Author’s response to reviews

Title: Effects of motor imagery training of gait in Parkinson´s disease: a protocol for a randomized clinical trial

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Response to Reviewers:

Reviewer #1

1. Is the EG group instructed to continue motor imagery on their own in daily life and after the 4 weeks as well? Are the authors assessing this fact? It might be possible that patients would try this at home as well if they experience satisfying results during the Physiotherapy sessions.

EG individuals will be instructed to continue to practice MI of gait in their daily lives during the training period. They will be instructed to fill in a diary with information on the quantity of days, number of repetitions and duration of the training performed at home, for analysis purposes, if we find satisfactory effects in this group. This information was added to the manuscript at page 13, lines 337 to 340.

2. Page 6, line 152: Inclusion criteria: why is the maximum age 75 years and not higher?

To minimize the repercussions of aging on participants' gait performance, reported in some studies:

3. Page 6, line 153: Antiparkinson medication is an inclusion criterion. Are the authors monitoring medication changes? How would the authors deal with possible medication changes or are the patients instructed to do not adapt medication during the course of the study?

Antiparkinsonian medications used by each participant will be recorded at the start of the study. Participants will be instructed not to make adaptations until finalization of their participation in the study. This information was added to the manuscript at page 6, line 173.

4. Page 6, line 161 ff: Exclusion criteria: Is there a special reason for testing and excluding hemodynamic instability, especially defined by hypertension? I would rather expect orthostatic problems. Please comment on that.

Cardiovascular autonomic symptoms such as orthostatic hypotension, supine hypertension and reduced heart rate variability are expected in these patients. Therefore, there will be a monitoring of these variables in these patients, so that they can perform the proposed training safely. Despite the fact that hypertension is not a symptom frequently reported in the literature, in the study by Giodano et al., Mov Disord., 2017, the authors compare two samples of patients with Parkinson's disease, one with hypertension and another not. They observed that hypertension is associated with more severe Parkinson's disease motor symptoms. Although there are few studies that relate hypertension to Parkinson's disease, it is important to consider that hypertensive symptomatology is frequent and shows a high prevalence in the Brazilian adult and elderly population.


Yes, the correct term is EEG. Correction was made on the page 7, line 200, and page 15, line 403.

6. The method, using Emotiv EPOC+ is in line with the innovative approach of the project, however a more extensive explanation of the expected findings would be valuable.

More information was added to the manuscript at “Background”, page 4, lines 95 to 101, 104 to 111, and page 5, lines 133 to 138.

For a more extended explanation, the reduction of Dopamina of the substantia nigra and its projections in Parkinson's disease (PD) results in electrophysiological changes in the activity of neurons involved in the cortico-striatal circuit and in motor and non-motor symptoms observed in the disease. While in healthy people, phasic movements, as gait, are modulated in the gamma rhythm (Pfurtscheller et al., 2003; Miller et al., 2007), pathological firing patterns in the beta rhythm (13–30 Hz) in the subthalamic nucleus (STN) have been linked to akinesia and rigidity in PD patients (Marsden et al., 2001; Kuhn et al., 2008). In addition, the beta rhythm is related to
memory, attention and learning, assumptions of the executive function, deficient in this pathology (Ros et al., 2014). It has been shown that MI can produce replicable EEG patterns over primary sensory and motor areas (Beisteiner et al., 1995; Pfurtscheller & Neuper, 1997). As an example, imagery of hand movements results in desynchronization of mu (8–12 Hz) and central beta rhythms (13–28 Hz), very similar to planning and execution of real movements. Few studies in PD investigated electroencephalographic functions during gait activity. Therefore, this study seeks to contribute to the literature on the pattern of brain activation of individuals with PD during gait activity, before and after the intervention with Motor Imagery. The Emotiv Epoc + can provide information in a practical way and is intended to make analysis of spectral power and coherence.

7. Page 9, line 237 ff: Is 'showing the gait cycle' comparable to action observation therapy? (Caligiore, 2016). If so, this should be commented as it could add a therapeutic effect.

The visualization of the gait is a previous stage of action observation to facilitate the MI of gait. The EG will need to visualize the movement itself and execute it before imagining it. These are resources to increase the perception of the stages of movement from the activation of a visual and kinesthetic memory, facilitating the imagination of the movement. We consider, therefore, that they are necessary for MI, not being additional therapy. In addition, the time used by EG to observe and imagine the movement will be the same as the CG will have to view the educational video.

8. Page 10, line 250: How do the patients compare their own gait to the presented videos? Are videos also made from the patient's gait?

The therapist will show a video of the normal gait (typical) of an adult man or woman with no pathologies, and will compare to the video made of the patient's own gait. When viewing both videos, patients will analyze and score the characteristics of their own gait that differ from the gait of the individual without pathology, such as step width, arm swing, posture and speed. This information was added to the manuscript at page 10, lines 254 to 257.

9. Page 10, line 257: I assume only the EG group, will perform the progressive relaxation? For completeness, the authors might clarify in the manuscript within this paragraph.

Both groups will do progressive relaxation. It was clarified at the manuscript at page 10, line 270.

10. Page 10, line 272: The authors report "3 sessions" of MI. This is confusing for readers, as I understood the patients will always do MI prior to physiotherapy sessions?

To facilitate the reader's understanding, the following information was added on page 11, lines 295 and 296: “Each MI session will be performed alternately with the PP sessions (described in the next topic: ‘5) PP OF GAIT’). The MI will always be prior to the PP of gait.”. This information is also reinforced on page 11, lines 301 and 302.
11. Page 12: The exact role of the physiotherapists in the CG is not entirely clear. Will the CG only receive advices from physiotherapists as well? It might be good to comment on that more extensively.

To facilitate the reader's understanding, new information was added to the manuscript at page 11, line 303.

12. Page 11, Line 282-289: I wonder, if this paragraph might fit better into the paragraph "MI of Gait".

Suggestion accepted. The paragraph was moved to the topic "MI of gait" on page 11, lines 286 to 287 and 289 to 294.

13. Page 12, line 324: Will the EG group do the MI prior to the gait testing/analysis as well? Or do the authors aim to test the longer lasting effect of MI?

Participants will not perform MI immediately prior to the gait test. It is intended to evaluate effects 24h, 7 days and 30 days after the last MI training session. The patient will be instructed during the gait test to walk as he has habitually done in the last days, since the beginning of the study participation. Because the evaluator is blind to allocation groups, he will not know whether the patient is making corrections or not in gait.

To facilitate the reader's understanding, new information was added to the manuscript at page 13, lines 343 to 345.

14. Figure: I suggest to add the training period (such as week 1-4) to the boxes 'Control group' and 'MI group' (week 1-4). Furthermore, "Baseline measures" are confusing in the boxes 'Post-intervention' and 'Follow-up measures'. The authors might add "Repetition of baseline measures". An explaining figure's legend is missing as well.

Suggestion accepted, the figure was redone to make it clearer. The legend of the figure is in the "Figure legends" section on page 20, line 546.

Reviewer #2

15. The rationale / background on the selection of EEG as outcome for this study needs to be spelled out and supported more clearly. Would EEG be used as biomarker, and if so what type of biomarker (target engagement? surrogate?)? This should be supported by references, etc.

In a recent review study, Bočková and Rektor (2019) concluded that, in PD, there is a general slowing of background activity, excessive synchronization of beta activity, and disturbed movement-related gamma oscillations in the basal ganglia and in the cortico-subcortical and cortico-cortical motor loops, suppressible by dopaminergic medication as well as by high-
frequency DBS. Although dopaminergic therapy is currently the best treatment in PD, gait dysfunctions are commonly resistant to drug therapy, especially in more advanced stages of the disease. It has been shown that motor imagery can produce replicable EEG patterns over primary sensory and motor areas (Beisteiner et al., 1995; Pfurtscheller & Neuper, 1997) and, in spite of deficits in the supplementary motor area from indirect effect of the basal ganglia, PD patients have preserved locomotor imagery observed during on state of medication (Snijders et al., 2011). The mesencephalic locomotor region, in the brainstem region and constituted by pedunculopontine and cuneiform nuclei, is modulated by changes in imagined locomotion in healthy humans (Jahn et al., 2008), which also modulates cortical networks similar to those involved during real gait (La Fougère et al., 2010). This study seeks to bring contributions to the literature regarding the pattern of brain activation of individuals with PD during walking activity and during motor imagery of gait after a period of MI intervention, discussing the potential of motor imagery training in gait rehabilitation.

These information was added to the manuscript at page 4, lines 95 to 101 and lines 104 to 111.

16. Sample size estimation: the study is powered based on previous observed effects of locomotor imagery training on degrees of hip excursions. In this referenced study, the difference between the means of hip excursion was apprx 6 degrees. Please justify the selection of this specific measure (over all other measures deployed in this previous study) to calculate the sample size, and provide a rational for relevance / clinical meaningfulness of this measure and the intended change.

Variations in hip angle, even if small, biomechanically, may reflect or influence angular changes in other joints, which together generate clinically important postural changes. Hip angulation was chosen to compose the calculation, considering also that it will be a parameter observed by the participants in the analysis of the gait movement during the experimental protocol, that is, they will analyze the video itself in the sagittal plane, which highlights the pattern common hip flexor in PD. The range of motion of the hip will also be the primary outcome of this study.

17. Clarify whether the inclusion criterion requirement subjects being "between stages 1.5 and 3" on the H&Y scales, allows subjects with a stage 1.5 or 3 can be included or not.

Individuals in phases 1.5 to 3 will be included. To facilitate readers' understanding, additional information was placed on page 6, line 172.

18. The specific primary and secondary outcomes should be listed - either in the text or in a table / box. "Kinematic variables" and "electroencephalographic activity" is to general, and the actual extracted and computed variables should be identified that go into the analysis. In particular, as the study was powered on the expected change of hip excursions, this outcome should be assessed. Also, in the data analysis section, specify the variables (EEG frequency bands are not an outcome measure).

Recommendations accepted. The primary outcome will be the hip range of motion, which corresponds to a kinematic variable. Secondary outcomes correspond to mobility (assessed
through Timed Up and Go Test), spectral power of alpha and beta rhythms and intra- and inter-hemispheric coherence between frontal and fronto-central channels.
These information was added to the manuscript at page 7, line 188 and lines 197 to 198.

19. Since the assessors and analysis staff will be blinded to the allocation, please elaborate on the blinding procedure, to ensure that there is protection from accidental or unintended unblinding.

The randomization process will be performed by a volunteer outside the research, who will maintain the confidentiality of the allocation until the end of the study. He will randomly separate individuals into control (CG) and experimental (EG) groups, using codes to represent the groups. He will also prepare sequentially numbered, sealed envelopes. The randomization sequence will be performed according to the coding created for the study groups (control and experimental).

The researcher in charge of the training will only open the envelope corresponding to the number of the patient who will be starting the training and he will know about the meaning of each code.

The researcher responsible for the statistical analysis, will only have access to the codification, not being informed which group corresponding to which code.

This information was added to the manuscript at page 8, lines 215 to 216, 218 to 219, and 222 to 223.