Reviewer’s report

Title: Depression pathogenesis and treatment: what can we learn from blood mRNA expression?

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Reviewer: Michael Maes

Reviewer’s report:

This is a very interesting paper reviewing the importance to examine blood mRNA expression in clinical depression. I have a few remarks which the authors should amend prior to publication of their paper.

1. Major compulsory revisions

The paper discusses that it is important to examine inflammatory, HPA-axis, and neuroplasticity biomarkers in depression. Therefore, the authors should start their Introduction with a description of the state-of-the-art, big picture in clinical depression, i.e. that inflammatory, oxidative and nitrosative stress (O&NS), HPA-axis, mitochondrial and neuroprogressive pathways are involved in the pathophysiology of depression. The authors can refer to for example Moylan et al. (2012) or Leonard and Maes (2012) and describe that interrelated aberrations in these pathways contribute to depression and staging of depression.


2.1. It is better to use the term neuroprogression, because this term describes aberrations in neuroprotective and neurogenesis pathways, neurodegeneration and apoptosis, which are all involved in depression (please discuss these factors).

2.2. It is indeed important to examine mRNA expression. However, it is even more important to use high-throughput methods applied on gene, mRNA and protein data and analyze these by means of systems biology methods (Leonard and Maes, 2012). This new methodology should be discussed at the end of their review.

2.3. The authors should enlarge their discussion on O&NS biomarkers and O&NS mRNA expression in depression.

2.4. The authors then state: “The inflammatory theory of MDD emphasizes the role of psychoneuroimmunological dysfunctions where there is an activation of the immune system and refer to [12 = themselves]. However, the authors should refer to the original cytokine-inflammatory findings dating back to 1990 or even better to the state-of-the art inflammatory-O&NS-neuroprogressive theories of clinical depression (Moylan et al., 2012; Leonard and Maes, 2012).
2.5. On page 5 the authors state “additionally, MDD is very common in the medically ill,
particularly in illnesses with an inflammatory component such as autoimmune
diseases and rheumatoid arthritis [13,14]. The authors should state that inflammatory and O&NS pathways explain the multiple comorbidities of depression with a) neuroinflammatory disorders (Alzheimer’s, Parkinson’s,
multiple sclerosis, stroke, etc); b) inflammatory / autoimmune disorders, including CVD, COPD, CFS, RA, psoriasis, SLE, IBD, diabetes, HIV, etc.

Quality of written English: Acceptable

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

Declaration of competing interests:
I have no competing interests