2023 45th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC) | 979-8-3503-2447-1/23/$31.00 ©2023 IEEE | DOI: 10.1109/EMBC40787.2023.10340128

Saccadic eye movement variables as biomarkers for cognitive decline in elderly individuals

Julius Opwonya, *Student Member, IEEE,* Boncho Ku, Kahye Kim, Kun Ho Lee, Joong Il Kim, and Jaeuk U. Kim, *Member, IEEE*

***Abstract*— Alzheimer's disease (AD) is the leading cause of Dementia, and mild cognitive impairment (MCI) is often considered a precursor to the development of AD dementia and other types of Dementia. Biomarkers such as amyloid beta are specific and sensitive in identifying AD and can identify individuals who have biological evidence of the disease but have no symptoms, but clinicians and researchers may not easily use them on a large scale. Ocular biomarkers, such as those obtained through eye tracking (ET) technology, have the potential as a diagnostic tool due to their accuracy, affordability, and ease of use. In this study, we show that eye movement (EM) metrics from an interleaved Pro/Anti-saccade (PS/AS) ET task can differentiate between cognitively normal (CN) and MCI subjects and that the presence of Aβ brain deposits, a biomarker of AD, significantly affects performance on these tasks. Individuals with Aβ deposits (Aβ+) performed worse than those without (Aβ-). Our findings suggest that eye-tracking measurements may be a valuable tool for detecting amyloid brain pathology and monitoring changes in cognitive function in CN and MCI individuals over time.**

***Clinical Relevance*— The PS/AS paradigm, which measures saccadic eye movements, can accurately detect subtle cognitive impairments and changes in the brain associated with Alzheimer's disease in CN and MCI individuals. This makes it a valuable tool for identifying individuals at risk for cognitive decline and tracking changes in cognitive function over time.**

I. Introduction

Alzheimer's disease (AD) is diagnosed by identifying specific neuropathological changes in the brain through biomarkers and postmortem examination [1]. These changes, including the presence of amyloid plaques and neurofibrillary tangles, are the standard for diagnosing AD and distinguishing it from other diseases that can cause dementia. The cognitive decline in AD dementia occurs continuously over a long period, and the progression of biomarker measures is also a continuous process that begins before symptoms appear.

Validated, widely used biomarkers exist that are proxies for AD neuropathologic changes: β-amyloid (Aβ) deposition, pathologic tau, and neurodegeneration. The biomarkers of β-amyloid (Aβ) plaques are cortical amyloid PET ligand binding or low cerebrospinal fluid (CSF) $A\beta_{42}$ [1]. The AD biomarkers are sensitive and specific for the neuropathological changes that define the disease and can identify individuals who have biological evidence of the disease but do not yet exhibit signs or symptoms. Notwithstanding their diagnostic potential, the broad and frequent use of these biomarkers is often impeded by their invasiveness, high cost, and limited accessibility. Additionally, further evidence is required to establish their performance and variations across different types of dementia.

There is an acknowledged need for biomarkers that can bridge this gap, capable of serving as early diagnostic markers for AD and, simultaneously, as parameters for monitoring the clinical progression and effects of therapy. One potential good candidate is ocular biomarkers since eye tracking (ET) technology is becoming popular due to the development of accurate, affordable, moveable, and easy-to-use eye trackers. Several studies suggest that neurodegenerative pathophysiology may be present earlier in vision-related brain structures than in other structures [2, 3]. Furthermore, a previous study found AD pathology in the occipital cortex of healthy adult subjects and patients with mild cognitive impairment (MCI) [4].

Whereas previous work has shown that prosaccade/antisaccade (PS/AS) paradigms of eye movement (EM) tasks could distinguish cognitively normal (CN) controls from patients with MCI using latency and error saccade parameters [5], no study has shown the effect Aβ brain deposition has on eye movements and whether these changes, if any, could be used to distinguish between subjects with and without Aβ deposits based on the EM metrics. Therefore, we sought to determine how performance on an eye-tracking task relates to biomarker profile status by examining eye movement metrics of cognitively unimpaired controls and cognitively impaired patients with MCI during interleaved PS/AS tasks.

As a step forward in improving the clinical utility of ET for preclinical and prodromal AD screening and monitoring, the present study had three primary aims. First, to investigate the impact of brain Aβ deposition, as measured by PET, on performance in an ET task. Secondly, the study seeks to identify the specific ET metrics affected by Aβ biomarker status, and thirdly, to explore the relationship between Aβ deposits and EM in both CN and MCI groups.

* This research was supported by a grant (KSN1823130) from the Korea Institute of Oriental Medicine funded by the Korean government.

J. Opwonya, B. Ku, K. Kim, J. Kim, and J.U. Kim are with Korea Institute of Oriental Medicine (KIOM), Daejeon, South Korea.

J. Opwonya* and J.U. Kim** are with University of Science and Technology (UST), Daejeon, South Korea (corresponding authors to provide email: *jopwonya@kiom.re.kr, **jaeukkim@kiom.re.kr) .

K. Lee is with Gwangju Alzheimer's Disease and Related Dementias (GARD) Cohort Research Center, Chosun University, Gwangju, South Korea.

II. METHODS

A. Participants

A total of 231 participants recruited at the Gwangju Alzheimer's Disease and Related Dementia (GARD) center (Gwangju City, South Korea). We examined all the participants through detailed clinical consultations, incorporating the Clinical Dementia Rating scale and the Seoul Neuropsychological Screening Battery-Second Edition (SNSB-II) [6], including the Korean version of the mini–mental state examination (MMSE), administered to all participants. The participants also underwent magnetic resonance imaging (MRI) scanning, and Aβ plaque burden was measured using PET.

Participants with less than three years of education, ongoing acute or chronic illnesses, mental health instability, or excessive alcohol consumption were excluded; as a result, 25 subjects diagnosed with AD dementia and 60 participants with visual impairments or who failed the preliminary exercise and calibration test were excluded. The remaining 146 participants were divided into a CN group with a CDR score of 0 and no signs of brain atrophy or other focal brain lesions on MRI scans and an MCI group with a CDR score of 0.5 and an SNSB-II z score of no less than -1.5 in at least one domain. Informed consent was obtained from all participants or their legal guardians, and the study was approved by the Chonnam National University Hospital Institutional Review Board (IRB no. CNUH-2019-279).

Table 1. Participants' demographic information, neuropsychological scores, and biomarker profiles

Characteristic	**CN**, N = 94[1]	**MCI**, N = 52[1]	**p-value**
Age	70.76 (5.27)	71.79 (6.92)	0.3[2]
Sex (Female)	51 (54%)	29 (56%)	0.9[3]
Education	13.8 (4.7)	14.9 (12.7)	0.5[2]
MMSE	27.65 (1.97)	26.08 (2.92)	**0.001[2]**
Amyloid PET (Negative)	65 (69%)	31 (60%)	0.2[3]

[1]The values represent the mean (SD) for continuous variables and n (%) for categorical variables. The p values for the continuous variables were obtained using the Wilcoxon rank sum test. For the categorical variables, the p values were derived from the Chi-squared test statistics. [2]Pearson's Chi-squared test; [3]Wilcoxon rank sum test. The bold fonts indicate a p value lower than 0.05.

B. Experimental design

In the study, participants were asked to perform prosaccade (PS) and antisaccade (AS) tasks in response to visual stimuli presented on a Tobii Pro Spectrum screen (EIZO FlexScan EV2451) with a refresh rate of 300 Hz and a resolution of 1920 × 1080 pixels (See Figure.1). The screen was positioned approximately 65 cm away from the participants. Each task began with the presentation of a fixation target (1.5° in diameter) on a black background in the center of the screen, which the participants were instructed to fixate on for 500 ms. This was followed by the presentation of a cue (2° in diameter) in either green (for the PS task) or red (for the AS task) for 800 ms, after which the stimuli disappeared for a 200 ms gap period. Finally, a target (1° in diameter) was presented 10° from the center of the screen for 1500ms. Participants were instructed to make a prosaccade or antisaccade according to the cue color in response to the target appearance. The experimental procedure consisted of 30 blocks of PS/AS tasks, in which trials were randomized and counterbalanced. Each block included two PS trials and one AS trial, totaling 60 PS trials and 30 AS trials. The trial and target location (left/right) were interleaved pseudo-randomly with equal frequency within each block. Eye movements of both eyes were recorded using the Tobii Pro Spectrum, and participants were seated with their heads on a chin rest to maintain an appropriate viewing angle.

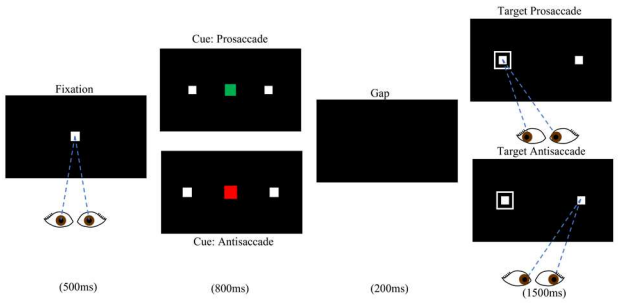

Figure 1 Schematic representation of interleaved prosaccade/antisaccade task. Each trial began with the appearance of a fixation point (FP) in the center of the screen for 500ms. The color of the cue indicated the trial condition. Following a 200ms gap, a stimulus appeared 10° to the left or right of the FP position and remained on the screen for an additional 1500ms.

C. Data acquisition and preprocessing

The preprocessing of eye movement data and all subsequent analysis steps were implemented in MATLAB (by MathWorks) using a customized algorithm to extract several parameters of interest, including fixation duration, correct responses, anticipatory errors, omissions, self-corrected-inhibition errors, and uncorrected-inhibition errors. We developed an algorithm to classify correct and incorrect responses based on gaze variation and fixation duration. The algorithm defined invalid responses as those with less than 80% valid trials. It included trials with a minimum fixation duration of at least 100 milliseconds within less than or equal to a 1° radius centered on the fixation target before the onset of the saccade targets. We defined correct responses as those with a saccade onset time between 80 and 500 milliseconds and a maximum gaze variation of within less than or equal to a 1° radius centered on the target. We classified responses as anticipation errors if the saccade onset time was less than 80 milliseconds and omission errors if no saccade movement occurred within 500 milliseconds. We also identified corrected-inhibition errors as instances where the gaze shifted within 400 milliseconds from the incorrect direction to the correct direction. The gaze variation was within less than or equal to a 1° radius

centered on the target. Finally, we defined uncorrected-inhibition errors as instances where the gaze shifted within 400 milliseconds to the incorrect direction, and no correction was made. Additional details have been published elsewhere[7].

D. Statistical Analyses

Statistical analyses were performed in R V.4.2.2 (R Foundation for Statistical Computing, Vienna, Austria (https://www.R-project.org/). Figures were generated using the R package *ggplot2*. The Wilcoxon rank sum test was used for continuous variables to compare baseline demographics, and Pearson's Chi-squared test was used for categorical variables. A two-way analysis of the covariance model was used to compare eye tracking metrics across groups, with the main effect of diagnostic group and Aβ status being tested while accounting for MMSE as a covariate using the *rstatix* package. Post-hoc pairwise comparisons were conducted using the Bonferroni correction method for each eye movement metric and PET Aβ biomarker.

III. Results

A. Participant characteristics

Baseline demographics, cognitive scores, and amyloid beta (Aβ) positron emission tomography (PET) status are shown in Table 1. The CN group had 94 subjects (51 females), and their mean age was 70.76±5.27 years; the MCI group had 52 subjects (29 females), and their mean age was 71.79±6.92. There was no difference in age, sex, and years of education of the groups. The PET Aβ status did not show any differences between the groups. However, the MMSE scores showed a significant difference, as shown in Table 1.

B. Prosaccade

In the prosaccade task, we observed a significant main effect of group in the number of correct prosaccades ($F(1,141)=5.753$, $p=0.018$). There was also a significant main effect of PET Aβ status ($F(1,141)=7.538$, $p=0.007$). Post-hoc comparisons using the Bonferroni correction method revealed a significant difference in the number of correct saccades between the CN Aβ+ and Aβ- subgroups but not between the MCI participants with Aβ+ and Aβ-. See Figure 2 for a schematic representation of these results.

We observed significant main effects of group ($F(1,141)=4.159$, $p=0.043$) and PET Aβ status ($F(1,141)=7.986$, $p=0.005$) on the number of errors. Post-hoc comparisons revealed a significant difference in the errors between the CN Aβ+ and Aβ- subgroups but not between the MCI subgroups. In the analysis of self-monitoring variables, we did not find any significant difference between the two groups regarding inhibition errors that were corrected and uncorrected. However, those with Aβ+ in the MCI subgroup had significantly fewer uncorrected errors. In addition, there was no significant difference between the groups when we compared the anticipations and omissions. However, those

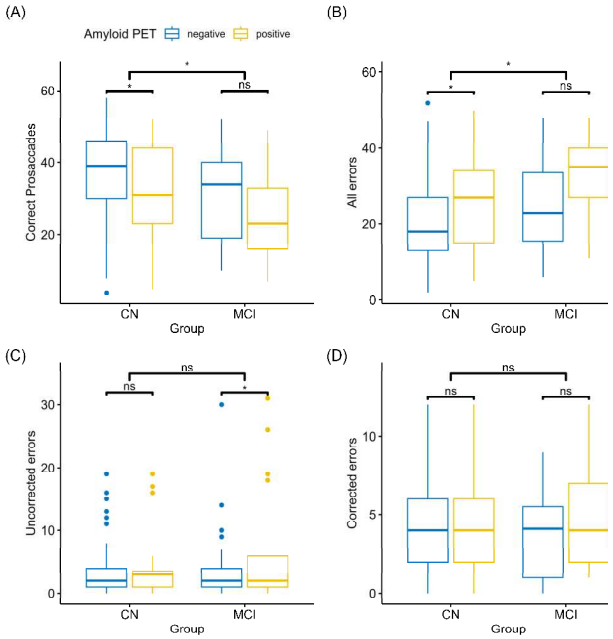

Figure 2 Prosaccade responses in CN controls and patients with MCI. (A) Number of correct PS (B) Number of all errors committed. (C) Number of uncorrected errors. (D) Number of corrected errors.

with Aβ+ in the CN subgroup had significantly higher omissions.

C. Antisaccade

We found a significant main effect of group in the number of correct antisaccades during the antisaccade task ($F(1,141)=6.299$, $p=0.013$), with no significant difference in PET Aβ status ($F(1,141)=1.335$, $p=0.250$). Post-hoc comparisons using the Bonferroni correction method showed no significant difference in the number of correct saccades between Aβ+ and Aβ- for both subgroups (see Figure 3). We also observed a significant main effect of group on the number of all errors made ($F(1,141)=6.562$, $p=0.011$), but no significant difference in PET Aβ status ($F(1,141)=1.670$, $p=0.198$). The post-hoc analysis did not reveal significant differences in the number of all error antisaccades between Aβ+ and Aβ- for both subgroups.

We found a significant main effect of group in the number of uncorrected antisaccades ($F(1,141)=6.885$, $p=0.010$) and a trend towards an effect of PET Aβ status in the number of uncorrected errors ($F(1,141)=3.657$, $p=0.057$). Post-hoc comparisons revealed a significant difference in the number of uncorrected saccades between the MCI Aβ+ and Aβ- subgroups but not in the CN subgroups. We also observed a significant main effect of group in the number of corrected errors ($F(1,141)=8.521$, $p=0.004$), but no significant difference in Aβ status ($F(1,141)=0.226$, $p=0.635$). In addition, there was no significant difference in the number of anticipations ($F(1,141)=0.715$, $p=0.399$) but a significant main effect of group on the number of omissions ($F(1,141)=4.998$, $p=0.027$). The post-hoc analysis using the Bonferroni correction method did not reveal significant

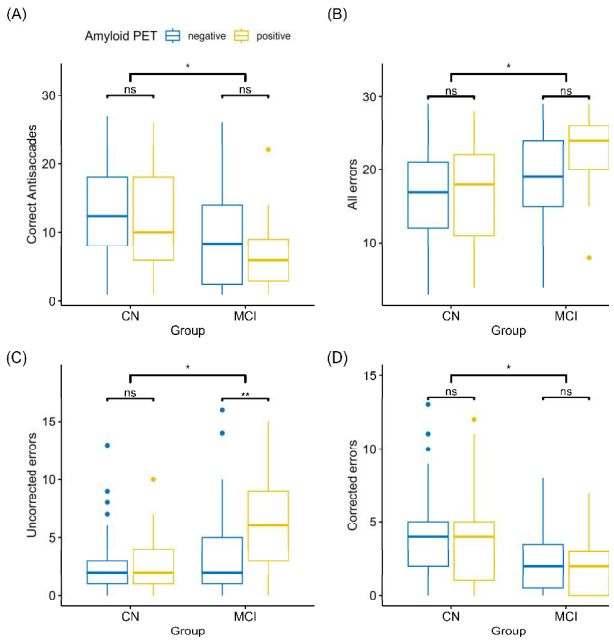

Figure 3 Antisaccade responses in CN controls and patients with MCI. (A) Number of correct PS (B) Number of all errors committed. (C) Number of uncorrected errors. (D) Number of corrected errors.

differences in the number of omissions between Aβ+ and Aβ- for both groups.

IV. Discussion

This study demonstrates that metrics from an interleaved PS/AS eye-tracking task can differentiate between cognitively unimpaired and impaired subjects. Furthermore, we show that Aβ brain deposits, a biomarker of Alzheimer's disease, significantly affect performance on these tasks. Individuals with Aβ deposits (Aβ+) performed worse than those without (Aβ-). These findings suggest that eye-tracking measurements may help detect amyloid brain pathology.

Our findings support previous research that indicates that metrics from the voluntary saccade task (AS) differentiate between groups more effectively than metrics from the visually guided saccade task (also known as prosaccades)[5].

We observed a main effect of amyloid status on prosaccade metrics, such as the number of correct responses and errors committed. To further investigate this relationship, we divided the CN and MCI groups into subgroups based on Aβ status and found significant differences in the CN subgroups but not in the MCI subgroups.

Our findings demonstrate that when analyzing uncorrected errors based on amyloid status in the PS and AS tasks, significant differences were observed in the MCI subgroups, with a trend towards an effect of amyloid status in the AS task.

The current study highlights the utility of eye tracking (ET) in distinguishing between cognitively normal (CN) and mild cognitive impairment (MCI) groups through the examination of visually guided saccades and voluntary saccade parameters, as well as identifying which ET metrics are most effective in differentiating subgroups of individuals with and without Alzheimer's disease (Aβ) pathology in both cognitively unimpaired and impaired groups.

Previous studies have shown that individuals with abnormal amyloid biomarkers and cognitively normal tend to experience a more rapid decline in brain atrophy, metabolism, and cognitive function compared to those without evidence of Aβ deposition[1]. Therefore, eye tracking may be a valuable and non-invasive method for detecting early signs of amyloid plaque buildup and cognitive decline and monitoring changes in cognitive function in cognitively normal individuals over time. However, as our study is cross-sectional, further longitudinal research is needed to confirm and refine the use of eye tracking as a proxy for amyloid burden and cognitive status and to identify the most effective eye-tracking metrics for this purpose. Additionally, further research is needed to understand the specific factors that contribute to variations in eye-tracking performance and how they relate to cognitive status and brain function.

V. Conclusion

In conclusion, we proposed that ET metrics may offer valuable insights into amyloid plaque burden and other AD pathology since neurodegenerative pathophysiology is present mainly in brain structures related to vision at an early stage. In this regard, incorporating ET into a larger diagnostic framework alongside other established biomarkers or tests could provide a more comprehensive understanding of the risk of progression for individuals with preclinical disease and subtle cognitive impairment and aid in differentiating the diverse forms of dementia.

Acknowledgment

This research was supported by a grant (KSN1823130) from the Korea Institute of Oriental Medicine funded by the Korean government.

References

[1] Jack Jr, C.R., et al., *NIA-AA research framework: toward a biological definition of Alzheimer's disease.* Alzheimer's \& Dementia, 2018. **14**(4): p. 535--562.

[2] Albers, M.W., et al., At the interface of sensory and motor dysfunctions and Alzheimer's disease. Alzheimers Dement, 2015. **11**(1): p. 70-98.

[3] Kusne, Y., et al., *Visual system manifestations of Alzheimer's disease.* Acta Ophthalmol, 2017. **95**(8): p. e668-e676.

[4] McKee, A.C., et al., *Visual association pathology in preclinical Alzheimer disease.* Journal of Neuropathology \& Experimental Neurology, 2006. **65**(6): p. 621--630.

[5] Opwonya, J., et al., *Saccadic Eye Movement in Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis.* Neuropsychol Rev, 2021. **32**(2): p. 193-227.

[6] Kang, Y., D.L. Na, and S. Hahn, *Seoul neuropsychological screening battery.* Incheon: Human brain research \& consulting co, 2003.

[7] Opwonya, J., et al., Inhibitory Control of Saccadic Eye Movements and Cognitive Impairment in Mild Cognitive Impairment. Front Aging Neurosci, 2022. **14**: p. 871432.