Reviewer’s report

Title: Conditioning cortisol in humans: design and pilot study of a randomized controlled trial

Version: 0 Date: 24 Oct 2018

Reviewer: Urs Nater

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This is an intriguing study, aimed at conditioning of cortisol responses in humans. As such, I can see numerous applications in both basic research (improved understanding of the HPA axis) and clinical research (stress-related conditions known to go together by HPA axis dysregulation). The paper is well-crafted, and the design is logical. The pilot study is of great interest for this endeavor, as it indicates that the study is feasible. I have some questions that the authors could address in a revised version of their manuscript:

1. The background section is brief and succinct, but I think it would be important to outline in a few sentences what the basic and clinical research applications of being able to condition cortisol responses could be. If the authors think that the background section is not an ideal place for that, then this should be picked up in the discussion.

2. Not all readers will be familiar with the substances that are being mentioned in the text (e.g. sumatriptan). This should be briefly explained. More important, though, is that the rationale for selecting hydrocortisone should be mentioned in the background section. It does not necessarily follow from the literature summary that this is the ideal choice.

3. I am not sure whether it is correct to conclude that previous studies have "shown inconsistencies" (page 4) and leave it at that. It becomes clear from the literature summary that these studies had very different aims and rationales. It is thus not necessarily surprising that the findings are "inconsistent". It would probably more to the point if the authors would state that the studies/findings are not comparable.

4. The background section should briefly introduce the reason why the response to stress was examined. It becomes clear later on, but the reader is somewhat surprised at the end of the background section about this part of the design.

5. Since only women are going to be examined, are the authors going to test them in a specific part of the menstrual cycle? If not, why not? Also, are they going to incorporate BMI and/or smoking as covariates?

6. I can see that the authors chose to use a 100mg dose of hydrocortisone, because this dose has been shown to lead to marked cortisol increases in other studies. However, do they need to take into account body weight, and if not, why not? What were the reasons deciding against body weight-adjusted doses?
7. The collection of sAA has its own intricacies. Some argue that salivary flow rate needs to be measured and controlled for (and some argue that this is not necessary). What is the authors´ stance on this question? Also, how exactly is saliva going to be collected (passive drool, chewing on salivettes, etc.)?

8. More details are needed on the assessment of HR and EDA. Are the authors interested in SCR/SCL? Sampling rates?

9. Figure 2 was not incorporated in the review material. I am not sure how long the baseline/accommodation phase is at the beginning. Maybe I overlooked it, but it should be at least 30 minutes.

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