Author’s response to reviews

Title: So depression is an inflammatory disease, but where does the inflammation come from?

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Author’s response to reviews: see over
Reviewer's report 1
Title: So depression is an inflammatory disease, but where does the inflammation come from?
Version: 1 Date: 3 March 2013
Reviewer: Carmine M Pariante

Reviewer's report:
I enjoy reading this thorough and at times innovative reviews. I have a few suggestions.

Major compulsory revisions:
The literature on this topic, including this review, seems to project a picture where only depression is associated with inflammation. However there is ample evidence that similar, or even higher, levels of inflammation are present in psychosis and schizophrenia, at least in the acute phases. The authors should add a subtitle called "Inflammation across psychiatric disorders" or something similar, where this issue is described and discussed. I suspect that many of the mechanisms described here could also apply to psychosis.

As requested by this referee we have added a new section on Inflammation and immune activation across major psychiatric disorders. It reads:

12. Inflammation and immune activation across major psychiatric disorders.

There is also evidence that many other major psychiatric disorders are accompanied by activation of inflammatory and cell-medaited immune pathways, e.g. mania, schizophrenia, post-traumatic stress disorder (PTSD). The first papers showing inflammation (increased levels of pronflammotory cytokines, such as IL-6 and acute phase proteins; [229, 230] and immune activation (increased levels of sIL-2Rs levels [229, 231] in acute and euthymic manic patients were published in the 1990s. A recent metaanalysis confirmed that mania and bipolar disorder are accompanied by activation of
inflammatory, cell-mediated and negative immunoregulatory cytokines [232]. Based on the first results obtained in schizophrenia, Smith and Maes in 1995 launched the monocyte-T lymphocyte theory of schizophrenia, which considered that activation of immuno-inflammatory processes may explain the neurodevelopmental pathology related to gestational infections. Results of recent meta-analyses showed that schizophrenia is accompanied by activation of inflammatory and cell mediated pathways [233]. PTSD patients also show higher levels of proinflammatory cytokines including IL-1 [234], IL-6 [235, 236] and TNFα [237].

It is evident that the sources of inflammation and immune activation, which play a role in depression, may contribute to the inflammatory burden in patients with mania. Schizophrenia is also associated with some but not all sources of inflammation and immune activation that play a role in depression. For example, a recent review showed that stress and trauma (first and second hits), nutritional factors and vitamin D may play a role in schizophrenia [238]. The strong association between schizophrenia and smoking [239], obesity [240], some atopic disorders [241], sleep disorders [242] and poor periodontal and oral health [243, 244] may further contribute to the inflammatory burden in schizophrenia patients. Other factors, however, may be more specific to mood disorders than to schizophrenia. For example, there is no significant association between schizophrenia and increased bacterial translocation [Maes et al., personal data]. There is strong comorbidity between depression and PTSD and patients with this comorbidity show increased inflammatory responses as compared with those with PTSD or depression alone [235, 236]. The severity of stress and trauma [235], and the association between PTSD and smoking [245], obesity/metabolic syndrome [246], oral health status [247], and sleep disorders [248] may further aggravate the activation of immuno-inflammatory pathways in PTSD or comorbid PTSD and depression.

Likewise, at the end of the Abstract we have added a new sentence:

Some, but not all of the abovementioned sources of inflammation may play a role in other psychiatric disorders, such as mania, schizophrenia and post-traumatic stress disorder.
Minor revision:
I know that it is tricky for a referee to suggest authors to comment on their own papers, but may I invite the authors in this case to consider including in the review the paper by Cattaneo et al., Neuropsychopharmacology. 2013 Feb;38(3):377-85. This paper is the first gene-expression paper on depression and it specifically deals with many topics raised by the reviews, including the link between inflammation and lack of response and the effects of antidepressants on immune function.

A section on gene expression has been added as requested:

They additionally alter leucocyte mRNA gene expression of some immune markers. Galecki (2012) first documented altered expression of mRNA coding for cyclooxygenase-2, myeloperoxidase, inducible nitric oxide synthase and secretory phospholipase A2 type IIA in people with recurrent depressive disorder [12]. Additionally, inflammatory gene expression secondary to antidepressant therapy has been examined, with lowered levels of IL-1β and macrophage inhibiting factor seen after treatment, changes which were not associated with treatment response. However lowering of IL-6 levels was associated with antidepressant response [13].

Quality of written English: Acceptable

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

Declaration of competing interests:
I declare that I have no competing interest
Reviewer's report 2
Title: So depression is an inflammatory disease, but where does the inflammation come from?
Version: 1 Date: 20 March 2013

Reviewer: Juan C Leza
Reviewer's report:
Interesting review about one of the hot topics in translational psychiatry. The senior authors are recognized scientists in the topic.

General: too much information about inflammatory basis of diet, excercise, smoking... and les about the link between these and depression. I would suggest tuning down generalized aspects on these topic (why not age?) and more on relationships between depression in humans with these other pathologies or status os depressive behaviors in animal models. Similarly, too much is known about cytokines, that is ok, but probably adding more information about other mediators of inflammation (prostaglandins, transcription factors....) will increase impact of the review.

We have not addressed age, as there is no linear link between age and depression risk, in particular, depression peaks in middle age, and drops in the elderly, and there is no clear and linear link to inflammation in this regard.

We have chosen to provide some detail about the inflammatory basis of diet, exercise, smoking, as these are novel hypotheses, not well documented in the extant literature, and are the focus of this paper.

We have added more information on transcriptional factors and other inflammatory mediators and added one reference (i.e. Kubera et al., 2011):
Moreover, the onset of depressive-like behaviors following external stressors (e.g. learned helplessness and chronic mild stress) is associated with activated transcriptional factors (e.g. nuclear factor κB), activation of other inflammatory pathways (e.g. cyclooxygenase 2 and prostaglandin production), and increased apoptosis (e.g. lowered levels of Bcl-2 and Bcl-2-associated athanogene 1) [24].

Also, commentaries about the breaking in the balance between proinflammatory and anti-inflammatory equilibrium are needed.

There is no evidence that there is “a breaking in the balance between proinflammatory and anti-inflammatory equilibrium” in depression. As stated in the first sentence, depression is accompanied by activation of immuno-inflammatory pathways and activation of negative immuno-regulatory pathways, i.e. activation of the CIRS (HPA-axis, lower tryptophan, increased TRYCATs, increased sIL-2R, PGE2, etc) which tends to downregulate the primary immune activation. However, the equilibrium between both factors certainly determines the detrimental effects of the immuno-inflammatory pathways. Therefore, we have added the following sentence:

Any processes that activate chronic inflammatory and cell-mediated processes without a concomitant activation of the CIRS may further aggravate the detrimental effects of activated immuno-inflammatory pathways.

Please, revise the specificity of each reference, i.e, the first one Maes, 1995 is a really important reference, somehow seminal in the topic, but there is no reference in this work about antiinflamamtory pathways, as stated in the first sentence of the ms.

The Maes (1995) paper described the negative immunosuppressive pathways in depression, e.g. HPA-axis, lowered tryptophan and DPP IV, increased PGE2, etc. (see pages 24-25). Nevertheless it is correct that the term “CIRS” was first applied by Maes et al. (2012). Therefore we have added the 2012 reference (reference 209 □ 2).
There is now an extensive body of data showing that depression is associated with both a chronic low-grade inflammatory response, activation of cell-mediated immunity and activation of the compensatory anti-inflammatory reflex system (CIRS), characterized by negative immunoregulatory processes [1, 2].

In general, various of the inflammatory conditions presented in the review have been "related" with depression, but most of these relations are not based in strong statistical analysis taking into account, i.e. possible confounders, so clear statement should be done when strong, sound works are cited. Other cases should be presented as coexisting questions, not totally proved cause-effect connexion.

We completely agree with this comment. As a consequence, we have added:

The aim of this review was, therefore, to collate extant data on the role of inflammation and O&NS as possible mediators of known environmental risk factors in depression, and to discuss potential implications of these findings, acknowledging the exploratory nature of these relationships.

Of special importance the subheading 7, about gut permeability and the microbiome.

This section started and starts with a sentence suggesting that this a putative new pathway, i.e. “A new potential pathway mediating depression pathogenesis is increased immune responses against lipopolysaccharides (LPS) of different commensal, gram negative bacteria”.

Meanwhile new translational data have been published and these are now added to the text:
Recently, translational data further underscore the importance of increased gut permeability in mediating stress-related behavioural responses including depression [156]. Thus, stress activates the TLR-IV pathway and associated inflammatory and O&NS pathways including central neuroinflammation. These effects are at least in part mediated by stress-induced intestinal permeability and bacterial translocation [156].

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests