Barcelona, August 5, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4372-review.doc).

Title: Brain-derived neurotrophic factor as a potential biomarker of cognitive recovery in schizophrenia

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated (tittle, key words, 100 references, etc.)

2 Revision has been made according to the suggestions of the Reviewers.

Reviewer # 1

(1) Thank you for noting us the unfortunate typing mistakes in our previous manuscript. We tried to mend all of them.

(2) We entirely agree on this point with the reviewer, so we have included two paragraphs in the Introduction section to better clarify which biomarkers have been described in the scientific literature, and to relate them with the current increasing interest in the study of BDNF as potential biomarker adding more references to the previous text. We have implemented in the manuscript the following text:

> *One of the most important challenges of research in schizophrenia is to establish biological markers which can predict clinical outcome and to identify clinical stages in these patients. Molecular genetics, analysis of serum and cerebrospinal fluid (CSF), structural and functional neuroimaging have provided an attractive field of research for biomarkers [1]. For many reasons, such as small effect sizes and individual rarity, gene studies have traditionally shown that genetic markers are not suitable as diagnostic markers [2]. In this line, the study of CSF parameters has yielded a number of interesting candidate biomarkers, but this research is still in a recent onset [3]. On the other hand, despite of a particular promising research on neuroimaging, available techniques evaluating structural and functional brain changes make them actually unsuitable as current biomarkers in schizophrenia [4]. Further research is needed in biomarker research in schizophrenia. However, evidence suggests the relevance of BDNF in the pathophysiology of schizophrenia and the potential utility of BDNF as a suitable biomarker for diagnostic and prognostic purposes, in comparison with other potential biomarkers [5].*

(3-4) In pages 8 and 9, we have added information not only about dopaminergic but also glutamatergic and serotoninergic systems as suggested. Additionally, the role of BDNF as a potential biomarker for schizophrenia and cognition is discussed at the discussion section.

> *It has been confirmed that BDNF plays a crucial role as a regulator of synaptic transmission and seems to be related with dysfunctions in the principal neurotransmitter systems such as the dopaminergic, glutamatergic and serotonergic neurotransmitter systems. Particularly, BDNF has been associated with disruptions in brain structure, neurodevelopmental process and some studies suggest that BDNF levels are altered in schizophrenia patients.*

(5-6) We strongly agree with the reviewer about the lack of suitability of the Table 1 for the current review. In the revised version we have just removed it and a new and more explicative figure has been added instead. Thus, Figure 1 shows now the interaction between BDNF and dopaminergic, glutamatergic and serotonergic systems, and its relationship with findings in recent reviewed studies in schizophrenia.

Reviewer # 2

(1-2) We have tried to specify more clearly those facts that could be relevant for the understanding of the review, especially when reporting those studies relating cognitive activity and BDNF levels and treatments. For instance, when describing the unique study about cognitive training and BDNF we have added data from BDNF levels, cognitive improvement in terms of effect sizes, etc:

> *In sum, in a repeated-measures analyses of variance approach, subjects following cognitive training showed a statistically significant gain in global cognition (about 0.36 standard deviations) from baseline to endpoint, compared with subjects in the control group who showed no change (0.01 standard deviation). After 10 weeks, subjects following the neurocognitive training were able to increase their mean serum BDNF levels (Mean: 25.27; Standard deviation: 10.34) to the same level than healthy controls (Mean: 31.30; Standard deviation 8.95), whereas the control group showed no change. After the treatment, authors calculated standardized mean difference (Cohen's d) in BDNF level between the control group and the therapeutic group and they showed to find a medium effect size of 0.67.*

(3) We have tried not to use expressions that could be potentially unethical. Always we have used the term schizophrenia for describing the condition or when we wanted to point the persons with the condition we have used the term persons diagnosed of schizophrenia.

3 References and typesetting were corrected

Thank you again for revising and publishing our manuscript in the *World Journal of Psychiatry*.

Sincerely yours,

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