Author's response to reviews

Title: Pain and sensory detection threshold following acupuncture are modulated by the association between coping strategy and acupuncture sensation

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Response to Review Comments

First of all, we appreciate the editor and reviewers for the constructive comments and suggestions. These comments and suggestions were very helpful for us to improve our manuscript and we have revised our manuscript accordingly. We believe this revised version has been improved in its quality, which was possible with your constructive comments and thorough review.

Below are point-by-point response to the reviewer’s comments and suggestions.

Reviewer 1:

We would like to thank the reviewer for the constructive, insightful and important comments. The following is our point-by-point response.

1. The manuscript described that subjects were randomized into two groups while Figure 1 indicated that there are 13 subjects not blinded so the data were excluded. It is hard to know whether the integration of the study was maintained.

Response: Thanks for the insightful comment. First of all, the term ‘not blinded’ was not fully illustrated in this manuscript. To make the reason of exclusion clear, we add following sentence to the in the Methods (Physiological and psychological response) and Figure 1 was updated:

“If the subjects in the AC group thought the stimulation intensity was reduced on demand, we considered that the active coping condition was induced successfully regardless of the acupuncture sensations they felt so that only these subjects were included in the analysis. If they did not consider the stimulation intensity was not reduced on demand, we decided that the active coping condition was not induced experimentally (Figure 1, not blinded). In case the subjects did not ask to reduce the intensity, induction of experimental active coping condition could not be determined (Figure 1, not determined blindness).”

Plus, to response the main question, the difference between excluded (n=13) and included/analyzed (n=18) subjects’ data was calculated if there are significant differences. If there are significant difference between those two groups (i.e., excluded and included), that means exclusion from the original pool of AC group can make meaningful influence on the observation. However, in this study, we cannot find any significant differences in their baseline features: “age”, “perception of bodily sensations”, “belief in the effectiveness of acupuncture treatment”, “expected acupuncture sensations”, “perceived acupuncture sensations”, and “previous experience of acupuncture treatment”. Thus, we believe that the exclusion does not make any influence on our observation, and the integration was maintained.

2. The research groups did focus on the level of belief, expectation, toward acupuncture, however, there is no baseline anxiety level assessment as anxiety is another factors
can affect the interpretation of QST.

Response: Besides the factors that we concerned such as the level of belief and expectation toward acupuncture, anxiety and depression can be psychological factors that can influence of the QST measures and its interpretation. In this study, however, was designed and performed in healthy subjects. Thus, subjects with anxiety and depression were excluded from this study. To clarify this exclusion criteria, we revised the previous into following sentence in the Methods (Subjects):

“Subjects who have pain and autonomic/psychological disorder (e.g., depression or anxiety), and have difficulties in sensory perception and recognition were excluded.”

3. There is description about the assessment of individual electrical pain threshold but where was/were testing sites were they consistent for all subjects, at the same location?

Response: Thanks for the considerable comment. Electrical pain threshold was measured at the same location of EA stimulation (ST36 and GB39) across the subjects to set the EA stimulation intensity. After the needles inserted, the individual pain threshold was tested using EA stimulator, then the EA stimuli was applied (95% of the pain threshold) during the EA stimulation session. Thus the testing site was maintained consistent across the subjects. To make this clear, we added sentences in the Methods and Figure legend (Figure 2C):

“To find the individual’s electrical pain threshold, the EA was applied before the EA session (Figure 2A, Electrical Pain Threshold test at ST36 and GB39).”

“C: Locations of electrical pain threshold test and EA stimulation (stimulation: ST36, reference: GB39), and quantitative sensory testing (QST-measurement) in the left leg. All test and stimuli were applied at a same location across the subjects. n.b. ISI: inter-stimulation interval”

4. The detail of all the QSTs were not described especially whether the location(s) were consistent between subjects and/or how long the break between repetitive testing.

Response: QST was assessed at the same location between subjects (Figure 2C, QST-measurement). To make this clear, we revised the manuscript in Methods (Quantitative sensory testing). Thanks for the constructive comment.:  

“Each QST parameter was assessed (five times for MPT, ten times for MDT, and three times for others during 30 minutes) at the same location across the subjects (Figure 2C, QST-measurement) by a trained single technician. The break between repetitive test was decided considering the individual’s wash-out duration (<30sec).”

5. Owing to the fact that not all QST devises were available for every subjects, there are different data from QST being collected. Thus the researchers decided to analyze data based on the availability of QST were all the subjects, do they have a subjects with full assessments of all QSTs at all and how many of them have pre-post f same QST?
Response: We regret that we had to employ all the QST measures but the devices were not available through the sequent experiments. Unfortunately, no subject has full QST measures in the AC and PC groups. Thus, we used paired $t$-test when we calculate the individual threshold change (postACUP – preACUP, see below), and used unpaired $t$-test when we compare the AC and PC groups. Please see the following paragraph in the Methods (Quantitative sensory testing):

“Because of the limitation of the use of QST devices through two separate subject recruitment, some data were omitted from the analysis (collected number of data in the AC group: n=15 for CDT, WDT, HPT, and CPT measurement, and n=3 for MDT and MPT measurement; collected number of data in the PC group: n=15 for CDT, WDT, HPT, and CPT measurement, and n=12 for MDT and MPT measurement; VDT and PPT were collected from all the subjects).”

6. The AC group has greater “expected acupuncture sensation” than PC, how does research account for this differences in their data analysis especially in the data analysis.

Response: Thanks for the important comment. It could be very critical problem that we noticed. We reanalyzed the correlation between “expected acupuncture sensation” and change in QST as well as autonomic responses in our entire subjects (n=61), but no evidence was found from the analysis that the “expected acupuncture sensation” can affect the results including QST measures and autonomic responses. To make this point clear, we revised our previous as followed:

“The greater “expected acupuncture sensations” was observed in AC than PC (in MASS Index: AC=5.73±1.55, PC=4.49±2.02, P<0.05), but it was not significantly correlated to any other measures of QST and autonomic activity.”

7. While the manuscript described (page 12) that “Even though no significant difference of acupuncture intensity between the AC and PC groups was found in the first-phase and the second-phase, it seemed that the AC group had greater intensity in the second phase compared to the first phase while the PC group had less intensity. There was a tendency that AC group showed greater change of acupuncture intensity (the second 4mins phase – the first 4mins phase) than the PC group did (acupuncture intensity change from the first phase to second phase; $\Delta AC=0.69\pm2.84$ in AC and $\Delta PC=-0.84\pm2.60$ in PC, $P=0.06$). And the AC group didn’t show significantly different acupuncture sensations compared to the PC group.” --- in a scientific study, “its seems” may not be the best descriptive about the study results.

Response: Thanks for the valuable comment. We removed the sentence because we found redundancy with the very next sentence. Thus the paragraph was modified as followed:

“Even though no significant difference of acupuncture intensity between the AC and PC groups was found in both the first-phase and second-phase, there was a tendency that AC group showed greater change of acupuncture intensity (the second 4mins phase – the first 4mins phase) than the PC group did (acupuncture intensity change from the first phase to second phase; $\Delta AC=0.69\pm2.84$, $\Delta PC=-0.84\pm2.60$, $P=0.06$).”
8. It may be best to put figure 5 under hypothesis move to introduction.

Response: Thanks for the constructive suggestion. We think it is a good idea if it is in the instruction, because it shows the big picture of this study findings. Then the reader can easily capture the idea and understand the rest of the manuscript. The figure, However, is the explanatory model for our hypothesis and findings so that it includes our results and discussions. If the Figure 5 is not proper for the discussion section, we will revise the figure and move it to the instruction as a hypothetical diagram. But we think it would be better for the figure in the discussion.

9. please consider add ISI in the figure 2B and add the full description into the list of abbreviations.

Response: Thanks for the constructive suggestion. As recommended, we updated the Figure 2, and added ISI in the legend for obviousness in paradigm. Follow is the added sentence in Figure 2:

“n.b. ISI: inter-stimulation interval”

10. May want to reanalyze the data only include subjects with all QST, autonomic data in both AC and PC groups.

Response: Thanks for the important suggestion. Unfortunately and regretfully, no subject has full QST measures in the AC and PC groups so that we were not able to rerun our analysis with subjects who has all QST and autonomic measures. Thus, we used paired $t$-test when we calculate the individual threshold change (postACUP – preACUP), and used unpaired $t$-test when we compare the AC and PC groups. Our analysis was from the available subjects who has QST measure (both pre and post) and who has autonomic responses (HR and SCR). Follows are the specification of the numbers that were used for analysis (in the Methods, ‘Quantitative sensory testing’, and ‘Physiological and psychological response’):

“Because of the limitation of the use of QST devices through two separate subject recruitment, some data were omitted from the analysis (collected number of data in the AC group: n=15 for CDT, WDT, HPT, and CPT measurement, and n=3 for MDT and MPT measurement; collected number of data in the PC group: n=15 for CDT, WDT, HPT, and CPT measurement, and n=12 for MDT and MPT measurement; VDT and PPT were collected from all the subjects).”

“Among the subjects, 6 from the AC group and 7 from the PC group were excluded from the analysis of autonomic response due to the acquisition error.”

11. Please clarify the description about what were subjects perceptions from the stimulations

Response: Thanks for the constructive suggestion. To clarify the sensations induced by
EA stimulation, we added the name of items of the scale (MGH Acupuncture Sensation Scale) in the Methods (Physiological and psychological response):

“And to quantify the intensity of each acupuncture-induced sensation and the gross intensity of EA stimulation, the “perceived acupuncture sensations” (0-10 scale, including aching, soreness, deep pressure, heaviness, fullness, tingling, warmth, numbness, dull and sharp pain etc.) were collected after EA session using MGH Acupuncture Sensation Scale [4].”

In the Results (Psychophysics during EA stimulation), the perceived sensation intensities were also reported for more clarity:

“The AC group didn’t show significantly different acupuncture sensations compared to the PC group (e.g., soreness: AC=4.4±2.0, PC=3.2±2.6, P=0.10, deep pressure: AC=6.1±1.5, PC=5.4±2.1, P=0.26, heaviness: AC=6.1±1.7, PC=5.6±2.3, P=0.52, fullness: AC=4.6±2.5, PC=4.8±2.5, P=0.80, numbness: AC=4.8±2.0, PC=4.1±2.6, P=0.37).”

Reviewer 2:

We would like to thank the reviewer for the constructive, insightful and important comments. The following is our point-by-point response.

1. In the method, this study included three sessions: EA, Quantitative sensory testing was performed before and after EA. QST consisted of vibration (VDT), mechanical (MDT), warm (WDT), and cold (CDT) detection thresholds, and pressure (PPT), mechanical (MPT), heat (HPT) and cold (CPT) pain thresholds. Autonomic measures such as skin conductance response (SCR). It is not clear why the study need so many indices, how long to be finished, how to keep testing finished during the similar testing time for so many subjects. How many subjects or the PC group.

Response: Thanks for the valuable and important comment. As questioned above, we have many QST and autonomic measures in this study. Each parameter of QST was collected to estimate the sensory processing of each modality (such as vibration, light touch, pressure, and low and high temperature detection) which is mediated by Aβ, Aδ, and C-fibers, respectively. Lang et al [20], also measured QST parameters as many as we did for investigation of acupuncture analgesic effect. Thus, it is important to collect various range of data which can be used for estimation of acupuncture analgesic effect, because the effect can be broad or can be specific to the sensory modality. To make this clear, we revised our manuscript in the Background and Methods (Quantitative sensory testing) as followed:

“Quantitative sensory testing (QST) was performed to evaluate the sensory threshold change in various modalities [20],”

“The averaged values and their changes were calculated to estimate the sensory processing of each modality (mediated by Aβ, Aδ, and C-fibers) as well as hyperalgesic mechanism [20].”

References:
Autonomic activity was estimated by heart rate (HR) and skin conductance response (SCR) during the EA stimulation session. It has been know that acupuncture stimulation modulates autonomic activity [21], producing sympathetic increase after the stimulation. While HR is modulated by the interaction of sympathetic and parasympathetic activity, SCR is only represent the sympathetic activity. Thus, SCR is as important as HR in that relative sympathetic and parasympathetic activity can be estimated from those measures. To make this more clear, we sited Knardahl’s study and revised the Background:

“autonomic activity was estimated to explore the influence of acupuncture stimulation [21] as well as the underlying neural physiology in coping strategies [22], and the influence on acupuncture effects on QST variables.”

References:

The QST test was performed by a trained technician, and the test takes around 30 minutes to get the whole QST measures including break between measures. Thus, QST takes 30 minutes to be finished, electrical pain threshold test takes 2 minutes, EA stimulation session takes 8 minute, and another QST test takes 30 minutes. It takes around one and a half hour to finish this experiment per subject. So four subjects were tested a day in maximum. To make this clear, we revised the Figure legend (Figure 2A):

“A: Overview of the entire experiment procedure. Considering the duration of each session (two 30 minutes for QSTs, 2 minutes for electrical pain threshold test, and 8 minutes for electroacupuncture stimulation), two-hour-slot was allocated for the test of each subject, and 4 subjects were tested per day in maximum.”

Finally 18 subjects in the AC group and 30 subjects in the PC group were included in the analysis. The subjects in the PC group were only asked to hold the applied EA stimulation and to press the button once after the visual cue and all performed as instructed (i.e., no not-blinded in PC).

2. The author thought it was a new point for acupuncture, but the placebo effects of acupuncture in many previous studies include this phenomenon (psychological hint).

Response: Thanks for the constructive and insightful comment. In terms of acupuncture effect, placebo effect is one of important needling non-specific effect. But we believe the coping condition itself is not a part of placebo, even though the coping condition can affect the placebo effect. Here, in our study, we did not consider the interaction between expectancy and coping effects on acupuncture treatment. Thus, coping condition can be
an another needling non-specific component of acupuncture but it is not similar to placebo effect in that coping condition itself does not include any positive expectancy of acupuncture efficacy. Additionally, we reanalyzed and calculated the difference in terms of correlation between anticipation of acupuncture efficacy (by “belief in the effectiveness of acupuncture treatment” score) and QST measures to see the possible link between coping and placebo effect. As a result, no significant correlation was found in both groups, and no significant difference between groups. Thus, we have no evidence to consider the coping is similar to the placebo effect.

3. How to explain the negative correlation of PC group in the acupuncture effect? The results indicate that acupuncture intensity and acupuncture sensation plays a negative role in the patients without the active coping strategy. It seems that the coping strategy instead of the acupuncture stimulation has the effect of analgesia. How to explain it.

Response: Thanks for the insightful comment. We found a negative correlation between acupuncture sensations and acupuncture effect (QST increase). The same amount of acupuncture stimulation was applied (i.e., 95% of individual electrical pain threshold) to all subjects so that the effect of the acupuncture stimulation (in terms of intensity) was not investigated in this study. In fact, no significant increase in QST measures were found in the AC and PC groups, and this does not support the idea that coping strategy instead of the acupuncture stimulation has the effect of analgesia. What we found was the influence of interaction between coping and acupuncture sensation on acupuncture effect, and this is the main findings in our study.

4. In this MS, there was not any test using fMRI or other functional methods, why did the author pay more attention on PAG in the abstract, discussion and inclusion?

Response: Thanks for the constructive and important comment. Even though our study is not directly related to the PAG, its involving was speculated through our result findings so that the PAG was mentioned in the discussion and conclusion as a hypothetical possibility. We hope further research can be proceeded on the coping strategy and PAG in fMRI study.

Sincerely yours,
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