Working Memory and Executive Functions in Parkinson's disease after intervention with non-immersive virtual reality

Memória Operacional e Funções Executivas na doença de Parkinson: desempenho após intervenção com realidade virtual

Memoria Operativa y Funciones Ejecutivas en la enfermedad de Parkinson: desempeño tras intervención con realidad virtual

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ABSTRACT: To analyze Working Memory (WM) and Executive Function (EF) scores after and before intervention with non-immersive virtual reality in patients with Parkinson's disease (PD). Longitudinal study, with 13 subjects, of both sexes. Fourteen sessions of interventions based on Nintendo games. Cognitive functions were assessed using the Cambridge Cognitive Examination (CAMCOG). Statistical analysis of Wilcoxon was used to compare the performance of WM and EF scores before and after intervention. Results: Improvement in EF and VF scores after intervention was observed with statistically significant differences p= 0.004 and p=0.037, respectively. There were no differences between the interventions for WM scores (p= 0.609). Conclusion: Training with virtual games is suggested as a therapeutic approach that offers cognitive stimulation that improve EF.
Keywords: Aged; Cognition; Virtual reality exposure therapy; Parkinsonian Disorders.

RESUMO: *Analisar os escores da Memória Operacional (MO) e Funções Executivas (FE), antes e depois da intervenção com realidade virtual, em pacientes com doença de Parkinson (DP). Estudo longitudinal com 13 participantes, de ambos os sexos. Quatorze sessões de intervenção através de jogos do Nintendo. As funções cognitivas foram avaliadas por meio do Cambridge Cognitive Examination (CAMCOG). As análises estatísticas foram realizadas por meio da prova de Wilcoxon, para comparar o desempenho da MO e FE, antes e depois das intervenções. Os resultados mostraram uma melhora nos escores de FE e FV, após a intervenção com diferenças estatisticamente significativas de p= 0,004 e p=0.037, respectivamente. Não foram encontradas diferenças estatisticamente significativas entre os escores de MO (p= 0,609). Treinamentos por meio de realidade virtual podem contribuir com uma abordagem terapêutica que ofereça estimulação cognitiva que melhora funções executivas.*

Palavras-chave: *Idosos; Cognição; Terapia de exposição mediante realidade virtual; Transtornos Parkinsonianos.*

RESUMEN: *Analizar los escores de la Memoria Operativa (MO) y las Funciones Ejecutivas (FE), antes y después de la intervención con realidad virtual, en pacientes con enfermedad de Parkinson (DP). Estudio longitudinal con 13 participantes, de ambos sexos. Catorce sesiones de intervención a través de juegos de Nintendo. Las funciones cognitivas se evaluaron a través del Cambridge Cognitive Examination (CAMCOG). Los análisis estadísticos se realizaron a través de la prueba de Wilcoxon, para comparar el desempeño de la MO y FE, antes y después de las intervenciones. Los resultados mostraron una mejora en los escores de FE y FV, después de la intervención con diferencias estadísticamente significativas de p = 0,004 y p = 0.037, respectivamente. No se encontraron diferencias estadísticamente significativas entre los escores de MO (p = 0,609). Los entrenamientos a través de la realidad virtual pueden contribuir con un enfoque terapéutico que ofrezca estimulación cognitiva que mejora las funciones ejecutivas.*

Palabras clave: *Ancianos; la cognición; Terapia de exposición mediante realidad virtual; Trastornos del Parkinson.*

Introduction

Parkinson's disease (PD) is a neurodegenerative pathology, in which death of neurons located in the substantia nigra occurs and impairment of dopamine production is the main aggression that the disease produces (Pinheiro, 2011). The result of this dopamine deficiency is deficient communication in the neural circuit, generating motor symptoms such as bradykinesia and hypokinesia freezing, stiffness, posture instability, rest tremor among others (Ostrosky-Solis, Madrazo, & Ardila, 1991; Redmond, *et al.*, 2010; Rochester, *et al.*, 2007).

In addition to motor impairments, there are changes in cognitive functions characterized by inability to make decisions and control of attention, performance in dual tasks (Shi, Huber, & Brain, 2010), as well as psychological changes such as demotivation and depression (Ostrosky-Solis, Madrazo, & Ardila, 1991). Fengler, *et al.* (2016) describes the importance of cognitive alterations during the clinical investigation process of the patient, mainly because the cognitive decline contributes to the worsening of the clinical picture in patient with PD.

The authors used the Montreal Cognitive Assessment (MoCA) to investigate cognitive abilities and found that executive functions (EF), language, and abstract thinking (finding similarities in different things) were the major roles involved in their research.

In a recent study conducted by Santos, Cecato and Martinelli (2013) with 24 patients with PD, evaluating cognitive functions through the Mini Mental State Examination (MMSE) and verbal fluency tests, it was verified language deficits, visuospatial skills, and Attention of the participants.

In the literature is notoriously described the impairment of some cognitive functions in PD (Fengler, *et al.*, 2016; Melo, Barbosa, & Caramelli, 2007; Santos, Cecato, & Martinelli, 2013). Fengler, *et al.* (2009) and Melo, Barbosa and Caramelli (2007) report that several cognitive functions are impaired in PD, of which one can quoting memory and EF.

Cognition functions are responsible for the interaction of human behavior with the environment, that is, it allows the individual to be motivated to execute a plan of action that has been learned through previous experiences.

However, it is important to note that this behavioral action plan needs to be flexible and responsive to the demands or environment's requirements.

This flexibility of behavior, strategies to plan and organize the action plan, and the ability to regulate information processing is conceptualized as EF (Gazzaniga, Ivry, & Mangun, 2002). Working memory (WM) is classified as a short-term memory and it is responsible for manipulating information in a short period of time. WM is used, for example, to calculate the change during a market purchase (Baddeley & Hitch, 1974).

A justification for the impairment in WM and EF in patients with PD is the involvement of the neurotransmitter (dopamine) in mediating these cognitive functions (Ellis, & Nathan, 2001).

A resultant of PD is the association of motor and cognitive impairment. To better rehabilitate the cognitive and motor functions of patients with PD, Santos, *et al*. (2013) dates that walking, for example, is a motor task that suffers external influence, been considered a dual task ability and Bruin, *et al*. (2010) quotes that deficience in attention capacity to performance multi tasks can lead the patient to a higher fall risk and suggests that interventions based on virtual reality, can contribute for a better improvement in motor behavior for PD patients.

The use of virtual exposure as a therapeutic tool has been the subject of recent review (Haydu, Kochhann, & Borloti, 2016).

It is known that video game intervention allows the patient to interact in a real-time, two-dimensional environment in order to provide an intervention that involves both cognitive and motor functions at the same time.

The video game exercises are challenging and allowing greater engagement in the execution of virtual tasks, presenting the possibility of repeating the same exercises (movements) in a gradual way and accompanying the therapeutic evolution through the scores shown at the end of each game.

In other words, video game provides conditions for the functional reorganization of motor and pre-motor systems, by stimulating non-injured motor areas or by recruiting alternative, peri or anti-injury neuronal networks, which are difficult to attain in the real world (Cameirão, Badia, Oller, & Verschure, 2010; Fong, *et al*., 2010).

The importance of studying non-drug interventions for PD is because 30% of these patients progress to dementia (Aarsland, & Kurz, 2010).

Because WM and EF functions are two of the most frequently impaired cognitive functions in PD, this study aimed to analyze the cognitive aspects of pre and post intervention WM and EF with the Nintendo Wii Fit Plus® console of patients diagnosed with PD.

Objective

To analyze the working memory and executive functions' scores, pre- and post-interventions, with non-immersive virtual reality in patients with Parkinson's disease.

Methods

Participants

A longitudinal study was conducted between January and December 2016, in which 17 elderly people, both sexes, over 60 years of age who were diagnosed with PD were evaluated. The study protocol was previously approved by the Research Ethics Committee of the FIEO Center (UniFIEO) and the subjects participated in the research of their own free will. The study is part of a larger project that was submitted and approved by the Ethics Committee of the University Center FIEO - UniFIEO under the number 853.742 and CAAEE 34669514.0.000.5435.

The mean age of the sample was 70.62 years (minimum = 60, maximum = 80, standard deviation [sd] = 5.87), with 11.76% (n = 2) females and 88.24% (N = 15) males. All participants had high schooling (over 9 years of schooling). The mean time of PD diagnoses was 6.5 years.

Instruments and Procedures

After the clinical anamnesis, the elderly underwent in a neuropsychological evaluation with Cambrigde Cognitive Assessment (CAMCOG) (Roth, *et al*., 1986) and then began sessions with the Nintendo Wii Fit Plus® video game console.

The sessions were held twice a week, with a duration of 40 minutes, respecting the same times for all patients. In total, 14 sessions were performed, which lasted approximately 3 months (for each patient).

Regarding the type of games, Soccer Head® was selected, which requires lateral displacements and inhibitory control, being predominant frontal movements, the Ski Slalom® that requires lateral displacements, with cognitive requirement of processing speed and attention, Snowball Fight® that requires displacements with the feet and concomitantly movements with one of the arms with cognitive requirement of inhibitory control, processing speed and attention, the Table Til Plus® that require control of the center of gravity with displacements in all the directions of the patient's axis (front, back, right and left) with cognitive demands of processing speed, attention and draw a mental path to make the ball fall into the hole, Balance Bubble Plus® that requires shifting with processing speed time and Big Top Juggling® that in addition to lateral displacement with legs, still requires attention, inhibitory control and alternating hands movements according to the stimuli presented by the video game (Figure 1).

Figure 1: Selected video game games for the search
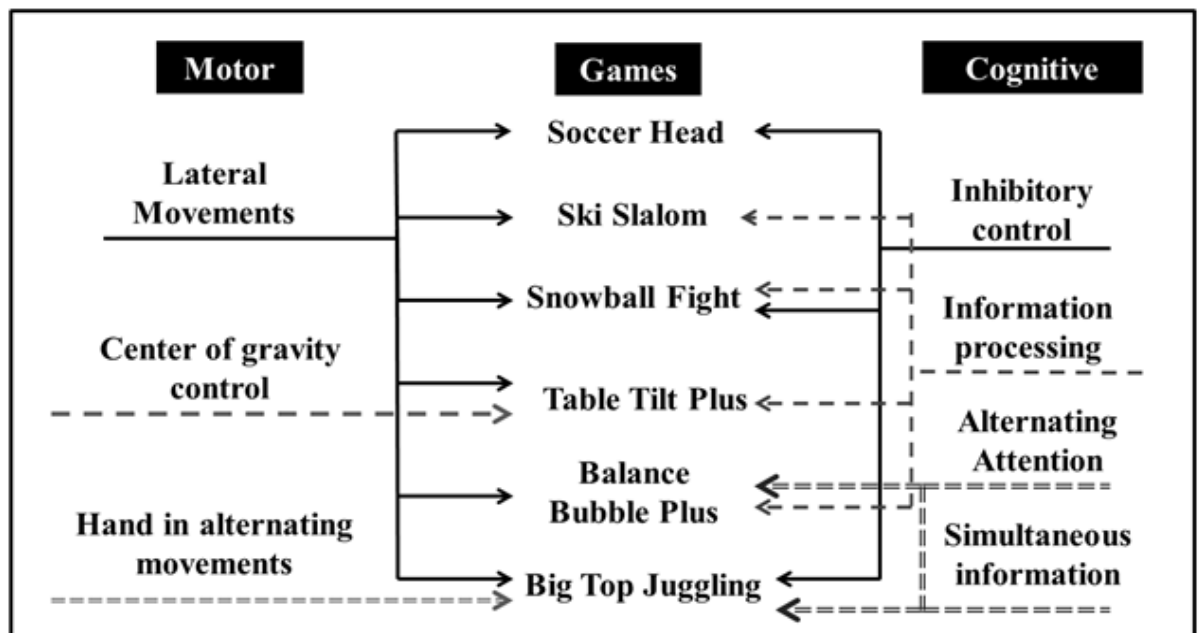
The selection of the Nintendo Wii Fit Plus® console games was made by the research team, which seek to find those who worked the most movements of laterality, balance, operational memory and EF.

Out of total 17 participants, 4 elderly were included in the control group (CG), since they participated in the pre neuropsychological evaluation and, after 6 months, performed the post neuropsychological evaluation only, that is, they did not perform the intervention with the Nintendo Wii Fit Plus®. However, at the end of the research, these four participants were invited to perform the video game intervention.

Procedures for analyzing cognitive functions

To evaluate Working Memory and EF, the cognitive battery of Cambridge Cognitive Examination (CAMCOG) (Roth, *et al*., 1986) and the Verbal Fluency test were used according to the suggestions of Brucki, *et al*. (2003).

The WM evaluation corresponded to five mental calculations (total of 5 points), writing a sentence (1 point), performing three successive commands (3 points) and counting down (2 points). The total WM score was 11 points. A higher score on this scale indicates more WM ability.

For the evaluation of EF, semantic (20 points) and phonological (20 points) verbal fluency, command planning and organization (22 points) and similarity were found in different forms (total of 8 points). The total EF score was 70 points. A higher score on this scale indicates more EF ability.

Statistical analysis

SPSS program (20.0) was used to analyze patient performance in pre and post video game interventions. Descriptive analyzes were performed regarding age and gender through mean, minimum, maximum, standard deviation and percentages. For the comparative analysis of WM and EF before and after intervention, the Wilcoxon test was used, testing the unilateral hypothesis (H1> H0), where H_0 represents Pre-Inverting and H_1 corresponds to Post-intervention.

It was decided to use a non-parametric analysis since it corresponds to a sample of only 17 participants, that is, the Wilcoxon test would be ideal for a small sample.

Results

Table 1: Characterize of the 13 participants on the cognitive performance

Participants (Education)/ Age	Group	Hoehn, & Yard	Working Memory		Executive Function	
			Before	After	Before	After
N.º 1 (9 to 11 years) / Age 73	CG	1.5	6	10	38	32
N.º 2 (9 to 11 years) / Age 68	CG	1.5	11	10	38	32
N.º 3 (9 to> 11 years) / Age 72	CG	1.5	8	7	33	29
N.º 4 (9 to 11 years) / Age 68	CG	1.5	10	7	34	25
N.º 5 (5 to 8 years) / Age 77	Nintendo	1.5	12	12	41	53
N.º 6 (1 to 4 years) / Age 75	Nintendo	1.5	12	10	50	67
N.º 7 (> 11 years) / Age 65	Nintendo	1.5	12	13	40	48
N.º 8 (9 to 11 years) / Age 80	Nintendo	1.5	12	12	54	60
N.º 9 (9 to 11 years) / Age 72	Nintendo	1.5	12	12	18	19
N.º 10 (> 11 years) / Age 70	Nintendo	1.5	13	10	29	35
N.º 11 (9 to 11 years) / Age 66	Nintendo	1.5	12	13	32	40
N.º 12 (> 11 years) / Age 71	Nintendo	1.5	12	13	29	37
N.º 13 (9 to 11 years) / Age 64	Nintendo	1.5	12	12	41	49

Table 2: Descriptive analysis (means and standard deviation) between pre- and post-intervention
with the 13 participants of the Nintendo Wii® and the 4 participants in the control group

Groups	Cognitive Functions	Pre intervention Mean (sd)	Post intervention Mean (sd)	P
Nintendo Wii® Group	WM	12,15 (±9,48)	11,92 (±6,55)	0,609
	EF	37,08 (±14,35)	45,38 (±13,25)	**0,004**
	EF fluency	25,15 (±9,21)	29,38 (±9,61)	**0,037**
	EF plan/org.	20,08 (±2,30)	20,69 (±2,17)	0,337
	EF Similarities	4,46 (±2,93)	5,0 (±2,91)	0,141
Control Group	WM	8,75 (±2,22)	8,50 (± 1,73)	0,713
	EF	35,75 (± 2,63)	29,50 (± 3,32)	0,066
	EF fluency	21,50 (± 2,65)	18,25 (± 3,86)	0,144
	EF plan/org.	18,25 (± 3,50)	18,0 (± 2,45)	0,713
	EF similarities	4,0 (± 2,0)	3,0 (± 3,83)	0,713

Table 2: Comparative analyzes using the Wilcoxon test, testing the hypothesis $H_1 > H_0$

Groups	Hypotheses $H_1 > H_0$	Z	p
Nintendo Wii® Group	WM	-0,512[b]	0,609
	EF	-2,904[a]	**0,004**
	EF fluency	-2,081[a]	**0,037**
	EF plan/org.	-0,960[a]	0,337
	EF similarities	-1,473[a]	0,141
Control Group	WM	-0,368[c]	0,713
	EF	-1,841[a]	0,066
	EF fluency	-1,461[c]	0,144
	EF plan/org.	-0,368[c]	0,713
	EF similarities	-0,368[c]	0,713

a Post intervention > Pre intervention
b Pre intervention = Post intervention
c Post intervention < Pre intervention

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Table 2 describes mean and standard deviation (SD) of the cognitive functions evaluated, namely WM and EF. A higher mean was observed in relation to the total EF score after the intervention when compared to the pre intervention (p= 0.004). The total WM item did not show statistically significant differences (p= 0.609).

In the CG, participants who did not perform the intervention with the video game, showed a cognitive deterioration after the re-test. This data corroborates with that described by Fengler, *et al.* (2016) and Melo, Barbosa, and Caramelli (2007) on the subtle cognitive decline even in the early stages of Parkinson's disease.

As the total EF score, in the group that underwent intervention, presented statistically significant differences, we chose to assess its subitems: EF fluency, EF planning and organization (EF plan / org.) and EF similarities. Table 2 shows absence of significance among the subgroups EF plan / org (p = 0.337) and EF similarities (p= 0.141). However, the verbal fluency item showed statistically significant differences between pre- and post-interventions (p=0.037).

The Wilcoxon test showed that the EF total score after the intervention with virtual reality is higher when compared to the total EF score before the intervention (Z= -2.904; p= 0.004). Among the EF subitems, improvement of the scores after the Verbal Fluency test intervention was significant (Z= -2.081; p= 0.037). These data allow us to affirm that the intervention through virtual reality improves the EF, especially with regard to processing speed, of patients diagnosed with PD (Table 2). Carbon and Marie (2003) and Nieoullon (2002) describe that the frontal brain areas are responsible for the mechanism of regulation of emotions, cognitive flexibility, processing speed, ie the frontal region mediates EF.

One hypothesis to justify the EF impairment described in this study is in relation to the deficit of dopaminergic neurons production and consequently reduction of this neurotransmitter in the substantia nigra, also reducing its effectiveness in the basal ganglia circuitry that passes through the striatum and impairs the fronto-striatal circuitry (Pillon, Czernecki, & Dubois, 2003). In other words, dopaminergic neuronal loss impairs frontal circuitry and consequently affects EF.

In relation to CG (participants who did not perform virtual reality training), there was no significant difference between the pre- and post-tests for WM (Z= -0.368, p= 0.713), EF (Z= -1.841, p= 0.066), EF fluency (Z= -1.461, p= 0.144), EF plan /org (Z= -0.368, p= 0.713) and EF similarities (Z= -0.368, p = 0.713).

Working memory did not show statistically significant differences in both CG ($Z= -0.368$, p= 0.713) and in the intervention group ($Z= -0.512$, p= 0.609). In addition to the WM item, the sub-items of the EF also did not show significant differences in the group that performed the intervention with virtual reality, EF plan / org ($Z= -0.960$, p= 0.337) and EF similarities ($Z= -1.473$; p= 0.141). WM and EF are mediated mainly by the frontal lobe and dysfunction of this brain region may lead to a decline in the functions observed in PD (Carbon, & Marie, 2003; Nieoullon, 2002).

Although the WM and EF subitems (EF plan / org and EF similarities) did not present statistically significant differences between pre- and post-interventions, the impairment of these cognition functions in PD is described in the literature (Ellis, & Nathan, 2001). One hypothesis for the absence of significance for WM is the fact that the patients are active in their daily life, that is, the maintenance of the functionality resulted in satisfactory scores, both in WM and EF subitems (Nickel, *et al.*, 2010), even after undergoing virtual reality intervention.

Discussion

The objective of this study was to analyze the effectiveness of the intervention with virtual reality as a tool to improve cognitive functions in PD. According to Assis, *et al.* (2015), 70 articles on the effect of training with cognitive intervention with video games in elderly individuals over 65 years of age, of which 26 studies focused on PD were reviewed. The results of our research proved the effect of the intervention with virtual reality, based on videogame, comparing to Control Group (CG, without intervention).

In Assis`s review (2015), cognitive improvements were verified regarding memory, EF, language and perception. Our findings demonstrated that the Experimental Group (submitted to virtual reality training) obtained post-training cognitive improvement in EF (total score) and verbal fluency. The studies with games evidenced the cognitive abilities that are able to provide interaction between player and the machine becoming relevant for the contribution of non-pharmacological treatment (Assis, 2015; Abreu, 2015; Bruin, *et al.*, 2010; Martinelli, *et al.*, 2014).

Our findings corroborate with other studies in the literature referring to the benefits of technology (video game intervention) in gait improvement and cognition in PD (Martinelli, *et al*., 2014; Melo, Barbosa, & Caramelli, 2007).

Abreu (2015) idealized another study that corroborates with our findings. The author verified that healthy elderly showed a positive result of 70.97% in relation to video game use, 22.54% presented unbiased results for videogame intervention in the context of cognitive training, and 6.45% presented worse results compared to the control group, the improvement in EF and attention were highlighted as strengths. This information is in agreement with the findings of this research, which refers to the improvement of the EF after videogame training.

In our study, we evaluated the Working Memory and the EF, and in addition to the total EF score, we observed satisfactory performance after the intervention with EF verbal fluency. On Table XX, the VF subtest showed satisfactories results and psychometric significant results after intervention. The EF aspects are mediaded in the Forntal Lobe region, more speciffic in the Inferior Frontal Lobe, wich is considered one of the regions of motor behavior on verbal/speaking fluency. It´s kwon that patients with PD shows decline in motor behavior, including speaking skills, for involving motor participation by this function. One hyphotesis that can be related with the satisfatory performance of this function after intervention is that the neuroplasticity provided by virtual reality could have benefited the speak motor skills, and for this reason, those patients with PD showed better performance in this function (Hoogland, *et al*., 2018; Merola, *et al*., 2018).

Our results corroborate with the work of Toril, Reales and Ballesteros (2014), who analyzed 474 trained and 439 healthy and showed in both young and older adults that video game training improved the performance of cognitive functions. One hypothesis to justify this improvement in performance refers to neural plasticity. The study also indicated that older adults improved the reaction time, memory, attention and global cognition. Moreover, exergames can be a valuable intervention for cognitive improvement (Toril, Reales, & Ballesteros, 2014).

Martinelli, *et al.* (2014) after evaluating nine older adults over 60 years old with a diagnosis of PD, used virtual reality sessions twice a week for 40 minutes. Concluding that virtual games training highlights the motor and cognitive improvement of patients, showing that the games can be interpreted as non-pharmacological treatment, making it clear that conventional exercises presented performance limitations.

Mhatre, *et al.* (2013) verified the improvement of posture and balance in PD through virtual reality, including the improvement of depressive symptoms using the Geriatric Depression Scale. However, the authors did not mention cognitive assessment in their study.

Due to the aging of the population, there is an increasing volume of chronic and degenerative diseases, and PD is one of the highest incidence among elderly people. Based on the articles evaluated, virtual reality has been shown to be an important therapeutic tool for physical rehabilitations and for neurorehabilitation, in this sense it is important to consider that this kind of intervention offers visual and auditory cues, allowing a number of repetitions and integrated cognitive training (Vieira, *et al.*, 2014). In the present study, it was possible to develop motor skills and motor control through a playful form of therapy (Vieira, *et al.,* 2014).

The technological advances in the health area have shown the possibility of rehabilitation of patients with PD through virtual reality, using the two-dimensional interaction and direct sensory feedback generated by virtual reality. The main objectives in virtual rehabilitation would be the easy application and a high degree of motivation during the treatment. Usually, the monotony of the conventional exercises and the repetitions provided in the treatment cause demotivation for the patient. Studies shows the increase of the functional abilities and increased patient participation in daily life, improving their sensory, motor and cognitive functions (Batista*, et al*., 2012).

As part of the limitations of this study, we found a low number of patients included in the intervention program. Another fact of relevance is that we have considered for the research only participants in the early stages of PD. New studies should be conducted to elucidate the efficacy of a virtual reality program in patients diagnosed for more than 10 years and should also consider the development of specific games for the stimulation of patients with Parkinson´s disease.

Conflicts of interest

The authors declare that they have no conflicts of interest in their realization and publication.

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