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RESEARCH ARTICLE

A detection model of cognitive impairment via the integrated gait and eye movement analysis from a large Chinese community cohort

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Abstract

INTRODUCTION: Whether the integration of eye-tracking, gait, and corresponding dual-task analysis can distinguish cognitive impairment (CI) patients from controls remains unclear.

METHODS: One thousand four hundred eighty-one participants, including 724 CI and 757 controls, were enrolled in this study. Eye movement and gait, combined with dual-task patterns, were measured. The LightGBM machine learning models were constructed.

RESULTS: A total of 105 gait and eye-tracking features were extracted. Forty-six parameters, including 32 gait and 14 eye-tracking features, showed significant differences between two groups ($P < 0.05$). Of these, the Gait_3Back-TurnTime and Dual-task cost-TurnTime patterns were significantly correlated with plasma phosphorylated tau 181 (p-tau181) level. A model based on dual-task gait, dual-task smooth pursuit, prosaccade, and anti-saccade achieved the best area under the receiver operating characteristics curve (AUC) of 0.987 for CI detection, while combined with p-tau181, the model discriminated mild cognitive impairment from controls with an AUC of 0.824.

DISCUSSION: Combining dual-task gait and dual-task eye-tracking analysis is feasible for the detection of CI.

KEYWORDS
cognitive impairment, diagnosis, dual task, eye movement, gait

Highlights

- This is the first study to report the efficiency of integrated parameters of dual-task gait and eye-tracking for cognitive impairment (CI) detection in a large cohort.
- We identified 46 gait and eye-tracking features associated with CI, and two were correlated to plasma phosphorylated tau 181.
- We constructed the model based on dual-task gait, smooth pursuit, prosaccade, and anti-saccade, achieving the best area under the curve of 0.987 for CI detection.

1 | BACKGROUND

Dementia is a major public health concern that is also emerging as a growing burden owing to the consistent increase in the aging population in society, affecting approximately 57 million people worldwide.[1] Individuals with Alzheimer's disease (AD) comprise the largest segment of the population of dementia patients.[2–4] Mild cognitive impairment (MCI) is recognized as an intermediary phase between the typical processes of aging and dementia onset.[5] Early diagnosis of dementia, including the detection of MCI or even early-stage dementia, may substantially benefit patients. Currently, the prevalent and well-studied screening tools for cognitive impairment (CI) in China mainly include the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA); however, their sensitivity and specificity are not identical,[6,7] partially due to differences related to age, education level, and culture between studies.[8–10] These limitations hinder objective disease identification and necessitate the exploration of alternative methods that can overcome the weaknesses of existing techniques.

Recent technological advancements have led to the exploration of the use of eye tracking and gait characteristics as promising tools for CI detection. Previous findings have suggested that individuals with AD experience a gradual decline in effective attentional control, leading to impairments in their ability to correct eye movement errors.[11] Currently, three types of eye movements have been reported to be associated with cognition—namely, smooth pursuit, saccade, and anti-saccade. Smooth pursuit eye movements have been shown to play an important role in reflecting visual attention via saliency map modeling and have been proven to be associated with a superior colliculus, a midbrain area associated with attention and gaze.[12] Furthermore, recent pathological research on the connection between cognition and oculomotor control in smooth pursuit has provided consistent evidence,[13] and the association between AD-related pathologies and oculomotor route impairment has also been proven.[14,15] The saccade eye movement task has also been in use for decades.[16] Mosimann et al. observed that individuals with AD exhibited significantly shorter saccades than healthy controls.[17] Yang et al. conducted both horizontal and vertical saccadic tests among healthy elderly individuals and patients with MCI and AD, and observed that the gap effect resulted in longer saccade latency in patients, suggesting that abnormalities in latency and latency–accuracy–speed variability reflect deficits in cerebral areas involved in saccade initiation and execution.[18] Likewise, during the anti-saccade task, the latency of the pro-saccades for error correction was longer in the CI group than in the control group.[19,20] Moreover, individuals with AD exhibited smooth pursuit impairments, similar to their saccadic dysfunctions.[21] Together, these results indicate that smooth pursuit, saccade, and anti-saccade tasks can be used as potential tools to assess cognitive function.

Regarding gait analysis, Guimarães et al. found that most gait parameters enabled good discrimination of CI (area under the receiver operating characteristics curve [AUC]: 0.7–0.8); among these, the pushing ratio dual-task effect (DTE) was reported to have the highest AUC of 0.764.[22] In addition, a meta-analysis has shown that velocity, stride length, and stride time performed the best in differentiating between patients with MCI and healthy controls under single-task conditions and that the discriminative power increased under dual-task conditions.[23] Other studies have indicated that the DTE on gait speed was higher in the MCI group than in the cognitively normal (CN) group and presented a high sensitivity for the detection of MCI.[24,25] Moreover, studies using brain imaging have indicated that cognition and motor control are associated with overlapping brain networks, particularly within the prefrontal and temporal regions.[26] A recent study also found that combining gait and dual task could predict dementia progression.[27]

However, whether the integration of eye movement and gait assessment in screening for CI is feasible in the context of a large community cohort is unclear. The small sample sizes and outdated technologies used in previous studies limit the reliability and generalizability of their results—with limited access to patients, most studies only included < 100 participants;[27–30] additionally, the outdated infrared optical positioning and wearable sensor-based systems, such as Locometrix,[31] are often difficult to use. With improvements in technology and measurement techniques, such as those in the virtual reality (VR) headset system used in this study, many experimental biases can be minimized.[32]

Based on the enhanced predictive value of combining gait analysis and dual tasks,[27] we proposed the idea of merging eye-tracking and dual tasks for the first time in this study. Because cognition is affected by multidimensional factors, integrating eye tracking, gait, and their dual task in a large population is crucial for developing more sensitive screening tools for dementia. Moreover, a substantial sample of 1481 participants was included in our analyses. Eye movement and gait parameters were assessed and analyzed using LightGBM machine learning models. Based on the data, we identified crucial parameters for distinguishing individuals with CI from those who were CN. Finally, as plasma phosphorylated tau 181 (p-tau181) has been indicated as a non-invasive diagnostic biomarker of AD,[33,34] the associations between p-tau181 levels and key features were also evaluated. The combination of eye tracking, gait monitoring, and dual task demonstrated high accuracy in discriminating patients with CI, providing evidence for the feasibility of a new non-invasive method for the early detection of CI.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the available literature about the associations of gait and eye-tracking characteristics with dementia, while most studies focused on gait or eye-tracking independently; in addition, the limited sample size, the outdated technologies for features assessment, and incomplete parameters collection hindered their application for cognitive impairment (CI) detection.
2. **Interpretation**: We identified 46 gait and eye-tracking parameters significantly associated with CI group. Interestingly, the Gait_3Back-TurnTime and Dual-task cost-TurnTime patterns are found to be correlated to plasma phosphorylated tau 181 (p-tau181). In addition, the model based on dual-task gait, dual-task smooth pursuit, prosaccade, and anti-saccade achieved the best area under the receiver operating characteristics curve (AUC) of 0.987 for CI detection, while combined with plasma p-tau181, the model can discriminate mild cognitive impairment from controls with an AUC of 0.824.
3. **Future directions**: This novel approach, combining dual-task eye-tracking and dual-task gait analysis, represents a significant advancement in diagnostic capabilities and shows promising prospects for clinical applications.

2 | METHODS

2.1 | Participants

A total of 1481 Chinese participants of Han ethnicity from Jili County, Liuyang City, China were enrolled in this study. This is a longitudinal, community-based cohort established in 2022; as of 2023, the first year of participant follow-up has been completed. Gait and eye movement data for this study were collected during the first year of follow-up. The Jili subdistrict contains three villages (Xihu, Daowu, and Dongsha) and six urban communities (Gongjiaqiao, Xinwuling, Xihe, Baiyi, Shenxianao, and Jiliqiao). A total of 3233 residents aged ≥ 60 years from nine communities are participating in the baseline examination. According to the elderly resident population data collected by the local government, the coverage rate of the enrolled participants was 73%.

The inclusion criteria for the gait and eye-movement analysis were: (1) age ≥ 60 years at the time of enrollment, (2) independent availability of complete cognitive assessment test results, and (3) informed consent form signed by the participant or their guardian. The exclusion criteria for the gait movement analysis were: (1) history of stroke, Parkinson's disease, or other neurological conditions, such as brain injury and brain surgery, that could have affected the motor functions of participants and (2) history of other systemic diseases or conditions, such as osteoarthritis and limb or spinal trauma. The exclusion criteria for the eye movement analysis were: a history of (1) cataract, glaucoma, or other eye diseases and (2) other systemic conditions or diseases that could have caused ocular symptoms affecting eye tracking. More importantly, to eliminate the impact of vision-related or ocular conditions on the analysis, in the initial stage of eye tracking, eye movement was calibrated using a nine-point calibration procedure to ensure a maximum calibration error of 2° in radius. Eye movement was not evaluated for participants who did not correctly complete this step.

In total, 1224 individuals completed the gait task, 993 completed the pro-saccade and smooth pursuit task, and 392 completed the anti-saccade task. The patient inclusion flowchart is shown in Figure 1.

For MCI diagnosis, the following criteria were required to be met:[35] (1) expression of cognition-related concerns by the subject, informant, or physician (Clinical Dementia Rating [CDR] ≥0.5); (2) evidence of objective CI in at least one of the four cognitive domains; (3) essentially preserved daily activity functions; and (4) absence of dementia. The signs used to diagnose dementia were based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[36] Individuals who did not show signs of MCI or dementia were classified into the CN group. All participants provided written consent to participate in the study. The research protocol of this study was approved by the ethics committee of Xiangya Hospital of Central South University.

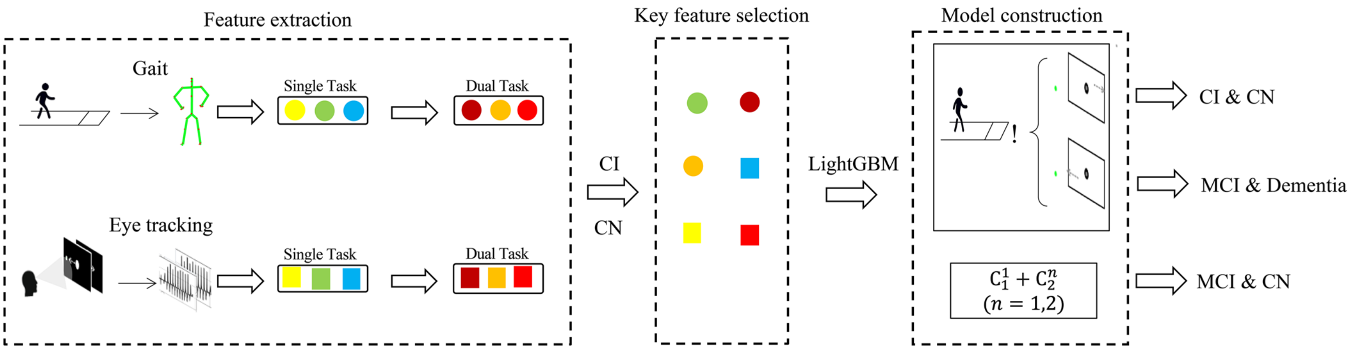

FIGURE 1 Overview of the procedures used for gait and eye movement data collection and model construction. CI, cognitively impaired; CN, cognitively normal; MCI, mild cognitive impairment.

2.2 | Neuropsychological assessments

The MMSE and CDR were used to assess the cognitive function of the participants. The trained investigators in this study included interviewers and neurologists who had received consistent training in neuropsychological assessment. First, an interviewer used the MMSE to assess global cognitive function, with the cut-off values for CI set according to the criteria reported in a previous Chinese population study (illiterate participants, $\leq$ 17 points; primary-education participants, $\leq$2 0 points; junior secondary school or higher education participants, $\leq$ 24 points).[37] Another interviewer conducted the CDR assessment, with the necessary information obtained through a semi-structured interview with the participant and a reliable informant. A CDR $\geq$ 0.5 was used to designate CI.[38] The final diagnosis of CI was made based on a consensus among three neurologists specializing in cognitive disorders according to disease history, education level, and neuropsychological scores.

2.3 | Eye movement assessment

Eye movements were recorded using an eye-tracking system (EyeKnow; Beijing CAS-Ruiyi Information Technology Co., Ltd.) at a sampling rate of 120 Hz. The EyeKnow system consists of a tablet computer paired with a VR headset that is equipped with an eye-tracking camera. The VR headset was used to guide eye movements and collect eye-movement data. This system requires only a chair and a table for testing. An initial nine-point calibration procedure was used to ensure a maximum calibration error of 2° in radius. Stimuli were displayed on a monitor integrated with the eye-tracking system, and eye-movement parameters were analyzed using an embedded data processing module. The assessment involved three tasks (the smooth pursuit, pro-saccade, and anti-saccade tasks) and their corresponding dual task.

2.4 | Smooth pursuit task

In the smooth pursuit task, a green dot moved along a sinusoidal trajectory with a horizontal amplitude of 20° and at a frequency of 0.2 Hz. Participants were asked to continuously track the sinusoidal movement of the target dot, and the pursuit accuracy and number of offsets were analyzed. Pursuit accuracy was defined as the ratio of the accurately tracked duration of the target dot to the total duration of the task; participant gaze points within a 2° radius from the center of the target were considered accurately tracked. The pursuit offset number was defined as the number of instances during the test of the gaze point deviating from the center of the target by more than 2° before accurate tracking subsequently resumed.

2.5 | Pro-saccade task

In the pro-saccade task, a green target dot was initially presented at the center of the display and then shifted randomly ± 15° horizontally and vertically away from the center. Participants were asked to direct their gaze promptly and accurately toward the target dot, and saccade accuracy, latency, and velocity were analyzed. Saccade accuracy was defined as the ratio of the number of successful saccades to the total number of saccade tests performed; saccade offsets falling within a 2° radius from the target dot were considered successful saccades. Saccade latency was operationally defined as the duration between target onset and saccade initiation. Saccade velocity was defined as the angular velocity of eye movement during the interval between saccade onset and offset.

2.6 | Anti-saccade task

The stimuli paradigms in the anti-saccade task followed the same experimental protocol as those in the pro-saccade task. However, participants were asked to initially fixate on the central target and then execute a saccade opposite to the position of the target dot as soon as possible. The key parameters examined in the analysis included anti-saccade accuracy, latency, corrective latency, and velocity. Anti-saccade accuracy was defined as the proportion of successful and direct saccades in the direction opposite to that of the target relative to the total number of anti-saccade tests conducted; eye movements toward the target prior to executing the anti-saccade in the opposite direction were regarded as task failures. Corrective latency was defined as the duration between a participant failing to inhibit a reflexive saccade toward the target and subsequent initiation of a voluntary saccade in the opposite direction. The definitions of saccade latency and saccade velocity were the same as those used in the pro-saccade task.

2.7 | Gait assessment

Gait parameters were assessed using a quantitative motor function assessment system (ReadyGo, Beijing CAS-Ruiyi Information Technology Co., Ltd.). The ReadyGo system uses only one set of cameras, consisting of a single RGB (red/green/blue) camera and a single-depth camera, to capture three-dimensional (3D) motion, along with deep learning for skeletal point positioning. Additionally, gait tests do not require a specific room to be set up because the system occupies less than 1 m^2 of space and functions effectively within a 1×5 m^2 area directly in front of the camera with no obstructions. This device can both observe and estimate 3D joints and landmarks through deep visual perception, uniquely track multiple skeletons, and eliminate the need for the subject to wear any sensors. For the single-gait test, participants were asked to walk at their usual pace on a 3 m walkway without using any mobility aids. Each participant performed one practice trial on the walkway.

2.8 | Dual-task tests

In the eye movement dual-task paradigm, participants were required to execute eye movement tasks and simultaneously engage in the following cognitive task: subtracting serial threes from 100. The rationale for the dual-task condition selection has been described elsewhere.[39] For the dual-task gait tests, participants walked at their usual pace while performing the same cognitive task. Dual-task cost (DTC) reflects the change in gait parameters relative to baseline values when participants perform the same gait task under dual-task conditions. The magnitude of the effect of the cognitive challenge on gait or eye movement performance was assessed by calculating the DTC (percent) as follows: ([single-task parameter – dual-task parameter] / single-task parameter) × 100%.[26]

2.9 | Plasma p-tau181 level assessment

The test kits called P-tau181 (#104111, Simoa® pTau-181 V2.1 Reagent Kit) were obtained from Quanterix Corp. and used correctly, and a 1:4 ratio was used to weaken the plasma tests for all trials. The following experiments were conducted in accordance with the protocol outlined in the test kit. A detailed inspection was carried out on the measuring tools and quality checks. The individuals in authority were unaware of the participants' illness.

2.10 | Statistical analysis

Demographics and clinical characteristics were summarized using either means and standard deviations or frequencies and percentages as appropriate. Characteristics in accordance with normal distribution were analyzed using a *t* test or otherwise using the Mann–Whitney *U* test. Statistical significance was set at $P < 0.05$.

The machine learning classification model LightGBM generated by different sets of input variables is used to distinguish between CN and CI, MCI and dementia, MCI and CN individuals. Specifically, models were based on the following input variables: single-task gait parameters, dual-task gait parameters, single-task eye movement parameters, dual-task eye movement parameters. The models were adjusted based on age, sex, and education level for all individuals, as well as body mass index for gait parameters. The performance of different machine-learning models was assessed by accuracy, specificity, sensitivity, and AUC.

Statistical analyses were conducted using Python version 3.8.10.

3 | RESULTS

3.1 | Baseline characteristics

We recruited 1481 participants from the Jili subdistrict in Liuyang City for this study. Of these, 724 were diagnosed with CI, including 487 with dementia and 237 with MCI; the other 757 individuals were designated as CN controls. The baseline characteristics of all participants are summarized in Table 1.

3.2 | Eye-tracking analysis

As previously mentioned, the smooth pursuit, pro-saccade, and anti-saccade tasks were conducted to assess eye movement. During these tasks, we observed discernible differences among the CN, MCI, and dementia groups. To illustrate these differences, typical eye movement trajectories during the smooth pursuit and pro-saccade tasks were derived. Because these two tasks involve fundamental eye movements, such as pursuit and saccade, intuitive differences indicating the distinctions among the three groups could be visualized. Figure 2 depicts the results of the eye-tracking analysis in the three groups. Figure 2A depicts the planar gaze trajectories (horizontal and vertical) plotted during the pro-saccade task for each group. The CN group showed regular and smooth eye movement trajectories; the MCI group exhibited slightly disorganized trajectories, suggesting less stable and coordinated eye movements; and the dementia group displayed highly erratic trajectories, with numerous microsaccades and unstable fixations during the pro-saccade task. Figure 2B presents the spatio-temporal plots of eye movement trajectories during the horizontal saccade task for each group. The trajectories illustrate the horizontal positional movement of the target point (gray line) and participant gaze position (red

TABLE 1 Baseline characteristics of enrolled participants.

Demographics	CI	CN	P-value
n	724	757	
Age, years	69.76 ± 6.54	68.82 ± 5.84	0.003
Female, n (%)	64.5	54.0	<0.001
Education, illiteracy and primary (%)	60.6	66.1	0.028
BMI	24.84 ± 3.24	24.65 ± 3.03	0.234
MMSE	19.67 ± 4.56	26.48 ± 2.33	<0.001
CDR	0.48 ± 0.42	0	<0.001
Plasma p-tau181 (pg/mL)	18.09 ± 9.10	15.69 ± 8.70	0.011

Abbreviations: BMI, body mass index; CDR, Clinical Dementia Rating; CI, cognitive impairment; CN, cognitively normal; MMSE, Mini-Mental State Examination; p-tau181, phosphorylated tau 181.

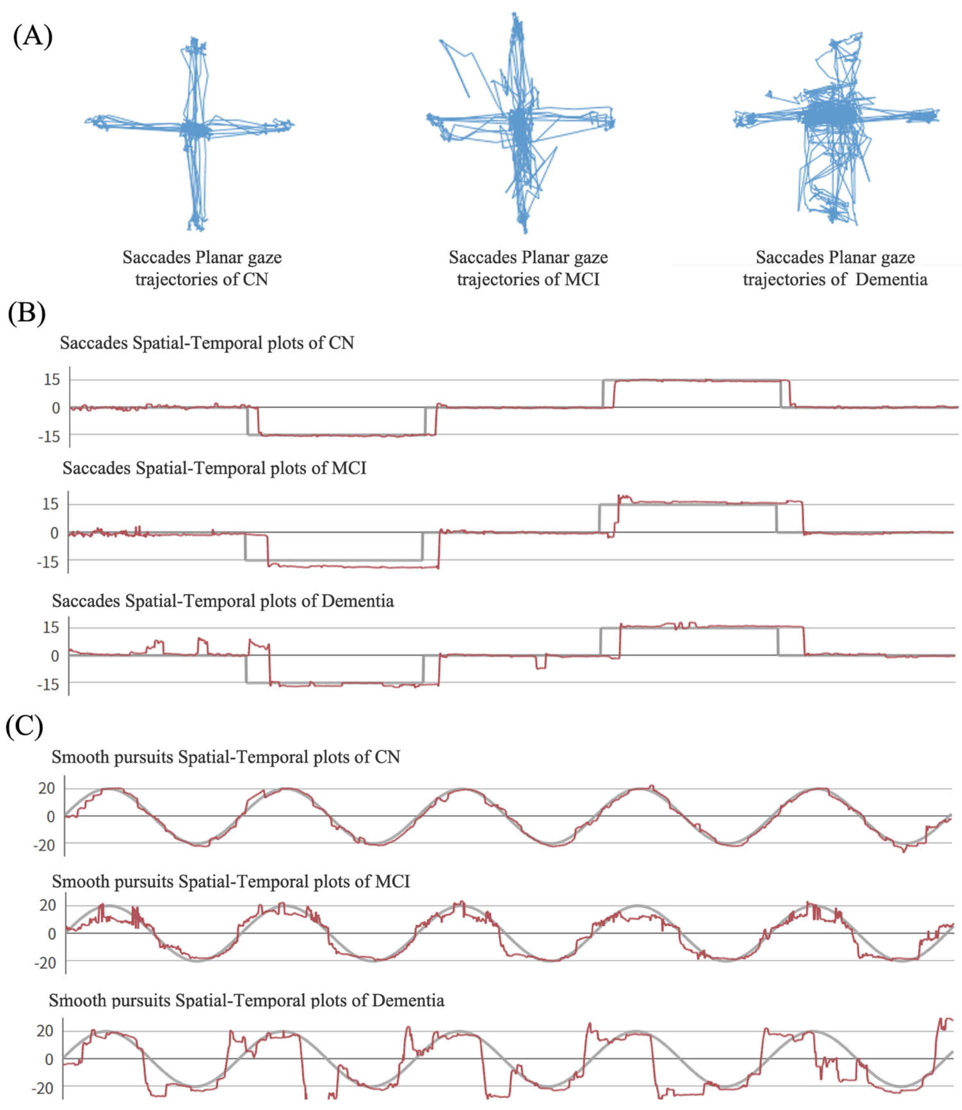

FIGURE 2 Visual evaluation of the smooth pursuit (SP) and pro-saccade (PS) tasks in the cognitively normal (CN), mild cognitive impairment (MCI), and dementia groups. (A) Plotted planar gaze trajectories (horizontal and vertical) in the PS task; (B) spatio-temporal plots of eye movement trajectories during the horizontal PS task; (C) spatio-temporal plots of eye movement trajectories during the horizontal SP task.

line) during two consecutive horizontal saccade tasks. The temporal gap between the target dot shifting and the onset of eye movement was higher in the MCI and dementia groups than in the CN group, reflecting longer latency periods. Figure 2C shows the spatio-temporal plots of eye movement trajectories during the horizontal smooth pursuit task for each group. The trajectories demonstrate the horizontal position changes of the target point (gray line) and participant gaze position (red line) over five cycles of horizontal sinusoidal motion. The CN group exhibited smoother and more accurate tracking performance, the MCI group showed a higher frequency of deviations and compensatory saccades, and the dementia group displayed more pronounced deviations along with pronounced hypermetria and hypometria (over- and under-shooting of the target) and compensatory saccades of greater magnitude.

3.3 | Differences in gait and eye movement features between the CI and CN groups

To obtain features with a high contribution to the classification model, 105 gait and eye movement features were extracted and divided into eight groups (Tables S1–S5 in supporting information)—the single-task gait, dual-task gait, single-task smooth pursuit, dual-task smooth pursuit, single-task pro-saccade, dual-task pro-saccade, single-task anti-saccade, and dual-task anti-saccade sets. Of these, 46 parameters, including 32 gait and 14 eye-tracking features, showed significant differences between the CI and CN groups ($P < 0.05$). The top 18 distinctive features ($P < 0.001$) are presented in Figure 3, including 14 gait features—Gait-TestTime, Gait-Stride_Left, Gait-Stride_Right, Gait-TurnTime, Gait_3Back-TestTime, Gait_3Back-Stride_Left, Gait_3Back-Stride_Right, Gait_3Back-Height_Left, Gait_3Back-Speed, Gait_3Back-StrideSpeed_Left, Gait_3Back-SwingSpeed_Left, Gait_3Back-TurnTime, DTC-TestTime, and DTC-TurnTime—and four eye movement features—Antisaccade (AS)-Lantency_Average (AVG), AS-Saccade_Velocity_AVG, AS_3Back-Lantency_AVG, and AS_3Back-Saccade_Velocity_AVG. All 46 features were used to construct the CI detection model.

3.4 | Associations between key features and plasma p-tau181 levels

The Pearson correlation coefficients between the 18 top key features and plasma p-tau181 levels were calculated, and two key features were found to be significantly correlated with p-tau181 level ($P < 0.05$): Gait_3Back-TurnTime and DTC-TurnTime. Results of the correlation analysis for these two features are shown in Figure 4. The correlation coefficient between Gait_3Back-TurnTime and p-tau181 level was 0.508 ($P = 0.045$), and that between DTC-TurnTime and p-tau181 level was −0.593 ($P = 0.016$). Considering that p-tau181 has been recognized as a detection biomarker for AD, our results suggest that Gait_3Back-TurnTime and DTC-TurnTime are associated with AD.

3.5 | CI detection effect based on single-task gait or eye movement and dual-task gait or eye movement

To evaluate the effect of CI detection based on the single task and dual task, we generated machine learning models with six sets of input key features. According to the situation of the valid samples, a total of six sets of features were used to construct the models and compare the evaluation indicators. We evaluated the discrimination power of these six sets of features as well as the p-tau181 level and MMSE score, as shown in Figure 5. The model based on dual-task gait features (AUC: 0.798) was better at distinguishing participants with CI from CN participants than a model based on single-task gait features (AUC: 0.544). Similarly, the model based on dual-task smooth pursuit and pro-saccade features (AUC: 0.909) was better than the model based on single-task smooth pursuit and pro-saccade features (AUC: 0.863); moreover, the combined smooth pursuit, pro-saccade, and anti-saccade single task and the dual task of these three eye movement types had high AUCs of 0.926 and 0.931, respectively. These results indicate that, for the classification models, the discrimination power of the dual task was better than that of the single task for both eye movement and gait measurement. The AUCs for plasma p-tau181 level and MMSE score were 0.615 and 0.914, respectively. A possible reason for the p-tau181 level having a lower discriminative accuracy is that plasma p-tau181 is recognized as an AD-specific marker, while the participants with CI in this study probably had other types of dementia. In contrast, the MMSE score was one of the measurements used to assess cognitive levels in this study and, thus, had a relatively high AUC value for classifying cognitive status.

3.6 | Power of the dual-task fusion model for CI detection

Considering the better results obtained from the dual-task models for eye movement and gait, we focused on the effect of dual-modal fusion models on CI detection. We fused the dual-task gait data with the dual-task smooth pursuit and pro-saccade data and verified the fusion model using the datasets with and without dual-task anti-saccade. The effect of the dual-modal fusion models was improved (Figure 6); in particular, the dual-modal fusion model containing all features had the best effect (accuracy: 0.929, sensitivity: 0.915, specificity: 0.941, and AUC: 0.987 for CI detection).

3.7 | Power of discriminating MCI from dementia and CN

To evaluate whether these models could discriminate MCI from dementia and CN, classification models were constructed based on the dual-modal fusion of gait and eye movement in three valid sample sets (Figure 7). Of these, the dual-modal fusion feature set including

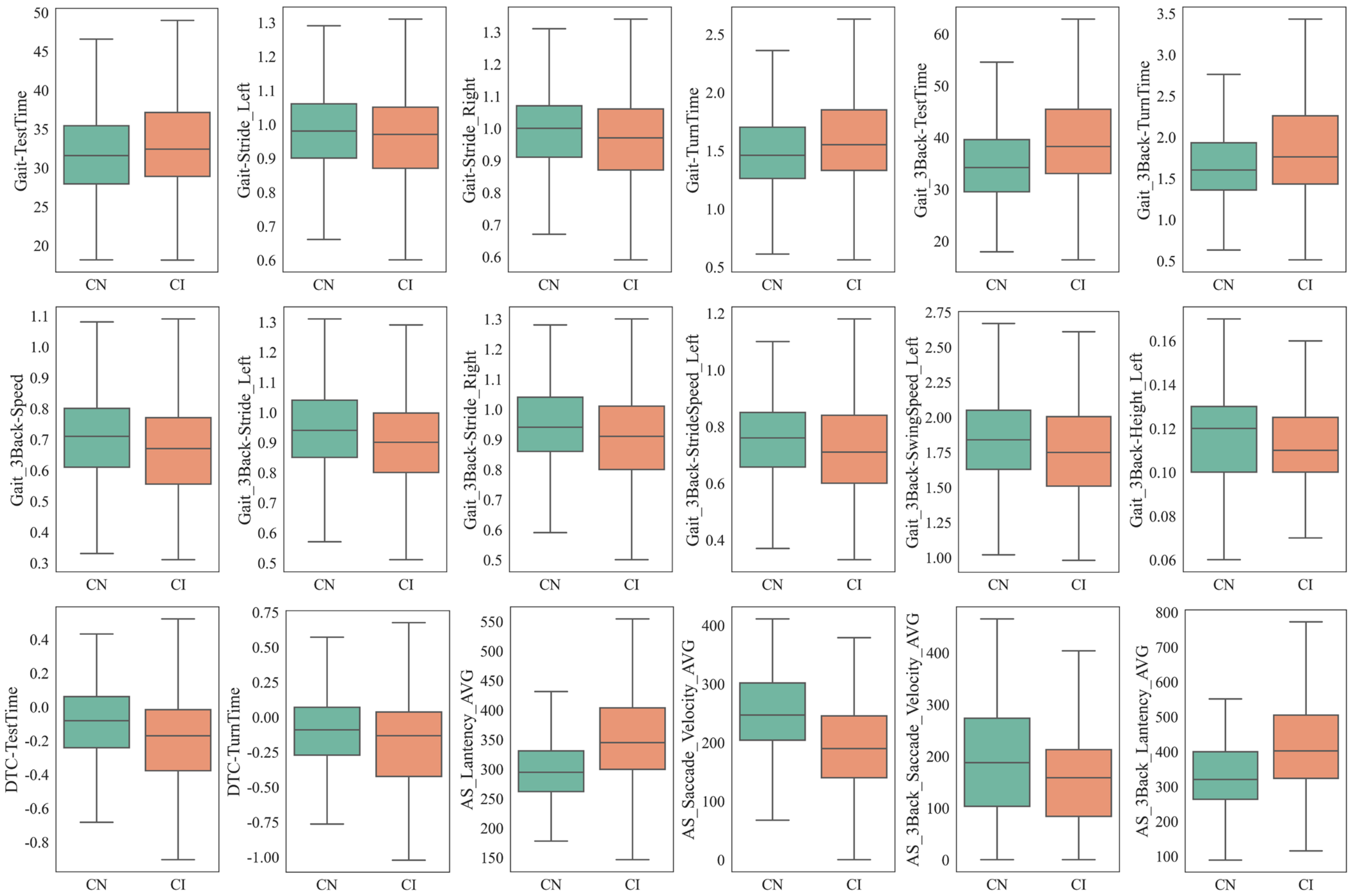

FIGURE 3 Top 18 distinctive gait and eye movement features ($P < 0.001$) between the CI and CN groups. CI, cognitively impaired; CN, cognitively normal.

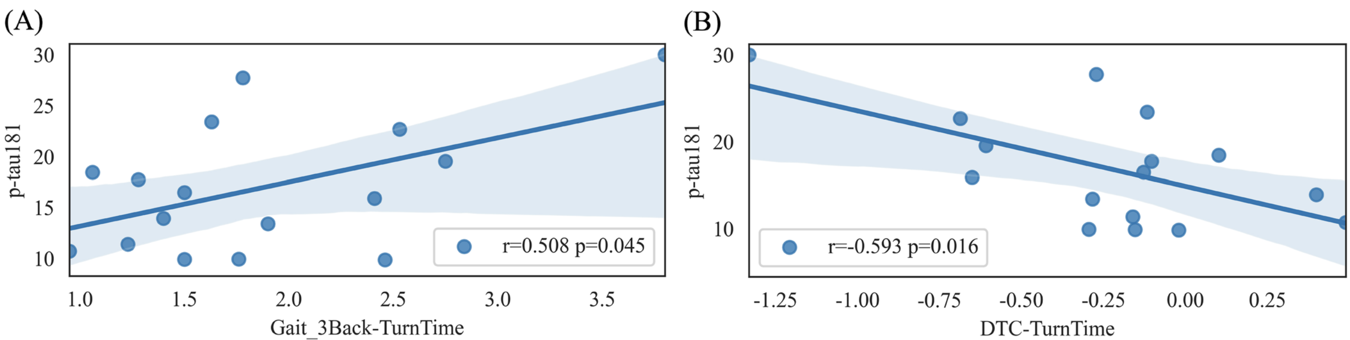

FIGURE 4 Linear correlations between gait features and plasma p-tau181 levels. The 3Back-TurnTime (A) and DTC-TurnTime (B) features were highly correlated with the p-tau181 level. p-tau181, phosphorylated tau 181.

dual-task gait, smooth pursuit, pro-saccade, and anti-saccade had the best AUC (0.893) for discriminating MCI from dementia. We further analyzed the power of the models in distinguishing individuals with MCI from CN individuals. Similarly, the model based on all dual tasks had the best AUC of 0.742, but when it was combined with the p-tau181 level, the power of discriminating MCI from CN improved (AUC: 0.824). This indicates that plasma p-tau181 level is helpful for differentiating between MCI and CN and improves the effect of the MCI identification model.

4 | DISCUSSION

This is the first study to focus on a new screening tool for CI using a combination of eye-tracking and gait analyses. Fourteen eye-tracking parameters and 32 gait features were identified as being significantly different between CN individuals and individuals with CI. At the same time, using the machine learning classification models constructed in this study, we found that combining dual-task eye-tracking and gait analysis can achieve an AUC of 0.987 in distinguishing between CN

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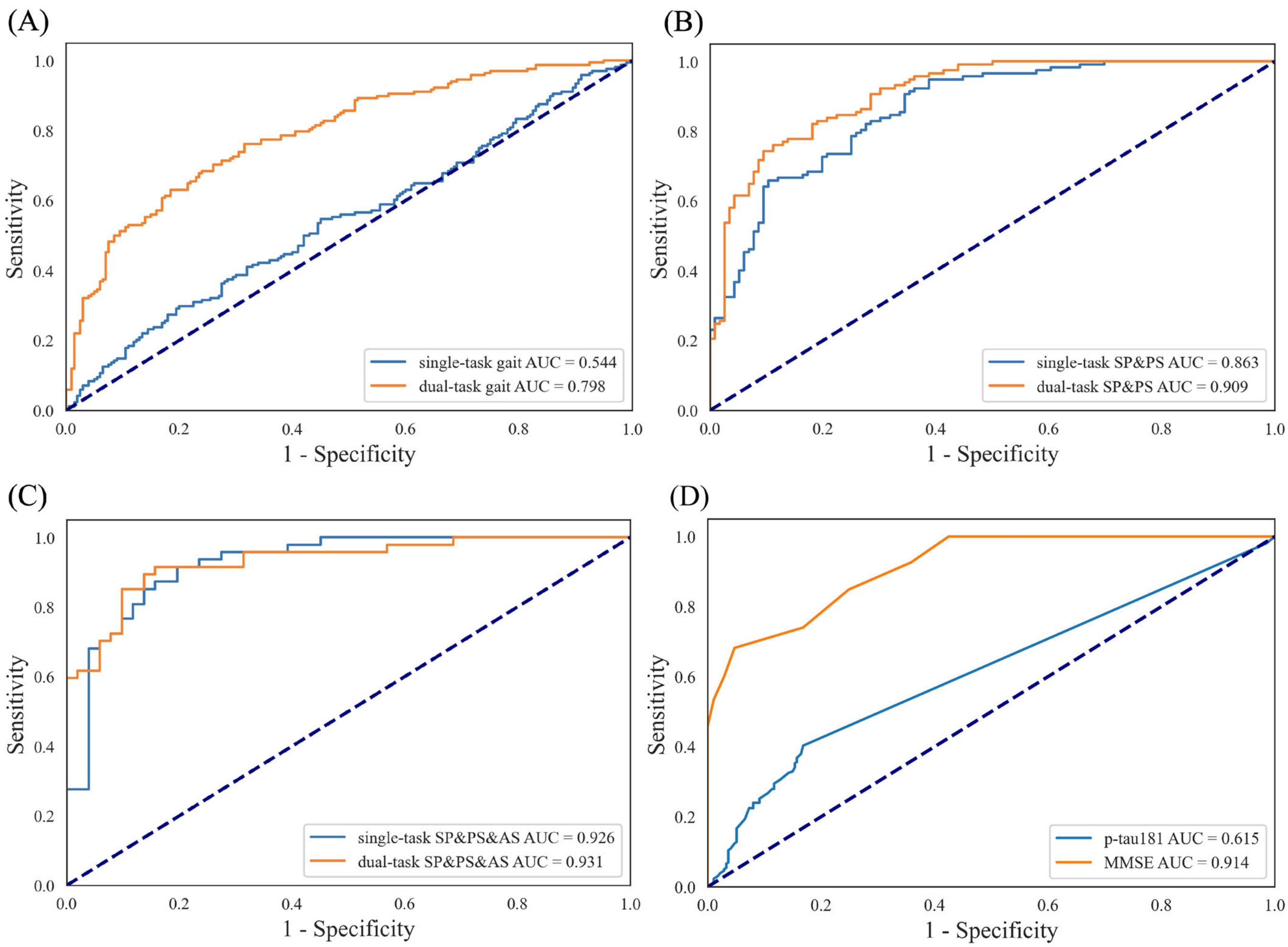

FIGURE 5 AUC comparison charts of single-task and dual-task models. (A) Models based on single task and dual task of gait features (AUC: 0.544 and 0.798, respectively); (B) models based on single task and dual task of SP and PS features (AUC: 0.863 and 0.909, respectively); (C): models based on single task and dual task of SP, PS, and AS features (AUC: 0.926 and 0.931, respectively); (D): models based on plasma p-tau181 level and MMSE score (AUC: 0.615 and 0.914, respectively). AUC, area under the receiver operating characteristic curve; AS, anti-saccade; MMSE, Mini-Mental State Examination; PS, pro-saccade; p-tau181, phosphorylated tau 181; SP, smooth pursuit.

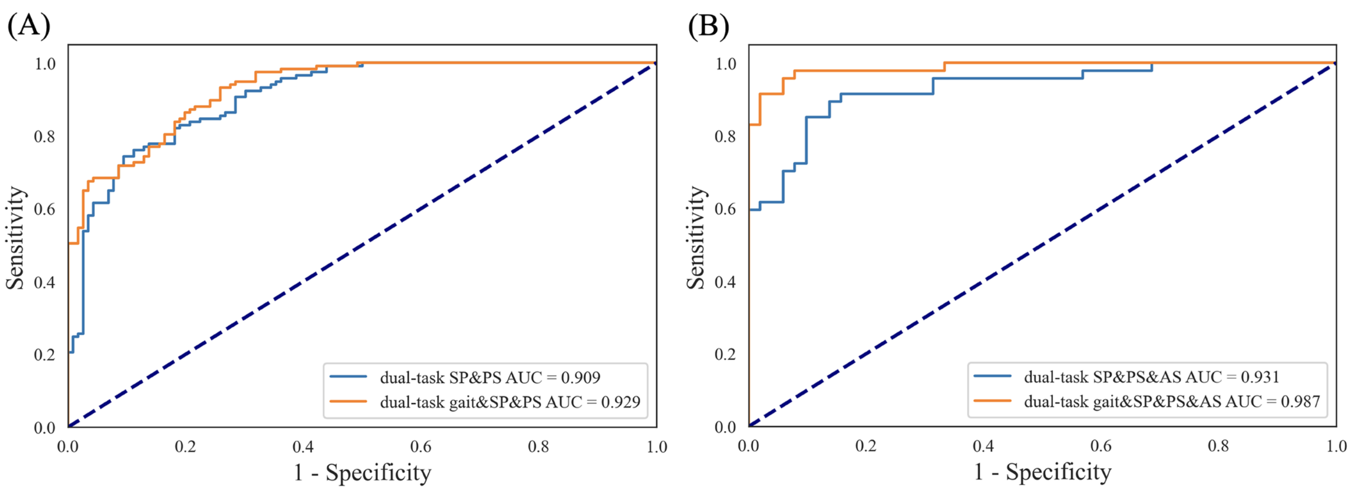

FIGURE 6 CI detection power of dual-task fusion models. (A) Models based on dual task of SP and PS features and gait features (AUC: 0.909 and 0.929, respectively); (B): models based on dual task of SP, PS, and AS features and gait features (AUC: 0.931 and 0.987, respectively). AUC, area under the receiver operating characteristic curve; AS, anti-saccade; CI, cognitive impairment; PS, pro-saccade; SP, smooth pursuit.

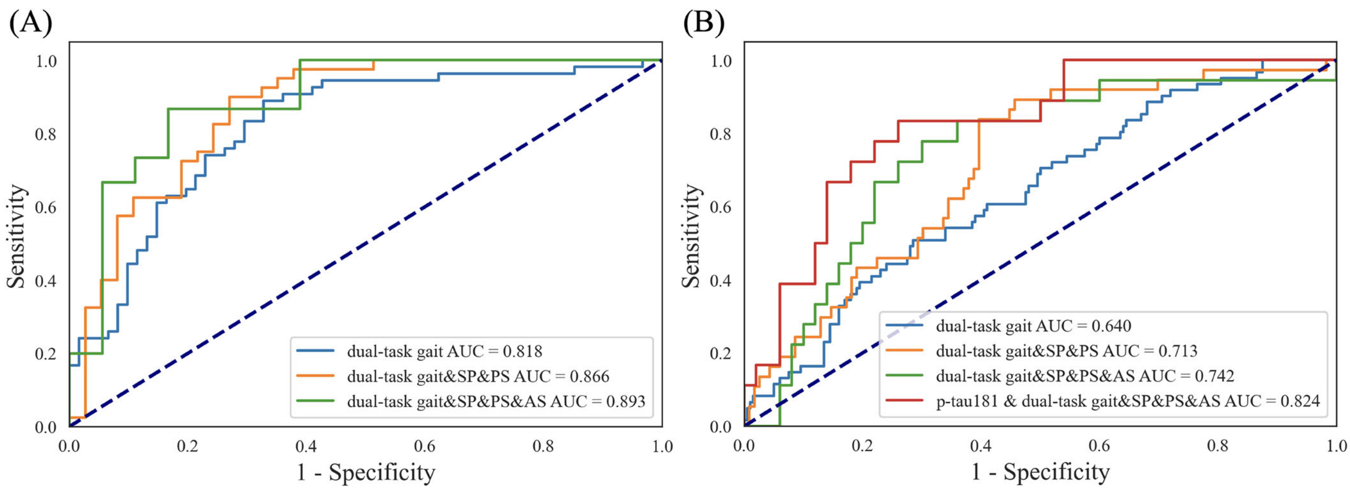

FIGURE 7 Power of dual-modal fusion for discriminating MCI from dementia and CN. (A) For the discrimination of MCI from dementia, the dual-modal fusion feature set including dual-task gait, SP, PS, and AS had the best AUC (0.893). (B) For the discrimination of MCI from CN, the model based on dual-task gait, SP, PS, and AS as well as the p-tau181 level had the best AUC (0.824). AUC, area under the receiver operating characteristic curve; AS, anti-saccade; CN, cognitively normal; MCI, mild cognitive impairment; PS, pro-saccade; p-tau181, phosphorylated tau 181; SP, smooth pursuit.

individuals and individuals with CI, which is much higher than those reported for MMSE and MoCA assessments;[40,41] thus, this screening tool is expected to be quite useful for CI identification in the elderly population. The complexity of CI was further indicated after investigating the feasibility of integrating eye-tracking and gait.

Previous studies have indicated that the eye-tracking technique can individually differentiate patients with CI from normal individuals with a test accuracy of 0.76 and an AUC of 0.802.[42–44] In this study, the AUC of eye tracking under dual-task conditions reached 0.931. The probable reason behind this high efficacy was that we first collected eye-tracking data for the smooth pursuit, pro-saccade, and anti-saccade tasks together, recognizing the added value of combining these parameters rather than relying on a single dimension.[44,45] Moreover, we discovered meaningful parameters within each of the three dimensions, and their combination resulted in the highest diagnostic value. Notably, this study is the first to incorporate a dual-task eye-tracking paradigm, which has not been previously reported. In this dual-task paradigm, participants were required to simultaneously perform eye movement tasks and the cognitive task of subtracting serial threes from 100. We found that the AUC of eye tracking for CI detection increased under dual-task conditions, providing strong evidence for a potential anatomical link between eye movement and cognition.[14,46] However, there was an obvious limitation of eye tracking for participants with eye diseases, and we plan to develop more optimized eye movement assessment methods in the future.

In addition, gait measurements were also found to have improved. Notably, there have been significant upgrades in gait monitoring equipment. The ReadyGo system used in this study did not require participants to wear any sensors; thus, it provided more objective and representative data independently compared to those obtained using the wearable devices used in other studies.[47,48] With advances in technology, more gait subtypes have now become measurable. Most previous studies only focused on a few specific gait traits, such as gait speed.[49–51] However, in this study, 20 traits, such as cadence, stance, swing, stride, and turn time, were observed and considered, which allowed for a more comprehensive analysis than in previous studies.[31,52] Test time, left stride, right stride, and turn time showed significant differences between the CI and CN groups, and the combination of multiple parameters also demonstrated superior performance compared to that reported previously. Previous reports have highlighted the advantages of dual-task gait assessments;[26] in this study, the AUC of a single gait measurement for detecting CI was only 0.544, whereas it increased to 0.798 after adding the cognitive task, which was similar to the results of previous studies. Muir et al. found that gait performance in a single task could not provide a significant distinction between individuals with CI and controls, whereas dual-task testing could provide a significant distinction.[24] Moreover, a meta-analysis showed that some gait parameters could allow the detection of MCI under a gait single task, but also that dual-task assessment significantly increased their discriminative power.[23] Another study indicated that the alternation in gait performance from single task to dual task could effectively discriminate CI.[53] Together, the findings of our study and previous studies suggest that gait dual-task tests could serve as an efficient way to improve the early detection of CI. Moreover, this further emphasizes an anatomical link between gait and cognition.[54]

Owing to the unexpected performance of combining eye tracking and dual tasks, the idea of integrating eye tracking, gait, and dual tasks became worthy of investigation. After combining all three characteristics, the results yielded an AUC of 0.987. Although this still cannot be compared to the prediction results of traditional examinations, such as those involving cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers,[55] it is superior to MMSE and MoCA and provides valuable suggestions for early CI identification. To explain this improvement in diagnostic efficiency, it is important to acknowledge that CI is associated with heterogeneity in various aspects. Consequently, it is highly unlikely that CI can be explained by a single pathological process.[56] Therefore, integrating multiple assessment methods allows for a more comprehensive understanding of the underlying pathology and improves diagnostic potential. Overall, our study is the first to report a connection among eye tracking, gait analysis, and cognitive function. This novel approach of combining eye tracking and gait analysis is likely to represent a significant advancement in diagnostic capabilities and shows promising prospects for clinical applications. In the future, potential anatomical links among the three domains involved will be explored further.

Differentiating between MCI and dementia is also of great importance. Previous studies have shown that the MMSE has limited effectiveness in distinguishing MCI, whereas the MoCA performs slightly better.[57] Because we observed the excellent discriminatory ability of the combined eye tracking, gait analysis, and dual task in differentiating individuals with CI from normal controls, we further explored the effectiveness of this combined approach in distinguishing between individuals with MCI and both controls and individuals with dementia. Both gait patterns and eye movements may serve as potential early markers of dementia. Among the features tested, 3Back-TurnTime and DTC-TurnTime showed positive and negative relationship with p-tau181 levels, respectively. This indicates that these traits are related to the severity of AD. In the future, we will delve deeper into the relationship between these two markers and amyloid, tau, and neurodegeneration (ATN) biomarkers to better understand their discriminatory roles. However, by comparing the results of the dementia and MCI groups, we determined that the combination of these methods was not that effective in distinguishing between patients with MCI and controls, and although there was an increasing trend in accuracy and specificity after integrating more parameters, they remained relatively low. After adding the potential AD marker plasma p-tau181 level, the AUC increased to 0.824, demonstrating a link between the model and AD. Although the results were not ideal, this study provides valuable insights into potential early indicators of CI. Future research efforts should focus on identifying and validating early markers that can contribute to more accurate and timely diagnoses, ultimately improving patient care and management in the early stages of the disease.

Overall, the integration of eye-tracking, gait analysis, and dual-task assessment holds promise for advancing the field of CI detection and may have broad applicability in community-based screening programs.

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CONFLICT OF INTEREST STATEMENT

All authors report no biomedical financial interests or potential conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants provided informed consent.

REFERENCES

1. Mulligan MD, Murphy R, Reddin C, et al. Population attributable fraction of hypertension for dementia: global, regional, and national estimates for 186 countries. *EClinicalMedicine*. 2023;60:102012.
2. Cheung CY, Ran AR, Wang S, et al. A deep learning model for detection of Alzheimer's disease based on retinal photographs: a retrospective, multicentre case-control study. *Lancet Digit Health*. 2022;4:e806-e815.
3. Jia J, Wang F, Wei C, et al. The prevalence of dementia in urban and rural areas of China. *Alzheimers Dement*. 2014;10:1-9.
4. Cao Q, Tan C-C, Xu W, et al. The prevalence of dementia: a systematic review and meta-analysis. *J Alzheimers Dis*. 2020;73:1157-1566.
5. Tábuas-Pereira M, Baldeiras I, Duro D, et al. Prognosis of early-onset vs. late-onset mild cognitive impairment: comparison of conversion rates and its predictors. *Geriatrics (Basel)*. 2016;1:11.
6. Yu J, Li J, Huang X. The Beijing version of the montreal cognitive assessment as a brief screening tool for mild cognitive impairment: a community-based study. *BMC Psychiatry*. 2012;12:156.
7. Huo Z, Lin J, Bat BKK, et al. Diagnostic accuracy of dementia screening tools in the Chinese population: a systematic review and meta-analysis of 167 diagnostic studies. *Age Ageing*. 2021;50:1093-1101.
8. Jia X, Wang Z, Huang F, et al. A comparison of the Mini-Mental State Examination (MMSE) with the Montreal Cognitive Assessment (MoCA) for mild cognitive impairment screening in Chinese middle-aged and older population: a cross-sectional study. *BMC Psychiatry*. 2021;21:485.
9. Maher C, Calia C. The effect of illiteracy on performance in screening tools for dementia: a systematic review and meta-analysis. *Alzheimer Dement*. 2021;17:e049670.
10. Appleman ER, Machizawa S, Chen Z, et al. geo-cultural influence on change in CDR and MMSE scores. *Alzheimer Dement*. 2022;18:e069363.
11. Wilcockson TDW, Mardanbegi D, Xia B, et al. Abnormalities of saccadic eye movements in dementia due to Alzheimer's disease and mild cognitive impairment. *Aging (Albany NY)*. 2019;11:5389-5398.
12. White BJ, Itti L, Munoz DP. Superior colliculus encodes visual saliency during smooth pursuit eye movements. *Eur J Neurosci*. 2019;54:4258-4268.
13. Schröder R, Keidel K, Trautner P, et al. Neural mechanisms of background and velocity effects in smooth pursuit eye movements. *Hum Brain Mapp*. 2023;44:1002-1018.
14. Beltrán J, García-Vázquez MS, Benois-Pineau J, et al. computational techniques for eye movements analysis towards supporting early

diagnosis of Alzheimer's Disease: a review. *Comput Math Methods Med*. 2018;2018:2676409.
15. Boxer AL, Garbutt S, Seeley WW, et al. Saccade abnormalities in autopsy-confirmed frontotemporal lobar degeneration and Alzheimer disease. *Arch Neurol*. 2012;69:509-517.
16. Hallett PE, Lightstone AD. Saccadic eye movements to flashed targets. *Vision Res*. 1976;16:107-114.
17. Mosimann UP, Felblinger J, Ballinari P, et al. Visual exploration behaviour during clock reading in Alzheimer's disease. *Brain*. 2004;127:431-438.
18. Yang Q, Wang T, Su N, et al. Specific saccade deficits in patients with Alzheimer's disease at mild to moderate stage and in patients with amnestic mild cognitive impairment. *Age (Dordr)*. 2013;35:1287-1298.
19. Crawford TJ, Taylor S, Mardanbegi D, et al. the effects of previous error and success in Alzheimer's disease and mild cognitive impairment. *Sci Rep*. 2019;9:20204.
20. Heuer HW, Mirsky JB, Kong EL, et al. Antisaccade task reflects cortical involvement in mild cognitive impairment. *Neurology*. 2013;81:1235-1243.
21. Fletcher WA, Sharpe JA. Smooth pursuit dysfunction in Alzheimer's disease. *Neurology*. 1988;38:272-277.
22. Guimarães V, Sousa I, de Bruin ED, et al. Minding your steps: a cross-sectional pilot study using foot-worn inertial sensors and dual-task gait analysis to assess the cognitive status of older adults with mobility limitations. *BMC Geriatr*. 2023;23:329.
23. Bahureksa L, Najafi B, Saleh A, et al. the impact of mild cognitive impairment on gait and balance: a systematic review and meta-analysis of studies using instrumented assessment. *Gerontology*. 2017;63:67-83.
24. Muir SW, Speechley M, Wells J, et al. Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges across the cognitive spectrum. *Gait Posture*. 2012;35:96-100.
25. Yang Q, Tian C, Tseng B, et al. Gait change in dual task as a behavioral marker to detect mild cognitive impairment in elderly persons: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2020;101:1813-1821.
26. Montero-Odasso MM, Sarquis-Adamson Y, Speechley M, et al. Association of dual-task gait with incident dementia in mild cognitive impairment: results from the gait and brain study. *JAMA Neurol*. 2017;74:857-865.
27. Åhman HB, Giedraitis V, Cedervall Y, et al. Dual-task performance and neurodegeneration: correlations between timed up-and-go dual-task test outcomes and alzheimer's disease cerebrospinal fluid biomarkers. *J Alzheimers Dis*. 2019;71:S75-S83.
28. de Castro Cezar NO, Hotta Ansai J, de Oliveira MPB, et al. Changes in executive function and gait in people with mild cognitive impairment and Alzheimer disease. *Dement Neuropsychol*. 2021;15:60-68.
29. Raichlen DA, Bharadwaj PK, Nguyen LA, et al. Effects of simultaneous cognitive and aerobic exercise training on dual-task walking performance in healthy older adults: results from a pilot randomized controlled trial. *BMC Geriatr*. 2020;20:83.
30. Readman MR, Polden M, Gibbs MC, et al. The potential of naturalistic eye movement tasks in the diagnosis of Alzheimer's disease: a review. *Brain Sci*. 2021;11:1503.
31. Gillain S, Warzee E, Lekeu F, et al. The value of instrumental gait analysis in elderly healthy, MCI or Alzheimer's disease subjects and a comparison with other clinical tests used in single and dual-task conditions. *Ann Phys Rehabil Med*. 2009;52:453-474.
32. Muro-de-la-Herran A, Garcia-Zapirain B, Mendez-Zorrilla A. Gait analysis methods: an overview of wearable and non-wearable systems, highlighting clinical applications. *Sensors (Basel)*. 2014;14:3362-3394.
33. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet Neurol*. 2020;19:422-433.
34. Janelidze S, Mattsson N, Palmqvist S, et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nat Med*. 2020;26:379-386.
35. Petersen RC, Roberts RO, Knopman DS, et al. Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. *Neurology*. 2010;75:889-897.
36. Bell C. DSM-IV: diagnostic and statistical manual of mental disorders. *JAMA*. 1994;272:828-829.
37. Katzman R, Zhang MY, Ouang Ya Q, et al. A Chinese version of the mini-mental state examination; impact of illiteracy in a Shanghai dementia survey. *J Clin Epidemiol*. 1988;41:971-978.
38. Cong L, Ren Y, Wang Y, et al. Mild cognitive impairment among rural-dwelling older adults in China: a community-based study. *Alzheimers Dement*. 2023;19:56-66.
39. Montero-Odasso M, Muir SW, Speechley M. Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. *Arch Phys Med Rehabil*. 2012;93:293-299.
40. Pinto TCC, Machado L, Bulgacov TM, et al. Is the Montreal Cognitive Assessment (MoCA) screening superior to the Mini-Mental State Examination (MMSE) in the detection of mild cognitive impairment (MCI) and Alzheimer's Disease (AD) in the elderly? *Int Psychogeriatr*. 2019;31:491-504.
41. Ciesielska N, Sokołowski R, Mazur E, et al. Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. *Psychiatr Pol*. 2016;50:1039-1052.
42. Haque RU, Pongos AL, Manzanares CM, et al. Deep convolutional neural networks and transfer learning for measuring cognitive impairment using eye-tracking in a distributed tablet-based environment. *IEEE Trans Biomed Eng*. 2021;68:11-18.
43. Tadokoro K, Yamashita T, Fukui Y, et al. Early detection of cognitive decline in mild cognitive impairment and Alzheimer's disease with a novel eye tracking test. *J Neurol Sci*. 2021;427:117529.
44. Liu Z, Yang Z, Gu Y, et al. The effectiveness of eye tracking in the diagnosis of cognitive disorders: a systematic review and meta-analysis. *PLoS One*. 2021;16:e0254059.
45. Gills JL, Bott NT, Madero EN, et al. A short digital eye-tracking assessment predicts cognitive status among adults. *Geroscience*. 2021;43:297-308.
46. 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;32:193-227.
47. Keogh A, Argent R, Anderson A, et al. Assessing the usability of wearable devices to measure gait and physical activity in chronic conditions: a systematic review. *J Neuroeng Rehabil*. 2021;18:138.
48. Weizman Y, Tirosh O, Beh J, et al. Gait assessment using wearable sensor-based devices in people living with dementia: a systematic review. *Int J Environ Res Public Health*. 2021;18:12735.
49. Li H, Zhang J, Zou X, et al. The bidirectional association between cognitive function and gait speed in Chinese older adults: longitudinal observational study. *JMIR Public Health Surveill*. 2023;9:e44274.
50. Jayakody O, Breslin M, Srikanth VK, et al. Gait characteristics and cognitive decline: a longitudinal population-based study. *J Alzheimers Dis*. 2019;71:S5-S14.
51. Chou M-Y, Nishita Y, Nakagawa T, et al. Role of gait speed and grip strength in predicting 10-year cognitive decline among community-dwelling older people. *BMC Geriatr*. 2019;19:186.
52. Darweesh SKL, Licher S, Wolters FJ, et al. Quantitative gait, cognitive decline, and incident dementia: the Rotterdam Study. *Alzheimers Dement*. 2019;15:1264-1273.

53. Lowe DA, MacAulay RK, Szeles DM, et al. Dual-task gait assessment in a clinical sample: implications for improved detection of mild cognitive impairment. *J Gerontol B Psychol Sci Soc Sci*. 2020;75:1372-1381.
54. Day BL, Stephen LR, Balance, Gait, and Falls: Amsterdam Etc, 2018.
55. Palmqvist S, Janelidze S, Quiroz YT, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. *JAMA*. 2020;324:772-781.
56. Ferrari C, Sorbi S. The complexity of Alzheimer's disease: an evolving puzzle. *Physiol Rev*. 2021;101:1047-1081.
57. Roalf DR, Moberg PJ, Xie SX, et al. Comparative accuracies of two common screening instruments for classification of Alzheimer's disease, mild cognitive impairment, and healthy aging. *Alzheimers Dement*. 2013;9:529-537.

SUPPORTING INFORMATION

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

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