Received: 28 May 2024 | Revised: 21 August 2024 | Accepted: 9 September 2024

DOI: 10.1002/dad2.70019

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Task-evoked pupillary responses as potential biomarkers of mild cognitive impairment

Julius Opwonya[1,2] | **Kahye Kim**[1] | **Kun Ho Lee**[3,4,5] | **Joong Il Kim**[1,2] | **Jaeuk U. Kim**[1,2]

[1]Digital Health Research Division, Korea Institute of Oriental Medicine, Daejeon, South Korea

[2]Korean Convergence Medical Science, University of Science and Technology, Daejeon, South Korea

[3]Gwangju Alzheimer's Disease and Related Dementias (GARD) Cohort Research Center, Chosun University, Gwangju, South Korea

[4]Department of Biomedical Science, Chosun University, Gwangju, South Korea

[5]Dementia Research Group, Korea Brain Research Institute, Daegu, South Korea

Correspondence
Joong Il Kim and Jaeuk U. Kim, Digital Health Research Division, Korea Institute of Oriental Medicine, 1672 Yuseong-daero, Yuseong-gu, 34054 Daejeon, South Korea.
Email: jikim@kiom.re.kr and jaeukkim@kiom.re.kr

Funding information
The Korean Government, Grant/Award Numbers: KSN1824130, KSN2312022; Korea Institute of Oriental Medicine

Abstract

INTRODUCTION: Eye movement alterations are effective biomarkers for Alzheimer's disease (AD). This study examines task-evoked pupillary responses (TEPRs) as potential biomarkers of the mild cognitive impairment (MCI), the symptomatic stage preceding AD.

METHODS: The prospective cohort study included 213 MCI patients and 514 cognitively normal controls (CNs). Participants performed a prosaccade (PS) or antisaccade (AS) task while their eye movements were tracked using a Tobii Pro Spectrum system.

RESULTS: The CNs showed unique TEPRs linked to better performance, characterized by larger baselines, greater PS target-onset variability, and smaller AS target-onset variability. Conversely, for MCI patients, better performance was linked to larger AS target-onset sizes. Furthermore, MCI patients displayed reduced dilation during the cue and target-onset periods compared to CNs.

DISCUSSION: MCI patients showed altered pupillary response patterns associated with cognitive task performance, highlighting the potential of oculomotor changes as a biomarker for early cognitive decline.

KEYWORDS
locus coeruleus, mild cognitive impairment, oculomotor, pretectal olivary nucleus, pupil size, saccades, superior colliculus

Highlights

- MCI patients displayed markedly smaller pupil dilation than CNs in response to cue and target stimuli.
- For MCI patients, larger pupil size upon target appearance during antisaccades correlated with better performance.
- Faster and more consistent prosaccades were linked to better performance in both groups.
- For MCI patients, the association between longer AS latencies and better performance was more pronounced than in CNs.

- Combined analysis of TEPRs and saccade performances in a sizeable cohort strengthens the generalizability of our findings to the broader MCI population.

1 | BACKGROUND

Cognitive impairment, particularly in the form of mild cognitive impairment (MCI), is a significant concern in our aging society.[1] MCI represents a transitional phase between normal aging and dementia, marked by subtle cognitive deficits, making the identification of early indicators imperative as the global population ages.[2] Recognizing subtle cognitive changes in MCI is essential for early intervention and effective management.[3]

Within this context, delving into intricate cognitive processes through innovative methodologies is crucial for advancing our understanding of MCI. Eye-tracking (ET) technology has emerged as a precise and noninvasive tool, providing a unique window into the functioning of the human brain.[4–6] One particularly promising avenue of exploration lies in analyzing saccades and pupillary responses.[6–8]

Pupillary responses, once regarded as mere physiological reflexes, are valuable indicators of cognitive states such as attention, emotional states, and motor planning.[6] The pupil size measurement has increasingly found applications in clinical investigations.[9–12]

The task-evoked pupillary response (TEPR) is an involuntary pupil dilation reliably reflecting a spectrum of cognitive processes during tasks like memory retrieval, attention, and problem-solving.[4,13] The TEPR is a transient dilation lasting seconds, typically under 0.5 mm.[14] Consistent with this, studies have shown increased pupil size with increasing cognitive load, reaching a plateau at peak demand.[15,16]

Pupil size modulation involves a complex network integrating sensory, attentional, and cognitive influences. The pretectal olivary nucleus (PON), superior colliculus (SC), and locus coeruleus (LC) pathways play a key role, dynamically adjusting pupil responses to reflect the interplay between visual processing and broader cognitive functions.[6]

While TEPR shows promise as a marker for Alzheimer's disease (AD),[17] its utility in MCI remains unclear. This study investigates the potential of TEPR during interleaved prosaccade (PS) and antisaccade (AS) tasks as early markers of MCI-related cognitive decline. We further explore the cognitive factors influencing AS performance. AS tasks, known to be more challenging than PS tasks, have shown greater efficacy in differentiating MCI from controls.[7] This is likely due to the increased activation of oculomotor networks and recruitment of additional brain regions during AS trials compared to PS tasks.

Investigating cognitive factors influencing AS performance in MCI holds significant value. First, it enhances our understanding of the neural mechanisms underlying MCI. Second, the sensitivity of AS tasks to subtle impairments allows for early detection, particularly in individuals at risk of AD. Finally, it aids in differentiating normal age-related decline from MCI, a crucial step for accurate diagnosis and intervention.

2 | METHODS

2.1 | Participants

The study recruited 832 participants categorized as MCI patients and age-matched controls (CNs) from the Gwangju Alzheimer's Disease and Related Dementia Center (GARD). All underwent clinical evaluations, including neuropsychological testing and Clinical Dementia Rating (CDR) scale assessment. CNs had a CDR score of 0, while MCI patients had a CDR of 0.5 with cognitive decline in specific domains according to Albert et al.'s[18] criteria.

MCI diagnosis was based on the Seoul Neuropsychological Screening Battery–Second Edition (SNSB-II). Patients had a z score less than −1.5 in at least one cognitive domain. All participants also completed the Korean Mini-Mental State Examination (MMSE) within the SNSB-II battery.[19]

Prospective participants underwent magnetic resonance imaging (MRI) scans to assess for brain atrophy or focal lesions. Individuals with MRI-identified lacunes or white matter hyperintensities graded two or more on established scales[20,21] were excluded. Participants with <3 years of education, and those diagnosed with AD, ocular conditions (eg, cataracts, glaucoma), or color blindness (due to color-coded task cues) were excluded. Additionally, 55 individuals were removed due to inadequate data quality or calibration failures (33 CNs, 22 MCI). Of the initial 832 participants, 105 were excluded, resulting in a final sample of 727 (see Figure 1).

The CNs group comprised 514 subjects, of which 287 were females whereas the MCI group consisted of 213 subjects, with 108 females (see Table 1). We obtained written informed consent from all participants or their legal guardians after providing a detailed description of the study, which was approved by the Chonnam National University Hospital Institutional Review Board (IRB no CNUH-2019-279).

2.2 | ET recordings and the experimental paradigm

Saccadic eye movement data were collected using a Tobii Pro Spectrum system and processed with Tobii Pro Lab version 1.118. Visual stimuli were presented on a monitor approximately 65 cm from the participants. Furthermore, we used a desk with adjustable chin and forehead rests to maintain a suitable angle between each participant's gaze and the ET monitor.

The experiment employed an interleaved PS/AS task design. Each session comprised 30 blocks of 3 trials, two PS, and one AS. PS and AS conditions and left/right peripheral targets (±10°) were randomized within blocks. Participants fixated centrally and executed saccades toward (PS) or away from (AS) targets cued by green or red colors,

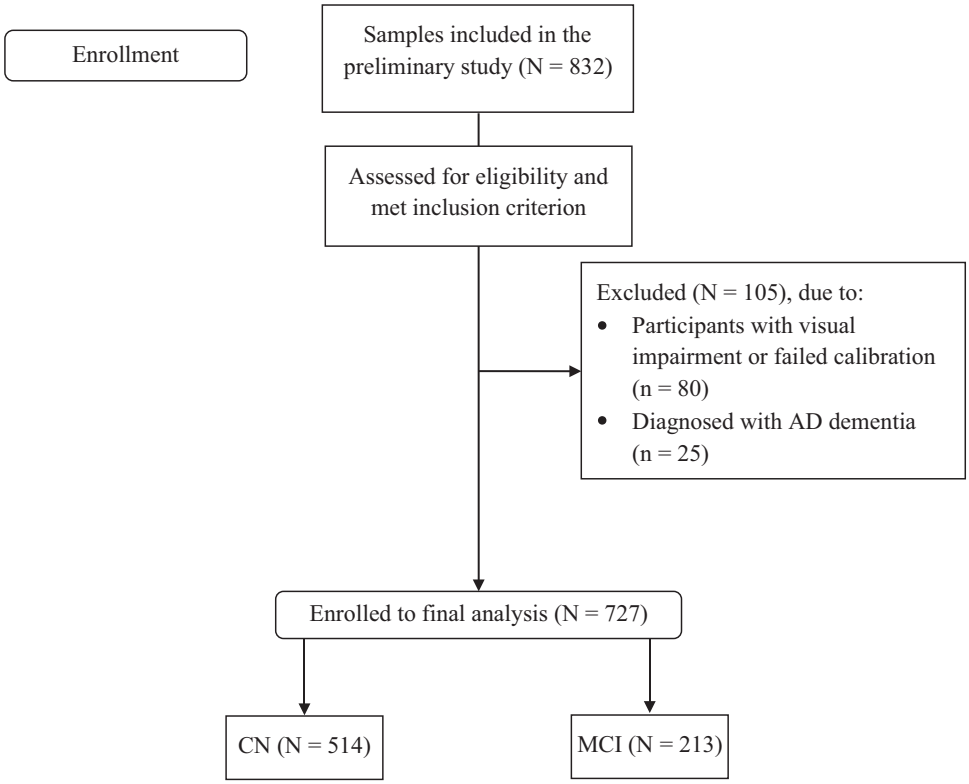

FIGURE 1 CONSORT flow chart illustrating enrollment and exclusion criteria for this study. AD, Alzheimer's disease; CN, cognitively normal (controls); CONSORT, Consolidated Standards of Reporting Trials; MCI, mild cognitive impairment.

TABLE 1 Cross-sectional demographic data for the CN and MCI cohorts.

Characteristic	CN, $N = 514$[a]	MCI, $N = 213$[a]	p-value[b]
Age	71.4 (6.2)	73.2 (6.8)	**<0.001**
Sex			0.2
Female	287 (56%)	108 (51%)	
Education	10.8 (4.3)	10.4 (4.6)	0.2
MMSE	27.69 (1.85)	25.92 (2.90)	**<0.001**
Attention	9.71 (2.17)	8.32 (1.88)	**<0.001**
Language	0.20 (0.29)	−0.10 (0.50)	**<0.001**
Visuospatial	0.53 (0.39)	0.29 (2.47)	0.2
Memory	0.33 (0.59)	−0.48 (0.67)	**<0.001**
Frontal	0.24 (0.57)	−0.34 (0.71)	**<0.001**

Abbreviations: CN, cognitively normal controls; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.
[a]The values represent the mean (standard deviation [SD]) for continuous variables and *n* (%) for categorical variables.
[b]The *p*-values for the continuous variables were obtained using the two-sample *t*-test. The *p*-values were derived from the chi-squared test statistics for the categorical variables. The bold fonts indicate a *p*-value lower than 0.05.

respectively (Figure 2). The timing of onset on the peripheral target was fixed, appearing immediately after the 200 ms gap period. The target remained visible for 1500 ms before the next trial began, with no inter-trial interval. Only trials where the gaze met the area of interest specifications were included in the final analysis. The standardized pipeline used to preprocess the gaze data has been described in detail elsewhere.[22]

2.3 | Data analysis

2.3.1 | Saccadic eye-movement data

Saccadic eye movement data were preprocessed using MATLAB. Eye movement responses were categorized using an area of interest (AOI)-based decision algorithm into correct saccades, anticipatory errors, omissions, and corrected/uncorrected inhibition errors.[22]

2.3.2 | Pupillary dynamics analysis

We used pupillometryR and GazeR packages[23,24] to preprocess pupil data. The preprocessing involved (1) blink artifact removal using a velocity-based algorithm with a 100 ms exclusion window, (2) consolidation via left and right pupil size averaging, (3) cubic interpolation smoothing, and (4) down-sampling from 300 to 30 Hz. Data cleaning included removing missing points and trials exceeding a 75% exclusion threshold.[23]

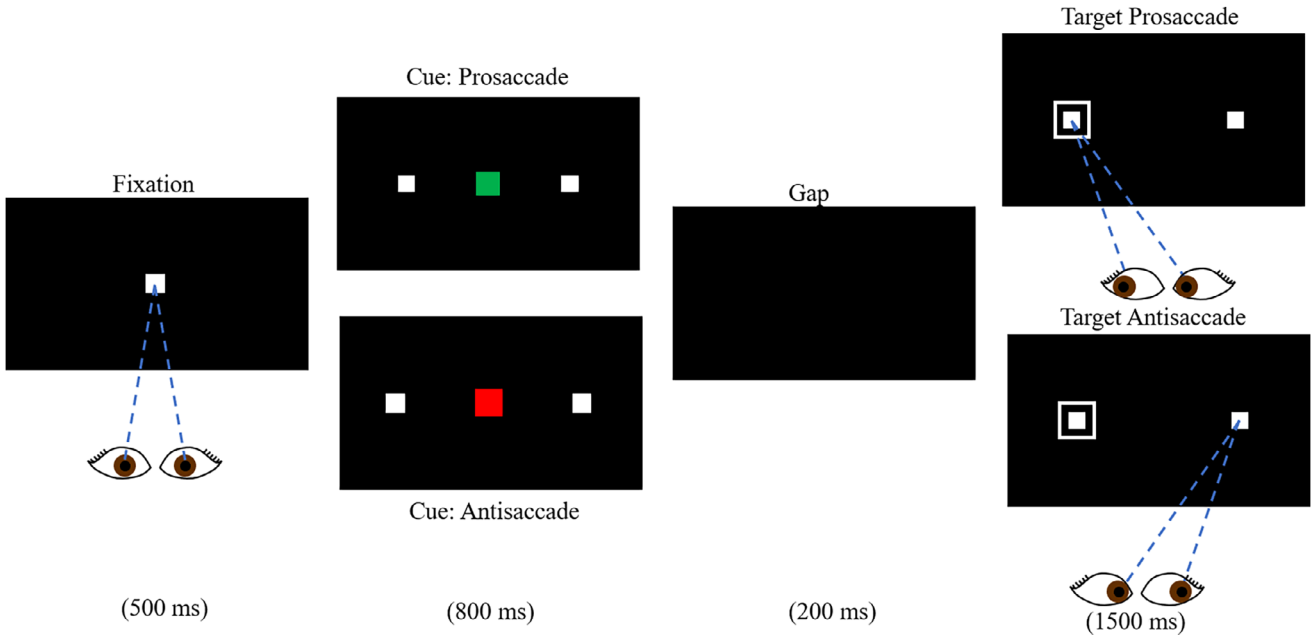

FIGURE 2 The interleaved PS/AS paradigm. The trial commenced with a 500 ms fixation point against a black background. Cue colors, green for PS and red for AS, indicated the trial condition. After a cue period of 800 ms, the stimuli disappeared for 200 ms before the target appeared, ± 10° from the center. The target remained on the screen for 1500 ms. AS, antisaccade; PS, prosaccade.

A robust baselining approach was applied to account for inter-participant variability in baseline pupil size. Pupil diameter data were then differentially subtracted from this baseline for each trial, enabling analysis of pupil dynamics within critical epochs—this subtractive correction aimed to isolate the contributions of constriction and dilation to observed pupil size differences.

Three key epochs were analyzed (Figure 3), labeled as follows: (1) FIXend (for "fixation end"), spanning 450 to 500 ms after fixation onset, reflecting early visual processing and gaze stabilization; (2) CUE epoch ("cue presentation"), extending from 700 to 1300 ms after fixation onset, capturing attentional shifts and cognitive processing triggered by the cue; and (3) TARon ("target onset"), focusing on 1500 to 1580 ms after fixation onset, reflecting responses to target presentation and potentially revealing insights into decision-making and motor preparation.[12,25,26]

2.3.3 | Statistical analysis

To investigate how task characteristics and cognitive status influence pupil size while accounting for age differences, we employed an age-adjusted linear mixed-effects model (LMM) using the lme4 package in R.[27]

We employed multiple linear regression analysis to assess the independent contributions of pupil size and saccade latency to task performance. Potential multicollinearity was evaluated using variance inflation factors (VIFs) with a threshold of <5.[28] We verified model assumptions by inspecting diagnostic plots for homoscedasticity (scale-location plot) and normality of residuals (Q-Q plot). If normality was violated, the outcome variable was log-transformed. Finally, influential cases were identified via residuals versus leverage plots and included in the analysis with and without them. Consistent results across models indicated no need for case removal.

Group differences in performance were examined using Student's *t*-test. Statistical significance was assumed as $p < 0.05$. Partial correlation coefficients and their associated *p*-values were computed for each oculomotor variable and cognitive score after controlling for age.[29]

3 | RESULTS

3.1 | AS performance variability

The multiple linear regression model included saccadic and pupillary metrics as predictors (Table 2). Due to our ET task's interleaved and counterbalanced nature, PS variables were incorporated to predict AS performance.

3.1.1 | Cognitively normal controls

The regression model significantly predicted task accuracy ($F(11, 412) = 12.07$, $p < .0001$), explaining 24.4% of the variance ($R^2 = .244$). This effect size remained substantial after adjusting for model complexity (adjusted $R^2 = .224$).

Our analysis revealed that a larger baseline pupil size during AS tasks was associated with better performance ($\beta = 0.093$, $p = 0.036$). Interestingly, task-induced cue dilation did not significantly predict accuracy in either PS or AS tasks. However, the variability in pupil size following target presentation emerged as a key factor. Higher

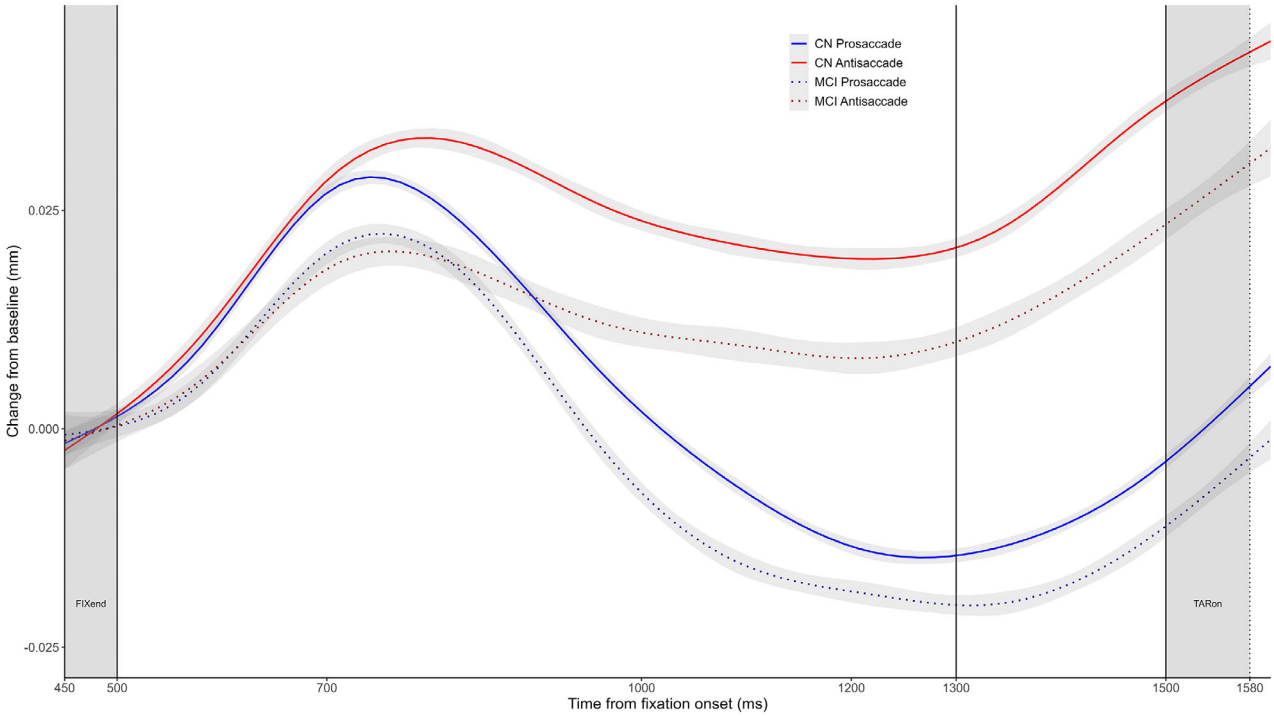

FIGURE 3 Pupillary measurements were employed to assess constriction and dilation responses. Three specific epochs were designated for pupil analyses: FIXend, 450 to 500 ms after fixation onset; CUE, 700 to 1300 ms after fixation onset; TARon, 1500 to 1580 ms after the initiation of the target stimulus. The solid/dashed-dotted lines depict the mean values of data points within each group, while the shadows represent the SE values associated with each group's data points. CN, cognitively normal (controls); CUE, cue presentation; FIXend, fixation end; MCI, mild cognitive impairment; SE, standard error; TARon, target onset.

variability in PS tasks and lower variability in AS tasks were linked to better accuracy ($\beta = 0.172$, $p < 0.0001$; $\beta = -0.100$, $p = 0.040$).

Saccadic latencies were critical in task accuracy, revealing distinct patterns for PS and AS. Shorter and less variable latencies in PS tasks were associated with better performance ($\beta = -0.259$, $p < 0.0001$; $\beta = -0.211$, $p < 0.0001$). Conversely, for AS tasks, longer latencies were linked to improved accuracy ($\beta = 0.158$, $p = 0.005$).

3.1.2 | Mild cognitive impairment

The model significantly predicted task accuracy ($F(11, 162) = 14.88$, $p < .001$), explaining 50.3% of the variance ($R^2 = .503$). This substantial effect size remained robust after adjusting for model complexity (adjusted $R^2 = .469$).

While baseline pupil size and average peak dilation during PS and AS tasks did not significantly predict accuracy, increasing pupil size following target presentation in AS tasks emerged as a significant predictor ($\beta = 0.179$, $p = 0.027$).

Saccadic latencies were critical in task accuracy, revealing distinct patterns for PS and AS. Shorter and less variable PS latencies were associated with better performance ($\beta = -0.281$, $p < 0.0001$; $\beta = -0.412$, $p < 0.0001$). Conversely, for the more demanding AS tasks, longer latencies and higher variability in latencies were both linked to improved accuracy ($\beta = 0.331$, $p < 0.0001$; $\beta = 0.129$, $p = 0.029$).

3.2 | Task-evoked pupil changes

Pupil size was examined within CNs and MCI groups during PS and AS tasks. CNs served as the group reference, with the PS task as the reference task. Besides the baseline pupil sizes, all TEPRs are measured as change from the baseline (Figure 4).

3.2.1 | Baseline pupil diameter

Baseline pupil size did not differ significantly between groups (mean difference [MD]: 0.026 mm, $p = 0.520$). Interestingly, the AS task elicited smaller baseline pupil sizes than the PS task (MD: −0.005 mm, $p = 0.024$). This effect was confirmed by estimated marginal means, although direct comparisons between tasks within each group revealed no significant differences (Figure 4A).

3.2.2 | Peak cue dilation size

Patients with MCI exhibited smaller maximum dilation than controls (MD: −0.0090, $p = 0.019$). In contrast, the type of cognitive task did not significantly affect pupil dilation (MD: 0.0016, $p = 0.442$).

We examined pupil dilation across tasks within each group. While no significant differences emerged between PS and AS tasks for CNs

TABLE 2 Pupillary and saccadic predictors of antisaccade performance in CN and MCI groups.

Cognitively normal controls					
Predictors	**Beta (β)**	**SE**	**Cohens f^2**	**95% CI**	***p***
Pupil					
AS baseline	0.093	0.044	0.011	0.006, 0.180	**0.036**
PS cue dilation	0.086	0.066	0.004	−0.043, 0.216	0.189
AS cue dilation	0.041	0.070	0.001	−0.096, 0.178	0.558
PS target	0.032	0.065	0.001	−0.096, 0.159	0.625
PS target SD	0.172	0.048	0.031	0.078, 0.267	**<0.001**
AS target	0.082	0.067	0.004	−0.050, 0.215	0.224
AS target SD	−0.100	0.049	0.010	−0.196, −0.004	**0.040**
Saccade					
PS latency	−0.259	0.064	0.040	−0.384, −0.133	**<0.001**
PS latency SD	−0.211	0.056	0.034	−0.322, −0.100	**<0.001**
AS latency	0.158	0.056	0.020	0.049, 0.268	**0.005**
AS latency SD	0.042	0.048	0.002	−0.052, 0.137	0.382
Mild cognitive impairment					
Predictors	**Beta (β)**	**SE**	**Cohens f^2**	**95% CI**	***p***
Pupil					
AS baseline	0.007	0.060	0.000	−0.111, 0.125	0.905
PS cue dilation	−0.034	0.079	0.001	−0.190, 0.123	0.673
AS cue dilation	0.071	0.077	0.005	−0.082, 0.224	0.363
PS target	−0.137	0.078	0.019	−0.291, 0.018	0.082
PS target SD	0.015	0.058	0.000	−0.099, 0.130	0.794
AS target	0.179	0.080	0.031	0.021, 0.338	**0.027**
AS target SD	−0.089	0.061	0.013	−0.209, 0.030	0.143
Saccade					
PS latency	−0.281	0.080	0.076	−0.439, −0.123	**0.001**
PS latency SD	−0.412	0.078	0.173	−0.566, −0.258	**<0.001**
AS latency	0.331	0.064	0.165	0.204, 0.457	**<0.001**
AS latency SD	0.129	0.058	0.030	0.014, 0.244	**0.029**

Note: The beta (β) estimates represent the standardized coefficients of the regression. Cohens f^2 represents the effect sizes. VIFs assessed multicollinearity among predictors. We eliminated predictors with VIFs over 5. Consequently, some predictors were not included in the final model.
Abbreviations: AS, antisaccade; CI, confidence interval; SD, standard deviation; SE, standard error PS, prosaccade; VIF, variance inflation factors.
The bold fonts indicate a *p*-value lower than 0.05.

or MCI participants, a group difference was observed during the AS task. Here, CNs displayed larger peak dilation than MCI patients (MD: 0.0173, $p < 0.001$) (Figure 4B).

3.2.3 | Maximum constriction magnitude

While cognitive status did not exert a significant effect (MD: −0.0032, $p = 0.531$), the task type had a substantial impact. Pupils were significantly less constricted during the AS task than the PS task (MD: 0.0270, $p < 0.001$).

Estimated marginal means analysis revealed no significant difference in pupil constriction magnitude between groups during PS tasks (Figure 4C). However, within each group, significant task-related effects emerged. CNs and MCI participants exhibited smaller constriction magnitudes during PS tasks than AS tasks (CNs: MD = −0.02696, $p < 0.0001$; MCI: MD = −0.01699, $p = 0.0004$). Additionally, CNs displayed smaller constriction magnitudes than MCI participants during AS tasks (MD = 0.01314, $p = 0.0476$).

3.2.4 | TARon pupil size

We found that cognitive status alone did not significantly alter pupil size (MD: −0.0011, $p = 0.832$). However, the type of task played a crucial role, with the AS task leading to a significantly larger increase in

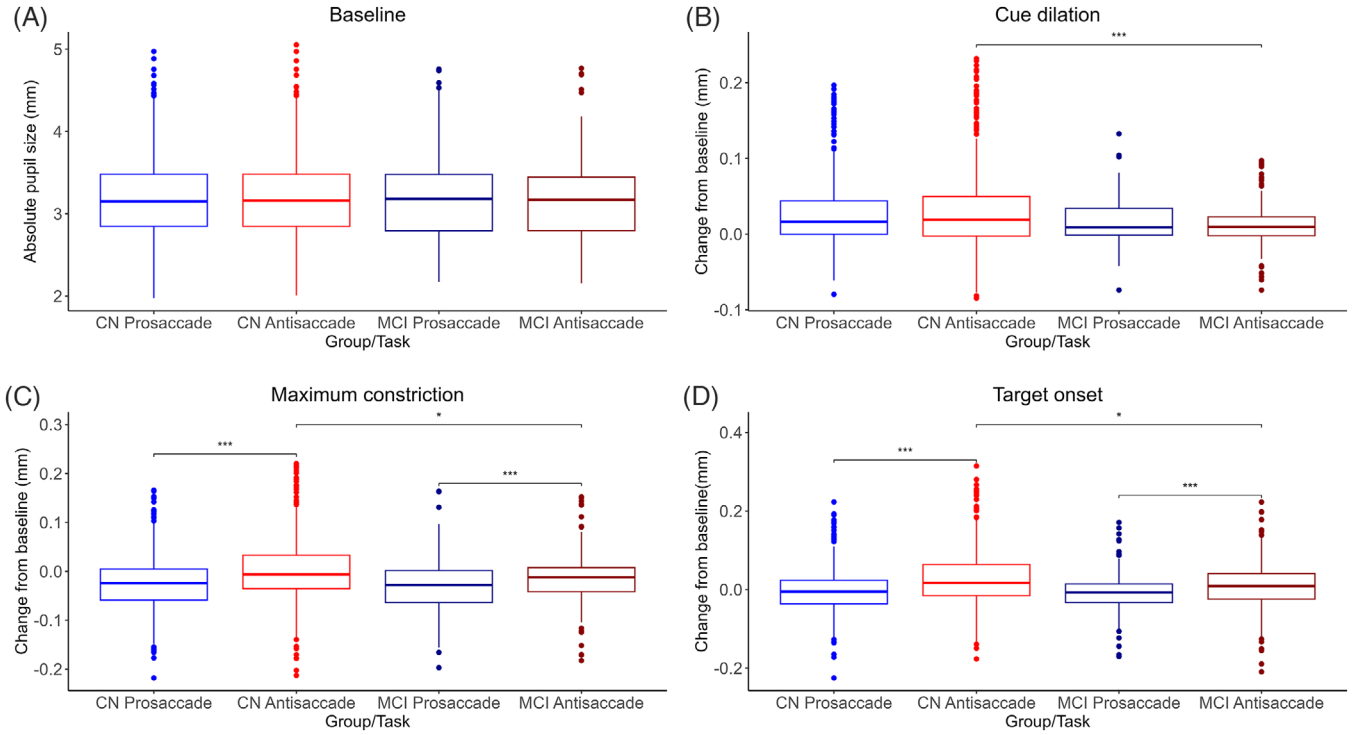

FIGURE 4 Pupil size during the task events. (A) Absolute pupil diameter during the fixation epoch (450 to 500 ms) after fixation onset. (B) Peak cue dilation. (C) Maximum constriction size. (D) Target onset pupil size between PS and AS for CN controls and individuals with MCI. AS, antisaccade; CN, cognitively normal; MCI, mild cognitive impairment; PS, prosaccade. $^{*}p < 0.05$, $^{**}p < 0.001$, $^{***}p < 0.0001$.

pupil size than the PS task (MD: 0.0294, $p < 0.001$). Additionally, we found a significant interaction between cognitive status and task type on pupil size. Specifically, the AS task resulted in a greater increase in pupil size among CNs than MCI (MD: −0.0154, $p = 0.004$).

Pairwise comparisons following TARon revealed no significant difference in pupil size between CNs and MCI participants during PS tasks (Figure 4D). However, pupil size was significantly smaller within each group during PS tasks than AS tasks. CNs displayed a more pronounced decrease (MD: −0.0292, $p < 0.001$) than MCI participants (MD: −0.0139, $p = 0.010$). Additionally, CNs had smaller pupil sizes overall during AS tasks than MCI participants (MD: 0.0165, $p = 0.011$).

3.3 | Partial correlation analysis

We observed significant correlations between oculomotor variables and cognitive scores in CNs and MCI groups. However, after adjusting for age, these associations substantially weakened in the MCI group (Figure 5).

4 | DISCUSSION

Current methods for detecting MCI often lack sensitivity to subtle cognitive decline. This study investigates the interplay between saccadic eye movements and pupillary responses during a cognitive task in MCI patients and CNs. We aim to identify how these oculomotor dynamics relate to the cognitive factors influencing AS performance. Building on prior research establishing TEPR as a marker of cognitive load and processing, we extend this by examining TEPR in conjunction with saccadic performance. By analyzing these combined responses, we seek to identify unique alterations in ocular patterns associated with MCI.

To examine the relationship between ocular measures and AS task accuracy in both groups, we analyzed pupil size during FIXend, CUE, and TARon epochs, along with saccadic latency. These epochs were selected to capture potential pupillary correlates of cognitive processes affected in MCI.

Our findings reveal differences in pupil variable influences on task performance between the CNs and MCI groups. CNs participants demonstrated that pupil metrics during fixation and postcue epochs predict task performance, suggesting a robust oculomotor system underpinned by efficient visual processing. High-level visual processing is deeply intertwined with cognitive processes, where memories, expectations, and goals shape our conscious visual experience. This integration allows us to see the world and interpret and act upon it in a contextually appropriate manner.[30] Conversely, MCI patients exhibited predictive pupil variables solely in later task stages. This observed shift in reliance from early to late task stages in MCI patients may reflect underlying deficits in visual processing. These results corroborate previous research indicating that visual processing, attention, and processing speed collectively influence AS task performance.[26,31]

Larger baseline pupil size during AS tasks correlated with improved accuracy in control participants. Additionally, higher pupil size variability following PS targets and lower variability following AS targets were

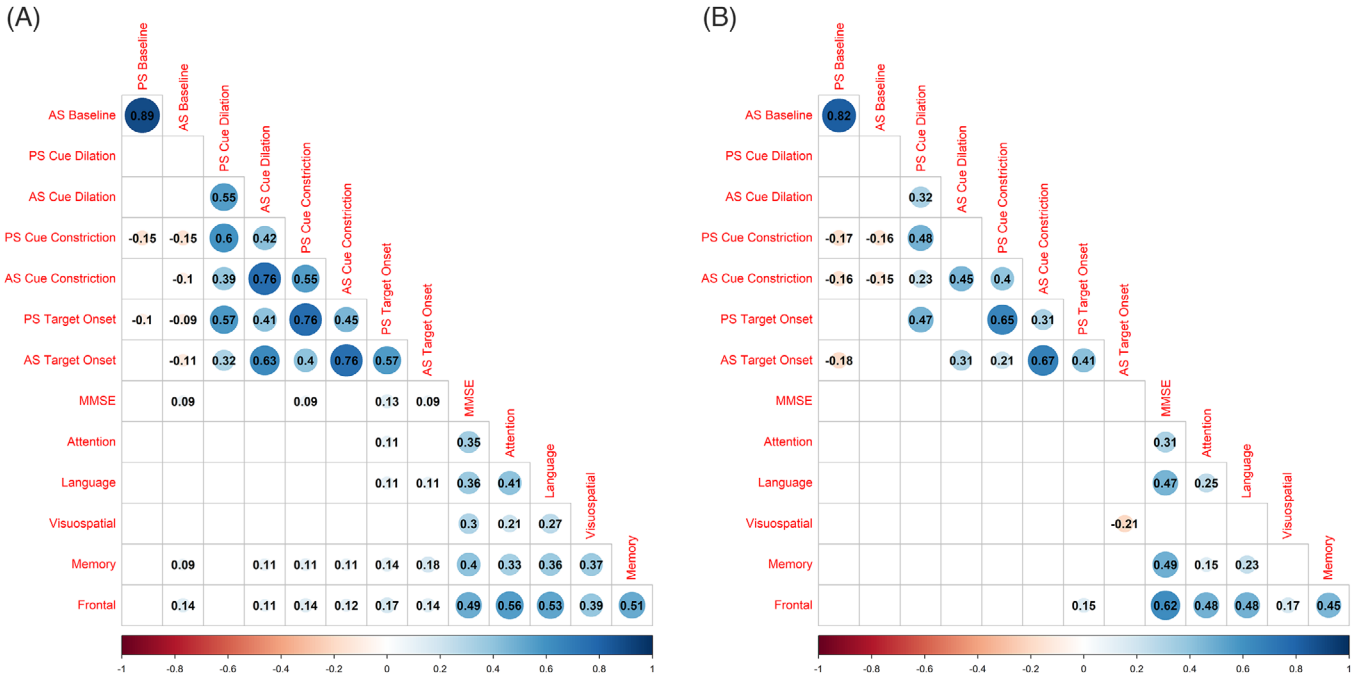

FIGURE 5 Significant partial correlations of oculomotor variables with cognitive scores for (A) cognitively normal and (B) mild cognitive impairment groups. AS, antisaccade; MMSE, Mini-Mental State Examination; PS, prosaccade.

linked to better performance. These findings suggest that increased baseline pupil size may reflect heightened arousal or attentional readiness, benefiting inhibitory control. In contrast, for the MCI group, improved accuracy was associated solely with larger pupil size at target presentation during AS tasks.

Saccadic latencies and their variability also played a role in both groups. Shorter latencies, lower latency variability in PS tasks, and longer latencies in AS tasks were linked to higher accuracy for both groups.

Our analysis of TEPR revealed a key difference in the CUE epoch. This peak pupil size, termed the cue peak size, reflects cognitive load/effort and is influenced by attention, working memory, and other cognitive processes.[32–34] Individuals with MCI displayed a smaller cue peak size than controls, suggesting altered information processing and resource allocation during the task. This aligns with known executive function deficits in MCI, particularly those affecting preparation for upcoming demands. The reduced cue peak size in MCI might reflect decreased attentional engagement with the cue due to difficulties inhibiting prepotent saccades and generating goal-directed saccades, both crucial for AS tasks.[22] These results implicate potential dysfunction in descending neural circuits from the cerebral cortex and the SC, critical in mediating attention shifts and eye movements. Abnormalities in these circuits, known to influence pupil size, could contribute to the observed differences in pupillary responses during the CUE epoch in MCI patients.

TEPR patterns during target presentation revealed a significant interaction between cognitive status and task type. Unlike controls, MCI participants struggled to adjust to the increased cognitive demands of AS tasks, suggesting impaired compensatory processes.[35] This pattern aligns with Granholm et al.'s findings of pupil dilation peaking near capacity and declining thereafter in a digit span task.[16] Such observations are consistent across various cognitive tasks, particularly those requiring attentional resources and language processing.[32–34]

TEPR analysis revealed distinct patterns of pupil size response between CNs and MCI participants, particularly during the more demanding AS task. During the AS CUE epoch, CNs displayed a larger pupil peak and less constriction than MCI. This suggests CNs engaged in more active cognitive processing in response to the increased demands of the AS task. Furthermore, larger pupil sizes in CNs during the AS TARon epoch potentially reflect enhanced saccade preparation and superior cognitive control mechanisms. These findings align with previous research showing reduced activation in brain regions crucial for AS tasks, such as the frontal eye field (FEF) in MCI individuals compared to CNs.[36]

In contrast, the PS task, known for its lower cognitive demands, did not reveal significant differences in pupil sizes between CNs and MCI subgroups. This observation aligns with the expectation that simpler tasks may not sufficiently reveal differences in pupillary responses between the groups, attributable to the minimal cognitive load imposed by the PS task.[34,37] For CNs and MCI participants, the AS task elicited smaller pupillary constrictions (CUE) and larger dilations (TARon) than the PS task. These findings highlight pupil size modulation by cognitive variables, with differences becoming particularly pronounced following task cues (CUE and TARon). These epochs mark critical moments where pupil size is linked to cognitive processing and attentional demands. The observed pupillary responses underscore the role of pupil size as a dynamic marker of cognitive load and attentional engagement.

The observed attenuation of significant correlations between oculomotor variables and cognitive scores after adjusting for age indicates that age is a critical confounder in the relationship between oculomotor dynamics and cognitive performance in MCI patients. The reduced significance of these correlations in the MCI group reveals the intricate interplay between aging and cognitive impairment, suggesting that age may obscure or interact with the oculomotor alterations linked to cognitive deficits. Consequently, it is imperative to account for age-related factors when interpreting oculomotor data in studies of cognitive decline. To disentangle the specific contributions of aging and cognitive impairment on oculomotor performance, future research should focus on isolating these effects in MCI and related populations.

Our findings highlight the complex interplay between TEPR, saccade measures, and cognitive functions mediated by brain regions crucial for AS task execution. This highlights the multifaceted nature of AS task performance and the impact of cognitive status on accuracy. ET using pupillary and saccadic measures may be valuable tools to detect dysfunction in neural substrates underlying AS performance in MCI, potentially reflecting abnormalities in these brain regions.

Furthermore, the AS task's sensitivity to cognitive variables like working memory, attention, and inhibitory control suggests its potential as a marker for neuropsychiatric disorders with similar impairments, such as schizophrenia, bipolar disorder, attention-deficit/hyperactivity disorder, autism spectrum disorder, and Parkinson's disease. Consequently, the AS task emerges as a sensitive and robust indicator of cognitive and neural dysfunction across a spectrum of disorders, underscoring its potential utility in clinical settings.

While our investigation offers valuable insights into the relationship between cognitive processes, ocular responses, and saccadic tasks, it is essential to acknowledge certain limitations. A primary limitation of the present study is the use of uncontrolled daylighting conditions. This introduces confounding luminance effects that can obscure cognitive influences on pupil size. Variation in room luminance due to incomplete blockage of outdoor solar luminance potentially affected participant comfort and task performance. While efforts were made to maintain consistent conditions, this remains a notable limitation. Future studies should consider employing head-mounted displays or virtual reality headsets with ET capabilities. These technologies offer controlled visual environments, mitigating the impact of external luminance variability. While ET offers a cost-effective and noninvasive method for studying cognitive function, pupil size is a composite measure influenced by cognitive load, arousal, and luminance. This limits its direct interpretation as a neural marker.

While saccadic deficits in MCI during AS tasks are well-documented, disentangling preparatory from execution process contributions remains unclear. Previous functional MRI research[38] revealed increased preparatory activation in frontal and parietal regions for AS compared to PS tasks. Discerning whether oculomotor dysfunction in MCI reflects preparatory or execution deficits requires further investigation considering these activation patterns.

In summary, while saccadic paradigms, particularly PS and AS tasks, have been extensively studied in relation to cognition and MCI, the novel contribution of this study lies in the exploration of pupillary responses during these tasks in a large cohort. The findings revealed that AS trials activate the oculomotor network more and are associated with greater cognitive demand than PS tasks. Furthermore, MCI patients displayed distinct pupil dilation patterns, suggesting potential deficits in attention allocation or processing capacity. Oculomotor dynamics, including pupil dilation, variability, and saccadic latencies, emerged as significant predictors of task accuracy in both CNs and MCI groups.

AUTHOR CONTRIBUTIONS

Julius Opwonya, Joong Il Kim, and Jaeuk U. Kim conceived the manuscript. Julius Opwonya, Kahye Kim, and Joong Il Kim carried out data verification. Julius Opwonya, and Jaeuk U. Kim performed the statistical analyses and generated the figures. Julius Opwonya, Joong Il Kim, and Jaeuk U. Kim drafted the manuscript. Kahye Kim, Joong Il Kim, Kun Ho Lee, and Jaeuk U. Kim oversaw the methodology and administration of the trial. All authors contributed to the critical editing of the manuscript and approved the final draft.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the staff of Gwangju Alzheimer's Disease and Related Dementia (GARD) center for their assistance with data acquisition and participant recruitment. The Korean Government funded this study under grants KSN1824130 and KSN2312022 to the Korea Institute of Oriental Medicine.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

We obtained written informed consent from all participants or their legal guardians after providing a detailed description of the study, which was approved by the Chonnam National University Hospital Institutional Review Board (IRB number CNUH-2019-279).

DATA AVAILABILITY STATEMENT

Data sharing is available for the datasets generated during the current study. However, the datasets are not publicly available. Interested parties may request access to the data from the corresponding author, and the data will be provided upon reasonable request.

REFERENCES

1. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2023;19(4):1598-1695. doi:10.1002/alz.13016
2. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. *Lancet*. 2006;367(9518):1262-1270. doi:10.1016/S0140-6736(06)68542-5
3. Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2023. *Alzheimers Dement*. 2023;9(2):e12385. doi:10.1002/trc2.12385
4. Klingner J, Kumar R, Hanrahan P. Measuring the task-evoked pupillary response with a remote eye tracker. Proceedings of the 2008 symposium on Eye tracking research & applications. ETRA; 2008:69-72.

5. Duchowski AT. *Eye Tracking Methodology: Theory and Practice*. Springer-Verlag; 2017.
6. Joshi S, Gold JI. Pupil size as a window on neural substrates of cognition. *Trends Cogn Sci*. 2020;24(6):466-480. doi:10.1016/j.tics.2020.03.005
7. Opwonya J, Doan DNT, Kim SG, et al. Saccadic eye movement in mild cognitive impairment and alzheimer's disease: a systematic review and meta-Analysis. *Neuropsychol Rev*. 2022;32(2):193-227. doi:10.1007/s11065-021-09495-3
8. Anderson TJ, MacAskill MR. Eye movements in patients with neurodegenerative disorders. *Nat Rev Neurol*. 2013;9(2):74-85. doi:10.1038/nrneurol.2012.273
9. Frost S, Kanagasingam Y, Sohrabi H, et al. Pupil response biomarkers for early detection and monitoring of Alzheimer's disease. *Curr Alzheimer Res*. 2013;10(9):931-939. doi:10.2174/15672050113106660163
10. Karatekin C, Bingham C, White T. Oculomotor and pupillometric indices of pro- and antisaccade performance in youth-onset psychosis and attention deficit/hyperactivity disorder. *Schizophr Bull*. 2010;36(6):1167-1186. doi:10.1093/schbul/sbp035
11. Granholm EL, Panizzon MS, Elman JA, et al. Pupillary responses as a biomarker of early risk for Alzheimer's disease. *J Alzheimers Dis*. 2017;56(4):1419-1428. doi:10.3233/JAD-161078
12. Wang CA, McInnis H, Brien DC, Pari G, Munoz DP. Disruption of pupil size modulation correlates with voluntary motor preparation deficits in Parkinson's disease. *Neuropsychologia*. 2016;80:176-184. doi:10.1016/j.neuropsychologia.2015.11.019
13. Sirois S, Brisson J. Pupillometry. *Wiley Interdiscip Rev Cogn Sci*. 2014;5(6):679-692. doi:10.1002/wcs.1323
14. Beatty J. Phasic not tonic pupillary responses vary with auditory vigilance performance. *Psychophysiology*. 1982;19(2):167-172. doi:10.1111/j.1469-8986.1982.tb02540.x
15. Kahneman D, Beatty J. Pupil diameter and load on memory. *Science*. 1966;154(3756):1583-1585. doi:10.1126/science.154.3756.1583
16. Granholm E, Asarnow RF, Sarkin AJ, Dykes KL. Pupillary responses index cognitive resource limitations. *Psychophysiology*. 1996;33(4):457-461. doi:10.1111/j.1469-8986.1996.tb01071.x
17. Zeeman M, Figeys M, Brimmo T, Burnstad C, Hao J, Kim ES. Task-evoked pupillary response as a potential biomarker of dementia and mild cognitive impairment: a scoping review. *Am J Alzheimers Dis Other Demen*. 2023;38:15333175231160010. doi:10.1177/15333175231160010
18. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008
19. Kang Y, Na DL, Hahn S. *Seoul neuropsychological screening battery*. Incheon: Human Brain Research \& Consulting Co; 2003.
20. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol*. 1987;149(2):351-356. doi:10.2214/ajr.149.2.351
21. Kim KW, MacFall JR, Payne ME. Classification of white matter lesions on magnetic resonance imaging in elderly persons. *Biol Psychiatry*. 2008;64(4):273-280. doi:10.1016/j.biopsych.2008.03.024
22. Opwonya J, Wang C, Jang KM, Lee K, Kim JI, Kim JU. Inhibitory control of saccadic eye movements and cognitive impairment in mild cognitive impairment. *Front Aging Neurosci*. 2022;14:871432. doi:10.3389/fnagi.2022.871432
23. Forbes SH. PupillometryR: an R package for preparing and analysing pupillometry data. *J Open Source Softw*. 2020;5(50):2285.
24. Geller J, Winn MB, Mahr T, Mirman D. GazeR: a package for processing gaze position and pupil size data. *Behav Res Methods*. 2020;52(5):2232-2255. doi:10.3758/s13428-020-01374-8
25. Unsworth N, Robison MK, Miller AL. Individual differences in baseline oculometrics: examining variation in baseline pupil diameter, spontaneous eye blink rate, and fixation stability. *Cogn Affect Behav Neurosci*. 2019;19(4):1074-1093. doi:10.3758/s13415-019-00709-z
26. Unsworth N, Miller AL, Robison MK. Oculometric indicators of individual differences in preparatory control during the antisaccade task. *J Exp Psychol Hum Percept Perform*. 2023;49(2):159-176. doi:10.1037/xhp0001070
27. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw*. 2015;67(1). doi:10.18637/jss.v067.i01
28. Thompson CG, Kim RS, Aloe AM, Becker BJ. Extracting the variance inflation factor and other multicollinearity diagnostics from typical regression results. *Basic Appl Soc Psychol*. 2017;39(2):81-90. doi:10.1080/01973533.2016.1277529
29. Kim S. Ppcor: an R package for a fast calculation to semi-partial correlation coefficients. *Commun Stat Appl Methods*. 2015;22(6):665-674. doi:10.5351/csam.2015.22.6.665
30. Albright TD. High-level visual processing: cognitive influences. In: Kandel ERS, James H, Jessell TM, Siegelbaum SA, Hudspeth AJ, eds. *Principles of neural science*. 5th ed. McGraw-Hill Education; 2013:621-637.
31. Hutchison KA, Moffitt CC, Hart K, Hood AV, Watson JM, Marchak FM. Measuring task set preparation versus mind wandering using pupillometry. *J Exp Psychol: Learn, Mem, Cogn*. 2020;46(2):280.
32. Porter G, Troscianko T, Gilchrist ID. Effort during visual search and counting: insights from pupillometry. *Q J Exp Psychol*. 2007;60(2):211-229. doi:10.1080/17470210600673818
33. Verney SP, Granholm E, Marshall SP. Pupillary responses on the visual backward masking task reflect general cognitive ability. *Int J Psychophysiol*. 2004;52(1):23-36. doi:10.1016/j.ijpsycho.2003.12.003
34. van der Wel P, van Steenbergen H. Pupil dilation as an index of effort in cognitive control tasks: a review. *Psychon Bull Rev*. 2018;25(6):2005-2015. doi:10.3758/s13423-018-1432-y
35. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage*. 2002;17(3):1394-1402. doi:10.1006/nimg.2002.1280
36. Alichniewicz KK, Brunner F, Klnemann HH, Greenlee MW. Neural correlates of saccadic inhibition in healthy elderly and patients with amnestic mild cognitive impairment. *Front Psychol*. 2013;4:467. doi:10.3389/fpsyg.2013.00467
37. Crawford TJ, Devereaux A, Higham S, Kelly C. The disengagement of visual attention in Alzheimer's disease: a longitudinal eye-tracking study. *Front Aging Neurosci*. 2015;7:118. doi:10.3389/fnagi.2015.00118
38. DeSouza JF, Menon RS, Everling S. Preparatory set associated with pro-saccades and anti-saccades in humans investigated with event-related FMRI. *J Neurophysiol*. 2003;89(2):1016-1023. doi:10.1152/jn.00562.2002

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Opwonya J, Kim K, Lee KH, Kim JI, Kim JU. Task-evoked pupillary responses as potential biomarkers of mild cognitive impairment. *Alzheimer's Dement*. 2024;16:e70019. https://doi.org/10.1002/dad2.70019