Dear Editor and Reviewers:

I am pleased to submit the revised research article entitled “Effect of Huperzine A on Cognitive Function and Perception of Effort During Exercise: A Randomized Double-Blind Crossover Trial” by Chadsley M. Wessinger, MS, RD; Cynthia L. Inman, MS, RD; Jeremiah Weinstock, PhD; and Edward P. Weiss, PhD for consideration for publication in the *International Journal of Exercise Science*. Please see below for point-by-point responses to both reviewers:

Reviewer 9:

* Methods: I would like the authors to add a figure showing a flowchart of the protocol. This will greatly help the reader to understand the research protocol.
  + We appreciate the suggestion and have added two figures, one to illustrate the study design, and another to illustrate the exercise protocol. All figures and in-text references to figures have been renumbered to accommodate this change.
* In the protocol section of the methods, please fix the following sentence: Outcome tests were performed for familiarization purposed and no-intervention baseline measures.
  + Thank you for pointing out this typo. The sentence has been corrected to the following: “Outcome tests were performed for familiarization purposes and for non-intervention baseline measures”.
* Protocol – 5th paragraph. Describe how you determined maximal heart rate. I’m assuming it was predicted.
  + This is explained in the 13th protocol paragraph, but the authors acknowledge it is advantageous to explain this sooner. The following statement was added to the 5th paragraph to describe how maximal heart rate was predicted: “Age-predicted maximal HR was predicted via 208 – 0.7 x age in years (30).”
  + Further, the authors noticed a typo in the 13th paragraph that has been revised.
* Protocol – 6th paragraph. Fix the formatting in the (15) reference.
  + The correct citation for the preceding statement is “Chang Y, Labban J, Gappin J, Etnier J. The effects of acute exercise on cognitive performance: a meta-analysis. Brain Res 1453:87-101, 2012”. This reference coincides with the citation number 4 and the correct in-text citation is now in place.
* On page 8, the paragraph preceding Figure 1 and the paragraph following figure one are confusing. It somewhat seems like a duplicate paragraph but some of the data are conflicting. Please address.
  + Thank you for your comment. There were three trials for each cognitive function test: baseline (at rest), placebo, and huperzine A. The first paragraph was referring to the percent change from baseline while the second paragraph was referring to the difference in percent change between the placebo and huperzine A trials. The authors have revised the text by integrating the two paragraphs so the information for a given test is presented together as one paragraph:

“Digit span did not improve from rest to exercise in either the placebo trial (5.22±5.43%, p=0.510) or huperzine A trial (5.04±4.69%, p=0.458). Furthermore, there was no difference (p=0.96) in percent change (Figure 3) observed between placebo (5.22±5.43%) and huperzine A (5.04±4.69%) trials for digit span. Letter fluency tended to improve in the placebo trial (22.93±10.02%, p=0.076) and improved significantly in the huperzine A trial (28.46±10.68%, p=0.018). However, there was no significant difference (p=0.49) in percent change observed between placebo (22.93±10.02%) and huperzine A (28.46±10.68%) trials for letter fluency. Category fluency did not improve in either the placebo (8.86±9.80%, p=0.756) or huperzine A trial (0.53±8.00%, p=0.609). Further, there was no significant difference (p=0.39) in percent change observed between placebo (8.86±9.80%) and huperzine A (0.53±8.00%) trials for category fluency. Stroop tended to improve in the placebo trial (9.91±4.30%, p=0.067) and improved significantly in the huperzine A trial (11.95±4.32%, p=0.022). Although, there was no significant difference (p=0.59) in percent change observed between the placebo (9.91±4.30%) and huperzine A (11.96±4.32%) trials for the Stroop test”.

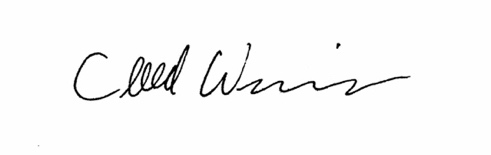
* Please fix this sentence in the discussion: Because nutritional supplements are not subject the same regulations as therapeutic medications...
  + Thank you for pointing out this typo. The sentence has been corrected and modified to the following “Because nutritional supplements are not subject to the same regulations as therapeutic medications, and because we did not analyze the content of the supplements used in our study, we cannot confirm the potency and purity of the supplement used in this study”.

Reviewer 14:

* In the abstract list the number of males and females in the study as well as give height and weight data.
  + Thank you for the suggestion. This information has been added to the abstract: “…(11 women [height 166±2 cm, weight 60.5±3.0 kg] and 4 men [height 173±4 cm, weight 82.0±11.0 kg], BMI 23.5±1.4 kg/m2, age 30.4±3.6 years)…”
* second paragraph of the introduction, what do you mean by "sport supplement" is this from protein powders to pre workouts? This seems to general.
  + Thank you for your feedback. This sentence has been revised with more specific terminology based on the reference cited: “Huperzine A is an ingredient found in ~11% of multi-ingredient pre-workout supplements (1)”.
* In the introduction, is this a double blind study?
  + Thank you for pointing out this error of omission. The second-to-last sentence in the introduction has been amended to indicate that this was a double blind study: “In this context, the purpose of this study was to use a double blind, randomized-sequence, placebo-controlled crossover trial to evaluate the hypothesis that huperzine A enhances cognitive function during exercise and reduces perception of effort”.
* Methods give mean and SD for age, list that it is the saint louis, missouri region.
  + Thank you for the feedback. Mean and SD have been added to this sentence.
* Did resistance training have a contribution to exercise trained classification?
  + No, because the primary goal of this study was to assess cognitive function during a bout of aerobic exercise, we only included individuals that participated in moderate to vigorous intensity endurance exercise (i.e. brisk walking, running, cycling, etc.), at least three days per week, for at least 20-minutes per session, for at least six months prior to this study. A statement has been added to this paragraph to further clarify that resistance training did not contribute to our exercise-trained definition: “Resistance training did not contribute to the definition of exercise-trained for the purposes of this study”.
* Don't be afraid to list the digestion rate and peak blood levels comment here when you introduce your huperzine supplementation approach.
  + Thank you for the suggestion. The following sentence has been added to 4th methods paragraph to indicate our rationale for the timing of exercise following ingestion: “Previous work has identified that orally ingested huperzine A appears in the blood within 15-minutes and reaches peak levels by 60-minutes (22)”.
* list maximal heart rate as estimated here since you did not test true maximal heart rate.
  + Thank you. Please see the response to Reviewer 9’s third comment.
* with the cognitive function tests did you homogenize how the test sequence was changed between tests?
  + Yes, thank you for the question. The following statement has been added to the 8th methods paragraph: “By using a randomization process, the test sequence was homogenized to ensure that the test sequence differed every time a given participant was tested”.
* On the push ups, what was the range of motion required and was there any set cadence?
  + The range of motion required was per the ACSM’s push-up test protocol, which requires the participant to continue downward until their chin touches the floor or a mat. Per the ACSM’s push-up test protocol, there is no set cadence for this test. The test is performed until the participant strains forcibly or is unable to maintain proper form. A statement has been added to this paragraph to clarify the range of motion that was required of the participants: “…the participant must continue downward until their chin touches the floor or a mat…”.
* In the aerobic capacity portion, I thought this was a walking test, so why use a treadmill running approach for prediction?
  + Initially, the treadmill started at 2.0 mph; at this pace all participants walked. However, the speed was increased incrementally until a self-defined “brisk” pace was achieved. For some participants, this was walking, for others this was running. From there, the percent grade was increased until 70% HRR was achieved. An expanded explanation has been added to the methods section via newly added Figure 2 and its description as well as an additional statement in the 7th methods paragraph: “. Participants were permitted to walk or to run based on their perception of ‘brisk’”.
* Dart throwing uses past tense verbiage of "will" and needs to be removed and change to "consisted" directly afterwards.
  + Thank you for pointing this out. The sentence has been revised: “Modelled after previous dart throwing procedures used in previous research, the dartboard consisted of ten concentric circles”.
* Heart rate was only monitored once every ten minutes during endurance testing? Effect size looks like a massive over estimate here.
  + Thank you for the question and comment. HR was monitored continuously during test and was recorded every 5-minutes. The authors have corrected this error in the methods paragraph immediately before the *Statistical Analysis* section: “…to monitor exercise heart, which was recorded at intervals of 5-minutes during endurance exercise…”.
  + Also, the authors have modified figure 4’s (previously figure 2) y-axis to depict a range of 100-200 bpm. This represents a broader range that better aligns with HR values for exercise. In the original figure, the range was too small(138-168 bpm), which was likely causing the small, statistically non-significant differences to appear inappropriately large. For the same reason, we have modified the y-axis of the RPE portion of this figure to depict a larger and more appropriate range of 10-20 RPE units. Similarly, this represents a broad range of light to vigorous exercise on the Borg RPE scale, as opposed to the previous range of 12-15.5. This is to ensure these small, statistically non-significant differences do not appear disproportionately large.
* Were any analysis of effects of supplementation examined relative to body size and mass?
  + Thank you for the question. No, no such analyses were conducted. The authors have revised the limitations paragraph to acknowledge this: “In the present study, the authors did not perform any analyses regarding the effects of the supplement relative to body size or body mass; this may be a potential avenue for researchers to pursue in the future”.
* For vertical jump numbers run them through the Harmon equation or any other jump power equation to see if changes in power might have occurred due to changes in mass between each visit.
  + Thank you for the suggestion. The authors acknowledge it may be worth probing further into this if there was a tendency for changes in vertical jump performance, but the means were very similar, and the p-value was 0.497. Futhermore, to our knowledge, there is no biological rationale to expect acute changes in body weight from a single dose of Huperzine A, nor is there evidence of such effects in this study. In this context, if any variations in body weight did occur between study trials, they were likely be random and wash out in the statistical analysis.
* In the second to last paragraph of the discussion add the word "to" between "not subject" and "the same regulations as therapeutic medications".
  + Thank you. Please see our response to Review 9’s last comment.

Thank you for your consideration.

Sincerely,



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