

DIGITAL GAME: A SCALE TO EVALUATE THE PERIOPERATIVE COGNITIVE FUNCTION (MentalPlus®)

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Abstract- Postoperative cognitive dysfunction (POCD) is a common multifactorial adverse event frequently in elderly patients. POCD diagnosis usually demands a long neuropsychological battery and specific professional for evaluate the results data as a neuropsychologist. As a tentative to overcome that issue, Mental Plus® video game was developed as a tool to assess cognitive function and future rehabilitation. The primary study objective was MentalPlus® reliability evaluation to assess cognition in healthy volunteers. **METHODS:** 163 volunteers were randomized to play MentalPlus® versions A and B with a week interval between both moments. Mini-Mental State Examination was applied to assess the volunteers mental state, and we excluded those with scores below 18 or 23 related to a determined educational level. MentalPlus® applicability and reproducibility were evaluated by kappa index and McNemar test. **RESULTS:** The patients had mean age of 36±16 years; 46 % male; School level mean of 5±2 years, the mean income of 4.6± 3 Brazilian minimum wage and the Mini-Mental score of 28±3, for an expectation of more than 25±3. The MentalPlus® A and B versions results revealed the subsequent kappa coefficients for reliability tests. For general cognitive function, kappa coefficient was 0.7122 ($p<0.005$); selective attention and alternating attention presented 0.4004 and 0.3998 ($p<0.005$); long-term memory and inhibitory control had comparable coefficients: 0.4103 and 0.4406 ($p<0.005$); executive function disclosed a kappa coefficient of 0.4406, through construct inhibitory control. The expected cognitive function scores in MentalPlus® were expressed as a mean and standard deviation and confidence interval of 95%, $\alpha=0.05$. MentalPlus® versions A and B values were similar when comparing with values adopted by researchers. **CONCLUSION:** MentalPlus® digital game presented reliable evidence for cognition evaluation. It might be a future accessible tool for POCD evaluation and probable future rehabilitation. Trial registration: www.clinicaltrials.gov Identifier: NCT02551952.

Keywords: Neuropsychological Tests, Surgery, Anesthesia, Cognition, Videogames.

I. INTRODUCTION

Postoperative cognitive dysfunction (POCD) is frequently reported following general anesthesia, especially in elderly patients and after cardiac surgery. POCD is defined as a cognitive decline in two or more neuropsychology functions, per the International Study of Postoperative Cognitive Dysfunction (ISPOCD) study group [1,2]. The ISPOCD demonstrated that in old patients submitted to non-cardiac surgery and general anesthesia, this adverse event affected up to 26% of them, one-week after the procedure. 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]. This may impair long-term results (outcomes). POCD etiology is multifactorial and some important cited causes are age, hypoxia, hypotension, anesthetics and depth of anesthesia,

surgical procedures and external factors such as quality of life [4]. Nowadays, POCD evaluation and diagnosis usually deserve an ample psychologic time consuming test battery. Full neuropsychological assessment often lasts more than 2 hours. It is a paramount limiting factor for POCD. The usual adverse perioperative patient's clinical conditions might

restrict the test battery applicability. The presence of pain or other perioperative factors does not provide a favorable environment associated with a reliable result. The stress associated with surgery might falsify the actual performance level of cognitive ability. [5] Furthermore, the psychologic battery application deserves specialized trained personnel. It is another factor for a decreased POCD diagnosis in much of health centers, mainly in low socioeconomic areas. Those issues related with 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]

Previous studies have shown that digital games might stimulate cognitive functions and enhance skills such as creativity, the search for strategies, decision-making, and skills aimed at visuoperception. [7] In clinical trials, the 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] However, the use of virtual games for assessing the integrity of neuropsychological functions is insufficient or non-existent. Most cognitive assessment available tools were developed and validated to diagnose cognitive impairment arising from neurological or psychiatric disorders. The development and validation of a neuropsychological test with the easy application as a digital game can contribute to a better cognition knowledge in different clinical situations, as in POCD. Early and accurate POCD are crucial, given that the rehabilitation might be started earlier. Later diagnosis and co-occurring conditions are related to a poor 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 objective 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 a near future. The data we are presenting here is part of a whole study that is registered in www.clinicaltrials.gov Identifier: NCT02551952

II. MATERIAL AND METHODS

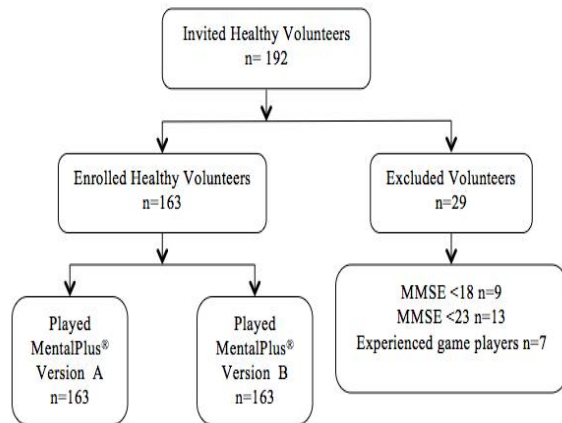
Study design and subject enrolment

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). (SI file)

There were 163 healthy people enrolled to play a free digital game, MentalPlus®, versions A and B, within a week interval, after invitation acceptance and a signed written informed consent. Minor age subjects 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 were healthy people who accepted the invitation to play a free digital game, MentalPlus®, versions A and B. (Fig 1)

Fig 1. Study Fluxogram. MMSE: Mini-Mental State Examination



The exclusion criteria were the presence of a history of brain disease or dementia, psychiatric disorders that affect cognition and the presence of some grade of visuomotor ability impairment to play video games. The Mini-Mental State Examination (MMSE) test, which assesses reasoning, spatiotemporal orientation, memory and education screened patients for enrolment in the study. For the Brazilian population, the cut-off point is considered for two types of schooling: up to 4 years of formal academic study and more than four years of schooling, with a cut-off point of 18 for the less educated and over 23 points for individuals with higher levels of education. [10,11,12] The healthy volunteers who presented the MMSE score below 18 or 23 by educational level [5] and the outstanding video game players were excluded from the study.

Randomization and video game versions

One hundred and sixty-three healthy volunteers included in the study were randomized to play two video game versions, MentalPlus® A and B in different moments. The same researcher applied both MentalPlus® versions, A and B, to the volunteers. There was a week interval between versions A and B application to prevent bias and the effect of the game learning. (Fig 1) 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

Demographic data were analyzed, including age, education and family income. The education evaluation was an index derived from the schooling years and the family income in Brazilian minimum wages.

The video game MentalPlus® characteristics

MentalPlus® is a digital game developed to evaluate and stimulate neuropsychological 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. Attention, resistance to distractor stimulus, sustaining attention and memory evaluation consist of a series of tasks in multiple digital game phases. The game phase tasks spend 25 minutes from its inception to the end, fulfilling all stages of the game through their difficulties. The CONSORT criteria (www.consort-statement.org) was followed.

Statistical analyses

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

III. Results

Per Fig 1, we recruited 163 healthy volunteers with a filling profile to participate in the study, according to inclusion criteria. We excluded 29 volunteers. 22 after failing to MMSE normative score (≤ 18 or ≤ 23 points) according to education levels and 7 for being outstanding video game players. 163 healthy volunteers played both versions within a week interval. The same researcher supervised both versions 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. (Table 2) The cognitive function categories evaluation revealed that attention function indicators presented a good agreement between the different game versions. The selective attention and alternating attention kappa index were 0.4004 and 0.3998 ($p < 0.005$). (Fig 3) Similarly, long-term memory and inhibitory control had comparable kappa index level. They were 0.4103 and 0.4406 ($p < 0.005$). (Table 2) 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)

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.

Cognitive Functions	Kappa	Z	Prob>Z
Total	0.7122	7.34	0.0000
Selective Attention	0.4004	12.40	0.0000
Alternating Attention	0.3998	12.81	0.0000
Long-term Memory	0.4103	13.39	0.0000
Working Memory	0.3796	12.21	0.0000
Inhibitory Control	0.4406	15.17	0.0000
Visual Perception	0.2029	9.27	0.0000
Visual Perception	0.2453	10.68	0.0000
Visual Perception	0.3974	18.93	0.0000

The researchers have established an expected average of score points for each cognitive function evaluated in MentalPlus®. The data was expressed in mean and SD. The significance level was $\alpha = 0.05$ 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 evaluated 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, it was expected a score of 30 ± 2 ; It was adopted 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 and the video game players. The cognitive function score results obtained for versions A and B corresponded to narrow ranges of values disclosing the both versions similarities. (Table 3)

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

MentalPlus Phases	PHASE I		PHASE II		PHASE III		PHASE IV		PHASE V		PHASE VI		PHASE VII*		PHASE VIII		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		Right		Left		*Training		Right		Left		A A A B		B B B B				
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	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	163
Minimum	8	6	31	28	9	9	9	9	10	9	10	9	3	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	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	20
75% Percentile	10	10	33	33	12	12	12	12	12	12	12	12	7	7	6	6	6	6	20	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	20
Mean	9.74	9.33	32.74	32.32	11.77	11.41	11.77	11.41	11.75	11.39	11.39	5.68	5.68	5.28	5.68	5.35	5.71	18.8	17	17.1	19	17	17.1	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	5.5	5.5	5.3	5.5	5.1	5.6	18.4	16	16.3	18	16	16.3	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	5.7	5.7	5.6	5.7	5.4	5.6	19	18	17.7	19	18	17.7	17.7	

4 Discussion

This study found sufficient evidence that MentalPlus® video game has reliability for use in neuropsychological evaluation as a diagnostic tool of cognitive dysfunction for mnemonic, attentional and executive functions. Data Analysis yielded interesting findings. The results presented an excellent agreement for a general cognitive function for MentalPlus® versions A and B, concerning scores concordance, with a Kappa coefficient of 0.7122 ($p < 0.005$). (Table 2) There was a good agreement for attention, long-term memory, and inhibitory control. (Table 2) It disclosed a low dispersion for executive function category through the construct inhibitory control. The visual perception presented a marked dispersion related to objects motion and resolution in versions A and B during the first two of 3

times it was evaluated. The last visuoperception evaluation phase with MentalPlus® revealed a better kappa index (0.3949), probably due the learning effect for the third time the volunteer was playing. (Table 2) These results might be influenced by the images resolution and definition for tablet screens and notebooks smaller than 10 inches. (S7 file) Both game versions values were very similar when compared with the values 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) The presented values favor MentalPlus® reliability. The use of the game in patients undergoing anesthetic and surgical procedures might favour the diagnosis and rehabilitation treatment for POCD. The main 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. MentalPlus® game presents many advantages through the extensive psychosocial 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 have an oriented health professional to apply the video game. Therefore, that justification would favour its usefulness in a broad of clinical settings, enabling 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. Afterwards, it might be evaluated for cognitive rehabilitation, in near future.

5 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 effective calibration of the game as for its validation.

6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7 Author Contributions

Conceived and designed the experiments: LSSV VFAP. Performed the experiments: LSSV, VFAP. Analyzed the data: LSSV VFAP. Wrote the manuscript: LSSV VFAP.

8 Acknowledgments

We wish to thank the timely help given by Professor Simone Kühn, Max Planck Institute and Professor Lars Simon Rasmussen, the University of Copenhagen in the support that we received for our study with MentalPlus®.

9 Funding Sources

Our Research was supported from Comissão de Análise de Projetos de Pesquisa da Universidade de São Paulo - CAPPesq-FMUSP (CAAE: 49463315.5.1001.0068), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES, Faculdade de Medicina - FMUSP, Pró-Reitoria de Pós-Graduação da Universidade de São Paulo - PRRG/USP.

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