Author's response to reviews

Title: Plasma brain-derived neurotrophic factor levels, learning capacity and cognition in patients with first episode psychosis

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Version: 2 Date: 8 January 2013

Author's response to reviews: see over
Dear Professor Majithia,

I am writing to you about the manuscript “Plasma brain-derived neurotrophic factor levels, learning capacity and cognition in patients with first episode psychosis” submitted to your journal for consideration as an original article.

We would like to thank you and the reviewers for their review of this manuscript, together with their comments and suggestions for its improvement. Please find below our detailed responses to each comment.

**Reviewer 1: Marie-Cecile BRALET**

The reviewer reported that the manuscript is clear and well-constructed, the limits are well described and that we gave some interesting hypothesis. She did not suggest any changes for the manuscript.

We are very grateful for the comments of this reviewer.

**Reviewer 2: Marcella Bellani** recommended two minor essential revisions:

1. **Better explanation of the blood collection methodology:**
   As the reviewer said, the methodology for blood collection was the same as in the article by Palomino et al., 2006, where blood collections were made four times in the first year. However, in the present study, we were only interested in the follow-up blood collection at 6 months, which was at the same time as the cognition evaluations. We decided to omit the other blood collection points to ensure the aims of the study were clear.

   We have added the following sentence in the “Blood collection” subsection of the Methods section:
   
   Plasma was prepared by centrifugation at 300 x g for 10 min and the resulting supernatant was removed and then frozen at -80 °C, as described previously [20].

2. **The discussion should be improved:**
   We have made several modifications to the text in the discussion to make it more comprehensive and to better explain the links between BDNF and cognition in patients with first episode psychosis.

   - **The possible role of biological marker of cognition is not sustained completely by results.**
     We have amended the text in the first two paragraphs of the discussion to explain why our results suggest that BDNF could be used as a biological marker of cognition:
A possible explanation for our findings is that healthy volunteers and patients with higher BDNF levels may have sufficient cognitive reserve to compensate for other possible deficits present in patients with low BDNF levels; i.e., the brains of individuals with higher BDNF have a greater resistance to damage. Higher cognitive reserve has been shown to have a protective effect against dementia, schizophrenia and depression [35, 36]. In the New Zealand Dunedin cohort, lower IQ was found to be a risk factor for the development of schizophrenia spectrum disorders [37]. In our sample, the healthy volunteer group had a higher IQ than the patient group and performed better in almost all of the cognitive tests. In both groups, IQ was positively associated with abstract thinking and processing speed.

Our results that patients with higher BDNF levels have better cognitive performance suggest that plasma BDNF levels could be used as a biological marker of cognition in patients with a first psychotic episode. Cognitive performance is an important clinical variable associated with prognosis in severe mental illness [3]. The nature of the relationship is unclear but, based on previous studies [38], we can hypothesize that lower BDNF functioning in the brain (e.g. during an acute episode of psychosis) can lead to cognitive impairment and could contribute towards the differences in cognition observed between different patients and between patients and healthy subjects. Other investigations have found positive relationships between BDNF levels and cognition in patients with diseases that result in cognitive impairment. One study found an association between maintained increases in serum BDNF levels and improved cognition in patients with schizophrenia, and suggested that serum BDNF levels could be used as a biological marker of cognitive improvement [38]. Another study found a positive correlation between serum BDNF levels and hippocampal volumes, which could explain the relationship between the BDNF and memory [8].

- The effect of medications has been discussed but not completely linked to the main idea of the discussion

We have amended the discussion to better link the effects of medication to our observations on BDNF levels and cognition. The relevant paragraph in the discussion now says:

Plasma BDNF levels vary over time in psychosis [20] and schizophrenia [18], as demonstrated in the present study, where mean BDNF levels were lower during the acute first episode of psychosis and increased to normal levels (comparable to those in healthy subjects) after 6 months of naturalistic treatment when patients were in remission. Plasma BDNF levels have a significant negative correlation with positive symptoms at psychosis onset [41]. A recent study found that after 6 weeks of antipsychotic treatment, BDNF levels did not increase in patients treated with risperidone, haloperidol or olanzapine, but increased significantly in the subgroup treated with olanzapine [7]. Another study found a significant increase plasma BDNF levels during the first 6 months of
follow-up after olanzapine treatment [15]. Recently, low serum levels of BDNF were found to be a state marker of depression that normalise during remission [42]. Our finding of a positive association between BDNF levels and cognition in FEP patients who have recovered from an acute episode of psychosis may be partly due to the effects of pharmacotherapy on BDNF levels in these patients.

Grammar and spelling mistakes in the manuscript have been corrected.

I hope that we have adequately addressed the reviewers’ comments and that the manuscript is now acceptable for publication in *BMC Psychiatry*. All authors have approved the changes to the manuscript.

Thank you again for your time, efforts and consideration of our work.

Regards

Sonia Ruiz de Azúa

Ana González-Pinto