PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of training involving patterned sensory enhancement on improving upper-limb movements in patients with Parkinson's disease: protocol of a randomised controlled trial
AUTHORS	FAN, Wei; Fong, Kenneth N. K.; Wang, Shu-Mei

VERSION 1 – REVIEW

REVIEWER	Fasano, Alessio Scuola Superiore Sant'Anna
REVIEW RETURNED	07-Mar-2023

GENERAL COMMENTS	The study protocol is well written and very interesting. The authors propose to investigate the effect of rhythmic auditory stimulation on the upper limb functionality in Parkinson's disease. They plan to do it by randomly assigned patients to two groups of training sessions. I appreciated he estimation of the sample size. Some minor comments follow: 1. How will you prevent the observer bias in the assessment of each group? You did not specified the distinction of personnel, and the blinding/masking. 2. Is phone-calls method enough to ensure the intervention compliance of the patients and their parents? Is the number of patients in each group enough to take into account potential confounders associated with this compliance? 3. Have you thought about a normalization of the tempo measure in order to mitigate individual differences in self-determined vigor, and assess properly the improvement in the PD-RAS group independently from this individual trait? Or do you already have a preliminary result on the same patients' speed distribution? Giving the clear utility of the study objective on the clinical point of view, the expertise of the authors and the statistical coherence emerging from the plan, I reckon this study protocol eligible for acceptance.

REVIEWER	Koshimori, Y University of Toronto
REVIEW RETURNED	28-Mar-2023

GENERAL COMMENTS	I acknowledge that I have included the comments from Dr. Michael Thaut. In Neurologic Music Therapy terminology, the current intervention would be called Patterned Sensory Enhancement (PSE), not RAS. The term “RAS” is reserved for gait, and “PSE” for the rest of the body where movement is cued by music/rhythm. Since only gait is

	biologically oscillatory, for the rest of the body, you have to create cyclical movement patterns to use rhythm. Please provide the rationale why outcome measures post-intervention, but not changes pre- and post-intervention between groups will be compared using t-test. The two groups will potentially be different in demographic and/or disease characteristics. How will these confounding effects be addressed in the statistics? Will this study collect other disease characteristics such duration of disease, more affected side, depression/anxiety that might affect the outcome measures? It would be useful to train both hands (because the left hand may be more affected by the disease to see the effects of training. Why will the distance between the target and main bowls be set at 30 cm instead of each participant's 50% of upper-limb length? Please indicate when (during the day) the participants will have a training session relative to their medication schedule. Please provide the rationale why blinding is not applicable. As Fan et al (2022) cited in this manuscript has acknowledged the issue of "speed/accuracy(variability) trade off" and considering the importance of accuracy/variability for upper-limb function, it would be useful if this study assesses it. To assess the effects of intervention on reduction in bradykinesia (the primary aim of this study), it would be useful to assess MDS-UPDRS III scores post-intervention.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

1. How will you prevent the observer bias in the assessment of each group? You did not specified the distinction of personnel, and the blinding/masking.
Reply:
Thank you for indicating this important point. To address this issue, we will ensure that a senior therapist conducts the assessments in a face-to-face manner both before and after the 21-day training. This therapist will be blinded to the group allocation, which will help to prevent any potential bias in the assessment process. We have revised our manuscript to clarify this information. Please see the revisions below.

METHODS AND ANALYSIS – Study design
"Assessments will be completed face-to-face before and after the 21-day training by a senior therapist who is blinded to the group allocation. Blinding of patients and people who provide training is not feasible in this study because patients and training providers know group allocation."

2. Is phone-calls method enough to ensure the intervention compliance of the patients and their parents? Is the number of patients in each group enough to take into account potential confounders associated with this compliance?
Reply:
Thank you for the valuable comments. We have added real-time video meetings to ensure the adherence of participants to the training program. In addition, in order to be conservative in estimating

the required sample size, we have selected the analysis of covariance in G*Power and taken into account all possible confounding factors in our study, including age, gender, the Hoehn and Yahr stage, disease duration, the more affected side (left or right; which is determined by inspection of an experienced physician), medication dosage (which is measured via calculation of the levodopa equivalent dose), the number of training sessions the participant completes, the score of the depression item in the first part of MDS-UPDRS at pretest, the score of the anxiety item in the first part of MDS-UPDRS at pretest, and a pretest score of an outcome variable (including BBT scores, the error rate during executing BBT, JHFT scores, and the domain score of the third part of MDS-UPDRS). We have described the collection of the aforementioned covariates in the manuscript. Please also see revisions below.

METHODS AND ANALYSIS – Study design:
"For all participants, training and assessments will be performed during the 'on' state of their anti-Parkinson medication. We will conduct weekly face-to-face meetings with patients and real-time video meetings during all home training sessions to ensure the adherence of participants to the training program. We will monitor muscle fatigue during home training by using a daily training log."

METHODS AND ANALYSIS – Participants
"Patients with PD will be recruited from hospitals through posters and physician referrals. At pretest, this study will collect demographic and clinical data, including age, gender, disease duration, the more-affected side, and medication dosage. The more-affected side (left or right) refers to the side of the body exhibiting more severe bradykinesia, which will be determined visually by an experienced physician. In addition, we will calculate the levodopa equivalent dose [33] to measure medication dosage."

METHODS AND ANALYSIS – Sample size estimation
"Because of no existing PD studies testing effects of training involving PSE on upper-limb movements, we calculated the effect size of training involving PSE (f = 0.255) according to data of the classic study [20] examining effects of training involving RAS on gait speed in PD patients. The G*Power software (version 3.1.9.7) was used to estimate the required sample size under the following conditions: analysis of covariance as the statistical test, an effect size f of 0.255, the power of 0.8, the alpha level of 0.05, two groups, and 10 covariates (age, gender, the Hoehn and Yahr stage, disease duration, the more-affected side, medication dosage, the number of training sessions the participant completes, the score of the depression item in the first part of the Movement Disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS) at pretest, the score of the anxiety item in the first part of MDS-UPDRS at pretest, and a pretest score of an outcome variable, including the score of the box and block test (BBT), the error rate during executing BBT, the score of the Jebsen hand function test (JHFT), and the domain score of the third part of MDS-UPDRS). The estimated total sample size was 124. Considering the dropout rate of 10%, the final total sample size was 138 patients (69 patients per group)."

METHODS AND ANALYSIS – Intervention
"On the first day of each subsequent training week, patients will be asked to return to the hospital to receive a face-to-face training session. We will conduct real-time video meetings during all home training sessions to ensure adherence to the treatment plan. We will also ask participants to complete daily training logs to record training completion and monitor the degrees of fatigue. In addition, we will calculate the number of training sessions the participant completes."

METHODS AND ANALYSIS – Outcome measures
"The MDS-UPDRS is a commonly used tool in clinical settings and research to assess influences of PD on multiple aspects in patients [35]. It consists of four parts, including (the first part) non-motor subjective experiences of daily living, (the second part) motor-related subjective experiences of daily

living, (the third part) the motor examination, and (the fourth part) motor complications [35]. We will calculate the domain score of the third part of MDS-UPDRS, which is used to reflect objective severity of movement symptoms in patients. Larger scores indicate more severe movement symptoms. We will also use the score of the depression item and that of the anxiety item separately in the first part of MDS-UPDRS to detect levels of depression and anxiety in patients."

METHODS AND ANALYSIS – Data collection and statistical analysis
"A one-way analysis of covariance will be conducted to examine effects of group (the PSE group versus the no-PSE group) on each dependent variable, including BBT scores, the error rate during executing BBT, JHFT scores, and the domain score of the third part of MDS-UPDRS at posttest. The 10 potential confounding factors are age, gender, the Hoehn and Yahr stage, disease duration, the more-affected side, medication dosage, the number of training sessions the participant completes, the score of the depression item in the first part of MDS-UPDRS at pretest, the score of the anxiety item in the first part of MDS-UPDRS at pretest, and a pretest score of an outcome variable (including BBT scores, the error rate during executing BBT, JHFT scores, and the domain score of the third part of MDS-UPDRS). The alpha level (two-tailed) will be set at 0.05. It is hypothesized that after controlling for confounding influences, PSE increases scores of BBT, and decreases JHFT scores, the domain score of the third part of MDS-UPDRS, and the error rate of BBT."

3. Have you thought about a normalization of the tempo measure in order to mitigate individual differences in self-determined vigor, and assess properly the improvement in the PD-RAS group independently from this individual trait? Or do you already have a preliminary result on the same patients' speed distribution?
Reply:
Thank you for raising this concern. When this study designed provision of PSE, one important consideration is to provide a tempo of PSE that is faster than each participant's baseline fastest movement speed. It has been indicated (Ghai et al., 2018) that providing a tempo of PSE that is slower than the baseline movement speed is detrimental to effects of movement training in people with PD. If tempi of PSE provided for all participants are unified and not tailor-made, the tempi of PSE are likely to be slower than baseline movement speed for some participants and thus may lead to negative effects on movement speed after training. Another reason for adopting tailor-made tempi of PSE for each participant in this study is lack of research showing the distribution of upper-limb movement speed on the picking-beads task.

Reference:
Ghai, S., Ghai, I., Schmitz, G., & Effenberg, A. O. (2018). Effect of rhythmic auditory cueing on parkinsonian gait: A systematic review and meta-analysis. Scientific Reports, 8(1), 506. https://doi.org/10.1038/s41598-017-16232-5

Reviewer #2:

1. In Neurologic Music Therapy terminology, the current intervention would be called Patterned Sensory Enhancement (PSE), not RAS. The term "RAS" is reserved for gait, and "PSE" for the rest of the body where movement is cued by music/rhythm. Since only gait is biologically oscillatory, for the rest of the body, you have to create cyclical movement patterns to use rhythm.
Reply:
Thank you for the valuable suggestion. We have revised the term from RAS to PSE in the manuscript.

2. Please provide the rationale why outcome measures post-intervention, but not changes pre- and post-intervention between groups will be compared using t-test. The two groups will potentially be different in demographic and/or disease characteristics. How will these confounding effects be

addressed in the statistics?
Will this study collect other disease characteristics such duration of disease, more affected side, depression/anxiety that might affect the outcome measures?

Reply:
Thank you for your comments. In order to take into account possible group differences at the pretest, we have revised the statistical analysis from the independent sample t-test to the one-way analysis of covariance to examine effects of group (the PSE group versus the no-PSE group) on each dependent variable, including BBT scores, the error rate during executing BBT, JHFT scores, and the domain score of the third part of MDS-UPDRS at posttest. We will taken into account 10 potential covariates in the analysis, including age, gender, the Hoehn and Yahr stage, disease duration, the more affected side (left or right; which is determined by inspection of an experienced physician), medication dosage (which is measured via calculation of the levodopa equivalent dose), the number of training sessions the participant completes, the score of the depression item in the first part of MDS-UPDRS at pretest, the score of the anxiety item in the first part of MDS-UPDRS at pretest, and a pretest score of an outcome variable (including BBT scores, the error rate during executing BBT, JHFT scores, and the domain score of the third part of MDS-UPDRS). We have added the collection of all the covariates in the manuscript. Please see revisions below.

METHODS AND ANALYSIS – Participants
“Patients with PD will be recruited from hospitals through posters and physician referrals. At pretest, this study will collect demographic and clinical data, including age, gender, disease duration, the more-affected side, and medication dosage. The more-affected side (left or right) refers to the side of the body exhibiting more severe bradykinesia, which will be determined visually by an experienced physician. In addition, we will calculate the levodopa equivalent dose [33] to measure medication dosage.”

METHODS AND ANALYSIS – Sample size estimation
“Because of no existing PD studies testing effects of training involving PSE on upper-limb movements, we calculated the effect size of training involving PSE (f = 0.255) according to data of the classic study [20] examining effects of training involving RAS on gait speed in PD patients. The G*Power software (version 3.1.9.7) was used to estimate the required sample size under the following conditions: analysis of covariance as the statistical test, an effect size f of 0.255, the power of 0.8, the alpha level of 0.05, two groups, and 10 covariates (age, gender, the Hoehn and Yahr stage, disease duration, the more-affected side, medication dosage, the number of training sessions the participant completes, the score of the depression item in the first part of the Movement Disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS) at pretest, the score of the anxiety item in the first part of MDS-UPDRS at pretest, and a pretest score of an outcome variable, including the score of the box and block test (BBT), the error rate during executing BBT, the score of the Jebsen hand function test (JHFT), and the domain score of the third part of MDS-UPDRS). The estimated total sample size was 124. Considering the dropout rate of 10%, the final total sample size was 138 patients (69 patients per group).”

METHODS AND ANALYSIS – Intervention
“On the first day of each subsequent training week, patients will be asked to return to the hospital to receive a face-to-face training session. We will conduct real-time video meetings during all home training sessions to ensure adherence to the treatment plan. We will also ask participants to complete daily training logs to record training completion and monitor the degrees of fatigue. In addition, we will calculate the number of training sessions the participant completes.”

METHODS AND ANALYSIS – Outcome measures
“The MDS-UPDRS is a commonly used tool in clinical settings and research to assess influences of

PD on multiple aspects in patients [35]. It consists of four parts, including (the first part) non-motor subjective experiences of daily living, (the second part) motor-related subjective experiences of daily living, (the third part) the motor examination, and (the fourth part) motor complications [35]. We will calculate the domain score of the third part of MDS-UPDRS, which is used to reflect objective severity of movement symptoms in patients. Larger scores indicate more severe movement symptoms. We will also use the score of the depression item and that of the anxiety item separately in the first part of MDS-UPDRS to detect levels of depression and anxiety in patients."

METHODS AND ANALYSIS – Data collection and statistical analysis
"A one-way analysis of covariance will be conducted to examine effects of group (the PSE group versus the no-PSE group) on each dependent variable, including BBT scores, the error rate during executing BBT, JHFT scores, and the domain score of the third part of MDS-UPDRS at posttest. The 10 potential confounding factors are age, gender, the Hoehn and Yahr stage, disease duration, the more-affected side, medication dosage, the number of training sessions the participant completes, the score of the depression item in the first part of MDS-UPDRS at pretest, the score of the anxiety item in the first part of MDS-UPDRS at pretest, and a pretest score of an outcome variable (including BBT scores, the error rate during executing BBT, JHFT scores, and the domain score of the third part of MDS-UPDRS). The alpha level (two-tailed) will be set at 0.05. It is hypothesized that after controlling for confounding influences, PSE increases scores of BBT, and decreases JHFT scores, the domain score of the third part of MDS-UPDRS, and the error rate of BBT."

3. It would be useful to train both hands (because the left hand may be more affected by the disease to see the effects of training).
Reply:
Thank you for your comments. Compared with the classic 30-minute RAS training program for gait (Thaut et al., 1996), the training protocol adopted in this study will last for 40 minutes because we added breaks to the training protocol. The major reason for this adaptation is that our pilot study showed that patients with PD had noticeable fatigue and reduced motivation when using upper limbs, in which muscles are smaller than those of lower limbs, in training without provision of breaks. We did consider combining the left-hand movement training via two options. The first option was to directly add separate daily 40-minute training for the left hand to the training protocol, which substantially elongated the total training period per day. According to the feedback in our pilot study, this first option was too demanding and thus reduced motivation of participation in PD patients. The second option was to divide the 40-minute training into two halves, one of which was for the right hand and the other for the left hand. Compared with our current protocol, only targeting the right hand, the second option resulted in shorter training time for each hand and increased the risk of insufficient training intensity and consequent no training effects. After deliberating influences of the two options, we determined to focus on the right hand training in this protocol as a first step in validating beneficial effects of PSE in patients with PD. Future research recruiting another sample of participants will be suggested to further explore effects of PSE on the left hand.

Reference:
Thaut, M. H., McIntosh, G. C., Rice, R. R., Miller, R. A., Rathbun, J., & Brault, J. M. (1996). Rhythmic auditory stimulation in gait training for Parkinson's disease patients. Movement Disorders, 11(2), 193–200. https://doi.org/10.1002/mds.870110213

4. Why will the distance between the target and main bowls be set at 30 cm instead of each participant's 50% of upper-limb length?
Reply:
Thank you for your comment. The distance between the target and main bowls on the picking-beads task was kept the same (that is, 30 cm) across all participants because the design of the training task

between the PES group and the non-PES group should be the same. The only difference between the two groups is the provision (yes versus no) of PES. Varying reaching distances on the picking-beads task (that is, 50% of each participant's arm length) becomes a confounding factor, which we would like to prevent when we designed this randomized controlled trial. The reason for selecting 30 cm to be the fixed reaching distance is that this distance is equal to 50% of the average arm length of Hong Kong women and thus reachable for all participants.

METHODS AND ANALYSIS – Intervention
"Three target bowls, labelled as the left, middle, and right target bowl, will be placed on the table at an equal distance from the main bowl. The distance between a target bowl and the main bowl will be set at 30 cm, which is 50% of the upper-limb length (from the shoulder to the middle finger tip) of Hong Kong women [41], to ensure that beads in the target bowls are reachable for research participants."

5. Please indicate when (during the day) the participants will have a training session relative to their medication schedule.
Reply:
Thank you for the important suggestion. We have added descriptions in the revised manuscript. Please see the relevant revisions below.

METHODS AND ANALYSIS – Intervention
"The training sessions will be conducted during the "ON" period of medication. Specifically, the participant will be required to conduct daily training after 1 hour of taking medications. Each daily training will consist of three rounds……"

6. Please provide the rationale why blinding is not applicable.
Reply:
Thank you for your comments. We have added descriptions regarding the blinding of assessors. Blinding of patients and people who provide training is not feasible in this study because patients and training providers know group allocation.

METHODS AND ANALYSIS – Study design
"Assessments will be completed face-to-face before and after the 21-day training by a senior therapist who is blinded to the group allocation. Blinding of patients and people who provide training is not feasible in this study because patients and training providers know group allocation."

7. As Fan et al (2022) cited in this manuscript has acknowledged the issue of "speed/accuracy(variability) trade off" and considering the importance of accuracy/variability for upper-limb function, it would be useful if this study assesses it.

Reply:
Thank you for the valuable comment. Although this study aims to improve and assess movement speed, we understand that movement quality in response to PSE also matters and is worth assessments. We will use the BBT of this study to assess movement quality in addition to movement speed. Specifically, we will additionally record the number of blocks dropping out in each hand task of the BBT and calculate the error rate of executing BBT. The lower error rate in each hand task indicates the higher movement accuracy. Please see the revisions below.

METHODS AND ANALYSIS – Outcome measures
"The score of BBT for each hand is the number of blocks that are successfully transferred between compartments in one minute. A higher BBT score indicates faster upper-limb movements and better dexterity. In addition, the number of dropping blocks during the blocks moving tasks of BBT in each hand will be recorded as the error score. We will calculate the error rate of executing BBT in each

hand by dividing the error score by the sum of the error score and the BBT score to assess the accuracy of upper-limb movements. The higher error rate indicates less accurate upper-limb movements."

8. To assess the effects of intervention on reduction in bradykinesia (the primary aim of this study), it would be useful to assess MDS-UPDRS III scores post-intervention.
Reply:
Thank you for your valuable comment. We have added the domain score of the third part of MDS-UPDRS as one dependent variable. Please refer to relevant revisions below and also in the revised manuscript.

METHODS AND ANALYSIS – Outcome measures
"The MDS-UPDRS is a commonly used tool in clinical settings and research to assess influences of PD on multiple aspects in patients [35]. It consists of four parts, including (the first part) non-motor subjective experiences of daily living, (the second part) motor-related subjective experiences of daily living, (the third part) the motor examination, and (the fourth part) motor complications [35]. We will calculate the domain score of the third part of MDS-UPDRS, which is used to reflect objective severity of movement symptoms in patients. Larger scores indicate more severe movement symptoms. We will also use the score of the depression item and that of the anxiety item separately in the first part of MDS-UPDRS to detect levels of depression and anxiety in patients."

METHODS AND ANALYSIS – Data collection and statistical analysis
"A one-way analysis of covariance will be conducted to examine effects of group (the PSE group versus the no-PSE group) on each dependent variable, including BBT scores, the error rate during executing BBT, JHFT scores, and the domain score of the third part of MDS-UPDRS at posttest. The 10 potential confounding factors are age, gender, the Hoehn and Yahr stage, disease duration, the more-affected side, medication dosage, the number of training sessions the participant completes, the score of the depression item in the first part of MDS-UPDRS at pretest, the score of the anxiety item in the first part of MDS-UPDRS at pretest, and a pretest score of an outcome variable (including BBT scores, the error rate during executing BBT, JHFT scores, and the domain score of the third part of MDS-UPDRS). The alpha level (two-tailed) will be set at 0.05. It is hypothesized that after controlling for confounding influences, PSE increases scores of BBT, and decreases JHFT scores, the domain score of the third part of MDS-UPDRS, and the error rate of BBT."

VERSION 2 – REVIEW

REVIEWER	Fasano, Alessio Scuola Superiore Sant'Anna
REVIEW RETURNED	16-Jun-2023

GENERAL COMMENTS	The authors revised the manuscript with clear and comprehensive modifications, following the reviewers' suggestions and mitigating all their concerns. I have no further comments. Thank you.