PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Study protocol of a randomized controlled trial of the effects of near-infrared spectroscopy neurofeedback training coupled with virtual reality technology in children with ADHD

Authors

Zheng, Que; Tsam-ling Kei, Kathy; Chiu, Ka Yu; Shum, Kathy KM

VERSION 1 - REVIEW

Reviewer	**1**
Name	**hasslinger, John**
Affiliation	**Karolinska Institutet**
Date	**27-Sep-2024**
COI	

Thank you for submitting your well-written manuscript titled “Study protocol of a randomized controlled trial of the effects of near-infrared spectroscopy neurofeedback training coupled with virtual reality technology in children with ADHD.” The study compares NIRS-based neurofeedback delivered in a VR-classroom environment with an active comparator and a passive waiting list. The protocol is overall well-structured and easy to follow. However, there are some areas that require clarification and improvement:

1. Please specify what constitutes “significant teacher- or parent-reported attention problems.” I assume you used a specific cut-off from a screening questionnaire. Clarification on this point would be helpful.

2. This section would benefit from a clearer structure. The current “The virtual classroom” section primarily describes how feedback from the NFT will be displayed and how successful trials are defined, while the “Training paradigm” section also describes the task. Merging these sections and providing a detailed description of the NFT-VR task would enhance readability.

3. Is the baseline measurement 2 minutes of resting state inside the VR-classroom? What are the instructions during the baseline? Are participants answering questions that appear

during the lessons? If so, how are these questions presented (text/audio), and will they be scored?

4. During the downregulation blocks, is the feedback also based on a brighter lamp, i.e., does the lamp get brighter when the oxy-Hb signal drops below the baseline?

5. It appears that participants' performance does not influence the increasing level of distractors, nor is the "compensation" performance-based. A discussion on the rationale behind this choice would be appreciated.

6. Will there be any discussion or inquiry of how the participants are performing their self-regulation, i.e., developing some sort of strategies? Or is the regulation assumed to take place on an implicit level? Furthermore, will there be some sort of transfer exercises taking place between sessions? Please clarify your rational for this.

7. Although Cogmed is well described elsewhere, it would be beneficial if the authors could describe its use in this study. Specifically, how many tasks/trials are included, what types of tasks are involved, and whether any performance-based incentives are given. Additionally, please clarify if the Cogmed training is conducted at home or in a clinic, and whether it is done alone or under supervision.

Thank you for addressing these points.

Reviewer	**2**
Name	**Aggensteiner, Pascal**
Affiliation	**Heidelberg University**
Date	**27-Sep-2024**
COI	

The Protocol is clear and well written. Here some minor comments and suggestions:

L15 - Please report as well worldwise prevalence. Not only for US.

L31, please cite as well the Review from Katya Rubia, Sam Westwood, Pascal Aggensteiner and Brandeis, Cell, 2022 I think.

Pg8- L22 Typo in NIRS

P10- L49 - specify which kind of standard protocol.

Pg 11 - Stats- Latent growth curve modeling. Specify why not linear mixed model.

Pg- 11 Exclusion criteria - Add info about medication

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pg18-L14- Typo futility

pg19 - L 24 typo - will not be involved

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Dr. John Hasslinger, Karolinska Institute

Comments to the Author:

Thank you for submitting your well-written manuscript titled "Study protocol of a randomized controlled trial of the effects of near-infrared spectroscopy neurofeedback training coupled with virtual reality technology in children with ADHD." The study compares NIRS-based neurofeedback delivered in a VR-classroom environment with an active comparator and a passive waiting list. The protocol is overall well-structured and easy to follow. However, there are some areas that require clarification and improvement:

1. Please specify what constitutes "significant teacher- or parent-reported attention problems." I assume you used a specific cut-off from a screening questionnaire. Clarification on this point would be helpful.

Authors' response:

- We have now provided more details on the screening criteria on p.11: "*or significant ADHD symptoms, as reported by parents in the Swanson, Nolan, and Pelham Version IV Scale (SNAP-IV) [40]. Specifically, at least 6 out of 9 items must be rated "2" or above in either the "inattention" or "hyperactivity/impulsivity" subscale of the SNAP-IV, in accordance with the diagnostic criteria for ADHD in the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) [1].*"

2. This section would benefit from a clearer structure. The current "The virtual classroom" section primarily describes how feedback from the NFT will be displayed and how successful trials are defined, while the "Training paradigm" section also describes the task. Merging

these sections and providing a detailed description of the NFT-VR task would enhance readability.

Authors' response:

- Thank you for your suggestion. These two sections are merged (pp.12-14) and hopefully the revised paragraphs will facilitate readability.

3. Is the baseline measurement 2 minutes of resting state inside the VR-classroom? What are the instructions during the baseline? Are participants answering questions that appear during the lessons? If so, how are these questions presented (text/audio), and will they be scored?

Authors' response:

- The 2-min baseline measurement does not occur within the VR classroom scenario. The baseline measure is taken in a simulated garden setting during which the participants are asked to relax for 2 minutes. The description is added on p.12: *"During the 2-min baseline measurement, participants are asked to relax in a simulated garden within the VR environment."*
- Yes, participants are answering questions appearing during the lessons and questions are presented in a visual format. A more detailed description is now included on p.13: *"Each block consists of 5 minutes of upregulation (lesson time in the VR classroom), during which participants will answer multiple-choice questions displayed in text or picture formats on the screen by pressing a specific button on the VR controller. Participants' performance in answering the questions is recorded but will not be disclosed to them at any point during the training. "*

4. During the downregulation blocks, is the feedback also based on a brighter lamp, i.e., does the lamp get brighter when the oxy-Hb signal drops below the baseline?

Authors' response:

- In downregulation blocks, the feedback is based on the brightness of the lamp as well. Participants are asked to keep the lamp dim during the 2-min downregulation time. This information is now presented on p.13: *"In the 2-min downregulation, depicted as break time in the VR classroom, participants are asked to decrease the brightness of the lamp and keep it dim. A dim lamp indicates that the oxy-Hb level is below*

baseline, which is achieved through the downregulation of hemodynamic activity in the prefrontal cortex."

5. It appears that participants' performance does not influence the increasing level of distractors, nor is the "compensation" performance-based. A discussion on the rationale behind this choice would be appreciated.

Authors' response:

- Thank you for your suggestion. We have added a discussion on the rationale behind this design on pp.13-14: *"To simulate a real classroom environment where distractions naturally emerge, visual and auditory distractors are introduced in the VR classroom. The types of distractors (distant, near, peer) and their occurrence frequency are designed to follow a standardized protocol that is replicable and applicable to all participants. The level of distraction difficulty is set to progressively increase across the 16 training sessions."*

6. Will there be any discussion or inquiry of how the participants are performing their self-regulation, i.e., developing some sort of strategies? Or is the regulation assumed to take place on an implicit level? Furthermore, will there be some sort of transfer exercises taking place between sessions? Please clarify your rational for this.

Authors' response:

- Thank you for raising these questions. We have now included a more detailed discussion addressing these questions on p.14: *"Participants will receive continuous performance feedback in the form of lamp brightness during the first three sets of upregulation and downregulation blocks. In the fourth regulation block, however, the brightness of the lamp will be fixed to encourage the generalization of self-regulation skills in the absence of neurofeedback. Importantly, participants will not be explicitly instructed on how to regulate the brightness of the lamp in either the upregulation or downregulation blocks; they will simply be asked to alter it.*

  The self-regulation learning process is purposefully designed to be implicit, aiming to reduce cognitive load, as explicit instructions on regulation strategies might divert children's attention from the tasks at hand [45,46]. By not explicitly instructing

children on how to regulate their brain activity, cognitive load is minimized, creating a more natural and less stressful learning environment."

7. Although Cogmed is well described elsewhere, it would be beneficial if the authors could describe its use in this study. Specifically, how many tasks/trials are included, what types of tasks are involved, and whether any performance-based incentives are given. Additionally, please clarify if the Cogmed training is conducted at home or in a clinic, and whether it is done alone or under supervision.

Authors' response:

- We have now provided more details for the Cogmed training design in the current study on p.15: *"To match the training duration of the NFT-VR group, each training session in the Cogmed group will last approximately 30 min. During each session, participants will play five working memory games selected from a total of ten available in the Cogmed software, which train both visual and auditory working memory. Participants will attend training sessions at the university laboratory twice a week for eight weeks. Each session is conducted in a one-on-one format, similar to the NFT-VR group, with a trainer who will explain the instructions for each game and monitor the entire training process. Participants in the Cogmed training group will receive performance-based reinforcement in the form of digital tokens, which they can use to build a simulated city within the software in each session."*

Reviewer: 2

Dr. Pascal Aggensteiner, Heidelberg University

Comments to the Author:

The Protocol is clear and well written. Here some minor comments and suggestions:

L15 - Please report as well worldwide prevalence. Not only for US.

Authors' response:

- Thank you for your suggestion. We agree that it is important to report the ADHD prevalence from a global perspective and the introduction is revised as follows on p.6: *"A recent umbrella review revealed that the global prevalence of ADHD among*

children and adolescents was estimated to be 8% [2], with the inattentive presentation of ADHD (ADHD-I) identified as the most common type of ADHD."

L31, please cite as well the Review from Katya Rubia, Sam Westwood, Pascal Aggensteiner and Brandeis, Cell, 2022 I think.

Authors' response:

- Thank you for your recommendation on the meaningful read. We have cited the paper in the revised manuscript (see p.7).

Pg8- L22 Typo in NIRS

Authors' response:

- Thank you for spotting the error. It has been corrected (p.8).

P10- L49 - specify which kind of standard protocol.

Authors' response:

- We have now specified this information on p.10: *"This manuscript, along with the described trial, are aligned with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)—the SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials [37]. Please see Supplementary Material 1 for the SPIRIT checklist."*

Pg 11 - Stats- Latent growth curve modeling. Specify why not linear mixed model.

Authors' response:

- Thank you for your valuable insights. We have reconsidered the analytical methodologies and believe that a linear mixed model would be sufficient for analysing the treatment effects. However, latent growth curve modeling will be used to analyse the changing patterns of brain activity, as measured by fNIRS during the neurofeedback training, in order to examine any trends in participants' neural activities.
- The statistical methods section is now revised as follows (pp.19-20): *"Chi-square tests and ANOVAs will be performed to compare the demographic characteristics (e.g., age,*

gender) and baseline variables among the three conditions. Intent-to-treat analyses will be conducted on the available data. Linear mixed-effects modeling will be employed to evaluate the treatment effects, specifying time (baseline, immediate post-test, follow-up), training group, and the time-by-group interaction as fixed effects, with a random intercept for each participant. Bonferroni corrections will be applied to adjust for multiple comparisons. The treatment effects will be assessed based on the time-by-group interaction effects from baseline to immediate post-test/follow-up. Within-group effects from baseline to immediate post-test/follow-up will be calculated for all three groups using paired sample t-tests to evaluate whether there are significant improvements in the outcome variables across the three time points for the training conditions. Latent growth curve modeling analyses will also be performed to evaluate changes in the success rate of feedback signal regulation across training sessions. Finally, to investigate whether changes in task performance correlate with changes in prefrontal cortical activation, Pearson's correlations will be examined."

Pg- 11 Exclusion criteria - Add info about medication

Authors' response:

- We have added the medication requirement in the exclusion criteria as follows (see p.11): *"Ongoing pharmacological treatment for ADHD is allowed during the intervention, provided that a 24-hour washout period is observed at each time point of outcome measurement."*

pg15 - L40 - here it is the first time that I read four timepoints. Earlier the authors only mention per-post-2 m fu.

Authors' response:

- We apologize for the confusion caused. We originally planned to collect data at time point 4 (T4) so that child participants and parents in the waitlist group would have both pre- and post-training assessments, similar to the other two groups. This data would be used to prepare personalized reports for participants, serving as incentives to encourage their continued participation in the study. However, the data collected at T4 are not intended to be analysed in the current study for evaluating treatment effects. As stated in the clinical trial registration, the randomized controlled trial will only use data

collected at three time points to examine the treatment effects. To avoid confusion, we have revised the manuscript accordingly (see pp.16-17), as well as Figure 1.

pg 18 -L15 Sure that the authors save data in hard disk? and not on the servers of the institute? If yes, please protect it with password and keep a copy. However this is not fulfilling any standard...

Authors' response:

- Thank you for your comments and suggestion. All digital data will be saved in a hard disk with our institute's encryption method so it is password-protected and a copy will be kept.

pg18-L14- Typo futility

Authors' response:

- The error has been corrected. The sentence on p.19 now reads: "*The principal investigator (the last author) is responsible for reviewing the initial findings from the interim analyses regarding efficacy and utility.*"

pg19 - L 24 typo - will not be involved

Authors' response:

- Thank you for your careful review. The typo has been corrected on p.20.