**Relational memory and hippocampal function in psychotic bipolar disorder by Avery et al.**

Avery et al.’s brain imaging study aims to determine whether relational memory deficits and abnormalities in hippocampal structure/activation, which are characteristic of schizophrenia, are also present in other psychotic illnesses, such as the bipolar disorder I. It is an exciting research question and Avery et al. address it by comparing the neurocognitive functioning of BDI patients to that of healthy controls. The authors did not find any differences between the two groups in either relational memory performance, hippocampal volume or hippocampal activation during a recognition memory task. Avery et al. interpret these findings by hypothesizing that relational memory deficits and hippocampal abnormalities are specific to schizophrenia. Although Avery et al.’s paper needs major revision, in particular in the methodology and conclusions sections (see below), their findings deserve to be published as they will assist researchers in finding a neurocognitive marker of bipolar disorder.

**Methods**

The section “*Participants*” should include age (M, SD) and gender. The section should refer to Table 1 for a more exhaustive description of the population. Table 1 should also include duration of illness or time since the last psychotic episode and medications.

Lines 43 to 51 at page 4 describe the participant’s diagnosis but the author does not provide the official SCID diagnosis. Further, the author should mention in Methods that 5 participants were euthymic (this piece of information is mentioned in the conclusions but does not appear to be mentioned in the methodology).

Table 1 shows that there are significant differences in Education and verbal IQ between the BD and healthy controls but the author does not discusses these differences in either the methodology or the conclusions.

*MRI/fMRI ACQUISITION (page 7)*

Please include description of the acquisition of structural brain images

Please replace milliseconds with ms, seconds with s, minute with min

Line 20: replace scans with tasks

Line 22: “each series” does the author mean run?

Line 22: remaining 4 min and 30 s (not 4.5 minutes)

Line 24: 130 functional brain images (instead of 130 BOLD functional brain images)

Line 26: Echo time = TE, Repetition time = TR

*Data analysis (Page 7)*

Please mention which statistical software was used

Accuracy: is this the percentage of correct responses? If so please clarify or mention it consistently in this section, in captions and tables

Did the author use a multiple comparison correction? What kind and what is the reference p-value?

Post-hoc one way ANOVA does not exist. The author should rather say “When a significant omnibus *F* statistic was observed, Bonferroni? *post hoc* comparisons were computed”

Post-hoc is always in italics

Since the authors conducted correlational analyses they should describe these in the data analyses section and mention if they are talking about Spearman/Pearson coefficient of correlation or rather a linear regression

Please mention the statistical threshold of significance (commonly *p* < .05)

The authors mention that “Diagnosis” is the between-subject factor, wouldn’t it be more appropriate to call it “Group” since the authors compares a clinical population to healthy controls?

**fMRI data Page 8**

Page 9: what’s the threshold p-value after correcting for multiple comparisons?

**Results page 9**

This section is extremely hard to read and understand because of the large number of irrelevant results. *Behavioural data:* Given the research question of this paper, I would recommend that the authors present their behavioural findings (mean reaction times and accuracy %, F, p-values for main effects) in a table. They could then discuss significant interactions/comparisons between healthy and clinical group in the result section.

Page 9, Line 59: is p =.053 significant? (unclear what the initial p-value was…)

Page 10: If the statistical threshold is .05 and results are not significant, p-values can be reported as p>.05. Hence, line 18 should be p>.05 instead p=.25. Please correct all the other non-significant values.

Page 10: Line 41: It would be best if the authors explained first why the author did the correlations (no explanation before Line 41). Also please mention r =, p = and possibly R2 as well

Page 10: Line 55: There is no need to include the first sentence “to investigate….whole brain” since it’s part of the authors’ hypotheses and has already been mentioned before. The authors could start with “In controls….”. Also since these results are presented in Table 2 there should be a reference to Table 2.

Page 11, line 4-10: did the authors consider changing the statistical threshold of activation to be able to compare activation between the two populations? Wouldn’t this have been more useful than comparing activation (in healthy controls) to no activation (in the clinical population)?

Page 11 line 12” please clarify what the author mean by “altered neural activity”

Page 11, line 35-36: please reformulate Sentence “bipolar patients did not show this pattern…difference”. Unclear what the author wants to say. Unclear if this result is of any relevance for this paper. If so, it should be discussed in the discussion

**Discussion**

Overall: I think that the authors should attempt to re-write the discussion and attempt a more critical evaluation of how 1) schizophrenia and bipolar disorder may differ in terms of neurocognitive functioning 2) the implications of these findings for neuropsychology/therapy, 3) explain whether there may be genetic/biological explanations that may help differentiate the two populations or that affect fMRI results? 3) discuss whether there are differences in age/gender/duration of illness similar between the current and previous studies in schizophrenia patients that may explain the different results? 4) are there other cognitive mechanisms that may explain the absence of memory deficits in this BD population?

Page 12: Line 47: What does the author mean by “cellular abnormalities”

Page 12 Line 47: Please replace small volumes with “brain volumes” or a more suitable formulation

Page 12 Line 47: “disrupted activation”: the author should define if they mean a reduction/elevation

Page 12 Line 48: differences…does the author mean reduction?

Page 12, line 10: How does the author explain the differences in cognitive performance between healthy controls and the clinical population? What about the differences in education and verbal IQ presented in Table1?

Page 12, line 53: Could the authors explain what they mean by “general affective and cognitive dysfunction”. Please provide references

Page 12: Line 61 (page 13) to Line 9: sentence is unclear, author should make explain that paired associate learning is a measure of relational memory. Also do the authors refer to the paired associate learning task of the WAIS? How old were the patients?

Page 12-13: Line 22 to Line 26: This paragraph should come first as it would clarify what the author wants to say in this paragraph

Page 13: Line 42 at page 13: the author should mention the precise diagnosis of patients in the participant description and not (only) in limitations

Page 13, Line 56: “the task proved very difficult in healthy controls, making it impossible to use in psychotic patients”, is the author referring to data collected in the current study or in Zalesak et al.? Please clarify why it was “difficult/impossible”.

Line 57: I would replace “matched” with “comparable with…” since the author here means that there were no significant differences between the two populations.

Page 14: line 9: please replace “the one” with “the finding”

Page 14 Line 9/10 add reference for the finding in chronic schizophrenia patients after the word patient

Page 14 Line 15: replace cellular with cell and please clarify if in vivo/in vitro…

Page 14 Line 18: Since the authors did not compare a population with schizophrenia to bipolar patients they cannot really claim that their data support functional separation of the two disorders. They may reformulate this sentence by talking of characterization of the neurocognitive functioning of a psychotic bipolar population.

Also in terms of consistency” the author speaks of psychotic bipolar in the conclusions but refers to Bipolar type I in the methodology, please adjust.

Figure 1: please add (% of correct answers) after accuracy and (ms) after response times. Please do it overall, also in graphics

Figure 2/3: The authors should explain that the yellow dots refer to task-specific regions of activation or contrasts between clinical and healthy controls

Table 2: The author should add a sentence in the column “Bipolar group” to clarify that there were no regions of activation for this population for Transitive Inference

Figure 3: Unclear what Y=-15 refers to