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A Pilot Study to Improve Cognitive Performance and Pupil Responses in MCI Patients Using Gaze-Controlled Gaming

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Abstract: Mild Cognitive Impairment (MCI) may progress to severe forms of dementia, so therapy is needed to maintain cognitive abilities. The neural circuitry for oculomotor control is closely linked to that which controls cognitive behavior. In this study, we tested whether training the oculomotor system with gaze-controlled video games could improve cognitive behavior in MCI patients. Patients played a simple game for a month while a control group played the same game using a mouse. Cognitive improvement was assessed using the MoCA screening test and CANTAB. We also measured eye pupil and vergence responses in an oddball paradigm. The results showed an increased score on the MoCA test specifically for the visuospatial domain and on the Rapid Visual Information Processing test of the CANTAB battery. Pupil responses also increased to target stimuli. Patients in the control group did not show significant improvements. This pilot study provides evidence for the potential cognitive benefits of gaze-controlled gaming in MCI patients.

Keywords: attention; digital treatment; MCI; visual oddball; pupil

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Mild Cognitive Impairment (MCI) may progress to severe forms of dementia, so therapy is needed to maintain cognitive abilities. The neural circuitry for oculomotor control is closely linked to that which controls cognitive behavior. In this study, we tested whether training the oculomotor system with gaze-controlled video games could improve cognitive behavior in MCI patients. Patients played a simple game for 2-3 weeks while a control group played the same game using a mouse. Cognitive improvement was assessed using the MoCA screening test and CANTAB. We also measured eye pupil and vergence responses in an oddball paradigm. The results showed an increased score on the MoCA test specifically for the visuospatial domain and on the Rapid Visual Information Processing test of the CANTAB battery. Pupil responses also increased to target stimuli. Patients in the control group did not show significant improvements. This pilot study provides evidence for the potential cognitive benefits of gaze-controlled gaming in MCI patients.

Mild Cognitive Impairment (MCI) is a condition that affects cognitive function, including attention, memory, and executive function. While MCI does not typically interfere significantly with daily activities, it may progress to more severe forms of cognitive decline, such as dementia. As such, there is a need for therapy or treatment for patients with MCI to maintain their mental abilities and potentially delay the onset of more severe cognitive impairment.

Cognitive improvement may involve various approaches, such as cognitive training, physical exercise, and diet modifications, and there is growing interest in the use of computerized tasks and video games as a potential intervention to improve cognitive functions. Research has suggested that

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video gaming and computerized task can improve attention, working memory, executive function, and visuospatial abilities (Green & Bavelier, 2003; Boot et al., 2008; Basak et al., 2008; Li et al., 2009; Kueider et al., 2012; Anguera et al., 2013; Kühn et al., 2014). Enhancements have been observed not only in healthy individuals but also in patient populations with attention problems (Bertoni et al., 2021), including MCI patients (Park & Park, 2018; Ferreira-Brito, et al., 2021; Lin et al., 2022). However, meta-analysis studies revealed small to moderate positive treatment effects in MCI patients (Coyle et al., 2015; Zhang et al., 2019; Hu et al., 2021; Li et al. 2022; Kletzel, 2021) and some studies found no positive effects of computerized training tasks in healthy subjects nor in MCI patients (Coyle et al., 2015; Hill et al., 2017; Gates et al. 2019). Thus, although video games are a promising technology, they need to be further developed to become a tool for intervention.

Patients with cognitive disorders typically demonstrate altered pupil responses (Jimenez et al., 2021; Guath et al., 2023) and oculomotor deficits (Johnson et al., 2016; Myles et al., 2017; Kapoula et al., 2014; Varela et al., 2018; Jimenez et al., 2021; de Vries et al., 2021). Ample evidence shows that modulation in pupil size manifest cognitive processing and likely reflects the functioning of the Locus Coeruleus (Joshi & Gold, 2020; Strauch et al., 2022), which is a key structure in attentional processing. In addition to pupil responses, eye movements also play a role in perception and attention. (Martinez Conde et al., 2006; Hafed & Clark, 2002; Enbert & Kliegl, 2003; Solé-Puig et al., 2013; Bonneh et al., 2015; Scholes et al., 2015). It is thus plausible that the oculomotor system can be used as a means of cognitive intervention. Indeed, recent evidence shows that training the oculomotor system with gaze-controlled video games can be effective in improving attention in ADHD patients (Garcia-Baos et al., 2019). The goal of this study is to determine whether gaze-controlled games can improve cognitive behavior in patients with MCI.

Materials and Methods

Participants

A total of 50 patients with MCI were recruited. Thirteen patients withdrew from the study before completion and their data were therefore excluded from the analysis. Of the remaining 37 patients, 29 (19 female) participated in the experimental group and 8 (5 female) in the control group. All participants had a history of cognitive decline confirmed by their Montreal Cognitive Assessment (MoCA) scores (see Results). They were 63-86 years old (mean±SD: 77.91±6.85) and were recruited from three different private day care centers in Barcelona, Spain.

Ethics statement

Participants and their relatives received detailed instructions for the experiments. Prior to enrollment, patients or their relatives signed a written informed consent for their participation, in accordance with the tenets of the Declaration of Helsinki. The ethics committees of the University of Barcelona approved the study.

Video game

The video game (Figure 1) consisted of a stationary or moving (left to right or vice versa) target (dartboard-like picture) and a distractor (picture of an owl). Participants had to look at or follow the moving target with their eyes for 1 second and avoid looking at the (moving) distractor. If successful, the target would "explode" and the participant receives points, or the owl would disappear. If unsuccessful, the target would disappear or the owl would "explode" and the participant would lose points. Only one target or distractor was presented at a time. Eye position was recorded with a remote eye tracker (5L, Tobii Danderyd, Sweden) and fed back to the presentation software to control the game. The actual eye position was indicated by a pointer on the screen. In the control group, participants played the same game but used a mouse cursor as a controller instead of eye gaze. Participants played 3 sessions per week of approximal 15 minutes each over a period of one month.

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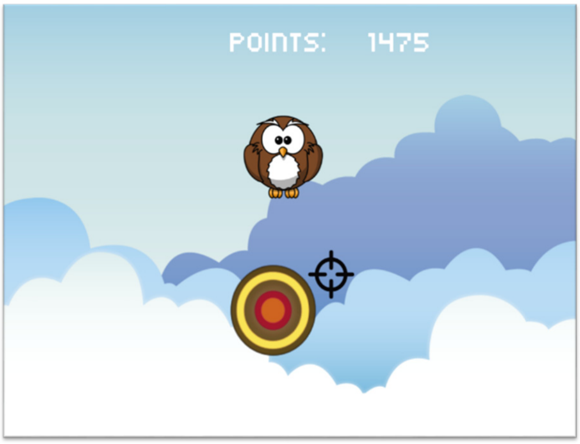

Figure 1. Illustration of the video game Note that in the actual game only 1 target (dartboard) or distractor (owl) was presented. The pointer indicated position of eye gaze or mouse cursor in real-time.

Neuropsychological pre and post assessment instruments

Global cognitive performance of participants was assessed using the Montreal Cognitive Assessment (MoCA) and the Cambridge Neuropsychological Test Automated Battery (CANTAB®; Cambridge Cognition Ltd., UK)

MoCA

MoCA is a widely used cognitive screening tool that assesses various aspects of cognitive function, including attention, memory, language, visuospatial abilities, and executive function. It was designed to detect MCI and early dementia in adults. The maximum score on the test is 30, with a score of 26 or above considered normal.

CANTAB

CANTAB is a computerized cognitive assessment battery. The CANTAB battery consists of a series of tests that assess various cognitive domains, including attention, memory, executive function, and visuospatial abilities. The battery has been extensively validated and is widely used in both research and clinical settings to assess cognitive function in a range of populations.

For this study we used the following tests:

- Rapid Visual Information Processing (RVP) is a measure of sustained attention.
- Paired Associates Learning (PAL) assesses visual memory and new learning.
- Motor Screening Task (MST) provides a general assessment of sensorimotor deficits.
- Pattern Recognition Memory (PRM) is a test of visual pattern recognition memory in a 2-choice forced discrimination paradigm.
- Reaction Time (RT) provides assessments of motor and mental response speeds, as well as measures of movement time, reaction time, response accuracy and impulsivity.
- Spatial Working Memory (SWM) requires retention and manipulation of visuospatial information.
- Delayed Matching to Sample (DMS) assesses both simultaneous visual matching ability and short-term visual recognition memory.

Visual oddball paradigm

To assess possible changes in pupil and eye vergence responses, patients performed a visual oddball task before and after the gaming sessions (Jimenez et al., 2021). The task was a sequence of 100 trials. Each trial started with a grey screen (Mask) for 2000ms followed by the stimulus screen for 2000ms. The central stimulus consisted of a series of randomly selected letters forming a string of 11

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characters in upper or lower case. Letter strings did not represent acronyms or meaningful words. In the distractor condition, the color of all characters of the string was blue (80% of trials), whereas in the target condition, the color of the characters was red (20% of trials). Target and distractor stimuli were randomly presented. Participants were instructed to press a response button when the characters of a string appeared in red. The total duration of the task was about 6 minutes.

The BGaze (Braingaze SL, Mataró, Spain) system was used to present the visual oddball task. Eye position data was recorded with X2-30 (30Hz) remote eye tracker (Tobii Technology AB, Sweden) mounted below the screen. Screen resolution was 1024 x 768 pixels. Patients were seated 50-60 cm from the stimulus screen. Patients could wear corrective lenses. Before starting the recording, the eye tracker was calibrated (5 points, binocular) for each participant. No chinrest was used during the task.

The eye data obtained during the oddball task was used to calculate pupil and vergence responses. In order to calculate vergence changes, we transformed the coordinates of left and right eye, supplied by the eye tracker, into angular magnitudes (degrees). The subtraction of initial values from every response, which was applied both to vergence and to pupil data, served the purpose of obtaining relative changes. Only correct trials were analyzed.

Statistical analysis

One-tailed t-test was used to evaluate improvement in MoCA scores. Raw scores of CANTAB test measures were selected for statistical evaluation. For comparisons between baseline and post-game CANTAB scores, the one-tailed Wilcoxon signed rank test was used. For the analyses of pupil and vergence responses, two sided paired t-test was applied. The significance level was set at $p<0.05$. MATLAB (MathWorks) was used for data and statistical analysis.

Results

Gaming

On average (mean±SD) 11.7±2.20 (min: 9; max: 16) sessions were completed. The mean session duration was (mean±SD) 16.12±3.22 minutes. The mean number of correctly identified targets was 55.25%. Participants did not improve over the course of therapy, as there was no significant ($p > 0.05$) correlation (Spearman rank) between the number of sessions played and the number of correct responses ($R^2 = 0.21$).

MoCA

The total MoCA score improved from (mean±SD) 14.64±4.28 at baseline to 15.52±4.76 after gaming ($p<0.03$). When comparing the scores for the different items, we observe that the improvement is mainly in the visuospatial domain ($p<0.002$). The effect sizes are small for total MoCA scores (Hedges' g factor: 0.20) and moderate for the visuospatial domain (Hedges' g factor: 0.52). Of the participants, 55% improved and 10% worsened on this domain. None of the other domains showed significant improvement. Results of the MoCA assessment per cognitive function tested are shown in Figure 2.

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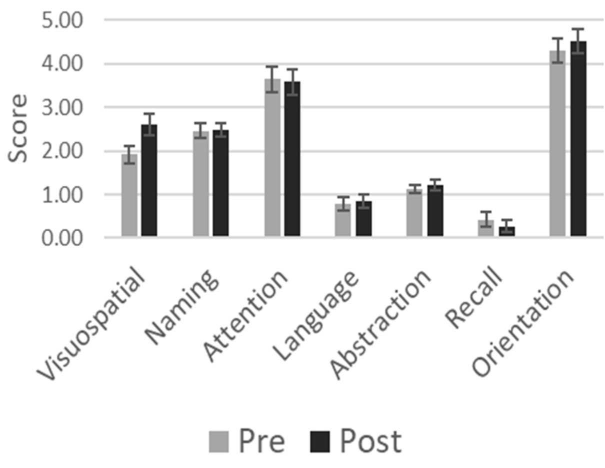

Figure 2. MoCA scores obtained before (pre) and after (post) the gaming sessions.

There was no significant ($p > 0.05$) correlation (Spearman rank) between the number of game sessions played and improvement in either the overall MoCA score ($R^2 = 0.067$) or the visuospatial domain score ($R^2 = 0.155$).

CANTAB

Of the various CANTAB tests used, only Rapid Visual Information Processing (RVP) showed significant improvements after the end of the game session (Table 1). The most significant improvement was observed in Subject's Sensitivity (RVPA), which is a measure of how well the subject is able to detect target sequences. The effect size for RVPA was 0.67 (Hedges' g-factor). Except for a few scores, all other tests (Paired Associates Learning, Motor Screening Task, Pattern Recognition Memory, Reaction Time, Spatial Working Memory, and Delayed Matching to Sample) showed no statistically significant improvement after the gaming sessions (Tables 2–6 in Annex 1).

Table 1. Measures obtained from the Rapid Visual Information Processing (RVP) test, presented as Mean ± SD of the Raw Score.

Type	Pre-treatment	Post-treatment	Participants	Test statistics		
	Mean(SD)	*Mean(SD)*	*N*	*Ties*	*Z*	*P*
RVPML	887.00(340.36)	787.89(205.26)	29	0	1.6866	**0.0458**
RVPLSD	409.24(138.68)	337.10(145.22)	29	0	2.1842	**0.0145**
RVPA	0.75(0.07)	0.79(0.05)	27	2	-3.4476	**<0.001**
RVPTH	16.59(10.29)	22.89(15.58)	27	2	-2.1403	**0.0162**
RVPTFA	35.81(36.73)	65.30(99.65)	25	3	-0.4858	0.3136
RVPPH	0.31(0.19)	0.42(0.29)	27	2	-1.9646	**0.0247**
RVPTM	34.83(13.84)	30.59(15.63)	27	2	1.5505	0.0605

Control group

To assess whether the improvements observed on the MoCA test and the RVP task of the CANTAB battery were specific to the gaze-controlled game, we tested a small group of MCI patients who played the same game but controlled it with the mouse instead of their eyes.

Overall MoCA scores did not improve significantly between baseline (mean±SD: 22.50±6.82) and post-game (23.00±6.93; p=0.37). No significant changes were observed in any of the individual domains of the MoCA, including the visuospatial domain (mean±SD: baseline: 4.13±0.83; post-gaming: 4.13±0.64; p=0.5). Note that the overall MoCA score and the visuospatial score are higher than in the experimental group. The RVP task of the CANTAB battery also showed no significant differences in any of the measures. For example, sensitivity (RVPA) at baseline was (mean±SD)

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0.84±0.07 and 0.81±0.10 after the game (Z: -1.007; p: 0.8309). On the other administered CANTAB tasks, no significant improvements were observed.

Pupil and vergence responses

We next evaluated whether pupil size and vergence responses had changed after the gaming sessions. We observed modulatory pupil responses where responses were stronger to targets than to distractors (Figure 3). After gaming, there was a significant increase in the late period (average window of 1500-2000ms) of the pupil responses to targets (mean±SD: pre: -0.012±0.24; post: 0.032±0.17; t= -2.41, p= 0.016). Responses to distractor stimuli did not change after gaming (mean±SD: pre: -0.034±0.168; post: -0.039 ± 0.155; t= -0.064, p= 0.94).

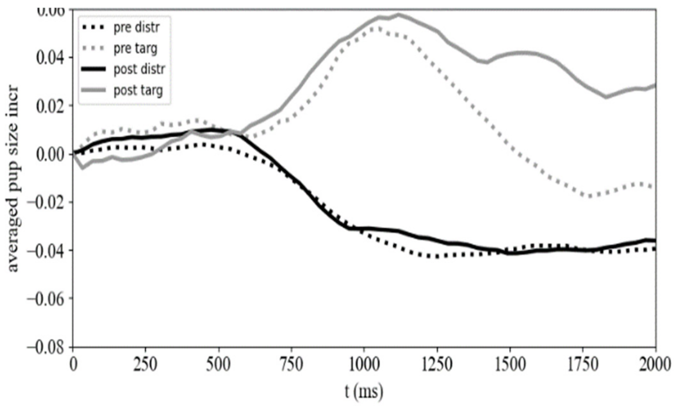

Figure 3. Pupil responses before (pre) and after (post) the gaming sessions to targets (targ) and distractors (distr).

Vergence responses to target stimulus were not significantly (t= -0.51, p= 0.61) different after gaming (mean±SD: 0.186 ± 2.34) compared to baseline responses (mean±SD: 0.062 ± 3.33). Neither distractor responses showed significant changes (mean±SD: pre: -0.034±2.77; post: 0.15±2.35; t=-1.9, p=0.057). The control group showed comparable pupil responses to distractors (mean±SD: pre: -0.050±0.16; post: -0.069±0.16; t= 0.838, p=0.109) and targets (mean±SD: pre: 0.032±0.18; post: 0.014±0.18; t=0.87, p=0.39) after gaming. Also, vergence responses were similar before and after the gaming sessions (target, mean±SD: pre: 0.16±2.6; post: 0.075±1.74; t= 0.35, p=0.73; distractor: mean±SD: pre: 0.12±2.32; post: 0.18±1.89; t=-0.50, p= 0.61).

Discussion

In the current study, we tested a gaze-controlled video game as a potential intervention tool to improve cognitive function in MCI patients. The gaze-directed game required participants to repeatedly maintain focus on a target for short periods of time, thus training sustained attention. The results show an increased score on the MoCA test specifically for the visuospatial domain after playing the game. This may indicate that the improvement with the gaze-controlled game is task specific, possibly due to the visual and spatial demands of the video game. Of the CANTAB battery, the Rapid Visual Information Processing test was the only test to show improvement. Again, the improvement may be task specific. The Rapid Visual Information Processing test primarily tests the ability to focus and maintain attention on a task over time. The other CANTAB test we used primarily tested short-term memory, which was not trained by the game. The results of the current report support our previous findings of cognitive improvement with gaze-controlled games (Garcia-Boas et al., 2019) and are consistent with previous studies (Park & Park, 2018; Ferreira-Brito, et al., 2021; Lin et al., 2022) showing that video games can have a positive effect on cognitive function.

Practice effects cannot be ruled out, as the MoCA test may be susceptible to practice effects in healthy older adults (Cooley et al., 2015, but see Bell 2019) and MCI patients (Lei et al., 2022). The CANTAB battery tests also show practice effects in patients with cognitive decline. In particular, the

Paired Associates Learning, Spatial Working Memory, and Motor Screening tests are associated with large practice effects (Gonçalves et al., 2016; Cacciamani et al., 2017). This is in contrast to our observations, which show no practice effects on these tasks. The Rapid Visual Information Processing and Reaction Time tests show no or weak practice effects in MCI patients (Cacciamani et al., 2017).

Thus, our findings suggest that the improvements observed in the current study are a true effect of playing a gaze-controlled game. This assumption is supported by the outcomes of the control group, in which participants showed no practice effects on the Rapid Visual Information Processing tests nor on any of the tests administered. However, the size of the control group was small and their scores were relatively high compared to the experimental group.

Both pupil and vergence responses are manifestations of cognitive processing. Pupil dilation reflects the allocation of top-down attentional resources (Lisi et al., 2015) and has been linked to various cognitive processes, including perception (Sole Puig et al., 2021), cognitive effort (van der Wel & van Steenbergen, 2018), memory (Papesh et al., 2012; Pajkossy et al., 2020), prediction error (Koenig et al., 2018) and decision-making (Urai et al., 2017, Van Slooten et al., 2018; Strauch et al., 2020). Similarly, vergence responses are associated with attention and memory (Sole Puig et al., 2013; 2016; 2017). Our results on pupil responses are consistent with previous findings that show greater pupil dilation for target stimuli compared to distractor stimuli (Krebs et al., 2018; Strauch et al., 2020; Jimenez et al., 2021). This suggests that the larger pupil responses to targets in the experimental group may indicate a higher level of attention or extra cognitive effort to achieve performance (Kang et al., 2014; Angulo-Chavira, et al., 2017).

In conclusion, the present results provide evidence for the potential cognitive benefits of gaze-controlled gaming in MCI patients and suggest that further research in this area is warranted.

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Conflict of Interest/Disclosure Statement: HS is co-founder of Braingaze

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