Reviewer's report

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

**Version:** 1  **Date:** 23 December 2010

**Reviewer:** Daniel Sifrim

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Major Compulsory Revisions

1. The aims are not well defined in the context of the study, or of the title. If the aim was to assess differences in cerebral responses to intra-oesophageal acid and psychological stimuli, why was so much time spent assessing the psychological profile of 176 GERD patient? Or was an (undeclared) aim of the study to assess psychological comorbidity in GERD subgroups? If so perhaps it detracts from the study focus to present it in the same paper.

2. The authors should clarify their recruitment and selection process. It is not clear how 39 subjects were chosen for fMRI studies from the 176 recruited. How this group compares with the larger group of 176 patients?

3. I doubt that the NERD- SI- group truly are a GERD subgroup. It is highly likely that they represent a group with functional heartburn. This would be compatible with the well-documented increased psychological comorbidity in this group.

4. The “psychological stimulus” is a weak aspect of the study as presented. The running title and aim of the study imply a desire to test brain responses to stress in GERD. Do the authors have data to show that the stimulus used did indeed alter stress levels? This could easily have been tested using scores (e.g. VAS) during the course of the experiment. Demonstration of higher stress levels after the stimulus is essential to answer the study questions. It is possible that the stimulus used could be testing the subjects’ suggestibility, not response to stress?

5. The focus of the discussion regarding the fMRI studies appears to be misplaced. The authors appear keen to discuss differences between the NERD subgroups, whereas in fact little differences are present. Where differences are found, they do not follow a logical pattern (e.g. in response to acid stimulus the IC region was activated in RE, NERD- SI+ and NERD- SI- groups, but not in the NERD+ group) and no attempt was made to explain these differences. In fact, the study does appear to show differences between controls and GERD (taken as a whole), and this may be something the authors wish to explore further.

6. The discussion states that "cerebral activation response to acid stimulus in RE and NERD+ patients are more intensive than the other subgroups". This is a false statement that is not borne out in the results. The max stimulation seen in the RE group was only significantly more intense than one other group (remarkably it was the NERD+ group).
7. I believe that discussion of visceral hypersensitivity with respect to these results is potentially misleading. The study only supposes (but does not demonstrate) that activation of certain brain regions in the study setting are associated with visceral hypersensitivity. It should also be noted that very few subjects were actually able to perceive the acid stimulus.

8. The fact that acid perfusion provoked a more intense FMRI activation than psychological stimulus does not mean that hypersensitivity to acid is peripheral rather than central!!!

9. I believe it is wrong to suggest that NERD-SI- patients have an "acid sensitive esophagus with visceral hypersensitivity". By definition they do not show acid sensitivity. Their SI is negative.

10. The discussion regarding high CRH levels in NERD-SI- patients does not allow for the fact that they were no higher than in the other GERD subgroups.

11. The authors' concluding sentence is that "these results have important implications for improved understanding of the pathogenesis of NERD-, and for the development of more effective therapeutic approaches". Unfortunately, other than demonstrating higher psychological morbidity in NERD-SI- patients (not surprising, and not the stated aim of the study) the study as reported here does not appear to reveal key differences between the GERD subgroups with regards to fMRI (or at least any differences are not clearly explained or interpreted).

Minor Compulsory Revisions
1. There are many spelling and grammatical errors throughout the manuscript. As it stands the manuscript cannot be published without major editing.
2. The authors’ discussion on strengths and limitations of the study is not included.
3. The NERD-SI- group is now called functional heartburn. The authors should explain why they used different classification
4. Did the NERD patients received earlier PPI during the last month or they were naive to PPI treatment.
5. The authors enrolled only the NERD-SI- responsive to PPI but they did not check the PPI response in the other NERD groups.
6. Was there any difference in the SCL-90 between responders and not responders?

Discretionary Revisions
1. The symptom associated probability (SAP) is a more accurate tool than symptom index (SI) in assessment of symptom-reflux correlation. Perhaps the authors could define their subgroups more accurately using SAP rather than SI (or both).
2. The methodology for acid infusion could be more robust. The same sequence was followed in all cases (which does not control for changes which could conceivably be produced by the subjects’ acclimatization to the study conditions,
changes in stress levels over the course of the study etc.). A variation in sequence order and repetition of infusions would lead to more reliable data.

Recommendation
• This is an interesting study. It requires major revision before acceptance for publication.

Level of interest
• The article has a significant level of interest

Quality of written English
• Not suitable for publication unless extensively edited.

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.

Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

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