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Livia Valentin
Instituto do Coração

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MentalPlus® digital game is reliable to measure cognitive function in healthy adults. A future accessible tool to assess postoperative cognitive dysfunction and rehabilitation.

Livia Stocco Sanches Valentin[12*] and Valeria Fontenelle Angelim Pereira[1 2]

[1]*LIM 8 – Laboratory of Anesthesiology, Department of Anesthesia, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.*

[2]*Cognition Dysfunction and Rehabilitation Group, Alphacor Cardiologia Clínica e Diagnóstica, MentalPlus Project Association, Barueri, Brazil.*

[*]Corresponding author
Livia Stocco Sanches valentin: Department of Anesthesia, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil Email: lssv@usp.br

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Abstract

Postoperative cognitive dysfunction (POCD) is a multifactorial adverse event most frequently in elderlypatients. POCD diagnosis usually demands a long neuropsychological battery. Mental Plus® video game was developed to evaluate cognitive function. It might also be a tool to use in future neuropsychological rehabilitation. The primary study objective was MentalPlus® reliability evaluation to assess cognition in healthy volunteers. METHODS: 163 volunteers were randomized to play MentalPlus® theme versions A and B with a week interval. The volunteer's mental state was first evaluated applying Mini-Mental State Examination, and the study excluded volunteers with scores below 18 or 23 related to educational scores. Kappa index and McNemar test evaluated MentalPlus® applicability and reproducibility. RESULTS: The results disclosed the following characteristics: mean age of 36±16 years; 46 % male; School rank level mean of 5±2 years, the average benefits of 4.6± 3 Brazilian minimum wages. The Mini-Mental score was 28±3, for an expectation of more than 25±3. The MentalPlus® A and B theme versions results disclosed resulting kappa coefficients assessing reliability tests. General cognitive function presented a kappa coefficient of 0.7122 (p<0.005); selective attention and alternating attention revealed 0.4004 and 0.3998 (p<0.005); long-term memoryand inhibitory control had similar coefficients: 0.4103 and 0.4406 (p<0.005); and executive function, through constructing inhibitory control presented a kappa coefficient of 0.4406, There was a marked dispersion for visual perception, concerning to motion and resolution of objects: 0.2029 and0.2453 (p<0.005). The cognitive function scores in MentalPlus® were displayed as a mean and standard deviation and confidence interval of 95%, α=0.05. MentalPlus® theme versions A and B results were comparable with values utilized by researchers. CONCLUSION: MentalPlus® digital game displayed reliable evidence for cognitive function evaluation. It might be a future feasible instrument for POCD assessment and rehabilitation. Trial registration: www.clinicaltrials.gov Identifier: NCT02551952.

Keywords: NeuropsychologicalTests, Surgery, Anesthesia, Cognition, Videogames, Reproducibility of results, Experimental games.

Introduction

Recurrently, postoperative cognitive dysfunction (POCD) is reported following general anesthesia, particularly in elderly patients and after cardiac surgery. POCD definition is a cognitive decline in two or more neuropsychology functions, according to the International Study of Postoperative Cognitive Dysfunction (ISPOCD) study group [1,2]. The ISPOCD demonstrated that in geriatric patients after noncardiac surgery and general anesthesia, its frequency one-week after the procedure.is around up to 26% of them. After three months of operation, POCD remained in up to 10% of that group [2,3]. POCD increased the risk of comorbidities in elderly patients, in the first year after surgery [4]. Consequently, it is likely to be detrimental to the long-term outcomes. POCD etiology is multifactorial. Important causes are age, hypoxia, hypotension, anesthetics and depth of anesthesia, besides surgical procedures and external factors such as quality of life [4].

Nowadays, POCD diagnosis and evaluation usually justify an extensive and time consuming psychologic test battery. A complete neuropsychological evaluation usually spends more than 2 hours. POCD diagnosis has a paramount limiting factor due to that time-consuming necessity. The usual adverse perioperative patient's clinical conditions might restrict the test battery applicability. The presence of pain or other perioperative factors does not contribute to an encouraging environment associated with reliable psychological test battery outcomes. The stress associated with surgery might falsify the actual performance level of cognitive ability [5]. Furthermore, the psychologic battery application demands specialized trained health professional. That is a leading factor for a decreased POCD diagnosis in a majority of health centers, mainly in low socioeconomic areas. Those issues related to cognitive tests battery application reduces the viability to adopt measures to increase cognitive reserve and for prevention, diagnosis, and rehabilitation of POCD cases. The restriction to use and applicability of the psychological tests has led the scientific community to a constant search for alternative diagnostic methods. During a recent POCD study we have developed in our service, at the University of São Paulo – Brazil, our team, faced those cited technical difficulties [6].

Digital games motivate cognitive functions and enhance skills such as creativity, the search for strategies, decision-making, and expertise aimed at visuoperception [7]. In clinical trials, the video games have been used for neuropsychological function skill improvement. They have been able to modify the structure and functioning of the brain architecture [8,9]. Nonetheless, the use of virtual games for assessing the integrity of neuropsychological functions is insufficient or non-existent. Today, most cognitive evaluation tools were developed and validated to diagnose cognitive impairment from neurological or psychiatric health disorders. Not only in POCD but the evolution of a neuropsychological test of easy applicability, as a digital game might also contribute to cognition knowledge development in various clinical situations. Early and accurate POCD are crucial, given that the rehabilitation might start earlier. Later cognitive dysfunction diagnosis and co-occurring conditions are related to a worse prognosis [4].

As an alternative to overcome those issues, we developed a digital game named MentalPlus® as a possible tool to assess cognition and future cognitive dysfunction rehabilitation. The primary objective of this study aimed to estimate the MentalPlus® reliability to assess cognitive function in healthy volunteers. Afterward, the secondary purpose of the study would be to validate it as a tool to cognitive function evaluation and rehabilitation in patients undergoing surgery under general anesthesia in the near future. The data we are presenting here is part of a whole study that is registered in www.clinicaltrials.gov Identifier: NCT02551952 Manuscript Formatting (S0 file) [10].

Material and Methods

Study design and subject enrollment

The study was conceived as a randomized, double-blind exploratory trial. It received the approval of the Ethics Committee for Research Project Analysis (CAPPesq) of the Clinical Board, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP). (S1 file)

There were 163 healthy people enrolled to play a free digital game, MentalPlus®, theme versions A and B, with a week interval, after invitation acceptance and a signed written informed consent. Minor age volunteers had the consent signed by their parents. The volunteer recruitment to the study was from August 2015 to January 2016. The neuropsychological assessment phase study finished in February 2016.

Inclusion criteria: Healthy people who accepted the invitation to play a free digital game, MentalPlus®, theme versions A and B. (Fig 1)

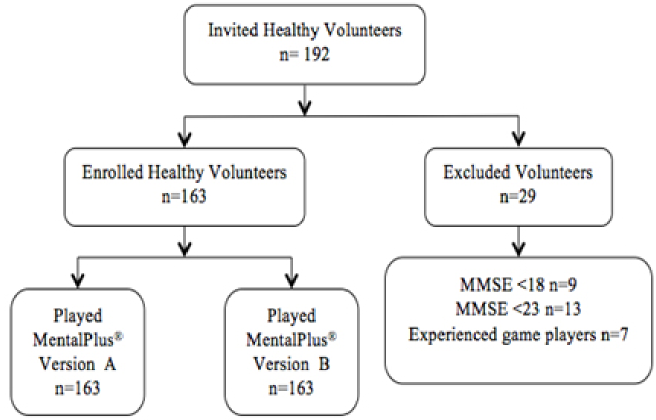


Figure 1: Study Fluxogram. Legend: MMSE: Mini-Mental State Examination

The exclusion criteria

The presence of a history of brain disease or dementia, psychiatric disorders affecting cognition and the presence of visuomotor ability impairment to play video games. The healthy volunteers who presented the MMSE score below 18 or 23 by educational level and the professional video game players were excluded from the study [5]. The Mini-Mental State Examination (MMSE) test, which assesses reasoning, spatiotemporal orientation, memory, and education screened patients for enrollment in the study. For the Brazilian population, the cutoff point is determined for two scores of schooling: up to 4 years and more than four years of academic study at school. The cutoff point is 18 and 23 points respectively. Consequently, it deserves a higher cutoff level for individuals with a better educational attainment [11-13].

Randomization and video game versions

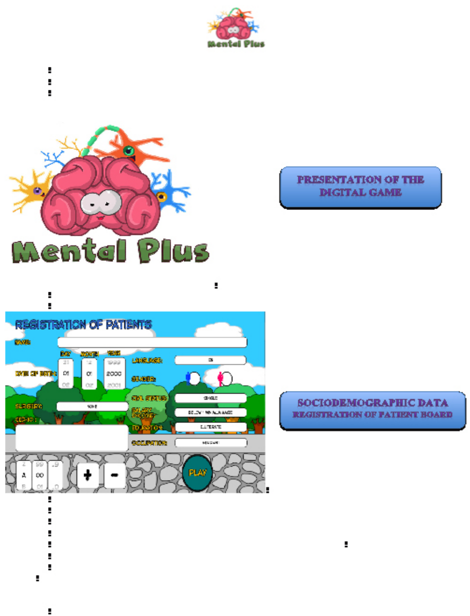
One hundred and sixty-three healthy volunteers included in the study were randomized to play two video game theme versions, MentalPlus® A, and B on different dates. The same researcher applied both MentalPlus®, A and B, to the volunteers with a week interval to prevent bias and the effect of the game learning.(Fig1) The randomization was performed using the website http://www.randomizer.org/form.htm, recorded on paper and stored in sealed opaque envelopes to be opened in the study room where volunteers would play the video game. The health professionals responsible for the game application were aware of the MentalPlus® game version arm, just after openness of the envelopes. However, patients, neuropsychologists, and outcome assessors involved in the study were kept blinded to the stratification group to which each patient belonged. The study groups were identified only after the evaluation of all patients and statistical analysis.

Sociodemographic evaluation and neuropsychological assessment

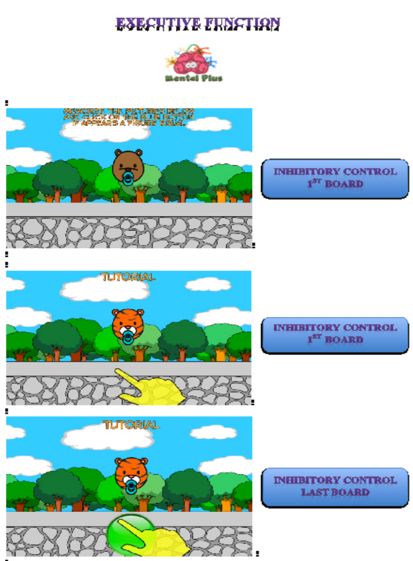
The evaluation data constituted of sociodemographic and neuropsychological assessment data. Demographic data included: age, education level, and family earnings. The education assessment was an index derived from the schooling years and the household income in Brazilian minimum wages.

The video game MentalPlus® characteristics

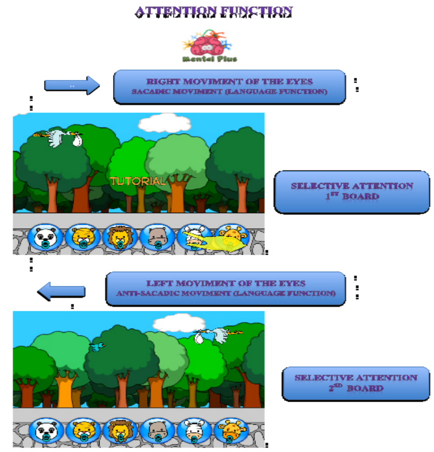
MentalPlus® is a digital game developed to evaluate and stimulateneuropsychological functions, patented and registered with the National Library Foundation by Law No. 9,610/98, under copyright No. 663,707. This digital game identifies the neuropsychological deficits in functions - Attention / Memory / Executive. Executive function evaluation consists of an analysis of planning and searching strategy, followed by thought flexibility and inhibitory control investigation. (S4File). Attention, resistance to distractor stimulus, sustaining attention and memory evaluation consist of a series of tasks in multiple digital game phases, shown detailed in the attached Files (S3, S4 and S5). The game stage tasks spend 25 minutes from its inception (S1 File) to the end, fulfilling all stages of the digital game through their difficulties. (S6 File Video).The CONSORT criteria (www.consort-statement.org) were followed. (S2 File)



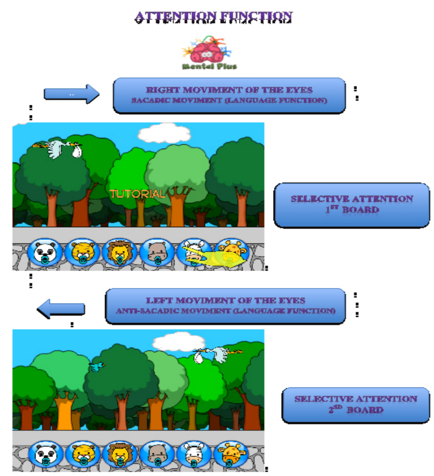
S1 File: MentalPlus Game



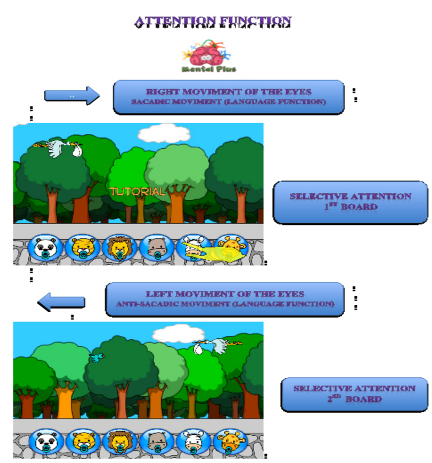
S2 File: Executive Function



S3 File: Attention Function



S4 File: Distractor Element



S5 File: Sustaining Attention and Memory Functio

S6 File: video-MentalPlus
https://www.youtube.com/watch?v=aJqvYb7jeHA&feature=youtu.be

Statistical analyses

We used the Kappa index for replicability analysis and reproducibility of the MentaPlus® results followed by McNemar test analysis to ensure homogeneous distribution of the outcome [13]. Data were expressed as mean and SD and confidence interval (CI) of 95%. The significance level was α = $p<0.05$. They were performed using SPSS12 and GraphPad Prism version 6.00 for Mac (GraphPad Software, La Jolla California USA www.graphpad.com).

Results

According to Fig 1, we recruited 163 healthy volunteers with an inclusion profile to participate in the study, according to previous criteria. We excluded 29 volunteers. 22 after failing to MMSE normative score (≤ 18 or ≤ 23 points) according to education levels and seven that were professional video game players. 163 volunteers played both theme versions with an interval of a week. Equal researchers followed versions A and B of each volunteer. Table 1 discloses sociodemographic data, which were expressed as the mean and standard deviation (SD). The 163 volunteer participants presented a mean age of 36±16 years, (mean; SD) and 46 per cent were male. They had a School level mean of 5±2 years, (mean; SD) and a mean income of 4.6 ± 3 (mean; SD) Brazilian minimum wage. They exhibited the MMSE score of 28±3 (mean; SD), for an expectation of more than 25±3 (mean; SD).

Table 1: Baseline sociodemographic profile. School Level: education in years of schooling; Income: number of Brazilian minimum wage=US$262,33; MMSE: Mini-Mental state examination.

Age(Years)	Gender	School Level (Years)	Income (minimum wage)	MMSE (>25±3.30)
Mean ±SD	Male(%)	Mean ±SD	Mean ±SD	Mean ±SD
35.06±16.50	46	5.00±1.60	4.63±0.65	28.15±3.30

The results obtained in reliability tests with both MentalPlus® versions, A and B, disclosed the following main features: In general, cognitive function evaluation, the Kappa coefficient was 0.7122 ($p<0.005$) what represents an excellent agreement. The cognitive function categories evaluation revealed that attention function indicators presented a good concordance between both game versions. The selective attention and alternating attention kappa index were 0.4004 and 0.3998 ($p<0.005$). Similarly, long-term memory and inhibitory control had comparable kappa index level. They were 0.4103 and 0.4406 ($p<0.005$). Data disclosed a low dispersion for executive function category through the construct inhibitory control and a marked dispersion for the categories of visual perception for aspects related to motion and resolution of objects:0.2029, 0.2453, 0.3949 ($p<0.005$), respectively in versions A and B.

Table 2: Reliability tests data with both MentalPlus® versions, A and B, concerning different cognitive functions. Kappa: Kappa coefficient – Coefficient level: > 0.70: excellent; 0.39-0.69: Average to good; <0.39: low; Z: Z-score; Prob: probability.

Congnitive Functions	Kappa	Z	Prob>Z
Total	0.7122	7.34	0.0000
Selective Atiention	0.4004	12.40	0.0000
Alternanng Alien	0.3998	12.81	0.0000
ong-trxm Memory	0.4103	13.39	0.0000
Wading Memory	0.3796	12.21	0.0000
lobibitory Control	0.4406	15.17	0.0000
Visual Perception	0.2029	9.27	0.0000
Visual Perception	0.2453	10.68	0.0000
Visual Percqition	0.3974	18.93	0.0000

The research group established a normal mean of scores for each cognitive function evaluated in MentalPlus®. The data was expressed in mean and SD. The significance level was α = 0.05 and the confidence interval (CI) of 95%. The data is exposed on (Table 3). Cognitive function was evaluated through 8 MentalPlus® game phases. (Table 4) The memory function was assessed through long-term and working memory. The expected scores were 9±3 and 4±2 points, (mean; SD) respectively. Attention function was analyzed by the selective and alternative attention. The expected scores for both were 10±2 points, (mean; SD). For executive function, the researchers adopted a score of 30±2 and a score of 20±3 points for visuoperception, (mean; SD). The values presented for versions A and B were similar, as also comparing with the values adopted by the researchers. The cognitive function score results obtained for versions A and B disclosed the both versions concordance.

Table 3: Cognitive functions score values for MentalPlus® with versions A and B.CI: confidence interval.

MentalPlus® Cognitive Function	Expected Score (mean ±SD)	Version A score (mean±SD)	Version B score (mean±SD)	95% CI Vcrsion A	95% CI Vcrsion B
Long-Term memory	9±3	9.75±0.602	9.3±1.03	9.655-9.842	9.178-9.497
Working Memory	4±3	5.68±0.64	5.33±0.96	5.58-5.78	5.18-5.48
Inhibitory Control	30±2	32.74±0.59	32.53±1.11	32.65-32.83	32.35-32.70
Selective Attention	10±2	11.77±0.57	11.4±0.86	11.68-11.86	11.28-11.54
Alternating Attention	10±2	11.75±0.47	11.39±0.96	11.68-11.83	11.24-11.54
Visual Perception	20±2	18.75±1.90	17.06±4.25	18.46-19.05	16.40-17.41

Table 4: Cognitive function evaluation and MentalPlus® video game phases.

MentalPlus Phases	PHASE I		PHASE II		PHASE III		PHASE IV		PHASE V		PHASE VI		PHASE VII*		PHASE VII				PHASE VIII			PHASE VIII		
Cognitive Functions	Long-term Memory		Inhibitory control		Selective Attention				Alternating attention				Working Memory						Visual Perception					
Side of Visual Seeking					Right		Left		Right		Left		*Training		Right		Left							
MentalPlus Version	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	A	A	B	B	B
Total number of values	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163	163
Minimum	8	6	31	28	9	9	9	9	10	9	10	9	3	3	3	3	3	3	13	8	8	13	8	8
25% Percentile	10	9	33	33	12	11	12	11	12	11	12	11	7	7	5	7	5	6	17	14	14	17	14	14
Median	10	10	33	33	12	12	12	12	12	12	12	12	7	7	6	6	7	6	20	20	20	20	20	20
75% Percentile	10	10	33	33	12	12	12	12	12	12	12	12	7	7	6	7	6	6	20	20	20	20	20	20
Maximum	10	10	33	33	12	12	12	12	12	12	12	12	7	7	7	7	7	7	20	20	20	20	20	20
Mean	9.74	9.33	32.74	32.52	11.77	11.41	11.77	11.41	11.75	11.39	11.8	11.39	5.68	5.68	5.28	5.68	5.35	5.71	18.8	17	17.1	19	17	17.1
Std. Deviation	0.6	1.03	0.59	1.11	0.56	0.86	0.56	0.86	0.47	0.96	0.47	0.96	0.64	0.64	0.96	0.65	0.94	0.66	1.9	4.3	4.25	1.9	4.3	4.25
Std. Error of Mean	0.047	0.08	0.04	0.08	0.04	0.06	0.04	0.06	0.03	0.075	0.03	0.07	0.05	0.05	0.07	0.05	0.07	0.05	0.14	0.3	0.33	0.1	0.3	0.33
Lower 95% CI of mean	9.6	9.1	32.6	32.3	11.6	11.2	11.6	11.2	11.6	11.2	11.6	11.2	5.5	5.5	5.3	5.5	5.1	5.6	18.4	16	16.3	18	16	16.3
Upper 95% CI of mean	9.8	9.5	32.8	32.7	11.8	11.5	11.8	11.5	11.8	11.5	11.8	11.5	5.7	5.7	5.6	5.7	5.4	5.6	19	18	17.7	19	18	17.7

Discussion

This study found enough evidence that MentalPlus® digital game has reliability for use in neuropsychological assessment for cognitive dysfunction for mnemonic, attentional and executive functions. (Fig 4) Data Analysis disclosed important findings. The results revealed an excellent concordance for a general cognitive function for both MentalPlus® versions with a Kappa coefficient of 0.7122 ($p<0.005$). There was a good agreement for attention, long-term memory, and inhibitory control. A low dispersion for executive function category through the construct inhibitory control was demonstrated.On the other hand, the visual perception disclosed a significant dispersion related to motion and resolution of the objects in versions A and B during the first two of 3 times of the complete evaluation. The last visuoperception evaluation phase with MentalPlus® disclosed a better kappa index (0.3949), probably due to the learning effect. These results might be influenced by the images resolution and definition for tablet screens and notebooks smaller than 10 inches. (S7 file) For that reason, we encourage researchers to evaluate volunteers only with larger screens. Both game versions presented very similar values when compared with the expected by the researchers.The cognitive function results for both MentalPlus® versions, A and B, correspond to narrow values ranges, disclosing similarity between versions. (Table 3) These published values favor MentalPlus® reliability. That is a fascinating result that encourages the researcher team to keep on the next research phase: to validate the digital game to diagnosis and future rehabilitation of cognitive dysfunction. The primary interest in developing that possible tool for cognitive function evaluation is its convenience when compared with extensive and time consuming psychological battery usually undertaken for that end. The mentalplus® game presents many advantages through the extensive psychological battery usually performed to evaluate those patients.The game only requires about 25 minutes to be played through all its phases. It would be enough to the health service to offer an oriented health professional to apply the video game. Therefore, that justification would favor its usefulness in a broad of clinical settings, enabling within many situations, a prompt POCD diagnosis. Future research might focus on direct neuropsychological assessment using the MentalPlus® digital game in patients undergoing surgery and general anesthesia procedures. Our next step is POCD patient evaluation with MentalPlus® digital game compared with a usual neuropsychological test battery. Although preliminary studies have shown that games can be used for that goal, there is a necessity for accurate measurements and calibrations to get reliable results of these cognitive functions. Afterward, it might be evaluated for cognitive rehabilitation, shortly.

Conclusion

MentalPlus® digital game presented reliable evidence for cognition evaluation like attention, memory and executive functions. It is a possible future accessible instrument to POCD diagnosis and rehabilitation use. Additional study will contribute for an adequate calibration of the game as for its validation.

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