



Research Paper

The use of cognitive mobile games to assess cognitive function of healthy subjects under various inspiratory loads

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ABSTRACT

Objective: The aim of this work was to determine if scoring mechanisms embedded in cognitive mobile games (CMG) designed for cognitive training are sensitive enough to detect changes in cognitive function induced by various acute respiratory loads in healthy subjects.

Material and methods: Thirty healthy subjects participated in this study (25 ± 4 years old, 13 women). A set of three brief CMG was used to assess cognitive function (Rush Back, Must Sort, True Color) in control situation and at four different inspiratory loads (through a mouthpiece without resistance and with 10, 50 and 70% of the maximal inspiratory pressure).

Results: Statistically significant decreases in CMG scores were observed in Rush Back ($p = 0.032$) and True Color ($p = 0.002$) when the subjects breathed through the mouthpiece without resistance compared to the control condition. A statistical difference was observed for Must Sort ($p = 0.003$) between baseline and 10% of Inspiratory Threshold Load (ITL). Significant differences for the three games were observed between the baseline and 50% of ITL and between baseline and 70% of ITL.

Conclusion: CMG designed for cognitive training are sensitive in detecting transitional changes in cognitive function induced by low, medium and high acute respiratory loads in healthy subjects. This offers interesting new possibilities for the assessment and long-term follow-up of patients suffering from chronic respiratory disease, since this type of assessment could easily be completed independently by patients in their own homes, and could be combined with rehabilitation exercises as an evaluative measure.

1. Introduction

The use of video games for cognitive training has been popularized by the “How old is your Brain”™ games by Dr Kawashima [1], among others. As a result of this, the use of entertaining video games to train cognition has gained the interest of young adults and older people in an attempt to slow down age-related cognitive decline [2]. One meta-analysis indicates that cognitive games training can have a positive, but limited, effect on several cognitive functions such as reaction time, attention and memory in the elderly [3]. A recently published Cochrane’s

review summarised the use of cognitive games in cognitively healthy people in late life (65 or older) and found little evidence from the included studies to suggest that 12 or more weeks of training improves cognition in healthy older adults [4]. Therefore, video games could be used to counter the natural age-related decline of cognitive function. One possible benefit of cognitive games is that they could be combined with cognitive assessments to provide regular screening and follow-up of cognitive function (since the results of the games correlate with scores in clinical scales [5]), at a lower cost and without the need of a healthcare professional.

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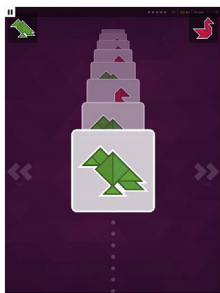
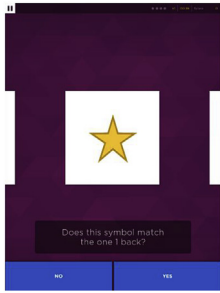
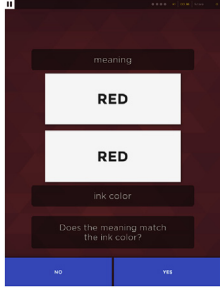
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Table 1
Screenshots, description, main objectives, score calculation and basis of the mobile games used in the study.

Games	Screenshot	Instruction	Score	Objective	Test based on
Must Sort		Sort the items correctly by tapping on the corresponding sides	Base score multiplied by streak multiplier, streak is incremented by correct answers and is reduced to 1 on incorrect or more than 5 s between answers.	<ul style="list-style-type: none"> • Response control • Task shifting 	Go/No-Go task
Rush Back		Memorize the card and respond to whether the current card matches the card that came before it	Base score with a multiplier which goes up and down based on streak. Streak up of 4 correct in a row but not changed during game play Bonus for end of game, current streak multiplier * bonus	<ul style="list-style-type: none"> • Sustained attention • Visual recognition • Working memory 	N-Back
True Color		Respond to whether the word on the bottom corresponds to the correct color(top word)	Base score with a multiplier which goes up and down based on streak. Streak up of 4 correct in a row but not changed during game play Bonus for end of game, current streak multiplier * bonus	<ul style="list-style-type: none"> • Inhibitory control • Mental flexibility 	Stroop Task

Furthermore, it is widely accepted that breathing can interfere with cognition on the short and long term [6–8]. When an inspiratory load is added, either artificially or due to respiratory disease, this induces the involvement of the pre-motor cortex, thus affecting the person’s cognition during activities of daily living [9]. On the long term, it has been shown that people with chronic respiratory diseases presented an increased risk of developing dementia [10].

The increase of inspiratory load on respiratory muscles is a common feature in some pulmonary pathologies (e.g. Chronic Obstructive Pulmonary Disease (COPD), asthma, etc.) [11]. This could have an impact on the multitask activities of daily living for these patients [12]. It is thus important to evaluate the impact of this inspiratory load on the cognition of these patients on a regular basis.

Therefore, the aim of this study was to determine whether or not specific Cognitive Mobile Games (CMG) demonstrate adequate sensitivity in detecting changes in cognitive function induced by various acute respiratory loads in healthy subjects.

2. Materials and methods

Thirty healthy young adults (25 ± 4 years old, 13 women) participated in this study. This study was approved by the Ethical Committee of Erasme Hospital (P2016/406/B406201629663) and written informed consent was obtained from all subjects prior to their participation.

Maximal inspiratory pressure (P_{Imax}) was measured following ATS/ERS recommendations close to the residual volume [13]. Mouth pressure was measured through an occluded mouthpiece (Hand-held spirometer; USB Pocket-Spiro® MPM100 MEC Medical Electronic Construction

R&D). The highest value of three consecutive 1-s attempts was recorded as the P_{Imax}.

Five different breathing conditions were tested: quiet breathing (baseline condition used as control), breathing through the mouthpiece with no resistance, and breathing through an Inspiratory Threshold Load (ITL; MAS Philips Respironics Threshold IMT Lung Muscle Trainer Adjustable Constant Pressure and POWERbreathe Plus Medium Resistance Breathing Muscle Trainer) at 10% (low resistance), 50% (mid resistance) and 70% (high resistance) of each subject’s P_{Imax}. For all conditions, subjects were equipped with a nose clip to restrict nasal compensation. This protocol has been previously validated in assessing the influence of increased respiratory loads on balance [14].

Three short (<1 min) CMG were used in this study, selected based on previous evidence of their similarities to neuropsychological assessment tools in identifying cognitive impairment [5]. The CMG were explained to the participants and they were invited to play one time before the start of the study to get familiar with the CMG. Each CMG was played one time for every condition. Screenshots and descriptions of the games are presented in Table 1. The outcome was the score obtained in the three CMG in each of the five different conditions. Each CMG has its own scoring system described in Table 1.

Both the order of the conditions and of the CMG were randomized to avoid fatigue or habituation bias. Subjects were unaware of the different loads, and were asked to breathe for 30s with the different loads before testing to allow acclimatization to these constraints.

The normality of each set of scores was assessed using graphical methods (boxplots, histograms and QQ-plots) and homogeneity of variances using Levene’s test. One-way multivariate ANOVA (MANOVA)

Table 2

Mean (standard deviations) scores of the games under the different inspiratory loads. P-values are the results of the ANOVA, ω^2 is the measure of the effect size ($\omega^2 < 0.01$ = small, between 0.01 and 0.06 = medium, $\omega^2 > 0.14$ = large).

Games	Baseline	Mouth-piece	10%	50%	70%	ANOVA	ω^2
Must Sort	5348 (1381)	4724 (1260)	4255 (1743)	3546 (1628)	3508 (1449)	F(4, 125) = 7.12, p < 0.001	0.17
Rush Back	21367 (3626)	19110 (4904)	19361 (3956)	15271 (6087)	17160 (5233)	F(4, 125) = 6.12, p < 0.001	0.07
True Color	9212 (3017)	7296 (3784)	8072 (3492)	6960 (3870)	5879 (3239)	F(4, 125) = 3.31, p = 0.012	0.10

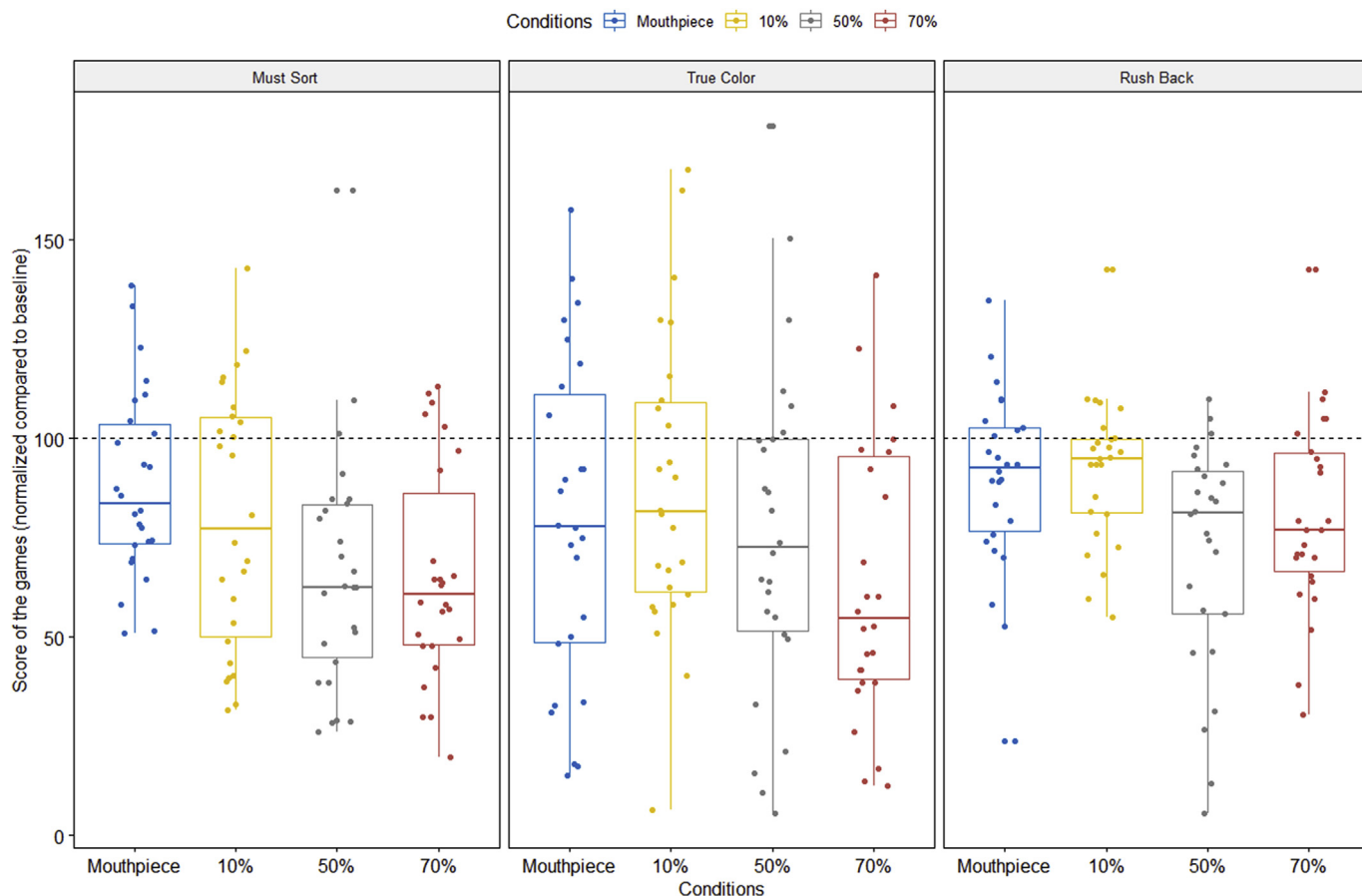


Fig. 1. Normalized scores (expressed in percentage) of the CMG for the different conditions compared to baseline results.

tests was applied to compare the five conditions. Omega-squared tests were computed to estimate the effect size. Finally, Bonferroni tests were used to correct for multiple comparisons in our post-hoc analysis. Statistical analyses were performed at an overall significance level of 0.05, and were computed in RStudio (version 1.1.442) with R version 3.4.4. To detect a difference of 10% in the CMG scores between the loads with 80%

power and a two-sided type I error of 5%, we calculated prior to the commencement of the study the need to include 28 subjects. This sample size estimation was calculated using STATA (StataCorp. 2015. Stata Statistical Software: Release 13. College Station, TX: StataCorp LLC).

Table 3

Difference [95% CI] and p-value of group comparisons after Bonferroni corrections (*p < 0.05, **p < 0.01, ***p < 0.001).

CMG	Conditions	Baseline	Mouthpiece	10%	50%
Must Sort	Mouthpiece	-624 [-1777; 528]			
	10%	-1093 [-2046; -140]**	-468 [-1621; 684]		
	50%	-1802 [-2956; -649]***	-1178 [-2131; -225]**	-709 [-1863; 443]	
	70%	-1840 [-2203; -687]***	-1215 [-2369; -63]***	-747 [-1900; 450]	-37 [-1190; 1115]
Rush Back	Mouthpiece	-2257 [-3975; -460]*			
	10%	-1736 [-4454; 981]	521 [-3197; 4239]		
	50%	-6096 [-9814; -2377]***	-3838 [-6556; -1120]***	-4359 [-7077; -1641]***	
	70%	-4207 [-7925; -490]***	-1949 [-4668; 768]	-2470 [-6189; 1247]	1888 [-1829; 5606]
True Color	Mouthpiece	-1915 [-2598; -1232]**			
	10%	-1139 [-2822; 544]	776 [-1907; 3459]		
	50%	-2251 [-3435; -1067]***	-336 [-3019; 2346]	-1112 [-3796; 1570]	
	70%	-3332 [-5016; -1649]***	-1417 [-2568; -266]*	-2193 [-4876; 489]*	-1080 [-3764; 1602]

3. Results

Results of the CMG scores under the different loads are presented in Table 2 and in Fig. 1. The differences between the different conditions are presented in Table 3. There was a highly significant effect of the breathing conditions on cognitive performance as indicated by our MANOVA ($F(4,125) = 3.51, p < 0.001$).

Statistically significant decreases in CMG scores were observed in Rush Back ($p = 0.032$) and True Color ($p = 0.002$) when the subjects breathed through the mouthpiece without resistance compared to the control condition but not for the Must Sort ($p = 0.09$).

A statistically significant difference in game scores was found between the baseline and 10% of ITL for Must Sort ($p = 0.003$) but not for Rush Back ($p = 0.098$) or True Color ($p = 0.063$).

There were highly significant differences in game scores between the baseline and 50% and 70% of ITL for the three CMG.

No difference was found between the mouthpiece condition and 10% of ITL, however, statistically significant differences were found between the mouthpiece and 50% of ITL for Must Sort ($p = 0.002$) and Rush Back ($p < 0.001$) but not for True Color ($p = 0.580$).

For the difference between the mouthpiece condition and 70% of ITL, only Must Sort presented a statistically significant difference ($p = 0.001$).

There was a highly significant difference between 10 and 50% of ITL for Rush Back ($p < 0.001$) but not for the other games.

No statistically significant differences were found between 50% and 70% of ITL for any of the games.

4. Discussion

The aim of this study was to determine if three CMG designed for brain training are sensitive enough to detect changes in cognition induced by different acute respiratory loads. Statistically significant differences in CMG scores were observed for the different inspiratory loads. Interestingly, no change in cognition was identified between the mouthpiece condition and 10% ITL. In addition, no difference was found between 50% ITL and 70% ITL. These results may indicate that the threshold of prefrontal cortex activation has not been reached at 10% ITL [7] and that a plateau has been reached at 50% ITL, but further studies using electroencephalography are necessary to confirm this.

It has previously been demonstrated that breathing under respiratory load interferes with cognition [6]. In fact, inspiratory load-induced dyspnea can interfere with performance in different cognitive tasks such as fearful face recognition [15], response inhibition [16] and with decreasing illusory effects [8]. A growing body of evidence appears to indicate competition for cortical resources between the loaded breathing and cognitive tasks. Research demonstrates that breathing under inspiratory load activates the cortex: when a respiratory load is imposed, there is a shift from the automatic neural processes to the cortical network [9]. This could explain the cognitive cost of loaded breathing, and this kind of task may therefore be considered a dual task paradigm. To the author's knowledge, this study is the first to describe a progressive alteration of cognitive function with increasing inspiratory load.

The present results are interesting from a clinical perspective as the increase of inspiratory load is one of the key characteristics of COPD patients [11], and we have succeeded in demonstrating that CMG are able to detect the cognitive impact of this load.

However, the inspiratory loads used in this study may be too high to recreate the same/exact? symptoms encountered by COPD patients. The choice of loads was based on the evidence that there is strong linear relationship between the increase of mouth inspiratory pressure and the increase of respiratory muscle activation in healthy subjects [17]. Furthermore, COPD patients show greater respiratory muscle activity than do healthy subjects for the same load [18]. Therefore the different loads used in this study (10%, 50%, and 70% of the P_{Imax}) were selected

to test the sensitivity of CMG using a wide spectrum of muscle activation. However, the fact that no cognitive differences were found between the mouthpiece and 10% ITL, and 50 and 70% ITL conditions, may indicate that the CMG are not sensitive enough to detect smaller changes.

To summarize, Must Sort can detect the effect of a 10%, 50% and 70% increase in inspiratory load compared to normal breathing, while Rush back and True Color were able to detect the effect of 50% and 70% loads. Must Sort thus appears to be the most sensitive game in detecting acute modification of the cognition. However, only Rush Back can distinguish between the effect of a 10% and 50% load. Therefore, to cover all of the effects of an unknown inspiratory load on cognition, all three CMG should be used. Since the CMG are short (a combined total of less than 5 min) the three games should be used in combination to ensure the highest assessment sensitivity [5].

5. Conclusion

We have shown that the CMG used in this study are sensitive enough to detect changes in cognitive function induced by various acute respiratory loads in healthy subjects. Further studies are needed to test this system more thoroughly in patients with respiratory disease.

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References

- [1] Nouchi R, Taki Y, Takeuchi H, Hashizume H, Nozawa T, Kambara T, Sekiguchi A, Miyauchi CM, Kotozaki Y, Nouchi H, Kawashima R. Brain training game boosts executive functions, working memory and processing speed in the young adults: a randomized controlled trial. *PLoS One* 2013;8(2):e55518.
- [2] Grillo FW. Long live the axon. Parallels between ageing and pathology from a presynaptic point of view. *J Chem Neuroanat* 2016;76(Pt A):28–34.
- [3] Toril P, Reales JM, Ballesteros S. Video game training enhances cognition of older adults: a meta-analytic study. *Psychol Aging* 2014;29(3):706–16.
- [4] Gates NJ, Rutjes AW, Di Nisio M, Karim S, Chong LY, March E, Martínez G, Vernooij RW RW. Computerised cognitive training for maintaining cognitive function in cognitively healthy people in late life. *Cochrane Database Syst Rev* 2019;3: CD012277.
- [5] Bonnechère B, Van Vooren M, Bier JC, De Breucker S, Van Hove O, Van Sint Jan S, Feipel V, Jansen B B. The use of video games to assess cognitive function of elderly with and without cognitive impairment. *J Alzheimer's Dis* 2018;64(4):1285–93.
- [6] Nierat MC, Demiri S, Dupuis-Lozeron E, Allali G, Morélot-Panzini C, Similowski T, Adler D. When breathing interferes with cognition: experimental inspiratory loading alters timed up-and-go test in normal humans. *PLoS One* 2016;11(3): e0151625.
- [7] Sharman M, Gallea C, Lehongre K, Galanaud D, Nicolas N, Similowski T, Cohen L, Straus C, Naccache L. The cerebral cost of breathing: an fMRI case-study in congenital central hypoventilation syndrome. *PLoS One* 2014;9(9):e107850.
- [8] Allard E, Canzoneri E, Adler D, Morélot-Panzini C, Bello-Ruiz J, Herbelin B, Blanke O, Similowski T. Interferences between breathing, experimental dyspnoea and bodily self-consciousness. *Sci Rep* 2017;7(1):9990.
- [9] Raux M, Straus C, Redolfi S, Morelot-Panzini C, Couturier A, Hug F, Similowski T. Electroencephalographic evidence for pre-motor cortex activation during inspiratory loading in humans. *J Physiol* 2007;578(Pt 2):569–78.
- [10] Zhang X, Cai X, Shi X, Zheng Z, Zhang A, Guo J, Fang Y. Chronic obstructive pulmonary disease as a risk factor for cognitive dysfunction: a meta-analysis of current studies. *J Alzheimer's Dis* 2016;52(1):101–11.
- [11] Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 2003;168(1):10–48.
- [12] Paes T, Machado FVC, Cavalheri V, Pitta F, Harnandes NA. Multitasks protocols to evaluate activities of daily living performance in people with COPD: a systematic review. *Expert Rev Respir Med* 2017;11:581–90.
- [13] American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002;166(4):518–624.
- [14] Van Hove O, Van Muylem A, Leduc D, Jansen B, Feipel V, Van Sint Jan S, Bonnechère B. Validation of the Wii Balance Board to assess balance modifications induced by increased respiratory loads in healthy subjects. *Gait Posture* 2019;68: 449–52.
- [15] Vinckier F, Morélot-Panzini C, Similowski T. Dyspnoea modifies the recognition of fearful expressions by healthy humans. *Eur Respir J* 2018;51(2):1702253. pii.
- [16] Sucec J, Herzog M, Van Diest I, Van den Bergh O, von Leupoldt A. The impairing

- effect of dyspnea on response inhibition. *Int J Psychophysiol* 2018;133:41–9.
- [17] Yokoba M, Abe T, Katagiri M, Tomita T, Easton PA. Respiratory muscle electromyogram and mouth pressure during isometric contraction. *Respir Physiol Neurobiol* 2003;137(1):51–60.
- [18] de Andrade AD, Silva TN, Vasconcelos H, Marcelino M, Rodrigues-Machado MG, Filho VC, Moraes NH, Marinho PE, Amorim CF. Inspiratory muscular activation during threshold therapy in elderly healthy and patients with COPD. *J Electromyogr Kinesiol* 2005;15(6):631–9.