Reviewer's report

Title: Delayed circadian phase is linked to glutamatergic functions in young people with affective disorders: A proton magnetic resonance spectroscopy study

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Reviewer: Fei Du

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Major Comments

In this manuscript, the goal of the authors was to find a biomarker that reflects the relationship between circadian rhythm, neuronal integrity, oxidative stress and neuronal-glial dysfunction through measuring NAA, GSH and Glu+Gln (Glx) with a 1H-MRS approach. No significant difference was observed among demography, MRS measurements and depressive symptoms between unipolar and bipolar subjects. The authors found that a strong correlation exists between later sleep midpoints and levels of Glx in the ACC. It is an interesting study, however, there are a few flaws in this manuscript. These need be considered and reconciled.

1. Medication effect. The sample size is quite a good number, 53 subjects participated in this study. However, the treatment history is complicated by multiple medications. Therefore, the authors should have more discussion about medication effects and do more data processing to check whether some kind of relationship exists between medication effects and MRS measurements.

2. Bipolar vs. unipolar. 53 subjects were recruited for this study, 32 of which were classified as unipolar and 21 as bipolar. The authors did group-group difference analysis and found no significant difference among demography, MRS measurements and depressive symptoms. The authors should provide more interpretation about why differences were not observed and give some possible explanations.

3. It is not clear how to do “Sleep-wake ambulatory assessment”, especially in Line 116-118’s description. How was sleeping monitored? Is each day of the month? And when (in the one month window) was 1H-MR performed? Did every subject follow the same procedures? This is particularly important for the female subjects considering females’ menstrual cycle.

4. The most interesting findings are the association between circadian and Glx in the ACC. The authors gave some interpretation of how sleep is involved in brain circuitry (including ACC) in Line 194-198, but they should give a clearer discussion of how Glx and ACC regulate sleep.

5. Limitations. More should be mentioned about how MRS measurements were
acquired at different stages of brain sleep-wake conditions and menstrual cycles for female subjects; 2) The method of measuring GSH by PRESS 35ms echo time is questionable and cannot be fully separated from Glu/Gln’s contribution.

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 have no competing interests