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Classification of MCI patients using vergence eye movements and pupil responses obtained during a visual oddball test

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ABSTRACT

In the current study, we tested the hypothesis that Mild Cognitive Impairment (MCI) patients can be identified based on the analysis of vergence eye movements and pupil responses. We recorded vergence and pupil responses in MCI patients ($N = 22$) and cognitive healthy elderly ($N = 18$) while performing a visual oddball task. Based on selected features, a classifier model computed probability scores predicting MCI. MCI patients were re-evaluated in a follow-up visit of 12–18 months. For validating the model, patients with Alzheimer's Disease (AD) ($N = 9$) were tested. High classification accuracy was obtained (AUC: 0.93). In addition, the probability scores showed significant predictive power of MCI conversion into possible AD. Our results show that MCI can be detected by assessing vergence and pupil responses during a simple and short task. Therefore, these responses could potentially be used as a marker tool for MCI diagnosis and to identify the risk of developing Alzheimer's Disease.

1. Introduction

To identify people with Mild Cognitive Impairment (MCI), brain imaging, as well as cerebrospinal fluid and blood biomarkers have shown promising results [1,2]. However, these marker tools require trained personnel to administer, and are invasive and expensive prohibiting their use in a clinical setting.

During gaze fixation participants briefly make a vergence eye movement, which may trigger a pupillary response [3]. Both vergence and pupil responses relate to cognitive processing [4–9], and are atypical in MCI patients when performing an attention task [10].

Here we recorded eye vergence and pupil responses of MCI patients and cognitive healthy older adults while performing a short attention task, and used the eye data for classification. To assess the potential of the classifier model to detect and predict Alzheimer's Disease (AD), additional patients with possible early AD were tested, and MCI patients were re-evaluated one year after testing.

2. Methods

2.1. Participants

The study group consisted of 40 participants (26 men and 14 women; mean±SD: 69.3 ± 7.8 years). Of these, 22 were diagnosed with MCI, and the remaining participants ($N = 18$) were cognitively healthy controls. In addition, 9 patients diagnosed as possible AD and 12 possible MCI patients were tested for evaluating the classifier model. For more details see supplementary information.

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2.2. Ethics statement

Prior to participating in the study, participants and/or care-takers received detailed instructions for the experiments and signed an informed consent in accordance with the Helsinki Declaration. The study was approved by the ethics committees of the Hospital Sanitas CIMA and of the University of Barcelona.

2.3. Neuropsychological testing

Cognitive performance was tested using a neuropsychological test battery and functional scales. Also, depression and anxiety issues were evaluated (see supplementary information for more details).

2.4. Clinical assessment

The clinical diagnosis of MCI and AD was established at a consensus meeting by neurologists and neuropsychologists of the hospital. After 12 to 18 months, MCI patients were re-evaluated and categorized as reversed, stable or progressed to possible AD (see supplementary information for more details).

2.5. Experimental task

The BGaze (Braingaze, Spain) system was used to present the visual task. The task was a visual oddball task (see appendix: 1.5,1.6; Fig A1). Eye position data was recorded with X2–30 eye tracker (Tobii Technology AB, Sweden).

2.6. Data analysis and classification

Vergence and pupil signals for every trial were calculated as the initial input for classification model. Based on the modulation of the vergence and pupil size responses, 5 aggregated features were used to build the classifier model. We used a decision tree classifier to fit a classification model (see also appendix: 1.7, 1.8, 1.9; Fig. A2).

3. Results

3.1. Demographics

Demographics of the patients from the hospital are shown in Table A1. Average age of the groups was similar. Gender differed between the control and MCI group. The GDS and MoCA scores were significantly different among the three groups. MMSE scores were only different between controls and MCI and AD patients.

3.2. Vergence and pupil size responses

In general, vergence and pupil responses have a similar modulation pattern but differ in amplitude (Fig. 1A-D). Correlation analysis suggests that the responses to distractor stimuli have higher potential to separate MCI patients from controls (see appendix: 2.1).

3.3. Feature aggregation

The first feature, i.e. the transient peak of the vergence response, is higher in MCI participants than in controls ($F_{(1,2128)} = 109.06$, $p<0.001$). The second feature (the minimum response strength after the initial vergence peak but before the onset of the delay response) is also different in MCI participants than in controls ($F_{(1,2128)} = 50.9$, $p<0.001$). Also the mean of the delay vergence response (third feature) is higher in MCI participants than in controls ($F_{(1,2128)} = 31.45$, $p<0.001$). The fourth feature, i.e. the average rate of the changes in pupil size after the

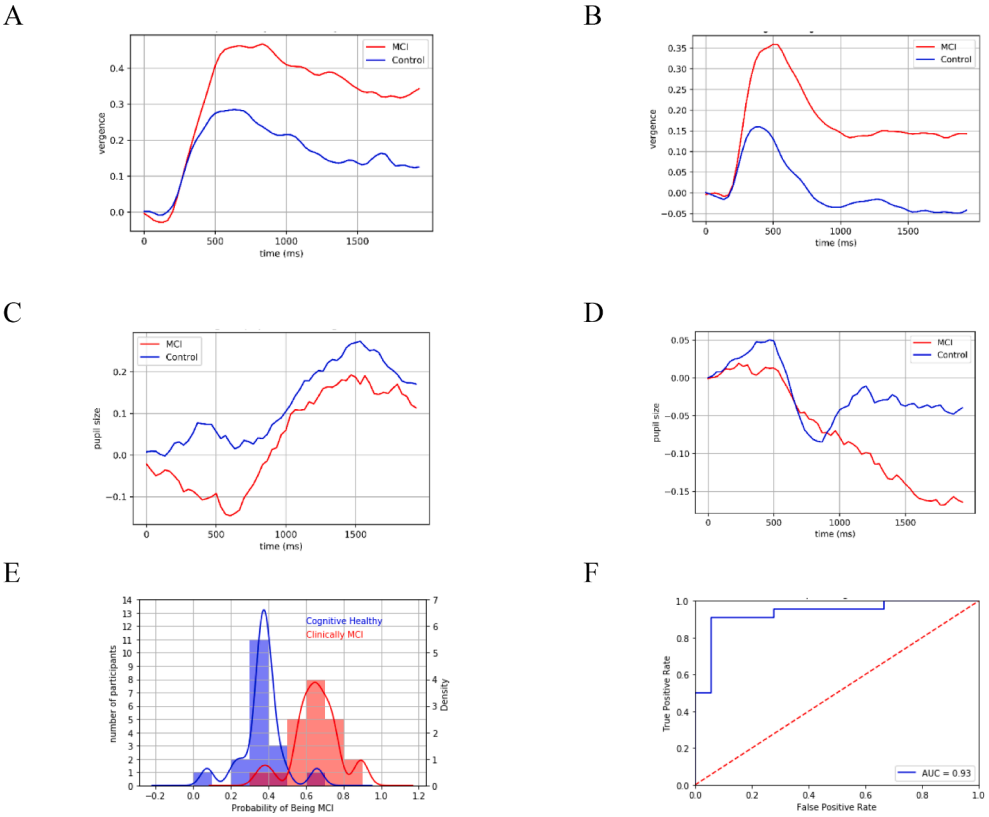

Fig. 1. Normalized average vergence (A,B) and pupil responses (C,D) of MCI patients (red traces) and control participants (blue traces), and probability scores (E) and ROC (F). A,B: Vergence responses to targets (A) and to distractors (B). C,D: Pupil responses to targets (C) and to distractors (D). E: Histograms and probability densities (using Kernel Density Estimation) derived from the result of the final model for MCI patients. D: ROC curve for the final model.

initial peak response, is different between MCI patients and controls ($F_{(1,2128)} = 16.67$, $p<0.001$). The fifth feature is the mean delay pupil response, and is higher in MCI patients than in control participants ($F_{(1,2128)} = 31.45$, $p<0.001$). Thus, all of the aggregated features for building the classification model were significant.

3.4. Probability scores of participants

Using the weighted average of the probability scores (appendix: 2.2; Figs A3, A4), a probability of being MCI for each participant was obtained (Fig. 1E). There was significant correlation (Pearson, r) between probability scores and MoCA scores ($r = - 0.53$, $p = 0.01$), and GDS ($r = 0.70$, $p < 0.001$). There was no significant correlation with MMSE scores ($r = 0.1$, $p = 0.75$).

3.5. Classification model

The classifier model detected MCI patients with a 92.5% accuracy (Table A2). The sensitivity (true positive rate) of the model is 0.91 and the specificity (true negative rate) is 0.94, and an AUC of 0.93 (Fig. 1F).

3.6. Verification of the model

MCI patients that progressed to possible AD (32% of the MCI patients; $N = 7$) had high probability scores compared to the mean, while MCI patients that reversed (23% of the MCI patients; $N = 5$) had low scores (appendix: Fig. A5). There was a significant correlation (Spearman rho $= -0.71$;$p = 0.0029$) meaning that people with high probability scores were more likely to progress to AD whereas people with low probability scores tend to reverse to being cognitive healthy. The two MCI patients that were incorrectly predicated as cognitive healthy by our model (Table 1, appendix: Fig. A6) did not progress to possible AD. Thus, all MCI patients that progressed to possible AD were classified as MCI. The AUC performance of our model for MCI patients that progressed to possible AD vs. MCI patients who did not was 0.85. The AUC performance for reversed MCI vs. stable/progressed MCI was 0.46. Thus, our model could predict progressed MCI better than reversed MCI.

We applied the final model trained with the data from control and MCI participants to classify the possible AD patients (appendix: Fig. A7). Results show that our model predicted 8 out of 9 CE patients correctly, i.e., labelled as patient. The final model was further validated with 12 new participants with cognitive impairment, confirmed by their MoCA scores (mean±std: 16.6 ± 2.3), from a private day care center. Of these participants, 10 (83.3%) were correctly classified as MCI patient by the model.

4. Discussion

We evaluated vergence eye movements and pupil responses as a potential marker for the detection of MCI. Based on these eye metrics, a classifier model was able to separate MCI patients from cognitive healthy controls with high accuracy. The classification outcomes cannot be explained by medication as MCI patients were not treated with medication that could affect vergence or pupil size.

Evidence shows that the locus coeruleus is the origin of MCI and AD or at least is one of the first regions to show signs of neurodegeneration [11,12]. For an early detection of MCI, it is therefore important to monitor the functioning of the locus coeruleus. Pupil diameter can be employed as a proxy measure of locus coeruleus activity [13,14]. Activity of the locus coeruleus can influence pupil responses by its noradrenergic connections to the Edinger Westphal nucleus [14]. Also, a pupil response may be triggered by vergence eye movement [3], which is hypothesized to have a role in phase resetting of functional neural connections [15] for cognitive processing [4–7]. Our current and previous [10] findings indicated that MCI patients show atypical vergence and pupil responses during a short cognitive test and thus may be an effect of the degeneration of the locus coeruleus.

We observed that within approximately 12–18 months after the initial diagnosis (the period in which we analysed the data and wrote the manuscript), MCI patients with the highest probability scores progressed to possible AD while MCI patients with the lowest scores recovered. This observation may indicate that vergence and pupil responses have a predictive power of detecting AD at an early stage. This idea is supported by the finding of accurate detection of possible AD patients by the MCI model.

Early intervention of MCI by pharmaceutical treatment, cognitive therapy, or adoption of healthy life style may help to prevent or delay the onset of AD [16–18]. Biomarker assessment of MCI is preferred for an early and objective diagnosis. However, available biomarker tools are expensive and invasive, and more accessible solutions are needed that can be applied in routine clinical practice. In line with previous reports [10,19] the assessment of vergence/pupil metrics could be a potential candidate to consider for further clinical research in developing an objective, non-invasive, low-cost marker tool for the early diagnosis of MCI and AD in a non-clinical setting.

4.1. Limitations and follow-up

We did not make a distinction between MCI subtypes. It was therefore not possible to know which MCI patients were at risk for progressing to AD. Nor did we include other types of dementia. Further and longitudinal studies are obviously needed to evaluate association of vergence and pupil responses with known MCI/AD biomarkers, and to demonstrate accurate classification of patients with non-dementias of comparable overall severity to address differential diagnosis.

5. Conclusions

The measurement of vergence and pupil responses can be a potential candidate to consider as a non-invasive and objective marker tool for MCI diagnosis and AD risk.

Declaration of Competing Interest

HS is co-founder of Braingaze, OL was an employee of Braingaze.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahr.2023.100121.

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