Does exergaming promote neurofunctional changes in Parkinson´s disease? A pilot clinical study

Os exergames promovem alterações neurofuncionais na doença de Parkinson? Um estudo clínico piloto

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Abstract

Introduction: Previous studies have demonstrated beneficial effects in people with Parkinson´s disease trained with exergames. However, to the best of our knowledge, none of them evaluated whether these effects are sustained by neurofunctional changes. **Objective:** To evaluate neurofunctional effects of a training, by means of functional magnetic resonance imaging, in people with Parkinson´s disease. **Methods:** This study was a blind, randomized, and controlled pilot clinical trial with crossover design. The participants were submitted to an evaluation including cognitive performance and functional magnetic resonance imaging before and after the WiiTM or control trainings. Trainings were applied for 10 days, in two consecutive weeks. Participants starting with WiiTM training were then moved to the control training and vice versa. A wash-out period of 45 days between the trainings was respected. **Results:** Memory, executive and visuo-spatial functions, and attention were significantly improved compared to baseline ($p < 0.05$). No differences were observed in cognition compared to the control training. Though not significant, results of functional magnetic resonance imaging analyses suggested that WiiTM training could promote improvements on the brain functional connectivity especially in areas involved in motor execution, planning, visual, memory and somatosensory functions. **Conclusion:** In people with Parkinson´s disease, an intensive WiiTM training improved cognitive performance that underlined neurofunctional changes in areas involved in cognitive processing.

Keywords: Cognition. Exergames. Magnetic resonance imaging (Functional). Parkinson Disease.

Resumo

Introdução: *Estudos anteriores demonstraram efeitos benéficos em pessoas com doença de Parkinson treinadas com exergames. No entanto, até onde sabe-se, nenhum deles avaliou se esses efeitos são sustentados por alterações neurofuncionais.* ***Objetivo:*** *Avaliar os efeitos neurofuncionais de um treinamento, por meio da ressonância magnética funcional, em pessoas com doença de Parkinson.* ***Métodos:*** *Trata-se de um ensaio clínico piloto cego, randomizado e controlado com delineamento* crossover. *Os participantes foram submetidos a uma avaliação incluindo desempenho cognitivo e ressonância magnética funcional antes e após treinamentos com Wii® ou controle. Os treinamentos foram aplicados durante 10 dias, em duas semanas consecutivas. Os participantes que começaram o treinamento com Wii® foram depois movidos para o treinamento de controle e vice-versa. Respeitou-se um período de* wash-out *de 45 dias entre os treinamentos.* ***Resultados:*** *Memória, funções executivas e visuoespaciais e atenção melhoraram significativamente em comparação com a linha de base ($p < 0,05$). Não foram observadas diferenças na cognição em comparação com o treinamento de controle. Embora não significativos, os resultados das análises de ressonância magnética funcional sugeriram que o treinamento com Wii® poderia promover melhorias na conectividade funcional do cérebro, especialmente em áreas envolvidas na execução motora, planejamento, funções visuais, de memória e somatossensoriais.* ***Conclusão:*** *Em pessoas com doença de Parkinson, um treinamento intensivo com Wii® melhorou o desempenho cognitivo, que destacou mudanças neurofuncionais em áreas envolvidas no processamento cognitivo.*

Palavras-chave: *Cognição. Exergames. Ressonância magnética (Funcional). Doença de Parkinson.*

Introduction

Parkinson's disease (PD) is a chronic, degenerative, and progressive condition characterized by motor (stiffness, tremor, bradykinesia, postural instability) and cognitive symptoms (attention, executive, and visuospatial functions impairments).[1]

Cognitive symptoms lead to increased disability and hinder the treatment of motor symptoms.[2] Treatment of PD involves medication, surgery, and rehabilitation. As medications and surgery may not prevent the progression of the disease or improve cognitive functions, the role of rehabilitation has become increasingly important.[3,4]

Among treatment modalities, virtual reality (VR) training has become a resource in cognitive-motor rehabilitation. VR allows the patient to interact with an artificial reality through computer simulation,[5] providing real-time feedback on performance in the virtual task and offering control over the intensity of exercises and an environment rich in sensory stimulation.[5,6] In the last decade, commercial exergames, due to low cost, positive effect on motivation and potential for home using,[7,8] have become an alternative to more sophisticated VR systems and might be considered a new intervention tool. Previous studies have shown that videogame training is beneficial, economical, and safe for PD patients,[8,9] demanding non only motor but cognitive skills such as memory, attention, and visuospatial functions.[9]

Among the commercial exergaming systems, potentially useful as rehabilitation tool, the most used is the Nintendo Wii Fit Plus™. It is a portable low-cost device, easy to handle and with good reliability.[10] Its interface incorporates manual wireless controls and a force platform, the Wii Balance Board (WBB), capturing the weight shifting and users´ resulting movements, and transferring them to the games in real time.[11] Some studies have used the Wii™ confirming it as an effective intervention tool in people with PD.[9,10,12-14] In general, these studies assessed balance,[9,10,12,13] gait,[9,14] and quality of life[9,12,14] using only clinical scales. Cognition was assessed by non-specific clinical tests.[12,14] Therefore, none of these studies verified the effects of training through specific cognitive tests that could identify changes in cognitive functions truly trained in exergaming (such as attention, memory, and visual-spatial skills), nor through objective measures such as neurofunctional and brain activity changes, as imaging tests can demonstrate.

Functional magnetic resonance imaging (fMRI) has been applied to PD to enhance the understanding of pathophysiological changes, including functional connectivity (FC), by detecting variations in cerebral blood flow. Among these, resting state (RS-fMRI) evaluates regional interactions and functional connectivity when the subject is not performing a specific task.[15] By means of RS-fMRI,[16] it has been demonstrated that one training session, with high intensity exercises, was able to promote changes in the brain activity of people with PD previously trained.

Thus, the objective of this study was to evaluate, in patients with PD, whether intensive virtual reality-based training would promote a superior effect on specific cognitive performances compared to those observed after an exclusively motor therapy, and to determine consequent possible neurofunctional changes. Our hypothesis was that the cognitive-motor training provided by the exergaming training could stimulate brain areas involved in both, motor and cognitive functions, and that this stimulation would be based on neural structure and connectivity changes.

Methods

This study, approved from the Ethics and Research Committee of the University of Palermo/Italy (No. 4/2014/ Comitato Etico Palermo 1), used a single-blind, randomized, controlled and cross-over, with a washout period.

Participants

Participants were consecutively recruited in the Movement Disorders outpatient clinic of University Hospital of Palermo according to inclusion and exclusion criteria. According to such criteria, ten patients were enrolled in the study (Table 1). All patients gave their consent to participate. The procedures for RS-fMRI were performed in the Radiology Section of the University Hospital of Palermo.

Inclusion criteria

PD diagnosis made according to criteria of the Movement Disorders Society (MDS);[17] being considered eligible after screen visit of a physiotherapist; being on stable treatment with antiparkisonian drugs; being classified as stage 1 to 3 according to the Hoehn and Yahr scale; presenting a Mini Mental State Examination score ≥ 24; having at least 4 years of formal education; having visual and auditory acuity consistent with the requirements of videogame training; being of male sex, to avoid brain heterogeneity in MRI scans.

Exclusion criteria

Having other neurological disorders or organic pathological conditions that prevented participation in the trainings; having previous experience with Wii games; attending another specialized rehabilitation program; having absolute or relative contraindications to MRI.

Table 1 - Demographic and clinical characteristics of the participants

Cases	Age (years)	Duration of the disease (years)	Level of education (years)	m-H&Y (staging)	Total UPDRS (scores)	MMSE (scores)
1	57	4	8	2	42	29
2	64	1	8	1	27	30
3	62	2	8	2	29	28
4	75	1	13	2	34	30
5	59	3	8	1	23	30
6	52	5	18	2,5	32	30
7	69	3	24	2	28	30
8	56	1	18	2	20	30
9	70	11	8	3	79	29
10	72	6	13	2	47	30
Mean	63.60	3.70	12.60	1.95	36.10	29.60
SD	7.68	3.09	5.72	0.60	17.14	0.70

Note: m-H&Y = Modified Scale of Hoehn and Yahr; UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini Mental State Examination; SD = standard deviation.

Study design

Participants first underwent cognitive tests and RS-fMRI (T0 the week prior to the beginning of the first training). They were then randomly allocated into the Nintendo Wii Group (WG) or the Wii-like Group (WLG).

After completion of the first part of training, patients of both groups underwent cognitive evaluation and RS-fMRI (T1, the week after the end of the first training). After a 45 days interval, the two groups started the second exercise sessions: those who initially started with Wii™ training completed the study with "Wii-like" exercises, and vice versa. When the second training session was completed, the two groups repeated cognitive evaluation and RS-fMRI (T2, the week after the end of the second training).

Figure 1 illustrates the stages of the study. The participants were instructed not to reveal to the evaluator about their allocation. The same physiotherapist was involved in both types of training.

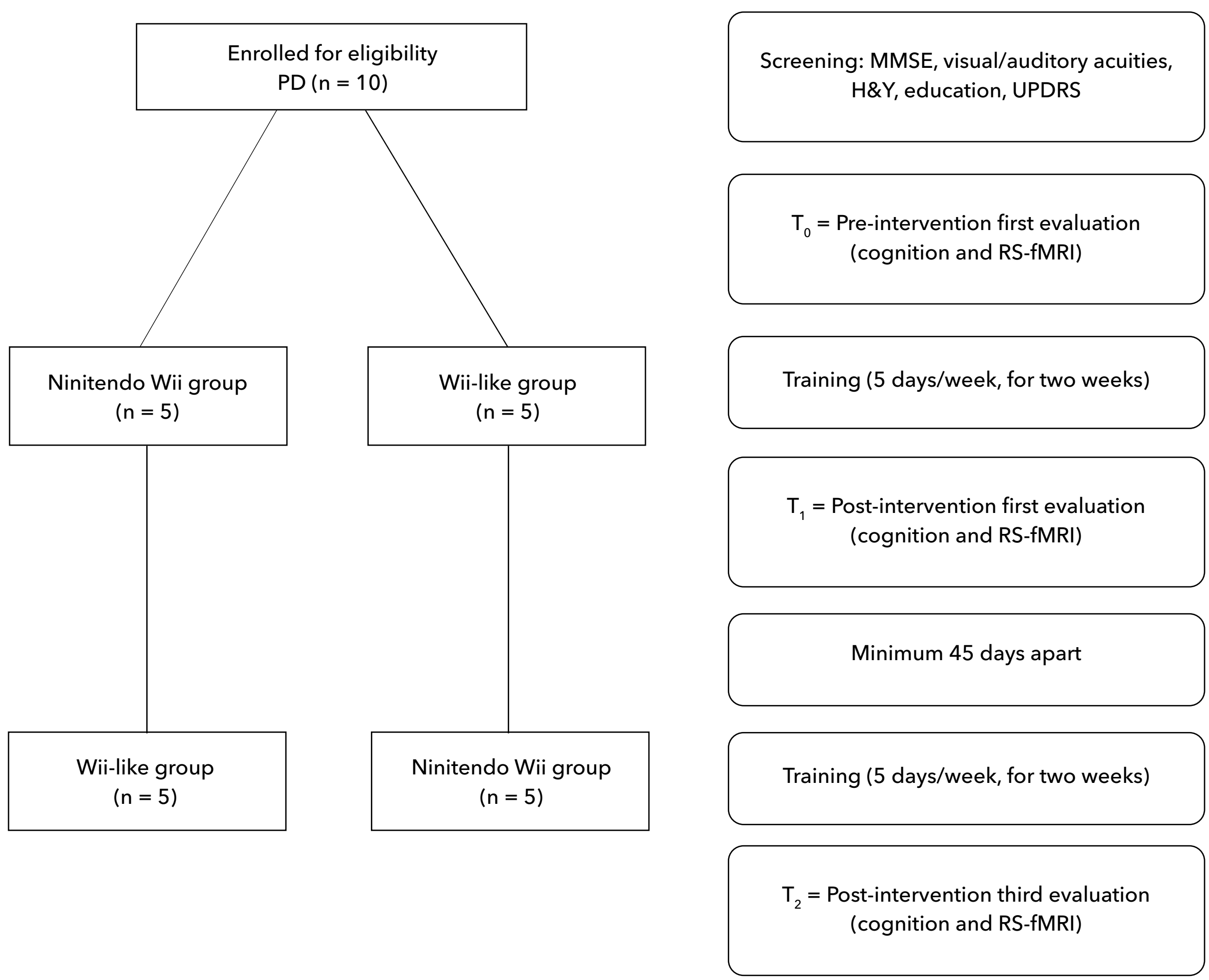

Figure 1 - Flowchart of the study procedures.

Note: PD = patients with Parkinson's disease; MMSE = Mini Mental State Examination; H&Y = Hoehn and Yahr Disability Scale; UPDRS = Unified Parkinson's Disease Rating Scale; RS-fMRI = Resting State Functional Magnetic Resonance Imaging.

Interventions

Wii training: the WG underwent 10 intensive individual training sessions, supervised by a physiotherapist, five times a week for two consecutive weeks, always in ON state of the dopaminergic medication. Four games of the Wii Fit Plus package of the Wii™ videogame (obstacle course, basic step, rhythm parade and tightrope walk) were previously selected according to the motor and cognitive demands established in the study by Alves et al.[13]

Table 2 describes the main tasks to be done and the motor and cognitive demands of the Wii games. The videogame device was connected to a multimedia projector projecting games images on a 2m x 2m canvas screen, positioned two meters away, in front of the participant. Participants repeated three times each game per session, and each session had a maximum duration of 45 minutes. The sequence of games trained in each session was randomized. Before starting of the first training session, the physiotherapist explained the objectives and allowed only one initial attempt in each game for familiarization with tasks and equipment, in which all participants should perform. During the attempts, the physiotherapist offered verbal and kinesthetic stimuli to promote correct posture and movements, for proper interaction with the games. Rest periods were observed if needed.

Table 2 - Main games tasks and demands

Games	Tasks	Main motor demands	Main cognitive demands
Obstacle course 	Walk as fast as possible and stop ona course, avoiding obstacles.	Fast stationary walk and suddenly stopping.	Response inhibition and planning.
Basic step 	Alternate steps according to the game's music rhythm and visual stimuli.	Alternate, coordinated steps.	Sustained attention, divided attention and visuospatial capacity.
Rhythm parade 	Marching in place to the sound of a beat while moving arms according to the visual stimuli.	Alternate coordinated steps while moving arms.	Divided attention.
Tightrope walk 	Keep balance while walking on a tightrope and avoid obstacles.	Shift center of gravity latero-laterally.	Sustained attention and decision making.

Wii-like training: WLG performed a set of exercises based on the same motor demands (described in Table 2), with similar number of repetitions, movement velocities and duration required by each of the four games selected for the Wii training. The same Wii´s controls and platform were used, but turned off, to increase the similarity with Wii training. Wii-like training occurred without the provision of external cues, feedback, or cognitive stimulation, offered by the games.

Cognitive performance assessment

A comprehensive battery of neuropsychological tests was applied, with a total duration of 1 hour, in a room reserved exclusively to the evaluator and to the patient. All tests were applied through forms A and B to avoid learning effects. The following tests were applied:

Attention and working memory: digit span forward; attentive matrix test; trail making test parts A and B; symbol digit modalities test;

Executive functions: frontal assessment battery; phonemic fluency (letters P, F and L); cognitive estimation test;

Visuo-spatial functions: Test of the Rey-Osterrieth C Com-plex Figure, that evaluates immediate and late recall;

Verbal memory: Rey´s list - immediate and late recall; revocation of the complex figure of Rey-Osterrieth;

Language: semantic fluency test (animals).

RS-fMRI acquisition and preprocessing

All participants underwent brain scan using a 1.5 T MRI scanner (Signa HDxt; GE Medical System, Milwaukee, Wisconsin, USA) at the Radiology Section of the University Hospital of Palermo. An eight-channel brain phased array coil was used. Foam pads were placed on both sides of the head, within the head coil, to limit head motion during the scan.

Structural images were obtained via a T1-weighted sagittal three-dimensional (3D), ultra-fast gradient echo 1mm thick Brain Volume Imaging (BRAVO) isotropic sequence (acquisition matrix 256 x 256; FOV 25.6 x 25.6; slice thickness 1 mm; TR 12.4 ms; TE 5.1 ms; IT 450 ms; FA 20; parallel imaging method: Array coil Spatial Sensi-tivity Encoding, ASSET). RS-fMRI data were acquired with a two-dimensional (2D) axial T2*-weighted gradient-echo Echo-Planar (EP) pulse sequence parallel to the anterior commissure-posterior commissure (AC-PC) line over the entire brain (acquisition matrix 64 x 64; 33 slices; slice thickness 3 mm; gap 1 mm; TR 3000 ms; TE 60 ms; FA 90); the first five scans were discarded to allow T1 saturation to reach equilibrium. All participants were explicitly instructed not to move during the MRI scan and quietly rest in the scanner with their eyes open and not to think of anything specific. A ten-minute (200 volumes) fMRI scan was performed on each participant. Scan parameters were consistent for all imaging sessions. All the preprocessing was performed at the Department of Physics and Chemistry of the University of Palermo, using FSL's recommended preprocessing pipeline from FMRIB's Software Library (FSL version 5.0.9).

The following preprocessing procedure was applied by employing different modules of the FSL-software package. The preprocessing of the resting-state data consisted of the standard FSL steps.[18,19]

Statistical analysis

All analyses were performed using the statistical package SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov, Levene and Mauchly tests were used to assess normality, variance homogeneity and data sphericity, respectively. Demographic and clinical characteristics were presented as descriptive measures. Results of the cognitive tests were analyzed by means of a repeated measure two-way Anova (group [WG x WLG] x time [pre x post]), followed by the post hoc Bonferroni test. The significance level was $p < 0.05$.

The analyses related to the processing of functional magnetic resonance images were made through FSL's MELODIC software, using independent component analysis (ICA). ICA was carried out using FSL's MELODIC toolbox implementing probabilistic independent component analysis (PICA). Multi-session temporal concatenated ICA (Concat-ICA) approach, as recommended for RS-fMRI data analysis was chosen.[20] We tested Resting State-Functional Connectivity (RS-FC) by performing a dual regression analysis in six different conditions: Baseline x Wii (stat1); Wii x Baseline (stat2); Baseline x Wii-Like (stat3); Wii-Like x Baseline (stat4); Wii x Wii-Like (stat5); Wii-Like x Wii (stat6).

As a statistical analysis, the different component maps are tested voxel-wise for statistically significant differences between the groups using FSL dual regression, which allows for a voxel-wise comparison of RS-fMRI.[19] Correction for multiple comparisons across space was applied assuming an overall significance of $p < 0.05$, using permutation testing and TFCE.

Results

No dropouts occurred during the study. Both WG and WLG trainings were well tolerated.

A significant improvement in cognitive performance (Table 3) was observed after both trainings, in the Rey List tests (immediate and later recall), Trail Making Test part B and Rey-Osterrieth Complex Figure Revocation test, with significant time effects (p = 0.00; p = 0.01; p = 0.005; p =0.00, respectively), but without significant group or interaction effects, for all these tests.

No significant differences were observed in the participants' performances in any other cognitive test (Table 3).

Table 3 - Performance of participants in cognitive tests, in the pre- and post-intervention moments, for each training modality

Test	Groups	Pre	Post	p-value
FAB (Score range: 0-18)	Wii	16.4 (2.2)	16.1 (2.5)	0.18
	Wii-like	16.4 (2.2)	17.1 (1.5)	0.06
DSF (Score range: 0-9)	Wii	5.8 (1.1)	5.5 (1.0)	0.52
	Wii-like	5.8 (1,1)	5.5 (1.6)	0.52
Rey – I (Score range: 0-75)	Wii	36.4 (5.9)	47.5 (8.7)	0.00
	Wii-like	36.4 (5.9)	46.2 (6.8)	0.01
Rey – D (Score range: 0-15)	Wii	7.2 (1.7)	8,8 (2.3)	0.01
	Wii-like	7.2 (1.7)	8,8 (2.3)	0.01
TMT-A (seconds)	Wii	85.9 (43.6)	66.6 (23.2)	0.11
	Wii-like	85.9 (43.6)	69.0 (47.5)	0.16
TMT-B (seconds)	Wii	259.4 (99.7)	134.5 (83.1)	0.01
	Wii-like	259.4 (99.7)	154.7 (130.1)	0.01
AM (Score range: 0-60)	Wii	46.2 (10.0)	48.9 (10.8)	0.15
	Wii-like	46.2 (10.0)	50.3 (7.8)	0.10
SD (Score range: 0-110)	Wii	33.1 (14.5)	40.2 (13.6)	0.05
	Wii-like	33.1 (14.5)	36.8 (10.8)	0.30
CET (Score range: 0-42)	Wii	15.5 (2.6)	14.1 (2.6)	0.14
	Wii-like	15.5 (2.6)	15.3 (2.1)	0.82
FF (number of evoked words)	Wii	30.4 (11.6)	32.0 (10.3)	0.53
	Wii-like	30.4 (11.6)	37.2 (13.3)	0.15
FS (number of evoked words)	Wii	36.8 (7.3)	37.2 (9.1)	0.80
	Wii-like	36.8 (7.3)	40.9 (10.5)	0.20
Rey Fig Cop (Score range: 0-36)	Wii	29.0 (8.6)	30.5 (7.2)	0.07
	Wii-like	29.0 (8.6)	29.0 (8.5)	0.07
Rey Fig Rec (Score range: 0-36)	Wii	13.6 (6.1)	16.3 (7.1)	0.05
	Wii-like	13.6 (6.1)	18.6 (7.4)	0.01

Note: Values are represented as mean and standard deviation. p = Bonferroni post hoc test to compare post-training evaluation with pre-training evaluation. FAB = Frontal Batery Assessment; DSF = Digit Span forward; Rey-I = List of Rey-immediate evocation; Rey-D = List of Rey- late evocation; TMT-A = Trail Making Test part A; TMT-B = Trail Making Test part B; AM = Attentive Matrix; SD = Symbol digit Modalities Test; CET = Cognitive Estimation Test; FF = Phonetic Fluency Test; FS = Semantic Fluency Test; Rey Fig Cop = Rey-Osterrieth Complex Figure Copy Test; Rey Fig Rec = Revocation of the Complex Figure of Rey-Osterrieth. For all tests, the higher the score, the better the performance, except for TMT-A and TMT-B.

Neurofunctional changes

Visual inspection of IC maps allowed us to identify common RS-fMRI networks reported in literature.[21,22] The dual regression analysis did not show any statistically significant RS-Functional Connectivity changes using a p-value of 0.05 and a cluster threshold of 0.95. However, by lowering the cluster threshold significance to 0.7 and considering only those clusters equal or higher to five voxels, some interesting results has emerged. Increased RS-FC were verified in the Wii group when compared to the Wii-like group, in the following components (Figure 2):

a) Motor and default mode networks: IC002 in the left precentral gyrus (mesial aspects) and left cingulate gyrus (peak at x, y, z: 48, 55, 58; cluster size = 5 voxels (Figure 2A).

b) Cerebellar and visual networks: IC008 in the left cerebellar crus II (peak at x, y, z: 49, 18, 15; cluster size = 151 voxels (Figure 2B). Left lingual gyrus and left retrosplenial cortex (hyppocampus tail) (peak at x, y, z: 55, 42, 37; cluster size = 40 voxels (Figure 2C).

c) Fronto-parietal network: IC0031 in the left postcentral gyrus (peak at x, y, z: 74, 52, 51; cluster size = 7 voxels (Figure 2D).

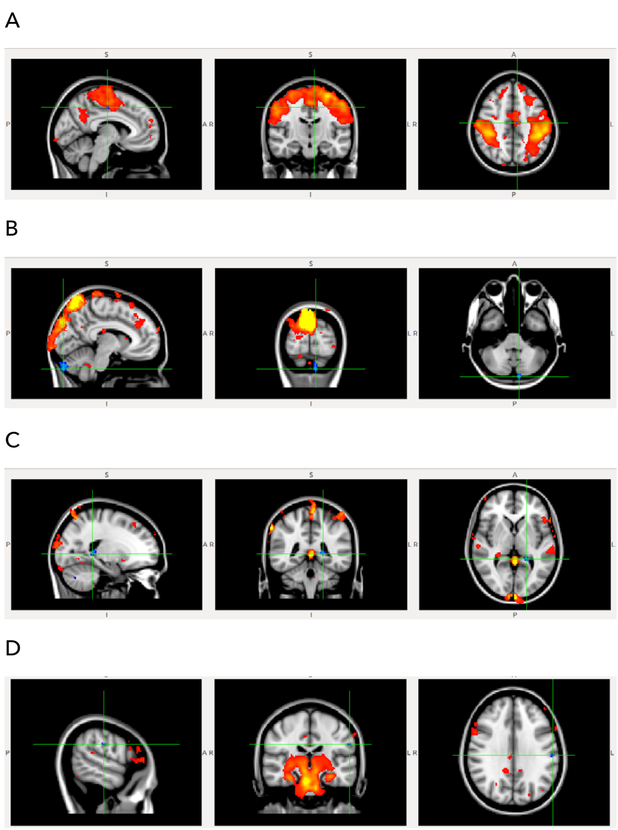

Figure 2 - Functional magnetic resonance imaging at resting state.

Note: A = Motor and default mode networks; B,C = Cerebellar and visual networks; D = Fronto-parietal networks. In the yellow-red color scale, the networks detected in a resting state are observed. Overlapping in light blue/dark blue color scale, variations in the functional connectivity detected.

Discussion

To the best of our knowledge, this is the first study that evaluated both a comprehensive battery of cognitive tests and neurofunctional changes in people with PD underwent to exergaming training. Results of the cognitive tests showed a significant improvement in the performance of the participants, after both trainings, in the Rey List Tests (in immediate and late evocation), Part B of the Trail Making Test and in the Revocation of the Complex Figure of Rey-Osterrieth. The Rey List Test includes a list of 15 words and uses five consecutive learning tests and a late test. The initial part of the learning mainly involves frontal executive functions, while the late recall test assesses verbal memory. The TMT-B, on the other hand, investigates attentional skills, spatial planning capacity of a visuo-motor task and its ability to rapidly shift from a numerical stimulus to an alphabetic stimulus. Revocation of the Complex Figure of Rey-Osterrieth test involves visuo-spatial memory.

These results indicate that both trainings probably stimulated the participant's cognitive functions such as executive, memory, attentive and visuo-spatial skills. These findings are, therefore, in line with those of previous studies showing that VR used as rehabilitation tool can have important effects on memory, attention and spatial orientation in people with PD.[23] Rehabilitation with the use of exergames seems to have an effect, especially improving the spatial perception of participants.[24] In fact, studies showed that each training session contributes, in the short term, with a slight improvement in cognitive functions,[25] and that chronically significant improvements can be achieved with more prolonged training.[24]

Regarding the results of the RS-fMRI, small changes in connectivity were detected in different networks, in T1. Thus, RS-fMRI analysis did not show any statistically significant RS-FC changes when using a p-value of 0.05 and a cluster threshold of 0.95. However, by lowering the cluster threshold significance to 0.7 and considering only those clusters equal or higher to five voxels, some interesting results has emerged. Thus, considering the relevance and novelty of the results, we will discuss the results speculatively, highlighting those ones in which there were an increase in the connectivity in participants of the WG in relation to those of WLG.

An increase in the FC was detected in the left precentral gyrus and left cingulate gyrus, in the motor and default mode networks. Such data suggest a global increase in the connectivity of the area involved in motor control (pre-central area) and in processing of emotions and behavior regulation (cingulate gyrus). An increase in the FC was detected also in the left cerebellar crus II, left lingual gyrus and left retrosplenial cortex (hippocampus tail), in the cerebellar and visual networks, respectively. Some studies[26,27] found increased FC of the cerebellum with motor and sensorimotor areas in people with PD compared to healthy controls.[28] This increase observed after Wii training, in the present study, could therefore reflect a beneficial effect of exergaming, promoting a greater cerebellar neurofunctional activity, helping in motor planning in this population. Additionally, the increase in the FC lingual gyrus could be related to gains in the visual function, possibly linked to the high visual stimulation of the games used. Guimarães et al. have already showed that the retrosplenial cortex is associated with verbal memory performance in people with PD.[29]

So, we could infer that the repetitive stimulation promoted by the exergaming training could have improved this function in our sample. Taken together, these findings can reflect the results in the cognitive clinical tests performed, in which we were able to verify in both groups improvements in memory and visuospatial functions.

Finally, we found increased FC in the left postcentral gyrus, in the frontoparietal network, greater in the WG in relation to the WLG. Guimarães et al.[29] have showed that people with mild PD symptoms already present cortical structural and functional damage. In PD, areas such as the postcentral gyrus present cortical thinning. Therefore, considering the increase in FC in this area, verified in the present study, it is plausible to infer that the Wii training could be a strategy to reduce the functional loss in that population, minimizing the structural damage.

From the authors' knowledge, this is the first study that aimed to evaluate neurofunctional changes, through RS-fMRI, after exergaming training, in patients with PD and its correlations with cognitive modifications. Main limitations of the study are the reduced sample size, which results in greater variability of results and reduction of statistical power, and the lack of a verification of the first participants´ impressions about the games used and of their performance in them before the familiarization process.

Conclusion

In conclusion, we observed that an intensive exergaming training is efficacious to improve cognitive performance, particularly memory functions, executive functions, attention, and visuospatial function, without advantages on the conventional training. Despite the low significance of the neurofunctional changes observed through RS-fMRI exams, cognitive improvement underlined neurofunctional changes of brain connectivity among areas involved in specific cognitive domains.

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Authors' contribution

FASM, RD, GC, MM, CG and MDA were responsible for the conception, design, analysis and interpretation of data; FASM, RD, CG, ALF, and MDA, for writing and reviewing the manuscript. All authors approved the final version.

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