Author's response to reviews

Title: Neurodevelopmental and environmental hypotheses of negative symptoms of schizophrenia

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Author's response to reviews: see over
Dear Editor,

I carefully revised the manuscript, following the referees’ comments. You will find below the response to each of the referees’ points. I hope that the revised MS will satisfy you and the referees, and be of interest for the readers of the journal.

Best Regards,

Frederic Limosin

Answers to the referees

Referee 1.

1. The manuscript represents potentially interesting review and many of its parts are developed very well. But on the other hand some parts of the manuscript regarding some important topics are significantly underestimated and very short. For example part of the text about psychosocial factors and some others.

Answer: We thank the referee for this comment. Following the referee’s suggestion, we enriched the "2.1. Psychological factors" section, page 5, as follows:

- "The psychological effect of an urban environment may also interact with levels of reality distortion and depressive symptoms in people experiencing first-episode psychosis and may affect the syndromal presentation of psychotic disorders [4]. For individuals suffering from psychosis, spending time in an urban environment makes them think more negatively about other people and increases their paranoia [5]."
- "The role of disturbances in early parent/child relationships, whether it be early separation, a lack of emotional support and physical contact, or abuse, has also been invoked in the later development of the disorder. Zugno et al. showed that rats subjected to maternal deprivation had an increased risk for schizophrenia-like behavior and cholinergic alteration [6]."


2. Also very important explanations regarding a basic concept of the manuscript are missing, for example basic definitions of negative symptoms compared to positive ones and origin of this definition in the work of Hughlings Jackson, who established these terms would be very helpful to understand the topic in sufficient details.

Answer: Following the referee’s comment, we added the definition of "negative symptoms" and the origin of this definition according to Hughlings Jackson in the "3. The neurodevelopmental hypothesis applied to negative symptoms" section, pages 7-8:

"The negative symptoms of schizophrenia include avolition, alogia, apathy and impaired or nonexistent social functioning. The negative symptoms are so called because they are an absence as much as a presence: inexpressive faces, monotone and monosyllabic speech, few gestures, seeming lack of interest in the world and other people, inability to feel pleasure or act spontaneously. Origin of the definition of the negative symptoms can be found in the work of John Hughlings Jackson [21]. From 1874 to 1876, Hughlings Jackson adapted Herbert Spencer's evolutionary theory to neurological disease and addressed the relationship between the centres in his hierarchy. Following Spencer, Hughlings Jackson concluded that the highest nervous centres evolved out of the lower. Patients with diseases of the highest centres develop two types of symptoms, negative symptoms due to the loss of higher centres and positive symptoms due to the emergence of lower centres. Positive symptoms are simpler and less differentiated than the negative symptoms which they replace [21]."

We thank the referee for this comment. Following the referee's suggestion, we enriched the conclusion section as follows:

"Additionally, given the modest impact of drug treatments for negative symptoms to date [51], psychological factors associated with the development of these symptoms are of considerable importance and may be viable treatment targets [52]."


2. “...and dysfunction corticostriatal glutamatergic transmission” should be “...dysfunction of corticostriatal...”

Answer: We thank the referee for this comment. Following this comment, we modified the text in the abstract as suggested.

3. Major Compulsory Revisions. The major limitation of this analysis is the treatment of negative symptoms as a unitary construct. This is at odds with current evidence that suggests the presence of two distinct components comprising experiential and expressive factors (Kring et al. 2013 Am J Psychiatry 170:2). Furthermore, the distinction between primary versus secondary negative symptoms is left unaddressed and no attention is paid to the contentious issue of whether a distinction should be drawn between prominent and predominant negative symptom profiles (Marder et al. 2013 Schizophrenia Research 150 328–333). There is a distinct possibility, as yet largely unaddressed, that the relative lack of impact of pharmacological interventions to date is due to presence of negative symptom subtypes with differing underlying causal mechanisms. A clearer analysis of these issues will help make this discussion paper make a greater contribution to current debates.

Answer: Following the referee's suggestion, we enriched the "3. The neurodevelopmental hypothesis applied to negative symptoms" section, page 8, as follows:

"Furthermore, recent data suggest that negative symptoms should not be considered only as a unitary construct, and that measure of these symptoms should distinctly assess motivation, pleasure, and emotion expression factors [22]. Moreover, particular attention should be paid to the distinction between primary versus secondary negative symptoms and between prominent and predominant negative symptom profiles [23]."


**Referee 3.**

We thank the referee for his positive comments on our work.