**Schizophrenia Research**

*Title:* Inflammatory markers are associated with general cognitive abilities in severe mental disorders and healthy controls by Hope et al.

*Overall:* the authors investigate the relationship between inflammatory markers and cognition in individuals with schizophrenia and bipolar disorder. The study design is novel and the findings compelling and worth being published in this journal. Major revisions are however required.

*Introduction:* I would encourage the authors to provide their theory or working hypothesis in relation to the link between inflammation and cognition in mental health. Also examples of which cells (e.g. T cells, leukocites, cytokines) they think they are involved in inflammatory processes associated with bipolar/schizophrenia and why. Additional information on cognitive functioning in bipolar and schizophrenia and reference to the current literature suggesting that cognitive deficits are persistent across acute and chronic phases of bipolar disorder would also be helpful.

Also one could briefly discuss the link between mood or affective processing and such mental health disorders. Since the authors decided to include individuals with bipolar disorder and schizophrenia I would highly recommend that they provide a rationale as to why they did so and what their hypotheses would be. Did they expect different results for each population? If so why?

Some mention of pharmacokinetics or fluctuations of inflammatory marker levels would be good since they mention that *serum* was used. Why serum and not plasma for instance? Do the authors think that medication may affect serum markers of inflammation (considering that they should be relatively stable over time)?

At the level of the cognitive measures, the WASI is used to determine premorbid intellectual functioning but is not a measure of cognitive functioning *per se*. I would recommend that the authors define what kind of high-order cognitive function they measured as “cognitive abilities” is a very broad term. Also, since IQ and education have been shown to affect domains such as memory and verbal fluency, it would be wise to address these variables in the introduction.

Also why did the authors include participants aged 18 to 65 knowing that cognitive functioning varies across the lifespan? This is an important aspect to address because some measures of the WASI tap into fluid intelligence while others assess crystallized intelligence. Fluid intelligence changes over time, while crystallized intelligence is a relatively stable measure. A correlation between such heterogeneous measures of functioning and inflammation may have different meanings. The authors should discuss this both in the introduction and in the discussion.

*Methods and results:* I wonder if the authors considered entering an estimate of verbal abilities (WRAT score if available) in their analyses. If not this could be mentioned in the conclusions as a possible confounding effect. Further, could the authors define whether they used the WASI score only or also subscores of the WASI? If not why? Are there scores of clinical questionnaires that they could report in table 1?

*Discussion:* I would recommend that the authors mention the choice of cognitive tool as one of the limitations of this study. Other measures such as the BAC-S or BAC-A could have provided a better and relatively fast measure of cognitive functioning. Also it would be helpful to have some background information related to sTNF-R1 and IL-1RA and brain functioning. Possible mechanisms underlying the effects of these markers on the brain could be useful. Also how do the authors view the differences between bipolar disorder and schizophrenia (are they on a continuum, separate diseases etc.)? The authors could mention the advantages of examining psychiatric disease from a multidimensional level (biological/clinical) and how this relatives to the current RDoC model? were the authors surprised to find different markers associated with different disorders?

A mention of the possible role of the HPA axis response and genetics in terms of polymorphism, expression levels of specific genes etc. would be helpful. Another important concept that needs to be addressed is whether the authors expect these findings to be stable over time?