment of an index manic or depressive episode (longitudinal studies). We used Hedges’ adjusted g to calculate effect sizes and pooled results using random-effect models. We also did meta-regression analyses by mood state to investigate possible moderators of CRP concentrations.

Findings We identified 27 studies representing 2161 patients with bipolar disorder and 81 932 healthy controls. Compared with healthy individuals, CRP concentrations were moderately increased in people with bipolar disorder during depression (g 0.67, 95% CI 0.23 to 1.11; p=0.003) and euthymia (0.65, 0.40 to 0.90; p<0.0001) and more substantially increased during mania (0.87, 0.58 to 1.15; p<0.0001). The extent of the increases in CRP concentrations in mania and depression was not related to symptom severity (p=0.256 for mania and p=0.626 for depression). CRP concentrations were moderately decreased after resolution of an index manic episode (–0.36, –0.66 to –0.05; p=0.022) and slightly decreased after resolution of an index depressive episode (–0.18, –0.30 to –0.07; p=0.002).

Interpretation CRP concentrations are increased in bipolar disorder regardless of mood state, but are higher during mania than in depression and euthymia, suggesting an increased inflammatory burden in mania.

Funding None.

Introduction Inflammatory processes and neural–immune interactions are implicated in the pathogenesis of psychiatric disorders.1–3 Bipolar disorder is one of the psychiatric disorders with the most severe burden of illness,4 not only because of its effects on mood and cognition but also because of its association with clinical comorbidities such as obesity, diabetes, and cardiovascular disease. Such an association led to the suggestion that bipolar disorder is a systemic disease with an inflammatory component that could at least partly account for common risk pathways in bipolar disorder and comorbid conditions.5 In preclinical and clinical studies,6–9 concentrations of pro-inflammatory cytokines were found to be increased in bipolar disorder in both the brain and the peripheral blood. Additionally, results from several longitudinal studies10–13 showed that people with inflammatory clinical pathologies are at an increased risk of developing a psychiatric event in the future.

C-reactive protein (CRP) is an acute-phase protein produced in response to an inflammatory stimulus and is mostly induced by the pro-inflammatory cytokines interleukin-6 and interleukin-1β.14 Increased concentrations of CRP have been reported in meta-analyses of cross-sectional studies in schizophrenia15 and in major depressive disorder.16 Raised concentrations of CRP increase the risk of a first episode of depression,17 schizophrenia,18 and bipolar disorder.19 Findings from two mendelian randomisation studies19,20 suggested a causal relation between increased CRP concentrations and the occurrence of bipolar disorder; however, a longitudinal study21 published in 2016 reported no association between CRP concentrations in childhood and risk of manic symptoms in young adulthood. Several clinical studies22–24 have investigated the association between CRP concentration in the blood and different mood states in bipolar disorder. Although studies most found an increase in CRP concentration during manic states, the data regarding depressive and euthymic states are less certain, with both positive and null findings. Whether CRP concentrations are associated with the severity of mania or depression, or with age and...
Articles

**Research in context**

**Evidence before this study**

We searched MEDLINE, the Cochrane Library, Scopus, and Web of Knowledge for peer-reviewed articles on C-reactive protein (CRP) concentrations in bipolar disorder from inception of the database to Aug 14, 2016, with no language restrictions. The search term was “(CRP OR C-reactive protein OR hsCRP OR hs-CRP) AND (bipolar OR psychosis OR mania OR manic)”. We identified a meta-analysis on CRP concentrations in bipolar disorder that included 11 cross-sectional studies. Although the authors of this meta-analysis found some evidence of increased CRP concentrations in mania and euthymia, the number of studies included in each mood state (ie, mania, depression, and euthymia) was small and therefore no subgroup analysis was done. The authors reported no changes in CRP concentrations in depression, probably because only four studies involving this subgroup of patients were included. Longitudinal changes in CRP concentrations were not included. We identified 16 additional studies of CRP concentrations in bipolar disorder. However, most of these studies and those included in the meta-analysis had small sample sizes with conflicting results.

**Added value of this study**

To our knowledge, this study is the first to investigate the association between CRP concentrations and bipolar disorder that takes into consideration BMI, severity of mood episodes, and use of psychiatric medications. We were also the first to analyse dynamic changes in CRP concentrations with psychiatric medications after an index manic or depressive episode. We did five meta-analyses on CRP concentrations across the mood spectrum in bipolar disorder and included 27 studies with 84 093 participants. We found that CRP concentrations are moderately increased in people with bipolar disorder during depression and euthymia and more substantially increased during mania. In manic and depressive states, CRP concentrations are higher in people who have not taken psychiatric medication for at least 1 week. The extent of the increases in peripheral CRP concentrations in mania and depression showed no association with the severity of manic or depressive symptoms. We noted a moderate decrease in CRP concentrations with achievement of euthymia after an index manic episode, and a small decrease after an index depressive episode.

**Implications of all the available evidence**

Our findings provide further evidence for an increased inflammatory state in bipolar disorder across the mood states, with inflammation being particularly high during mania. Treatment of manic and depressive episodes with psychiatric medications is associated with a decrease in systemic inflammation, as shown by the decrease in CRP concentrations. Longitudinal studies are needed to clarify the association between CRP concentrations and the development of bipolar disorder.

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length of illness, is also uncertain, and such knowledge could shed light on the importance of CRP in the context of neuroprogression. Regarding changes in CRP concentrations after amelioration of symptoms of index manic or depressive episodes, the data are varied, with studies showing increase, decrease, or no changes in CRP concentrations. A meta-analysis of 11 cross-sectional studies of CRP concentrations in bipolar disorder found that CRP concentrations increased in mania and euthymia but not in depression. However, owing to the small number of studies included, it did not analyse effects of any moderators such as severity of symptoms or the effects of treatment.

In this study, we aimed to assess peripheral CRP concentrations in bipolar disorder across the mood states, whether concentrations are correlated with the severity of mood symptoms, and whether CRP concentrations change after resolution of an index mood episode.

**Methods**

**Search strategy and selection criteria**

In this systematic review and meta-analysis, we searched MEDLINE, the Cochrane Library, Scopus, and Web of Knowledge from database inception to Aug 14, 2016, for peer-reviewed articles on CRP concentrations in bipolar disorder, using the search term “(CRP OR C-reactive protein OR hsCRP OR hs-CRP) AND (bipolar OR psychosis OR mania OR manic)”. We did not apply any restrictions on language or study design. Studies were included if they recruited adult patients with bipolar disorder in mania, depression, or euthymia, as defined by DSM-IV-TR; did pairwise comparison to a control group of healthy volunteers; and measured circulating serum or plasma CRP and high-sensitivity CRP concentrations. Duplicate reports, studies using CRP assays that provide dichotomous results (ie, positive or negative), and studies without a control group were excluded.

We adhered to the PRISMA guidelines. Two authors (BSF and C-AG) independently did the literature search, decided on study inclusion, extracted the data, and performed quality control. Consensus was achieved through discussion between BSF and C-AG.

**Data extraction**

Two authors (BSF and C-AG) independently extracted summary estimates (n, mean, and SD) for diagnostic status, CRP concentration, sex, age, duration of illness, body-mass index (BMI), medication (such as antipsychotics, mood stabilisers, and antidepressants), Young Mania Rating Scale (YMRS) scores, and Hamilton Depression Rating Scale (HDRS) scores. All analyses were done according to mood state (ie, mania, depression, or euthymia). Patients with bipolar disorder were
considered drug free if they had not taken psychiatric medication for at least 1 week before the blood draw. BSF and C-AG double-checked discrepancies in data entry with the original published data, and consensus was reached by rechecking the original studies and contacting the study authors when necessary. When the necessary data were not available from the published reports, we contacted the authors and requested the information. If the results were graphically presented and the authors could not provide the data, we used a method for data extraction from the graphs explained by Sistrom and Mergo. Whenever multiple reports pertained to the same groups of patients, we retained only the most comprehensive report for analysis. For longitudinal studies, we included baseline and follow-up information for the between-group meta-analysis.

**Data analysis**

The meta-analyses consisted of three steps. First, we did the overall analysis for three between-group meta-analyses comparing serum and plasma CRP concentrations in people with bipolar disorder inmania, depression, or euthymia, with those in healthy controls (cross-sectional studies), and two within-group meta-analyses comparing changes in CRP concentrations before and after resolution of an index manic or depressive episode (longitudinal studies). Additionally, we did a prespecified subgroup analysis of patients in mania and depression by medication status.

We used the Newcastle-Ottawa Scale to assess the quality of the eligible observational studies, case-control studies for the between-group meta-analyses, and cohort studies for the within-group meta-analyses. Overall quality score was defined as the frequency of criteria that were met by the particular study. All studies were included in the posterior analyses. Methods to assess publication bias are described in the appendix.

Because studies used different measurement methods, we used standardised mean difference estimates of the differences in CRP concentrations between patients and healthy controls as the effect size. We used Hedges' adjusted $g^*$ for the calculation to provide unbiased effect sizes adjusted for small sample sizes, and also calculated the corresponding 95% CIs. An effect size of 0-2 was considered to indicate a low effect, meaning a small difference in CRP concentrations between patients and controls, 0-5 a moderate effect, and 0-8 a large effect. The level of significance for effect size estimates was set at p<0-05.

We assessed heterogeneity across studies using the Cochran Q test, a weighted sum of the squares of the deviations of individual study effect size estimates from the overall estimate, and considered a p value of less than 0-10 significant. Inconsistency across studies was then quantified with the $I^2$ metric. $I^2$ can be interpreted as the percentage of total variation across several studies as a result of heterogeneity, and heterogeneity was considered moderate when $I^2$ is between 50% and 75%, and high when $I^2$ is greater than 75%.

Since the analyses showed that the studies were heterogeneous, we pooled effect sizes from different studies according to the inverse variance method of accounting for random effects, which allows population-level inferences and is more stringent than fixed-effect models. Random-effect modelling assumes a genuine diversity in the results of various studies and incorporates a between-study variance into the calculations. The direction of the effect size was positive if patients with bipolar disorder had increased CRP concentrations, and negative if they had decreased CRP concentrations compared with controls in the between-group meta-analyses. In the within-group meta-analyses, the effect size was positive if CRP concentrations increased after treatment of the index mood episode, and negative if CRP concentrations decreased after treatment of an index mood episode.

Second, we did sensitivity analyses to ascertain whether the results of our analyses were strongly influenced by any single study or a cluster of studies sharing some characteristic. The overall significance was recomputed after each study or group of studies with a common characteristic. The results of our analyses were strongly influenced by any single study or a cluster of studies sharing some characteristic. The overall significance was recomputed after each study or group of studies with a common characteristic. When the necessary data were not available from the published reports, we contacted the authors and requested the information. If the results were graphically presented and the authors could not provide the data, we used a method for data extraction from the graphs explained by Sistrom and Mergo. Whenever multiple reports pertained to the same groups of patients, we retained only the most comprehensive report for analysis. For longitudinal studies, we included baseline and follow-up information for the between-group meta-analysis.

Third, we did meta-regression analyses, separately for each mood state, to investigate possible moderators of CRP concentrations. Restricted maximum likelihood random-effects meta-regressions of effect size were done with mean age, sex, BMI, duration of illness, and severity of disease (as assessed by YMRS and HDRS) as

![Figure 1: Study selection for meta-analysis of CRP in bipolar disorder](See Online for appendix)
CRP=C-reactive protein.

(A) Mania. (B) Depression. (C) Euthymia.

Healthy controls

Change in serum and plasma CRP concentrations in patients with bipolar disorder compared with healthy controls. Ten studies were included in the within-group meta-analyses, providing data on 83,669 participants, of whom 137 were individuals with bipolar disorder and 81,932 were healthy controls. Of those, 14 studies provided data for mania (500 subjects in mania and 11,696 controls), 11 for depression (408 in depression and 955 controls), and 17 for euthymia (829 in euthymia and 79,808 controls). Ten studies were included in our within-group meta-analyses, providing data on 424 subjects (141 for a manic index episode and 283 for an index depressive episode). Some studies provided more than one pairwise comparison.

The 23 studies included in the between-group meta-analyses were published between 2002 and 2016 and varied in sample size from 20 to 78,809 (appendix). Mean age of the participants ranged from 23 years to 63 years. 15 studies assessed CRP concentrations in serum, and eight in plasma. 11 studies assessed CRP concentrations in serum, and eight in plasma. Only three studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals. In 16 studies, the control group was matched by age and BMI to the case group. Five studies provided data on drug-free individuals.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 176 studies after duplicates were removed, all of which had an English abstract (figure 1). Of those, 137 were excluded on the basis of title and abstract, and another 12 after full text assessment (figure 1). 27 studies were included in the meta-analyses. 23 studies fulfilled our inclusion criteria for the between-group meta-analyses, providing data on 83,669 participants, of whom 1737 were individuals with bipolar disorder and 81,932 were healthy controls. Of those, 14 studies provided data for mania (500 subjects in mania and 11,696 controls), 11 for depression (408 in depression and 955 controls), and 17 for euthymia (829 in euthymia and 79,808 controls). Ten studies were included in our within-group meta-analyses, providing data on 424 subjects (141 for a manic index episode and 283 for an index depressive episode). Some studies provided more than one pairwise comparison.

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Overall, random-effects between-group meta-analysis showed that serum and plasma CRP concentrations were increased substantially in patients with bipolar disorder in mania compared with healthy controls (g=0.87, 95% CI 0.58–1.15; p<0.0001), and moderately in depression (0.67, 0.23–1.11, p=0.003) and euthymia (0.65, 0.40–0.90, p<0.0001; figure 2; table 1). Since differences in BMI and age between the patient and control groups could confound results, we re-ran the analysis including only the studies with a control group matched by BMI and age to the patient group. After such an adjustment, CRP concentration remained higher in patients than controls across all mood states (table 1). When only studies paired by age and BMI were considered, the effect size increased slightly in the depression group and from moderate to large in the euthymia group (table 1). In subgroup analyses of patients with mania and depression by medication status, the crude effect size was higher in drug-free participants than in those on medication (table 1). However, even though the general effect size of the drug-free group in depression was twice as high as that of the medicated group, it was not significant, probably because of a loss of power, since only three studies were included in this subgroup. We could
not perform subgroup analysis of euthymia by medication status because of the small number of studies (table 1).

To investigate whether CRP concentrations were increased across the mood states to the same extent, we directly compared the effect sizes of each study. Although CRP concentrations were increased across mood states compared with controls, the extent of the increase differed (p=0.021), with CRP concentrations being higher in mania than in depression and euthymia (figure 3). No significant difference in CRP concentrations was seen between depression and euthymia (figure 3).

We did meta-regression analyses to explore the sources of heterogeneity between studies. In univariable meta-regression models, neither severity of manic symptoms as assessed by YMRS, nor severity of depressive symptoms as assessed by HDRS, was related to the magnitude of the effect size, indicating no association between severity of symptoms and CRP concentrations (figure 4). Additionally, we found no relation between duration of illness in euthymia and CRP concentration. Age, sex, and BMI were not associated with CRP concentration in any mood state (table 2).

To determine whether CRP concentrations decreased or increase after the treatment of an index manic or depressive episode until euthymia is achieved, we did two additional within-group meta-analyses. A moderate decrease in CRP concentration was seen following an index manic episode, and a small decrease in CRP concentration was noted following an index depressive episode (figure 5). However, CRP concentrations did not return to those measured in the control groups. For within-group meta-analyses, we did not perform any meta-regression because of the small number of studies included (four for index manic episode and six for index depressive episode).

Results from the rating of quality of the included studies, sensitivity analyses, and publication bias are shown in the appendix.

Discussion

Serum and plasma CRP concentrations were moderately increased in people with bipolar disorder during depression and euthymia, and more substantially increased during mania. In both manic and depressive states, CRP concentrations were higher in patients who were not taking psychiatric medication. The size of the increases in peripheral CRP concentrations in mania and depression was not associated with the severity of symptoms or with duration of illness in euthymia. Additionally, CRP concentration was moderately decreased with achievement of euthymia after an index manic episode, and slightly decreased after an index depressive episode, but concentrations did not fall to those in the control groups.

High peripheral concentrations of CRP can increase the permeability of the blood–brain barrier, allowing CRP to enter the CNS and directly affect the brain. In primary cell culture, CRP induces reactivity of microglia and astrocytes and exacerbates gliosis. The hyper-reactivity of microglia and astrocytes leads to increased release of cytokines such as interleukin-6 and interferon-γ increasing quinolinic acid synthesis and decreasing synthesis of brain-derived neurotrophic factor, ultimately leading to risk of neuronal damage.
increase with chronicity of the disease. Our finding suggests that CRP-mediated inflammation is not a cause of neuroprogression and is consistent with results from the Netherlands Study of Depression and Anxiety (NESDA) study. In the NESDA study, BMI was not associated with persistence of depression in a population sample (n=2447), although high BMI at baseline was associated with an increased risk of developing depression over 6 years of follow-up. Our finding that CRP concentration does not increase with duration of illness in bipolar disorder might suggest that, although raised CRP concentrations increase the risk of development of bipolar disorder, it is not a major cause of neuroprogression. This interpretation agrees with a report that high serum CRP concentrations in 84 individuals with bipolar disorder are not associated with worse prognosis at 15 month follow-up, regardless of whether the patients had euthymia or a mood episode at baseline.

In our study, mania seemed the most robustly linked to inflammation, as assessed through relatively high CRP concentrations in serum and plasma. This result is supported by the findings of a longitudinal study in which raised baseline serum CRP concentrations were a strong predictor of occurrence of mania in 957 people with depressive disorder. One of the pathways involved in the occurrence of mania could be the kynurenine pathway. Microglia, once activated by CRP, can produce interferon-γ, which in turn induces the enzyme indoleamine 2,3-dioxygenase, increasing quinolinic acid production and activating NMDA glutamate receptors. In this scenario, the inflammatory hypothesis would complement the glutamatergic hypothesis in the occurrence of mania. Psychiatric medications, such as mood stabilisers and antipsychotics, can increase serum and plasma CRP concentrations. However, in our study, CRP concentrations in mania and depression were higher in people not taking such medications than in those using these types of medications, possibly because psychiatric treatment of a disorder associated with low-grade inflammation, such as mania and depression, decreases inflammation. This explanation is consistent with the results of both our longitudinal meta-analyses, in which resolution of an index manic or depressive episode was associated with decreases in CRP concentrations. An implication of mania and depression being associated

Table 2: Between-group meta-regressions, by moderator

<table>
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<th>Number of</th>
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<tr>
<td>Sex (proportion of women)</td>
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BD=bipolar disorder. HC=healthy controls. BMI=body-mass index. YMRS=Young Mania Rating Scale. HDRS=Hamilton Depression Rating Scale.

Figure 5: Changes in serum and plasma CRP concentrations following (A) an index manic episode and (B) an index depressive episode

The sizes of the squares are proportional to sample size. CRP=C-reactive protein.
with high inflammation is the possibility of treating mood symptoms in bipolar disorder with anti-inflammatory agents such as aspirin and statins. On the basis of results from our previous meta-analysis,\textsuperscript{7} we suggested that statins as an add-on treatment could improve depressive symptoms in moderate-to-severe depression. Whether statins and other anti-inflammatory agents have a role in the treatment of depression in the context of bipolar disorder remains to be determined.

Finally, in the meta-regressions we found no association between CRP concentration and severity of manic or depressive symptoms.

Our study has some inherent limitations. First, the meta-regressions might have failed to achieve statistical significance because of a lack of power in these specific analyses, thus giving a false-negative result. Second, the three meta-analyses on CRP concentrations in patients with bipolar disorder compared with healthy controls provided us with pooled results originating from cross-sectional studies, and we therefore cannot draw any conclusions on causality. Obesity is only one of the factors known to drive inflammation, with smoking, low concentrations of vitamin D, low level of physical activity, poor diet, atopy, leaky gut, stress, sleep disorder, and subclinical infections (including dental caries) as additional drivers.\textsuperscript{1,72} Data for these factors were not available in most of these studies. Third, waist circumference is more accurate than BMI for assessment of visceral adiposity. Since most studies included in our analysis did not provide data on waist circumference, we used BMI as a surrogate for visceral adiposity. Finally, any meta-analysis is dependent on the quality of the analysed studies, and our results need to be verified by studies specifically designed to test the points we raised.

To conclude, our meta-analyses of 27 studies comprising 84,093 participants provide evidence that serum and plasma CRP concentrations are increased in patients with bipolar disorder regardless of mood state, with highest concentrations during mania. Future studies need to investigate whether changes in CRP concentrations have a causal relation to the development of bipolar disorder and recurrence of a mood state, or whether they are an epiphenomenon of low-grade inflammation in this condition, its risk factors, or comorbidities.

\textbf{Contributors}
All authors contributed to the study design. BSF and C-AG did the literature search and extracted the data. BSF did the statistical analysis and prepared the figures. All authors interpreted the data, wrote the report, and approved the final version of the manuscript.

\textbf{Declaration of interests}
We declare no competing interests.

\textbf{Acknowledgments}
We thank all authors of the papers included in our study, particularly Domenico De Berardis (Department of Neurosciences and Imaging, Chair of Psychiatry, University “G D’Annunzio” of Chieti, Chieti, Italy), Nilay Herpalg (King’s College London, Institute of Psychiatry, Psychology and Neuroscience, Department of Psychological Medicine, London, UK), Valeria Mondelli (King’s College London, Institute of Psychiatry, Psychology and Neuroscience, Department of Psychological Medicine, London, UK), and Jaana Suvisaari (Mental Health Unit, National Institute for Health and Welfare, Helsinki, Finland), who kindly provided us with unpublished data. BSF is supported by a postdoctoral scholarship and a research grant (MCTI/CNPq/Universal 14/201461833/2014-0) from CNPq, Brazil. CAX received a postdoctoral fellowship from CAPES, Brazil. AFC received a research fellowship from CNPq (Brazil, level II). MB is supported by a Senior Principal Research Fellowship 105660 from the Australian National Health and Medical Research Council.

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