OPEN PEER REVIEW REPORT 3

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Title: Efficacy and safety of transcutaneous auricular vagus nerve stimulation paired with conventional rehabilitation training in acute stroke patients
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COMMENTS TO AUTHORS

I think the authors are to be commended for having successfully carried out a logistically challenging study, combining intensive rehabilitation with (in the experimental group) transcutaneous auricular vagus nerve stimulation, and following the subjects for one year with virtually no attrition. The sample size is nicely justified by the power calculation. The finding that 20 days of stimulation just prior to rehabilitation was still having positive effects at 1-year follow-up is, needless to say, incredibly useful.

There were a few areas that I felt should be addressed in the write-up:

1. Although there were extensive, very good efforts to conceal group assignment to the participants, rehabilitation therapists, and the researchers, it sounds like the control group had the TENS-type device "without stimulation" (section 2.4, line 24), which I am assuming means that the unit was inserted but not switched on. In contrast, the experimental group was adjusting the parameters of stimulation to tolerance. This seems rather limited blinding (as opposed to, say, stimulation of a sham location, or using some other stimulus not expected to be effective. I feel this limitation of blinding should be mentioned in the "limitations" section at the end of the Discussion.

2. (Section 2.7, line 25): The various dependent measures were each analyzed with a 2-way ANOVA. Am I correct in assuming that for each measure there was a separate ANOVA at each post-baseline time point? If so, I feel this should be stated explicitly.

3. (Section 3.3, first paragraph): So, the two groups differed throughout the study on heart rate and systolic and diastolic blood pressure? Figure 2 is very helpful. I think this difference at baseline and throughout the study should be discussed a bit. I assume there is no reason to believe it could have affected outcome, but this, too, should be mentioned.

4. (Section 3.4). As you no doubt know, when conducting a statistical test to determine that two groups are comparable at baseline, the p value is often set to .10 rather than .05, because the concern is for Type II error (not seeing a difference that is there) rather than Type I error (seeing a difference that is not there). Even without this adjustment, there is a strong trend ($p = .06$) for the experimental group to have higher SIS quality of life and lower anxiety at baseline than the control group. I assume the difference is too small to have likely affected the rehabilitation outcome, but I feel the issue should be treated in the Discussion section.

5. (Section 3.5): I feel the results for the HADS should be described in a bit more detail.

6. (Third page of Discussion section, line 28): The authors contend that the improvement in depression

and anxiety, and improvement in function, confirms that depression and anxiety have a negative effect on treatment outcome. However, the reverse causality is also possible - depression and anxiety might have improved because functioning was getting better. I feel the Discussion should mention this possibility also.

7. Forgive me for not understanding but, Section 2.1, line 9: What is a "pragmatic" trial? Do you mean parallel groups?

8. Conflict of interest: To be explicit, then, you have no connection with the manufacturer of the unit, yes?