Reviewer's report

Title: Neurodevelopmental and environmental hypotheses of negative symptoms of schizophrenia

Version: 2
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Reviewer: Hamish McLeod

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This is a discussion paper examining some possible precursors and causes of negative symptoms in people with schizophrenia spectrum disorders. Emphasis is placed on the neurobiological processes that may lead to alterations in brain structure and/or functioning (e.g. stress mediated excess synaptic pruning, toxic effects of substance use). The description of studies using animal models provides an overview of the ways that experimental laboratory based work has attempted to gain traction on the mechanisms by which in utero and post-natal stressors may influence the development of negative symptom analogues (e.g. social functioning impairments, problems with sensory gating). However, no data are presented and it is not clear whether the papers selected for analysis were extracted in a systematic manner.

1. Discretionary Revisions
1.1 The major aim of the paper appears to be to elucidate biological mechanisms of negative symptom development. However, this ignores the accumulating evidence from both experimental studies and RCTs that psychological factors are of considerable importance and may be viable treatment targets (e.g. Klingberg et al (2011) Schizophrenia Bulletin vol. 37 suppl. 2 pp. S98–S110, doi:10.1093/schbul/sbr073). Acknowledgement of the potential benefit of developing multimodal therapies may stimulate a more productive debate about the ways that negative symptoms can be modeled and treated. This is particularly salient for practicing clinicians given the considerable challenges in translating findings from animal research into human clinical phenomena (O’Tuathaigh et al. (2013) Cell Tissue Res, 354:247–257 DOI 10.1007/s00441-013-1652-4) and given the modest impact of drug treatments for negative symptoms to date (Davis, M.C., et al., (2013) Psychopharmacology of the negative symptoms: Current status and prospects for progress. European Neuropsychopharmacology http://dx.doi.org/10.1016/j.euroneuro.2013.10.010).

2. Minor Essential Revisions
2.1 Abstract.
“…and dysfunction corticostriatal glutamatergic transmission” should be “…dysfunction of corticostriatal…”

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.

Level of interest: An article of limited interest

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