Reviewer's report

Title: The study of visceral hypersensitivity and psychological stress in gastroesophageal reflux disease

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Reviewer: Zhuo Wang

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Major compulsory revisions
1. Only 4 out of 34 patients reported heartburn during acid infusion. It brings up the question whether 5-minute infusion of 0.1 N HCl is a sufficient stimulus. Considering that the aim here is to study neural correlates of visceral hypersensitivity in GERD, using subthreshold stimuli doesn’t seem optimal. The authors need to elucidate their rationale for not using a stronger stimuli (i.e., longer duration) and limitations that may be associated with the current protocol. There seems to be a fair range (up to 20 minutes of infusion) before inducing discomfort in healthy controls (page 14, cited work by Ho et al.)
2. The rationale for excluding some NERD-SI- patients based on their responses to PPI treatment is not clear. Furthermore, since subjects in other groups didn’t go through this 7-day omeprazole treatment, the authors need to discuss this as a possible confounding factor when interpreting the data.
3. A major weakness in the analysis of fMRI data is inadequate secondary analysis to statistically assess between-group differences. The group differences in the time course of brain activation as presented in Table 4 are important. But equally important are group differences in the intensity and extend of regional activation. The authors may want to consider additional analysis addressing these questions.

Minor essential revisions.
1. Acronyms should be spelt out in the Abstract as well as main body on their first appearance. E.g., PFC in the Abstract.
2. There are some corrupted characters in the PDF file. E.g., page 2, Abstract, (P = 0.003 ?0.000).
3. NERD-SI- is misspelled as “NERD-SI” in several places. E.g., page 2, line 3.
4. Redundant sentences “The RE subgroup had the shortest …”, page 2, line 10-14.
5. Should cite work by Dr. Emeran A. Mayer and colleagues using functional brain imaging to study brain substrates of visceral nociception in healthy subjects and IBS patients. (Introduction, page 3, last paragraph.)
7. The use of the term “psychological stress” seems ambiguous. “At the
beginning of the psychological stimulation, the participant was informed by an earphone that some fluid which might cause heartburn would be infused ...”. This appears to this reviewer as a paradigm to investigate pain anticipation, a subject of much brain imaging research by Dr. Mayer and many others.

8. Unit of measurement should be given. E.g., page 11, unit for plasma SP and CRH. Table 4, unit for time.

9. Figure 1: Need to label X- (Time) and Y-axis (V %). The three horizontal arrows and the three vertical line marks for different time point are redundant. Consider removing the arrows. What are the yellow lines for? What are the numbers under the figure, “X: 39” etc.? Should use the same font in all figures.

10. Figure 3: Add graph for the control group response to acid. A – E labeling is not necessary. Use NERD-SI+ and NERD-SI- rather than SI+ and SI- for consistency. Remove minor tick marks in the X-axis. Fix the major tick mark labels for the X-axis. Label X-axis as Time (s). Remove markers from the data lines for clarity (like in Figure 1).

Discretionary revisions

1. The title doesn’t summarize the contents very well. The running title looks better. A better title should make it clear that this is a functional brain imaging study of brain responses to actual and anticipated visceral stimuli in GERD patients.

2. Consider changing “P = 0.000” to “P < 0.001” in text.

3. Consider listing number of female subjects as well. E.g., page 5, “9 RE (7 males, …)” to 9 RE (7 males / 2 females …).

4. Page 13, Discussion: why limit epidemiological data to China? What about for the world population in general?

5. Figure 2: Consider simply using A and B to label upper and lower panel, and labeling individual activation map with group name, e.g. Control, RE, etc.

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 declare that I have no competing interests.