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: JAN scott

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Delayed circadian phase and glutamatergic functions in young people with affective disorders…Naismith et al.

Review by Jan Scott

Declarations- I have undertaken research projects and written papers with the group submitting this paper. I have an interest in young people with emerging bipolar disorders and have undertaken clinical and actigraphy studies of sleep. I have only a general knowledge of research on neuronal integrity, oxidative stress etc.

Review:

This is an admirably short paper reporting on the associations between a selected marker of circadian functioning/proxy marker of melatonin onset (sleep midpoint) and various neuronal/oxidative parameters in 53 individuals with affective disorders (60% UP; 71% female).

An interesting and significant correlation is reported between sleep midpoint and ACC Glx. This finding was re-analysed when controlling (separately) for age and then severity of depression.

I have some comments and questions for the authors- BUT some of the issues may be difficult to provide detailed answers for if there is a word limit for this paper (I was not informed if this was a ‘short report’ or if a longer paper is acceptable).

Comments-

1. The introduction is too brief, and the 2nd paragraph is too general. Individuals with limited knowledge of NAA, GSH, Glx will be left behind. I would suggest a some redrafting of th e2nd paragraph to give

(a) a better insight into what is related to eg development (would young adults show relationships between sleep midpoint and neurobiological change even in the absence of mental disorders? Are abnormalities being investigated disorder specific?)

(b) a set of hypotheses that give some insights into how eg circadian dysregulation or delayed melatonin onset may relate to the selected neurobiological markers….or a clear statement that this is a proof or principle
study and you are running a range of statistical tests (given this is the first study combining these measures I do not think the latter affects a decision on publication)

2. Methods-

a) Sample- the sample is described as a tertiary referral population, the reference provided (#23) is about primary care. Given that most of those interested in this paper are not likely to be health service research experts, it may makes sense to rewrite this bit… the main issue is whether this is a convenience/consecutive sample, how did you arrive at the sample size and were cases selected in any way on the basis of their history of affective disorder and etc- additional information to enable readers to understand the sample might include duration of illness or mean number of prior depressive or affective episodes

b) L103-113: if the sample comprises both UP and BD, were any measure of manic symptoms used. Also, overall how many individuals would currently be regarded as in a depressive episode or in any other mood episode? Were alcohol or substance use comorbidities excluded?

c) Did the authors examine any other correlations between sleep parameters and neurobiological parameters? I think that the novelty of the study would allow some additional exploration of other variables…so it would be quite acceptable to have a single line in the results to state that other tests were not significant.

3. In the results section, the significant correlation between ACC Glx and sleep midpoints was tested in separate partial correlations using severity and age- why not run one partial correlation with both variables… were these confounders selected because they have previously been shown to have any association? Given that some sleep abnormalities may be more common in males than females or in those with longer duration of illness or in BD rather than UP (??mood stabilizers or not etc)…is there a case for examining additional potential confounders? I appreciate the authors may wish to avoid multiple testing, but there needs to be clarity about why these two variables were seen as the most relevant.

4. The authors are clearly aware of limitations to the study- although I think two things may need to be made more of –

a) The sample size means that there is probably a lack of statistical power eg several separate rather than combined analyses were used.

b) The lack of a control group is commented on – BUT it would help if a further sentence were added about what we know about the associations of sleep midpoint and ACC Glx with age or gender in controls ie without a control group how certain are the researchers that they are looking at associations that are linked to affective disorder pathway rather than associations that would be seen as normal at this stage of individual development, (or within normal range).

Level of interest: An article whose findings are important to those with closely
related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have undertaken research projects and written papers with the group submitting this paper.