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Review

Homocysteine as a peripheral biomarker in bipolar disorder: A meta-analysis

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ABSTRACT

Background: Bipolar disorder (BD) is a psychiatric disorder with an uncertain aetiology. Recently, special attention has been given to homocysteine (Hcy), as it has been suggested that alterations in 1-carbon metabolism might be implicated in diverse psychiatric disorders. However, there is uncertainty regarding possible alterations in peripheral Hcy levels in BD.
Methods: This study comprises a meta-analysis comparing serum and plasma Hcy levels in persons with BD and healthy controls. We conducted a systematic search for all eligible English and non-English peer-reviewed articles.
Results: Nine cross-sectional studies were included in the meta-analyses, providing data on 1547 participants. Random-effects meta-analysis showed that serum and plasma levels of Hcy were increased in subjects with BD in either mania or euthymia when compared to healthy controls, with a large effect size in the mania group ($g = 0.98$, 95% CI: 0.8–1.17, $P < 0.001$, $n = 495$) and a small effect in the euthymia group ($g = 0.3$, 95% CI: 0.11–0.48, $P = 0.002$, $n = 1052$).
Conclusions: Our meta-analysis provides evidence that Hcy levels are elevated in persons with BD during mania and euthymia. Peripheral Hcy could be considered as a potential biomarker in BD, both of trait (since it is increased in euthymia), and also of state (since its increase is more accentuated in mania). Longitudinal studies are needed to clarify the relationship between bipolar disorder and Hcy, as well as the usefulness of peripheral Hcy as both a trait and state biomarker in BD.
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1. Introduction

In order to better understand the physiopathology underlying bipolar disorder (BD), increasing research efforts have attempted to identify potential biomarkers in the peripheral blood of those with BD and also to advance the elusive field of precision psychiatry [1–4]. Neurotrophins such as BDNF [5–9] and inflammatory markers such as C-reactive protein [10–12] have

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consistently been proposed as promising peripheral biomarkers in BD. More recently, special attention is being given to homocysteine (Hcy) [13], as it has been suggested that alterations in 1-carbon metabolism might be implicated in psychiatric disorders, including BD [14–17].

In the 1-carbon metabolism, a carbon unit from serine or glycine is transferred to tetrahydrofolate (THF) to form methylene-THF. Homocysteine is a non-protein and nonessential amino acid sulfur with a central role in 1-carbon metabolism, and its regulation depends on multiple enzymes, with methylenetetrahydrofolate reductase (MTHFR) the most extensively investigated. Folate and vitamin B12 are also key elements of Hcy metabolism, since they act as enzymatic cofactors [18,19]. Accordingly, either a reduced enzymatic activity of MTHFR or a nutritional deficiency in folate or vitamin B12 may lead to hyperhomocysteinemia [19–21]. This may promote neurotoxic and vasculotoxic effects by several proposed mechanisms, including but not limited to mitochondrial dysfunction [22], oxidative stress induction [14,23,24], inflammation [25], neuroapoptosis [26,27], direct vascular damage [25,28], aberrant DNA methylation [29,30] and impaired DNA synthesis [31]. These pathways overlap considerably with those pathways documented as drivers of the process of neuroprogression evident in BD [32]. Equally, this is concordant with the notion of shared pathways to comorbidity of both psychiatric and common medical disorders [18,33].

Hyperhomocysteinemia is a known risk factor for cardiovascular diseases [34] and Alzheimer's dementia [35,36]. Additionally, several studies have described an association between higher levels of Hcy and depression [37–41], autism [42] and schizophrenia [17,29,43]. In addition, a recent meta-analysis by Numata et al. provided evidence that increased Hcy levels is causally related with an increased risk of developing schizophrenia using a Mendelian Randomization analysis [16]. In BD, higher levels of peripheral Hcy have been associated with worse cognitive performance [44,45].

Contrary to schizophrenia, where better evidence exists, data on peripheral levels of Hcy in BD are more limited, with discrepant findings across studies conducted to date; some studies show increased levels of Hcy in persons with BD when compared to healthy controls [46], while others find no evidence for this association [47]. The aim of this study was therefore to verify if alterations in peripheral Hcy levels are present in BD in the different mood states compared to healthy controls. To this end, we performed a meta-analysis of all available cross-sectional studies that measured peripheral Hcy levels in BD compared to healthy subjects in order to evaluate the potential of Hcy as a biomarker in BD. The null hypothesis was that there would be no difference between individuals with BD compared to healthy controls.

2. Methods

We performed a meta-analysis comparing peripheral levels of Hcy in subjects with BD across different mood states versus healthy controls. We adhered to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement and guidelines from the Cochrane Collaboration [48]. The literature search, decisions on inclusion, data extraction and quality control were all independently performed by two of the authors (E.S., B.S.F.). Disagreements were resolved through consensus. An a priori defined but unpublished protocol was followed.

2.1. Search strategy

We conducted a systematic search for all potentially eligible peer-reviewed articles using PubMed and SCOPUS in January 2016. We included studies published in English, Dutch, French, German, Italian, Portuguese and Spanish, with no year or country restrictions [48]. The Boolean terms used for the electronic database search were: (homocysteine or MTHFR or methylenetetrahydrofolate reductase or folate or folic acid or B12) and (bipolar or mania or psychosis). We manually searched bibliographies of the identified articles in order to identify further relevant references that might have been missed in the initial search. Study selection eligibility and exclusion criteria were pre-specified.

2.2. Study selection

We included studies meeting the following inclusion criteria:

- adult subjects with diagnosis of BD, as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM), regardless of current mood state;
- pairwise comparison with a control group of healthy volunteers
- studies that assessed homocysteine levels *in vivo*.

Exclusion criteria were:

- duplicate reports;
- studies conducted in subjects aged less than 18 years;
- reviews or meta-analyses articles;
- lack of a control group of healthy volunteers;
- genetic studies not measuring Hcy levels;
- studies that included samples with mixed psychiatric diagnoses unless data for BD were reported separately or were obtained after contacting the authors;
- studies not specifying the mood state of the subjects at the time Hcy was assessed;
- studies which did not report data on subjects with BD separately according to mood state;
- animal studies.

We used the Newcastle–Ottawa Scale (NOS) for case-control studies [49] as recommended by the Cochrane Collaboration [50] to assess the quality of the eligible studies. Overall, quality score was defined as the frequency of criteria that were met by the particular study. The NOS scale contains eight items for assessing the quality of case-control studies, categorised into the three domains of selection, comparability, and exposure. A series of response options is provided for each item. A star system was used to enable semi-quantitative assessment of study quality, such that the highest quality studies are awarded a maximum of one star for each item, with the exception of the comparability domain, which allows the assignment of two stars. As such, the Newcastle–Ottawa scale ranges between zero and nine stars [49]. Item "non-response rate" from Exposure in the case-control scale was not applicable; therefore, a maximum of eight stars was considered. The quality score of the included was four and five. All studies were included in the posterior analyses.

2.3. Data extraction

Two independent reviewers extracted data [*n*, mean and standard deviation (SD)] using a predesigned form [48]. Whenever necessary, authors of included studies were electronically contacted to provide data in at least two separate occasions. Whenever data on the same participants were provided by different articles, only the most comprehensive data set was included. When necessary, means and SD were calculated from available graphs using procedures described in details elsewhere [51].

All variables were extracted separately for each mood state (euthymia, mania or depression). We extracted the following data: sample size, age, sex, length of illness in years, body mass index

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