Reviewer’s report

Title: Systematic Review of Genome-wide Gene Expression Studies of Bipolar Disorder

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Reviewer: John Nurnberger

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This is a mega-analysis of all available data for brain gene expression in persons with bipolar disorder. The results (including 10 separate studies) identified 11 genes differentially expressed after correction for multiple testing. Pathway studies identified metallothionein genes and neuropeptides as enriched among nominally differentially expressed genes.

This is a carefully performed analysis. As the authors note, they were not provided raw data by some groups and this limits the dataset that may be included. This limitation is unfortunate, and somewhat difficult to understand, given that results have already been published (but this is not a criticism of the authors).

There are some questions, however, about the data that were analyzed.

Major compulsory

1. The major issue is that it should be clear to the reader what the actual N of subjects is for each data category. We have an N of arrays, but the text implies that some of these arrays were actually independent tests of gene expression from the same brain samples. The data should be presented in a form that makes this clear (e.g. were all the Stanley analyses from the same 30 samples?). It would also be of interest to know the variance within different analyses of the same sample as compared to the variance within groups of samples.

Minor essential:

2. What does “all brain” mean? Is that an average of pfc and hippocampus, or an average of all available brain areas or something else?

3. The list of 382 genes is of interest for the supplementary material, but since these are not FDR corrected it may not be appropriate to feature these in the abstract (I would suggest paying more attention to the list of 11).

Discretionary:

The pathway analysis should be described in somewhat greater detail. Apparently multiple pathways passed FDR but they are not listed.

Minor essential:

The authors should compare and contrast their results with those of similar
It should be discussed whether there is a need to control these analyses for such technical variables as PMI, pH as well as subject demographic variables.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I receive funding from NIMH.
I am in multicenter collaborative studies with Drs. Zandi and Potash.