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Early indicators of cognitive decline, Alzheimer's disease, and related dementias captured by neurophysiological tools

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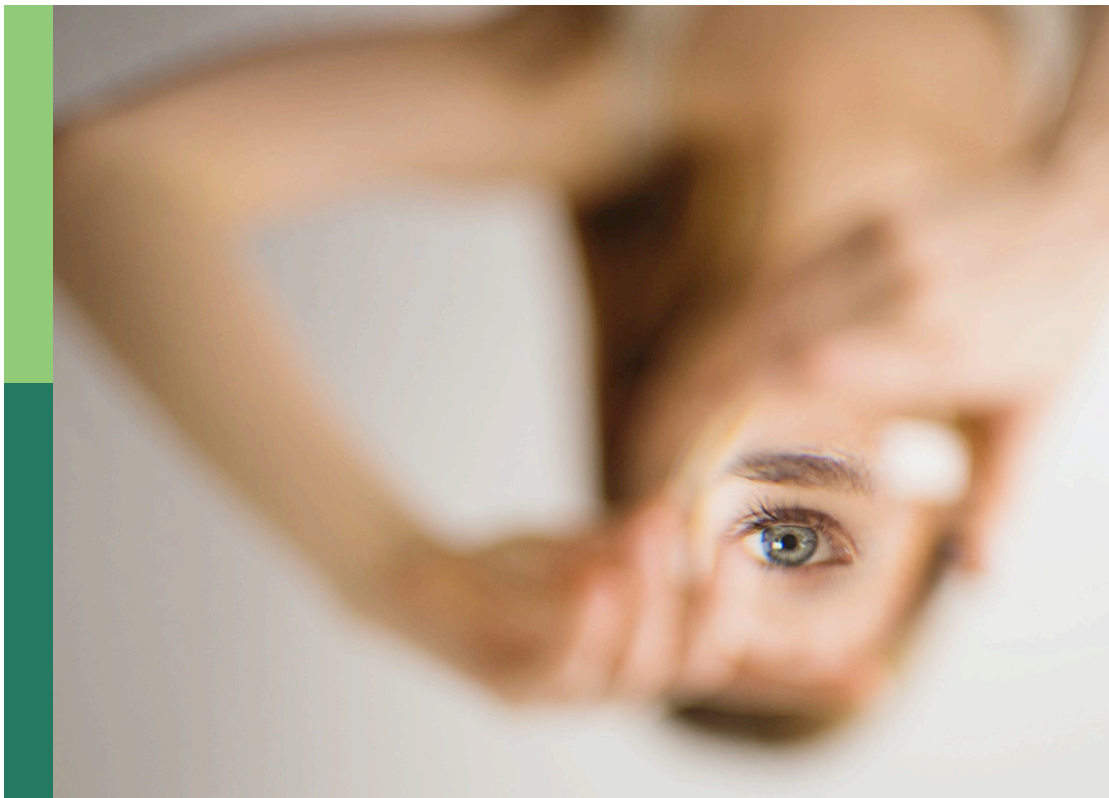

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Early indicators of cognitive decline, Alzheimer's disease, and related dementias captured by neurophysiological tools

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Editorial: Early indicators of cognitive decline, Alzheimer's disease, and related dementias captured by neurophysiological tools

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Editorial on the Research Topic
Early indicators of cognitive decline, Alzheimer's disease, and related dementias captured by neurophysiological tools

Major neurocognitive disorders represent a significant global challenge, impacting a substantial number of individuals and placing emotional and financial strain on caregivers (Werner, 2012; World Health Organization, 2017; Wright and O'Connor, 2018). In response to the imperative requirement for early detection and intervention, the editors of this Research Topic aimed to enhance comprehension of brain integrity, concentrating mainly on biomarker investigations targeting timely identification of the mild cognitive impairment (MCI) stage. As an accelerated cue, traditional diagnostic trajectories for dementia are often initiated with standardized cognitive assessments like the Mini-Mental State Examination and Montreal Cognitive Assessment (Wolf and Ueda, 2021; López-Cuenca et al., 2022; Whelan et al., 2022); yet their limited sensitivity to subtle cognitive impairments has become increasingly pronounced. Furthermore, the influence of pandemic-related lockdowns and lockdown-like measures during conflicts on dementia diagnosis rates cannot be overlooked (Bick and Nelson, 2016; Brown et al., 2020; Tani et al., 2020; Ismail et al., 2021; Corney et al., 2022; Górski et al., 2022). The global disruptions trigger a significant decline in individuals seeking treatment for dementia-related symptoms, resulting in dementia diagnoses falling below anticipated levels (Axenhus et al., 2022; Hazan et al., 2023). This highlights the urgent necessity for innovative yet cost-effective early-stage intervention strategies to adeptly confront the swiftly evolving global challenge (Irazoki et al., 2020; Tokunaga et al., 2021; Braun et al., 2024).

In this context, we recognize the urgency for practical strategies that will bridge subjective evaluations with objective physiological metrics. By presenting insights from 10 original research projects and three reviews, all focused on early indicators of cognitive decline, Alzheimer's disease (AD), and related dementias, our Research Topic holds the potential for significant individual and societal benefits. Synthesizing findings from various specializations (e.g., visual processing, language impairments) and techniques (EEG, eye-tracking, or optical coherence tomography angiography), this work addresses the multifaceted challenges associated with a dementia diagnosis and paves the way for more effective early intervention initiatives.

The study conducted by Ma et al. employed optical coherence tomography angiography to examine retinal vascular changes in AD and MCI. Significantly, their findings suggested that these alterations in retinal microvasculature hold potential as promising biomarkers for AD and MCI. Plaza-Rosales et al., on the other hand, contribute to the nuanced understanding of the visual narrative by examining visual-spatial processing in the initial stages of AD. The investigators employed a spatial navigation task, incorporating comprehensive behavior recordings, EEG, and eye-tracking. This research portends clinical promise for early diagnostic applications, thereby holding considerable importance in enhancing the quality of life for affected individuals and easing the associated healthcare costs. To zoom into the visual integration domain, Elvira-Hurtado et al. enhance the understanding of AD by investigating its continuum with visual implications, revealing the intricate interplay between visual factors and cognitive progression. Compared to a control group, the study assessed visual function differences at different AD stages, i.e., family history group (FH+), mild cognitive impairment (MCI), mild AD, and moderate AD. The results showed a significant decrease in visual acuity, contrast sensitivity, and visual integration scores in MCI, mild AD, and moderate AD groups. Notably, the research group underlined the utility of visual psychophysical tests alongside neuropsychological assessments as valuable tools for early AD diagnosis. Following that, posing that implementing automated electronic reports tailored to clinical needs will ensure swift responsiveness to patient requirements, Huang, Zhang et al. introduce the vestibular cognition assessment system (VCAS). This practical advancement provides a framework for improving visuospatial cognition in individuals with vestibular impairment, portraying VCAS as a potent instrument for comprehending the intricate interplay between spatial memory, navigation, and cognitive proficiency.

Language is intricately linked to brain function, making cognitive impairment a potential cause of language disorders (Baldo et al., 2015; Dronkers et al., 2017; Abe and Otake-Matsuura, 2021). Therefore, shifting readers' attention to language and memory, Kong et al. explore the role of spoken discourse in episodic autobiographical and verbal short-term memory. This linguistic investigation enriches understanding of cognitive functions beyond the visual domain, integrating language into the spectrum of cognitive research. The study highlights the intricate relationship between coherence in personal narrative and episodic autobiographical memory, suggesting potential interventions through conversation. Additionally, the research team identified indices like global coherence, informativeness, and empty speech as potential markers of memory functions in individuals with cognitive impairments. In light of other top-notch projects focusing on the positive effects of conversation-based interventions on cognitive function (Otake-Matsuura et al., 2021; Sugimoto and Otake-Matsuura, 2022; Sugimoto et al., 2023), this project deepens the grasp of how language, memory, and cognition interact and offer valuable insights into cognitive functions on a broader scale. In the foreseeable future, harnessing language processing during extended conversations facilitated by robots could prove pivotal in attaining profound insights into the health of elderly individuals (Kumagai et al., 2022; Figueroa et al., 2023). This forward-thinking strategy represents a transformative stride toward optimizing healthcare for an aging population worldwide.

Expanding on research by Eyamu et al., portable EEG devices show the potential to identify nuanced cognitive abnormalities and brain alterations in MCI patients. Moreover, a recent study by Zheng et al. utilized EEG attributes like spectrum, complexity, and synchronization to aid AD diagnosis, emphasizing EEG's pivotal role in detecting neurological markers across conditions. These findings align with previous research and show that EEG data hold promise in extending early diagnosis and management of cognitive diseases, offering clinicians additional avenues to strengthen diagnostic precision and patient care (Al-Qazzaz et al., 2014; Maestú et al., 2019).

Addressing the challenging differentiation between Alzheimer's dementia and dementia with Lewy bodies (DLB), which typically involves invasive and resource-intensive techniques, Iannaccone et al. demonstrate an original study utilizing quantitative EEG (qEEG) for the early differential diagnosis. The study investigates the sensitivity and specificity of electroencephalography quantified using the statistical pattern recognition method (qEEG-SPR). The outlined technique significantly enriches the diagnostic landscape, offering a non-invasive and cost-effective approach. The findings underscore the efficacy of qEEG-SPR as a sensitive and specific tool for diagnosing dementia and distinguishing DLB from other forms of dementia in the initial stages. Crucially, this procedure holds promise as a tool that could be readily implemented in local care settings, addressing the practical challenges associated with current diagnostic methods and paving the way for improved identification and intervention strategies.

Next, Gil-Peinado et al. offer a comprehensive examination of factors associated with cognitive impairment. The research acknowledges the dynamic nature of mental health factors by integrating an up-to-date analysis standardizing the assessment of psychosocial, clinical, and lifestyle variables. This multifaceted approach advances readers' understanding of cognitive decline and lays a foundation for targeted dementia prevention strategies.

Finally, machine learning, particularly long-short-term memory (LSTM) algorithms, holds considerable promise for analyzing data from older adults and forecasting dementia trajectory. In the work by Huang, Huanget al., LSTM algorithms have successfully predicted the risk of MCI using longitudinal datasets. This screening method not only enables early intervention to delay the progression from MCI to dementia but also holds the potential to reduce the incidence and treatment costs (associated with dementia) in the long term.

In addition to the original works, the narrative of this Research Topic is further complemented by three insightful reviews. Liu et al. evaluate ultra-brief screening tools, enhancing delirium detection rates, particularly in older patients, potentially reducing adverse prognoses. The review searches databases such as the Cochrane Library, PubMed, and EMBASE, employing rigorous assessment tools like the COSMIN checklist and the QUADAS-2 tool to evaluate the diagnostic accuracy of ultra-brief screening tools for delirium. Significantly, the review identifies two instruments, 4 'A's test and UB-2, showcasing exceptional sensitivity in delirium screening. These results offer crucial insights for the early identification of delirium, offering significant relevance within clinical practice while extending scientific guidance to healthcare professionals.

Recognizing the vast challenges of early detection, the review by Wolf et al. discusses the limitations of traditional pen-and-paper tests and explores technological advancements in cognitive scoring methodologies. The review protocol adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, systematically searching electronic databases for peer-reviewed articles, examining visual processing among the MCI population, and reporting gaze parameters as potential biomarkers. While consistent with current trends in remote healthcare technology, the authors also examined studies that used non-commercial eye-tracking hardware to detect information processing problems in elderly people with MCI. In short, this high-quality literature synthesis suggests that eye-tracking-based paradigms can ameliorate screening limitations inherent in traditional cognitive assessments, paving the way for early AD detection.

The final review focuses on chromatic pupillometry, providing a unique viewpoint on particular photoreceptor functions in neurodegenerative diseases. Romagnoli et al. describe the use of chromatic pupillometry as a non-invasive method for assessing melanopsin retinal ganglion cells (mRGCs) in a variety of clinical contexts, including Parkinson's disease, rapid eye movement (REM) sleep behavior disorder, and Alzheimer's disease. The authors suggest that assessing mRGC-system functioning using chromatic pupillometry might serve as an early indicator of malfunction in neurodegenerative conditions characterized by circadian and sleep disturbance, setting the framework for future longitudinal cohort investigations.

In summary, the in-depth exploration of the Research Topic represents a significant step in understanding the subtle details of neurophysiological tools for identifying early signs of cognitive decline, Alzheimer's disease, and related dementias. The collective research articles set a path toward a future where integrating early detection, targeted intervention, and preventive strategies becomes fundamental in longevity research. Such direction holds the potential to revolutionize the approach to cognitive wellbeing, introducing an era where proactive and far-seeing neurophysiological measures redefine the landscape of healthcare and research (Moqri et al., 2023).

Author contributions

AW: Conceptualization, Investigation, Project administration, Supervision, Writing—original draft, Writing—review & editing. KR: Writing—review & editing. ES-G: Writing—review & editing.

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Conflict of interest

KR is employed by Vanaya NeuroLab Brain & Behavior Research Center.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Visual-spatial processing impairment in the occipital-frontal connectivity network at early stages of Alzheimer's disease

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Introduction: Alzheimer's disease (AD) is the leading cause of dementia worldwide, but its pathophysiological phenomena are not fully elucidated. Many neurophysiological markers have been suggested to identify early cognitive impairments of AD. However, the diagnosis of this disease remains a challenge for specialists. In the present cross-sectional study, our objective was to evaluate the manifestations and mechanisms underlying visual-spatial deficits at the early stages of AD.

Methods: We combined behavioral, electroencephalography (EEG), and eye movement recordings during the performance of a spatial navigation task (a virtual version of the Morris Water Maze adapted to humans). Participants (69–88 years old) with amnesic mild cognitive impairment–Clinical Dementia Rating scale (aMCI–CDR 0.5) were selected as probable early AD (eAD) by a neurologist specialized in dementia. All patients included in this study were evaluated at the CDR 0.5 stage but progressed to probable AD during clinical follow-up. An equal number of matching healthy controls (HCs) were evaluated while performing the navigation task. Data were collected at the Department of Neurology of the Clinical Hospital of the Universidad de Chile and the Department of Neuroscience of the Faculty of Universidad de Chile.

Results: Participants with aMCI preceding AD (eAD) showed impaired spatial learning and their visual exploration differed from the control group. eAD group did not clearly prefer regions of interest that could guide solving the task, while controls did. The eAD group showed decreased visual occipital evoked potentials associated with eye fixations, recorded at occipital electrodes. They also showed an alteration of the spatial spread of activity to parietal and frontal regions at the end of the task. The control group presented marked occipital activity in the beta band (15–20 Hz) at early visual processing time. The eAD group showed a reduction in beta band functional connectivity in the prefrontal cortices reflecting poor planning of navigation strategies.

Discussion: We found that EEG signals combined with visual-spatial navigation analysis, yielded early and specific features that may underlie the basis for understanding the loss of functional connectivity in AD. Still, our results are clinically promising for early diagnosis required to improve quality of life and decrease healthcare costs.

KEYWORDS

mild cognitive impairment (MCI), spatial memory, virtual navigation, EEG, eye-tracking, Alzheimer's disease

Introduction

Alzheimer's disease (AD) is the primary cause of dementia and one of the leading sources of social and economic impact worldwide (Tahami Monfared et al., 2022). However, the pathophysiology and mechanisms related to some of the major clinical manifestations of AD remain elusive, as does the development of practical biomarkers to apply at early stages in the course of the disease. AD generates alterations in neuronal connectivity at early stages by damaging neuronal circuits and creating aberrant networks (Sarter and Bruno, 2004), contributing to memory loss and higher-order cognitive dysfunctions due to the neural circuits' disconnection (Dauwels et al., 2010, 2011). Spatial memory loss represents one of the earliest signs of its clinical syndrome (Klimkowicz-Mrowiec et al., 2008; Hamilton et al., 2009; Etchamendy et al., 2012). It has been proposed that AD patients generate, at very early stages, detectable physiological changes during memory encoding processing (Bangen et al., 2012). The core network for navigation is constituted by the hippocampus, parietal, prefrontal, and occipital regions, which are activated in young and elderly controls, but not in AD and Mild Cognitive Impairment (MCI) subjects. This network impairment affects several frontal lobe areas of action planning sequences, including executive functioning, organization, error monitoring, and global response decision-making (Vann et al., 2009; Coughlan et al., 2018; Sneider et al., 2018).

We aimed to identify early behavioral and cerebral activity signs of AD by assessing electroencephalographic features recorded during the performance of patients at early AD (eAD) stages in a hippocampus-dependent, virtual spatial memory task [the Virtual Morris Water Navigation (VMWN)]. We conjectured that fixation-event-related potentials (fERPs) would reflect alterations in the sensory coding needed to perform this task successfully. We found that electroencephalography (EEG) signals, combined with visual-spatial navigation analysis, yielded early and specific features. These characteristics are not only the basis for understanding the loss of functional connectivity in AD; they are also clinically promising for early diagnosis and fall in line with the attributes suggested by health organizations, to improve patient's quality of life and avoid significant healthcare costs (Cummings et al., 2013; Alberdi et al., 2016; Jack et al., 2018).

Materials and methods

Participants

The Scientific and Ethics Committee approved all procedures involving participants of the Clinical Hospital of the Universidad de Chile, Protocol number: 26/2015. A total of 38 individuals were initially recruited for this study. All participants signed informed consent. Participants were classified by a dementia-specialized neurologist blind to the participant's performance in the navigation task. A total of 18 individuals, 9 at the early phase of AD and 9 cognitively healthy controls (HCs) aged 61–88 years, considering a strict criterion of EEG signal quality, were included. A total of 18 participants (11 from the control and 7 from the eAD group) were excluded because of artifactual or technical problems with the EEG recordings, due to the lack of posterior clinical confirmation of AD, or finally, to have an age-matched control group. The exclusion criteria for the eAD group were evidence of non-degenerative dementia (e.g., inflammatory, metabolic, or vascular dementia), non-amnestic MCI or cognitive impairment of doubtful origin, or severe medical conditions that limited their ability to participate in the study. Only the records of those patients who progressed to AD clinical diagnosis were included in the analyzes presented in this study. Control participants underwent the same neurological and neuropsychological evaluations as the eAD group. The demographic data are shown in **Supplementary Table 1**.

Neuropsychological testing

Subject cognitive status was evaluated with the Clinical Dementia Rating scale (CDR) (Morris, 1993), CDR Sum-of-Boxes (CDR-SOB) (O'Bryant et al., 2008), the mini-mental state examination (MMSE) (Llamas-Velasco et al., 2015), the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) validated in our country (Delgado et al., 2019), and the MoCA Memory Index Score (MoCA-MIS) (Julayanont et al., 2014). The maximum score of the MoCA test is 30; a score equal to or greater than 26 is considered normal according to normed and validated scales for its administration; however, the cutoff was lower (<21) in the validation in our population (Delgado et al., 2019). The early stage AD group, hereafter designated as eAD, consisted of patients with cognitive impairment with memory deficits confirmed by an informant. The global CDR in all eAD participants was 0.5; the CDR-SOB was $\geq$ 1.5, and the MoCA-MIS $\leq$ 11, with two or fewer out of five words recalled spontaneously. All eAD participants had a very mild loss of instrumental activities in daily living but did not comply with the diagnosis of dementia.

Behavioral task: Virtual Morris Water Navigation (VMWN) task

Spatial exploration by the eAD and control participants was assessed with the VMWN task, implemented through an open-use

program adjusted under the same parameters described in (Hamilton et al., 2009), and with support provided by its author. The virtual environment simulates the traditional Morris water maze navigation task, consisting of a circular pool inside a room with visual cues on its four walls. By convention in the study, measurements are described in arbitrary units. The room measured 16 units wide and length by 3 units high, while the visual cues measured 3 × 3 units. The circular pool was 3.2 units in diameter, with a perimeter wall of 0.66 units above the pool surface. The square platform was 0.66 units wide and long and extended approximately 0.33 units above the pool surface. This description is the same for both the training and the task, where the only difference is the content of the visual cues (a figure of distinctive design). The virtual task is presented through a computer screen that the user must navigate by pressing keyboard buttons to find a platform hidden under the water. After finishing the task, the program stores the information about the route traveled in the text. The navigation task was divided into three stages. Stage I (Training): this task consisted of finding the hidden underwater platform in a room with visual clues on each of its walls, starting each repetition from a different location. Participants had to reach the platform and had 2 s to turn on the spot and visually explore their position in the environment. The platform became visible after 1 min if the participants did not find it. This training task comprised four trials, keeping the platform in the same hidden position inside the pool. Stage II (Task I): the participants had to find the hidden platform in the same pool based on a different set of visual cues. As in the previous stage, the platform became visible if not found after 1 min. The task comprised 20 trials divided into 4 blocks, allowing rest and eye-tracking recalibration. The platform's location was the same throughout the task, and participants started each repetition from different positions. Stage III (Task II): in an equivalent virtual room with other visual cues, participants had to select between two visible platforms; only one represented the correct option. This task also consisted of 20 trials divided into 4 groups. Both platforms always maintained the same position. The participants started each repetition from a different location in the pool. We used this task to control each participant's visual and psychomotor functioning, making it possible to rule out any deterioration in these parameters as possible explanations for faulty performance in Task I.

EEG recordings and eye-tracking

An EEG system of 32 + 8 channels was used (32 EEG channels, 8 external channels to measure electro-ocular activity, and for referential mastoid recording; BioSemi®).[1] The EEG electrodes were positioned with an elastic cap over the head. EEG activity was continuously acquired during the tasks. The acquired analog signal was filtered between 0 [real direct current (DC)] and 1,000 Hz, sampled at 2,048 Hz, and digitally converted with a precision of 24 bits. The recording system used a specific reference system Common Mode Sense (CMS) active electrode and Driven Right Leg (DRL) (CMS/DRL) that allows information storage. Each participant was placed in a comfortable seat in front of the monitor where the VMWN task was deployed. Their heads were positioned with chin support to minimize movement during the task and to allow optimal detection and recording of eye movements. Eye-tracking was accomplished by employing an Eyelink® 1000 system, which digitizes and stores eye-tracking data in a binary file convertible to text, from which the bi-dimensional position of the pupils was obtained at a frequency of 500 Hz. The system automatically recorded blinks, fixations, and saccades based on user-defined initial parameters. The proximity to the platform was calculated by the software as a rank-sum test for all pixels of the heat map.

Data analysis

All data analyses, including behavioral parameters of space navigation in the VMWN task, electroencephalographic signals, and eye-tracking data, were performed with MATLAB® (The MathWorks, Inc., Natick, MA, USA). The data parsing pipeline was the same for the eAD and control groups. Text files of behavioral tasks were imported and analyzed using custom algorithms. Binary EEG files were imported and preprocessed using the Fieldtrip open-source toolbox. The EYE-EEG MATLAB toolbox was used as a plugin of the EEGLAB package to import, visualize, and verify the detected eye-tracking events and synchronize them with the EEG signals (Delorme and Makeig, 2004).

Sample sizing and analyzed data

We used convenience sampling and recruited data from 38 participants classified by a specialist into control and AD groups under neuropsychological testing and fulfilling different inclusion criteria. Subjects who did not have a recording of adequate quality for EEG analysis were ruled out, including the loss of electrodes necessary for the study and artifacts that significantly affect the signal. Eighteen subjects, nine control, and nine AD subjects, were then analyzed.

For the behavioral data, each subject contributed 20 trials to the analysis. For the ocular data, for each subject, the total number of fixations, and saccades for each trial was calculated for each subject. For electrophysiological analyses, fERP, time-frequency (TF) decomposition, and coherence, nearly 300 epochs for each participant were obtained. Each epoch corresponds to one eye fixation. The initial EEG data matrix was, therefore, made up of a $M \times N \times O$ matrix, where the dimension M is given by the EEG channels (Perrochon and Kemoun, 2014), N by the time points sampled for each epoch of ocular fixation (1,500), and O by the number of epochs of eye fixation throughout the 20 trials of the task (typically close to 3,000 epochs of eye fixation). The eye movement matrix, in turn, consisted of an $M \times N$ matrix for each eye, where M is the time points sampled during the task (1,200,000 points), N is the position variables on the X-axis, on the Y-axis, and acceleration of eye movement. Finally, the motor behavior matrix was made up of an $M \times N$ matrix, where M is the number of temporary samples taken throughout the task (1,200,000 points), and N is the position variables on the X-axis and position on the Y-axis of the navigation environment. Therefore, each of these million-point matrices has been sampled by each subject for the entire set of subjects in each analysis group.

Behavioral analysis

The parameters quantified were: (i) error rate corresponding to the fraction of trials where the participants could not find the platform within the first 60-s, (ii) latency in finding the platform (total time traveled); (iii) travel speed; (iv) length of the route followed to

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reach the platform; (v) resting time, defined as the total period in which participants visually explore the maze environment without moving; and (vi) latency after the platform became visible.

Eye-tracking analysis

We studied ocular parameters in terms of the number, duration, and frequency across trials. Fixations and saccades were automatically identified based on the velocity (30°/s) and acceleration threshold (8,000°/s2). Saccades longer than 5 ms and smaller than 100 ms and fixations between 50 and 800 ms were picked for further processing. In addition, blinks were defined as the absence of pupil data.

EEG analysis

Electroencephalography signals were inspected by a clinical neurophysiologist to evaluate the acquired signals' quality. This procedure allowed the discard of abnormal recordings, including epileptiform activity and abnormal basal rhythms. Then the segments of data were marked for exclusion from the analysis. Offline filter settings were bandpass filter at 1–40 Hz (Butterworth, FIR). Next, artifact elimination was applied using the independent component analyses (ICA) decomposition (fieldtrip toolbox) over the continuous record. Finally, noise components were semi-automated, utilizing algorithms executed in the EYE-EEG package to detect ocular movement-related components.

Eye-tracking signals synchronized with segments of the continuous EEG signal, between −1,000 and 3,000 ms around the ocular fixations, were used. For each trial, we evaluated the first 30 s of recording to avoid variability in each participant's time. Fixation-related epochs were subsequently subjected to analyses in the time and frequency domains: (1) fERPs were computed. For the fERP analysis, a reference correction was calculated by removing the baseline difference between −200 to 0 ms before eye-fixation (onset time). The resulting fERP between groups was compared in terms of amplitude, latency, phase, and scalp distribution, (2) the TF decomposition on the EEG epochs tapered by a sliding Hanning window, using a fixed window length for the frequency range from 1 to 40 Hz in 1 Hz steps between −750 and 1,500 ms, was computed. (3) We implemented a multitaper analysis based on multiplication in the frequency domain, obtaining output power spectra. (4) For each frequency, values of power-spectra were transformed to Z scores, normalizing by the corresponding mean and standard deviation (SD) of pre-stimulus time between −750 and −450 ms. (5) The normalized values for each time, frequency, and electrode between groups were compared. (6) For the amplitude of fERP and the TF charts between groups, a region of interest was defined as O1-Oz-O2 electrodes as the place of maximal amplitude for visual stimuli.

Also, we computed the coherence by performing TF analysis on any time series trial data using the multitaper method, based on conventional Hanning tapers, to obtain the power and the cross-spectral (fieldtrip toolbox). The estimated coherence ranges from 0 to 1, where 0 means that both signals are linearly independent, and 1 means that the frequency components of the signals have a maximum linear correlation. Thus, coherence estimation is a valuable tool for observing and quantifying the synchrony property of two EEG series, mainly when they are limited to particular frequency bands (Dauwels et al., 2010). Coherences for delta (2–4 Hz), theta (4–7 Hz), alpha (7–13 Hz), beta (13–30 Hz), and gamma bands (30–40 Hz) as the mean coherence values of the epochs between 0 and 300 ms, were calculated. The EEG coherence calculation for each electrode pair generates a 14 × 14 (channels selected) matrix showing the connectivity between all possible functional independent brain areas in each frequency band. To estimate whether the changes were primarily related to alteration of short- or long-range coherences reported to be affected in AD progression, the following electrodes were used: (O1, O2, PO3, PO4, CP1, CP2, C3, C4, F3, F4, F7, F8, Fp1, Fp2). Finally, we measured the effect sizes of the beta coherence spectrum (Cohen's d) between groups.

Statistical analyses

Demographics and neuropsychological performance were divided into continuous variables expressed as mean and SD, while the categorical variables were expressed as frequencies (%). Wilcoxon rank-sum test was used for age, education, CDR-SOB, MoCA, MoCA-MIS, and MMSE comparison between groups. A chi-square test was used for gender comparison (Fisher's exact test). Differences in ocular behavior as the frequency of ocular movements (fixations and saccades), were measured using a Wilcoxon rank-sum test between groups. Additionally, we obtained a heat map of the probability of differences and a map of significant differences between the exploration performed by both groups. Finally, we performed a rank-sum test as a statistical approach pixel by pixel on the image at the 0.05 significance level.

Statistical tests based on permutations were applied to evaluate the differences in the oscillatory activity between groups. The Montecarlo method was considered an estimator of the permutation's significance probabilities (two-tailed, alpha: $p < 0.01$, cluster correction, cluster-alpha: $p < 0.05$). Given many comparisons applied by the number of electrodes between groups, we used cluster as a correction method that solves the Multiple Comparison Problem (MCP) (Maris et al., 2007). Moreover, we calculated effect sizes (Cohen's d) as the difference of the means of groups divided by the weighted pooled SDs of the groups. Cohen's d effect size of 0.2–0.3 is a "small" effect, around 0.5 a "medium" effect, and from 0.8 to infinity, a "large" effect. We estimated significant differences in intragroup for the baseline in a beta-band coherence region of interest (15–20 Hz and between 0 and 300 ms) using a statistical threshold criterion of effect size (>0.5) and one-sample t-test (<0.05). A chi-square test for intragroup ratios was applied to this threshold. We processed the data with MATLAB and Fieldtrip toolbox.

Results

The detailed demographic and neuropsychological assessment information is presented in **Supplementary Table 1**. Nine patients diagnosed with eAD, and nine matched control participants were included in this analysis. We found no significant differences in age, sex subgroups, and years of education. Neither were differences in the prevalence of diabetes, hypertension, or tobacco use between groups. In contrast, the MoCA and MoCA-MIS scores of the eAD group were significantly different from the control group (see **Supplementary Table 1**).

Spatial navigation performance

The experimental protocol and the setup are illustrated in Supplementary Figure 1. Representative examples of the trajectories taken by the eAD and the control participants in the VMWN are shown in Figure 1A. Control participants typically learned to find the hidden platform within the first 60 s of the task across trials. The error rate was significantly higher in eAD patients when compared to controls (Wilcoxon Rank sum test, $p < 0.001$) both across trials (Figure 1B) and between the groups along all the trials (Figure 1C). The eAD group displayed higher resting times than the control group. These results may indicate that eAD participants may need more time for visual processing and orientation before moving their position within the maze (Figure 1D). Accordingly, navigation speed was consequently reduced in the eAD group (Figure 1E). The average latency to find the platform also showed differences. For the eAD group, the average latency exceeded 60 s in most trials, indicating that these participants did not encounter the platform before it became visible (Figure 1F). Thus, in the case of the control group, participants found the hidden platform after five trials, while the AD group could never achieve the goal during the 60 s of the task, but they could find the platform once it became visible. Subsequent analyses based on this background consider similar exploratory behavior times for both groups, i.e., the first 30 s. This result suggests that most of the latency displayed by the eAD participants was mainly due to hesitation to execute the navigation task. After the platform became visible at 60 s, significant differences in latency were found only in the first trials, which were no longer significant after the sixth trial (Figure 1G). This result suggests that both groups could adequately execute the basic motor programs necessary for navigation, albeit with a slower improvement over time in the eAD group. Therefore, we can infer that the difficulty in carrying out the initial navigation task in the eAD group was not due to changes in the motor spectrum abilities.

Ocular movement parameters and visual exploring strategies

To explore whether differences in spatial learning could be explained by changes in the ocular behavior of the groups, we compared the number and duration of fixations and saccades made during the task. Given the variation in reaching the platform over time, we calculated the total number of occurrences and their duration in the first 30 s. For fixations and saccades, participants showed no significant differences between groups in frequency and duration, indicating that the differences did not stem from alterations in basic ocular parameters. However, higher dispersion was observed in the eAD group (Supplementary Figure 2).

We obtained a graphical representation of the distributions of ocular fixations by group using heat maps. Eye fixations in the control group were focused on a central region located at the representation of the water where the platform should be hidden (Figure 2A). Instead, in the eAD group, visual scanning was much more heterogeneous, with no clear preference (Figure 2B). We calculated absolute differences in the visual exploration between the groups, finding that although both groups visually scanned the center of the image in contrast to the periphery, the main differences were observed in the intermediate image region. Notably, the control group preferred to fix the central area, where the platform could be placed. In contrast, the eAD group focused on the upper midline without a defined focus on the target platform (Figure 2C).

In addition, we performed a pixel-by-pixel comparison of the visual scan of the groups. We used level curves for the eye fixation heat maps with the normalized values. Furthermore, we applied a rank-sum test for all pixels of the heat map to obtain a probability of differences. This result highlights the lower central region with statistical differences, which could correspond to an area close to the hidden platform (Figure 2D). We analyzed the distribution to confirm that the visual scanning behavior of participants with eAD differs from controls who fixate more on a specific position. Eye fixation frequency distribution revealed a significant difference between groups (K–S test; $D = 0.11$, $p = 0.001$). The eAD group had more eye fixations over the middle line relative to controls (Figure 2E). These results confirm that both groups differ behaviorally in their visual exploration, reflecting their ability to process visual information.

Fixation event-related potentials (fERPs)

We explored early neuronal responses of the visual cortex elicited during each visual fixation performed along the task. This ERP reflects the visual processing that is putatively needed to properly extract the visual characteristics of the environment to complete the task. Thus, it was chosen as an integrity marker of cortical signals to differentiate between the eAD and control groups. fERP signals were computed as the average activity at the onset of fixations during the first 30 s of each trial (with 800–1,200 occurrences across the 20 trials).

We found a lower amplitude of occipital fERP signals in eAD participants compared to the control group, as shown in Figure 3A. Significant differences were observed in the period that preceded the fixation onset, including but not limited to the preceding saccade, meaning that the influence of the prior motor behavior was differentially observed in both groups. Another significant difference was observed between 0 and 200 ms from the onset of visual fixations, demonstrating that the early visual activity during each visual fixation displays a larger magnitude in controls than in eAD participants. We also found differences in the amplitude of potentials after the P100 component. Because brain signals have reached extra striate association cortices at these latencies, we examined the scalp distribution of fixational evoked potentials at different latencies to determine whether there were differences in the propagation of the electrical dipole (Figure 3B). In the control group, we observed an early activation of the occipital cortex compatible with the arrival of the visual input at 60 ms, then a maximum response near 100 ms, and finally, the frontal propagation occurring at about 135 ms. Remarkably, there was a shallow spreading of occipital activity to parietal and frontoparietal regions at later times in the eAD group compared to that observed in the control group, with a clear occipitofrontal dipole. These spatial differences suggest that visual processing differs between eAD and HCs at early visual cortices and higher spatial association cortical areas.

Time-frequency analysis

We performed a power spectra analysis to identify differences in the frequency band. The TF decomposition was achieved by

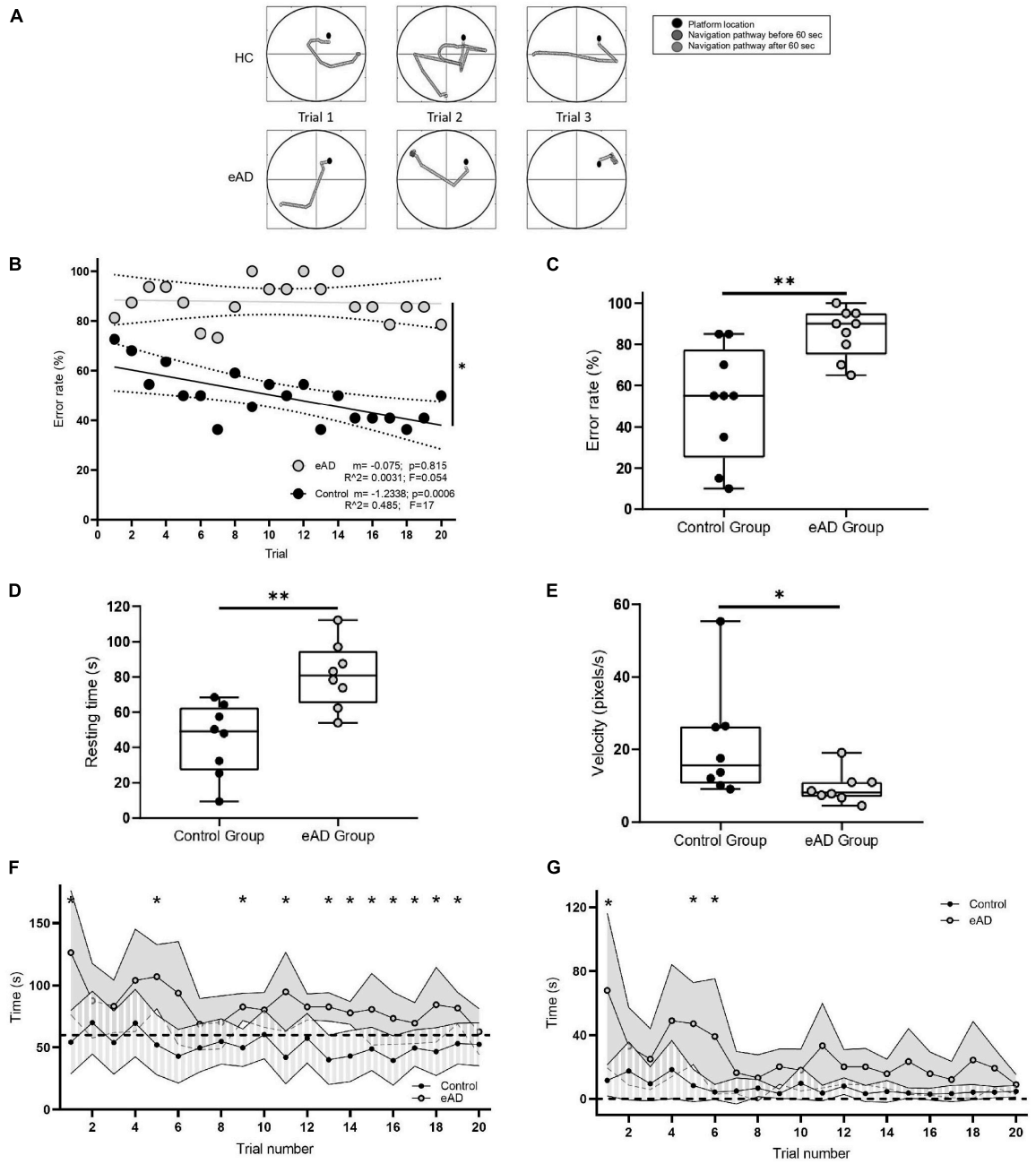

FIGURE 1
Navigation performance. **(A)** Examples of navigation paths to find the platform during the performance of the Virtual Morris Water Navigation (VMWN) memory task for the early Alzheimer's disease (eAD) and the healthy control (HC) groups in three different trials. Trajectories when the platform was hidden (dark gray) and when the platform became visible after 60 s of navigation (light gray). **(B)** Multiple learning linear regression analysis for the control and eAD groups. The decrease in the error rate was significantly different between both groups [multiple lineal regression (MLR), F (1, 36) = 7.072, p = 0.0116]. **(C)** Error rate. Percentage of participants who could not find the platform. For panels **(C–E)**, the box-whisker plot represents the median error rate of the nine participants in the 20 trials for each group, and the statistical significance, determined by the Mann–Whitney test (*$p < 0.05$, **$p < 0.01$). **(D)** Average resting time in which the participants in each group were not performing movements. **(E)** The speed at which the participants moved to the supposed position of the hidden platform. **(F)** Time spent to reach the platform in each of the 20 trials. Dashed line: 60 s–limit to fail (Wilcoxon rank-sum test, *$p < 0.05$). **(G)** Time spent by the participants to reach the platform after it became visible. Dashed line: time 0–the moment when the platform becomes visible (60 s after the initiation of the original trial). Points joined by the continuous line represent the mean per group, and for each group, the variance is also plotted. The eAD group showed a latency greater than the HC at the beginning of the test (Sidak corrected, *$p < 0.05$). **(B–F)** Gray: eAD participants (n = 9); black: HC participants (n = 9).

generating epochs in the signal associated with the eye fixation and taking a baseline of −750 to −450 ms. Two examples of TF maps for each group are shown in Supplementary Figure 3. Both the control and the eAD group showed a marked predominance of activity for the Oz channel in the low-frequency spectrum, particularly in theta and alpha bands, but also an activity relevant in the beta band that went only recognized in the control group (Figures 4A, B).

A two-tailed non-parametric cluster-based permutation test for the Oz channel was performed to test for differences in the power between the groups. This test considered the TF data from −250 ms

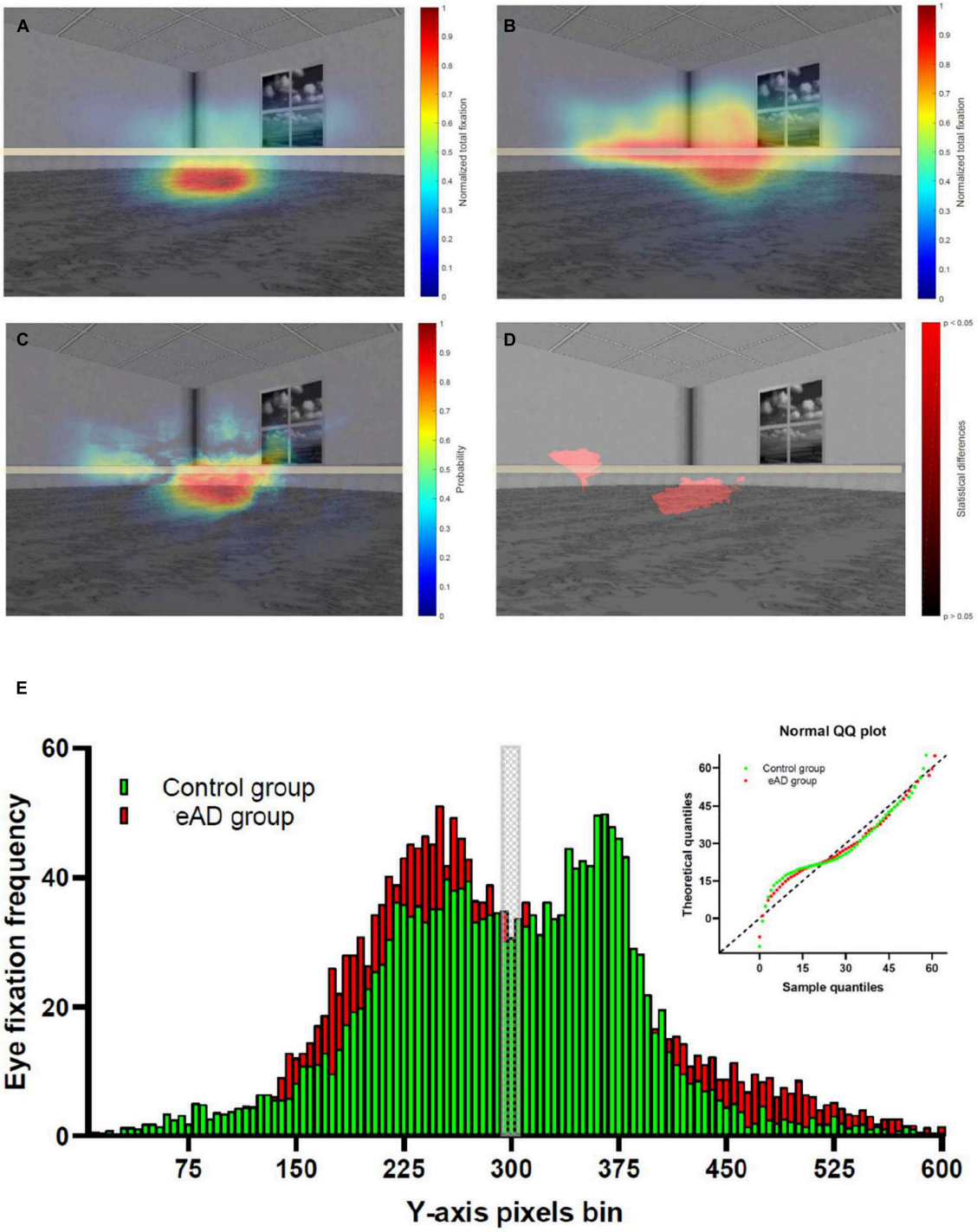

FIGURE 2
Heat map of the spatial distribution of eye-fixation of the control and early Alzheimer's disease (eAD) group. **(A)** Heat map of eye-fixation of the control group, with high fixation density in the center. **(B)** Heat map of eye fixation of the eAD group demonstrated a less localized exploration. Warmer colors represent a higher number of fixations. **(C)** Heat map of the probability differences in the visual exploration. Warmer colors represent a higher probability and in panel **(D)** regions with statistical differences in visual exploration between control and eAD group. The red path represents statistical differences (Wilcoxon rank-sum test, $p < 0.05$). The horizontal gray line represents the central region of the image. **(E)** Comparison eye fixation frequency distribution in *Y*-axis pixels bin between control and eAD group, Kolmogorov–Smirnov test comparison cumulative fixation fraction (K–S test; $D = 0.11$, $p = 0.0014$). The gray block represents the central region of the image, while control group and eAD group results are represented in green and red, respectively.

to 600 ms, which means that we include the window to involve the visual event and its early cognitive processing, and this is for a frequency range that considers low frequencies 2–25 Hz. A Monte Carlo estimate of the permutation *p*-value was computed by randomly permuting condition labels ($N = 1{,}000$). We observed significant differences in the beta band between 15 and 18 Hz for the first 250 ms post-fixation and the same effect between 17 and 20 Hz for the 250– 600 ms post-fixation (Figure 4C). Additionally,

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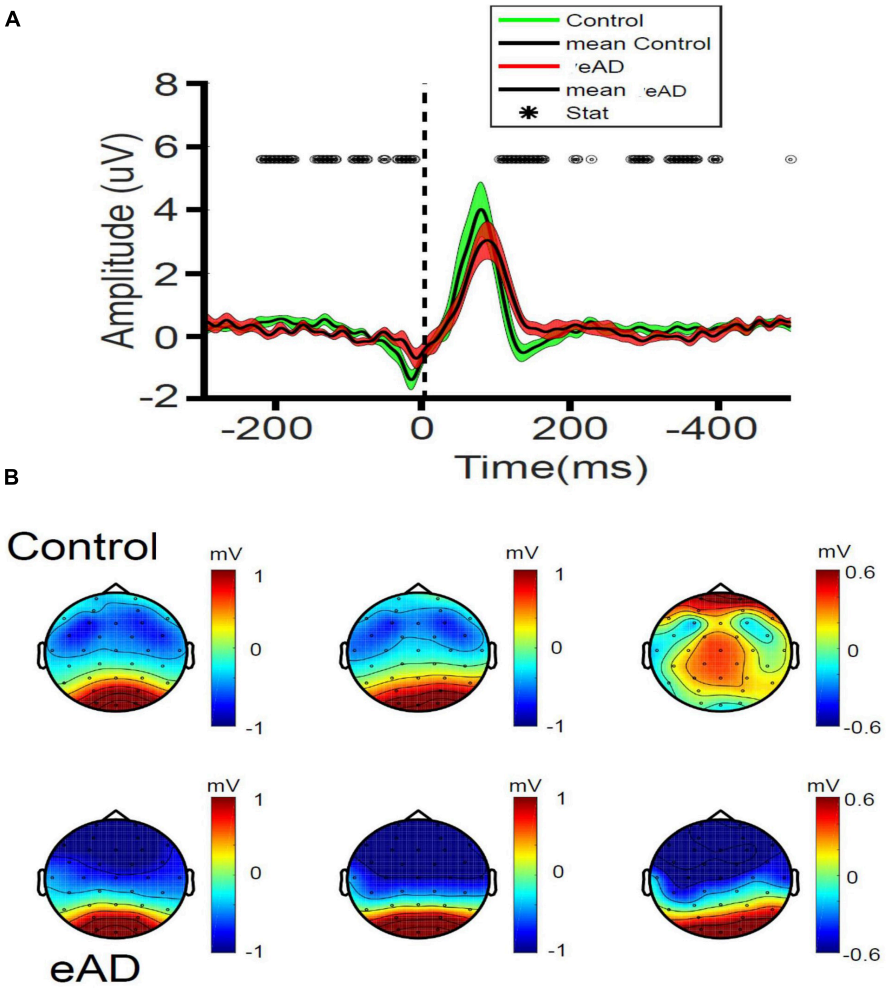

FIGURE 3
Fixation related potentials (RPs) recorded in early Alzheimer's disease (eAD) and control participants. **(A)** Amplitude of the occipital potentials (mean of O1, O2, and Oz channels). The central black line represents the mean, and the colored shade the variance. For each curve, time 0 represents the onset of visual fixation. Statistical differences in time are indicated as black open circles at the top (Wilcoxon test, $^*p < 0.05$). For panels **(A,B)**, red represents eAD patients ($n = 9$); and green, elderly controls ($n = 9$). **(B)** Scalp topographic maps of fixational-event RPs (fERPs) recorded at 60, 100, and 135 ms post-fixation. 2-D spatial color maps of voltage scalp distributions of fERP (in μV), from negative (blue) to positive voltages (red), at different latencies after the onset of fixation, are shown. Almost no spreading of the occipital dipole to parietal or frontoparietal regions is observed at later latencies in the eAD group compared to the control group.

the power difference (control–eAD) is shown in a topographic map for the beta frequency band, within the range of 15–20 Hz in the time interval between 0 and 200 ms (Figure 4D). This difference could be associated with difficulties in spatial navigation when the reactivation of memories is necessary to find the platform using visual cues.

Functional connectivity analysis

We applied a pairwise electrode coherence analysis for the eAD and control groups in the frequency beta-band. These pairwise electrodes were principally related to the frontoparietal activity, whose functions are widely associated with working memory and are particularly relevant to visual working memory and visual attention. Evidence suggests that the activity of this component correlates with visual processing. The mean coherence between 14 channels of eAD and the control group in the beta frequency (15–20 Hz) showed in Figures 5A, B. We calculated the connectivity matrices with the baseline correction from −750 to −450 ms and the *p*-value matrix (one-sample *t*-test between groups). We found significant uncorrected differences in coherence distributed in frontal and frontoparietal areas for the beta band. We estimated the effect size (Cohen's *d*) for the coherence spectrum in the frontoparietal-occipital axis to understand the impact of these results (Supplementary Figures 4A–D).

Only the high values of Cohen's *d* were used in a topographic map highlighting which areas could impact the participants' behavioral performance (Figure 5C). We found that most of the changes in eAD coherence were essentially frontoparietal and that less activation or synchronization in the prefrontal cortices will account for poorer spatial navigation. In addition, we created a binary connectivity matrix, where the threshold represents a combination of previously calculated values in the beta frequency band; an effect size (>0.5), and the *P*-value matrix for the one-sample *t*-test (<0.05). The scale represents significant coherence differences from the baseline in black color. The statistical analysis results of the intragroup coherence for the control connectivity matrix show many pairwise comparisons

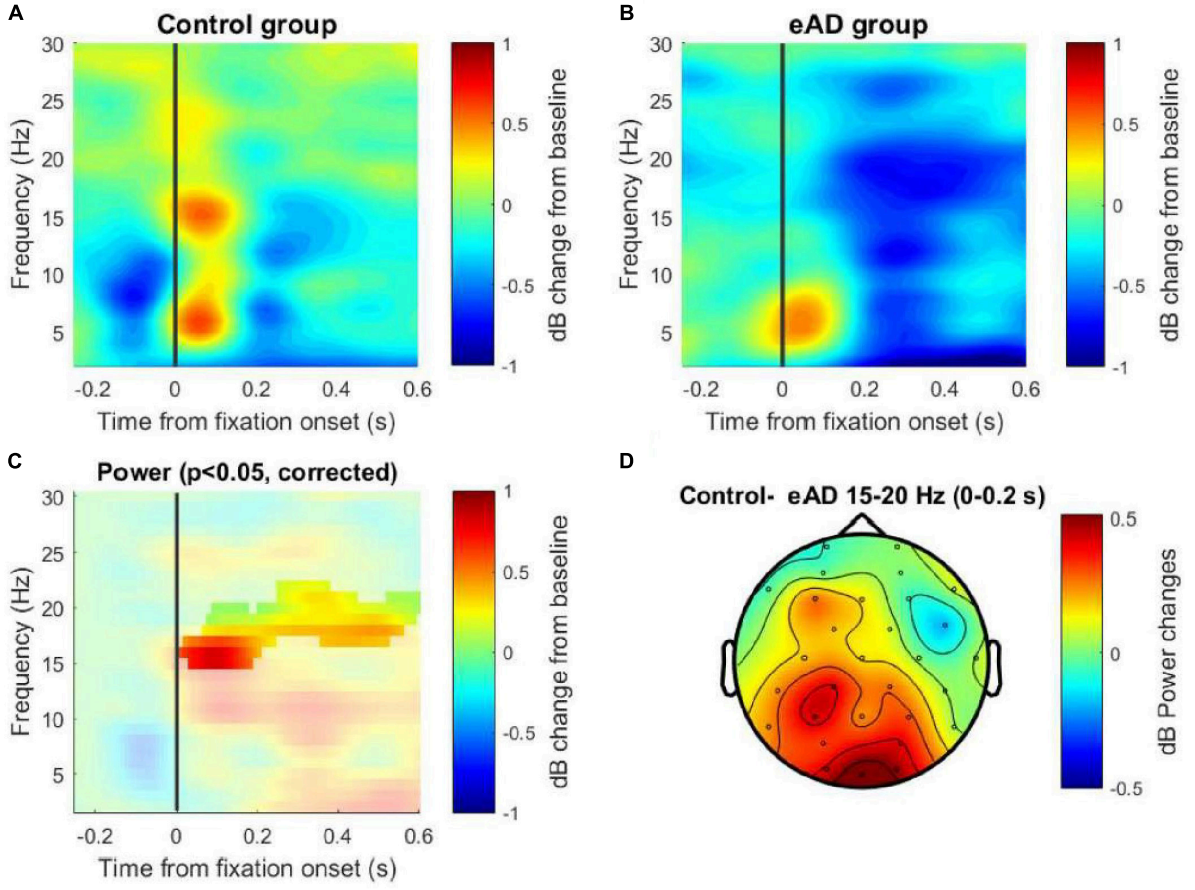

FIGURE 4
Time-frequency (TF) maps of the Oz channel. **(A)** Power spectral decomposition of the electroencephalography (EEG) data for the control group and **(B)** for the early Alzheimer's disease (eAD) group. **(C)** Cluster-based permutation test on TF activity of the Oz channel. The analysis considered 1,000 permutations to determine the cut-off alpha = 0.025, to two tails, resulting in significant differences in the beta band between 15 and 20 Hz. **(D)** Topographical map from the differences in power data averaged. The solid line (vertical line) represents the zero time at the beginning of the eye fixation. The color scale represents the percentage of change relative to the baseline period of −750 to −450 ms and normalized in decibels.

with significant differences (Figure 5D). The eAD matrix shows only one electrode pair with significant brain activity changes (Figure 5E). Finally, we show the topographic distribution of electrode pairs with significant coherence differences from baseline time by groups (Figure 5F). Based on these results, we suggest that long- and short-distance synchrony exhibits a higher degree of coherence differences in the frontoparietal region of the brain. That could affect less effective planning of navigation routes since this region is critical for executive functions, including planning, organization, error monitoring, and decision-making.

Discussion

Despite the vast progress in recent years in the study of AD, the principal mechanisms involved in cognitive deficits still need to be clarified. This study compared behavioral performance, ocular behavior, and functional connectivity in control vs. eAD subjects in a sensitive early detection test of cognitive impairment (Laczó et al., 2011; Weniger et al., 2011; Gazova et al., 2012, 2013; Tarnanas et al., 2015). Our results showed significant differences between groups in the prefrontal area in beta-band coherence, a consequence of less effective planning of navigation strategies.

Early Alzheimer's disease and spatial navigation in the virtual maze

Patients with a diagnosis of eAD performed significantly worse in the VMWN task than the control group, as they did also in all the behavioral aspects evaluated in this work. Although differences in speed were observed between the two groups, we attribute the worse performance of AD patients in the spatial navigation task to memory problems and how they use visual cues to find the platform. Performance of AD participants had more erratic trajectories and longer reaction times before initiating spatial navigation strategies in AD participants. Moreover, the results presented in Figure 1G show that their latency to find the platform after it became visible was not different from control subjects, which supports the idea that it is not a locomotor problem for the AD subjects managing to execute basic motor navigation programs. This lower latency time could be related to the increased speed of response in searching the platform. These results reaffirm that a deficit in space coding used for navigation learning is an early disease feature. In support of our findings, recent studies have used virtual tools to indicate that the performance of participants at high risk of developing AD is worse than that of the control groups (Gazova et al., 2012; Laczó et al., 2012; Tarnanas et al., 2012, 2015; Vlček and Laczó, 2014), as is reported in a study that has

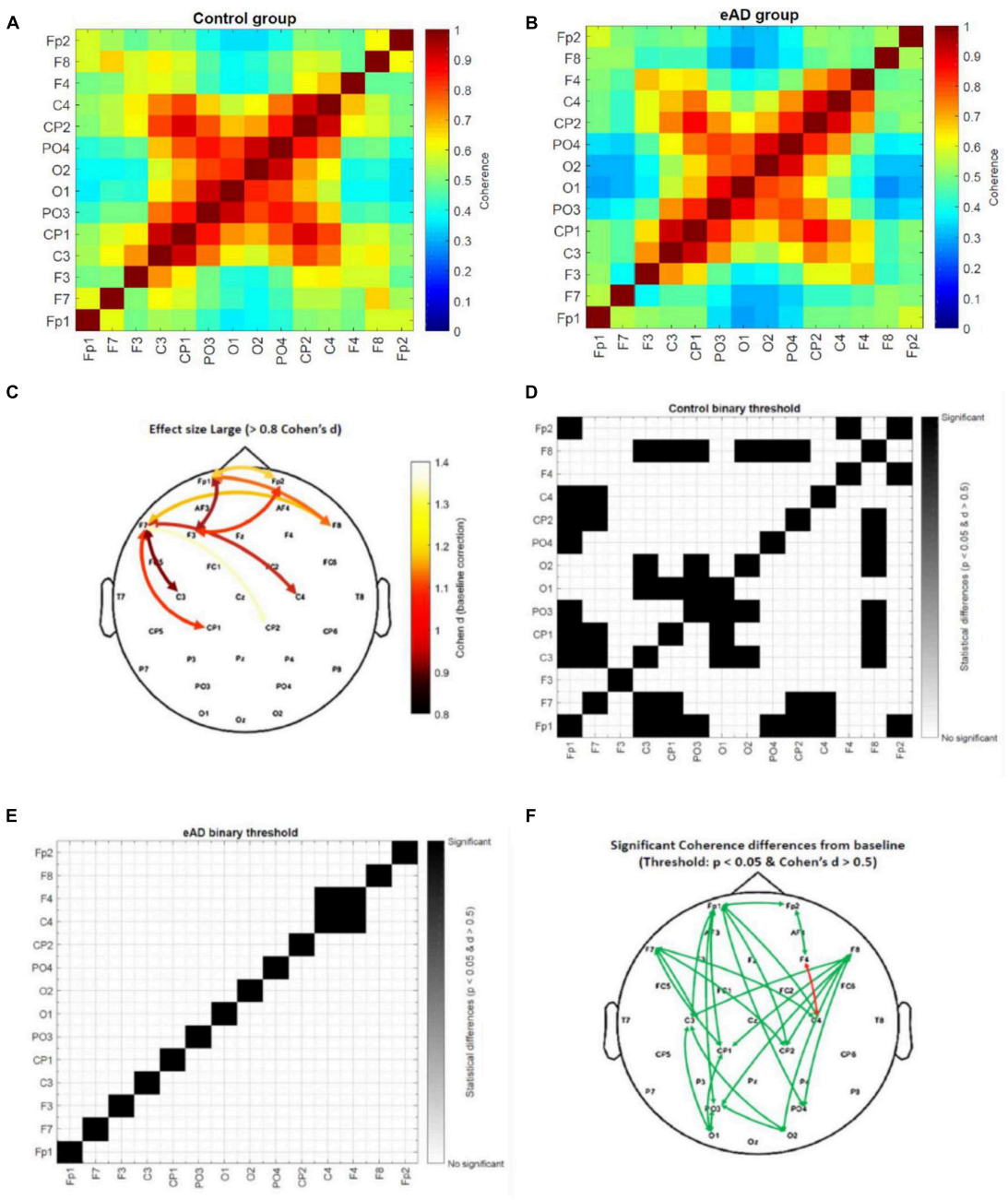

FIGURE 5
Coherence beta (15–20 Hz) connectivity matrices from 0 to 300 ms. **(A)** Absolute coherence matrix for the control group, and **(B)** early Alzheimer's disease (eAD) group. The color scale represents low coherence in blue and high coherence in red between a pair of electrodes. **(C)** Topographic distribution of electrode pairs with large value effect size (>0.8 Cohen's *d* statistic). Threshold value matrix. **(D)** Matrix of control group and **(E)** matrix of eAD group. The color scale represents significant coherence differences for the baseline time (−750 to −450 ms) in black. In white, there is no difference in baseline time for the activity of the electrode pair, using as a threshold the $p < 0.05$ and Cohen's *d* statistic > 0.5. **(F)** Topographic distribution of electrode pairs with significant coherence differences from baseline time by groups. The green arrow represents the control group, and the red arrow the eAD group.

patients walk through a real maze (Benke et al., 2014). Our results strongly suggest that a virtual task based on spatial labyrinths may constitute a practical and sensitive tool for eAD detection.

Analyzing the different aspects recorded during navigation, eAD participants displayed some well-marked characteristics: (i) lower orientation capacity, estimated from a higher latency in finding the platform, higher error rates, and lower travel speeds. (ii) Lower capacity for spatial learning, evidenced by the lack of an improvement in the error rate throughout the repetitions of the task, a capability observed in the control group. (iii) Reduced avidity to find the platform, manifested as shorter average run lengths and slower speed, elicited after the platform appeared in the scene. In other studies comparing healthy-elderly people to participants with MCI, these features were also detected (Perrochon and Kemoun, 2014; Vlček and Laczó, 2014; Tarnanas et al., 2015).

It is worth noting that evidence indicates gender differences in spatial memory. Men perform better than women in spatial navigation tasks, and they also travel longer distances without making

course changes, pause less often, and return less to previously visited places (Munion et al., 2019). Differences in performance in navigation tasks could be explained by the fact that they produce different way finding behaviors. Nevertheless, considering that AD affects both men and women and that our data have shown no significant differences between the number of them in the groups, we decided to analyze the overall group performance.

Ocular behavior in early Alzheimer's disease

Early AD patients performed significantly different exploration strategies to reach the visual keys in the task. These findings reassert an increased instability in fixations, enhanced latency of voluntary exits, the erratic direction of microsaccades, a higher number of anti-saccadic errors, and decreased correction of this anti-saccadic error in AD participants (Anderson and MacAskill, 2013; Kapoula et al., 2014). The eye fixations of the control group focused on task-relevant objects (visual keys and possible platform location). Instead, in the eAD group, the visual exploration was more heterogeneous on the image and without a clear preference for regions of interest that could guide solving the task. All these deficits might represent an early manifestation of AD impairments in executive functions and visual parameters such as visuospatial skills, processing, and selective visual attention (Chehrehnegar et al., 2020). Furthermore, the participants with eAD had more eye fixations over the middle line and less on the bottom relative to controls. This difference can be due to attention deficiencies and the involvement of prefrontal networks and visual attention (Belleville et al., 2008).

Early electrophysiological features of spatial navigation in Alzheimer's disease

We found a significantly lower amplitude of the P100 component in eAD participants. These results differ from other studies measuring classical evoked potentials (not fERP), in which there are usually no differences in such components as the P100 (Quiroz et al., 2011). Our results also differ from another study that did not detect a decrease in the P100 amplitude in very mild AD. However, the participants in that study did not have any executive function requirements (Cheng and Pai, 2010). In another study, a virtual exploration model showed significant differences in late components of the classical ERP in patients with amnestic cognitive impairment associated with non-visual events (Tarnanas et al., 2015). The appearance of such early differences in the ERP associated with fixation is difficult to attribute to the learning of the task at the hippocampus level but instead to an altered visual-executive system of the participants with eAD that prevents their optimal processing in the early stages of visual processing. This finding has implications for the entorhinal cortex and hippocampal activity and, thus, for the consolidation and retrieval of sensory information. In agreement with this hypothesis, a study that evaluated ERP variables in a visual exercise demonstrated that those AD participants who had disturbances in the resting state, in turn, presented lower amplitudes of ERP (Tartaglione et al., 2012). There are, therefore, detectable electrophysiological features recorded with surface EEG during space exploration in participants with eAD.

Prefrontal beta-band coherence and its role in eAD

Our spectral power analysis through the TF maps presented differences in activity in the theta frequency ranges, alpha, and significantly in the beta band (15–20 Hz), confirmed by the analysis of cluster-based permutations tests. These results are consistent with a study that reported increases in the theta band and decreases in the alpha and beta-band in AD patients (Aghajani et al., 2013). Other studies even attributed the reduction in the alpha band and reduced beta power in the parietal and occipital regions as a differentiating factor between normal aging, MCI, and AD (Jeong, 2004; Kwak, 2006; Rossini et al., 2006; Babiloni et al., 2011; Ruiz-Gómez et al., 2018; Li et al., 2019). The beta-band was related to memory processes in our study, and their decrease in the eAD group could be associated with difficulties in spatial navigation when the reactivation of memories is necessary to find the platform by visual cues (Guran et al., 2019).

Although a single process could not entirely explain beta oscillations, its role in the interneural communication of inhibitory networks and high executive demands has been ascribed (Guevara et al., 2018; Hou et al., 2018). Synchronization, instead, might be involved in sensory processing (Singer, 1993; Hou et al., 2018). Our results showed a reduction in beta band functional connectivity in the eAD group in the prefrontal cortices. Both alpha and beta frequencies are associated with many functions representing downstream influences. However, beta oscillations are crucial for long-distance communication between cortical regions, maintaining a constant update of the state of the brain (Guran et al., 2019).

Our results, as well as previous studies, showed that selective visual attention is sensitive in eAD. Additionally, the prefrontal cortex (PFC) could be involved in associative learning in navigation and changing strategies and might be engaged in processes to search for specific objectives, such as selecting the best route or trajectories in space navigation processes (Zhong and Moffat, 2018). Besides, disconnections between brain regions playing an essential role in cognitive impairment in AD, with reduced synchrony as a marker, were described (Delbeuck et al., 2007; Wang et al., 2014; Engels et al., 2016; Tait et al., 2019). Some studies have proposed activating the right PFC during spatial working memory (WM) tasks in young adults. In contrast, older adults presented bilateral activation of PFC as a compensatory response to cognitive impairment. Likewise, healthy older adults also showed bilateral hyperactivation of the frontal cortex during a particular memory task (such as coding complex visual scenes). During the progression from MCI to AD, it has been proposed that the disintegration of compensatory networks occurs due to the lack of activity observed in the lateral regions of the prefrontal cortex (PFC), precuneus, and posterior parietal cortex. These regions are all involved in the executive function compared to controls (Clément et al., 2013; Kirova et al., 2015). These findings are consistent with our proposal that the symptoms observed in patients with eAD are closely related to a loss of functional connectivity, reflected by physiological changes and an attenuation of the electrical activity (Babiloni et al., 2010; Wang et al., 2014; Engels et al., 2016; Blinowska et al., 2017).

It is interesting to note that recent studies have shown that the brain undergoes significant structural and functional changes at older ages, and neurodegenerative processes can accelerate these changes. Many of these functional changes are found in the PFC as a compensatory response to the processes of cognitive scaffolding, enhancing activity in these areas *via* the recruitment of additional

regions or networks (Ferreira and Busatto, 2013; Sala-Llonch et al., 2015). This occipitofrontal desynchronization in subjects with AD is part of this compensatory mechanism rather than just a poor visual-spatial ability during navigation tasks. Although our results are task-dependent, we suppose that with additional resting-state studies, it is possible to show similar patterns of functional brain connectivity in subjects with AD.

As we conjectured, spatial navigation impairments can be associated with early mechanisms of cognitive deterioration in the progression to AD. This task joints the functions of the occipital, parietal, and frontal cortices. We already know that navigation abilities depend on the occipital cortices for the early processing of visual information and the parietal and hippocampal cortices for the generation of the cognitive map and egocentric/allocentric navigation strategies. At the same time, the frontal cortex is relevant for deciding, developing, and planning actions (Vann et al., 2009). A study by Coughlan et al. (2018) showed that morphological changes (in particular, the accumulation of Aβ in the cerebral cortex) follow a typical course of progression, which coincides with the structures involved in spatial navigation. Thus, the spatial navigation impairments are consistent with the loss of cognitive skills and less functional connectivity in eAD (Pai and Jacobs, 2004; Klimkowicz-Mrowiec et al., 2008; Hamilton et al., 2009; Etchamendy et al., 2012; Alberdi et al., 2016; Tait et al., 2019). In summary, we propose an operational model whose functionality depends on the structural integrity but further on the functional connectivity generated.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Clinical Hospital of the Universidad de Chile, Protocol number: 26/2015. The patients/participants provided their written informed consent to participate in this study.

Author contributions

IP-R, EB, AP-L, and PM: conceptualization and funding acquisition. IP-R, EB, and PM: methodology. IP-R, RM-S, and SM: formal analysis. IP-R, RM-S, SM, EB, MB, AP-L, and PM: investigation and writing—review and editing. IP-R: writing—original draft and visualization. PM: supervision. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Vestibular cognition assessment system: Tablet-based computerized visuospatial abilities test battery

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Introduction: The vestibular system is anatomically connected to extensive regions of the cerebral cortex, hippocampus, and amygdala. However, studies focusing on the impact of vestibular impairment on visuospatial cognition ability are limited. This study aimed to develop a mobile tablet-based vestibular cognitive assessment system (VCAS), enhance the dynamic and three-dimensional (3D) nature of the test conditions, and comprehensively evaluate the visuospatial cognitive ability of patients with vestibular dysfunction.

Materials and methods: First, the VCAS assessment dimensions (spatial memory, spatial navigation, and mental rotation) and test content (weeding, maze, card rotation, and 3D driving tests) were determined based on expert interviews. Second, VCAS was developed based on Unity3D, using the C# language and ILruntime hot update framework development technology, combined with the A* algorithm, prime tree algorithm, and dynamic route rendering. Further, the online test was built using relevant game business logic. Finally, healthy controls (HC) and 78 patients with vertigo (VP) were recruited for the VCAS test. The validity of VCAS was verified using the test results of random controls.

Results: In the weeding test, the HC group had a significantly longer span and faster velocity backward than did the VP group. In the 12 × 12 maze, statistically significant differences in step and time were observed between the two groups, with VP taking longer time and more steps. In the mental rotation task, no significant difference was observed between the two groups. Similarly, no significant difference was found in the performance of the two groups on maps 2, 3, and 4 in the 3D driving task.

Discussion: Thus, impaired visuospatial cognition in patients with vestibular dysfunction is primarily related to spatial memory and navigation. VCAS is a clinically applicable visuospatial cognitive ability test for VP.

KEYWORDS

vestibular dysfunction, visuospatial cognition, cognition, tablet-based test, computerized system

1. Introduction

The vestibular system consists of three semicircular canals and two otolithic organs (the utricle and balloon), all of which contribute to movement stability. Specifically, the vestibulo-ocular reflex maintains clear vision, while the vestibulo-spinal reflex maintains body stability and postural balance during exercise. The vestibular system is anatomically connected to vast regions of the cerebral cortex, hippocampus, and amygdala. The vestibulo-thalamo-cortical pathway transmits spatial information from the vestibular system through the parietal and entorhinal cortices to the hippocampus (Shinder and Taube, 2010; Hitier et al., 2014). Thus, reduced vestibular input could impair these cognitive and affective circuits. Studies have demonstrated that patients with vestibular diseases exhibit cognitive deficits, such as object recognition and memory. Several researchers have conducted cross-sectional studies of the National Health Interview Survey in 2012 and found a corresponding association between vertigo, cognition, and mental illness (Bigelow et al., 2020). In contrast to healthy controls (HC), people with vertigo were three times more likely to have difficulty with mood, concentration, or behavior. Furthermore, patients with vertigo (VP) often have comorbid disorders, such as mental disorders, fatigue, and sleep disorders. However, studies have discovered that short-term memory impairment in VP can occur independently of these disorders (Smith et al., 2019). Despite the various dimensions of cognitive impairment in patients with vestibular dysfunction, research has primarily focused on visuospatial ability and memory, particularly spatial memory, and navigation ability aspects (Bigelow and Agrawal, 2015; Bigelow et al., 2015).

This study used the most available clinical test questionnaires, namely, the dizziness handicap inventory, the vertigo symptom scale, and the vestibular activities and participation. The questionnaires primarily assess the functional, emotional, and physical impacts of vertigo on patients' daily life, which rarely involve the cognitive dysfunction caused by vertigo (Lacroix et al., 2016). Therefore, cognitive evaluation tools in neuroscience are predominately used to evaluate cognitive function in patients with vestibular dysfunction. Some multi-dimensional testing tools focus on language and memory ability, such as the Montreal cognitive assessment and repeatable battery for the assessment of neuropsychological status. However, visuospatial assessment is considered less in some of these tools. Single-domain tools for assessing visuospatial ability, including the Benton visual retention test (BVRT) and clock drawing test, are predominately limited to assessing one dimension of spatial cognition, such as spatial memory or structural ability. However, most available visuospatial testing tools operate in an offline mode, which makes it impossible to accurately measure reaction time. In these tools, the stimulus presentation is relatively simple, insufficiently dynamic, and unable to control irrelevant variables. Therefore, these traditional scales may have insufficient sensitivity in patients with vestibular dysfunction (Dobbels et al., 2019).

In contrast to other cognitive dimensions tests, visuospatial tests require a greater transmission of sensory information. Furthermore, using three-dimensional (3D) simulations rather than two-dimensional (2D) simulations in perceptual-cognitive tests is more beneficial (Put et al., 2014). Computerized tests can address the lack of sensory stimulation observed in the traditional visuospatial scales, present test scenes in 3D that are more dynamic, and better capture the visuospatial cognitive ability of the participants. Thus, a more realistic experimental scene can be simulated using computer 3D presentation, enriching sensory stimulation (García-Betances et al., 2015). In addition, participants can move their position in a virtual reality environment. This can enhance the simulation of spatial navigation movement, yielding a stronger interactive experience. Navigation tests in real environments are more effective than in virtual reality environments; however, experimental conditions in real environments are variable and uncontrollable. Moreover, offline, real-world environments require a large test site, the management of which is often complicated and time-consuming. Therefore, computerized cognitive tests can mitigate the traditional visuospatial scale's lack of dynamic and stereoscopic aspects and avoid the disadvantages of the variability of experimental conditions in real environments. Researchers have innovated online visuospatial tests; for example, Morganti (2018) transformed the money roadmap into a virtual reality version, while Claessen et al. (2015) adapted the Corsi block tapping task (CBTT) into a computerized version. Researchers have improved the traditional Morris Water Task and developed a virtual Morris Water Task (vMWT) for humans (Gazova et al., 2013; Daugherty et al., 2015). However, studies have focused on visuospatial cognition problems caused by aging, with less emphasis on the impact of vestibular impairment on visuospatial cognition ability.

According to previous literature, visuospatial domain impairment of patients with vestibular dysfunction is concentrated primarily in the three dimensions of spatial memory, spatial navigation, and mental rotation (Bigelow and Agrawal, 2015; Smith, 2017). Spatial memory denotes the ability to use visual external information and non-visual personal information to store and organize data regarding the surrounding environment (including the relative position, size, and distance of objects), which comprises the basic condition necessary to complete spatial navigation (Iachini et al., 2009). Spatial navigation is a fundamental animal and human behavior that involves planning routes and executing movements toward environmental goals. Many components of successful navigation rely on perception, memory, and executive functions to build spatial representations in the brain, integrate spatial information, and select appropriate navigation strategies. Spatial navigation predominately includes two navigation strategies: self-centered strategy and object-centered strategy (Iachini et al., 2021). Finally, mental rotation refers to an imaginative process in which people use representations to mentally rotate objects in two or three dimensions (Searle and Hamm, 2017). In this study, the conventional visuospatial tests used to evaluate these three dimensions in patients with vestibular dysfunction in previous clinical studies were summarized, screened, improved, and placed online. Finally, a test system was developed for evaluating the three sub-dimensions of visuospatial cognition in patients with vestibular dysfunction.

Abbreviations: VCAS, vestibular cognitive assessment system; HC, healthy controls; VP, patients with vertigo; 3D, three-dimensional; BVRT, Benton visual retention test; 2D, two-dimensional; CBTT, Corsi block tapping task; vMWT, virtual Morris water task; MCI, mild cognitive impairment; AD, Alzheimer's disease; BVP, bilateral vestibulopathy.

The present study developed an effective and convenient vestibular cognition assessment system (VCAS). Through this complete, combined testing system, the performance of VP can be efficiently and accurately evaluated simultaneously for the three spatial cognitive sub-dimensions of spatial memory, spatial navigation, and mental rotation. Furthermore, the system can comprehensively assess the visuospatial cognition of patients with vestibular dysfunction. Consequently, VCAS enhances dynamic and rich sensory stimulation and improves the human-computer interaction experience for the participants. Moreover, the test is presented on a mobile tablet terminal, increasing the convenience for the clinician. Particularly, accurate data recording and digital storage of test results facilitate the maintenance and management of patient data. The test results of patients with vestibular dysfunction can be accumulated to perform data mining and big data analysis to assist in smart medical care development.

2. Materials and methods

2.1. Visuospatial tools summary

The cognitive assessments of patients with vestibular dysfunction published in PubMed, Web of Science, and other literary resources over the past 15 years were reviewed. Consequently, this study discovered that visuospatial dysfunction might comprise the main cognitive impairment in patients with vestibular dysfunction. Table 1 summarizes the use of visuospatial ability testing tools in previous clinical studies that investigated patients with vestibular dysfunction. These tools primarily assess three dimensions of visuospatial ability in patients with vestibular dysfunction: spatial memory, spatial navigation, and mental rotation.

Despite the widespread use of cognitive tools for visuospatial testing in patients with vestibular dysfunction, these tools have the following limitations:

(1) Most of the assessments are paper and pencil tests. This cannot accurately control the experimental conditions and is inconvenient for managing statistical test data.

TABLE 1 Application of visuospatial tools in patients with vestibular dysfunction in previous clinical studies.

Dimension	Research	Tool
Spatial memory	Bigelow et al. (2015); Popp et al. (2017); Guidetti et al. (2020); Pineault et al. (2020)	Corsi block tapping task, Benton visual retention test
Spatial navigation	Wei et al. (2018); Pineault et al. (2020); Lacroix et al. (2021)	Money road map test, maze task
Mental rotation	Grabherr et al. (2011); Bigelow et al. (2015); Deroualle et al. (2019)	Card rotation test, mental transformation tasks and control task, third-person perspective taking
Spatial memory and navigation	Brandt et al. (2005); Kremmyda et al. (2016)	virtual Morris water task

(2) Traditional visuospatial scales cannot sufficiently stimulate the senses. Furthermore, the test conditions are predominately composed of static graphics, lack 3D and dynamic sense, and cannot accurately reflect visuospatial cognition.
(3) Some online tests have been improved; however, most are limited to computer presentations, an inconvenient medium for bedside evaluation.
(4) Many tests solely assess one dimension of visuospatial cognition, while few multi-dimensional combined test systems comprehensively evaluate visuospatial ability.

2.2. Semi-structured interview

This study invited six experts in vertigo and cognition to discuss the test tools presented in Table 1. Two and four of the six experts were from Peking University First Hospital and Beijing Friendship Hospital, respectively. Based on their in-depth experience in vertigo diagnosis and treatment and spatial cognition assessment, a semi-structured interview was performed with the experts to screen the test methods and indicators with high sensitivity and develop the subsequent test system. Table 2 presents the interview questions.

2.3. VCAS design

This study designed the VCAS to assess the visuospatial cognitive abilities of VP to assist clinical diagnosis, improve the efficiency of clinicians, and provide guidance for subsequent treatment, care, and rehabilitation. The assessment method, test dimensions of the test system, and the indicators to be collected for each test were determined according to feedback

TABLE 2 Interview questions.

Interview outlines
1. Which dimensions do you think should be assessed, and which tests should be included?
2. What existing test or experimental paradigms do you think can be online or improve innovation?
3. In these tests, which indices do you think are more important?
4. In addition to the common indicators, which indicators do you think should be included?

TABLE 3 Description of test items and indicator indexes.

Test	Dimension	Index
Weeding test	Spatial memory	Span forward, span backward, velocity forward, velocity backward
Maze test	Spatial navigation	Time, step
Card rotation test	Mental rotation	Score, time
3D driving	Spatial memory and navigation	Response time, errors

3D, three-dimensional.

from the interviews (Table 3). The development of the system was user-centered. After several comparative experiments, several visuospatial tests were administered online or modified, resulting in a combined test system suitable for clinical use. Consequently, the VCAS framework was designed in this study (Figure 1). The flat panel has the characteristics of a large visual screen area and high operability. This design used a flat panel to enhance the test experience of the participants. In addition, VCAS identifies relevant research information upon touching the screen and triggers the corresponding event. The touch screen is easier to operate and manage than a keyboard and mouse. Furthermore, it enhances the participants' sense of mastery and is highly adaptable. Furthermore, the hot update framework development VCAS is an Android-based system built with the 2019 version of Unity3D,[1] using the C# language and ILRuntime. ILRuntime is a framework used by application software developers that permits hot updates. The C# language version used was 4.x. The system includes three main sections: the information input, test, and result query.

2.4. Information input section

This section contained the participants' basic information, including demographic information such as name, age, and sex. The confirmation button was clicked to commence the formal test after creating the participant's profile. Participants with pre-existing profiles could discover their corresponding accounts through the existing database for the formal test (Figure 2).

2.5. Test section

2.5.1. Experimental design of the weeding test

The weeding test is used to assess spatial memory and is inspired by the CBTT, which determines memory breadth. Specifically, the weeding test is divided into two main sessions, a forward and a backward session. The test uses simulation teaching to help beginners better understand the rules and methods of the test. The American psychologist, George A. Miller, proposed that the maximum capacity of short-term memory lies between 5 and 9 items (Manoochehri, 2021). Based on this hypothesis, the longest span of the weeding game was set to nine in this study. Specifically, a background image of nine sections of grass in the form of squares with weeds growing on them appeared on the screen. The system automatically demonstrated the square jumping, with the jumping interval set to 1 s. After the demonstration, the participants were instructed to reproduce the sequence in the same or reverse order. When participants clicked correctly, the weed on the square automatically disappeared. However, when the participants clicked incorrectly, the weed exhibited an "×" (Figure 3).

The system randomly generated squares to jump, with the number of squares starting at two. Subsequently, the weeding sequence to be memorized gradually increased as the difficulty of the test increased. The sequence length increased progressively; namely, each sequence had two levels, and the game automatically proceeded to the next level when one of the two levels was passed. The game automatically stopped when two sequences of the same level failed or the maximum click limit sequence set by the game was reached. The system automatically registered the dependent variables of the longest series (span) recalled, the total number of blocks clicked, and the total time for the correct item in the forward and backward directions. The weeding test collected two metrics, namely, the longest correct series (span) and the clicking speed (total blocks/total time). Specifically, the longer and faster the longest correct series (span), the better the spatial memory.

2.5.2. Experimental design of the maze test

The maze test was used to evaluate spatial navigation and was inspired by the money road map test and maze task. The maze game used the most basic heuristic global path search A* algorithm for the shortest path solution. The A* algorithm is the most efficient direct search method for shortest-path solving in static routing (Ou et al., 2022). The system randomly generated the corresponding maze map using a prime tree algorithm and dynamic route rendering to avoid learning effects. The principles of the A* algorithm are as follows:

This paradigm consists of per-node priority calculations, for example:

$$f(n) = g(n) + h(n) \tag{1}$$

where n denotes the node and $f(n)$ represents the integrated priority of the node n. In the process of implementing the algorithm, a smaller value of $f(n)$ node indicates its higher integrated priority. During the algorithm's operation, the node with the smallest $f(n)$ value is preferred. Specifically, $g(n)$ represents the distance of node n from the initial point, and $h(n)$ represents the distance of node n from the target point, where the heuristic function $h(n)$ is computed using the Manhattan distance.

$$c = |x_1 - x_2| + |y_1 - y_2| \tag{2}$$

$$h(n) = D * c \tag{3}$$

where x and y denote the corresponding horizontal and vertical coordinate values of the two nodes, respectively, and D denotes the movement cost between the two neighboring nodes.

The researcher created mazes with the starting point of the maze located in the lower left corner, the ending point in the upper right corner, and the game roulette in the lower right corner (Figure 4). The test participants created mazes based on different difficulty factors according to the study's purpose (Figure 5). After creating the maze, the participant clicked the game roulette and manipulated the cow to move to the end of the maze (Supplementary Figure 1). The total time and number of steps the participant used to complete the maze were automatically registered in the system. Subsequently, the maze test captured the total number of steps and total time as metrics. Specifically, the shorter the total time and the fewer the total number of steps, the better the spatial navigation.

2.5.3. Experimental design of the card rotation test

This study used an online card rotation test to assess mental rotation. The test comprised eight questions, divided into six 2D

1 https://docs.unity.cn/cn/current/Manual/index.html

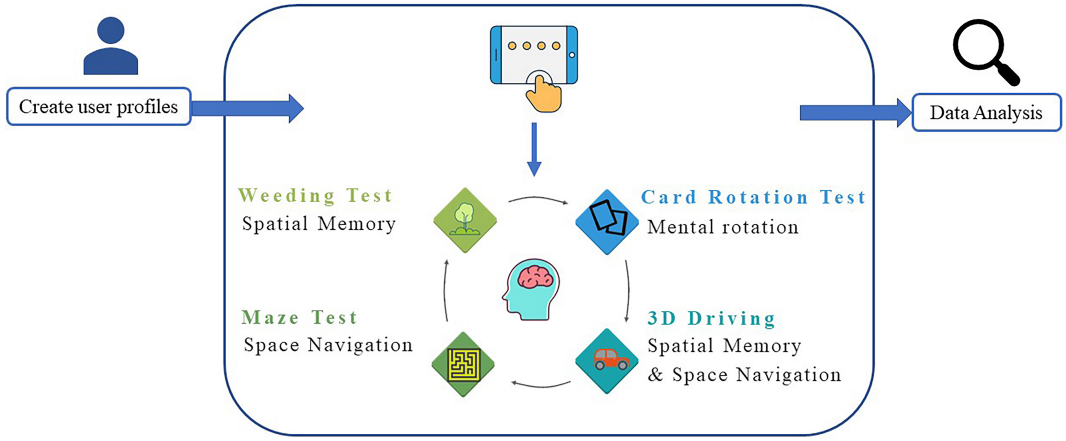

FIGURE 1
Vestibular cognitive assessment system (VCAS) frame. The system includes three main sections: Information input, test, and result query.

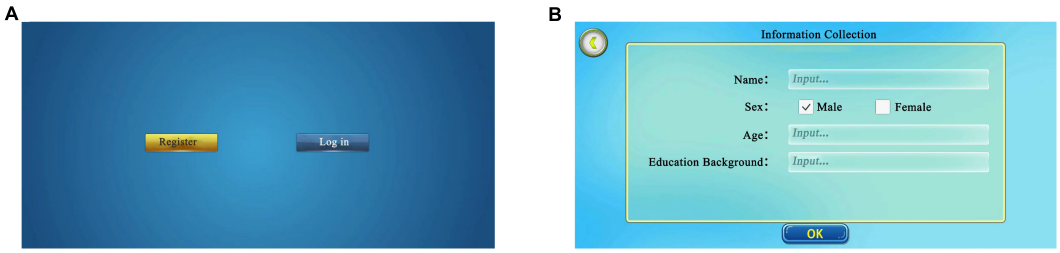

FIGURE 2
Initial login interface. **(A)** Login interface. New participants select "register", former participants select "log in" and find their page. **(B)** Information collection. New participants log in and fill in basic information, including name, sex, and age. Adapted from https://unity.com/.

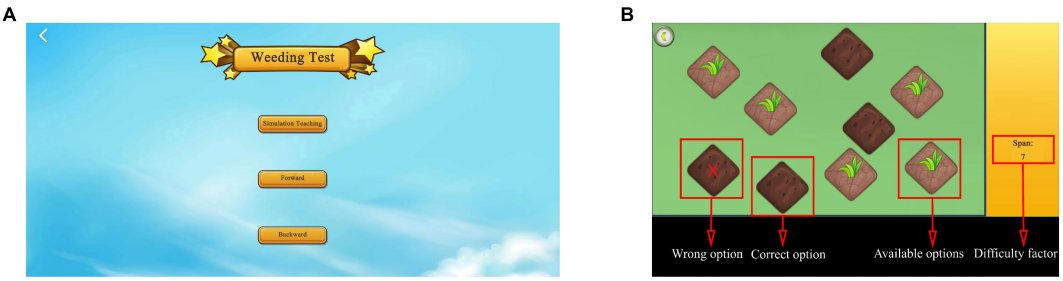

FIGURE 3
Weeding test. **(A)** Login to the weeding test interface. The weeding test includes forward and backward, and simulation exercises are required before the test. **(B)** Test interface. The screen in the weeding test. Weeds will disappear when selected correctly; when selected incorrectly, the weed will exhibit "×". Adapted from https://unity.com/.

and two 3D test questions (Figure 6). The system provided a reference figure in the upper right corner of the interface, with four figures of the same color and size as the reference figure but with different rotation angles.

The first question was used for the explanation and was not scored. The timing and scoring commenced after the explanation. One point was awarded for each correct answer, with a maximum of eight points. Subsequently, the total score and time were recorded backstage. Consequently, higher scores and shorter time spent indicated improved mental rotation.

2.5.4. Experimental design of the 3D driving test

The 3D driving test was inspired by the vMMT and used to evaluate spatial memory and navigation. The test used the Unity3D engine and accessed the ILruntime hot update framework development to build virtual 3D maps and physical car models. An artificial intelligence pathfinding system was used to realize the car model autopilot function.

The system displayed a map connected to a turntable with three directions at each intersection before the test commenced. The participants were required to memorize the map's contents

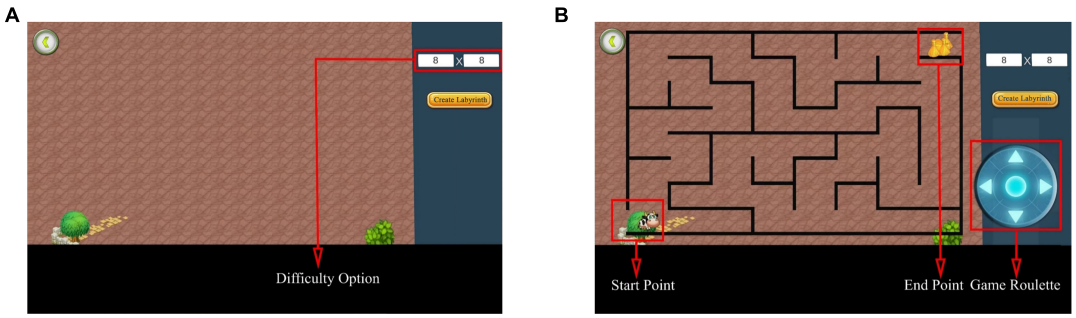

FIGURE 4
Maze test interface. **(A)** Before creating a maze. Select the difficulty of the maze to be tested by adjusting the difficulty option. **(B)** After creating the maze. The interface after generating the maze using 8 × 8 as an example. Adapted from https://unity.com/.

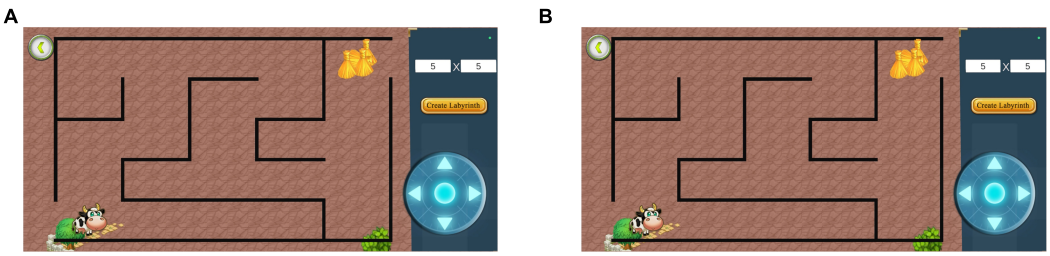

FIGURE 5
Diagram of different difficulty mazes. **(A)** Difficulty factor 5 × 5 maze. **(B)** Difficulty factor 12 × 12 maze. The higher the difficulty factor, the more complex the maze. Adapted from https://unity.com/.

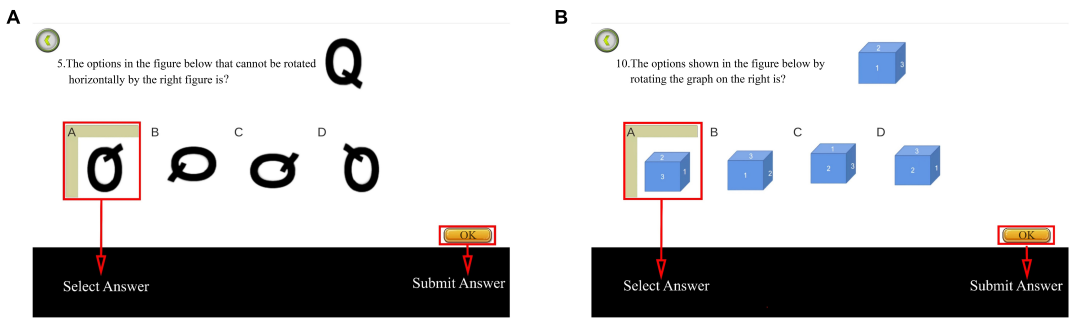

FIGURE 6
Diagram of card rotation test. **(A)** Two-dimensional (2D) test question. **(B)** Three dimensional (3D) test question. In total, the test comprised eight questions, namely six 2D and two 3D test questions. Adapted from https://unity.com/.

within 5 s. After the map disappeared, the participant selected a direction from each intersection based on the memorized content (Figure 7). Each intersection had only one correct direction, and the car could only be driven after the participant had chosen it. The test was designed to ensure that the participant did not need to steer the car to avoid experimental errors caused by the inflexible fingers of some older adults. Particularly, the 3D driving had four maps of the same difficulty level, each with different starting and ending positions (Figure 8). The system recorded the number of selection errors and the response time required to complete the test. Consequently, fewer selection errors and shorter response time indicated better spatial memory and navigation.

2.6. Result query section

Figure 9 shows the module display with indicators for each test and controls that permit the selection of different tests on the right to view the test results. The system data were stored in the Tencent Cloud storage bucket.

2.7. System verification

2.7.1. Participants

In this study, VP were diagnosed with vestibular dysfunction-related diseases at the Department of Otolaryngology and Head and

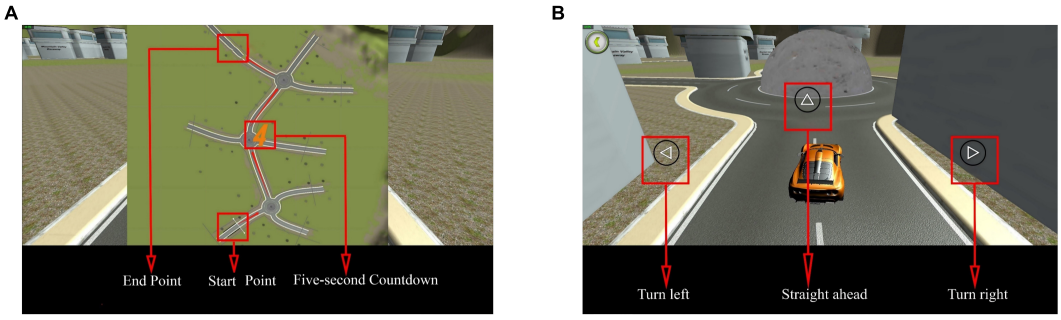

FIGURE 7
Three dimensional (3D) driving diagram. **(A)** Map style. The map includes the start and end points and is presented in 5 s. **(B)** Road turntable. At the round turntable, participants must choose a direction, including straight ahead, turning left, or turning right. Adapted from https://unity.com/.

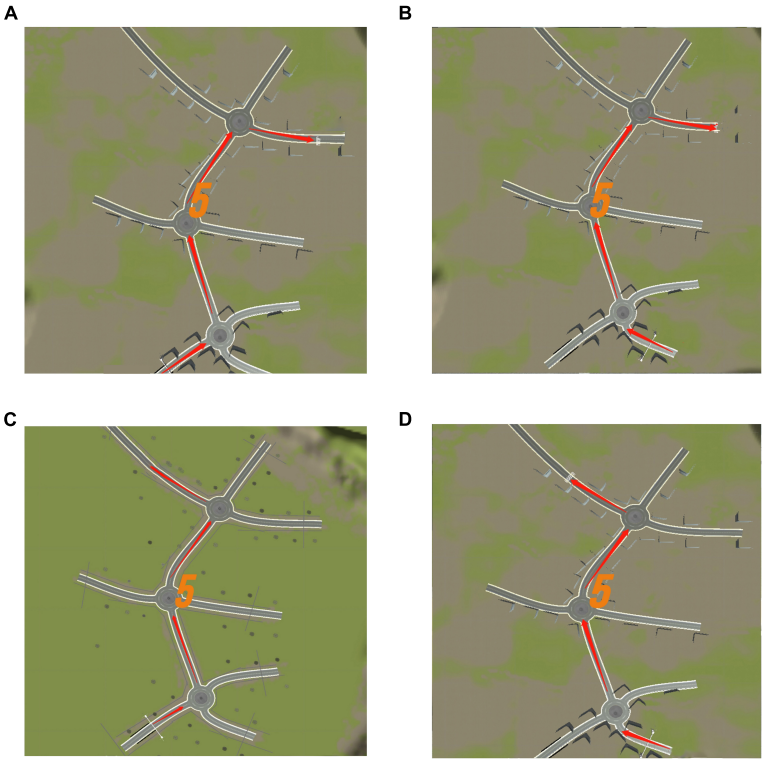

FIGURE 8
Three dimensional (3D) driving memory map diagram. **(A)** Map 1. **(B)** Map 2. **(C)** Map 3. **(D)** Map 4. Each map has a different starting and ending point. Adapted from https://unity.com/.

Neck Surgery, Peking University First Hospital, between December 2021 and June 2022. Each patient had a history of dizziness or vertigo, and at least one routine vestibular function test with abnormal results, including:

(1) The cervical vestibular evoked myogenic potential test failed to elicit obvious P1 and N1 waves at 100 dB nHL intensity in monaural or binaural tests (Vanspauwen et al., 2011);
(2) Video-head impulse test with compensatory saccades or abnormal gain (Macdougall et al., 2013);
(3) Unilateral weakness value of > 25 in caloric tests (Shepard and Jacobson, 2016);
(4) Positioning nystagmus evoked in dynamic position test.

The VP group mainly included common vestibular disorders such as otoliths, Meniere's disease, sudden deafness with vertigo, and vestibular neuritis. The HC were recruited *via* adverts and had no history of dizziness, vertigo, or hearing impairment. For the VP and HC groups, the following exclusion criteria were applied: (1) age < 18 years; (2) inability to understand and cooperate with tests; (3) history of anxiety or depression; (4) related dementia diseases (such as Alzheimer's disease (AD) and vascular dementia); (5) noticeable visual impairments; (6) motor dysfunction disorder (especially of the upper limbs); (7) central nervous system diseases such as cerebral infarction or neurological

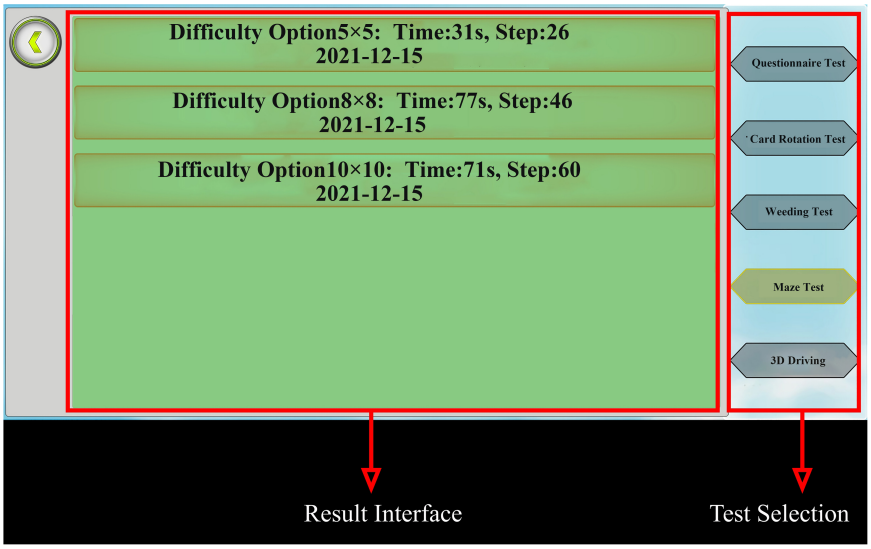

FIGURE 9
Result display module. Taking the 8 × 8 maze test results as an example, the results include the number of steps and time for different difficulties of the maze test. Adapted from https://unity.com/.

disease. We only included adults with concomitant vestibular dysfunction because vestibular disorders are more predominant in adults and are relatively rare in children and adolescents. Moreover, VCAS requires a certain level of cooperation and understanding; thus, we excluded individuals who could not cooperate.

All procedures in this study were approved by the hospital Ethics Committee, and informed consent was obtained from all participants. The test duration for this study was approximately 40 min. Specifically, the weeding, maze, card rotation, and 3D driving tests took approximately 10, 10, 8, and 12 min, respectively. Appropriate breaks were provided, if necessary, during the testing period. This study was conducted in the hospital's outpatient department. However, some of the tests were not completed because of schedule conflicts for some participants. In the maze test, a maze with a 5 × 5 difficulty was used to familiarize the participants with the test rules. Subsequently, tests of three difficulty levels were conducted, namely 8 × 8, 10 × 10, and 12 × 12. In the 3D driving test, the participants were informed about the test rules using map 1. The tests of maps 2, 3, and 4 were conducted after understanding the rules. The study was conducted on a Lenovo TB-J606F tablet with a resolution of 2,000 × 1,200 and a screen size of 11 inches.

2.7.2. Statistical analyses

SPSS 25.0 was used for the statistical analysis of the data. Quantitative variables were distributed normally using mean (SD) and non-normally using M (P_{25}, P_{75}). Categorical variables were expressed as frequencies and percentages, n (%). Normality was tested using the Shapiro–Wilk test, and quantitative variables with normal distributions were tested using two independent-sample *t*-tests and those with non-normal distribution using the Mann–Whitney *U* test. For the demographic data, *t*-tests were used to assess age and years of education, and a chi-square test was used to assess sex. Maze and card rotation test data with normal distribution were assessed using *t*-tests, whereas the weeding and 3D driving test data with non-normal distribution were assessed using Mann–Whitney *U* test. Statistical significance was set at $P < 0.05$. GraphPad Prism 9.0 was used to display the overall distribution of the data between the two groups.

3. Results

3.1. Participants' characteristics

This study investigated 154 participants: 75 HC (21 males and 54 females) and 79 VP (25 males and 54 females). There were no statistically significant differences between the groups in terms of age ($P = 0.079$), sex ($P = 0.621$), or education ($P = 0.398$; Table 4).

3.2. Comparison of the results of the HC and VP groups

3.2.1. Comparison of weeding test results

All the participants completed the weeding test, and the Mann–Whitney *U* test was used to compare the results between the two groups. As shown in Figure 10 and Supplementary Table 1, the median span forward was 5 (4.00, 6.00) for the VP group and 6 (5.00, 6.00) for the HC group; the difference was significant ($z = -3.85$, $P < 0.001$). Similarly, a significant difference was observed in the span backward between the groups ($z = -1.97$, $P < 0.05$). However, the median velocity forward was 0.44 (0.39, 0.48) for the VP group and 0.44 (0.40, 0.49) for the HC group; the difference was insignificant ($z = -0.86$, $P = 0.392$). Finally, the VP group had a lower negative weeding rate than the HC group ($P < 0.05$).

3.2.2. Comparison of maze test results

In total, 67 HC and 66 VP completed the 8 × 8, 10 × 10, and 12 × 12 maze tests in this study. Ten individuals did not

TABLE 4 Demographic characteristics of the study population.

	Patients with vertigo (n = 79)	Healthy controls (n = 75)	
Age: mean (SD)	55.01 (12.05)	51.63 (11.56)	$P = 0.079$
Sex (n, %)			$P = 0.621$
Male	25 (32)	21 (28)	
Female	54 (68)	54 (72)	
Educational level: mean (SD)	12.77 (2.56)	12.38 (2.99)	$P = 0.398$

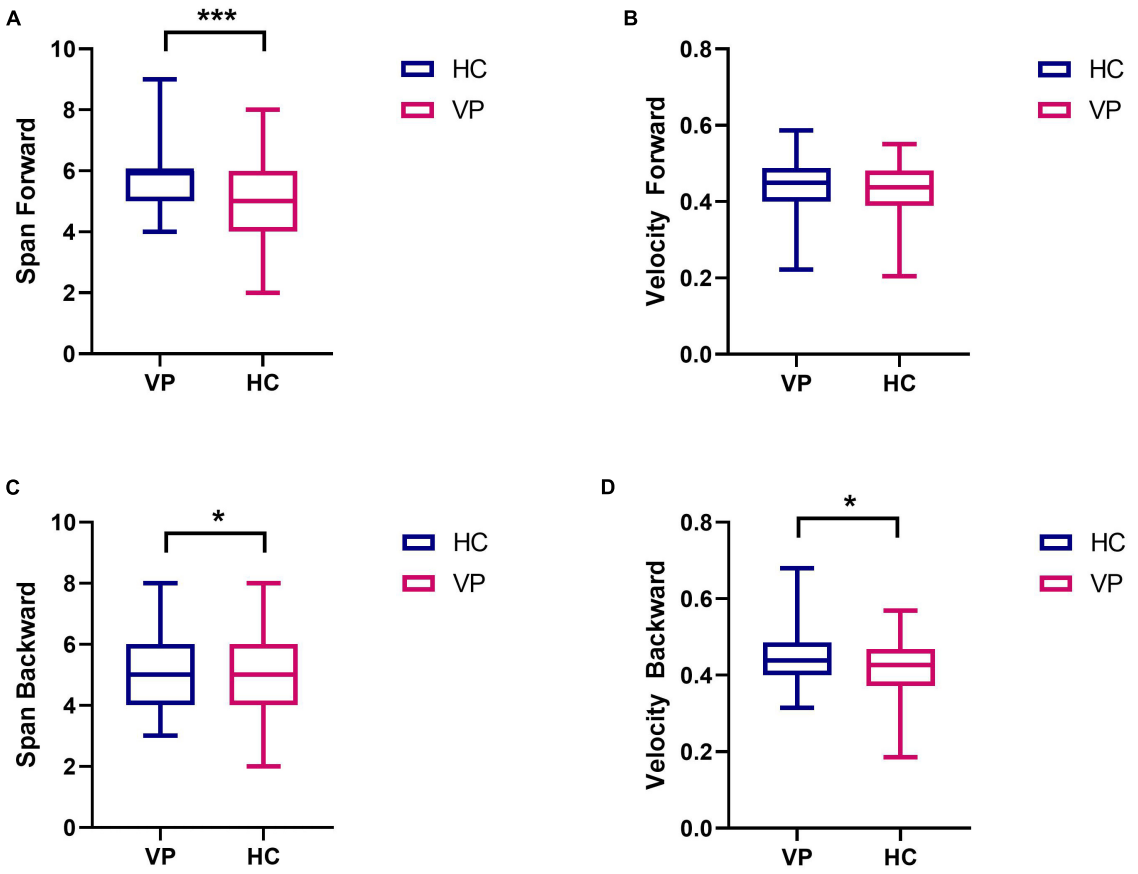

FIGURE 10
Comparison of weeding test indexes between VP and HC. **(A)** Span forward. **(B)** Velocity forward. **(C)** Span backward. **(D)** Velocity backward. The upper and lower lines represent the 95th and 5th percentiles, respectively, and the horizontal line within the box is the median. VP, patients with vertigo; HC, healthy controls. ***$P < 0.01$, *$P < 0.05$.

complete the weeding test because of schedule conflicts. For the 8 × 8 maze, the mean times (s) for the VP and HC groups were 40.48 (18.26) and 34.75 (15.97), respectively, with no significant difference between the groups (t = 1.93, P = 0.056). Further, for the 8 × 8 maze, the mean steps of the VP and HC groups were 28.39 (8.63) and 27.10 (11.53), respectively; the difference was insignificant (t = 0.73, P = 0.467). For the 10 × 10 maze, the mean times (s) and steps of the VP and HC groups showed no significant difference ($P > 0.05$). For the 12 × 12 maze, the mean times (s) of the VP and HC groups were 85.76 (48.35) and 69.57 (31.01), respectively, and the mean steps were 58.06 (25.20) for the VP group and 49.52 (16.45) for the HC group; all showed significant differences (P all < 0.05). Figure 11 and Supplementary Table 1 show the maze test results for the two groups.

3.2.3. Comparison of the card rotation test results

Due to the pre-experimental replacement of some question items, only 41 HC and 38 VP completed the card rotation test in this study. These results are shown in Figure 12 and Supplementary Table 1. The mean scores were 4.31 (1.65) for the VP group and 3.84 (1.65) for the HC group; the difference was insignificant (t = 1.28, P = 0.205). The mean times (s) were 252.21 (99.62) for the VP group and 234.88 (98.70) for the HC group; the difference was insignificant (t = 0.655, P = 0.515).

3.2.4. Comparison of the 3D driving test results

Maps 2, 3, and 4 were completed by 42 HC and 40 VP, 40 HC, and 39 VP, and 42 HC and 40 VP participants, respectively. The reason for this was that we initially only had map 1, and we

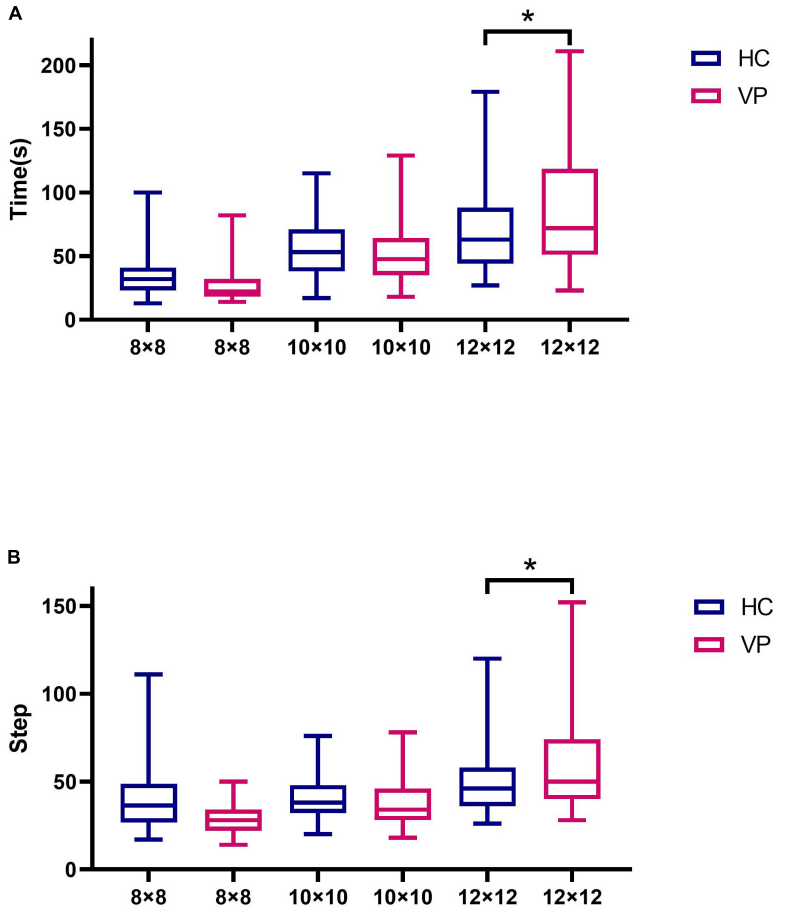

FIGURE 11
Comparison of maze test indexes between VP and HC. **(A)** Time spent in maze tests of 8 × 8, 10 × 10, and 12 × 12 difficulty for VP and HC, respectively. **(B)** The number of steps in maze tests of 8 × 8, 10 × 10, and 12 × 12 difficulty for VP and HC, respectively. The upper and lower lines represent the 95th and 5th percentiles, respectively, and the horizontal line within the box is the median. VP, patients with vertigo; HC, healthy controls. *$P < 0.05$.

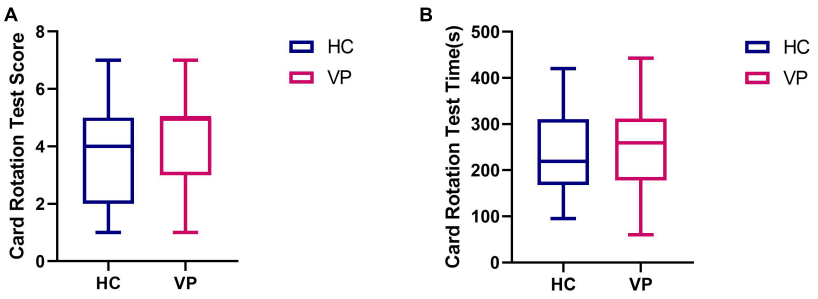

FIGURE 12
Comparison of card rotation test indexes between VP and HC. **(A)** Score. **(B)** Time (s). The upper and lower lines represent the 95th and 5th percentiles, respectively, and the horizontal line within the box is the median. VP, patients with vertigo; HC, healthy controls.

subsequently added maps 2, 3, and 4. We compared the response time and the number of errors between the two groups, and because these data did not conform to a normal distribution, we used the Mann–Whitney *U* test. In map 2, the median response time (s) of the VP and HC groups were 17.00 (8.00, 33.25) and 15.00 (10.00, 22.50), respectively, with no significant difference observed ($z = 0.84$, $P = 0.399$). Furthermore, the median errors of the VP and HC groups for map 2 were 1.50 (0.00, 2.25) and 1.40 (1.27), respectively, with no significant difference ($z = 0.90$, $P = 0.371$). For map 3, the median response times (s) of the VP and HC groups were 11.50 (6.00, 24.50) and 17.00 (8.00, 30.00), respectively, with no significant difference ($z = 1.19$, $P = 0.235$). The median errors of the VP and HC groups for map 3 were 1.00 (0.00, 3.00) and 2.00 (0.00, 3.00), respectively, with no significant difference ($z = 1.35$,

P = 0.177). However, we found no difference between the two groups in terms of response time and the number of errors in map 4 ($P > 0.05$) (**Figure 13** and **Supplementary Table 1**).

4. Discussion

Animal and clinical studies have indicated that visuospatial abilities are the most relevant in vestibular dysfunction. In a clinical study, Guidetti et al. (2020) used CBTT to evaluate 263 patients with vestibular dysfunction and 430 healthy people. Their study results revealed that the CBTT span was significantly lower in patients than in HC. Furthermore, they discovered that vestibular disease significantly influenced spatial working memory ability. Pineault et al. (2020) used the BVRT to evaluate the spatial memory of participants. The experimental results demonstrated that the BVRT errors were significantly higher in patients with bilateral semicircular canal injury than in the HC group. Moreover, Kremmyda et al. (2016) found that in contrast to the HC, patients with bilateral vestibulopathy (BVP) took longer to reach the exit in the vMWT task and exhibited significant difficulties in spatial memory and navigation. Consistent with these findings, Brandt et al. (2005) used magnetic resonance imaging technology on 10 patients with chronic BVP and discovered that the hippocampus was significantly atrophied. In the vMWT task, patients with BVP exhibited significant heading deviation errors. Researchers in related animal studies also underscored the impact of vestibular impairment on visuospatial cognition. A study found that rats with chronic unilateral vestibular dysfunction had impaired spatial memory during foraging tasks in a dark environment (Zheng et al., 2006). In addition, several studies have demonstrated impaired hippocampal function in rats with bilateral vestibular deafferentation, affecting their spatial learning and memory (Zheng et al., 2007). Similarly, Nguyen et al. (2021) found that unilateral labyrinthectomy impairs spatial memory, navigation, and motor coordination in mice.

The influence of vertigo on cognitive function is an emerging field and represents a novel scientific problem related to cognition, discovered by researchers. For basic research and clinical application, developing and implementing tools to detect the impact of vestibular dysfunction on cognitive function is necessary. VCAS serves as a comprehensive and objective test system to detect the effects of vertigo disorders and vestibular dysfunction on cognitive function. In contrast to previous cognitive function assessments, the VCAS permits comprehensive detection and evaluation of the dimensions underlying visuospatial cognitive ability, such as spatial memory, spatial navigation, and mental rotation. These aspects specifically pertain to the effects of vertigo and vestibular dysfunction on cognitive function. Furthermore, visuospatial cognition research in clinical and related fields is important because it can provide clinical tools for spatial cognitive ability testing with a high clinical diagnostic and early warning value. Lacroix et al. (2021) preliminarily explored spatial cognitive assessment for children with vestibular dysfunction. In contrast, this study investigated adult patients with vestibular dysfunction, emphasizing older adults. In addition, we hope that VCAS will be used in the future to assess visuospatial cognition in patients with other diseases, such as mild cognitive impairment (MCI) or AD. Moreover, studies have shown that visuospatial cognitive testing may be a reliable technique and screening tool for identifying MCI or AD (Lester et al., 2017; Li et al., 2022). Plácido et al. (2021) found that compared with the Mini-Mental State Examination, the visuospatial test had better sensitivity for distinguishing patients with AD from HC, indicating that visuospatial cognitive decline could be independent of general cognitive decline. In addition, Wei et al. (2019) found that the odds of impaired vestibular function were three to four times higher in patients with MCI compared to HC. Further, the degree of vestibular impairment was higher in patients with AD than in controls and patients with MCI. Hence, a relationship might exist between AD, vestibular dysfunction, and cognitive decline (Agrawal et al., 2020). Therefore, the VCAS should be modified and updated accordingly to discover a convenient screening version for AD or MCI. For example, patients with MCI or AD should only perform the 8 × 8 maze test, and the number of questions in the card rotation test should be reduced. In addition, they should be able to perform the weeding test; however, the 3D driving test might be skipped for now to save time. Hence, further exploration and verification are required.

First, the experimental design of the mobile-based VCAS can improve clinicians' efficiency. Among these designs, the weeding test was inspired by the experimental paradigm of CBTT, which is used to evaluate spatial memory ability. Upon computerizing CBTT, sensory stimulation was primarily provided by flashing square lights (Brunetti et al., 2014; Claessen et al., 2015). In VCAS, the sensory stimulus for the weeding test is provided using "dancing" cubes. As opposed to simple visual light stimulation, jumping cubes provide a stronger sense of spatial dynamics, which can better reflect the role of the vestibular system. The maze test evaluated participants' spatial navigation abilities and used the A* algorithm combined with the prime tree algorithm and dynamic route rendering to randomly generate different mazes with the same difficulty level, avoiding learning effects and thereby improving test accuracy. The maze task developed by Lacroix et al. (2021) can only be completed using an electronic pen to draw lines. In contrast, the maze test of VCAS allows the simulated villain to move by manipulating the direction arrows. This can enhance the simulation of spatial navigation in real life and interactivity. The card rotation test evaluated the participants' mental rotation ability using 2D and 3D graphics. The 3D driving test evaluated the spatial memory and navigation ability of the participants and used the Unity3D engine and ILruntime hot update framework development technology to enhance the testing experience for the participants. Compared with traditional paper-and-pencil tests, VCAS digitally stores the data of patients. Capturing, analyzing, and predicting these electronic medical record data is possible by continuously accumulating the data of patients with vestibular dysfunction, permitting more direct and accurate diagnosis and treatment suggestions for clinical practice and rich data support for scientific research (Gamache et al., 2018). We hope that in the future, VCAS will be useful for cognitive screening and the detection of issues in patients with vestibular dysfunction.

Second, the test results indicated that the spatial memory performance of the VP in the backward weeding test was worse than that of the HC. In the forward weeding, no difference in velocity was observed between the groups, whereas the HC group had a shorter span forward than the VP group, indicating that vestibular dysfunction affected spatial memory ability. Popp et al. (2017) also found that patients with BVP performed worse than normal controls in CBTT. Furthermore, the maze test revealed

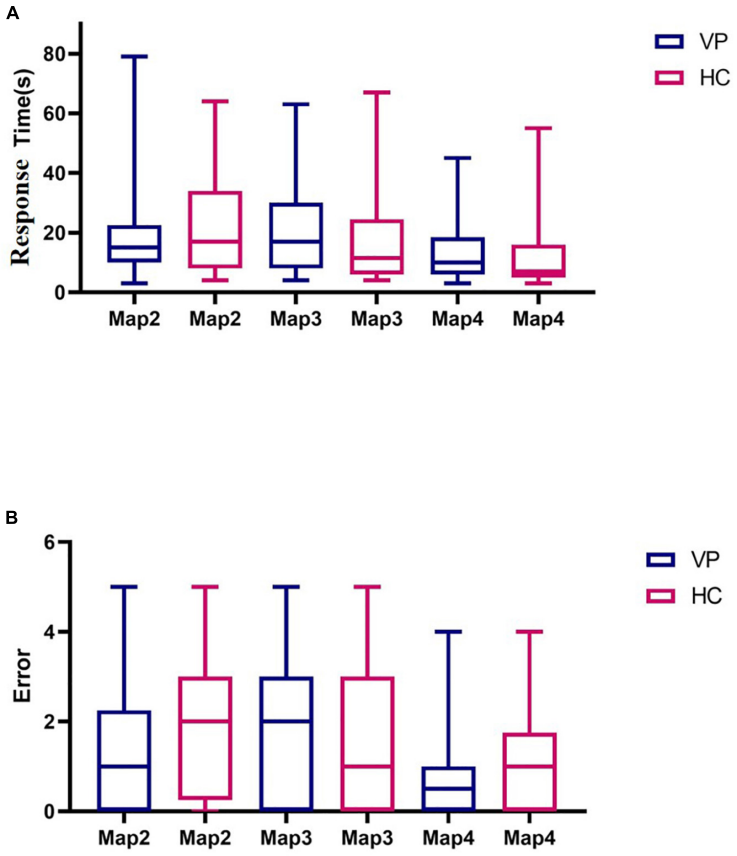

FIGURE 13
Comparison of three dimensional (3D) driving test indexes between VP and HC. **(A)** Response time spent in Maps 2, 3, and 4 for VP and HC, respectively. **(B)** The number of errors in Maps 2, 3, and 4 of VP and HC, respectively. The upper and lower lines represent the 95th and 5th percentiles, respectively, and the horizontal line within the box is the median. VP, patients with vertigo; HC, healthy controls.

no significant differences in steps or times between the VP and HC for the two difficulties of the 8 × 8 and 10 × 10 mazes. However, the 12 × 12 maze exhibited significant differences in the steps and times between the two groups, with VP requiring more time and steps. Consequently, this suggests that the 12 × 12 maze is more sensitive than the 8 × 8 and 10 × 10 mazes. In the mental rotation test, no significant difference was found between the groups, which could be attributed to the relatively few stimuli, and hence poor sensitivity. Thus, future studies should appropriately increase the number of questions for card rotation and establish a corresponding test question bank. In contrast to spatial memory and navigation, vestibular dysfunction may have a relatively lower impact on mental rotation. This may be because the head orientation and position cells in the hippocampus may receive more vestibular information, whereas the retrosplenial cortex, which is responsible for mental rotation, may be less influenced by vestibular information (Hitier et al., 2014). In the 3D driving test, no significant difference was found in the performance of the two groups on maps 2, 3, and 4, which could be due to the low number of patients with chronic vertigo among the VP. Previous studies have revealed that chronic unilateral vestibulopathy or patients with BVP and persistent postural-perceptual dizziness significantly affect brain structure and function, while cognitive impairment may be more significant (Li et al., 2020; Si et al., 2022). Therefore, more data on patients with chronic vertigo should be collected for future comparative experiments.

This study also demonstrated that patients with vestibular dysfunction could experience changes in cognitive function in addition to their balance and sensorimotor disorders. Thus, the routine balance exercise rehabilitation of patients with vestibular dysfunction should be prioritized. Furthermore, research ought to actively advocate for corresponding cognitive assessment and rehabilitation. Age is a common cause of the cognitive decline. However, no significant difference was found in age between the two groups in this study, in which experimental errors due to age factors were avoided. In addition to age factors, this experiment excluded other diseases affecting cognitive function, such as dementia. Notably, hearing loss could also mediate cognitive decline, increasing the risk of dementia (Kim et al., 2018; Maharani et al., 2018). Thus, this study excluded people with moderate or higher levels of hearing loss while controlling for the influence of hearing factors. Moreover, this study has clinical value and indicates the social significance of evaluating and identifying risk factors for cognitive function in VP.

This research had several limitations: (1) The VP recruited in this study had a relatively short disease course and a mild degree of vertigo. Consequently, these participants could not be

distinguished from HC in some tests. (2) The test trials must be made more intensive, such as increasing the response time in the maze test and total number of trials in the weeding test to ensure that each participant answers before the test is terminated. (3) The VP were not classified according to disease. In the future, the performance of people with different vestibular diseases for each visuospatial dimension and the impact of different vestibular organ damage on visuospatial cognition could be explored.

5. Conclusion

In conclusion, VCAS can assess the visuospatial abilities of VP in multiple dimensions and at multiple levels. VCAS can provide more 3D and dynamic simulation conditions than traditional visuospatial tests. Vertigo research is a growing discipline and has developed rapidly in recent years. Furthermore, vertigo diseases primarily involve neurology, otolaryngology, head, and neck surgery, neurosurgery, and orthopedics. Despite significant advances in understanding vertigo disease and its related effects, there are many areas to explore and study in the future. The research team that conducted this study is also developing a corresponding visuospatial clinical screening questionnaire, which will be embedded in the test system in the future to permit subjective and objective evaluations. Currently, VCAS is used primarily on mobile phones or tablets, which are convenient to carry. Hopefully, devices can be interconnected in the future so that test results can be accessed across several devices. Moreover, according to clinical needs, a corresponding electronic report is automatically generated, which is convenient for printing and enables timely response to patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of Peking University and the Peking University First Hospital (Approval no. 2021-390).

Author contributions

YH: experimental design, data collection, data processing, and manuscript writing. JT, XZ, and YX: data processing. XY, YZ, CW, RR, and HY: data collection. YL: experimental design and project implementation management. All authors contributed to the article and approved the submitted manuscript version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1095777/full#supplementary-material

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A cross-sectional study of retinal vessel changes based on optical coherence tomography angiography in Alzheimer's disease and mild cognitive impairment

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Background: The involvement of retina and its vasculature has been recently described in Alzheimer's disease (AD). Optical coherence tomography angiography (OCTA) is noninvasively used to assess the retinal blood flow.

Objective: This study was to compare vessel density (VD) and blood perfusion density (PD) of the macular in AD patients, mild cognitive impairment (MCI) patients and healthy controls by OCTA, which may provide new ideas for diagnosis of AD or MCI.

Methods: AD patients, MCI patients and healthy controls underwent a comprehensive ophthalmic and neurological evaluations, including cognitive function assessments as well as visual acuity, intraocular pressure (IOP), slit lamp examinations, and OCTA. General demographic data, cognitive function, retinal VD and PD were compared among three groups. The correlations among retinal VD, PD and cognitive function, amyloid-beta (Aβ) protein and phosphorylated Tau (p-Tau) protein were further evaluated. The correlations between retinal superficial capillary plexus and cognitive function, Aβ protein and p-Tau protein were also explored.

Results: A total of 139 participants were recruited into this study, including 43AD patients, 62 MCI patients, and 34 healthy controls. After adjusting for sex, age, history of smoking, history of alcohol intake, hypertension, hyperlipidemia, best corrected visual acuity, and IOP, VD and PD in the nasal and inferior regions of the inner ring, superior and inferior regions of outer ring in the AD group were significantly lower than in the control group ($p<0.05$). PD in nasal region of outer ring also significantly decreased in the AD group. VD and PD in superior and inferior regions of inner ring, superior and temporal regions of outer ring in the MCI group were markedly lower than in the control group ($p<0.05$). After adjusting for sex and age, VD and PD were correlated with Montreal Cognitive Assessment Basic score, Mini-mental State Examination score, visuospatial function and executive function ($p<0.05$), while Aβ protein and p-Tau protein had no relationship with VD and PD.

Conclusion: Our findings suggest that superficial retinal VD and PD in macula may be potential non-invasive biomarkers for AD and MCI, and these vascular parameters correlate with cognitive function.

KEYWORDS

optical coherence tomography angiography, Alzheimer's disease, mild cognitive impairment, vessel density, perfusion density, cognitive function

Introduction

Alzheimer's disease (AD) is a common progressive degenerative disease of the central nervous system, and has been the most common cause of dementia, accounting for 50–75% (Lane et al., 2018). It has a high prevalence in the elderly and early old age, and is mainly characterized by progressive cognitive dysfunction and behavioral impairment (Lane et al., 2018). Mild cognitive impairment (MCI) is the transitional stage between normal aging and dementia (Gauthier et al., 2006). It is characterized by cognitive decline but the ability to live a normal life is not affected (Kim et al., 2017). Of note, people with MCI have a high risk of developing dementia. It is estimated that 32% of MCI patients will develop AD within the next 5 years (Ward et al., 2013). AD patients bring great economic and social burdens to the family and even the whole of society. It is estimated that the annual total cost of nursing AD patients is more than US $507.49 billion in 2030 in China (Jia et al., 2018). Prevention and treatment of AD are still a worldwide problem. These may be ascribed to the difficult early diagnosis of AD. Because its onset is insidious, with pathological changes in the brain occurring 20 years or more before clinical symptoms (Villemagne et al., 2013; Gordon et al., 2018). The identification of these pathological changes in the brain requires expensive positron emission tomography/computed tomography (PET-CT) and invasive cerebrospinal fluid (CSF) tests, which are not widely available in clinical practice (Jack et al., 2018). Therefore, it is imperative to develop economical and noninvasive tests for the early recognition of AD and MCI.

The retina and the brain share some features in embryology, anatomy and physiology (Lee et al., 2020). First, the retina develops from the neuroectoderm, having the same embryonic origin as the brain, and is a sensory extension of the brain (Hart et al., 2016). Secondly, the retina is an extension of the diencephalon and has a blood-retinal barrier similar to the blood–brain barrier (Baker et al., 2008). Retinal small blood vessels and small cerebral blood vessels also have similar physiological properties (Patton et al., 2005). The microcirculation systems of both are hyperoxic extraction systems, and their blood flow depends on regional neuronal activity (Patton et al., 2005). The automatic regulation mechanism makes the perfusion pressure of the vessels maintain relatively constant blood flow even if it changes (Yan et al., 2021). Moreover, autopsy has indicated the amyloid-beta (Aβ) protein deposits in the retinal vessels of AD patients (Shi et al., 2020). This suggests that retinal vascular disease can objectively reflect the vascular disease in the brain, and is a window to study cerebral vasculopathy (Newman, 2013).

Studies have revealed that changes in brain perfusion exist long before the clinical symptoms of AD, and may even predate Aβ protein accumulation or brain shrinkage (Hays et al., 2016). However, the changes of blood flow in the brain cannot be directly observed. Based on the similarity between the retina and the brain, it is possible to detect the blood flow in the retina to reflect the changes of blood flow in the brain. Optical coherence tomography angiography (OCTA) is a non-invasive, rapid and high-resolution fundus angiography technique, which can observe the structure and morphology of blood vessels at different levels of the retina in layers, and quantify the blood flow index and diseased blood flow area within a certain range (Boeckaert et al., 2012). OCTA can be used to collect information on blood vessel density (VD) and blood vessel morphology of the retina in macular area. Studies have indicated that, compared with normal controls, the blood VD in the superficial and deep retina of macular area in AD and MCI patients significantly reduced, and the foveal avascular zone (FAZ) area was significantly enlarged, which is a sign of macular ischemia (Bulut et al., 2018; Jiang et al., 2018; Lahme et al., 2018; Zabel et al., 2019). In addition, the fractal dimension (FD) of the superficial vascular network also significantly reduced in AD patients (Chua et al., 2020), while FD reflected the complexity of retinal vascular branches and the density of the entire retinal vascular system. However, the changes in FD in MCI patients remain controversial. One study shows that FD in the superficial vascular network significantly reduces in MCI patients as compared to normal controls (Chua et al., 2020). But another case–control study shows a significant increase in the retinal FD in patients with MCI due to AD (Biscetti et al., 2021). There are also some changes in the choroid in AD and MCI patients. Compared with normal controls, choroid thickness was significantly thinner in AD patients (Trebbastoni et al., 2017; Salobrar-Garcia et al., 2020). However, the choroid thickness of MCI patients tends to become thinner although there is no statistical significance (López-de-Eguileta et al., 2020).

Therefore, this study was to compare VD and blood perfusion density (PD) of macular retinal superficial capillary plexus (SCP) in AD patients, MCI patients and healthy controls by OCTA. The relationships among the retinal microvascular network and cognitive function, Aβ protein and phosphorylated Tau (p-Tau) protein were also investigated.

Materials and methods

Participants

This study design was approved by the Clinical Research Ethics Committee of Tongji Hospital, Shanghai [(Tong) Audit No. (K-2017-003-XZ-190130)], and conducted according to the Declaration of Helsinki. All participants signed informed consent forms before the study. Inclusion criteria: (1) Patients were 50–90 years; (2) Patients were diagnosed with AD or MCI; (3) Scanning signal intensity index on OCTA was >4; (4) Healthy controls (HC) had no history of dementia and had normal cognitive function. Exclusion criteria: (1) History of diabetes mellitus, uncontrolled hypertension, heart disease, or other serious chronic medical conditions; (2) Refractive error > ±6 spherical equivalent; (3) Intraocular surgery within 6 months; (4) A history of glaucoma or intraocular pressure (IOP) >21 mmHg; (5) Macular disease or retinopathy,

such as age-related macular degeneration, macular anterior membrane, retinal vascular obstruction, etc.; (6) Other neurological diseases or severe psychiatric illnesses. (7) Apparent media opacification.

Diagnosis

The study participants were all from the Department of Neurology or Ophthalmology of Tongji Hospital in Shanghai. Data were collected from July 2020, to August 2022. The diagnoses of AD and MCI was based on 2011 guidelines of the National Institute of Aging-Alzheimer's Association workgroups (NIA/AA) (McKhann et al., 2011) and the quantitative criteria proposed by Jak/Bondi in 2014 (Bondi et al., 2014).

Alzheimer's disease: (1) Insidious onset and slow progression of symptoms; (2) A clear history of cognitive deterioration; (3) Impaired ability to function in daily life; (4) Cognitive impairment was classified into the following categories when the medical history and neuropsychological assessment were reviewed: (a) Amnestic presentation; (b) Nonamnestic presentations: language disorders, visuospatial disorders, and executive dysfunction; (5) Exclusion of other causes of dementia, such as metabolic disorder and encephalopathy.

Mild cognitive impairment: (1) Cognitive concern reflecting a change in cognition reported by the patient or relatives or clinicians; (2) Mini-Mental State Examination (MMSE) scores: illiterate ≤17, elementary school ≤20, middle school and above ≤24; or Montreal Cognitive Assessment Basic (MoCA-B) scores: elementary school and below ≤19, secondary school ≤22, college ≤24; (3) Clinical Dementia Rating Scale (CDR) = 0.5, not enough to diagnose dementia; (4) Meeting any one of the following three criteria: (a) impairment of 2 metrics in the same cognitive domain [score are 1 standard deviations (SD) below the mean for their age and education matched peers]; (b) impairment of 1 test score in 2 or more of the four cognitive domains (score are 1 SD below the mean for their age and education matched peers); (c) instrumental activities of daily living (IADL) score: more than one item score of 1 or more.

Neurological and ophthalmic examinations

All participants underwent neurological tests. A full set of cognitive scales were used to assess their cognitive status, including: MoCA-B, MMSE, IADL, Hamilton anxiety scale (HAMA), Hamilton depression scale (HAMD), Hopkins Verbal Learning Test (HVLT), Wechsler memory scale (WMS), Boston naming test (BNT), Verbal fluency test (VFT), Shape trails test (STT), and Rey-Osterrieth complex figure test (ROCFT). In addition, medical history, and results from laboratory and neuroimaging examinations were collected to aid the diagnosis. Furthermore, with the consent of some participants, CSF was collected and tested for Aβ and p-Tau proteins. CSF samples were collected from 23 patients, including 16 AD patients and 7 MCI patients.

A complete ophthalmic examination was administered, including the measurement of best-corrected visual acuity (BCVA), IOP, slit lamp examination and conventional OCTA of the macula. An international standard logarithmic visual acuity chart was used to measure the BCVA. IOP was measured three times with a hand-held tonometer, and the average value was taken. OCTA images and slit lamp examination were used to rule out other eye diseases.

Procedures for OCTA

The ZEISS Angioplex™ OCTA (Carl Zeiss Meditec, Dublin, CA) was used to scan the macula of all the participants. It has a scan rate of 68,000 A-scans per second, a central wavelength of 840 nm, and motion tracking to reduce motion artifacts. 6 × 6 mm images centered on the fovea were acquired. This study focuses on retinal SCP, which was defined as the area from the internal limiting membrane (ILM) to the inner plexiform layer (IPL). We subdivided the macula into 1 × 1 mm fovea subregion, 3 × 3 mm inner ring and 6 × 6 mm outer ring. Meanwhile, the inner ring and outer ring were divided into superior, inferior, nasal and temporal subregions (Figure 1). VD was defined as the ratio of total length of blood vessels in the region to the area of the region, whereas PD was defined as the ratio of covered area of blood vessels in the region to the area of the region. The built-in software automatically calculates the area of the macular foveal avascular zone (FAZ), VD and PD.

All the examinations are performed by the same skilled clinicians. The clinician input the patient's name, gender and date of birth, and informed the patient of the precautions for examination to relieve the patient's nervousness and clear images were captured. Participants were seated with their mandible placed on the mandibular support and their forehead pressed against the front support. The position was adjusted so that the patient's lateral canthus was at the same height as the horizontal line. Good fixation is required during the scanning. After each scan, the operator determines whether rescanning is needed depending on the image quality. The high-quality images were captured and saved in the computer.

Statistical analysis

The enumeration data are represented by the number of cases, and the Chi-square test was used for comparisons between groups. The measurement data are expressed as mean ± standard deviation, and Shapiro–Wilk test was used to test the normality of these data. If the data were normally distributed, one-way analysis of variance (ANOVA) was used for comparisons among groups. If the data were not normally distributed, Kruskal–Wallis H method was used for comparisons between groups. Multiple logistic regression models for each of the OCTA parameters with adjustments for confounding factors were used to compare AD, MCI and HC subjects. Partial correlation analysis was used to evaluate the correlations among OCTA parameters and neuropsychological assessment scores, Aβ and p-Tau protein. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using Statistical Package for Social Sciences (version 20.0, SPSS Inc., Chicago, IL, United States).

Results

Patient characteristics

A total of 139 subjects were included in this study, including 43 AD patients, 62 MCI patients and 34 HC. The eye with high-quality image was selected from each participant. Of AD patients, there were 21 (48.8%) males, and 58.1% were older than 70 years. Of MCI patients, there were 25 (40.3%) males, and 53.2% were older than

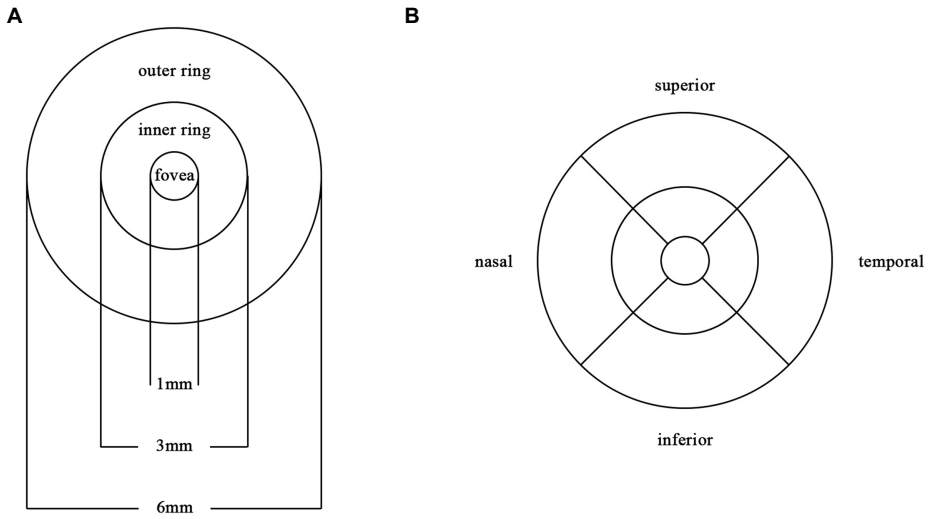

FIGURE 1
Partition diagram Partition diagram of the macula. **(A)** The macula is divided into 1×1mm fovea, 3×3mm inner ring and 6×6mm outer ring. **(B)** The inner ring and outer ring are divided into superior, inferior, nasal and temporal subregions.

TABLE 1 Patient's demographic characteristics.

	AD (*n*=43)	MCI (*n*=62)	HC (*n*=34)	*P*
Sex				0.449
Female	22(51.2%)	37(59.7%)	16(47.1%)	
Male	21(48.8%)	25(40.3%)	18(52.9%)	
Age				0.767
50–70 years	18(41.9%)	29(46.8%)	17(50%)	
>70 years	25(58.1%)	33(53.2%)	17(50%)	
History of smoking (Yes)	11(25.6%)	13(21%)	11(32.3%)	0.469
History of alcohol intake (Yes)	3(6.9%)	2(3.2%)	1(3.0%)	0.608
Hypertension (Yes)	15(34.9%)	24(37.5%)	13(38.2%)	0.918
Hyperlipidemia (Yes)	12(27.9%)	11(17.7%)	13(38.2%)	0.085
Years of education	10.3 ± 5.32	11.05 ± 4.15	10.68 ± 3.86	0.76
BCVA	0.63 ± 0.26	0.74 ± 0.22	0.76 ± 0.23	0.037*
IOP	14.12 ± 1.80	14.4 ± 1.84	14.53 ± 1.75	0.349
FAZ	0.34 ± 0.14	0.35 ± 0.14	0.34 ± 0.15	0.978

Data are shown as mean ± standard deviation or number. AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy controls; F, female; M, male; BCVA, best-corrected visual acuity; IOP, intraocular pressure; FAZ, foveal avascular zone. *Significant at $p < 0.05$. The bold values indicate that the number is < 0.05, indicating a statistical difference.

TABLE 2 Assessment of cognitive function in each group.

	AD (*n*=43)	MCI (*n*=62)	HC (*n*=34)	*P*
MMSE	16.56 ± 6.68	25.19 ± 2.48	27.15 ± 2.23	**<0.001***
MoCA-B	10.67 ± 6.09	19.23 ± 4.68	22.85 ± 3.78	**<0.001***
HAMD	9.28 ± 6.29	7.90 ± 4.95	5.41 ± 4.31	**0.009***
HAMA	9.67 ± 6.42	9.02 ± 5.82	6.62 ± 4.79	**0.089***
Memory function				
HVLT-immediate	2.49 ± 1.76	4.06 ± 1.58	4.47 ± 1.58	**<0.001***
HVLT-5 min delay	0.84 ± 2.06	4.45 ± 3.38	6.65 ± 2.87	**<0.001***
HVLT-20 min delay	0.74 ± 2.18	4.03 ± 3.35	6.74 ± 2.80	**0.001***
WMS	3.98 ± 2.69	7.03 ± 2.93	8.71 ± 2.74	**<0.001***
Language function				
BNT	16.09 ± 6.71	21.56 ± 3.78	23.76 ± 3.39	**<0.001***
VFT	7.21 ± 3.28	11.76 ± 3.29	14.32 ± 3.19	**<0.001***
Executive function				
STT-1	95.67 ± 47.55	67.84 ± 25.94	56.03 ± 17.30	**<0.001***
STT-2	182.08 ± 48.02	155.53 ± 47.48	135.29 ± 39.97	**0.001***
Visuospatial function				
ROCFT-copy	22.35 ± 13.91	32.92 ± 4.73	34.88 ± 1.49	**<0.001***
ROCFT-recall	4 ± 7.65	11.6 ± 7.96	18.06 ± 6.79	**<0.001***

Data are shown as mean ± standard deviation or number. AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy controls; MMSE, Mini-mental State Examination; MoCA-B, Montreal Cognitive Assessment Basic; HAMD, Hamilton depression scale; HAMA, Hamilton anxiety scale; HVLT, Hopkins Verbal Learning Test; WMS, Wechsler memory scale; BNT, Boston naming test; VFT, Verbal fluency test; STT, Shape trails test; ROCFT, Rey-Osterrieth complex figure test. *Significant at $p < 0.05$. The bold values indicate that the number is < 0.05, indicating a statistical difference.

70 years. Of healthy controls, there were 18 (52.9%) males, and 50% were older than 70 years. The demographic characteristics of AD patients, MCI patients, and HC are shown in Table 1. There were no significant differences in the age, sex, history of smoking, history of alcohol intake, hypertension, hyperlipidemia, years of education, IOP and FAZ among AD, MCI and HC groups ($p > 0.05$). The BCVA was 0.63 ± 0.26 in the AD group, 0.74 ± 0.22 in the MCI group, and 0.76 ± 0.23 in the HC group ($p = 0.037$).

The scores of neuropsychological assessments in each group are shown in Table 2. There was no significant difference in the HAMA score among three groups ($p = 0.089$). There were significant differences in the MMSE score ($p < 0.001$), MoCA-B score ($p < 0.001$), HAMD score ($p = 0.009$), HVLT score ($p < 0.001$), WMS score

($p < 0.001$), BNT score ($p < 0.001$), VFT score ($p < 0.001$), STT score ($p < 0.001$) and ROCFT score ($p < 0.001$) among AD, MCI and HC groups.

Vessel density

Compared with HC group (14.13 ± 3.00), the VD of the whole circle region (12.26 ± 2.87) significantly decreased in the AD group ($p < 0.05$). The whole circle was divided into three regions: fovea subregion, inner ring and outer ring. The results showed that, compared with HC group, the VD in the inner ring (AD:10.74 ± 3.42, HC:13.02 ± 3.70, $p < 0.05$) and outer ring (AD:13.07 ± 2.92, HC:14.83 ± 2.91, $p < 0.05$) regions significantly decreased in the AD group. Then, the inner ring and the outer ring were divided into four regions, respectively (Figure 1). In the AD group, the VD also significantly reduced in the nasal (AD:10.96 ± 3.79, HC:13.43 ± 4.12, $p = 0.008$) and inferior (AD:9.66 ± 4.03, HC:12.95 ± 3.80, $p = 0.001$) regions of inner ring, nasal (AD:15.72 ± 2.87, HC:17.39 ± 2.95, $p = 0.011$), superior (AD:12.99 ± 3.12, HC: 15.00 ± 3.03, $p = 0.009$) and inferior (AD: 12.2 ± 3.78, HC: 14.48 ± 3.39, $p = 0.017$) region of outer ring as compared to HC group (Table 3 and Figure 2). There were no significant differences in other areas. There was no significant difference between MCI group and HC group, and between AD group and MCI group ($p > 0.05$) (Table 3 and Figure 2). After adjusting for confounding factors such as sex, age, history of smoking, history of alcohol intake, hypertension, hyperlipidemia, BCVA, and IOP, multiple logistic regression analysis showed that the significant differences remained in the AD group except for the nasal (OR = 0.829, 95%CI: 0.683, 1.005) region of outer ring (Figures 3, 4). Compared with HC group, VD decreased significantly in the nasal (OR = 0.853, 95%CI: 0.740, 0.984) and inferior (OR = 0.821, 95%CI: 0.714, 0.943) regions of the inner ring and in the superior (OR = 0.825, 95%CI: 0.694, 0.981) and inferior (OR = 0.846, 95%CI: 0.725, 0.987) regions of the outer ring in the AD group (Figures 3, 4). Compared with HC group, VD also decreased significantly in the superior (OR = 0.870, 95%CI:0.763, 0.993) and inferior (OR = 0.869, 95%CI: 0.765, 0.988) regions of the inner ring and in the temporal (OR = 0.866, 95%CI: 0.753, 0.995) and superior (OR = 0.836, 95%CI: 0.709, 0.987) regions of the outer ring in the MCI group (Figures 3, 4).

Perfusion density

Perfusion density showed the same results to VD. Compared with HC group (0.338 ± 0.077), the PD (0.29 ± 0.07) in the whole circle region significantly decreased in the AD group ($p < 0.05$). The whole circle was divided into three regions. Compared with HC group, the PD in the inner ring (AD: 0.24 ± 0.08, HC: 0.302 ± 0.093, $p < 0.05$) and outer ring (AD: 0.31 ± 0.07, HC: 0.358 ± 0.076, $p < 0.05$) regions significantly decreased in the AD group. Then, the inner and outer rings were further explored. In the AD group, the PD also significantly reduced in nasal (AD: 0.25 ± 0.09, HC: 0.309 ± 0.102, $p = 0.007$) and inferior (AD: 0.22 ± 0.1, HC: 0.305 ± 0.097, $p = 0.001$) regions of inner ring, nasal (AD: 0.37 ± 0.08, HC: 0.421 ± 0.078, $p = 0.006$), superior (AD: 0.31 ± 0.08, HC: 0.364 ± 0.080, p = 0.007) and inferior (AD: 0.29 ± 0.1, HC: 0.351 ± 0.087, $p = 0.017$) regions of outer ring as compared to the HC group (Table 4 and Figure 5). There were no significant differences in other areas. There was no significant difference between MCI group and HC group, and between AD group and MCI group ($p > 0.05$) (Table 4 and Figure 5). After adjusting for confounding factors such as sex, age, history of smoking, history of alcohol intake, hypertension, hyperlipidemia, BCVA, and IOP, multiple logistic regression analysis showed that significant differences remained in the AD group. Compared with HC group, VD decreased significantly in the nasal (OR = 0.001, 95%CI: $3.62*10^{-6}$, 0.406) and inferior (OR = $1.89*10^{-4}$, 95%CI: $6.48*10^{-7}$, 0.055) regions of the inner ring and in the nasal (OR = $4.41*10^{-4}$, 95%CI: $3.50*10^{-7}$, 0.554), superior (OR = 0.001, 95%CI: $8.15*10^{-7}$, 0.423) and inferior (OR = 0.001, 95%CI: $2.76*10^{-6}$, 0.450) regions of the outer ring in the AD group (Figures 6, 7). Compared with HC group, VD also

TABLE 3 Comparison of vessel density in macular among the three groups.

VD	AD (n=43)	MCI (n=62)	HC (n=34)	P	AD vs. HC	MCI vs. HC	AD vs. MCI
					P	P	P
Whole circle	12.26 ± 2.87	12.68 ± 3.36	14.13 ± 3.00	**0.011***	**0.009***	0.085	0.872
Fovea	3.2 ± 2.24	3.43 ± 2.22	4.32 ± 2.91	0.239	>0.05	>0.05	>0.05
Inner ring	10.74 ± 3.42	11.35 ± 3.73	13.02 ± 3.70	**0.013***	**0.012***	0.078	1.000
Nasal	10.96 ± 3.79	11.77 ± 3.68	13.43 ± 4.12	**0.009***	**0.008***	0.068	0.887
Temporal	11.1 ± 3.66	11.28 ± 4.34	12.68 ± 4.04	0.172	>0.05	>0.05	>0.05
Superior	11.18 ± 3.62	11.33 ± 3.94	13.02 ± 3.92	0.07	>0.05	>0.05	>0.05
Inferior	9.66 ± 4.03	11.03 ± 4.07	12.95 ± 3.80	**0.002***	**0.001***	0.065	0.321
Outer ring	13.07 ± 2.92	13.42 ± 3.37	14.83 ± 2.91	**0.018***	**0.017***	0.091	1.000
Nasal	15.72 ± 2.87	16.15 ± 3.33	17.39 ± 2.95	**0.013***	**0.011***	0.086	0.958
Temporal	11.31 ± 3.26	10.97 ± 4.06	12.46 ± 3.64	0.184	>0.05	>0.05	>0.05
Superior	12.99 ± 3.12	13.54 ± 3.67	15.00 ± 3.03	**0.011***	**0.009***	0.135	0.585
Inferior	12.2 ± 3.78	12.94 ± 3.77	14.48 ± 3.39	**0.019***	**0.017***	0.114	1.000

Data are shown as mean ± standard deviation or number. VD, vessel density; AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy controls. *Significant at $p < 0.05$. The bold values indicate that the number is < 0.05, indicating a statistical difference.

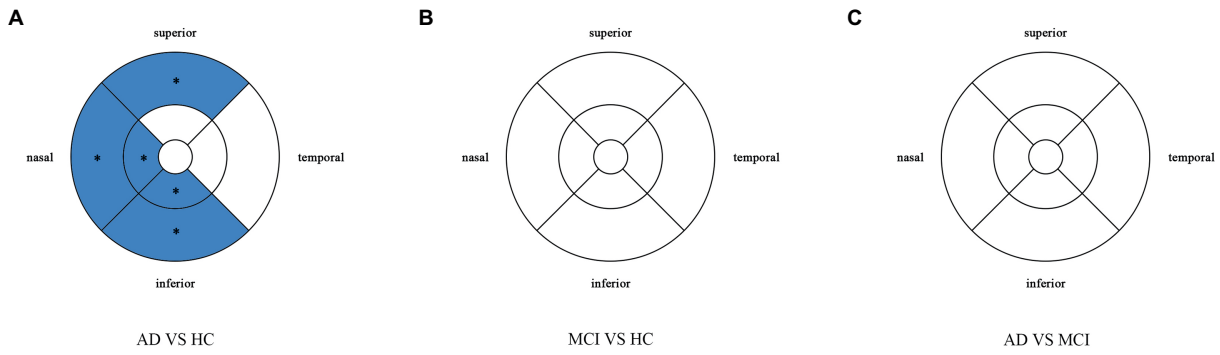

FIGURE 2
Comparison of vessel density in macular among the AD, MCI, and HC groups. Blue regions indicate that the vessel density of the former decreases significantly in these areas compared to the latter. **(A)** In the AD group, the vessel density significantly reduces in the nasal and inferior regions of inner ring, and in the nasal, superior and inferior regions of outer ring as compared to HC group. **(B,C)** There is no significant difference between MCI group and HC group, and between AD group and MCI group. *Significant at $p<0.05$. AD, Alzheimer's disease; MCI, mental cognitive impairment; HC, healthy controls.

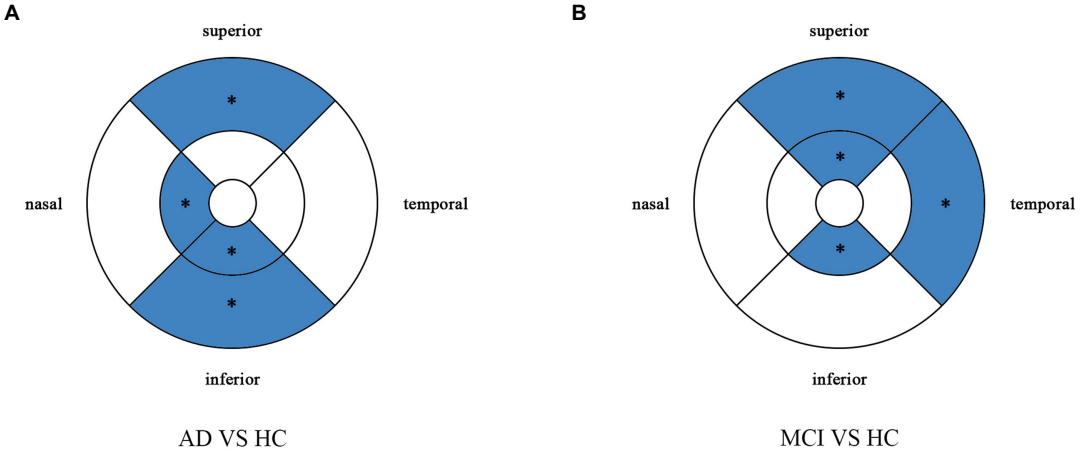

FIGURE 3
Multiple logistic regression was used to assess the association between retinal vessel density and clinical diagnosis, adjusted for confounders of sex, age, history of smoking, history of alcohol intake, hypertension, hyperlipidemia, BCVA, and IOP. Blue regions indicate decreases significantly compared with the HC group. **(A)** Compared with HC group, vessel density decreases significantly in the nasal and inferior regions of the inner ring and in the superior and inferior regions of the outer ring in the AD group. **(B)** Compared with HC group, vessel density decreases significantly in the superior and inferior regions of the inner ring and in the temporal and superior regions of the outer ring in the MCI group. *Significant at p<0.05. AD, Alzheimer's disease; MCI, mental cognitive impairment; HC, healthy controls.

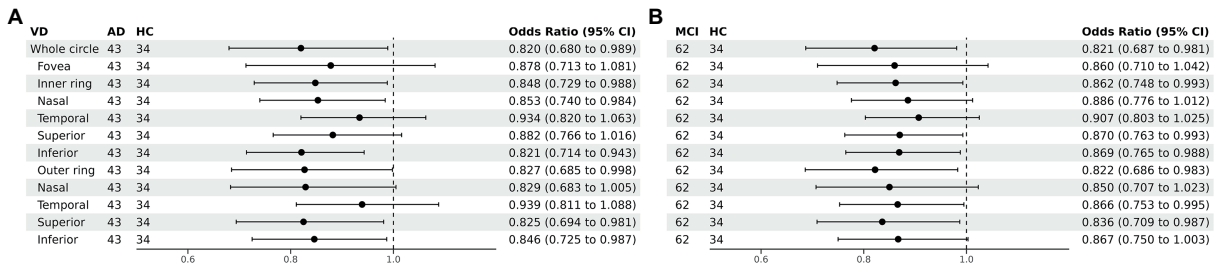

FIGURE 4
Forest plot of vessel density comparison among three groups. Multiple logistic regression was used to access the association between retinal vessel density and clinical diagnosis, adjusted for confounders of sex, age, history of smoking, history of alcohol intake, hypertension, hyperlipidemia, BCVA, and IOP. **(A)** Compared with HC group, vessel density decreased significantly in the nasal and inferior regions of the inner ring and in the superior and inferior regions of the outer ring in the AD group. **(B)** Compared with HC group, vessel density decreased significantly in the superior and inferior regions of the inner ring and in the temporal and superior regions of the outer ring in the MCI group. VD, vessel density; AD, Alzheimer's disease; MCI, mental cognitive impairment; HC, healthy controls; CI, confidence interval.

TABLE 4 Comparison of perfusion density in macular among the three groups.

PD	AD (*n*=43)	MCI (*n*=62)	HC (*n*=34)	*P*	AD vs. HC	MCI vs. HC	AD vs. MCI
					P	*P*	*P*
Whole circle	0.29 ± 0.07	0.3 ± 0.08	0.338 ± 0.077	**0.009***	**0.007***	0.092	0.676
Fovea	0.07 ± 0.05	0.07 ± 0.05	0.093 ± 0.066	0.218	>0.05	>0.05	>0.05
Inner ring	0.24 ± 0.08	0.26 ± 0.09	0.302 ± 0.093	**0.012***	**0.01***	0.078	0.970
Nasal	0.25 ± 0.09	0.27 ± 0.09	0.309 ± 0.102	**0.009***	**0.007***	0.078	0.798
Temporal	0.25 ± 0.09	0.26 ± 0.1	0.293 ± 0.101	0.144	>0.05	>0.05	>0.05
Superior	0.26 ± 0.09	0.26 ± 0.1	0.302 ± 0.096	0.076	>0.05	>0.05	>0.05
Inferior	0.22 ± 0.1	0.25 ± 0.1	0.305 ± 0.097	**0.001***	**0.001***	0.062	0.266
Outer ring	0.31 ± 0.07	0.32 ± 0.09	0.358 ± 0.076	**0.017***	**0.014***	0.116	0.897
Nasal	0.37 ± 0.08	0.39 ± 0.09	0.421 ± 0.078	**0.008***	**0.006***	0.091	0.647
Temporal	0.27 ± 0.08	0.26 ± 0.1	0.297 ± 0.093	0.194	>0.05	>0.05	>0.05
Superior	0.31 ± 0.08	0.33 ± 0.1	0.364 ± 0.080	**0.01***	**0.007***	0.194	0.374
Inferior	0.29 ± 0.1	0.31 ± 0.1	0.351 ± 0.087	**0.021***	**0.017***	0.163	0.776

Data are shown as mean ± standard deviation or number. PD, perfusion density; AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy controls. *Significant at $p < 0.05$. The bold values indicate that the number is < 0.05, indicating a statistical difference.

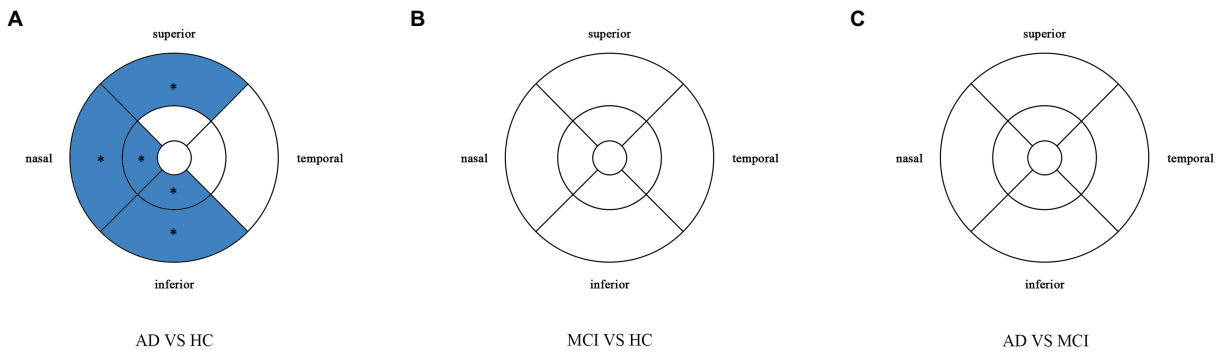

FIGURE 5
Comparison of perfusion density in macular among the AD, MCI, and HC groups. Blue regions indicate that the perfusion density of the former decreases significantly in these areas compared to the latter. **(A)** In the AD group, the perfusion density significantly reduces in the nasal and inferior regions of inner ring, and in the nasal, superior snd inferior regions of outer ring as compared to HC group. **(B,C)** There is no significant difference between MCI group and HC group, and between AD group and MCI group. *Significant at $p<0.05$. AD, Alzheimer's disease; MCI, mental cognitive impairment; HC, healthy controls.

decreased significantly in the superior (OR = 0.004, 95%CI: $1.73*10^{-5}$, 0.883) and inferior (OR = 0.002, 95%CI: $1.39*10^{-5}$, 0.445) regions of the inner ring and in the temporal (OR = 0.004, 95%CI: $1.57*10^{-5}$, 0.938) and superior (OR = 0.002, 95%CI: $3.53*10^{-6}$, 0.975) regions of the outer ring in the MCI group (Figures 6, 7).

Correlation analysis

The correlations between OCTA parameters and cognitive function were further evaluated using partial correlation analysis. After adjusting for sex and age, VD and PD of the inner ring region were correlated with MoCA-B score, MMSE score, STT-A score and ROCFT score. VD of the outer ring region was correlated with MoCA-B score and STT-A score. PD of the outer ring region was correlated with MoCA-B score, STT-A score and ROCFT-recall. VD and PD of the fovea region were correlated with MoCA-B score and ROCFT-recall (Table 5).

The CSF was collected for the detection of Aβ and p-Tau protein. The correlation between OCTA parameters and Aβ or p-Tau protein was further evaluated. After adjusting for sex and age, the results showed no correlation between them (Table 6).

Discussion

In this cross-sectional study, changes in blood vessels and blood flow of the SCP were investigated in patients with AD and MCI. VD and PD of the SCP significantly reduced in patients with AD and MCI compared with healthy controls. This suggests that the retinal microvascular system is damaged in patients with AD and MCI. And these blood flow indicators correlated with cognitive

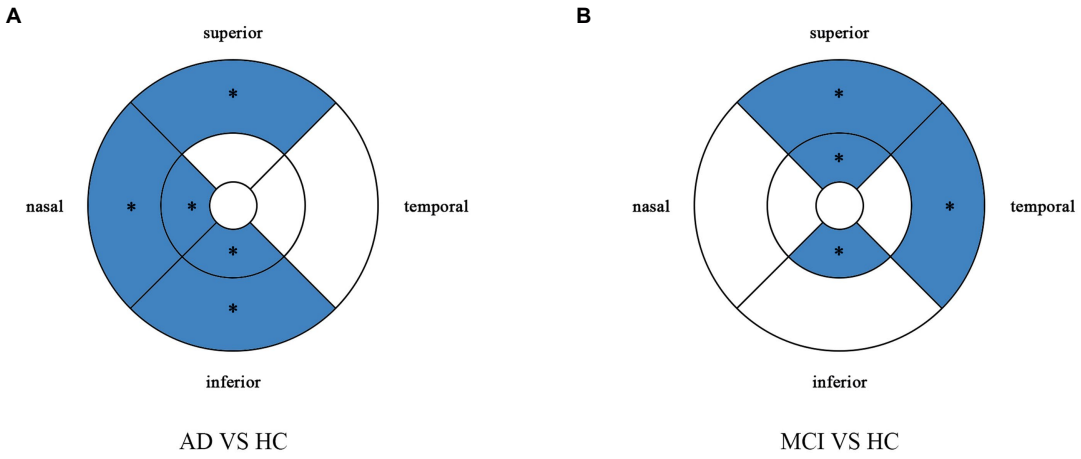

FIGURE 6
Multiple logistic regression was used to assess the association between retinal perfusion density and clinical diagnosis, adjusted for confounders of sex, age, history of alcohol intake, hypertension, hyperlipidemia, BCVA, and IOP. Blue regions indicate decreases significantly compared with the HC group. **(A)** Compared with HC group, perfusion density decreases significantly in the nasal and inferior regions of the inner ring and in the nasal, superior and inferior regions of the outer ring in the AD group. **(B)** Compared with HC group, perfusion density decreases significantly in the superior and inferior regions of the inner ring and in the temporal and superior regions of the outer ring in the MCI group. *Significant at $p<0.05$. AD, Alzheimer's disease; MCI, mental cognitive impairment; HC, healthy controls.

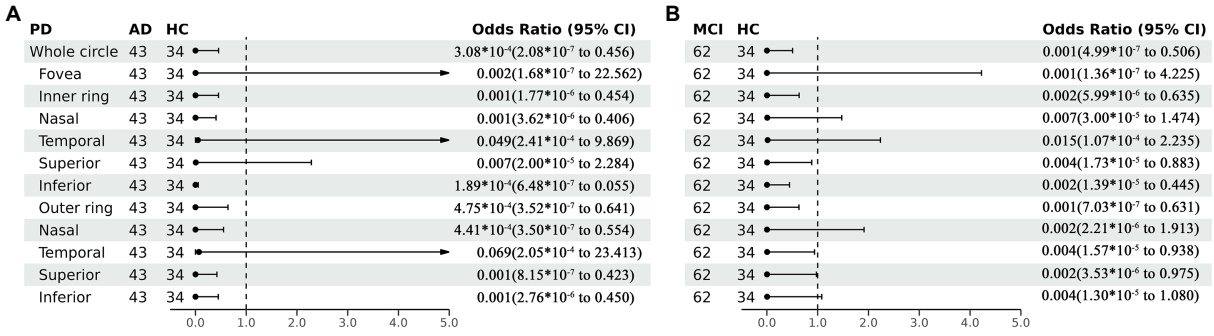

FIGURE 7
Forest plot of perfusion density comparison among three groups. Multiple logistic regression was used to assess the association between retinal perfusion density and clinical diagnosis, adjusted for confounders of sex, age, history of smoking, history of alcohol intake, hypertension, hyperlipidemia, BCVA, and IOP. **(A)** Compared with HC group, perfusion density decreased significantly in the nasal and inferior regions of the inner ring and in the nasal, superior and inferior regions of the outer ring in the AD group. **(B)** Compared with HC group, perfusion density decreased significantly in the superior and inferior regions of the inner ring and in the temporal and superior regions of the outer ring in the MCI group. PD, perfusion density; AD, Alzheimer's disease; MCI, mental cognitive impairment; HC, healthy controls; CI, confidence interval.

function. However, no correlation was revealed among these blood flow indicators and Aβ, p-Tau protein.

The mechanism underlying the decreased retinal blood flow in AD patients remains unclear. It has been proposed that Aβ protein may be deposited in the retina, causing damage to blood vessels. Autopsy results and AD animal experiments have shown that AD is accompanied by the deposition of retinal Aβ protein (Grimaldi et al., 2018; Chiquita et al., 2019; Shi et al., 2020), and the retina may have the deposition of Aβ protein before the Aβ accumulation in the brain (Koronyo-Hamaoui et al., 2011; Mirzaei et al., 2019). Aβ protein deposits in the vascular walls, resulting in decreased blood flow, hypoxia and nutrient deficiency. The hypoxic retina promotes angiogenesis by producing vascular endothelial growth factors (VEGF) to ensure essential oxygen and nutrient supplies. However, this process is stopped by the Aβ protein. VEGF is mechanically blocked by the diffuse accumulation of Aβ plaques, and Aβ protein competitively binds to VEGF receptor 2. Therefore, VEGF cannot bind to their corresponding endothelial receptors to restore retinal blood supply to normal levels (Bulut et al., 2018; Yoon et al., 2019). A recent study (Shi et al., 2020) has also suggested that Aβ protein accumulation in retinal blood vessels leads to decreased expression of platelet-derived growth factor receptor-β and pericyte loss, vascular cells that regulate blood flow in capillaries, coupled with decreased expression of LDL receptor-related protein-1(LRP-1), which leads to impaired blood-retinal barrier. The ability to clear Aβ protein is reduced, causing vascular damage. This may be the reason why retinal VD and PD are reduced in patients with AD.

TABLE 5 Correlation between retinal blood flow and cognitive function.

		VD				PD			
		Whole circle	Fovea	Inner ring	Outer ring	Whole circle	Fovea	Inner ring	Outer ring
MoCA-B	*r*	**0.200**	**0.224**	**0.234**	**0.176**	**0.207**	**0.223**	**0.240**	**0.188**
	p	**0.019***	**0.009***	**0.006***	**0.039***	**0.015***	**0.009***	**0.005***	**0.028***
MMSE	*r*	0.146	0.132	**0.185**	0.122	0.152	0.131	**0.189**	0.132
	p	0.088	0.125	**0.03***	0.154	0.077	0.127	**0.027***	0.123
Memory function									
HVLT-immediate	*r*	0.029	0.009	0.068	0.012	0.029	0.006	0.066	0.015
	p	0.739	0.921	0.429	0.892	0.736	0.946	0.445	0.861
HVLT-5 min delay	*r*	0.092	0.112	0.139	0.069	0.099	0.115	0.143	0.08
	p	0.285	0.192	0.104	0.426	0.251	0.182	0.096	0.355
HVLT-20 min delay	*r*	0.108	0.127	0.163	0.082	0.115	0.131	0.168	0.092
	p	0.208	0.139	0.057	0.339	0.181	0.128	0.05	0.284
WMS	*r*	0.145	0.152	0.159	0.131	0.151	0.152	0.165	0.140
	p	0.091	0.077	0.063	0.126	0.077	0.076	0.054	0.102
Language function									
BNT	*r*	0.120	0.099	0.097	0.121	0.128	0.104	0.103	0.131
	p	0.164	0.248	0.258	0.159	0.137	0.225	0.229	0.128
VFT	*r*	0.043	0.088	0.077	0.026	0.049	0.09	0.082	0.035
	p	0.615	0.307	0.374	0.762	0.568	0.297	0.338	0.688
Executive function									
STT-A	*r*	**−0.226**	−0.158	**−0.208**	**−0.222**	**−0.225**	−0.166	**−0.206**	**−0.223**
	p	**0.011***	0.076	**0.019***	**0.013***	**0.011***	0.064	**0.021***	**0.012***
STT-B	*r*	−0.045	−0.149	−0.063	−0.034	0.046	−0.155	0.058	0.039
	p	0.633	0.115	0.508	0.723	0.625	0.099	0.538	0.684
Visuospatial function									
ROCFT-copy	*r*	0.163	0.111	**0.168**	0.153	0.168	0.112	**0.173**	0.160
	p	0.058	0.196	**0.049***	0.074	0.050	0.194	**0.043***	0.061
ROCFT-recall	*r*	**0.180**	**0.180**	**0.202**	0.163	**0.183**	**0.180**	**0.203**	**0.169**
	p	**0.036***	**0.036***	**0.018***	0.058	**0.033***	**0.035***	**0.017***	**0.049***

Partial correlation analysis was used to evaluate the correlations between retinal blood flow and cognitive function, adjusted for confounders of sex, age. VD, vessel density; PD, perfusion density; MMSE, Mini-mental State Examination; MoCA-B, Montreal Cognitive Assessment Basic; HVLT, Hopkins Verbal Learning Test; WMS, Wechsler memory scale; BNT, Boston naming test; VFT, Verbal fluency test; STT, Shape trails test; ROCFT, Rey-Osterrieth complex figure test. *Significant at $p < 0.05$. The bold values indicate that the number is < 0.05, indicating a statistical difference.

Studies have indicated that the distribution of Aβ protein is not uniform in the retina, but analyzing the changes in the whole retina may ignore the changes in local areas (Lad et al., 2018; Chan et al., 2019). In the present study, the densities of different retinal regions were calculated. After adjusting for confounding factors, the VD and PD in the inner ring (especially in the nasal and inferior regions), and outer ring (especially in the superior and inferior regions) significantly decreased in the AD group compared with HC group. VD and PD in the inner ring (especially in the superior and inferior regions), and outer ring (especially in the superior and temporal regions) significantly decreased in the MCI group compared with HC group. Wu et al. (2020) also conducted a similar study. They also divided the macula into many areas, but their study results showed that the superficial retinal vascular plexus in AD and MCI groups showed no significant difference compared with the normal control group, while the trend of blood flow decline was more obvious in the deep retinal capillary plexus (Wu et al., 2020). But the study did not adjust for confounding factors, and the two studies used different OCTA cameras. This may account for the differences between the two studies. Lahme et al. (2018) also divided the blood vessels of macular retina into superficial layer and deep layer for analysis, and their results were consistent with our results about AD. The blood vessel density in the superficial layer of macular retina in AD patients was lower than that in the control group. Another study also supports our conclusion (Wang et al., 2020). Changes in retinal small vessels may reflect changes in brain small vessels in Alzheimer's disease. These parameters may be used as alternative non-invasive biomarkers for AD diagnosis. We speculate that the localized changes may be caused by the thinning

TABLE 6 Correlation between retinal blood flow and Aβ, p-Tau protein.

	Aβ protein (*n*=23)		p-Tau protein (*n*=23)	
	r	*P*	*r*	*P*
VD				
Fovea	−0.074	0.743	−0.215	0.336
Inner ring	0.009	0.968	−0.305	0.168
Outer ring	0.078	0.730	−0.067	0.767
Whole circle	0.065	0.772	−0.147	0.514
PD				
Fovea	−0.053	0.815	−0.233	0.297
Inner ring	0.012	0.957	−0.318	0.150
Outer ring	0.077	0.734	−0.07	0.759
Whole circle	0.063	0.781	−0.146	0.517

Partial correlation analysis was used to evaluate the correlations between retinal blood flow and Aβ, p-Tau protein, adjusted for confounders of sex, age. Aβ, amyloid-beta protein; p-Tau, phosphorylated Tau protein; VD, vessel density; PD, perfusion density.

of ganglion cell layer in AD patients, which changes the retinal blood flow in the corresponding area. The SCP provides nutrients and oxygen to the layers of nerve fiber and ganglion cell in the retina (Jiang et al., 2018). Yoon et al. (2019) investigated the ganglion cell and inner plexiform layer (GC-IPL) thickness in AD patients, and results showed that GC-IPL thickness significantly reduced in AD patients, and the decreased areas were concentrated in the superonasal, inferior and inferonasal regions around the macula. It is roughly consistent with the decreased areas of retinal VD and PD in AD patients in this study. Our study also showed that retinal VD and PD decreased in patients with MCI. This indicates that MCI patients have developed vascular lesions before the onset of clinical symptoms of AD. Therefore, the retinal microvascular network may reflect the early signs of microvascular injury in the MCI and AD patients.

There was no significant difference in the FAZ area between the groups in this study, which was inconsistent with previous findings. Bulut et al. (2018) found that, as compared to healthy controls, the FAZ area in AD patients increased, and a significant negative correlation was noted between FAZ area and MMSE score, suggesting that the lower the MMSE score, the larger the FAZ area is. Similar results were reported by O'Bryhim et al. (2018). In his study, the cognitively healthy subjects were into two groups based on the biomarkers, and results showed significant difference in the FAZ area between two groups, with patients in the biomarker positive group having larger FAZ area (O'Bryhim et al., 2018), but there was no difference in average annual change of FAZ area between the two groups during the 3-year follow-up period (O'Bryhim et al., 2021). Another study showed that the FAZ area remained unchanged (van de Kreeke et al., 2020). But FAZ size varies greatly in healthy people and can be affected by a number of factors (Laatikainen and Larinkari, 1977; Wagner-Schuman et al., 2011; Sampson et al., 2017). Therefore, whether FAZ can be used as a noninvasive retinal marker for AD remains controversial. And more studies with larger sample sizes are needed to confirm the association between FAZ area and AD pathology.

In addition, we compared the correlation between retinal blood flow parameters and cognitive function. MoCA-B and MMSE are usually employed to measure overall cognitive function. HVLT and WMS are used to test the memory function of patients. HVLT-immediate is used to reflect immediate memory, while HVLT-delay is used to reflect delayed memory. BNT and VFT reflect language function. STT tests executive function. ROCFT reflects visuospatial function and memory function. After adjusting for age and sex, overall cognitive function, executive function and visuospatial function were correlated with VD and PD of the retinal SCP. Another study also investigated the correlation between macular retinal blood flow and cognitive function, but no correlation was observed (Yan et al., 2021). The discrepancy between two studies may be ascribed to the differences in diagnostic criteria, statistical methods and OCTA machines. Frontal lobe, temporal lobe and parietal lobe constitute the attention, memory and executive network of the brain (Bero et al., 2011). Regional decrease of cerebral blood flow in AD patients is also mainly manifested in the frontal lobe, temporal lobe, parietal lobe and medial temporal lobe (Kim et al., 2020), suggesting that retinal blood flow may reflect changes in cerebral blood flow. However, this study had a small sample size, and prospective cohort studies with large sample size was still needed to further clarify the correlation between cognitive function and macular blood flow density.

In this study, the CSF was collected from 23 patients and the Aβ protein and p-Tau protein were detected. The correlations of retinal OCTA parameters with CSF Aβ protein and p-Tau protein were further explored. Our results showed no correlation of retinal VD and PD with Aβ protein and p-Tau protein. In a study of Lahme et al. (2018), results also showed no correlation between retinal SCP blood flow density and Aβ protein, p-Tau protein. Whether this implies that AD vascular lesions are primary rather than secondary to Aβ protein deposition and tau protein phosphorylation is still unclear. Therefore, prospective cohort studies with large sample size are needed to further clarify the relationship between retinal blood flow density and pathological proteins.

There were several limitations in the present study. (1) The sample size was small, which may be related to the absence of differences in some parameters. In future studies, we will recruit more patients to expand the sample size. (2) OCTA requires a long shooting time, and patients cannot maintain fixation for a long time, especially patients with severe AD. So our study excluded patients who were unable to cooperate. That's one of the reasons why we had a low number of patients. (3) The patients were not followed up in this study. This was a cross-sectional study and the dynamic changes of retinal VD and PD were not investigated. In the following study, we will follow up the participants to monitor the dynamic changes in retinal vessel.

In conclusion, retinal SCP microvascular network density reduce in patients with AD and MCI patients as compared to healthy controls, suggesting retinal microvascular dysfunction in MCI and AD patients. Moreover, retinal VD and PD are correlated with some cognitive functional domains. This may be a potential non-invasive biomarker for AD and MCI. Changes in the retinal microvascular network density may offer a valuable insight on the brain in AD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Clinical Research Ethics Committee of Tongji Hospital, Shanghai. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XM and ZX were responsible for collecting patients' general information, cognitive information and ophthalmic examination information and writing this article. ZT and HW were responsible for statistical analysis of the data. LZ, YL, and YB were responsible for revising the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Quantitative EEG for early differential diagnosis of dementia with Lewy bodies

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Introduction: Differentiating between the two most common forms of dementia, Alzheimer's dementia and dementia with Lewy bodies (DLB) remains difficult and requires the use of invasive, expensive, and resource-intensive techniques. We aimed to investigate the sensitivity and specificity of electroencephalography quantified using the statistical pattern recognition method (qEEG-SPR) for identifying dementia and DLB.

Methods: Thirty-two outpatients and 16 controls underwent clinical assessment (by two blinded neurologists), EEG recording, and a 6-month follow-up clinical assessment. EEG data were processed using a qEEG-SPR protocol to derive a Dementia Index (positive or negative) and DLB index (positive or negative) for each participant which was compared against the diagnosis given at clinical assessment. Confusion matrices were used to calculate sensitivity, specificity, and predictive values for identifying dementia and DLB specifically.

Results: Clinical assessment identified 30 cases of dementia, 2 of which were diagnosed clinically with possible DLB, 14 with probable DLB and DLB was excluded in 14 patients. qEEG-SPR confirmed the dementia diagnosis in 26 out of the 32 patients and led to 6.3% of false positives (FP) and 9.4% of false negatives (FN). qEEG-SPR was used to provide a DLB diagnosis among patients who received a positive or inconclusive result of Dementia index and led to 13.6% of FP and 13.6% of FN. Confusion matrices indicated a sensitivity of 80%, a specificity of 89%, a positive predictive value of 92%, a negative predictive value of 72%, and an accuracy of 83% to diagnose dementia. The DLB index showed a sensitivity of 60%, a specificity of 90%, a positive predictive value of 75%, a negative predictive value of 81%, and an accuracy of 75%. Neuropsychological scores did not differ significantly between DLB and non- DLB patients. Head trauma or story of stroke were identified as possible causes of FP results for DLB diagnosis.

Conclusion: qEEG-SPR is a sensitive and specific tool for diagnosing dementia and differentiating DLB from other forms of dementia in the initial state. This non-invasive, low-cost, and environmentally friendly method is a promising diagnostic tool for dementia diagnosis which could be implemented in local care settings.

KEYWORDS

dementia, quantitative electroencephalography, cognition, EEG, dementia with Lewy bodies

1. Introduction

Alzheimer's disease (AD) and other forms of dementia are significant causes of disability and dependency among older people, worldwide (Lisko et al., 2021). While no curative therapies are currently available for dementia, there are considerable benefits to the early diagnosis of dementia and early differentiation between dementia subtypes. These benefits include better patient counseling and disease prognostication, appropriate selection of pharmacological and non-pharmacological options for symptomatic management, and early modification of cardiovascular risk factors which adversely affect disease progression. Early disease identification is also considered critical to develop both symptomatic and disease modifying therapies (Rasmussen and Langerman, 2019). The recent approval of aducanumab, a monoclonal antibody targeting amyloid-β fibrils, by the U.S. Food and Drug Administration, has been controversial; however, this potentially disease modifying treatment for AD further emphasizes the need for early and specific diagnosis of AD, as the phase 3 trial evidence for aducanumab suggests that it may exert a clinically significant effect, slowing the progression of cognitive decline in AD, but only in the early phase of the disease (Cummings et al., 2021).

After AD, the most common form of dementia is dementia with Lewy bodies (DLB) (Walker et al., 2015; McKeith et al., 2017; Arvanitakis et al., 2019). Reports suggest that DLB is under-diagnosed in clinical practice (Mok et al., 2004; Toledo et al., 2013) with difficulties in making an early diagnosis and differentiating DLB from AD posing the greatest challenge (Walker et al., 2015). Currently, the diagnosis of DLB is based on the identification of core clinical features: cognitive fluctuations (a particularly difficult clinical feature to elicit accurately), visual hallucinations, parkinsonism, and RBD (McKeith et al., 2017). Supportive clinical features and indicative biomarkers (including Positron Emission Tomography (PET), Single Positron Emission Computed Tomography (SPECT) and Magnetic Resonance Imaging (MRI), electroencephalography (EEG) and polysomnography (PSG)) can provide further indications for the diagnosis of DLB (McKeith et al., 2017). The accurate, early diagnosis of DLB is particularly important in order to ensure the appropriate selection of symptomatic pharmacotherapy as certain medications, namely most antipsychotics, which may be used to manage hallucinations or agitation, can generate potentially severe adverse reactions in approximately half of patients with DLB (Aarsland et al., 2008).

In the DLB diagnosis process, routine clinical assessments including physical examinations, blood tests, and basic neuropsychological tests must generally be supplemented by increasingly specialist assessments such as neuro-immunological analysis of cerebrospinal fluid (CSF), requiring an invasive lumbar puncture, complex neuropsychological and electrophysiological tests requiring specialist expertise and equipment and expensive, resource-intensive neuroimaging assessments (Walker et al., 2015; McKeith et al., 2017). These assessments, though effective, require many heavy resources and are therefore costly, in terms of time, money, and their environmental impact and are often only available in specialist centers. Thus, there is a need to develop and promote the use of robust but inexpensive, sustainable and easy-to-use diagnostic tools which can be implemented in small clinical centers and which can be used to streamline the assessment process, giving an indication of which patients warrant more in depth assessment or indeed a diagnostic tool which could provide a robust diagnosis without the other measures.

Electroencephalography (EEG) is a non-invasive diagnostic method which is relatively simple to implement, is inexpensive and therefore, could be provided in most clinical centers. Quantitative EEG analyses (qEEG), an EEG analysis methodology utilizing different computational algorithms such as fast Fourier transform (FFT) or auto regressive (AR) models, has been shown to be a reliable method for measuring modulations in cerebral activity in dementia, with the ability to differentiate AD from other forms of dementia, such as frontotemporal dementia or DLB (Caso et al., 2012; Engedal et al., 2015). EEG of patients with DLB are characterized by theta and delta activity in the posterior, anterior and temporal regions (van der Zande et al., 2018). Slower background activity has been constantly reported in DLB patients compared to AD with the mean dominant frequency ranging between 6.7–7.5 Hz for DLB and 7.5–8.8 Hz for AD (Law et al., 2020). Moreover, alpha relative power in occipital regions is reduced in AD compared to DLB while delta relative.

Power is higher in DLB than AD (Babiloni et al., 2017, 2018). Increased theta/delta power or activities would be more prominent in the posterior region in DLB patients (Kai et al., 2005; Bonanni et al., 2015; Babiloni et al., 2017). Although the dominant frequency was lower with more pre-alpha activities in the anterior region, the diagnostic accuracy of posterior pre-alpha rhythm was higher in differentiating DLB from AD (Bonanni et al., 2008, 2015, 2016). Studies of connectivity showed that phase lag index within the alpha range was lower in DLB than AD, indicating more severe changes in connectivity in DLB (van Dellen et al., 2015; Dauwan et al., 2018; van der Zande et al., 2018). Analyses of event-related potentials also showed differential abnormalities between DLB and AD patients, with delayed auditory or visual P300 in DLB patients (Bonanni et al., 2010; Kurita et al., 2010). Regarding the early stages of the various forms of dementia, EEG abnormalities have been reported to be more common in DLB, even at the mild cognitive impairment (MCI) stage (van der Zande et al., 2020). Thus, analysis of EEG features might have a good accuracy in differentiating DLB from other forms of dementia (Law et al., 2020). Regarding the association between EEG analyses and DLB clinical symptoms, EEG slowing has been correlated with cognitive fluctuations (Briel et al., 1999; Walker et al., 2000a,b; Stylianou et al., 2018). Hallucinations have been associated with slowing of dominant rhythm and decreased functional connectivity (Dauwan et al., 2018; Aoki et al., 2019). Regarding the relationship between EEG abnormalities and cognitive functions, severity of EEG abnormalities have been shown to correlate with MMSE scores (Law et al., 2020). Moreover, EEG features in DLB patients have been shown to correlate with specific domains of cognitive function, such as fronto-executive and visual abilities. The correlation coefficient values ranged between 0.29 and 0.60 indicating weak to moderate correlations (Law et al., 2020).

Thus, many EEG algorithms have been proposed to investigate the pathophysiology of DLB. Applying qEEG using the statistical pattern recognition (SPR) method (qEEG-SPR), where EEG data are processed and classified based on comparison with normative data from a well-defined group of patients with various dementia disorders and from healthy controls, has been shown to be effective in identifying patients with subjective cognitive decline and MCI that have a high risk of converting to dementia over a 5-year period (Ferreira et al., 2016). Moreover, in the last decade, several studies

have applied the qEEG-SPR method in order to identify patterns in AD, DLB or other dementias (Snaedal et al., 2010, 2012; Ommundsen et al., 2011; Engedal et al., 2015; Ferreira et al., 2016). Such methods could distinguish patients with dementia from healthy controls with a sensitivity of 76.9% and a specificity of 73.2%, and, among patients with dementia, to differentiate patients with DLB from other forms of dementia with a sensitivity of 90.9% and a specificity of 91.1% (Ferreira et al., 2016). To this aim, MentisCura have developed and tested in the last decade a qEEG-SPR protocol based on a database of 1,000 EEG recordings of patients with clinically confirmed dementia subtypes and 500 healthy controls (Gudmundsson et al., 2007). This database has been developed to identify various classifiers contrasting different sub-cohorts. These classifiers can then be applied to subsequent EEG recordings, constituting an independent estimate of the properties of the classifiers (Engedal et al., 2015).

In this study, we used retrospective clinical data to assess the use of the MentisCura qEEG-SPR protocol in a real-world sample of patients who had been referred for dementia assessment. We aimed to assess the utility of this protocol in identifying dementia and in distinguishing between DLB and other forms of dementia, using the clinical diagnosis [based on the diagnosis criteria for dementia and DLB diagnosis (American Psychiatric Association and American Psychiatric Association, 2013; McKeith et al., 2017)] obtained at the time of assessment as our diagnostic standard. We also aimed to assess whether the combination of neurological assessment, EEG, and neuropsychological tests could further improve the sensitivity and specificity of the results.

2. Materials and methods

2.1. Population

Thirty-two patients who visited the outpatient clinic of the Department of Rehabilitation and Functional Recovery of the San Raffaele Hospital (Milan, Italy) with suspected initial state of dementia or cognitive impairment were recruited for this study, as well as 16 healthy controls. To participate to this study, patients had to be aged 50 to 85 y.o. and present symptoms of dementia according to the DSM-5, i.e., substantial impairments in one or more cognitive domains, sufficient to interfere with independence in everyday activities (Hugo and Ganguli, 2014). Oral and written consents were obtained from participants, in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the study was approved by the local Ethics committee of the San Raffaele Hospital.

2.2. Assessments

Every participant underwent the following visits prior to the inclusion of their data in the study: clinic visit with neurologist, EEG recording visit, and follow-up clinic visit at 6 months. When available, neuropsychological evaluation of patients was gathered for analyses.

2.2.1. Neurological examination and clinical diagnosis

Medical history was obtained from both the patient and a close caregiver, in order to characterize the nature, course, and magnitude of cognitive changes (Arvanitakis et al., 2019). The neurologic examination aimed at identifying objective evidence of neurocognitive issues such as aphasia, apraxia or agnosia, and focal neurologic signs of parkinsonism and included a physical examination to identify systemic vascular disease and systemic signs of rare dementia (Arvanitakis et al., 2019). Based on the neurological examination and all the available data, such as neuropsychological evaluation or MRI/PET data, the neurologist gave a diagnosis of dementia or non-dementia. The majority of MRI or PET imaging was performed in different clinical centers, therefore images were not available for analysis in this study, but clinical reports were used for diagnosis. The diagnosis of probable or possible DLB was based on the diagnostic criteria for DLB (McKeith et al., 2017). A follow-up neurological assessment was performed after 6 months. At both visits, patients were seen by two neurologists, who gave their clinical diagnoses independently. At the time of the study, none of the patients were under benzodiazepines or acetylcholinesterase inhibitors.

2.2.2. EEG recording

EEG recordings were obtained the week following the neurological evaluation. EEGs were recorded from 19 Ag/AgCl electrodes fixed on an elastic cap accordingly to the 10–20 International System, referenced to CPz, with the ground in AFz. The 19 recording electrodes were the following: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz. Patients were seated on an armchair, with their arms and legs at rest, and were asked to close their eyes. Five-minute resting-state EEGs were recorded for each patient. Signals were sampled at 1 kHz and coded on 16 bits. Impedances were kept below 5 kΩ. EEG data were acquired using the NicoletOne EEG System from Natus®.

2.2.3. Neuropsychological evaluation

Some patients, included in the study, had previously underwent a detailed neuropsychological evaluation. The following tests for different cognitive domains were then analyzed: Mini Mental State Examination (MMSE) (Folstein et al., 1975), Attentive and Raven Matrices (Raven, 2003), Token test [36], Semantic fluency (Novelli et al., 1986), Phonemic fluency (Novelli et al., 1986), naming (Miceli et al., 1994), word picture matching test (Kaplan et al., 1983), Digit span test (Orsini et al., 1987), Digit Span Backward (Wechsler, 1955), Corsi block-tapping test (Corsi, 1972), Rey Complex Figure Test (Carlesimo et al., 1996), Trail making test (Reitan, 1955), Stroop test (Jensen and Rohwer, 1966; Heaton et al., 1993), and Wisconsin Card Sorting test [46].

2.3. qEEG data analyses

The analyses methods described below have been employed in previous studies (Snaedal et al., 2010, 2012; Ferreira et al., 2016; Engedal et al., 2020).

The EEG segment used for analysis was selected by a trained technician who chose a segment with minimal presence of artifact and a length of at least 150 s. Prior to feature extraction, the chosen segment was preprocessed by applying an 8th-order Butterworth band-pass filter with the chosen band (0.1–70 Hz) to eliminate potential low- and high-frequency disturbances from the signal. The features extracted from the EEG recording and used in the

evaluation of the dementia index (DI) were retrieved according to the recommendations of the Pharmaco-EEG society (Jobert et al., 2013). The society recommends that the signal is segmented into 2-s segments overlapping by 1 s. The signal is then analyzed segment by segment, and the feature values are estimated by evaluating the expected value over all the segments. This can be achieved by various means. For instance, using the average value or an alternative robust measure. Using a robust measure minimizes the impact of outliers and hence reduces the influence of potential signal artifacts. We used the simplest robust estimate, that is, the median of the feature values. The features used were all related to the spectral properties of the recording. Discrete fast Fourier transform was applied to estimate the spectral properties of the signal (Cooley and Tukey, 1965). The analysis relied on the recordings from the 19 electrodes. If the fast Fourier transform components for each of the electrodes, segments, and discrete frequencies considered are denoted by σ_{cij}, where $c \in \{1,2,\ldots, 19\}$ indicates the channel, $i \in \{1,\ldots, N\}$ the segment of the N segments considered, and $j \in \{1,\ldots, 90\}$ the discrete frequencies (0.5, 1,…, 45 Hz), the full spectral resolution covariance between channels *c* and *k* is then expressed by xij $ck = \sigma_{cij} \times \sigma^*_{kij}$. These covariances constituted the base features used for analysis and evaluation of the classification index values.

The aim of the qEEG-SPR protocol was to sort patients within two classifier indices. The first classifier, the "dementia index" (DI), was constructed to separate healthy individuals from patients presenting with any dementia disorder. This index showed good diagnostic capacity for AD (Snaedal et al., 2012). The second classifier, the "DLB index," was constructed to detect patients with DLB among the clinical cohort of patients with dementia. To determine the core features relied on, principal components (PCs) were determined based on the Mentis Cura database of EEG recordings. PC analysis was performed on data from dementia subjects in the database. This was done separately for each covariance. PCs were then ranked according to their individual discriminatory properties in separating the subjects in the database. The discriminatory properties were determined according to the area under curve (AUC) of the receiver-operating characteristic curve (ROC). We use the 2 best performing components from each of the covariances to extract the core features used for evaluation of the index. If $P_{ck\alpha j}$ denotes the 2 chosen PCs, $\alpha \in \{1, 2\}$, for electrode pair (c, k) at frequencies $j \in \{1,\ldots, 90\}$, the core features considered for analysis then become $C_{ck\alpha} = Ei\ \{\Sigma 90\ j = 1\ xij\ ck\ Pck\alpha j\}$. The PCs can be related to the classical EEG power bands, δ (1–4 Hz), θ (4–8 Hz), α (8–13 Hz), and β (13–30 Hz). Then, PC1 corresponds to the difference between the combined δ and θ power and the β power, while PC2 is a weighted measure of the total power with slightly more emphasis on α and β power. The index value for an individual recording is evaluated from these features by $I = \Sigma_{ck\alpha} C_{ck\alpha} \beta_{ck\alpha} + \beta^A_1 A + \beta^A_2 A^2 + \rho$, where A is the age of the subject in years. The classification coefficients $\beta_{ck\alpha}$, β^A_i, and ρ were determined using a combination of genetic algorithms to optimize the number of features used, and SVM (support vector machine), an SPR, was applied in the Mentis Cura database, which contains EEG data from people with various dementia diagnoses and HC. This was done separately for men and women, resulting in separate gender-dependent indices.

Analyses were done with Sigla v.3.3®, by an experimenter blinded for all clinical symptoms, medical history, and diagnosis of patients.

2.4. Statistical analyses

Confusion matrices were built to evaluate the performance of EEG algorithm for the diagnosis of dementia and DLB compared to the clinical diagnosis representing current clinical practice (reference category: clinical diagnosis; predictor: EEG results). Neuropsychological assessments were compared between DLB and non-DLB patients using Mann–Whitney test. Measures of concordance between EEG and neuropsychological tests were performed using Cohen's test. A correlation analysis between MMSE scores and the Dementia Index was performed using Pearson's correlation test.

Data were considered significant when $p < 0.05$. The commercially available software IBM SPSS Statistics v.23 (IBM Corp.©) was used for all statistical tests.

3. Results

3.1. Demographic and clinical data

Clinical and EEG data from 32 patients, who were visited in our memory outpatient clinic between September 2019 and January 2021, were utilized for this study. Twenty-four out of 32 patients were male, patients' mean age was 73.6 ± 7.6 y.o. and their mean education level was 11.7 ± 4.2 y. Sixteen controls were also included in the study (6 female, mean age 70.1 ± 7.6 y.o., mean education level 12.3 ± 5.1 y.).

Patients' demographic and clinical data are summarized in Table 1.

Clinical diagnoses for each patient, given after neurological examination at the first visit (V1) are listed in Table 1. At V1, 30 out of 32 patients were diagnosed with dementia. All patients were in the initial phase of the disease (symptoms' onset <1 year). Of those diagnosed with dementia ($n = 30$), 2 patients were diagnosed with possible DLB, 14 with probable DLB and 14 had DLB excluded. No diagnoses were revised at follow-up.

3.2. EEG reports

3.2.1. Dementia index

qEEG results were reported as a Dementia Index (positive or negative) and a DLB index (positive or negative). Twenty-six out of 32 patients showed a positive Dementia Index result, 3 patients showed a negative Dementia Index result, and 3 showed an inconclusive result (Table 1). Negative Dementia Index was obtained in 13 out of the 16 controls and inconclusive results were obtained for 3 controls.

When comparing qEEG results and the clinical diagnoses of all participants, the EEG dementia index reported 2 false positive (6.3%) and 3 false negative results (9.4%) in the patients' group.

The confusion matrix indicated a sensitivity of 80%, a specificity of 89%, a positive predictive value of 92%, a negative predictive value of 72% and an accuracy of 83% (Figure 1).

3.2.2. DLB index

Among patients with a positive or inconclusive Dementia Index result ($n = 29$), 12 patients presented with a positive DLB Index result,

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TABLE 1 Reports demographic and clinical data of all patients, including EEG results for dementia index and DLB index and clinical diagnosis at follow-up.

Patients				EEG results		Clinical diagnosis	
#	Gender	Age (year)	Education (year)	Dementia index	DLB index	DLB clinical criteria	Clinical diagnosis (dementia/DLB)
1	M	70	17	Positive	Inconclusive	Fluctuating cognition: YES, cerebral atrophy; neuropsychological deficits; REM behavior disorders; hallucinations: YES	Dementia: YES. DLB: probable
2	M	71	17	Positive	Positive	Patient with dementia due to hemorrhagic stroke in 2016 + neurosurgical intervention (for evacuation)	Dementia: YES. DLB: NO (hemorrhagic stroke)
3	M	75	13	Inconclusive	Negative	Fluctuating cognition: NO, cerebral atrophy: NO, neuropsychological deficits: YES	Dementia: YES. DLB: NO (Initial Alzheimer)
4	M	76	13	Positive	Positive	Fluctuating cognition: YES, hallucinations: YES; sleep disorders: YES; neuropsychological deficits: YES; parkinsonism: YES	Dementia: YES. DLB: Probable
5	M	80	5	Positive	Positive	Fluctuating cognition: YES, cerebral atrophy: YES; neuropsychological deficits: YES; parkinsonism: YES	Dementia. YES. DLB: Probable
6	M	70	11	Positive	Negative	Fluctuating cognition: NO, hallucinations: NO; sleep disorders: NO; neuropsychological deficits: YES; parkinsonism: NO; PET: positive	Dementia: YES DLB: NO (Alzheimer disease)
7	M	71	13	Positive	Negative	Dementia: YES, Fluctuating cognition: NO, hallucinations: NO; sleep disorders: NO; parkinsonism: NO	Dementia: YES DLB: NO
8	M	69	N/A	Positive	Positive	Dementia: YES, REM disorders: YES; Parkinson: NO	Dementia: YES. DLB: Possible
9	F	68	N/A	Positive	Negative	Dementia: YES, Hallucinations: YES; Parkinson: NO	Dementia: YES. DLB: NO
10	M	71	5	Inconclusive	Inconclusive	Cognitive deficits: yes (mild), Fluctuating cognition: NO, hallucinations: NO; sleep disorders: NO; parkinsonism: NO	Dementia: YES. DLB: NO (Alzheimer)
11	M	69	10	Positive	Inconclusive	Cognitive deficits: yes, Fluctuating cognition: NO, hallucinations: NO; sleep disorders: NO; parkinsonism: NO	Dementia: YES. DLB: NO (frontotemporal dementia)
12	M	56	8	Positive	Positive	Cognitive deficits: YES, Fluctuating cognition: NO, hallucinations: NO; sleep disorders: NO; parkinsonism: YES	Dementia: YES. Probable DLB
13	F	62	N/A	Negative	Non calcolato	Cognitive deficits: YES, Fluctuating cognition: NO hallucinations: NO sleep disorders: NO parkinsonism: NO	Dementia: YES. DLB: NO (frontotemporal dementia)
14	M	80	18	Positive	Positive	Cognitive deficits: YES, Fluctuating cognition: NO; hallucinations: NO; sleep disorders: NO; parkinsonism: NO	Dementia YES. DLB: NO
15	M	76	18	Positive	Negative	Cognitive deficits: YES, Fluctuating cognition: YES; hallucinations: NO; sleep disorders: YES; parkinsonism: NO	Dementia: YES. DLB: probable
16	M	71	N/A	Positive	Inconclusive	Cognitive deficits: YES, Fluctuating cognition: YES; hallucinations: NO; sleep disorders: YES; parkinsonism: NO	Dementia: YES. DLB: probable

(Continued)

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TABLE 1 (Continued)

Patients				EEG results		Clinical diagnosis	
#	Gender	Age (year)	Education (year)	Dementia index	DLB index	DLB clinical criteria	Clinical diagnosis (dementia/DLB)
17	F	75	13	Inconclusive	Negative	Cognitive deficits: YES, Fluctuating cognition: NO; hallucinations: NO; sleep disorders: YES; parkinsonism: YES	Dementia: YES. DLB: probable
18	F	69	N/A	Positive	Inconclusive	Cognitive deficits: YES, Fluctuating cognition: NO; hallucinations: YES; sleep disorders: NO; parkinsonism: YES	Dementia: YES. DLB: probable
19	M	77	8	Positive	Positive	Cognitive deficits: YES, Fluctuating cognition: YES; hallucinations: YES; sleep disorders: NO; parkinsonism: YES	Dementia: YES. DLB: probable
20	M	77	N/A	Positive	Positive	Cognitive deficits: YES, Fluctuating cognition: NO; hallucinations: NO; sleep disorders: NO; parkinsonism: YES	Dementia: YES. DLB: probable
21	M	75	N/A	Negative	Non processed (negative dementia index)	Cognitive deficits: NO, Fluctuating cognition: NO; hallucinations: NO; sleep disorders: NO; parkinsonism: YES (no tremor)	Dementia: YES. DLB: possible
22	F	80	N/A	Positive	Inconclusive	Cognitive deficits: YES, Fluctuating cognition: NO; hallucinations: YES; sleep disorders: NO; parkinsonism: NO	Dementia: YES. DLB: NO (vascular dementia)
23	M	51	N/A	Negative	Non processed (negative dementia index)	Cognitive deficits: YES, Fluctuating cognition: YES; hallucinations: NO; sleep disorders: NO; parkinsonism: NO	Dementia: YES. DLB: NO
24	M	82	N/A	Positive	Positive	Cognitive deficits: YES, Fluctuating cognition: YES; hallucinations: NO; sleep disorders: YES; parkinsonism: YES	Dementia: YES. DLB: probable
25	M	75	13	Positive	Negative	Cognitive deficits: YES, Fluctuating cognition: NO; hallucinations: NO; sleep disorders: NO; parkinsonism: NO	Dementia: YES. DLB: NO
26	F	73	13	Positive	Negative	Cognitive deficits: YES, Fluctuating cognition: NO; hallucinations: NO; sleep disorders: NO; parkinsonism: NO	Dementia: YES. DLB: NO (Vascular dementia)
27	F	73	13	Positive	Negative	Cognitive deficits: YES, Fluctuating cognition: YES; hallucinations: NO; sleep disorders: YES; parkinsonism: NO	Dementia: YES. DLB: probable
28	M	86	N/A	Positive	Positive	Cognitive deficits: YES, Fluctuating cognition: NO; hallucinations: NO; sleep disorders: YES; parkinsonism: NO	Dementia: YES. DLB: probable
29	M	80	8	Positive	Positive	Cognitive deficits: YES, Fluctuating cognition: NO; hallucinations: NO; sleep disorders: NO; parkinsonism: NO	Dementia: YES. DLB: NO (vascular dementia)
30	F	84	N/A	Positive	Positive	Cognitive deficits: YES, Fluctuating cognition: YES; hallucinations: YES; sleep disorders: YES; parkinsonism: YES	Dementia: YES. DLB: probable
31	M	80	13	Positive	Inconclusive	Cognitive deficits: YES, Fluctuating cognition: NO; hallucinations: NO; sleep disorders: NO; parkinsonism: YES (+ restless legs syndrome)	Dementia: NO. DLB: NO (Parkinson patients with chronic cerebral vasculopathy)

(Continued)

TABLE 1 (Continued)

Patients				EEG results		Clinical diagnosis	
#	Gender	Age (year)	Education (year)	Dementia index	DLB index	DLB clinical criteria	Clinical diagnosis (dementia/DLB)
32	M	84	5	Positive	Negative	Cognitive deficits: YES, Fluctuating cognition: NO; hallucinations: NO; sleep disorders: NO; parkinsonism: NO	Dementia: NO. DLB: NO (post ictus)

M: Male, F: Female. Age and education are reported in years.

10 patients showed a negative DLB Index result, while the DLB index was inconclusive for 7 patients.

Regarding the DLB index, the confusion matrix indicated a sensitivity of 60%, a specificity of 90%, a positive predictive value of 75%, a negative predictive value of 81%, and an accuracy of 75% (Figure 1).

Among the 22 patients who obtained a positive or negative DLB index, 3 patients obtained false positive results (13.6%) and 3 other patients obtained false negative results (13.6%).

3.2.3. Secondary analyses

Two out of the three patients who presented with false positive DLB index had a history of hemorrhagic stroke or head trauma. The third patient suffered from vascular dementia.

We thus removed from the data analyses patients who had a history of stroke or head trauma ($n = 3$). Moreover, since only probable DLB is diagnosed as DLB in clinical settings, we also removed patients with possible DLB diagnoses ($n = 2$).

After removing these patients, when analyzing results of the dementia index, the confusion matrix indicated a sensitivity of 81%, a specificity of 94%, a positive predictive value of 95.5%, a negative predictive value of 76%, and an accuracy of 87.4%.

Regarding the DLB index, the confusion matrix indicated a sensitivity of 657%, a specificity of 96.3%, a positive predictive value of 88.9%, a negative predictive value of 81.2%, and an accuracy of 76.7% of the EEG reports.

3.3. Neuropsychological tests

Eighteen out of 32 patients underwent neuropsychological tests. Out of these 18 patients, all were diagnosed with dementia, and 6 out of 18 received a diagnosis of DLB at V1. Neuropsychological scores did not differ significantly between patients with or without DLB (Table 2). Cohen's coefficient indicated a poor concordance between the EEG reports of dementia (dementia index and DLB index) and neuropsychological test scores (Table 2). The correlation analysis showed a tendency for a negative correlation between the Dementia Index and the MMSE scores ($R = -0.463$, $p = 0.053$).

4. Discussion

This study reports the successful application of machine learning derived indices to a separate and novel clinical dataset. Our data demonstrated that qEEG, using the statistical pattern recognition method, could constitute a sensitive indicator of dementia in a real-world clinical sample and had a high positive predictive value for differentiating DLB from other forms of dementia, even in the initial phase of the disease. This suggests that qEEG has the potential to be a robust method for screening patients for dementia and DLB.

These data confirmed previous evidence showing good sensitivity and specificity for both the dementia and DLB indexes (Engedal et al., 2015, 2020; Ferreira et al., 2016). These diagnoses were confirmed by the clinical examination of patients with clinical diagnoses expressed by two blinded neurologists at V1 and at 6 months follow-up. Our data reported higher sensitivity of the dementia index and lower sensitivity of the DLB index at point value, compared to previous studies (Ferreira et al., 2016). Lower DLB index might have been due to the small number of patients. This method has the advantage to capture multivariate features of the EEG recordings. This leads in general to more robust feature combination allowing for increased test re-test reliability. This particular algorithm of qEEG-SPR utilizes full spectrum analysis of inter-electrode covariances and direct spectral properties at individual electrodes. In this manner, the strategy captures the degrees of freedom related to both classical qEEG features and connectivity/coherence related features through the covariances. The connectivity/coherence related features are functionals of the covariances.

This study demonstrated the robustness and transferability of the qEEG dementia and DLB indices in an outpatient clinic, demonstrating the practical use of such technique for the diagnosis of dementia.

We also observed that the inclusion of patients with a previous history of head trauma, stroke, or neurosurgery might induce false positive results, especially for the DLB index. Indeed, previous evidence has shown that head trauma or chronic stroke can induce long-term changes in the EEG oscillatory activity, such as reduction of the mean alpha frequency or an increase of theta activity (Tebano et al., 1988; Chen et al., 2006; Gosselin et al., 2009; Petrovic et al., 2017; Livint Popa et al., 2020). Similar EEG changes have been evidenced in patients presenting with dementia. In Alzheimer disease, a generalized slowing of the EEG is observed at rest and is expressed by an increased power in the delta and theta frequency bands and a decreased power of the upper alpha and beta bands (Schreiter-Gasser et al., 1993; Huang et al., 2000; Caso et al., 2012). Early EEG slowing may be specific to MCI with Lewy Bodies compared to MCI with AD (Massa et al., 2020; Schumacher et al., 2020). Indeed, in MCI with AD patients, the slowing-down of the qEEG was less severe than in MCI with Lewy Bodies (Massa et al., 2020). These EEG slowing down are especially expressed by the lowering of the alpha/delta ratio. In MCI-DLB, such EEG slowing-down has been mainly observed in the centro-parietal, temporal, and occipital regions (Babiloni et al., 2011; Benz et al., 2014; Massa et al., 2020), although it seems that the slowing observed in the posterior regions might be particularly specific of DLB, compared to AD (Bonanni et al., 2008, 2015, 2016).

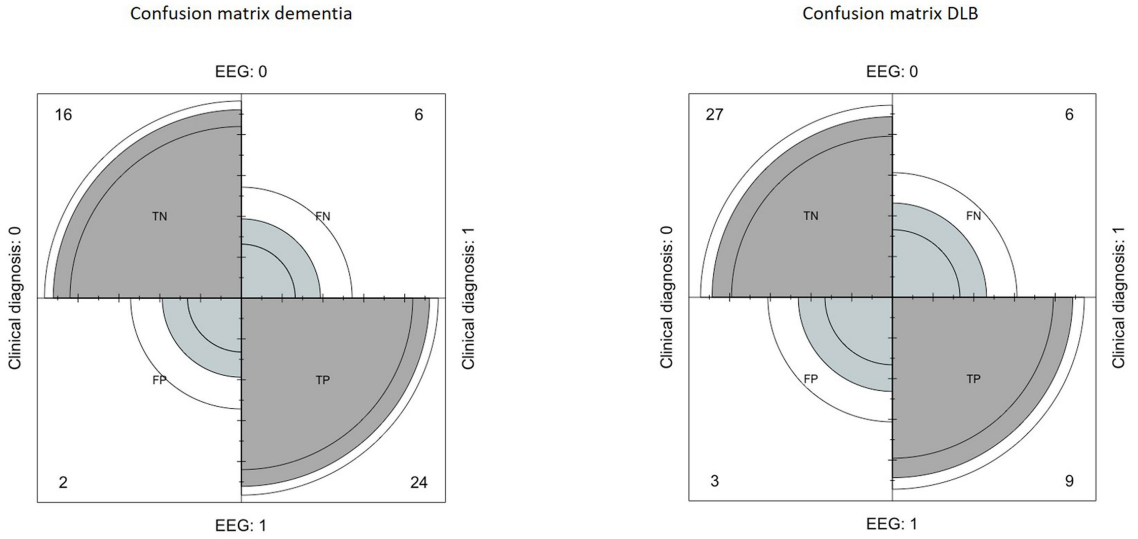

FIGURE 1
Left: confusion matrix built to evaluate the performance of EEG in the diagnosis of dementia, compared to clinical diagnosis. Right: confusion matrix built to evaluate the performance of EEG in the diagnosis of Lewy Body Dementia, compared to clinical diagnosis.

TABLE 2 Reports median scores and (interquartile range) for neuropsychological tests undergone by 18 out of the 32 patients.

	No DLB	DLB	*p*	Cohen's significance
Mini mental state examination	22.5 (11)	22 (9)	0.478	poor (−0.1)
Token test	27.75 (8.3)	26.75 (6.9)	0.925	poor (0.11)
Semantic fluency	19 (14)	24 (17)	0.111	poor (0.1)
Phonemic fluency	14 (17)	19.5 (12)	0.205	poor (0.1)
Naming	42 (7)	43 (9)	0.849	poor (−0.1)
Word picture matching test	48 (0)	48 (0)	0.48	poor (0)
Digit span test	5 (2)	5 (1)	0.92	poor (−0.1)
Digit span backward	3 (1)	3 (1)	0.557	poor (0.1)
Corsi block-tapping test	4 (1)	3 (3)	0.13	poor (0.11)
Raven matrices	24.5 (9)	18.5 (14)	0.174	poor (0.03)
Attentive matrices	36 (15)	26 (15)	0.111	poor (−0.11)
Rey complex figure test	30.5 (17)	15.5 (14)	0.061	poor (−0.1)

"*p*" refers to the statistical differences between DLB and non-DLB patients at Mann–Whitney's testing. Measures of concordance between EEG and neuropsychological tests are reported in the Cohen's significance column.

Cholinergic deficits, which are more severe and occur earlier in DLB compared to AD, may be the cause of the EEG slowing (Mesulam et al., 2004). EEG frequency is accelerated by cholinergic function and responds to therapy with acetylcholinesterase inhibitors in AD (Fogelson et al., 2003; Babiloni et al., 2013). In DLB, acetylcholinesterase inhibitors may improve global cognitive function, cognitive fluctuations, hallucinations and activities of daily living (Taylor et al., 2020), although only half of patients benefit from this type of treatment (McKeith et al., 2000; Mori et al., 2012; Stinton et al., 2015). These differences in qEEG as well as in EEG connectivity between DLB and AD would explain the strong accuracy of quantitative EEG analyses to differentiate DLB from AD or other dementia (Benz et al., 2014).

Excluding patients with a history of head trauma or stroke, the specificity of the DLB index greatly improved from 90 to 94%. Specificity is of particular importance in the diagnostic process of DLB as it indicates that 94% of the patients with a negative outcome, really do not suffer from DLB. The accuracy of the DLB index also greatly improved from 75 to 87.4%. Such data are similar to previous evidence showing that higher alpha power and lower delta power differentiate AD from DLB with sensitivity and specificity of 65–78% (Babiloni et al., 2017, 2018).

According to clinical criteria for DLB diagnosis, biomarkers are obtained by PET, SPECT, MRI, polysomnographic exams, or EEG. EEG analysis is considered as a supportive biomarker, meaning that EEG data is not considered as indicative as PET or SPECT reports. PET diagnosis of DLB has been shown to have a sensitivity of about 83–92% and a specificity of about 80–87%, similar to previously reported qEEG results (Minoshima et al., 2001; Ishii et al., 2007; Mosconi et al., 2008; Caminiti et al., 2019). Since qEEG has a good accuracy, a high

sensitivity and specificity in diagnosing dementia and DLB, considerations could be made to evaluate the possibility to upgrade qEEG analyses from supportive biomarkers to indicative biomarkers. More studies with higher number of patients would be required. Moreover, qEEG analysis represents a diagnostic tool that is non-invasive for the patients, environment-friendly, has a low cost both for the hospital/clinic and patient and can be easily repeated several times a year. Moreover, commercially available software can be used to perform such qEEG-SPR analyses, in order to promote these analyses even in small clinical centers. In these times of pandemic, attention has been brought to patients' protection and reduction of patients' displacements to reduce exposure of sensitive populations of patients. Quantitative EEG is a diagnostic tool that can be used even in small clinic centers and could be used as a systematic screening tool for those patients who are suspected of dementia or DLB following neurologic exam and neuropsychological evaluation. Based on the spoke/hub organization of hospitals and clinical centers, patients could undergo neurologic exam, neuropsychological evaluation, and qEEG in spoke centers. Only in the case of positive EEG results, PET/SPECT or MRI could be prescribed in hub centers to confirm the diagnosis.

Our data did not show significant concordance between EEG results and neuropsychological scoring, maybe due to the low number of patients. However, we showed a tendency toward a negative correlation between the EEG Dementia Index and the MMSE scores: the higher the Dementia index, the lower the MMSE. In order to better define such relationship between the Dementia Index and gravity of dementia, such analyses should be reproduced on a larger sample of patients. Evidence has shown that neuropsychological data are highly relevant in dementia and DLB diagnosis (Benz et al., 2014; Zorick et al., 2020; Howard et al., 2021). According to the literature, DLB subjects would have better performance on recall but worse on praxis than patients with AD (Walker et al., 1997). In the early stages, DLB patients present with more visuospatial deficits, compared to AD patients, as shown with the Rosen drawing test (Yoshizawa et al., 2013). Indeed, visuospatial or constructional impairment is present in 74% of patients with early-stage pathologically confirmed DLB compared with 45% of those with AD (Tiraboschi et al., 2006). Moreover, the authors showed that, among clinical variables, history of visual hallucinations was the most specific symptom to DLB (99%), and visuospatial impairment was the most sensitive (74%) (Tiraboschi et al., 2006). MCI patients with AD might have more memory storage impairments, as shown by the Free and Cued Selective Recall Reminding Test (FCSRT), testing for verbal episodic memory (Sarazin et al., 2007). In our study, FCSRT showed a minimal concordance with the EEG results. Such analyses should be replicated on a larger group of patients to further investigate the potential of neuropsychological testing associated with qEEG analyses to improve the sensitivity and specificity of such screening method.

This study presented several limitations, the first of which being the small number of patients. We also showed that certain pathologies or conditions could confound DLB index, such as head trauma or stroke, showing the necessity for exclusion criteria before running qEEG testing. To address these issues, future studies should involve larger cohort of patients, including non-demented patients. Comorbidities should be evaluated to exclude patients with a history of head trauma or stroke. Neuropsychological data should be gathered in all patients to define whether the combination of clinical data, qEEG, and neuropsychological tests could further improve the sensitivity and specificity of differential dementia diagnosis.

5. Conclusion

This study confirmed previous findings that qEEG constitutes a highly sensitive and specific tool to perform diagnosis of dementia and differential diagnosis of DLB in the early phase of the disease [12,13,15]. Additional studies, with larger cohorts of patients and control subjects, should be conducted to further confirm the present results to assess whether qEEG algorithms, such as qEEG-SPR, could be upgraded from supportive to indicative biomarker in the process of DLB diagnosis, since its sensibility and specificity are similar to the ones of MRI and PET/SPECT analyses. Quantitative EEG is a non-invasive, low-cost, environment-friendly tool that can be easily installed and used in small clinical centers (spoke). EEG tools should thus be used to streamline the assessment process in dementia diagnosis: EEG exams should be run first and give an indication whether or not more invasive assessments should be undergone to further define the diagnosis. Such invasive assessments are often available only in major clinical centers (hub). Conversely, EEG analyses can be easily implemented in small memory clinics.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Comitato Etico San Raffaele, San Raffaele Scientific Institute. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SI: participated in study design, data collection, interpretation of data, and paper writing. EH: participated in data collection, data analyses, interpretation of data, and paper writing. AS: participated in data analyses. GN: participated in data analyses. FA: participated in study design, data interpretation, and paper writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Detecting delirium: a systematic review of ultrabrief identification instruments for hospital patients

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Objective: Early identification of delirium, which often occurs in older patients, can effectively reduce adverse prognoses. One way to increase the detection rate of delirium is to use an effective ultrabrief instrument for higher-frequency screening. The purpose of this review is to evaluate the diagnostic accuracy of ultrabrief screening tools for delirium.

Methods: The Cochrane Library, PubMed and EMBASE were searched from January 1, 1974, to November 31, 2022. We assessed the measurement properties of screening instruments using the consensus-based standards for selecting health measurement instruments (COSMIN) checklist and evaluated the risk bias of the included studies using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. The diagnostic test accuracy of instruments for delirium was reported using sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR).

Result: Of the 4,914 items identified, 26 met the eligibility criteria, resulting in 5 different delirium identification tools. The overall study quality assessed by the QUADAS-2 tool was moderate to good. Of the five screening tools, two instruments had sensitivity ≥80% and specificities ≥80%: 4AT and UB-2. The most comprehensive is the 4AT scale, which has a sensitivity of 0.80 [95% confidence interval (CI):0.68, 0.88] and a specificity of 0.89 (95%CI: 0.83, 0.93) and contains 4 items. UB-2 has a sensitivity of 0.88 (95%CI: 0.72, 0.96) and a specificity of 0.64 (95%CI: 0.56, 0.70).

Conclusion: UB-2 and MOTYB had excellent sensitivity for delirium screening at an early stage. In terms of sensitivity and intentionality, the 4AT is the best recommended scale.

KEYWORDS

delirium, measurement, systematic review, psychometrics, older patients

Introduction

Delirium is the clinical manifestation of acute encephalopathy, which is characterized by acute disorders of consciousness, attention, and cognition that fluctuate over time and are fundamental criteria in delirium diagnosis (Oh et al., 2017). It is a common disease that affects many hospitalized patients, especially those aged 65 and over. Prolonged hospitalization and decreased cognitive ability are considered risk factors for delirium, while delirium itself is a known complication of dementia and is associated with an increased risk of death (Breitbart et al., 2002). Many cases of delirium are not recognized, which means that the opportunity for

prevention has been lost (MacLullich and Hall, 2011). Early detection is helpful for treatment and could reduce the duration and adverse effects of delirium. Although delirium screening is the standard procedure in many hospitals, up to 72% of delirium events have not been found or misdiagnosed (de la Cruz et al., 2015). The failure may be due to the fluctuation of delirium symptoms. The patient may not have developed delirium at routine screening. Therefore, it is particularly important to screen for delirium multiple times per day or every day, as well as obtain collateral history from a reliable caregiver, to detect its fluctuating nature.

At present, there are more than 40 delirium instruments for different purposes (e.g., screening, diagnosis and severity), for different clinical environments (e.g., intensive care units, emergency departments and medical wards), and for different users (e.g., psychiatrists, geriatricians, nurses, and caregivers; Helfand et al., 2021). Such a large number of instruments not only makes the direct comparison of evaluation results challenging but also increases the difficulty of selecting instruments for clinical staff. To detect delirium more efficiently, it is best to use a simple and rapid instrument to screen delirium. We named this rapid delirium screening instrument with an evaluation time $\leq$2 min and a number of items $\leq$4 the ultrabrief delirium screening instrument. This means that they can be routinely used 2–3 times a day in clinical situations. Thus, the recognition of delirium by clinical staff can be improved.

At present, many delirium screening scales are committed to simplifying and improving delirium detection. The MOTYB (the months of the year backwards test) is a commonly used attention test (Ryan et al., 2018). The 4 'A's test or 4AT is a short delirium assessment tool intended for clinical use in general settings when delirium is suspected and was initially published on a dedicated website in 2011 (Bellelli et al., 2014). UB-2 (ultrabrief screen), consisting of the two most sensitive items in the 3 min diagnostic CAM (3D-CAM) (Fick et al., 2015), was used recently and shown to be useful in delirium screening. While many systematic reviews of delirium instruments exist, they all focus on a certain instrument or comprehensive evaluation (Wong et al., 2010; Morandi et al., 2012; LaMantia et al., 2014; De and Wand, 2015; Jeong et al., 2020; Helfand et al., 2021). However, to the best of our knowledge, no systematic reviews have comprehensively compared the diagnostic accuracy between those different ultrabrief delirium screening instruments.

The objective of this review is threefold. First, we assessed the measurement properties of screening instruments using the consensus-based standards for selecting consensus-based standards for the selection of health status measurement instruments (COSMIN) checklist (Mokkink et al., 2009). Second, we evaluated the risk bias of study quality using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. Third, we examined the diagnostic accuracy of ultrabrief delirium screening instruments in various care settings. The findings of this investigation provide recommendations for the choice of ultrabrief screening tools for delirium.

Materials and methods

Literature search strategy

Two authors conducted independent literature searches. The Cochrane Library, PubMed and EMBASE were searched from January 1, 1974, to November 31, 2022. Studies were included when they met the following criteria: (1) reported at least one delirium screening instrument; (2) examination of diagnostic accuracy against a widely accepted diagnostic criterion of delirium, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM, Version III, IV or V), the International Classification of Diseases (ICD), or recognized instruments for delirium assessment, such as the confusion assessment method (CAM) and delirium rating scale (DRS). Exclusion criteria were: (1) case series, comments, letters, protocol, meeting reports; (2) non-English-language publications; (3) studies on delirium in children; (4) the scales involved in the study do not meet the requirements that the average use time is $\leq$2 min and the number of items is $\leq$4. The search terms included the keywords "delirium" and "instrument," as well as their known synonyms. The detailed search strategy is shown in the Supplementary material (supplement 1).

Study selection and data extraction

Two independent authors (YaL and ZL) screened the relevant literature by title and abstract and then read the full text to select eligible articles. Any disagreement was resolved by consulting a third author (JY). We collected the following information: sample size, language, study design, study sites, country, application of reference standard and examiner specialty. We also calculated/extracted the sensitivity, specificity, area under the ROC curve (AUC), and other diagnostic accuracy indices of each study.

Risk of bias assessment

Two independent review authors (YaL and ZL) assessed the methodological quality of the studies using the Diagnostic Accuracy Study Quality Assessment (QUADAS-2) tool. This tool is available at https://www.bris.ac.uk/quadas. The QUADAS-2 tool assessed the study quality from four aspects: participant selection, index test, reference standards, flow and timing. Differences were resolved by a third author (JY).

Measurement property assessment

We used the COSMIN guidelines to rate the measurement properties for each delirium screening instrument. The COSMIN checklist is a tool for assessing the reliability and validity of the screening instrument, which is available at https://www.cosmin.nl. We evaluated the screening instrument from six aspects: (1) content validity; (2) structural validity; (3) reliability; (4) internal consistency; (5) cross-cultural validity; and (6) criterion validity. We reviewed all relevant articles about each instrument to make an accurate decision. The ratings on each of the COSMIN criteria were summed and reported as a 0 to 6 score (Appendix 2) using an adaptation of the COSMIN scoring procedure published previously (Helfand et al., 2021). For reporting on each of these categories, the instruments were given one point; failure to report on these categories resulted in no points. Two authors carefully extracted information from each article according to the COSMIN framework.

Statistical analysis

Meta-analyses were performed using the Stata (version 16.0, StataCorp, TX, United States) MIDAS module. Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and area under the curve (AUC) were used to report diagnostic test accuracy for delirium instruments. Sensitivity, specificity, and likelihood ratios were calculated from the raw data and then rounded for display in the data tables. In general, larger PLRs and smaller NLRs indicate better diagnostic performance. AUC ≥0.9 indicates high diagnostic accuracy, 0.7–0.9 indicates moderate diagnostic capability, and 0.5–0.7 indicates low accuracy.

Heterogeneity was divided into low, moderate, and high with I^2 values of 25%, 50%, and 75%, respectively. To explore the sources of heterogeneity, we performed a subgroup analysis for different sites (ICU or non-ICU). To investigate the robustness we found, we performed sensitivity analyses. We analysed only DSM standard studies. We evaluated the publication bias of all eligible studies using Deek's funnel plot.

Results

Selection process

Figure 1 displays the PRISMA flowchart of the literature search and selection. We retrieved 4,914 potentially relevant records. A total of 2,265 records were excluded after title and abstract screening. Finally, 2,649 full texts were screened, of which 26 articles reporting five delirium screening instruments met the eligibility criteria and were included in this review. Five screening tools are 4AT (Robson et al., 2017), MOTYB (Marra et al., 2018), O3DY (Bédard et al., 2019), AMT-4 (Swain and Nightingale, 1997) and UB-2 (Fick et al., 2015).

Study characteristics

Table 1 shows the characteristics of all 26 included studies. A total of 7,262 participants were included. Eight studies (30.8%) were developed in ICUs, 3 studies (11.5%) were developed in stroke units, and 15 studies (57.7%) were conducted in non-ICUs. The gold standards used in each of the 26 articles include DSM (46.2%), CAM (50%), and DRS (3.8%).

Study quality assessed By The QUADAS-2 tool

Table 2 summarizes the study quality risk biases assessed by the QUADAS-2 tool. The overall risk of bias was rated as low to moderate. Eight studies were considered to have low-risk bias. Fourteen studies were rated as having a high risk. Potential biases for our systematic review were listed as follows: (1) participant selection (e.g., ICU or non-ICU patients); (2) secondary analysis of retrospective studies was also considered high risk. The retrospective design may have introduced selection bias.

COSMIN assessment of screening instruments

We used the COSMIN standards to assess the psychometric properties (reliability and validity) of five screening tools.

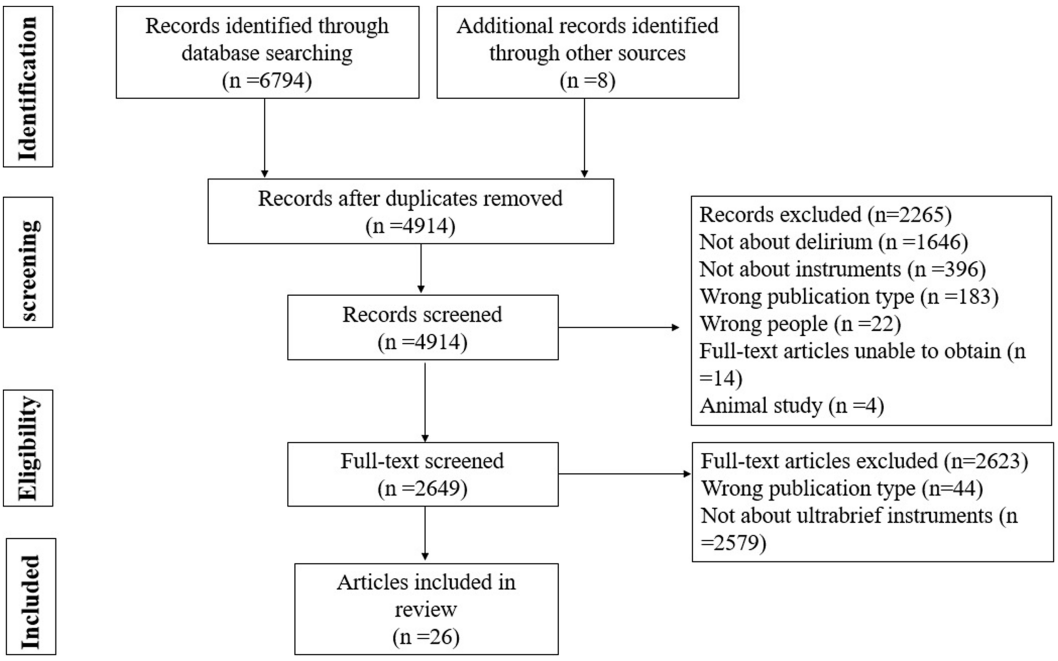

FIGURE 1
PRISMA flow chart diagram of the study selection process.

TABLE 1 Characteristics of the included studies and main findings.

Source	Study design	Study site	Country/ Language	Sample size	Examiner specialty	Delirium prevalence, %	Reference standard	Sensitivity	Specificity	PLR	NLR
4AT											
Asadollahi (2016)	Cross-sectional study	Nursing homes and daily care centers	Iran/Persian	293	Nurse	56	DSM	0.35 (0.28–0.43)	0.97 (0.92–0.99)	11.21 (4.18–30.08)	0.67 (0.60–0.76)
Bellelli et al. (2014)	Prospective consecutive patient study	Acute geriatric and rehabilitation wards	Italy/Italian	234	Expert assessors	12.4	DSM	0.90 (0.73–0.98)	0.84 (0.78–0.89)	5.62 (4.02–7.87)	0.12 (0.04–0.36)
Myrstad et al. (2019)	Retrospective, quality improvement study	Acute geriatric wards	Norway/ Norwegian	49	Nurse	42.8	DSM	0.50 (0.27–0.73)	0.86 (0.68–0.96)	3.63 (1.32–9.95)	0.58 (0.37–0.92)
Casey et al. (2019)	Prospective study	Multi-site health service	Australia/English	559	Nurse	16.3	CAM	0.65 (0.54–0.75)	0.90 (0.87–0.92)	6.32 (4.65–8.60)	0.39 (0.30–0.92)
MacLullich et al. (2019)	Prospective, double-blind diagnostic test accuracy study	Emergency departments or in acute general medical wards	UK/English	392	Expert assessors	–	CAM	0.76 (0.61–0.87)	0.94 (0.91–0.97)	13.63 (8.56–21.71)	0.26 (0.16–0.42)
Kuladee and Prachason (2016)	Cross-sectional study	General medical wards	Thailand/Thai	97	Psychiatrist	24.7	CAM	0.83 (0.63–0.95)	0.86 (0.76–0.93)	6.08 (3.33–11.12)	0.19 (0.08–0.47)
Hendry et al. (2016)	Prospective consecutive patient study	Geriatric hospital wards	UK/English	434	Clinician	18.6	CAM	0.87 (0.78–0.93)	0.70 (0.64–0.74)	2.85 (2.38–3.40)	0.19 (0.11–0.33)
De et al. (2017)	Prospective study	Geriatric and orthogeriatric hospital wards	Australia/English	257	Expert assessors	61.9	DSM	0.87 (0.81–0.92)	0.80 (0.70–0.87)	4.25 (2.86–6.32)	0.17 (0.11–0.25)
Gagné et al. (2018)	Prospective study	Emergency departments	Canada/French	319	Expert assessors	15.4	CAM	0.90 (0.78–0.97)	0.60 (0.54–0.66)	2.24 (1.89–2.67)	0.17 (0.07–0.39)
O'Sullivan et al. (2018)	Prospective nonconsecutive study	Emergency departments	Ireland/English	350	Clinician	11	DSM	0.93 (0.83–0.98)	0.91 (0.88–0.94)	10.87 (7.43–15.92)	0.08 (0.03–0.19)
Saller et al. (2019)	Prospective consecutive study	Recovery room	Germany/ German	543	Expert assessors	10.5	CAM	0.95 (0.77–1.00)	0.99 (0.98–1.00)	124.33 (46.64–331.42)	0.05 (0.01–0.31)
Infante et al. (2017)	Prospective and Cross-sectional study	Stroke units	Italy/Italian	100	Neurologist	52	DSM	0.96 (0.96–1.00)	0.76 (0.62–0.87)	4.00 (2.43–6.57)	0.05 (0.01–0.21)
Lees et al. (2013)	Prospective consecutive study	Stroke units	UK/English	100	Nurse	11	DSM	1.00 (0.74–1.00)	0.82 (0.72–0.87)	5.19 (3.31–8.12)	0.05 (0.00–0.72)

(Continued)

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TABLE 1 (Continued)

Source	Study design	Study site	Country/ Language	Sample size	Examiner specialty	Delirium prevalence, %	Reference standard	Sensitivity	Specificity	PLR	NLR
Shenkin et al. (2019)	Prospective study	Emergency room and acute geriatric wards	UK/English	395	Nurses or trained associates	12.4	CAM	0.45 (0.35–0.56)	0.96 (0.93–0.98)	10.45 (5.87–18.58)	0.57 (0.48–0.69)
Koca et al. (2022)	Cross-sectional study	Hospital	Turkey/Turkish	123	Nurse	13.8	DSM	0.67 (0.41–0.87)	0.94 (0.88–0.98)	11.67 (5.02–27.10)	0.35 (0.18–0.68)
Johansson et al. (2021)	Cross-sectional study	Hospital	Swedish/Swiss	159	Expert assessors	19	DSM	0.43 (0.23–0.66)	0.81 (0.73–0.87)	2.27 (1.27–4.06)	0.70 (0.48–1.01)
AMT-4											
Hendry et al. (2016)	Prospective consecutive patient study	Geriatric hospital wards	UK/English	408	Clinician	18.6	CAM	0.93 (0.85–0.97)	0.54 (0.48–0.59)	2.00 (1.75–2.28)	0.14 (0.06–0.30)
Lees et al. (2013)	Prospective consecutive study	Stroke Units	UK/English	111	Nurse	11	DSM	0.83 (0.52–0.98)	0.55 (0.44–0.65)	1.83 (1.31–2.56)	0.31 (0.09–1.10)
Dyer et al. (2017)	Cross-sectional study	Emergency departments	Germany/ German	196	Research assistants	26	CAM	0.92 (0.75–0.99)	0.82 (0.75–0.87)	5.06 (3.61–7.09)	0.09 (0.02–0.36)
MOTYB											
Hendry et al. (2016)	Prospective consecutive patient study	Geriatric hospital wards	UK/English	406	Clinician	18.6	CAM	0.91 (0.83–0.96)	0.50 (0.44–0.55)	1.81 (1.60–2.06)	0.18 (0.09–0.36)
Marra et al. (2018)	Prospective observational study	Emergency departments	US/English	235	Clinician	10.6	DSM	0.84 (0.64–0.95)	0.52 (0.45–0.59)	1.75 (1.40–2.18)	0.31 (0.12–0.76)
O'Regan et al. (2017)	Cross-sectional study	Hospital	UK/English	440	Expert assessors	39	DRS	0.85 (0.78–0.90)	0.58 (0.52–0.64)	2.04 (1.75–2.37)	0.26 (0.18–0.39)
Voyer et al. (2016)	Cross-sectional study	Acute care hospital and LTC facility	Canada/English	191	Expert assessors	12	CAM	0.83 (0.61–0.95)	0.38 (0.30–0.45)	1.32 (1.06–1.65)	0.46 (0.19–1.15)
O'Regan et al. (2014)	Cross-sectional study	Hospital	UK/English	265	Expert assessors	19.6	DSM	0.83 (0.70–0.93)	0.91 (0.86–0.94)	9.04 (5.84–13.99)	0.27 (0.17–0.44)
O3DY											
Bédard et al. (2019)	Cross-sectional study	Emergency departments	French/French	313	Expert assessors	6	CAM	0.84 (0.75–0.91)	0.58 (0.52–0.64)	2.01 (1.71–2.37)	0.27 (0.17–0.44)
UB-2											
Marcantonio et al. (2022)	Prospective cohort study	Hospital	US/English	293	Certified nursing assistants	22	CAM	0.35 (0.28–0.43)	0.97 (0.92–0.99)	11.21 (4.18–30.08)	0.67 (0.60–0.76)

4AT, 4 attention test; AMT-4, 4-point abbreviated mental test; MOTYB, months of the year recited backwards; O3DY, Ottowa day, date, WORLD BW and year; UB-2, ultra-brief 2-item screen; DSM, diagnostic and statistical manual of mental disorders; CAM, confusion assessment method; DRS, delirium rating scale. PLR, positive likelihood ratio; NLR, negative likelihood ratio.

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TABLE 2 Risk bias of included studies by the QUADAS-2 tool.

	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Asadollahi (2016)	?	?	?	h	?	?	?
Bellelli et al. (2014)	l	?	l	l	l	?	l
Myrstad et al. (2019)	h	?	?	h	h	?	?
Casey et al. (2019)	l	l	l	l	l	l	l
MacLullich et al. (2019)	?	l	l	?	?	l	l
Kuladee and Prachason (2016)	?	l	l	l	?	l	l
Hendry et al. (2016)	l	?	l	l	l	?	l
De et al. (2017)	l	l	l	l	l	l	l
Gagné et al. (2018)	h	?	?	?	h	?	?
O'Sullivan et al. (2018)	l	?	l	l	l	?	l
Saller et al. (2019)	l	l	l	l	l	l	l
Infante et al. (2017)	h	?	?	?	h	?	?
Lees et al. (2013)	l	l	l	?	l	l	l
Shenkin et al. (2019)	l	l	l	l	l	l	l
Koca et al. (2022)	l	l	l	l	l	l	l
Johansson et al. (2021)	l	l	l	l	l	l	l
Hendry et al. (2016)	l	?	l	l	l	?	l
Lees et al. (2013)	l	l	l	?	l	l	l
Dyer et al. (2017)	l	l	?	?	l	l	?
Hendry et al. (2016)	l	?	l	l	l	?	l
Marra et al. (2018)	l	l	l	l	l	l	l
O'Regan et al. (2017)	l	l	l	l	l	l	l
Voyer et al. (2016)	l	l	l	h	l	l	l
O'Regan et al. (2014)	l	l	l	l	l	l	l
Bédard et al. (2019)	l	l	l	l	l	l	l
Marcantonio et al. (2022)	l	?	?	l	l	?	?

h, high risk; l, low risk; ?, uncertain.

We chose the single earliest publication for each instrument. The summarized COSMIN assessment results are shown in Table 3. None of the included studies reported internal reliability. All five instruments have internal consistency and effect indicators. The 4AT and MOTYB have good content validity. The AMT-4 and UB-2 have adequate construct validity. For external validity, the MOTYB is the only one that lacks it.

TABLE 3 COSMIN checklist of screening instruments.

Scale	Effect indicators	Content validity	Internal consistency	Interrater reliability	Construct validity	External validity*
4AT	+	+	+	–	–	+
MOTYB	+	+	+	–	–	–
O3DY	+	+	–	–	–	+
AMT-4	+	+	–	–	+	+
UB-2	+	+	–	–	+	+

+, have this item; –, does not have this item.

TABLE 4 Summary estimates of pooled diagnostic accuracy.

Instrument	Study (sample)	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Pooled PLR (95% CI)	Pooled NLR (95% CI)
4AT	16 (4404)	0.80 (0.68, 0.88)	0.89 (0.83, 0.93)	7.3 (4.7, 11.4)	0.23 (0.14, 0.37)
4AT (ICU subgroup)	5 (1505)	0.76 (0.54, 0.89)	0.90 (0.78, 0.96)	7.38 (3.63, 15.01)	0.27 (0.13, 0.55)
4AT (non-ICU subgroup)	11 (2899)	0.82 (0.67, 0.91)	0.89 (0.81, 0.94)	7.36 (4.18, 12.96)	0.20 (0.11, 0.39)
AMT-4	3 (715)	0.93 (0.85, 0.97)	0.54 (0.48, 0.59)	2.02 (1.63, 2.36)	0.13 (0.06, 0.37)
MOTYB	5 (1537)	0.87 (0.83, 0.90)	0.61 (0.44, 0.76)	2.2 (1.5, 3.4)	0.22 (0.15, 0.30)
O3DY	1 (313)	0.84 (0.75, 0.91)	0.58 (0.52, 0.64)	2.01 (1.71, 2.37)	0.27 (0.17, 0.44)
UB-2	1 (293)	0.88 (0.72, 0.96)	0.61 (0.44, 0.76)	2.26 (1.28, 4.00)	0.20 (0.05, 0.64)

4AT, 4 attention test; AMT-4, 4-point abbreviated mental test; MOTYB, months of the year recited backwards; O3DY, Ottowa day, date, WORLD BW and Year; UB-2, ultra-brief 2-item screen; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

Diagnostic accuracy of screening tools

Studies have reported data on the diagnostic accuracy of all five screening tools for delirium: the 4AT, the MOTYB, the AMT-4, the O3DY, and the UB-2 (Table 3).

The 4AT ($n = 16$ studies) had a pooled sensitivity of 80% [95% confidence interval (CI): 68%–88%] and a pooled specificity of 89% (95% CI: 83%–93%); the pooled PLR and NLR were 7.3 (95% CI: 4.7–11.4) and 0.23 (95% CI: 0.14–0.37), respectively. The pooled estimates of sensitivity and specificity for the MOTYB ($n = 5$ studies) were 87% (95% CI: 83%–90%) and 61% (95% CI: 44%–76%), respectively; the pooled PLR and NLR were 2.2 (95% CI: 1.5–3.4) and 0.22 (95% CI: 0.15–0.30), respectively. The AMT-4 had a sensitivity of 93% [95% CI: 85%–97%] and a specificity of 54% (95% CI: 48%–59%); the O3DY had a sensitivity of 84% [95% CI: 75%–91%] and a specificity of 58% (95% CI: 52%–64%); and the UB-2 had a sensitivity of 88% [95% CI: 72%–96%] and a specificity of 61% (95% CI: 44%–76%). More details, such as the pooled PLR and NLR, are shown in Table 4.

The summary receiver operating characteristic (SROC) curves can eliminate the threshold effects of the instrument to predict overall accuracy. By the SROC curves of Figure 2, the 4AT had a higher AUC ($n = 16$ studies, AUC = 0.92) than MOTYB ($n = 5$ studies, AUC = 0.87). AMT-4, O3DY and UB-2 did not conduct SROC due to the lack of relevant research.

Subgroup analysis

We performed a subgroup analysis of different sites (ICU or non-ICU) where 4AT was used. In the ICU, 4AT had a sensitivity of 76% (95% CI: 54%–89%) and a specificity of 90% (95% CI: 78%–96%); in the non-ICU, 4AT had a higher sensitivity of 82% (95% CI: 67%–91%) and a lower specificity of 89% (95% CI: 81%–94%). The PLR and NLR of the ICU were 7.4 (95% CI: 3.6–15.0) and 0.3 (95% CI: 0.1–0.6); those of the ICU were 7.4 (95% CI: 4.2–13.0) and 0.2 (95% CI: 0.1–0.4), respectively.

Sensitivity analysis and publication bias

After the exclusion of non-DSM standard studies, the pooled sensitivity, specificity, PLR, and NLR for the 4AT were 80% (95% CI: 61%–92%), 88% (95% CI: 82%–92%), 6.5 (95% CI: 4.5–9.2), and 0.22 (95% CI: 0.10–0.48), respectively. MOTYB, AMT-4, O3DY and UB-2 did not conduct sensitivity analysis due to the lack of enough studies.

Deeks' funnel plots revealed no evidence of publication bias, as shown in Figure 3 (4AT $p = 0.3$, MOTYB $p = 0.66$). We did not assess the publication bias of the AMT-4, O3DY and UB-2 because not enough studies were included.

Discussion

Accurate recognition of delirium is clinically important to effectively provide clinical care and reduce late complications. To promote the detection rate of delirium, it is important to select appropriate methods and use them at least twice a day. Five instruments were included in our systematic review and showed that they may be used for multiple rapid screenings of delirium in clinical practice. The study quality of this meta-analysis was moderate to good overall, according to the QUADAS-2 assessment. Of the five screening

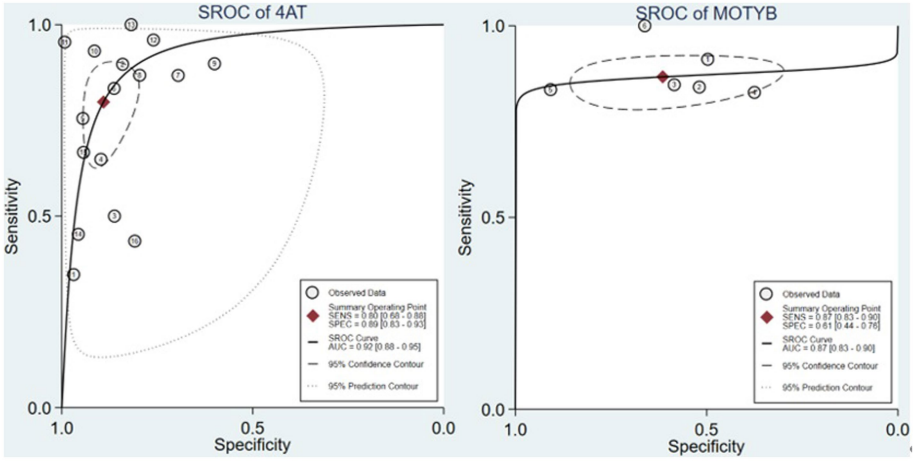

FIGURE 2
The SROC curves of 4AT and MOTYB.

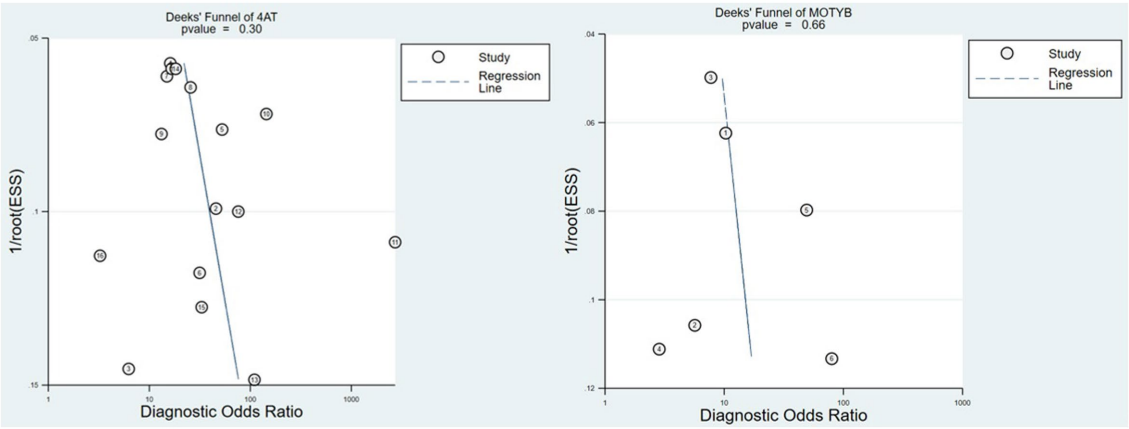

FIGURE 3
Deeks' funnel plot of 4AT and MOTYB.

tools, two instruments had sensitivity ≥80% and specificities ≥80%: 4AT and UB-2. These two instruments have unique strengths and limitations, and several potential scenarios for their use are provided here. Based on our recommended principles, we recommend 4AT as a clinical daily multiple rapid screening instrument.

The 4AT test includes two simple cognitive screening items. It is short (only 4 items and generally <2 min; Tieges et al., 2021), does not need special training, is easy to manage (including people with visual or hearing impairment), does not need physical response, and allows the evaluation of patients who "cannot be tested" (those who cannot be tested or interviewed due to severe sleepiness or excitement). 4AT has experienced several pilot rounds and has been used in many hospitals in the United Kingdom and internationally. The 4AT had a sensitivity of 80% and specificity of 89%, with a PLR of 7.3 and an NLR of 0.22. Although the 4AT has high sensitivity and specificity, it has the longest use time among the five scales included. There is a dynamic balance between performance and simplicity. Fortunately, we limited the ultrabrief scale when we included the article and then chose the best performance from it.

At present, there are few relevant studies on UB-2, which has only been verified in the United States. UB-2 is extracted from 3D-CAM (Fick et al., 2015), but the author does not recommend using UB-2 alone to diagnose delirium but uses the UB-CAM framework. Even UB-2 had a sensitivity of 88% and specificity of 64%, with a PLR of 2.4 and an NLR of 0.34. Another important item excluded by the author is "Does the patient report feeling confused?" That is, if these three items are positive, delirium can be directly diagnosed. More evidence of this screening tool is needed in the future.

Among the remaining five scales, MOTYB is the most studied. However, MOTYB, as a scale with only one test item, is extremely simplified in operation, but it has a low specificity of 61%. The five scales involved do not involve delusion, while a scale involving delusion, Nu-DESC, does not meet the criteria of the ultrasimple scale. The remaining three scales involved in this study have a

common problem: there are too few original studies directly related to delirium, of which UB-2 lacks relevant studies due to its late launch.

Notably, AMT-4 itself is a part of the 4AT. Although the number of entries in the strict sense of the word is more than 4, in the practical application of the 4AT, the four questions about the AMT-4 can be asked in one question in one book,[1] and it is not necessary to count the scores of each question but only the number of wrong answers, so it can be regarded as one item. This is different from using the RASS to evaluate the level of consciousness. RASS cannot be simplified into one problem (Ely et al., 2003).

This study has several advantages. First, we evaluated all screening tools' COSMIN quality and evaluated the QUADAS-2 risk bias of the included studies. Second, we also followed the principle of a double review process and developed an evidence-based process for quality assessment. The methodological quality of the included studies was moderate to good overall. There have been many systematic evaluations of delirium screening instruments before (Wong et al., 2010), and they are constantly updated; however, this paper focuses on simplifying the instrument and achieving the screening effect as efficiently as possible.

There are several limitations to this study. First, the description of the use duration in each study is different, which is different from the actual use duration in other institutions. For this reason, after the description of the original literature and the actual simulation of the expert team, we have comprehensively set the duration and set it as the interval value after discussion. Second, many scales were designed for different user groups at the beginning of the design when the scale was included, so some scales had design defects, which led to poor final results and were finally eliminated. For example, the Delirium Triage Screen (DTS)/Brief CAM (b-CAM) itself was a simple enough screening strategy (Rieck et al., 2020), but the combination of the two parts exceeded the limit of items and was eliminated. This part of the scale should be classified and discussed in detail. Then, the evaluation of consciousness level in many scales is unclear (such as BCS). After we replace RASS, the number of items and operation time will be exceeded, and we have to abandon it. If there is a simpler way to assess the level of awareness, this part of the scale should also be included in the discussion. Finally, the scale recommended in this study is the 4AT. Although there is no language restriction, the scale included in this study is all in English, which obviously limits the strength of evidence for the use of the scale in other language regions.

This article provides an overview of the delirium scale that can be used for daily multiple screening in clinical work. Different assessors will choose different scales for screening in different clinical environments, but these scales may not be suitable for multiple use every day. This paper recommends a comprehensive and ideal scale "4AT," which has a very high coverage of standard diagnostic criteria, which means that under ideal conditions, it can be used as the final diagnostic scale without requiring a professional doctor to diagnose. Moreover, because of the ultrasimple characteristics of 4AT, it can be used in clinical practice many times a day, which can reduce the delirium ignored due to the fluctuation of delirium, improve the detection rate, and ensure a good prognosis through early prevention.

In view of the high specificity of 4AT in the subgroup of nondementia patients and the high sensitivity of the subgroup of dementia patients, an important area of future research may be to improve the scale to improve its ability to identify delirium in dementia patients. It is hoped that the work of this paper will help improve the detection rate of delirium in clinical work and lay a foundation for promoting research in the field of delirium.

This study comprehensively summarized delirium screening tools based on the COSMIN guidelines. Five screening instruments were available, and the methodological quality assessment of the included studies by the QUADAS-2 tool was moderate to good. UB-2 and MOTYB had excellent sensitivity for delirium screening at an early stage. In terms of sensitivity and intentionality, the 4AT is the best recommended scale according to the results of this study.

Author contributions

YaL and JY: study concept and design. YaL, ZL, and YiL: acquisition of data. YiL and YaL: analysis and interpretation of data. YaL and ZL: drafting of the manuscript. JY and NG: critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1166392/full#supplementary-material

1 www.the4AT.com

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The A-to-Z factors associated with cognitive impairment. Results of the DeCo study

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Introduction: Cognitive impairment (CI) is known to be mediated by several risk and protective factors, many of which are potentially modifiable. Therefore, it is important to have up-to-date studies that address a standard assessment of psychosocial, clinical and lifestyle variables.

Materials and methods: We conducted a cross-sectional observational study, with a 24-month timeframe, to estimate the relationship between risk and protective factors associated with dementia, according to the A-to-Z Dementia Knowledge. Participants were considered at CI risk if they tested positive for at least one of three validated CI screening tests: The Memory Impairment Screening, Short Portable Mental State Questionnaire, and Semantic Verbal Fluency. The A-to-Z data Collection included Mediterranean Diet Adherence Screener and Geriatric Depression Scale.

Results: The estimated prevalence of CI was 22.6% in a sample of 709 patients with an average of 69.3±10.3 years. The risk factors gradually associated with cognitive decline were hypertension, loneliness, and depression. In contrast, the protective factors gradually associated with less cognitive decline were internet use, reading, and intellectually stimulating jobs. Finally, living alone, having diabetes, taking benzodiazepines, and sleeping more than 9 h were statistically significant associated with CI, whereas to do memory training or a family history of dementia was characteristic of patients without CI.

Conclusion: A joint assessment of the influence of psychosocial, clinical, and lifestyle-related factors is needed to develop dementia prevention strategies.

KEYWORDS

dementia, cognitive impairment, risk factors, protective factors, prevention, screening

1. Introduction

According to the 2021 World Alzheimer Report, "dementia", a major neurocognitive disorder, is not a specific disease, but a collection of symptoms resulting from an underlying condition. Dementia significantly affects memory, behavior, thinking, and social abilities severely enough to interfere with one's activities of daily living and social autonomy (Prince et al., 2016; Alzheimer Disease International, 2021).

In 2020, the National Institute on Aging and the Alzheimer's Association published a toolkit with six distinct stages of Alzheimer's disease (AD) (Jack et al., 2018). The first stage of the disease is characterized by the absence of subjective or objective evidence of cognitive

impairment (CI) or behavioral disturbances. The second transitional stage includes people who exhibit subjective memory complaints (SMC), subtle objective impairment, or mild behavioral symptoms. These two are the so-called "prodromal stages", while the third phase is the so-called "mild cognitive impairment" (MCI). Finally, stages 4 to 6 represent different clinical periods of dementia: mild, moderate, and severe (Jack et al., 2018; Jessen et al., 2020).

MCI is a syndrome defined as a cognitive decline that exceeds what is expected for an individual's age and education level but without notably interfering with daily life activities (Lopez et al., 1999). It is characterized by objectively measured CI using validated neuropsychological tests (Jessen et al., 2020). Patients with CI are at a higher risk of developing AD or other types of dementia compared to the general population (Petersen, 2006).

Dementia is a progressive neurodegenerative disease that can manifest up to 20 years before diagnosis. CI stands out as a prelude to the pathology, characterized by a decline in cognitive abilities when the patient does not meet the criteria for dementia diagnosis (Jessen et al., 2020). Thus, early detection of CI is essential as it is during this preclinical phase where a more significant benefit can be expected with disease-modifying or slowing therapies (Ramos et al., 2021b).

SMC is defined as the subjective perception of a decline cognitive abilities compared to previous levels of functioning in individuals with normal cognition. Evidence suggests that SMC may represent the first preclinical manifestation of AD (Warren et al., 2022). Nowadays, There is a growing awareness about AD, leading to an increasing number of individuals expressing concerns about a reduction in their cognition function (Jessen et al., 2020). Furthermore, individuals with personal exposure to dementia may develop heightened sensitivity to specific signs of memory loss (Lee et al., 2021). In this respect, it has been suggested that individuals who express concerns about perceived decline in cognitive function have an increased risk of developing cognitive decline or dementia (Jessen et al., 2020).

Although the progression of dementia is unstoppable because there is not yet a definitive treatment available, certain risk and protective factors associated with dementia are potentially modifiable (Livingston et al., 2020; Ramos et al., 2021b). It is possible to reduce the risk through specific lifestyle changes, delay the onset or slowing down the progression of the disease (World Health Organization, 2019). In this regard, the sooner a patient with cognitive dysfunction is identified, the earlier an appropriate intervention can be carried out to control risk factors and promote a healthy lifestyle. For this reason, screening for CI should be established early to prevent its development at later ages (World Health Organization, 2012).

Up-to-date research knowledge and dissemination of information about modifiable risk factors are crucial to promote effective prevention programs (Rosenberg et al., 2018). In addition, it has been reported that the development and greater accessibility of valuable tools and training would better equip community pharmacists to use their existing knowledge and improve their comfort in managing patients with or at risk of dementia (Chong et al., 2021).

With this purpose in mind, the *A-to-Z Dementia Knowledge list* was elaborated to facilitate memorizing factors associated with dementia (Ramos et al., 2021b). In addition to the clear evidence for the usefulness of 12 factors reported by the Lancet Commission, Alzheimer's Disease International (ADI), and the World Health Organization (WHO) (Morley et al., 2015; Prince et al., 2016; World Health Organization, 2017; Livingston et al., 2020), the *A-to-Z Dementia Knowledge list* includes five more significant factors forming an alphabet and make them easier to remember. To better understand the factors associated with dementia, they are classified according to their influence on cognitive dysfunction into non-modifiable factors (age, sex, genetic), factors that are difficult to modify (education level, job), protective factors (healthy habits such as exercise or good nutrition, cognitive stimulation such as quizzes and mind games, surfing on the internet, reading, meeting friends or playing music to keep mentally active, patient's knowledge of dementia) and risk factors (diseases such as depression, hypertension, insulin resistance, lipid profile alterations, brain injuries, hearing loss, obesity or viral and bacterial infections, memory complaint, environmental exposure to pollution, use of certain pharmaceuticals like anticholinergic drugs or benzodiazepines, toxic habits such as smoking and alcohol consumption, poor sleep hygiene) (Ramos et al., 2021b).

Psychosocial variables are major contributors to cognitive decline and general health status and should be considered as relevant as other biological variables in healthy aging and dementia (Deaton and Stone, 2015). The joint assessment of the influence of psychosocial, clinical, and lifestyle-related variables provides relevant information for the CI course analysis. These include physical activity, nutrition, social interaction, and occupation (García et al., 2022).

The main purpose of this study was to measure the influence of factors included in the *A-to-Z Dementia Knowledge list* in patients at risk of CI concerned about their cognition who were screened in healthcare facilities (including Community Pharmacy, Primary Care Health Centre, and Hospital).

2. Materials and methods

2.1. Type of study and target population

A cross-sectional observational study was conducted to estimate whether patients were at CI risk for having obtained in the CI assessment a score compatible with CI within a 24-month timeframe and whether it was related to risk and protective factors associated with dementia according to the *A-to-Z Dementia Knowledge*. Individuals with at least one test result compatible with CI were referred to primary care for evaluation as patients with CI after cognitive assessment were considered to have an increased risk of developing dementia.

As summarized in Figure 1, the following validated CI screening tests were carried out: Memory Impairment Screen (MIS) (Böhm et al., 2005), Semantic Verbal Fluency (SVF) (López Pérez-Díaz et al., 2013), and Short Portable Mental State Questionnaire (SPMSQ) (Martínez de la Iglesia et al., 2001). Using tests with different sensitivity and specificity is essential to obtain diagnostic

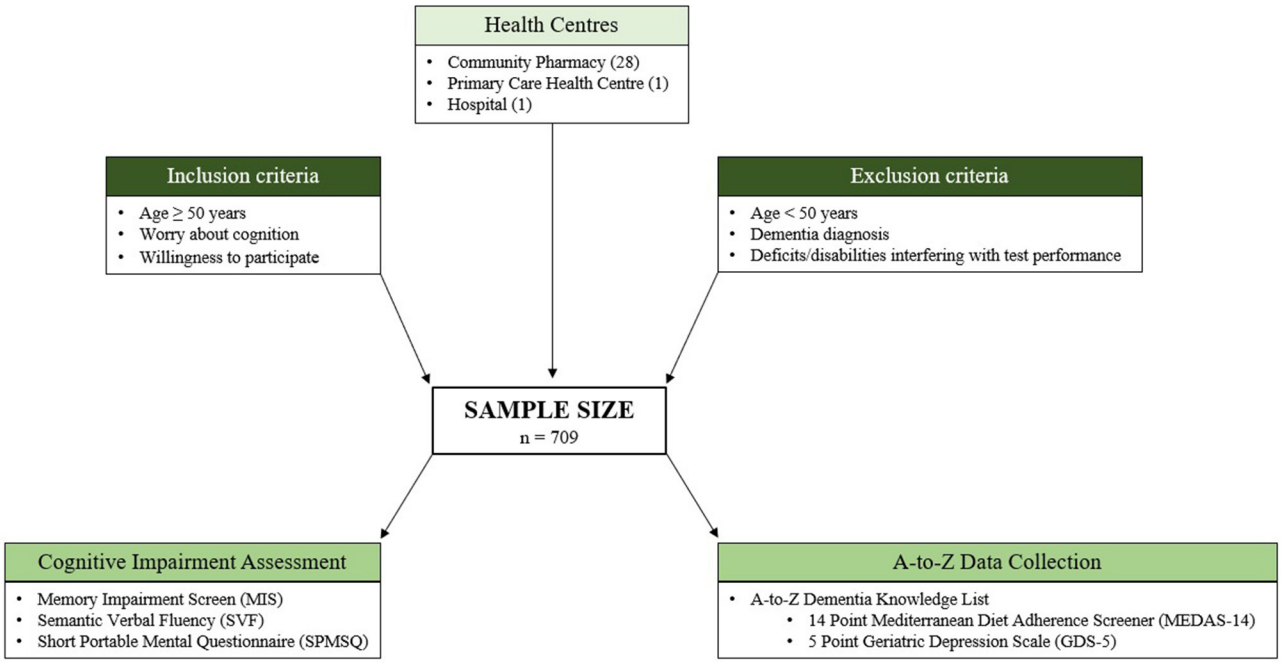

FIGURE 1
Diagram showing our inclusion criteria and analysis methodology.

accuracy. In order to gather information about factors associated with dementia, the interview included additional lifestyle variables and dietary habits and two more screening tests: Mediterranean Diet Adherence Screener (MEDAS-14) (Ferreira-Pêgo et al., 2016) and Geriatric Depression Scale (GDS-5) (Ortega Orcos et al., 2007).

The inclusion criteria, defining the target population were age 50 or older, worried about their cognition, and willingness to participate. Conversely, exclusion criteria were diagnosis of dementia, severe sensory deficits such as blindness or deafness, and physical disability interfering with the performance of the tests. The inclusion age (50 years or older) was decided to detect patients in the early stages of CI (Climent et al., 2018).

The service was offered to regular participating healthcare facility patients (28 Community Pharmacies, 1 Primary Care Health Centre, and 1 Hospital) who met the selection criteria. Likewise, patients directly referred by their physician were included.

2.2. Cognitive impairment assessment

2.2.1. Memory impairment screen

The MIS is a short 4-item test that measures the free and selectively facilitated recall, scoring on a 0–8 range. It uses the techniques of controlled learning and selectively facilitated recall to optimize encoding processes. The accepted cut-off point is ≤4 points, in which the sensitivity shown for dementia in the Spanish population was 80%, with a specificity of 96% (Buschke et al., 1999). Therefore, the MIS is proper as a screening instrument for memory problems such as cognitive impairment. In a blinded study, it showed a sensibility of 91.9 (IC95% 83.4–96.4) and a specificity of 81% (IC95% 70.3–88.6). Moreover, this questionnaire also has a sensitivity and specificity for AD, the most common cause of CI, that ranges from 86 to 96%, respectively (Buschke et al., 1999; Böhm et al., 2005).

2.2.2. Semantic verbal fluency

The SVF questionnaire assesses the number of items of a specific category (e.g., animals) within a limited time (1 min). This questionnaire is easy and fast to apply and is very sensitive (74%) and specific (80%) for cognitive impairment (López Pérez-Díaz et al., 2013), which justifies its use for the detection of CI with a cut-off point of fewer than 10 points. Furthermore, as it is a very specific questionnaire for temporal lesions, it is widely used in patients with amnesic mild cognitive impairment, where there is a progressive loss of semantic memory due to alterations in the frontal and temporal lobes (Price et al., 2012; López Pérez-Díaz et al., 2013).

2.2.3. Pfeiffer's short portable mental STATE questionnaire

The SPMSQ assesses different intellectual aspects, including short-term memory, long-term memory, orientation to surroundings, information about recent events, and the ability to perform serial mathematical tasks (Pfeiffer and Short Portable Mental, 1975). This questionnaire is characterized by its brevity and portability, as it assesses ten simple items and it presents a cut-off point of 3 or more errors. The Spanish version of this test obtained a sensitivity of 85.7% and a specificity of 79.3%, respectively (Martínez de la Iglesia et al., 2001).

Participants were considered cognitively impaired if they tested positive for at least one of these tests.

2.3. A-to-Z data collection/information collection questionnaires

2.3.1. A-to-Z dementia knowledge list

A data collection booklet was used to gather information on all factors covered in the *A-to-Z Dementia Knowledge List* (Table 1) (Ramos et al., 2021b).

Regarding the job factor, the categorization of occupations by social class was based on the Spanish Society of Epidemiology classification (Regidor, 2001). Additionally, to classify postcodes according to urban or rural areas, we use the criteria of the Ministry of Agriculture, Fisheries and Food of the Spanish Government, according to which "rural areas are defined as the geographical space formed by the aggregation of municipalities with a population of fewer than 30,000 inhabitants and a density of fewer than 100 inhabitants per km^2" (Ministerio de Agricultura, 2021).

In addition, MEDAS-14 and GDS-15 were used for nutrition and depression factors, respectively, to provide objective data.

The MEDAS was developed to assess compliance with the nutritional intervention of the *Prevención con Dieta Mediterránea* (PREDIMED) study, a multicenter clinical trial aimed at assessing the effects of the Mediterranean diet on the prevention of cardiovascular disease (Schröder et al., 2011). This questionnaire was validated in the Spanish population (Schröder et al., 2011) and recently in other countries such as Germany (Hebestreit et al., 2017). A face-to-face interview adequately classifies individuals according to their PREDIMED score by means of 14 simple response questions—"yes" or "no"—and allows the quality of the entire dietary pattern to be considered. It offers a score from 0 to 14 points (the higher the score, the better the adherence). On the other hand, GDS-5 is the short version of GDS-30 and quantifies depressive symptoms in older adults through 5 questions. It has a maximum score of 5 points and a cut-off point 2. The Spanish version obtained a sensitivity of 82% and a specificity of 98% in a population over 64 years (Ortega Orcos et al., 2007).

2.4. Statistical treatment

The information collected from the participants was stored in a Microsoft Excel spreadsheet designed for the study. After the data purification phase, we proceed with the statistical treatment using the advanced statistical software R. First, the categories of the qualitative variables are described with the sample size as the total and available percentages [n (% total, % available)]; that is, without considering and considering missing data, respectively. Quantitative variables are described with the mean and standard deviation (mean ± SD). The association of each qualitative factor from the A-to-Z Dementia Knowledge list with the CI is analyzed with the Chi-square or the Fisher tests. The association of the quantitative variables with the CI is studied with the T-test for independent samples. Finally, the association of the quantitative variables with the number of positive tests of CI is studied with the Kruskal Wallis test. The significance level is indicated with the following code *: p-value < 0.05; **: p-value < 0.01; ***: p-value < 0.001.

2.5. Ethical considerations

Information processing guarantees both the protection of the data and its security. These data were treated confidentially and lawfully and were used for the purpose for which the respondent had been informed. Thus, this work complied with the European General Data Protection Regulation (RGPD) and Organic Law 3/2018 on the Protection of Personal Data and the Guarantee of Digital Rights. Furthermore, the study complied with the basic principles of the Declaration of Helsinki: respect for the individual (Article 8) and recognition of their right to self-determination and their right to make informed decisions (informed consent, contained in Articles 20, 21, and 22), including participation in research, both at its beginning and throughout the work. The study was reviewed and approved by the Institutional Review Board (IRB) of Universidad CEU Cardenal Herrera (CEII18/027) and by the Research Ethics Committee of Arnau de Vilanova Hospital (CEIm 7/2022). All subjects gave written informed consent following the Declaration of Helsinki.

3. Results

After data collection, information is available from a sample of 709 patients. These patients range in age from 50 to 94 years (69.3 ± 10.3). Of them, 523 are female (73.8%), representing the general population of patients over 50 years of age who come to healthcare facilities with concerns about their cognition.

As shown in Figure 2, after CI screening, according to the three tests mentioned in the methodology (MIS, SVF, and SPMSQ), 160 patients were detected with at least one positive test, and therefore, at risk for CI (22.6%). Concretely, 16 of these patients have all three positive tests (2.3%), 32 have two positive tests (4.5%) and, 112 have a single positive test (15.8%).

Table 2 describes the distribution of patients in the groups with and without risk of CI by age range. As can be seen, patients older than 65 accumulate more than expected in the group with CI, contrary to younger patients.

Although Table 3 analyses the association of all the A-to-Z factors concerning having or not having CI, the text only details those factors that have obtained a statistically significant association and can be modified to reduce CI risk. Qualitative variables are described with the sample size and percentage, n (%), while quantitative variables are described with the mean and standard deviation (mean ± SD).

For example, the mean number of months with hearing loss is significantly lower among those with CI (32.9 ± 49.7) vs. those without CI (64.1 ± 105.9).

GDS-5 determines a statistically significant association in patients at risk of depression: the group with CI is higher than those without CI (39.9 vs. 26.1%).

The percentage of patients living alone is significantly higher in the group with CI than in the group without CI (30 vs. 18.2%). Therefore, living alone is significantly associated with being at risk of CI.

Among patients with a family history of AD, there is a significantly higher percentage in the group without CI compared

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TABLE 1 Questions included in the A-to-Z booklet according to the factors' classification.

Alphabet letter	A-to-Z Factor	Type of factor	Data collection booklet
A	Audition	Risk	Hearing loss YES/NO
B	Brain injury	Risk	Brain injury YES/NO
C	Complaint of memory	Risk	Complaint of memory YES/NO
D	Depression	Risk	Depression diagnosis YES/NO GDS-5 result compatible with depression YES/NO
E	Exercise	Protective	Hours of exercise/week
F	Friends	Protective	Do you feel alone? YES/NO Do you feel lonely? YES/NO N°. of friends met the last week
G	Genetics	Non-modifiable	Family history of dementia YES/NO
H	Hypertension	Risk	Hypertension diagnosis YES/NO Hypertension treatment YES/NO
I	Insulin resistance	Risk	Diabetes diagnosis YES/NO Diabetes treatment YES/NO
J	Job	Difficult to modify	Occupation
K	Knowledge	Protective	
L	Lipid profile alteration	Risk	Hipercolesterolemia diagnosis YES/NO Hipercolesterolemia treatment YES/NO
M	Musician	Protective	Plays a musical instrument YES/NO Hours/week playing a musical instrument
N	Nutrition	Protective	MEDAS-14 result
O	Obesity	Risk	BMI
P	Pharmaceutical drugs	Risk	Benzodiazepines consumption YES/NO Benzodiazepines use: Insomnia YES/NO Benzodiazepines use: Anxiety YES/NO Anticholinergic consumption YES/NO Anticholinergic burden (ACB Scale) Antiinflamatory consumption YES/NO Antidepressants consumption YES/NO
Q	Quiz	Protective	Memory training YES/NO
R	Reading	Protective	Reading habit Hours reading/week
S	Sleep	Risk	Hours reading/day
T	Toxics	Risk	Smoker/Nonsmoker/Former smoker Smoker: N°. of cigarettes/day Smoking cessation: How many years ago? N°. of alcohol cups/week
U	Universal task	Protective	
V	Virus and infections	Risk	In HSV treatment YES/NO
W	Web	Protective	Internet use YES/NO Hours of internet use/week
X	Xx	Non-modifiable	Woman YES/NO
Y	Your cognitive reserve	Difficult to modify	
Z	Zip code	Risk	Zip code (urban/rural)

GDS-5, 5 Point Geriatric Depression Scale; MEDAS-14, 14 Point Mediterranean Diet Adherence Screener; BMI, Body Mass Index; HSV, Herpes Virus Simplex.

with the group with CI (38 vs. 22.6%). Not having a family history of AD is significantly associated with having CI.

The percentage of patients with hypertension in the group with CI is also significantly higher compared with the group without CI (62.7 vs. 47.6%). According to this result, having hypertension is significantly associated with having CI. Likewise, the number of patients who have diabetes is significantly higher in the group with CI compared with the group without CI (30.2 vs. 17.9%). Thus, having diabetes is also significantly associated with having CI.

Regarding the occupation role in CI, Level 4 (skilled manual worker) and Level 6 (unskilled manual worker) are observed

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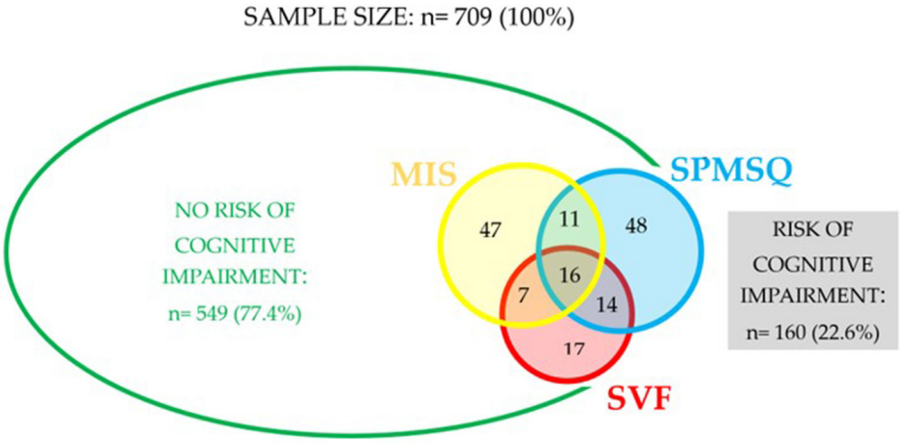

FIGURE 2
Scheme on the distribution of participating patients between risk and non-risk of cognitive impairment (MIS, Memory Impairment Screen; SPMSQ, Short Portable Mental Status Questionnaire; SVF, Semantic Verbal Fluency).

TABLE 2 Distribution of patients by age range in groups with and without CI (*p*-value of Chi-square test).

	Totals *n* (% total) 709 (100)	Cognitive impairment		*p*-value
		No	Yes	
		549 (100)	160 (100)	
Age				
(50, 65)	236 (33.2)	220 (40.1)	16 (10.0)	<0.001***
(65, 80)	340 (48.0)	258 (47.0)	82 (51.2)	
(80, 94)	133 (18.8)	71 (12.9)	62 (38.8)	

***p-value < 0.001.

more than expected in the group with CI. However, occupations Level 1 (professions associated with second and third-cycle university degrees), Level 2 (professions associated with a first-cycle university degree), Level 3 (unskilled non-manual worker and self-employed worker), and Level 5 (semi-skilled manual worker) are observed more than expected in the group without CI. We can observe that the type of occupation performed is associated with CI.

Since the percentage of patients taking benzodiazepines is significantly higher in the group with CI compared with the group without CI (39.6 vs. 31%), benzodiazepine use is significantly associated with having CI.

There are significantly more patients who routinely train their memory in the group without CI compared with the group with CI (50.8 vs. 40.3%). Hence, lack of memory training is significantly associated with having CI. The same applies to patients who read regularly (72.5 vs. 52.5%).

Sleeping more than 9 h per day is significantly higher in the group with CI than the group without CI (10.6 vs. 3.9%). Oversleeping is significantly associated with having CI. In addition, the mean sleep time in the group with CI is significantly higher than in the group without CI (7.3 ± 2.1 vs. 6.8 ± 1.5).

Former smokers and smokers are observed more than expected in the group without CI. However, non-smokers are observed more than expected in the group with CI. Therefore, tobacco exposure is associated with not having CI.

The percentage with a diagnosis of HSV is significantly higher in the group without CI compared with the group with CI (28.1 vs. 15.6%). In this regard, a diagnosis of HSV is significantly associated with not having CI.

More patients regularly use the internet. As a result, it is significantly higher in the group without CI risk compared with the group with CI risk (79.4 vs. 40.3%). Consequently, not using the internet is significantly associated with CI risk.

The association of the A-to-Z factors with the number of positive CI tests was also analyzed to identify trends. Table 4 summarizes the A-to-Z factors that have shown statistically significant associations and can be modified to reduce CI risk.

For example, the percentage of patients at risk of depression increases significantly as the number of positive CI tests grows. The same applies to the percentage of patients living alone, with a hypertension diagnosis, or with an unskilled manual worker.

Similarly, the percentage of diabetic patients is significantly higher among patients with a positive CI screening test. However, the higher percentage of people with diabetes accumulates in the group with a single positive test rather than among those with more positive tests.

On the other hand, the percentage of patients who read, use the Internet regularly or have intellectual work decreases as the number of positive CI tests increases.

Using the information described in Table 4 for hypertension, loneliness, depression, Internet use, reading, and intellectual work, Figure 3 graphically represents the evolution of the percentages of patients as the number of positive IC tests increases. As can be seen, the first three factors are risk factors for CI since the percentages tend to increase as the number of positive CI tests increases. On the contrary, the other three factors below are protective factors because the tendency of the percentages decreases as the number of positive CI tests increases.

TABLE 3 Association of the A-to-Z factors vs. having or not having CI.

			Totals *n* (% total; % available) 709 (100; 100)	CI risk		*p*-value
				No	Yes	
				549 (100)	160 (100)	
Audition (Hearing loss)		No	464 (65.4; 65.4)	356 (64.8)	108 (67.5)	0.572[a]
		Yes	245 (34.6; 34.6)	193 (35.2)	52 (32.5)	
Brain injury		No	681 (96.1; 96.5)	528 (96.4)	153 (96.0)	1.000[c]
		Yes	25 (3.5; 3.5)	20 (3.6)	5 (3.2)	
		Missing	3 (0.4; —)	—	—	
Complaint of memory		No	88 (12.4; 12.4)	75 (13.7)	13 (8.1)	0.076[c]
		Yes	621 (87.6; 87.6)	474 (86.3)	147 (91.9)	
Depression	Diagnosis	No	519 (73.2; 73.3)	403 (73.5)	116 (72.5)	0.839[a]
		Yes	189 (26.7; 26.7)	145 (26.5)	44 (27.5)	
		Missing	1 (0.1; —)	—	—	
	Risk (GDS-5)	No	479 (67.6; 70.9)	390 (73.9)	89 (60.1)	**0.001**[a***]
		Yes	197 (27.8; 29.1)	138 (26.1)	59 (39.9)	
		Missing	33 (4.7; —)	—	—	
Exercise		No	147 (20.7; 21.3)	106 (19.9)	41 (26.0)	0.180[a]
		<7 h	313 (44.1, 45.4)	250 (46.8)	63 (40.4)	
		>7 h	230 (32.4, 33.3)	178 (33.3)	52 (33.3)	
		Missing	19 (2.7; —)			
		Hours/week	7.3 ± 7.0	7.1 ± 6.9	7.8 ± 7.1	0.344[b]
Friends	Lives alone	No	561 (79.1; 79.1)	449 (81.8)	112 (70.0)	**0.002**[a***]
		Yes	148 (20.9; 20.9)	100 (18.2)	48 (30.0)	0.200[a]
	Feels lonely (Lives alone)	No	60 (8.5, 60.6)	42 (65.6)	18 (51.4)	0.130[a]
		Yes	39 (5.5; 39.4)	22 (34.4)	17 (48.6)	
		Missing	49 (6.9; —)	—	—	
	N°. of friends met last week (Lives alone)		2.6 ± 4.3	3.1 ± 5.0	1.6 ± 2.1	0.065[b]
Genetics		No	463 (65.3; 65.5)	340 (62.0)	123 (77.4)	**<0.001**[a***]
		Yes	244 (34.4; 34.5)	208 (38.0)	36 (22.6)	
		Missing	2 (0.3; —)	—	—	
Hypertension	Diagnosis	No	346 (48.8; 49.0)	287 (52.4)	59 (37.3)	**0.001**[a***]
		Yes	360 (50.8; 51.0)	261 (47.6)	99 (62.7)	
		Missing	3 (0.4; —)	—	—	
	Treatment in those who are diagnosed	No	17 (2.4; 4.7)	15 (5.7)	2 (2.0	0.171[c]
		Yes	343 (48.4; 95.3)	246 (94.3)	97 (98.0)	
		Missing	3 (0.4; —)	—	—	
Insulin resistance	Diagnosis	No	561 (79.1; 79.3)	450 (82.1)	111 (69.8)	**0.001**[a***]
		Yes	146 (20.6, 20.7)	98 (17.9)	48 (30.2)	
		Missing	2 (0.3; —)			
	Treatment in those who are diagnosed	No	4 (0.6; 2.7)	3 (3.1)	1 (2.1)	1.000[c]
		Yes	142 (20.0; 97.3)	95 (96.9)	47 (97.9)	
		Missing	2 (0.3; —)	—	—	

(Continued)

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TABLE 3 (Continued)

			Totals *n* (% total; % available) 709 (100; 100)	CI risk		*p*-value
				No	Yes	
				549 (100)	160 (100)	
Job		Level 1	54 (7.6; 7.8)	47 (8.8)	7	**<0.001**[c***]
		Level 2	110 (15.5,15.9)	93 (17.4)	17 (10.8)	
		Level 3	108 (15.2; 15.6)	89 (16.6)	19 (12.0)	
		Level 4	129 (18.2; 18.6)	96 (17.9)	33 (20.9)	
		Level 5	87 (12.3; 12.6)	72 (13.5)	15 (9.5)	
		Level 6	199 (28.1; 28.7)	132 (24.7)	67 (42.4)	
		Missing	22 (3.1; —)	—	—	
Lipid profile	Diagnosis	No	380 (53.6; 53.6)	303 (55.2)	77 (48.1)	0.126[a]
		Yes	329 (46.4; 46.4)	246 (44.8)	83 (51.9)	
	Treatment in those who are diagnosed	No	24 (3.4; 3.4)	20 (8.1)	4 (4.8)	0.464[c]
		Yes	305 (43.0; 43.0)	226 (91.9)	79 (95.2)	
Musician		No	668 (94.2; 94.2)	513 (93.4)	155 (96.9)	0.124[c]
		Yes	41 (5.8; 5.8)	36 (6.6)	5 (3.1)	
		Hours/week	8.4 ± 7.6	8.8 ± 7.5	5.9 ± 8.9	0.437[b]
Nutrition (MEDAS-14)		Low	71 (10.0; 12.1)	52 (11.3)	19 (15.0)	0.527[a]
		Intermediate	374 (52.8; 63.5)	296 (64.1)	78 (61.4)	
		High	144 (20.3; 24.4)	114 (24.7)	30 (23.6)	
		Missing	120 (16.9; —)	—	—	
Obesity (BMI)		Insufficient	11 (1.6; 1.6)	7 (1.3)	4 (2	0.705[c]
		Normal	189 (26.7; 27.9)	146 (27.9)	43 (27.7)	
		Overweight	271 (38.1; 39.8)	211 (40.2)	60 (38.7)	
		Obese	207 (29.3; 30.7)	159 (30.6)	48 (31.0)	
		Missing	31 (4.4; —)	—	—	
		Score	27.5 ± 4.6	27.5 ± 4.6	27.5 ± 4.7	0.981[b]
Pharmaceutical drugs	Benzodiazepines	No	474 (66.9; 67.0)	378 (69.0)	96 (60.4	**0.045**[a*]
		Yes	233 (32.9; 33.0)	170 (31.0)	63 (39.6)	
		Missing	2 (0.3; —)	—	—	
	Anticholinergic	No	559 (78.8; 81.6)	436 (81.6)	123 (81.5)	1.000[c]
		Yes	126 (17.8; 18.4)	98 (18.4)	28 (18.5)	
		Missing	24 (3.4; —)	—	—	
		ACB score	1.8 ± 1.1	1.7 ± 1.1	2.0 ± 1.1	0.214[b]
	Antiinflamatories	No	559 (78.8; 79.5)	433 (79.4)	126 (79.7)	1.000[c]
		Yes	144 (20.3; 20.5)	112 (20.6)	63 (39.6)	
		Missing	6 (0.8; —)	—	—	
	Antidepressants	No	540 (76.2; 76.3)	417 (76.1)	123 (76.9)	0.916[a]
		Yes	168 (23.7; 23.7)	131 (23.9)	37 (23.1)	
		Missing	1 (0.1; —)	—	—	

(Continued)

TABLE 3 (Continued)

			Totals *n* (% total; % available) 709 (100; 100)	CI risk		*p*-value
				No	Yes	
				549 (100)	160 (100)	
Quiz (Memory training)		No	364 (51.3; 51.6)	269 (49.2)	95 (59.7)	**0.019**[a]*
		Yes	342 (48.2; 48.4)	278 (50.8)	64 (40.3)	
		Missing	3 (0.4; —)	—	—	
Reading		No	227 (32.0; 32.0)	151 (27.5)	76 (47.5	**<0.001**[a]***
		Yes	482 (68.0; 68.0)	398 (72.5)	84 (52.5)	
		Hours/week	6.4 ± 7.5	6.5 ± 7.5	6.2 ± 8.0	0.801[b]
Sleep		<6 h	112 (15.8; 17.7)	87 (17.8)	25 (17.6)	**0.013**[c]*
		(6–9 h)	486 (68.5; 76.9)	384 (78.4)	102 (71.8)	
		<9 h	34 (4.8; 5.4)	19 (3.9)	15 (10.6)	
		Missing	77(10.9; —)	—	—	
		Hours/day	7.0 ± 1.6	6.8 ± 1.5	7.3 ± 2.1	**0.002**[b]**
Toxics	Tobacco	Non smoker	388 (54.7; 54.8)	278 (50.6)	110 (69.2	**<0.001**[c]***
		Former smoker	236 (33.3; 33.3)	198 (36.1)	38 (23.9)	
		Smoker	84 (11.8; 11.9)	73 (13.3)	11 (6.9)	
		Missing	1 (0.1; —)	—	—	
		Years without smoking (Former smoker)	21.3 ± 12.5	21.0 ± 12.0	22.6 ± 14.9	0.483[b]
		Cigarettes/day (Smoker)	12.4 ± 9.0	11.8 ± 7.8	16.1 ± 14.0	0.141[b]
	Alcohol	No	260 (36.7; 55.0)	199 (52.6)	61 (64.2)	0.050[c]
		Yes	213 (30.0; 45.0)	179 (47.4)	34 (35.8)	
		Missing	236 (33.3; —)	—	—	
		Cups/week (Those who drink)	1.6 ± 2.7	1.6 ± 2.7	1.6 ± 2.7	0.891[b]
Universal task (Useless feeling)		No	239 (33.7; 83.6)	174 (84.1)	65 (82.3	0.723[c]
		Yes	47 (6.6; 16.4)	33 (15.9)	14 (17.7)	
		Missing	423 (59.7; —)	—	—	
Virus or infection	HVS diagnosis	No	527 (74.3; 74.8)	392 (71.9)	135 (84.4)	**0.001**[c]**
		Yes	178 (25.1; 25.2)	153 (28.1)	25 (15.6)	
		Missing	4 (0.6; —)	—	—	
	Treatment in those who are diagnosed	No	47 (6.6; 28.0)	37 (25.7)	10 (41.7)	0.139[c]
		Yes	121 (17.1; 72.0)	107 (74.3)	14 (58.3)	
		Missing	14 (2.0; —)	—	—	
Web (Internet use)		No	208 (29.3; 29.4)	113 (20.6)	95 (59.7)	**<0.001**[a]***
		Yes	500 (70.5; 70.6)	436 (79.4)	64 (40.3)	
		Missing	1 (0.1; —)	—	—	
		Hours/week	10.0 ± 10.7	10.0 ± 11.1	9.5 ± 7.9	0.701[b]
XX (Woman)		No	186 (26.2; 26.2)	139 (25.3)	47 (29.4)	0.309[a]

(Continued)

TABLE 3 (Continued)

		Totals *n* (% total; % available) 709 (100; 100)	CI risk		*p*-value
			No	Yes	
			549 (100)	160 (100)	
	Yes	523 (73.8; 73.8)	410 (74.7)	113 (70.6)	
Zip code	Rural	129 (18.2; 21.3)	101 (22.0)	28 (18.9)	0.488[a]
	Urban	478 (67.4; 78.7)	358 (78.0)	120 (81.1)	
	Missing	102 (14.4; —)	—	—	

Numerical results are described as means and standard deviations (mean ± SD) while qualitative results are described with sample sizes and percentages [n (%)]; a: Chi-square test; b: T-test for comparison of two independent means (one-sided); c: Fisher exact test; MEDAS-14: 14 Point Mediterranean Diet Adherence Screener; BMI: Body Mass Index; HVS: Herpes Virus Simplex.
*p-value < 0.05.
**p-value < 0.01.
***p-value < 0.001.
Statistical significance marked in bold.

TABLE 4 Association of the A-to-Z factors vs. the number of positive tests for CI.

		Number of positive tests				
		0	1	2	3	*p*-value
		n = 549	*n* = 112	*n* = 32	*n* = 16	
Depression (GDS-5)	No	390 (73.9)	66 (64.1)	14 (46.7)	9 (60.0)	0.003[a**]
	Yes	138 (26.1)	37 (35.9)	16 (53.3)	6 (40.0)	
Do you live alone	No	449 (81.8)	82 (73.2)	21 (65.6)	9 (56.2)	0.004[a**]
	Yes	100 (18.2)	30 (26.8)	11 (34.4)	7 (43.8)	
Hypertension	No	287 (52.4)	40 (36.4)	15 (46.9)	4 (25.0)	0.004[a**]
	Yes	261 (47.6)	70 (63.6)	17 (53.1)	12 (75.0)	
Insulin resistance	No	450 (82.1)	75 (67.6)	23 (71.9)	13 (81.2)	0.004[a**]
	Yes	98 (17.9)	36 (32.4)	9 (28.1)	3 (18.8)	
Job	Intellectual work (Levels 1, 2, 3)	229 (43.3)	36 (32.4)	4 (12.9)	3 (18.8)	0.001[a**]
	Manual work (Levels 4, 5, 6)	300 (56.7)	75 (67.6)	27 (87.1)	13 (81.2)	
Obesity	Insufficient	7 (1.3)	1 (0.9)	3 (10.3)	0 (0.0)	0.036[a*]
	Normal	146 (27.9)	30 (27.3)	7 (24.1)	6 (37.5)	
	Obese	159 (30.4)	37 (33.6)	9 (31.0)	2 (12.5)	
	Overweight	211 (40.3)	42 (38.2)	10 (34.5)	8 (50.0)	
Reading	No	151 (27.5)	49 (43.8)	16 (50.0)	11 (68.8)	<0.001[a***]
	Yes	398 (72.5)	63 (56.2)	16 (50.0)	5 (31.2)	
Web	No	113 (20.6)	57 (50.9)	24 (77.4)	14 (87.5)	<0.001[a***]
	Yes	436 (79.4)	55 (49.1)	7 (22.6)	2 (12.5)	
Depression score (GDS-5)		1.1 ± 1.3	1.3 ± 1.4	1.8 ± 1.3	1.6 ± 1.2	0.008[b**]
Nutrition score (MEDAS-14)		9.0 ± 2.1	8.8 ± 2.3	7.6 ± 2.9	8.9 ± 2.2	0.039[b*]
Sleep (hours/week)		6.8 ± 1.5	7.2 ± 2.3	7.6 ± 1.7	7.6 ± 1.4	0.012[b*]

Numerical results are described as means and standard deviations (mean ± SD), while qualitative results are described with sample sizes and percentages [n (%)]; CI: cognitive impairment: GDS-5: 5 Point Geriatric Depression ScALE; BMI: Body Mass Index; MEDAS-14: 14 Point Mediterranean Diet Adherence Screener; a: Fisher test; b: Kruskal Wallis test.
*p-value < 0.05.
**p-value < 0.01.
***p-value < 0.001.

4. Discussion

The main contribution of this work is the estimation of factors included in the *A-to-Z Dementia Knowledge list* in a sample of cognitively concerned patients screened for CI. Various factors influence this estimation in addition to regular age-related degenerative changes (Cheon, 2022). Therefore, addressing a combination of modifiable factors is currently suggested to be the

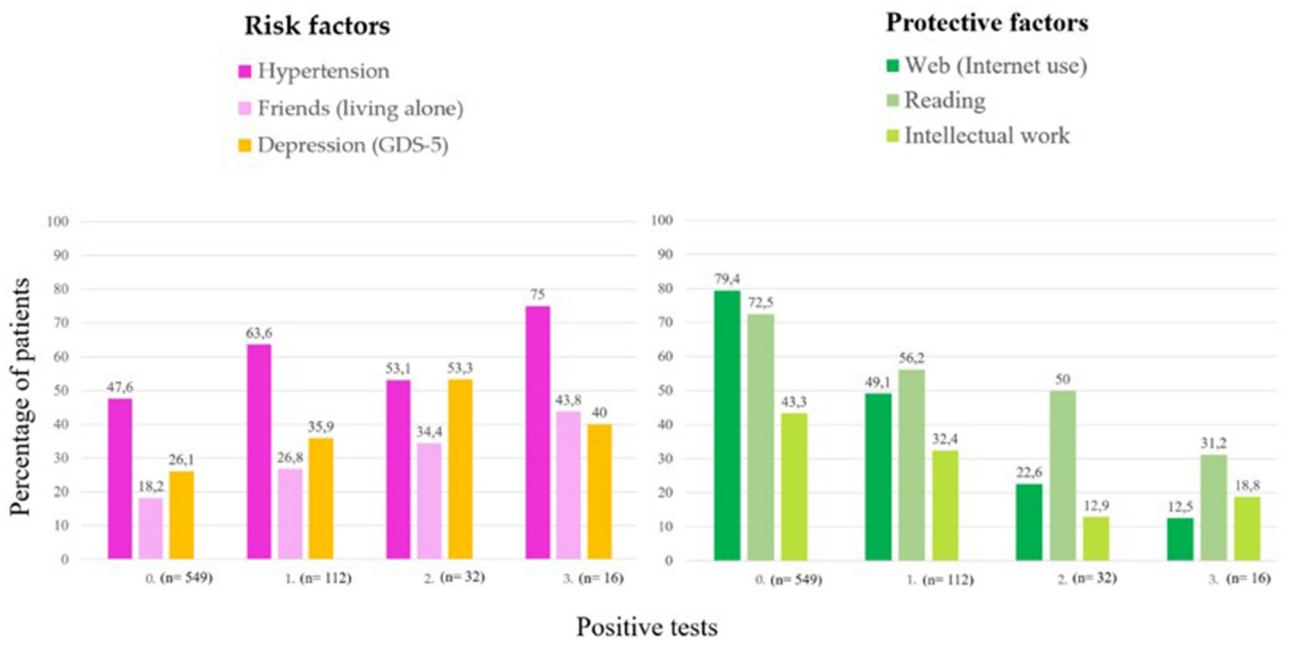

FIGURE 3
Evolution of the percentage of patients with hypertension, loneliness, depression, Internet use, reading, and intellectual work, as the number of positive CI screening tests increases.

best approach for mitigating or preventing the onset of dementia (Iadecola and Parikh, 2020). Our study found that hypertension, loneliness, and depression were gradually associated with cognitive decline as potential risk factors. In contrast, internet use, reading, and type of job were gradually associated with less cognitive decline, suggesting a protective effect (Figure 3).

According to the 2020 report of the Lancet Commission, there are specific potentially modifiable risk factors for dementia. As stated in this report, risk factors during early life, midlife, and later life can contribute to increased risk of dementia, as indicated by the following population attributable fraction (PAFs): less education (7.1%), hearing loss (8.2%), traumatic brain injury (3.4%), hypertension (1.9%), more than 21 units of alcohol/week (0.8%), obesity with BMI $\geq$ 30 (0.7%), smoking (5.2%), depression (3.9%), social isolation (3.5%), physical inactivity (1.6%), diabetes (1.1%) and air pollution (2.3%) (Morley et al., 2015).

Firstly, factors related to metabolic syndrome are highlighted. These include hypertension, insulin resistance, an altered lipid profile, and obesity. Reducing cardiovascular risk represents one of the most viable and promising strategies, as its association with CI is well known (Farnsworth Von Cederwald et al., 2022). The detrimental effect of vascular risk in mid-life on the future development of dementia has also been highlighted (McGrath et al., 2020). Hypertension is one of the most important risk factors for dementia, as it can be controlled and modified (Cheon, 2022). In addition, long-term cumulative blood pressure has been associated with subsequent cognitive decline and risk of dementia (Li C. et al., 2022). Given the high prevalence of dementia and its impact on quality of life, treating hypertension to reduce CI may be a clinically relevant intervention, Observational and randomized trials have shown that reducing blood pressure is associated with less dementia and CI (Iadecola and Parikh, 2020; Cheon, 2022), suggesting a 7–11% relative risk reduction in the incidence of dementia with antihypertensive treatment (Canavan and O'Donnell, 2022). On the other hand, numerous studies have linked type 2 diabetes with an increased risk of CI and dementia (Fink et al., 2022). Therefore, by reducing the incidence of diabetes, we can also reduce the incidence of dementia in diabetes patients (Fink et al., 2022). Moreover, diabetes mellitus has been identified as one of the risk factors responsible for up to one-third of AD cases and represents an important modifiable target for preventing dementia at the population level (McGrath et al., 2020). Cognitive-behavioral therapy for lifestyle modification in patients with metabolic syndrome effectively reduces cardiovascular risk (Garcia-Silva et al., 2022).

Regarding depression, this condition is closely associated with the incidence of dementia, and there are several potential mechanisms involved. These mechanisms include increased cortisol levels, vascular difficulties, inflammation, decreased brain-derived neurotropic factor, telomere shortening, increased plasma levels of amyloid ß42, and neurofibrillary tangles (Linnemann and Lang, 2020). Different studies have found positive associations between depression and dementia. It remains to be determined whether depression is a prodromal symptom of dementia, a risk factor, or a consequence of cognitive decline. They could also coexist due to a common underlying pathology or similar symptoms in both conditions (Sjöberg et al., 2020). In our study, we observed statistically significant differences in the reported depressive state as measured by GDS-5 but not in the diagnosis of depression itself. It could be because the depressive state directly influences the assessment of depression diagnosis. On the other hand, depression may be underdiagnosed in some patients, or the

effectiveness of pharmacological treatment in diagnosed patients could lead to a positive score on the GDS-5.

The main difference between depression and other cognitive risk factors is the availability of various therapeutic options, as some antidepressants may worsen the cognitive impact of depression. Therefore, studies have shown that using social supports, such as reducing social isolation, can delay the onset of dementia (Hakim, 2022). The potential increase in loneliness due to population aging and social isolation may harm brain health (Tao et al., 2022). Although living alone does not necessarily imply social isolation, loneliness feeling, or poor social networks, it is essential to note that social networks tend to diminish in later life due to factors such as adult children becoming independent, the loss of close social contacts through death and increased selectivity of social interactions with age. In addition, late-life implies health deterioration and limited mobility, which can further limit engagement in social activities and reinforce feelings of isolation (Evans et al., 2019). While living alone is an objective observation, loneliness refers to subjective dissatisfaction with social relationships and can be perceived differently by individuals. In line with our results, it has been suggested that living alone in later life may increase the risk of poor cognitive function. From a cognitive reserve perspective, living with others may enhance cognitive stimulation through social interaction, as there are more opportunities for social engagement (Evans et al., 2019). Socially stimulating environments promote neuroprotective mechanisms by activating alternative pre-existing or compensatory cognitive processes (Samtani et al., 2022). Frequent social activity has also been associated with improved memory, executive function, visuospatial ability, and processing speed, whereas frequent social support has been linked to improved memory (Kelly et al., 2017).

Concerning the protective factors gradually associated with reduced CI, certain variables related to cognitive stimulation stand out. These include internet use, reading, and type of job. Given the lack of effective pharmacological treatment, non-pharmacological activities are an important alternative to consider for promoting cognitive stimulation and delaying the onset of dementia (Yu et al., 2022). In this context, the concept of cognitive reserve becomes significant. Cognitive reserve refers to the varying susceptibility to exhibit dementia symptoms during the same phases of the disease (Stern, 2013; Stern and Barulli, 2019; Stern et al., 2021). Cognitive reserve is not immutable but is influenced by different exposures throughout life. These include general cognitive ability in early life, education, occupation, physical exercise, leisure activities, and social engagement (Cheng, 2016). As observed in our study, cognitive stimulation variables such as internet use, reading, quizzes, and mind games are statistically significantly associated with reduced CI. These data are consistent with previous studies, suggesting that modifiable lifestyle factors, like reading and daily Internet use, can slow cognitive decline in patients aged 50 and above with SMC (Ramos et al., 2021a).

Recent findings have also highlighted the interaction between technology, social environment, and cognitive functioning in later life (Kim and Han, 2022). Computerized cognitive training has also recently become a potential cognition stimulation instrument (Li R. et al., 2022). While internet use has shown cognitive benefits, discontinuation of internet use has been found to have adverse effects (Kim and Han, 2022). Different levels of internet use could have different relationships with cognitive function in middle-aged and older adults (Yu et al., 2022). Furthermore, social networking sites can also contribute to social support and connection and reduce perceived social isolation (Yu et al., 2022).

On the other hand, the results obtained regarding reading are in line with previous studies. A longitudinal study with 14 years of follow-up linked reading to a protective effect on cognitive function in late life (Chang et al., 2021). Furthermore, another cross-sectional study revealed that reading, writing, and technology use frequencies were significantly associated with language, attention, and memory proficiency after adjusting for demographic characteristics (Iizuka et al., 2021). In line with these findings, a 6-year follow-up study in Japan associated a lower risk of cognitive decline among individuals who reported being readers, regardless of whether they considered reading a hobby (Sugita et al., 2021). Finally, a mixed-effects model revealed that more frequent and earlier cognitive activity during a 5.8-year follow-up was associated with slower cognitive decline (Wilson and Boyle, 2013). Among the cognitive activities considered reading books, visiting a library, and writing letters were consistent with the cognitive reserve hypothesis.

Regarding the type of work, several studies have found that the risk of dementia is lower in people with cognitively stimulating jobs than those with non-stimulating jobs (Huang et al., 2020; Kivimäki et al., 2021). In a sample of 2261 participants, cognitive stimulation was associated with lower levels of plasma proteins that potentially hinder axonogenesis and synaptogenesis, consequently increasing the risk of dementia (Kivimäki et al., 2021). Moreover, a systematic review and meta-analysis concluded that engaging in mentally challenging work is linked to a reduced risk of MCI. Furthermore, working with more complex data and interacting with people may also decrease the risk of dementia (Huang et al., 2020). However, it is worth noting that job strain may influence cognitive performance decline in (Huang et al., 2020). Therefore, our findings, which show a significant inverse association between intellectual work and CI, align with previous research studies.

There is accumulating evidence linking sleep disturbances to the risk of dementia. Consistent with our findings, prolonged sleep duration (9 h per night) has been associated with an increased risk of late-life dementia (Sindi et al., 2018).

To date, the literature supports that hearing loss is a modifiable risk factor interrelated with dementia, and hearing aids can play a significant role in cognitive health. Both hearing loss and CI include aging, mitochondrial dysfunction, microvascular factors, and inflammation (Tarawneh et al., 2022). Given that mid-life hearing loss precedes the onset of dementia and may may contribute to up to 9.1% of dementia cases worldwide, it should be targeted as a preventive strategy for managing dementia (Ford et al., 2018; Pichora-Fuller, 2020). Although we did not observe statistically significant differences, this could be attributed to our homogeneous sample of health-conscious patients.

Our study did not observe statistically significant differences between memory complaints and CI. Nevertheless, it is worth noting that memory complaint is a variable that may be present in stage 2 of AD (Jessen et al., 2020). This factor has been associated with a twofold increase in the likelihood of dementia (Mitchell et al.,

2014). In addition, it has been observed that preclinical AD patients with memory complaints had a 62% higher risk of progression from MCI to dementia within 3 years (Wolfsgruber et al., 2017).

Regarding genetics, statistically significant differences were observed in our study between the absence of family history and CI. Although AD has an estimated heritability of 58–79% in early-onset AD and 90% in late-onset AD, the reality is that purely genetic AD is <1%, which can be explained by Mendelian inheritance pattern (Van Cauwenberghe et al., 2016; Potter et al., 2020). However, it is known that potentially modifiable risk factors play an important role in this disease, influencing 40% of the risk of dementia (Morley et al., 2015). Therefore, the obtained results could be attributed to patients with a family history having a better understanding of the disease and its associated risk factors.

Although numerous studies have associated anticholinergic drugs with CI (Chatterjee et al., 2020; Pasina et al., 2020; Sargent et al., 2020; Weigand et al., 2020), we did not find a statistically significant association in our study, which aligns with a previous study conducted by our group, where an association between CI and the anticholinergic burden was observed when measured using the newly developed CRIDECO Anticholinergic Load Sclae (CALS), which includes 129 new drugs with anticholinergic effects. However, no association was found when using the currently most widely used anticholinergic scale, the Anticholinergic Burden Scale (ACB). It is important to note that our study collected data before developing the new scale (Ramos et al., 2021b). In contrast, we observed an association between CI and the consumption of benzodiazepines, which is consistent with previous studies (Tapiainen et al., 2018; Baek et al., 2020).

Concerning smoking, despite being a known cardiovascular risk factor and, therefore, a risk factor for dementia, it is also known that nicotine may have a protective role in CI (Dong et al., 2020; Rao et al., 2022). In a recent study, nicotine has been found to prevent stress-induced damage in the hippocampus suggesting a potential neuroprotective role (Dong et al., 2020). Moreover, nicotine has shown promise as a treatment for cognitive deficits caused by traumatic brain injury. It can reverse altered signaling pathways in the brain, involving nicotinic receptors, tyrosine hydroxylase, and dopamine (Rao et al., 2022). Therefore, we hypothesize that in the stage of cognitive decline that patients are at, the long-term risks associated with smoking may not be evident, and we only observe the short-term neuroprotective effects of nicotine.

Treatment with antiherpetic medication has been associated with a decreased risk of dementia (Tzeng et al., 2018). In this 2018 study, antivirals were statistically significant in reducing the risk of dementia, highlighting the importance of treating HSV infection when it manifests. However, our study did not find any association.

Age is widely recognized as the primary risk factor for dementia. According to the Comprehensive Plan for Alzheimer's and other Dementias (2017–2023), the prevalence of this disease is around 0.05% among people aged 40–65 years, 1.07% among those aged 65–69 years; 3.4% in 70–74 years; 6.9% in 75–79 years; 12.1% in 80–84 years; 20.1% in 85–89 years; and 39.2% among those over 90 years. As shown in Table 2, our study population consisted of a higher percentage of individuals with cognitive impairment, as one of the inclusion criteria was a concern for cognition (Ministerio de Sanidad Consumo y Bienestar Social., 2019).

In our sample, among all the factors identified in the scientific literature as risk factors, the following are associated with gradual cognitive deterioration: hypertension, living alone, and depression. On the other hand, scientifically identified protective factors include internet use, daily reading, and intellectual work.

This study has several limitations. We could not collect data on the following factors in our patient's: knowledge and universal task. In addition, the results pertain to the CI risk, reflecting a decline in cognitive function in the patients because we do not have data on the diagnosis of CI by a neurologist. Notably, our sample consisted of homogeneous patients concerned about their memory, which may represent a specific group of patients for screening purposes. Future studies with a prospective approach and patient follow-up are needed.

5. Conclusion

This study identified the most influential variables that can be modified to reduce CI risk. Our results suggest that a joint assessment of the influence of psychosocial, clinical, and lifestyle-related factors is needed to develop dementia prevention strategies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board (IRB) of Universidad CEU Cardenal Herrera (CEII18/027) and by the Research Ethics Committee of Arnau de Vilanova Hospital (CEIm 7/2022). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: MA and MG-P. Methodology, software, and formal analysis: MA. Validation: MG-P and JS-L. Investigation: MG-P, HR, GG-L, CG, TL, and MS. Resources: JS-L. Data curation: MG-P and CG. Writing—original draft preparation: MG-P and HR. Writing—review and editing and Funding acquisition: JS-L and LM. Supervision and project administration: LM. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Alzheimer's disease: a continuum with visual involvements

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Introduction: Alzheimer's disease (AD) is the most common form of dementia affecting the central nervous system, and alteration of several visual structures has been reported. Structural retinal changes are usually accompanied by changes in visual function in this disease. The aim of this study was to analyse the differences in visual function at different stages of the pathology (family history group (FH+), mild cognitive impairment (MCI), mild AD and moderate AD) in comparison with a control group of subjects with no cognitive decline and no family history of AD.

Methods: We included 53 controls, 13 subjects with FH+, 23 patients with MCI, 25 patients with mild AD and, 21 patients with moderate AD. All were ophthalmologically healthy. Visual acuity (VA), contrast sensitivity (CS), colour perception, visual integration, and fundus examination were performed.

Results: The analysis showed a statistically significant decrease in VA, CS and visual integration score between the MCI, mild AD and moderate AD groups compared to the control group. In the CS higher frequencies and in the colour perception test (total errors number), statistically significant differences were also observed in the MCI, mild AD and moderate AD groups with respect to the FH+ group and also between the control and AD groups. The FH+ group showed no statistically significant difference in visual functions compared to the control group. All the test correlated with the Mini Mental State Examination score and showed good predictive value when memory decline was present, with better values when AD was at a more advanced stage.

Conclusion: Alterations in visual function appear in subjects with MCI and evolve when AD is established, being stable in the initial stages of the disease (mild AD and moderate AD). Therefore, visual psychophysical tests are a useful, simple and complementary tool to neuropsychological tests to facilitate diagnosis in the preclinical and early stages of AD.

KEYWORDS

Alzheimer's disease, mild cognitive impairment, family history, visual function, visual acuity, contrast sensitivity, PDT

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that affects the central nervous system and is the most common cause of dementia in the world (Cunha et al., 2016). This neurodegenerative disease is histologically characterized by the accumulation of beta-amyloid (Aβ) and intracellular neurofibrillary tangles of hyperphosphorylated tau protein (pTau) (Walker, 2020). The main risk factor for developing AD is the age (Capizzano et al., 2004; Chen et al., 2009), following this, two of the genetic risk factors are: having a first-degree family history of AD and carrying at least one ε4 allele for the ApoE gene (Sano et al., 1991; Donix et al., 2010). These subjects with a parent with AD have a 4 to 10 times higher risk of developing the disease (Huang et al., 2004). Some of these high-risk individuals may develop the pathology over time. Therefore, it could be considered that these subjects may be in a preclinical phase, since the first biochemical changes occur even 20 years before cognitive decline appears.

AD is a continuum because it is a progressive neurological disorder that develops gradually over time. This continuum begins when the subject is cognitively healthy, although there are molecular changes that already foreshadow the progression toward cognitive decline, to a phase in which the patient has cognitive impairment that cannot be independent in their daily life (Alzheimer's association, 2020; Alzheimer's Association, 2022). MCI can be considered as the stage of cognitive status prior to AD (Sperling et al., 2011). MCI is characterized by impairment of cognitive functions in the performance of everyday activities, that is greater than what would be expected for a person's age and education level, but not severe enough to interfere significantly with daily activities or independent functioning (Sanford, 2017; Alzheimer's Association, 2022). When dementia is established current criteria describe three stages: mild AD, moderate AD and severe AD (McKhann et al., 2011; Alzheimer's Association, 2022).

The retina is a projection of the brain, and it is known that in some brain neurodegenerative diseases there are retinal changes (Ramirez et al., 2017; Colligris et al., 2018; Salobrar-García et al., 2019; Rojas et al., 2020a,b; Alves et al., 2023). In recent decades, numerous studies have investigated retinal alterations in AD, observing that there is neuronal death that first affects the macular region in early stages of the disease, and later, as AD progresses, it affects the peripapillary region of the retina (Blanks et al., 1989; Garcia-Martin et al., 2014; Salobrar-García et al., 2015, 2019; Koronyo et al., 2017). These structural changes are often accompanied by functional visual changes, which have been described in patients with MCI and AD compared to healthy subjects, reporting decreased visual acuity (VA) and contrast sensitivity (CS), as well as poorer colour perception and impaired visuospatial integration (Sadun et al., 1987; Risacher et al., 2013, 2020; Salobrar-García et al., 2015, 2019; Chang et al., 2022). These visual functional tests are easy to perform, quick and non-invasive and can provide information on the onset, stage and evolution of the neurodegeneration.

These changes in visual function can have a significant impact on the daily lives of individuals with AD and their caregivers. It is important to monitor and manage visual changes in individuals with AD to help maintain their quality of life.

Currently, the continuum of AD is well understood in terms of biochemical changes, brain atrophy, and cognitive decline. However, what is not clearly established is how visual function changes in these patients throughout the evolution of the pathology, from preclinical stages to advanced disease. It is therefore crucial to understand the visual changes that occur in these patients, given their importance for maintaining independence in daily life. By gaining a better understanding of visual changes in the context of the disease continuum, we can improve patient care and outcomes. Despite the existence of numerous reports detailing the examination of retinal biomarkers in AD, as evidenced by numerous articles and reviews, the literature concerning the evaluation of visual perception in AD remains limited. This may be attributed to the challenge of obtaining subjective measurements in individuals with cognitive decline. Nonetheless, investigating these visual perceptual variables in early-stage cases may be worthwhile in order to determine whether they can be utilized as supplementary biomarkers for AD. Thus, the aim of this study is to analyze the differences in visual function in the different stages of the disease continuum, from healthy subjects with high genetic risk for the development of the disease to patients with moderate AD.

2. Materials and methods

2.1. Subjects

The study subjects were recruited from the Memory Unit of the Hospital Clínico San Carlos in Madrid and from the COGDEM study "The cognitive and neurophysiological characteristics of subjects at high risk of developing dementia: a multidimensional approach."

All patients were ophthalmologically examined at the Ramon Castroviejo Institute for Ophthalmic Research clinic of the Complutense University of Madrid and signed the informed consent form. The research followed the tenets of the Declaration of Helsinki, and the studies were approved by the local ethics committee (HCSC) with the internal code 11/372-E, 18/422-E_BS, and 20/698-E_Tesis.

The cognitively healthy subjects were divided into two groups: (i) controls with no family history of AD ($n = 53$); (ii) healthy subjects with a first-degree history of AD ($n = 13$) (Figure 1). Cognitively healthy subjects had a normal T2-weighted brain magnetic resonance imaging (MRI) without evidence of brain injury or pathology and a Mini Mental State Examination (MMSE) above 26.

Subjects with cognitive impairment were categorized according the National Institute of Neurological and Communicative Disorders and Stroke-AD and Related Disorders Association and

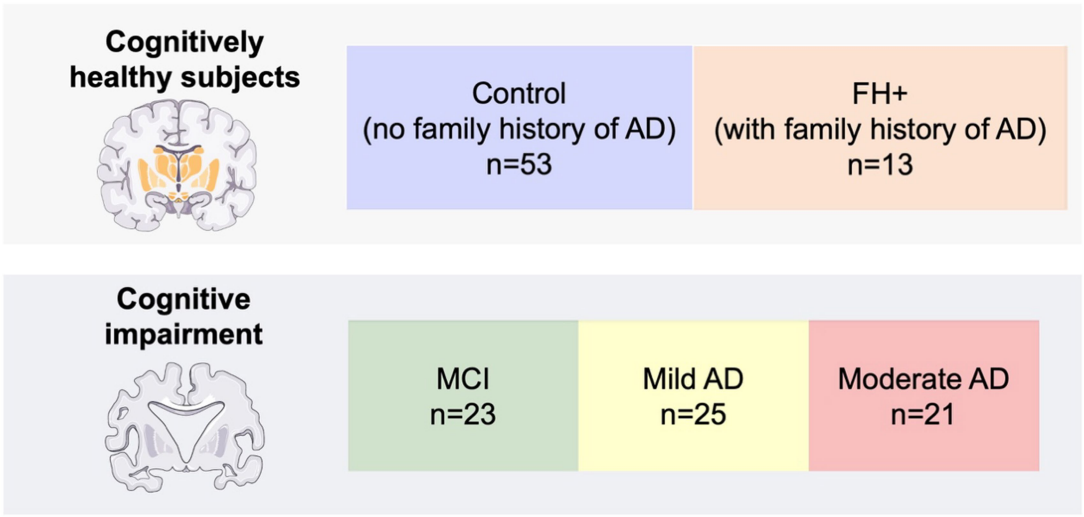

FIGURE 1
Number of participants per group. FH+, family history positive; MCI: mild cognitive impairment; AD, Alzheimer's disease.

the Diagnostic (NINCDS-ADRDA) and Statistical Manual of Mental Disorders V (DSM V) to the guidelines into patients with MCI ($n = 23$), mild AD ($n = 25$), and moderate AD ($n = 21$) (Figure 1). All cognitively impaired participants had a MMSE score between 25 and 17.

All participants had no history of neurological or psychiatric disorders or a serious medical condition and being free of systemic disorders affecting vision in their medical record. In all study groups, subjects met the following ophthalmologic inclusion criteria: be free of ocular disease or posterior pole pathology (macular degeneration, drusen, glaucoma or suspected, epiretinal membrane, congenital malformation) have best corrected VA better than 0.5 decimal, have less than ±5 spherocylindrical refractive error, have intraocular pressure less than 20 mmHg.

2.2. Ophthalmological tests

The complete ophthalmologic examination included: measurement of VA, refraction, slit lamp examination, applanation tonometry (Perkins MKII tonometer, Clement Clarke International, Essex, England), CS analysis with CSV-1000E, colour perception test with Farnsworth 28 Hue test, perception digital test (PDT), fundus examination and optical coherence tomography (OCT).

The analysis of visual function was performed through the results obtained in psychophysical tests which are described below.

2.2.1. Visual acuity

The best corrected VA was determined using the Snellen test (decimal scale), as previously described by Salobrar-García et al. (2015). The subjects have to identified the set of letters of each VA level up to his or her maximum, recognizing at least five letters out of eight in a given row, that is the point of highest gradient on the psychometric acuity function approximately of 56.25%. Decimal VA is expressed as a decimal number, where 1.0 represents normal vision, and lower numbers indicate poorer vision.

2.2.2. Contrast sensitivity

To analyze CS, it was used CSV-1000E system (VectorVision, Greenville, OH, United States) with the patient's best corrected VA. The manufacturer's recommendation for viewing distance and illumination levels was followed and four spatial frequencies [3, 6, 12, and 18 cycles per degree (cpd)] were analysed. The result provides us with a sensitivity curve in logarithmic values that is provided by the manufacturer.

2.2.3. Colour perception test

It was used the Farnsworth 28-Hue test (Luneau, Paris), that is a color vision test that measures a person's ability to distinguish differences in color hues. It consists of 28 color tiles, arranged in four rows of seven tiles each, that must be arranged in a specific color order. The test is used to assess color vision deficiencies, such as color blindness, and to evaluate a person's color discrimination ability. During the test, there were no time restrictions and the subject was permitted to make corrections. To determine the extent of tritan and deutan errors, the manufacturer's manual blue axis errors were taken into consideration when caps 43 to 64 were malpositioned, and deutan axis errors were considered for caps 42 to 85.

2.2.4. Perception digital test

Perception digital test (PDT) (Rami et al., 2007) was used to analyse visual integration. It is a quick, simple and sensitive test used in patients with AD. The test consists of 15 slides. Each slide shows the same distorted image (special effects: geometric effects (tile) and the effect of the frame 24/48 of the MGI Photo Suite III program) in different positions in space. The patient had to identify the image that was correctly oriented in space.

2.3. Statistical analysis

Statistical analysis was performed in Prism 9.0.1 (GraphPad Prism, La Jolla, CA, United States). Data were indicated as median ± interquartile range. The Kruskal-Wallis test with the Dunn's

test for multiple comparisons was used to analyze differences between the study groups (control, FH+, MCI, mild AD and moderate AD) in VA, Colour vision and PDT; CS was analyze using 2way-ANOVA test with the Tukey multiple comparison test. The sensitivity at 90% specificity and the area under the receiver operator characteristic (aROC) analysis were computed for all the psychophysical tests that were examined, with the aim of distinguishing between healthy individuals and those diagnosed with AD. Furthermore, these calculations were performed to compare the control group with the other groups. Correlation was applied using Spearman's correlation coefficient to study the possible association between MMSE and visual function test (VA, CS, color vision and PDT). A p-value of <0.05 was considered statistically significant after correction for multiple comparison. The notations used for the different levels of significance were $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

3. Results

3.1. Demographic analysis

When we analyzed age between the study groups, we found statistically significant differences (value of $p<0.01$) between the control group and: (i) FH+ group; (ii) MCI group and; (iii) moderate AD group. We also found significant differences (value of $p<0.01$) between FH+ group and: (i) MCI group; (ii) mild AD group and; (iii) moderate AD group (Table 1).

The MMSE scores showed significant differences (value of $p<0.001$) between the control, FH+ and MCI groups compared with: (i) mild AD and; (ii) moderate AD (Table 1; Figure 2).

3.2. Visual acuity

The VA analysis showed a statistically significant decrease ($p < 0.001$) between the MCI, mild AD and moderate AD groups with respect to the control group (Figure 3).

3.3. Contrast sensitivity

When comparing CS at the spatial frequency of 3 cpd, we found statistically significant differences between mild AD group and: (i) control group (value of $p<0.001$); (ii) FH+ group (value of $p<0.01$); and; (iii) MCI group (value of $p<0.01$) (Figure 4).

We observed a statistically significant differences in the 6 cpd contrast sensitivity (CS) between the control group and both the mild AD group and moderate AD group (value of $p<0.001$, in both) (Figure 4). Additionally, we observed a significant decrease in the mild AD group (value of $p < 0.001$) and moderate AD group (value of $p < 0.01$) in comparison with the FH+ group (Figure 4). Also, there is a decrease in the VA in the mild AD group compared with the MCI group (value of p <0.05) (Figure 4).

At the spatial frequency of 12 cpd, we observed statistically significant differences between the control group and: (i) MCI group, (ii) mild AD group and; (iii) moderate AD group ($p < 0.001$, in all instances). In addition, we also found a significant decrease when comparing the FH+ group and: (i) MCI group ($p < 0.01$); (ii) mild AD group ($p < 0.001$) and; (iii) moderate AD group ($p < 0.001$) (Figure 4).

Finally, significant differences were observed at a spatial frequency of 18 cpd between the control group and: (i) the MCI group, (ii) mild AD group, and (iii) moderate AD group. Additionally, compared to FH+ group a significant decrease ($p < 0.01$) was found in: (i) the MCI group, (ii) mild AD group, and (iii) moderate AD group (value of $p<0.001$, in all instances) (Figure 4).

3.4. Color perception

In the Farnsworth 28-hue Test, the analysis of the number of total errors shown an increase in the number of errors between the control group and moderate AD group (value of $p<0.001$). We also found a significant increase in the number of total errors between FH+ group and: (i) MCI group (value of $p<0.05$); (ii) mild AD group (value of $p<0.05$) and; (iii) moderate AD group (value of $p<0.001$) (Figure 5).

When we analyze the tritan axis, we found significant differences between the control group and: (i) mild AD group (value of p <0,05) and; (ii) moderate AD group (value of $p<0.001$). We also found significant differences between FH+ group and: (i) mild AD group (value of $p<0.05$) and; (ii) moderate AD group (value of $p<0,001$) (Figure 5).

On the deutan axis, we found significant increase in the error number between control group and: (i) mild AD group (value of $p<0.05$) and; (ii) moderate AD group (value of $p<0.0001$). We also found statistical significance increase when comparing FH+ group to the moderate AD group (value of p <0.001) (Figure 5).

3.5. Perception digital test

In the Perception digital test (PDT) median values we found that in comparison with the control group there was a decrease in: (i) mild AD group and (ii) moderate AD group ($p < 0.0001$, in all instances). We also found statistical significance decrease when comparing FH+ group and: (i) mild AD (value of p <0.05) and; (ii) moderate AD (value of p <0.01) (Figure 6).

TABLE 1 Demographics variables of the study.

Groups demographic variables	Control (n=53)	FH+ (n=13)	MCI (n=23)	Mild AD (n=25)	Moderate AD (n=21)
Age	75.00 (72.00–78.00)	68.00 (66.00–70.50)	79.00 (75.75–83.25)	76.00 (75.00–79.00)	77.00 (75.00–81.00)
Sex (n = Male/Female)	(n = 22/31)	(n = 5/8)	(n = 11/12)	(n = 10/15)	(n = 6/15)
MMSE	29.00 (28.00–30.00)	29.00 (29.00–30.00)	29.00 (26.00–30.00)	25.00 (21.00–26.50)	19.00 (18.00–23.00)

Median (interquartile range) MMSE, mini mental state examination; FH, family history positive; MCI, mild cognitive impairment; AD, Alzheimer's disease.

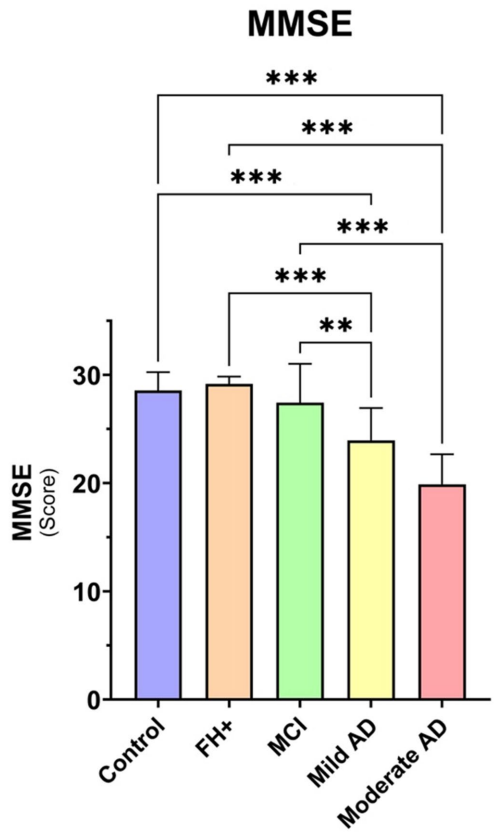

FIGURE 2
Median data of MMSE score in the study groups. FH+, family history positive; MCI, mild cognitive impairment; AD, Alzheimer's disease. Each bar represents the median±interquartile range. **p<0.01; ***p<0.001.

3.6. Correlation between MMSE and visual function

When analyzed the correlation between the MMSE score with the different visual function tests, we found a statistical significant direct correlation with: (i) VA (r = 0.402; value of p<0.001); (ii) CS in all spatial frequencies: 3 cpd (r = 0.4003; value of p<0.001); 6 cpd (r = 0.5634; p < 0.001), 12 cpd (r = 0.453; value of p<0.001) and; 18 cpd (r = 0.4182; value of p <0.001) and; (iii) PDT (r = 0.507; value of p<0.001).

Moreover, when we analyzed the correlation between the MMSE and the results in the Farnsworth color test, we found a statistically significant negative correlation in: total error number (r = −0.511; value of p <0.001); tritan axis errors (r = −0.448; value of p <0.001) and deutan axis errors (r = −0.461 and value of p <0.001).

3.7. Roc curves of the visual tests

The results indicated that the psychophysical tests had varying degrees of accuracy in discriminating between the different groups. For the cognitively healthy vs. cognitive decline comparison, all psychophysical tests showed statistically significant differences with p-values less than 0.01. The 18 cycles per degree (cpd) test had the highest aROC value at 0.8401, while the 3 cpd test had the lowest aROC value at 0.6991 (Table 2; Figure 7).

The results pertaining to the predictive value of VA test indicate that individuals with cognitive decline and the MCI, Mild AD, and Moderate AD groups exhibit a predictive value greater than 0.7283 when compared to the control group (Table 2; Figure 7).

When comparing the control group to those with MCI, mild AD, and moderate AD, the 12 cpd and 18 cpd tests showed the highest accuracy in distinguishing between groups with aROC values most above 0.8342. The Farnsworth total errors test also showed high accuracy, particularly in distinguishing between the control group and those with moderate AD with an aROC value of 0.8410 (Table 2; Figure 7).

The results of the study examining the Farnsworth Tritan Errors and Farnsworth Deutan Errors using the Area under the ROC curve reveal significant differences in the discriminative power of the Farnsworth tritan errors and Farnsworth deutan errors across the different comparisons. In the Cognitively Healthy vs. Cognitively decline comparison, both parameters demonstrate high discriminative power (p < 0.0001). However, in the Control vs. FH+ comparison, there is limited discriminative power for both parameters (p > 0.05). In the Control vs. MCI comparison, the Farnsworth tritan errors and Farnsworth deutan errors show moderate discriminative power (p < 0.05), while in the Control vs. Mild AD and Control vs. Moderate AD comparisons, both parameters exhibit significant discriminative power (p < 0.001) (Table 2; Figure 7).

4. Discussion

To our knowledge, this is the first study to analyze the visual function of 5 groups of subjects, corresponding to the different stages of the AD continuum ("Control," "FH+," "MCI," "mild AD" and, "moderate AD"). The study sample was carefully selected, and all participants met the inclusion criteria in terms of diagnosis of neurological disease or any ocular disease that could interfere with the results.

When analysing the MMSE of the study groups, we found statistically significant differences between the control group, the FH+ group and the MCI group, which had a higher MMSE score than the mild and moderate AD groups. The control, FH+ and MCI groups did not differ from each other. In the sample analysed in the present study, the mild AD group had an MMSE of 25.00 (21.00–26.50), a higher score than values reported in other studies (Cronin-Golomb et al., 1995, 2007; Lakshminarayanan et al., 1996), these values indicate that they are patients with a very early stage of the disease. The MMSE score of our patients is very high because our patients were newly diagnosed, and therefore, it is an early phase in each of the stages. All patients had a diagnosis given by a team of geriatricians and neuropsychologists after an extensive battery of tests, including magnetic resonance imaging. We specifically chose this population to reliably answer visual tests, as psychophysical visual tests require patient collaboration, and although the examiners had extensive experience with patients with cognitive impairment, minimal patient involvement was required.

Although there were differences among the different age groups, all patients were over 65 years old, including those in the FH+ group. This inclusion criterion was chosen because it is known that visual

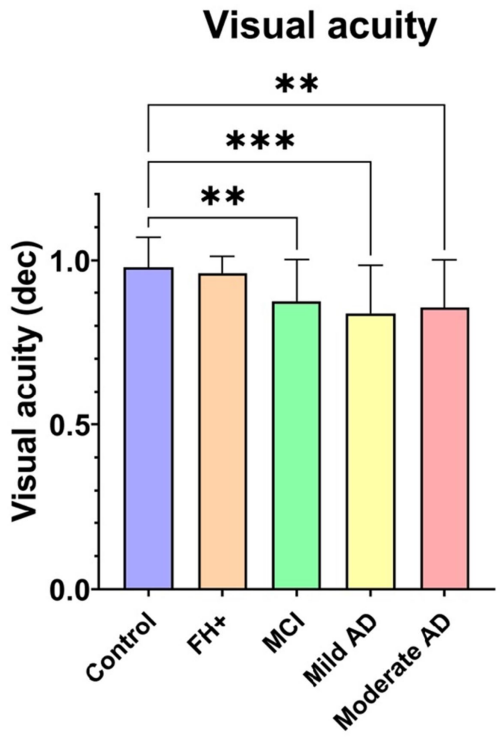

FIGURE 3
Median data of visual acuity in the study groups. FH+, family history positive; MCI, mild cognitive impairment; AD, Alzheimer's disease; dec, decimal. Each bar represents the median±interquartile range. **p<0.01; ***p<0.001.

function declines around this age range, and the population over 65 years old can be considered as a homogeneous group (Ross et al., 1985; Elliott, 1987; Liutkevičienė et al., 2013; Pelletier et al., 2016). It is noteworthy that subjects in the FH+ group had a younger age range because they were those whose parents had suffered from dementia, and although they had predisposing genetic traits, cognitive decline had not yet developed. That is precisely why the age of this group was lower, and it is interesting to understand what happens at this stage in order to detect possible early differences in visual function.

Patients with AD suffer from various symptoms at different stages, one of which is language problems, including nominative deficits. For this reason, the selection of visual tests was carefully considered in this study, choosing those with limited naming demands and easily performable by these patients. For the measurement of VA, the letters are presented in isolation for identification, as it has been observed that patients perform better on the test and obtain better results in this way (Sadun et al., 1987). Similarly, the analysis of CS with the CSV-1000E test, which has a low influence of VA compared to other existing CS tests (Neargarder et al., 2003) and the colour perception with the Roth 28-hue test that did not require verbalisation of the results by the patients (Berry, 2017; Salobrar-García et al., 2019).

A previous study performed in youngest AD relatives (average age of 56 years old), it was showed a hypersynchronization in functional connectivity measured by magnetoencephalography of high alpha band in comparison with the control group (Ramírez-Toraño et al., 2021). This alteration is caused by a possible imbalance of excitation/inhibition of GABAergic neurons located in the vicinity of Aβ plaques that are deposited very early in AD (Garcia-Marin et al., 2009; Busche and Konnerth, 2016). In the present study, we analysed the visual

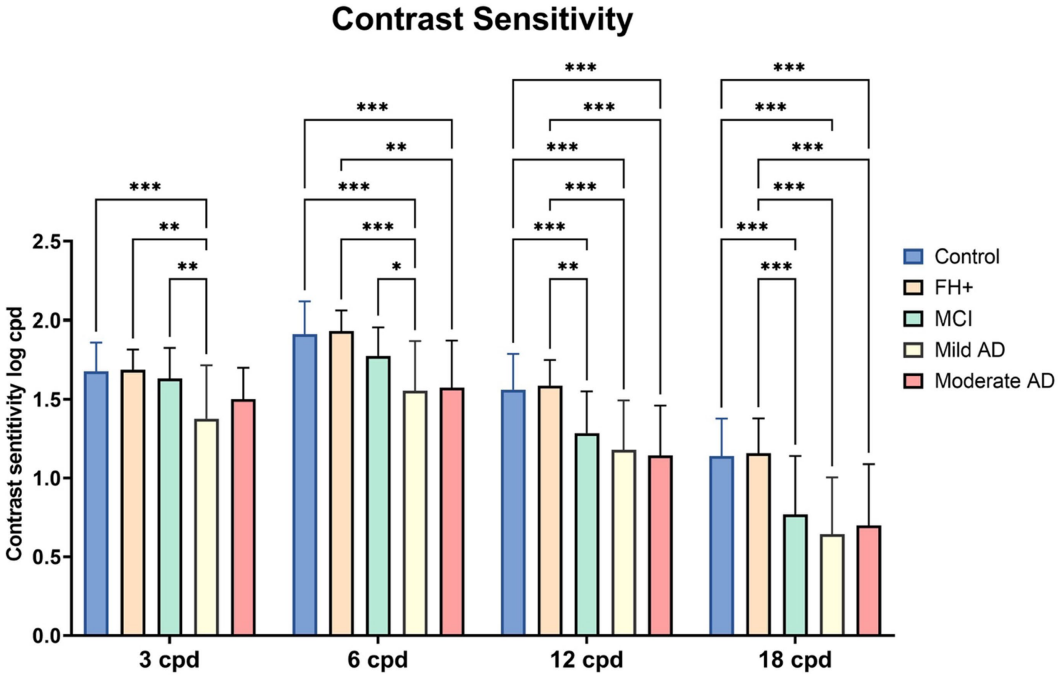

FIGURE 4
Median values of contrast sensitivity in the different groups. FH+, Family history positive; MCI, mild cognitive impairment; AD, Alzheimer's disease; CS, contrast sensitivity; cpd, cycles per degree. Each bar represents the median±interquartile range. *p<0.05; **p<0.01; ***p<0.001.

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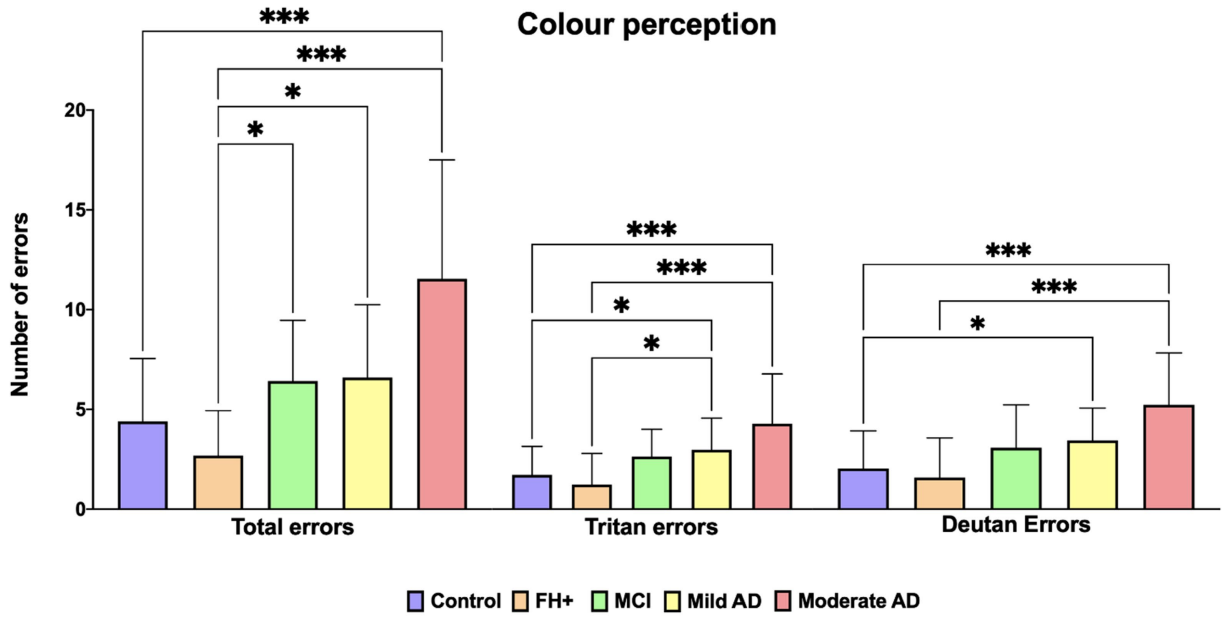

FIGURE 5
Median values of Farnsworth Roth 28-hue. FH+, family history positive; MCI, mild cognitive impairment; AD, Alzheimer's disease. Each bar represents the median±interquartile range. *p<0.05; ***p<0.001.

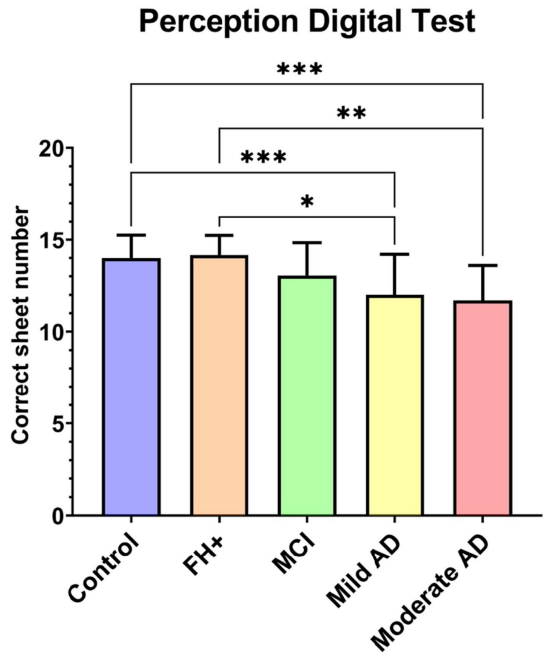

FIGURE 6
Median value of perception digital test between groups. FH+, family history positive; MCI, mild cognitive impairment; AD, Alzheimer's disease. Each bar represents the median±interquartile range. *p<0.05; **p<0.01; ***p<0.001.

function of subjects with a family history of AD and over 65 years of age, to test whether there are similar changes in the visual pathway as have been observed in the electric response of the brain.

The results obtained in VA showed a significant decrease in the MCI, mild and moderate AD patients with respect to the control group. This alteration that appears in both preclinical and early stages of the disease could be due to an alteration in the function of neurotransmitters, specifically acetylcholine. It is known that acetylcholine has a crucial role in the peripheral and central nervous systems, and in AD cholinergic neurons, are severely lost in AD (Ferreira-Vieira et al., 2016). In the retina, these neurotransmitter changes are mainly evident in the photoreceptor layer and in the inner nuclear layer and are associated with the loss of cholinergic cells in the retina (Nobili and Sannita, 1997; Schliebs and Arendt, 2006; Oliveira-Souza et al., 2017; Cerquera-Jaramillo et al., 2018). In the literature, according with our results, we found studies in which this loss of VA appears also in patients with cognitive decline and worsens as the disease progresses (Sadun et al., 1987; Salobrar-García et al., 2019; Rehan et al., 2021; Chang et al., 2022; Wu et al., 2022). Also, in the present work, we found a positive correlation between the MMSE score and the VA.

VA and CS impairment may be risk factor for cognitive decline (Ward et al., 2018; Swenor et al., 2019; Smith et al., 2021) and they may precede the onset of clinical cognitive impairment several years earlier. These findings suggest that reduced VA may be an early manifestation of central nervous system degeneration and/or that impaired visual function may contribute to cognitive impairment (Brenowitz et al., 2019; Naël et al., 2019; Swenor et al., 2019; Tran et al., 2020). Also the reduction in VA can be explained by cortical and subcortical dysfunction of the visual system further affecting writing, reading and face recognition (Cerquera-Jaramillo et al., 2018).

One of the earliest visual manifestations in patients with AD, are alterations in CS (Risacher et al., 2013; Jindal, 2015), which have been associated with impairment in more cognitive domains than other measures of visual functioning (Varadaraj et al., 2021). CS worsens

TABLE 2 aROC values of the different visual tests among the different study groups.

Area under the ROC curve		Cognitively healthy vs Cognitively decline	Control vs FH+	Control vs MCI	Control vs Mild AD	Control vs Moderate AD
VA	Area	0.7398	0.5653	0.7305	0.7713	0.7283
	p value	**<0.0001**	0.4681	**0.0015**	**0.0001**	**0.0028**
3 cpd	Area	0.6991	0.5155	0.5367	0.7988	0.7420
	P value	**<0.0001**	0.8633	0.6194	**<0.0001**	**0.0023**
6 cpd	Area	0.8002	0.5318	0.6888	0.8342	0.8478
	P value	**<0.0001**	0.7244	**0.0106**	**<0.0001**	**<0.0001**
12 cpd	Area	0.8378	0.5377	0.7911	0.8342	0.8750
	P value	**<0.0001**	0.6758	**<0.0001**	**<0.0001**	**<0.0001**
18 cpd	Area	0.8401	0.5118	0.8090	0.8600	0.8312
	P value	**<0.0001**	0.8956	**<0.0001**	**<0.0001**	**<0.0001**
Farnsworth total errors	Area	0.7618	0.6477	0.6886	0.6916	0.8410
	P value	**<0.0001**	0.1030	**0.0126**	**0.0071**	**<0.0001**
Farnsworth tritan errors	Area	0.7427	0.6038	0.6757	0.7216	0.8005
	P value	**<0.0001**	0.2516	**0.0201**	**0.0019**	**<0.0001**
Farnsworth deutan errors	Area	0.7439	0.5915	0.6462	0.7228	0.842
	P value	**0.0017**	0.3122	0.0531	**0.0017**	**<0.0001**

ROC, receiver operating characteristic; VA, visual acuity; cpd, cycles per degree; FH+, family history positive; MCI, mild cognitive impairment; AD, Alzheimer's disease. In bold significant values.

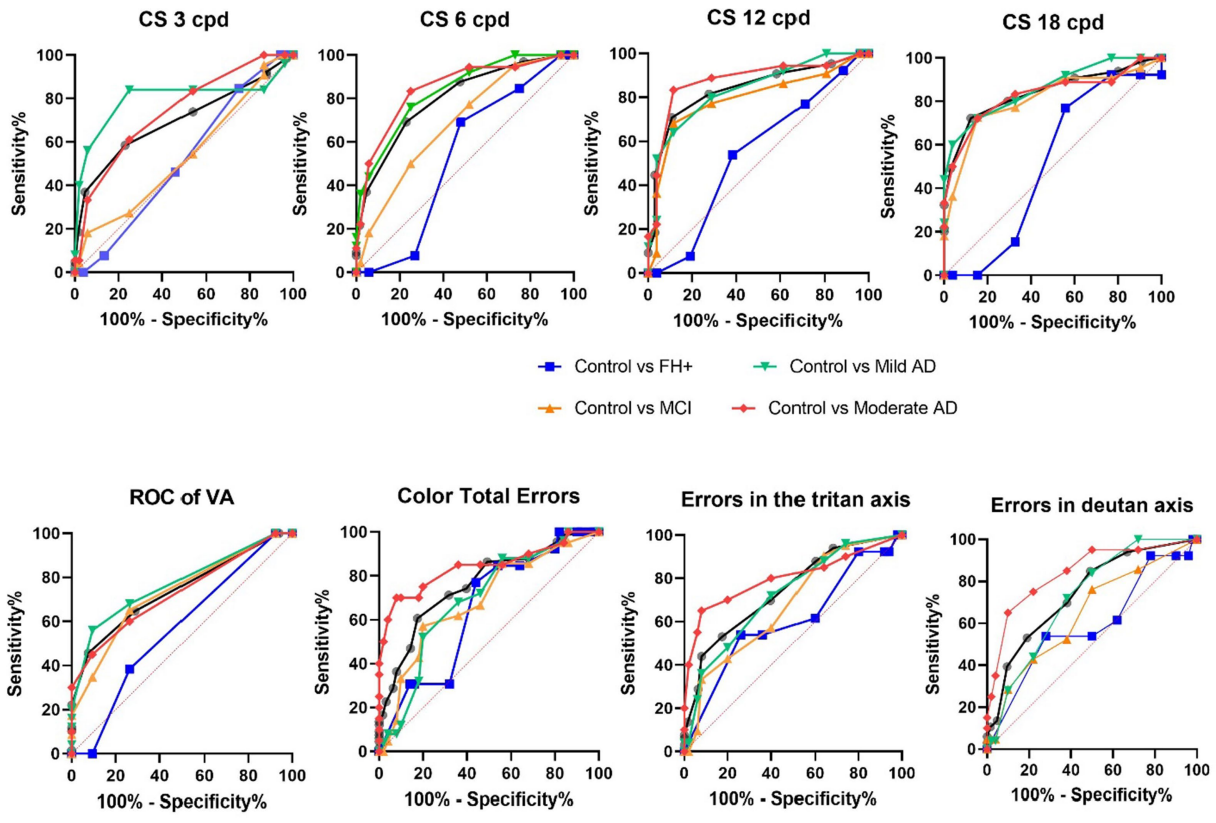

FIGURE 7
aROC curves of the different visual tests among the different study groups. FH+, family history positive; MCI, mild cognitive impairment; AD, Alzheimer's disease.

throughout the course of the disease, and is related to damage to the magnocellular pathway of the lateral geniculate nucleus of the central nervous system (Sartucci et al., 2010; Risacher et al., 2013). Epidemiological studies have shown that older adults with impaired CS are at increased risk of cognitive impairment at 10 years of follow-up (Fischer et al., 2016). It was also reported a strong association between brain areas involved in the disease with CS records which may be predictive of abnormal Aβ and p-Tau protein accumulation. In addition, a reduction in CS, measured by frequency doubling technology, has been associated with Aβ and P-Tau brain deposition as well as neurodegeneration, both throughout disease progression and alone in subjects at high risk for AD development (Risacher et al., 2020). In our study there are significant decreases in CS at both, low and high frequencies, between: (i) the control group and the AD groups and, (ii) the FH+ group and the AD groups; as reported in other studies in the literature associated with the MMSE score (Risacher et al., 2013; Salobrar-García et al., 2019). This correlation also has been found in the present study where in addition, we observed that high frequencies are decreased in all groups except for the comparison between the control vs. FH+ group. This decrease therefore already appears in the MCI group. The greatest reduction at higher spatial frequencies has been described by several authors (Hutton et al., 1993; Gilmore and Whitehouse, 1996; Salobrar-García et al., 2015, 2019), but others report that the higher reduction occurs at low spatial frequencies (Levine et al., 1993; Baker et al., 1997; Cronin-Golomb et al., 2007; Polo et al., 2017) and others find no differences with respect to the control group (Schlotterer et al., 1984; Rizzo and Nawrot, 1998; Massoud et al., 2002). The discrepancies observed in the literature in the analysis of CS at different stages of the disease may be due to the heterogeneity of the samples and the tests used to analyze it (Neargarder et al., 2003).

Another of the manifestations in AD patients are alterations in colour perception. These differences could be mainly due to participation both the parvocellular pathway, which is characterized by small axons of the optic nerve (Salamone et al., 2009) and the koniocellular pathway which is involved with the blue-yellow spectrum (Martin et al., 1997). One of the alterations linked to AD is a notable decrease in the cortical region V4, which plays a crucial role in the processing of chromatic information (Chan et al., 2001; Brewer and Barton, 2016). On the other hand, changes in colour vision in AD have been associated with variations in different retinal layers according to Köllner's rule. While changes in the retinal ganglion cells, optic nerve, visual pathway and visual cortex lead to a deficiency in the red-green axis, changes in the outer retina contribute to alterations in the blue-yellow axis (Huna-Baron et al., 2013; Kim et al., 2022). On the other hand, in the AD, it has been described that there is an degeneration on the photoreceptor cells that does not occur in only one type of cone, which is due to the reduction of melatonin levels and its antioxidant effects that occurs in AD (Savaskan et al., 2002).

When we analyzed colour perception in our patients, we observed that MCI, mild AD and moderate AD had a significant increase in the number of total errors in comparison to FH+ group. Also, the moderate AD group showed a significant increase in the total number errors related to control group. This diffuse involvement has been observed by different authors (Pache et al., 2003; Salamone et al., 2009; Polo et al., 2017; Salobrar-García et al., 2019) and recently Vidal et al. had found that individuals with AD and those with MCI display an acquired color vision deficiency, both in protan and tritan axism that is likely associated with compromised brain metabolism (Vidal et al., 2022).

In our patients, we found in the tritan axis errors, significant differences between the control group and mild and moderate AD groups, as well as between the FH+ and mild and moderate AD. However, we found no significant differences in this axis between the MCI group and the control group. In contrast, a loss in the tritan axis has been reported between the MCI subjects and the control group (Vidal et al., 2022). The MCI group is an intermediate stage between normal subjects and AD patients (Lewis et al., 1987; Black, 1996) that have worse MMSE scores (Vidal et al., 2022). In the present work, in all participants, we observed a negative correlation between the MMSE score and the total error number, tritan and deutan axis.

With respect to the deutan axis, we found statistically significant differences when we compared between the control group and both mild and moderate AD and when we compared between the FH+ and moderate AD groups. Similar than Vidal et al. (2022), we also found no significant differences in the number of errors between the control and MCI groups.

In a previous work, we found that in subjects with moderate AD the PDT showed a high direct correlation with the MMSE score and the aROC curves showed a good prognostic value (Salobrar-García et al., 2019). In the present study, our MCI patients showed no differences in PDT, however there were statistically significant differences between the mild and moderate AD groups and the control and FH+ groups. In addition, we also found a statistically significant positive correlation between the MMSE score and PDT. These results could be explained due to alterations in the visual processing in the AD pathology, that would take place in the regions involved in the magnocellular pathway (parietal and frontal brain areas) (Bar, 2003; Saumier et al., 2005).

Overall, our results of the aROC curves suggest that some psychophysical tests may be useful in identifying individuals with cognitive decline or disease, with the CS test analysing the 12 cpd and 18 cpd showing particular promise in distinguishing between control groups and those with mild or moderate AD.

As all the research works, this study shows strengths and some limitations. One of the first limitations is the low number of participants in each of the study groups. However, it should be noted that these have been carefully selected and that all participants met strict ophthalmological and memory criteria. We could be sure that all visual defects found are due to neurodegeneration and not to a visual problem. Despite having no biological biomarkers of the disease, the clinical diagnosis of the participants was made by professionals who followed standard criteria. It would be interesting for future studies to have bigger samples and to be able to correlate them with functional findings. On the other hand, it would be very interesting to carry out longitudinal studies of participants at high genetic risk for the development of AD and patients with MCI, so that we could learn about the evolution of the functional changes found in these early stages of the pathology. One of the strengths of this study is that the tests used in the present study to analyse visual function are easy to apply and could be useful together with neuropsychological tests and imaging tests for the diagnosis of AD, however, we are aware that other tests could be used for the analysis of visual function such as pupillometry, analysis of extraocular movements, and other tests for the analysis of visual function.

In conclusion, alterations in visual function appear already in subjects with MCI and evolve when AD disease is established. These differences seem to remain stable between the different early stages of AD (mild and moderate AD). Although in the present study we found no differences in visual function in the FH+ group, it would nevertheless be interesting to carry out longitudinal studies in these population to find out whether they develop the disease in the future. Therefore, visual psychophysical tests are a useful, simple and complementary tool to neuropsychological tests to facilitate diagnosis in the preclinical and early stages of AD and they correlated with the cognitive function.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the research followed the tenets of the Declaration of Helsinki, and the studies were approved by the local ethics committee (HCSC) with the internal code 11/372-E, 18/422-E_BS and 20/698-E_Tesis. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LE-H, IL-C, RH, MS, MD-L, AR, JS, FM, PG, JR, and ES-G: conceptualization and validation. LE-H, IL-C, RH, MS, LS-P, FR-T, JM, JF-A, PR, SA, MD-L, AR, JS, FM, PG, JR, and ES-G: methodology. LE-H, IL-C, RH, MS, FR-T, SA, MD-L, AR, JS, FM, PG, JR, and ES-G: formal analysis. LE-H, IL-C, RH, MS LS-P, FR-T, JM, JF-A, PR, SA, MD-L, AR, JS, FM, PG, JR, and ES-G: investigation. RH, MD-L, AR, JS, FM, PG, and JR: resources. LE-H, IL-C, MS, LS-P, FR-T, JM, JF-A, PR, SA, and ES-G: data curation. LE-H, IL-C, RH, LS-P, MD-L, AR, JR, and ES-G: writing—original draft preparation, LE-H, IL-C, RH, AR, JS, JR, and ES-G: writing—review and editing. RH, JR, and ES-G: supervision. RH, MD-L, AR, JS, FM, PG, JR, and ES-G: project administration. RH, FR-T, AR, JS, FM, PG, and JR: funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Eye-tracking paradigms for the assessment of mild cognitive impairment: a systematic review

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Mild cognitive impairment (MCI), representing the 'transitional zone' between normal cognition and dementia, has become a novel topic in clinical research. Although early detection is crucial, it remains logistically challenging at the same time. While traditional pen-and-paper tests require in-depth training to ensure standardized administration and accurate interpretation of findings, significant technological advancements are leading to the development of procedures for the early detection of Alzheimer's disease (AD) and facilitating the diagnostic process. Some of the diagnostic protocols, however, show significant limitations that hamper their widespread adoption. Concerns about the social and economic implications of the increasing incidence of AD underline the need for reliable, non-invasive, cost-effective, and timely cognitive scoring methodologies. For instance, modern clinical studies report significant oculomotor impairments among patients with MCI, who perform poorly in visual paired-comparison tasks by ascribing less attentional resources to novel stimuli. To accelerate the Global Action Plan on the Public Health Response to Dementia 2017–2025, this work provides an overview of research on saccadic and exploratory eye-movement deficits among older adults with MCI. The review protocol was drafted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Electronic databases were systematically searched to identify peer-reviewed articles published between 2017 and 2022 that examined visual processing in older adults with MCI and reported gaze parameters as potential biomarkers. Moreover, following the contemporary trend for remote healthcare technologies, we reviewed studies that implemented non-commercial eye-tracking instrumentation in order to detect information processing impairments among the MCI population. Based on the gathered literature, eye-tracking-based paradigms may ameliorate the screening limitations of traditional cognitive assessments and contribute to early AD detection. However, in order to translate the findings pertaining to abnormal gaze behavior into clinical applications, it is imperative to conduct longitudinal investigations in both laboratory-based and ecologically valid settings.

KEYWORDS

Alzheimer's disease, biomarker, dementia, eye-tracking, cognitive assessment, information processing, mild cognitive impairment, screening

> "Dementia research needs to be conducted within an enabling environment where collaborations are fostered, and equitable and sustained investment is realized (WHO, 2022)."

1. Introduction

The pathology of Alzheimer's disease (AD) may begin up to 20 years prior to the onset of severely debilitating symptoms (Jack et al., 2011). While potentially disease-modifying cognitive intervention therapies are being intensively developed, there is a need for sensitive and readily available screening tools that can detect AD in its initial stages (Otake-Matsuura et al., 2021). Mild cognitive impairment (MCI) is a term used to describe the transitional phase between the average cognitive decline that comes with normal aging and the onset of major neurocognitive disorder (commonly referred to as '*dementia*'; Petersen et al., 1999; Bruscoli and Lovestone, 2004; Roberts and Knopman, 2013; Kasper et al., 2020; Sabbagh et al., 2020a). Simply put, MCI can be portrayed as an early window for detecting cognitive impairment prior to the progression of neurodegenerative disease (see Figure 1; Roberts and Knopman, 2013; Ataollahi Eshkoor et al., 2015; Dunne et al., 2021). Neuropsychological symptoms may be absent during the latent phase, despite the presence of neuropathologic changes (including neurotic plaques and neurofibrillary tangles) that are primarily related to the overproduction and aggregation of amyloid beta (Aβ) peptide within the brain and to the hyperphosphorylation of Tau protein in affected neurons (Forlenza et al., 2010). As the pathology progresses, cognitive deterioration, such as worsening memory problems, poor judgment, confusion, difficulty in speaking, understanding, and expressing thoughts or reading and writing, begins to surface (*prodromal stage*). If not identified and addressed, a fully manifested clinical disease with irreversible consequences to one's daily living abilities may develop (Alzheimer's Association, 2019). Research has shown that after approximately 6 years, 80% of individuals with MCI progress to dementia (Petersen, 2003; Busse et al., 2006).

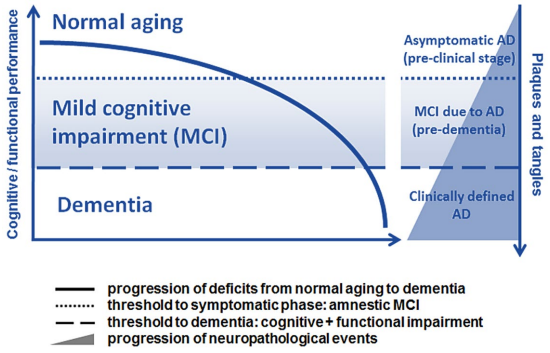

FIGURE 1
Schematic progression from normal aging to dementia, adapted with modifications in color from Forlenza et al., 2010 (available *via* license: CC BY 2.0). Relationship between the progression of cognitive and functional symptoms and the neuropathological events in the transition from the pre-clinical (silent) phase to mild cognitive impairment (MCI) due to AD and clinically manifest AD.

Furthermore, MCI is characterized by different subtypes, including amnestic MCI (aMCI), single-domain non-amnestic MCI (naMCI), and multiple-domain MCI. It has been postulated that the amnestic type presents itself predominantly with memory impairment (Kawagoe et al., 2017). Notably, although memory has been reported to be negatively affected in aMCI (Kahana Levy et al., 2018), impairments in other cognitive domains, such as executive function and visuospatial ability, may remain dormant if they do not affect the individual's activities of daily living (Gold and Budson, 2008; Johnson et al., 2009; Niu et al., 2013); hence, older adults may not complain about them (Kawagoe et al., 2017). The non-amnestic form of MCI, on the other hand, is reportedly accompanied by deficits in cognition and motor performance (with preserved memory; Petersen et al., 1999; Kluger et al., 2008; Readman et al., 2021). Since memory loss and cognitive decline occur in multiple-domain MCI (Kramer et al., 2006; Ataollahi Eshkoor et al., 2015), amnestic and multiple-domain MCI subtypes have been proposed to pose an equal risk for Alzheimer's disease (AD) progression (Petersen et al., 1999; Gauthier et al., 2006; Fischer et al., 2007; Ward et al., 2013; Ataollahi Eshkoor et al., 2015; Dunne et al., 2021). Notwithstanding, it has been suggested that the classification of aMCI as specific to AD and naMCI to other dementias (particularly vascular dementia) is *"conceptually too simplistic"* (Busse et al., 2006; Albert et al., 2007; Fischer et al., 2007; Rosenberg and Lyketsos, 2008). However, independent research groups exploring the structural differences between various MCI forms have provided scientific evidence to support the notion that separating these subtypes is not only a theoretical concept. For example, structural imaging and neuropsychological testing has supported the distinction between amnesic and non-amnesic forms of MCI. In the context of non-brain measures, such as eye-tracking, individuals with aMCI were found to be less accurate than controls and individuals with naMCI while performing a recognition task (McCade et al., 2018). Moreover, significant differences between aMCI and naMCI are highlighted by divergence in the percentage of uncorrected errors in the anti-saccade task (Wilcockson et al., 2019; Koçoğlu et al., 2021).

A variety of visual problems have been reported in patients with AD, including loss of visual acuity, abnormalities in contrast sensitivity, defects in fixation and saccadic eye movements, and disturbances of complex visual functions such as reading, naming, and identifying objects (Armstrong, 2009). Therefore, since visual cognitive dysfunctions transpire as an early indication of the transition from MCI to AD (Nakashima et al., 2010; Polden et al., 2020; Wolf and Ueda, 2021; Hannonen et al., 2022), visual testing holds promise for facilitating clinical diagnosis in future scenarios (Crutcher et al., 2009; Haque et al., 2019; Oyama et al., 2019; Readman et al., 2021; Tadokoro et al., 2021). Furthermore, and crucially, a deeper understanding of MCI subtypes may aid in predicting progression to AD and facilitate the development of targeted prevention strategies (Csukly et al., 2016; Kahana Levy et al., 2018; Opwonya et al., 2022b).

The problem of controlling AD-related healthcare costs while advancing health equity and quality has become an increasingly urgent issue to address (Pereira et al., 2020; Cilia et al., 2022; Kharroubi and Elbarazi, 2023). To visualize the pressing situation, in 2012, a new case of dementia was diagnosed every 7 s (Rashid et al., 2012), but more recent data indicate that every 3 s, someone in the World develops dementia (Alzheimer's Association, 2019). In addition, while significant efforts are being devoted to discover drugs to slow down

the progression of AD or alleviate its symptoms, few are authorized for clinical use (Ishikawa et al., 2022). Simultaneously, despite the vast research on AD, no single assessment measure is capable of predicting the onset of AD in a non-invasive, timely, and cost-effective manner (Bruscoli and Lovestone, 2004; Petersen, 2004; Panza et al., 2005; Zola et al., 2013; Ishikawa et al., 2022). Accordingly, clinicians are left with an arduous dementia diagnostic process based on a combination of laboratory tests, neuroimaging studies, and neuropsychological evaluations, which can take several months to complete (Petersen, 2003, 2004; Roberts and Knopman, 2013; Langa and Burke, 2019; Chen et al., 2021).

1.1. Eye-tracking as a potential solution to the challenges associated with assessment in MCI

According to the World Health Organization's first blueprint for dementia research: *"(…) addressing dementia comprehensively requires research and innovation to be an integral part of the response"* (WHO, 2022). Undoubtedly, there is a need for far-reaching and cost-effective innovations that reliably support the process of MCI diagnosis and facilitate the early application of cognitive interventions (Sabbagh et al., 2020b). With advances in eye-tracking technology and results from scientifically backed paradigms, health professionals may receive practical and effective screening tools for AD-related MCI in the future (Oyama et al., 2019; Wolf and Ueda, 2021). Eye-tracking technology provides a promising foundation for future cognitive assessment protocols (Hanazuka et al., 2021; Ehrlich et al., 2022) and carefully selected gaze parameters could accurately reflect changes in cerebral physiology (Leigh and Zee, 2015), reducing the risk of incorrect diagnoses (Samadani et al., 2015; Samadani, 2016).

In psychiatry research, gaze parameters have been shown to be promising biomarkers of diseases such as depression, bipolar disorder, and schizophrenia (Wolf et al., 2021a). Recently, eye-tracking has gained scientific attention as a potential technology to facilitate the diagnosis and management of AD-related MCI (Seligman and Giovannetti, 2015; Oyama et al., 2019; Ołownia et al., 2021; Wolf and Ueda, 2021). Notably, by mirroring thought processes, gaze can expose early cognitive impairments (Polden et al., 2020; Wolf and Ueda, 2021). A recent meta-analysis performed by Liu and colleagues showed that eye-tracking technology can detect a decline in patients' cognition (Liu et al., 2021). Concurrently, the passive monitoring of daily activity *via* smartphones, tablets, or smart-home devices provides portable means of tracking behavioral changes over time (Cichocki et al., 2008; Vashist et al., 2014; Miyake et al., 2020; Thabtah et al., 2020; Valliappan et al., 2020; Rutkowski et al., 2021; Wolf et al., 2021b). Following the digital healthcare trend, detecting cognitive deviations from the trajectory of normal aging through remote (non-face-to-face) channels has gained increasing interest (Rabinowitz and Lavner, 2014; Dagum, 2018; Huang et al., 2019; Kourtis et al., 2019). Eye-tracking technology represents a creative implementation of smart technologies that may support unsupervised at-home testing of cognitive performance (Dodge et al., 2015; Jekel et al., 2016; Rutkowski et al., 2020; Sabbagh et al., 2020a). Furthermore, advanced phone cameras combined with machine learning algorithms could support smartphone eye-tracking technology (Kong et al., 2021). Front-facing "selfie" cameras are particularly convenient for monitoring the performance of eye-movement tests on a more casual basis (Valliappan et al., 2020). Technological advances open up the possibility of particular gaze metrics being extracted from individuals while they perform experiments in front of a tablet or phone screen, contributing to a digital biomarker arsenal for disease detection (Kourtis et al., 2019; Kröger et al., 2020).

In recent years, the scientific literature has mounted in eye-tracking-based paradigms that aim to (i) gain insight into the visual abnormalities among cognitively unimpaired older adults, and (ii) improve the assessment of cognitive impairment due to AD. Hence, to accelerate the transition toward a globally accessible screening procedure for MCI (Sabbagh et al., 2020c, 2022; Liss et al., 2021), recent studies evaluating the potential utility of gaze metrics in the detection and characterization of MCI have been reviewed and discussed. Considering the multiple advantages of eye-tracking technology, it is hoped that presented compilation of impactful studies presented here, will spark interest among clinicians and foster future collaborations between neuroscience and machine learning, leading to an improved characterization of individuals along the Alzheimer's disease trajectory (Lagun et al., 2011; Zola et al., 2013; Wolf et al., 2021a; Ning et al., 2022; Przybyszewski et al., 2023).

2. Methods

This systematic review aimed to identify studies of MCI-related gaze behavior impairments published in the past 6 years (2017–2022). The protocol was drafted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). Electronic databases (Edith Cowan University Library, PubMed, Semantic Scholar, and Springer) were systematically searched to identify peer-reviewed literature that examined visual processing among older adults, as well as studies comparing cognitively unimpaired individuals to elderly individuals with MCI. Studies were found using a combination of the following terms: "mild cognitive impairment" or "MCI" AND "diagnosis" or "screening" AND "biomarker." Notably, the search term "eye-tracking" or "eye movements" were added to narrow the result to journal articles that reported gaze parameters as potential biomarkers for MCI. The search results (.csv file) obtained from each database were consolidated and saved as a single Microsoft Excel spreadsheet (.xls file). The spreadsheet was meticulously scrutinized for duplications through a manual inspection, which was carried out separately by AW and KT. Any disagreement was resolved by discussion and consensus. Certainly, following the preferred reporting items for PRISMA systematic review guidelines (Page et al., 2021), specific inclusion criteria were applied. To be included in this review, studies had to be relevant, original, peer-reviewed, and written in English. Furthermore, the studies had to include an MCI group (without comorbidities or other neurological disorders), which had to be evaluated by standardized diagnostic criteria and diagnosed with validated cognitive tests. Conference papers, letters, books, single case studies with a small sample (i.e., studies with less than 10 participants in the MCI and/or control group), and non-primary literature such as systematic reviews, meta-analyses, and editorials were excluded.

The PRISMA flow diagram, depicted in Figure 2, was generated using a web-based and free-to-use Shiny app (Haddaway et al., 2022), which allows users to create customized PRISMA flow

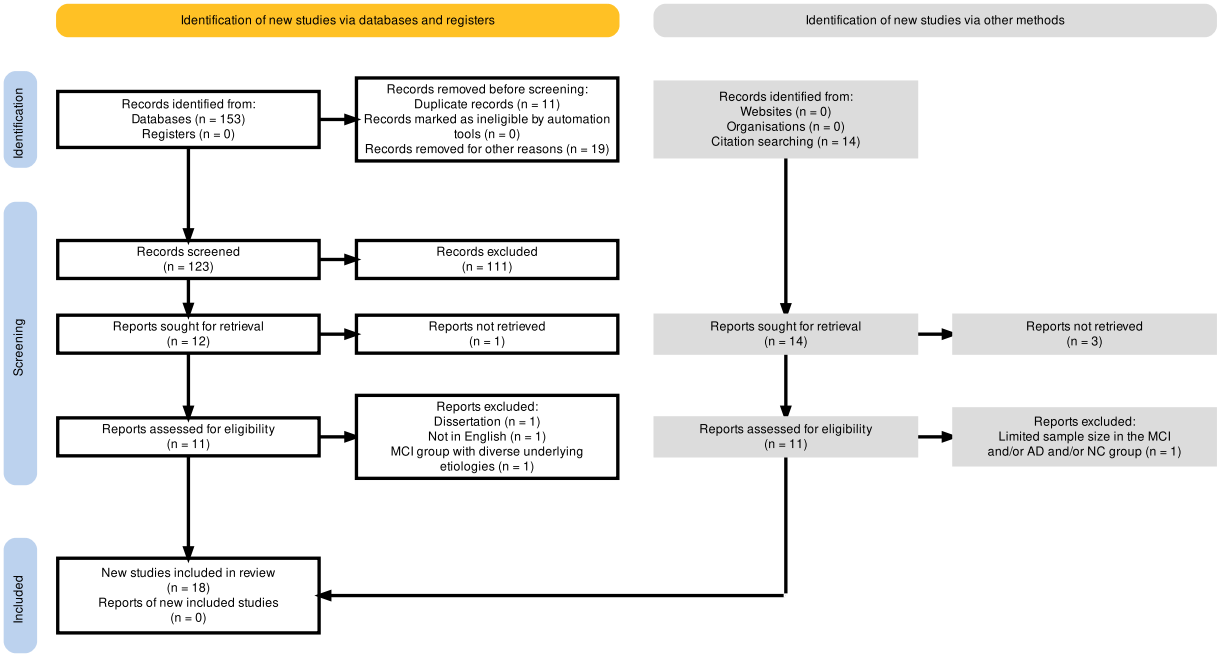

FIGURE 2
The full output plot from the PRISMA flow diagram, generated *via* the https://estech.shinyapps.io/prisma_flowdiagram/ (Haddaway et al., 2022).

diagrams for their systematic reviews. Out of the one-hundred fifty-three initially identified records ($n = 153$), a total of eleven duplicates were detected and consequently eliminated prior to the screening process. Furthermore, among the identified records, eighteen ($n = 18$) entries were excluded for varying reasons, including the classification of eighteen positions as conference proceedings and/or abstract book titles, while one entry ($n = 1$) lacked an available abstract. Next, the screening process involved reviewing the titles and abstracts of one-hundred twenty-three ($n = 123$) records. Out of these, fifty-five studies were deemed irrelevant to mild cognitive impairment (MCI) or focused on different clinical conditions, such as Autism Spectrum disorder, Parkinson's, schizophrenia, neurodevelopmental disorder or eating disorder. Additionally, four in-scope systematic reviews, two book chapters, and one study identified as a conference abstract, were rejected. Furthermore, the exclusion of forty-eight studies that examined various approaches for dementia screening was justified since these reports did not incorporate the use of eye-tracking technology. Also, one study focusing on the efficacy of a drug in enhancing visuospatial abilities among MCI patients through eye-tracking measurements was excluded. As a result, a total of one hundred and eleven records were excluded from the analysis due to their failure to meet the predetermined inclusion criteria. Next, a comprehensive search was undertaken to obtain twelve specific reports in the form of full-text papers. Out of the desired reports, eleven were successfully retrieved and checked for eligibility. Among the eleven reports, three were excluded (refer to the PRISMA flow diagram in Figure 2 for detailed reasons), resulting in the inclusion of eight reports (Oyama et al., 2019; Wilcockson et al., 2019; Nie et al., 2020; Gills et al., 2021; Haque et al., 2021; Chehrehnegar et al., 2022; Hannonen et al., 2022; Opwonya et al., 2022b). Notably, to supplement the identification of relevant studies, the reference lists of eight in-scope and full-text articles were independently screened by AW and KT for relevant publications. This practice, which is recommended in systematic review manuals (Horsley et al., 2011), served as an effective approach. In result, fourteen relevant studies for the systematic review have been identified. Eleven positions have been successfully retrieved as full-text documents for assessment of eligibility. After a detailed examination of the gathered works, one study was excluded due to the limited sample size in the MCI group ($n < 10$). Overall, the search of the reference lists has resulted in the addition of ten new studies (Galetta et al., 2017; Kawagoe et al., 2017; Bott et al., 2018; Noiret et al., 2018; Chehrehnegar et al., 2019; Gills et al., 2019; Haque et al., 2019; Pereira et al., 2020; Koçoğlu et al., 2021; Tadokoro et al., 2021).

In essence, this work presents a comprehensive review of the included studies, providing a thorough examination of the evidence on whether gaze metrics from eye-movement paradigms can distinguish between older adults with MCI, including those with the highest conversion rate to AD (aMCI subtype), and their age-matched counterparts. To combine the rising trend of eye-tracking technology with the challenges of AD diagnosis, the significant constraints of the currently used "ruling out" protocol have been elucidated. The research synthesis follows with an introduction of the human retina, capable of mirroring brain structure and revealing cognitive disturbances through human eye movements. Notably, the authors outline the fundamental point of gaze behavior as a reflection of one's attention and thought processes. A straightforward follow-up statement is presented on why eye-tracking should be considered an attractive technology for facilitating a non-invasive diagnosis of MCI by providing meaningful and objective outcome measures. Notably, this work highlights eye movement tests that provide information about saccadic and exploratory impairments among the elderly population with MCI. Furthermore, specific eye-movement

parameters, which show potential in distinguishing between patients with MCI and cognitively unimpaired elderly, have been identified.

3. "Ruling out" approach: the challenge of an early and accurate diagnosis

MCI is heterogeneous in its clinical spectrum (Kramer et al., 2006); therefore, this intermediate state is challenging to identify in clinical practice. Since some degree of cognitive slowing is typical in the context of healthy aging, identifying clinically significant cognitive impairments remains clinician's primary challenge (Hugo and Ganguli, 2014). An early and accurate diagnosis may give a patient the chance for improved quality of life and preserved independence in activities of daily living (Seligman and Giovannetti, 2015; Davis et al., 2018; Kasper et al., 2020; Budson and Solomon, 2021). However, there is a reported lack of technical support, infrastructure, training, and experience among primary care physicians to efficiently detect preclinical phases and manage AD along its clinical continuum (Olazaran et al., 2011; Kasper et al., 2020; Sabbagh et al., 2020b,c). For instance, a survey conducted in the United States revealed that only half of adults aged above 65 years undergo cognitive evaluations. This significant finding has been attributed to factors such as time constraints, the subtlety of patients' cognitive impairment, and resistance from elderly individuals towards being tested (Alzheimer's Association, 2019). Since the role of primary care physicians, being the first medical professionals that patients reach out to, is vital in the identification and management of MCI (Olazaran et al., 2011; Sabbagh et al., 2020c), rapid routine recordings of eye movements in the primary care setting could provide an objective and time-efficient method to facilitate diagnosis.

The necessity for a sharp demarcation between normal cognition and MCI as well as between MCI and AD remains crucial (Albert et al., 2011; Sabbagh et al., 2020b). To make these distinctions, several findings and clinical judgments must be integrated and interpreted. Extensive neuropsychological cognitive screening tests such as the Montreal Cognitive Assessment (MoCA), the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), Cognistat (formerly known as the Neurobehavioral Cognitive Status Examination), and the short Mini-Mental State Examination (MMSE) can be incorporated into the preliminary assessment (refer to Breton et al., 2019 for an insightful meta-analysis of diagnostic accuracy studies). These pen-and-paper tests contain elements related to executive functions, memory, orientation, learning, judgment, and perceptual motor function, and are commonly used in the clinical setting (Folstein et al., 1975; Bobholz and Brandt, 1993; Hanazuka et al., 2021). Furthermore, to evaluate verbal memory, two specific tests (the Rey Auditory Verbal Learning Test and Wechsler Memory Scale—IV—Logical Memory subset) may have utility during neuropsychological assessment (Rabin et al., 2005). Last but not least, the currently employed diagnostic protocols may require older adults to undergo a depression screening, since mood disorders can also cause dementia-like symptoms, including memory problems and a loss of interest in life (Dierckx et al., 2007, Defrancesco et al., 2009; for a review of putative neuropsychological mechanisms leading from depression to the development of AD, see Tetsuka, 2021).

In theory, a subject's score (performance) on a test is compared to a large general population normative sample derived from a population comparable to the person being examined. Based on this comparison, one's most recent cognitive functioning can be evaluated (Grossman et al., 1996; Hansen et al., 2018; Dunne et al., 2021). Nonetheless, despite being considered cost-effective and straightforward to administer, cognitive function tests are not sufficiently sensitive to identify the progression of MCI (for example, ADAS-Cog may be less responsive to change when used in people with MCI; Skinner et al., 2012; Thabtah et al., 2022b). Notably, as writing and drawing are required in some tests, motor impairments such as post-stroke paralysis (frequently observed in patients with dementia) can lead to lower scores and inaccurate diagnoses (Palsetia et al., 2018; Heyrani et al., 2022). Other factors that could potentially influence screening results have been discussed in the literature, such as the experience and training of the examining clinician as well as a potential dependency on the used screening test (Hoops et al., 2009). In addition, a further potentially confounding factor is the lack of a clear collateral history regarding prior peak occupational or educational attainments. Thus, relying on the neuropsychological score makes it challenging to detect MCI among high-functioning older adults (Tuokko et al., 2003; Dunne et al., 2021), where, simply speaking, impaired cognitive functioning in these individuals may not come to medical attention (Treves et al., 2005; Chary et al., 2013; Jessen et al., 2014; Dunne et al., 2021).

Patient evaluations remain challenging (Roberts and Knopman, 2013; Jekel et al., 2016; Oyama et al., 2019; Kasper et al., 2020) especially when taking into consideration that patients may (i) face problems with language comprehension or articulation while talking with healthcare professionals, (ii) experience high levels of psychological stress and fatigue while answering a series of questions during the assessment, or (iii) not have an accurate understanding of their own cognitive capabilities (Grossman et al., 1996; Gates et al., 2002; Hanazuka et al., 2021). Taken together, although neuropsychological screenings are still considered helpful in assessing respondents' cognitive functions, they are far from being objective.

Although this review does not aim to list all the advantages and shortcomings of the currently applied 'traditional pen-and paper' tests, note that inherent drawbacks of such tools have led to a concerted research effort to identify alternate diagnostic methods (Sonnen et al., 2008; Sabbagh et al., 2020b; Chen et al., 2021; Ning et al., 2022). For example, to confirm AD physicians may use a variety of approaches and tools, including blood and cerebrospinal fluid (CSF) biomarkers (Galasko, 2015; Hameed et al., 2020). Moreover, besides undergoing physically invasive assessments such as lumbar punctures, other intensive neuroimaging techniques including magnetic resonance imaging (MRI) are widely used to investigate brain changes (for example, cortical thickness) due to neurodegeneration (Raamana et al., 2014). Finally, diffusion tension imaging (DTI), positron emission tomography (PET), and proton magnetic resonance spectroscopy (^{1}H-MRS) are being investigated to define the biological AD construct (Jack et al., 2018). However, although PET is reportedly successful in characterizing cerebral Aβ plaques (Jansen et al., 2015), this particular technique is considered invasive, costly, and inaccessible; hence, it is unsuitable for population-based AD screening (Koronyo et al., 2017; Yang et al., 2019; Wang and Mao, 2021).

Overall, despite significant research efforts to acquire an early and more accurate AD diagnosis, the call for action to address the social and economic consequences of major neurocognitive disorders persists. AD remains incurable (Soleimani Zakeri et al., 2020), which increases the urgency for action. Moreover, although the Global Action Plan on the Public Health Response to Dementia 2017–2025 has been put in place (WHO, 2017), the majority of countries are yet to achieve the targets set in the plan (Werner, 2012; Lin and Neumann, 2013; Casagrande et al., 2022; see Global Status Report on the Public Health Response to Dementia, WHO, 2021). While policymakers around the world emphasize the importance of developing a successful diagnostic protocol, the authors would like to emphasize eye-tracking technology as a non-invasive, cost-effective, sensitive, and convenient response to the global call for action in addressing the extraordinary burden of AD (Wright and O'Connor, 2018; Tahami Monfared et al., 2022). Considering the fact that the retina is an optically accessible developmental outgrowth of the central nervous system (Eckstein et al., 2017), it has been postulated that changes in one's eye could reflect pathological processes occurring within the brain (Armstrong, 2009; Kumar et al., 2015; Nguyen et al., 2021; Wang and Mao, 2021; Wolf et al., 2021a). As a result, researchers seeking to distinguish between healthy and pathological aging have, in recent years, turned to the human eye (Criscuolo et al., 2018; Ramzaoui et al., 2018; Mirzaei et al., 2020; Hanazuka et al., 2021; Nguyen et al., 2021; Wolf and Ueda, 2021; Romaus-Sanjurjo et al., 2022).

4. The eye: anatomical extension of the brain

Although ancient scholars crowned the eyes with the title of the *windows to one's mind*, modern ocular-neural imaging techniques have scientifically confirmed that several well-defined neurodegenerative conditions as well as psychiatric disorders manifest themselves in the detailed structure of the human eye (Santos et al., 2018; Majeed et al., 2021). Furthermore, the fact that both the eye and the brain "*modify similarly with disease*" (Nguyen et al., 2021) creates a rich research opportunity. Hence, it stands to reason that investigating the human eye mirroring pathological processes that occur in the brain will become a rapidly expanding field of research. Recent ocular imaging studies, including methods such as optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA), have indicated that AD is associated with a decreased volume of the optic nerve, degeneration of retinal ganglion cells, loss in retinal nerve fiber layer (RNFL), and deposition of abnormally structured proteins (de Oliveira et al., 2020). Following the conclusion that the eye's microarchitecture is profoundly affected by AD and has the potential to harbor the earliest detectable disease-specific signs, the development of optical biomarkers for AD and other neurodegenerative disorders has gained significant interest in the context of clinical applications (for a comprehensive review on ocular biomarkers for AD diagnostics, readers are encouraged to read the work of Majeed et al., 2021).

Independent research groups have found a significant reduction in RNFL layer thickness in individuals with AD compared to cognitively unimpaired healthy controls (Garcia-Martin et al., 2014; Santos et al., 2018; Alber et al., 2020; Majeed et al., 2021). In parallel, this structural change has also been associated with Lewy body dementia, Parkinson's disease, multiple sclerosis, and conditions such as stroke and late-life depression. Therefore, it has been postulated that RNFL thinning alone is insufficient for a diagnosis of AD (Snyder et al., 2021) and – for the current state of knowledge – may only be a useful biomarker for a broader diagnosis of neurological pathologies (Ngolab et al., 2019). Additionally, it has been reported that ocular diseases such as glaucoma and non-glaucomatous optic neuropathology can also lead to pathological changes in the retina, making it challenging to develop clinically validated ocular biomarkers for AD. Some preliminary evidence suggests that Aβ deposits in the retina appear to be specific to patients with AD (Bilgel et al., 2016; Koronyo et al., 2017; Hadoux et al., 2019; Dumitrascu et al., 2020). However, the results of investigations that directly targeted Aβ accumulations were limited, leaving the scientific community with practically no clinically validated ocular biomarkers for AD (Wang and Mao, 2021).

The lack of sensitive and specific OCT/OCTA parameters as well as standardized imaging protocols (affecting the variability of structural markers) have been explicitly underlined in the scientific literature. Mentioned limitations hamper the use of ocular structures as influential and cost-effective biomarkers (Lee et al., 2020; Majeed et al., 2021). Moreover, the advice of using optical tomography in accordance with another technique such as MRI or biochemical analyses (Hashmi and Muzzammel, 2020) not only prolongs the diagnostic process, but also increases the number of involved medical doctors such as geriatricians, ophthalmologists, neurologists, and radiologists (Liss et al., 2021). This, in turn, generates high personnel- and equipment-related costs.

Eye-tracking devices, on the other hand, are regarded as relatively low-cost assessment tools, requiring only the presence of a technician who can be trained to explain and carry out the test. Moreover, the location of data collection can be extraordinarily flexible and take place in any comfortable environment, not restricted to the surroundings of a hospital, which is usually the case with neuroimaging apparatus. In addition, since most eye-tracking-based paradigms do not require verbal responses, scientists find gaze parameters extremely useful in assessing cognitive capacities among patients with language comprehension problems (Readman et al., 2021).

5. Objective

The utility of eye-tracking technology is receiving great interest in distinguishing people with neurocognitive disorders from their healthy counterparts (Anderson and MacAskill, 2013; Eckstein et al., 2017; Liu et al., 2021; Wolf and Ueda, 2021; Opwonya et al., 2022b). The concept is simple, and core brain damage associated with AD does not have to be directly evaluated through extensive physical assessments involving visualizations of the human eye or brain. Significant physiological changes, such as the accumulation of the pathological hallmarks of AD (intracellular neurofibrillary tangles, senile plaques), and the subsequent disruptions in synaptic transmission result in profound cognitive impairments (Baddeley, 2001; Forlenza et al., 2010; Kumar et al., 2015; Readman et al., 2021). Current evidence suggests that attention is the initial non-memory domain to be affected in AD, with visual information processing impairments occurring in the MCI phase (Ramzaoui et al., 2018;

Polden and Crawford, 2021; Readman et al., 2021). As attention and oculomotor control are thought to recruit overlapping brain regions, saccades (for example) are likely to be disturbed by the reductions in inhibitory control and executive function that occur in neurodegenerative disorders (Wollenberg et al., 2018).

In the light of a noticeable shift in focus to context-processing impairments and cognitive remediation for addressing cognitive impairments, the study of saccadic abnormalities and impairments in visual information processing has become a high-priority research area (Wolf and Ueda, 2021; Kim et al., 2022). Trends in eye-tracking assessment align well with evidence that human gaze gives powerful insights regarding one's information processing patterns (Eckstein et al., 2017; Marandi and Gazerani, 2019; Kröger et al., 2020; Nie et al., 2020; Chehrehnegar et al., 2022; Opwonya et al., 2022b). This opens new opportunities to provide proxy instrumentation to measure cognition (and its deficits) and disclose hidden aspects of aging (Molitor et al., 2015; Marandi and Gazerani, 2019). Therefore, apart from quantifying the parameters of an effectively stabilized (*frozen in time*) retina, scientists have begun to mirror the observer's brain integrity of sensory function and predict disease processes (Samadani et al., 2015; Lauermann et al., 2017; Marandi and Gazerani, 2019; Snyder et al., 2021; Wolf et al., 2021a; Opwonya et al., 2022b).

Undoubtedly, the scientific community requires more profound information regarding gaze metrics obtained from experimental paradigms that include older adults. While the next decade of clinical research is likely to lead to gaze parameters being included in clinical cognitive testing (Crutcher et al., 2009; Bott et al., 2017; Gills et al., 2019, 2021; Oyama et al., 2019; Tadokoro et al., 2021), the presented work introduces paradigms that incorporate eye-tracking technology into the challenging process of MCI assessment. These summarized insights from scientifically recognized and equally accessible protocols should support the future development of innovative response strategies and attenuate the dramatic financial burden of AD (Tarawneh and Holtzman, 2012; Klyucherev et al., 2022). Finally, the authors hope that the gathered evidence will spark interest among clinicians and foster cutting-edge, interdisciplinary collaborations to further research in this area.

6. Gaze: an indirect link to neural and cognitive functions

In recent years, to trace age-related irregularities associated with cognitive decline, researchers started to involve a variety of pupil-, fixation-, and saccade-related metrics serving as objective biomarkers (Marandi and Gazerani, 2019). Although human gaze is not a direct measure of their brain function, it does provide details on the association between the brain and behavior. Furthermore, in combination with attention-demanding tasks that demand one to act upon and manipulate given information, eye-tracking offers an interesting solution for future monitoring of the AD continuum (Ramzaoui et al., 2018; Opwonya et al., 2022a,b for scientific articles on bridging eye-tracking technology with cognitively informative paradigms and medical science, refer to works by Liu et al., 2021; Wolf and Ueda, 2021).

Yet, first and foremost, for an eye-tracking test to be an efficacious diagnostic tool, it must be able to differentiate those with preclinical cognitive decline (MCI) from cognitively unimpaired older adults as well as those with AD. It has been reported that changes in functioning of the frontal lobe and cingulate cortex can already lead to subtle impairments in inhibitory control. Since saccadic eye movements are primarily controlled by the frontal cortex, saccadic eye movements (SEM) have been suggested to offer important clues to facilitate the detection of the early signs of MCI. With this in mind, the authors hope that the referenced observations in the following section will be helpful to researchers and clinical practitioners who consider implementing saccade paradigms in order to expand the monitoring procedure of older adults at risk of MCI.

6.1. SEM impairments in MCI

Previous literature outlined robust findings demonstrating saccadic abnormalities among patients with AD (Noiret et al., 2018). Most of these findings are relative to well-known prosaccade (PS) and antisaccade (AS) tasks. These tasks are particularly popular due to their potential measures of cognitive capacities as well as the simplicity of the instructions. In short, participants are requested to first keep their gaze on a central fixation, then, as quickly as possible, look at a target appearing at the periphery of the fixation marker (immediate PS, see Figure 3 [A–D]), or to direct their gaze to another direction, which is opposite to the target's location (immediate AS, see Figure 3 [A–F]). A correct antisaccade performance consists of two main saccadic processes, namely, to restrain from making a saccade toward the target and voluntarily move the gaze in the opposite direction (Chehrehnegar et al., 2019; Si et al., 2022; Opwonya et al., 2022b). Hence, in the context of neurocognitive disorders such as AD, AS performance may reflect impairments in executive as well as attention functions, whereas PS performance may reflect the altered ability to rapidly trigger endogenous saccades toward a target, especially when viewer's attention remains on the central fixation sign (overlap conditions, see in Figure 3; Noiret et al., 2018).

To investigate the diagnostic value of saccadic eye movements, Chehrehnegar and colleagues carried out PS and AS tasks and used two variants of saccade tasks, *gap* and *overlap*. In the *gap condition,* a black fixation cross was presented in the middle of the screen and randomly stayed on for 1,000 or 1,500 milliseconds. In the last 500 milliseconds, the fixation cross changed its color to green (PS task) or red (AS task). The fixation cross disappeared for a period of 200 milliseconds (hence, *gap condition*), and re-appeared along with the peripheral stimulus. In the *overlap condition* however, the fixation cross remained displayed for 200 milliseconds combined in time with the onset of the target stimulus. In both tasks, the target was randomly displayed at the left or right side of the fixation cross. Notably, this procedure required the participants to remember instructions in order to (in case of an AS, for example) inhibit the visually guided exogenous saccade toward the target, and to trigger a saccade in the opposite direction. Therefore, only when the instruction was correctly remembered, could the urge of making a reflexive response towards a target have been suppressed with a volitional saccade carried out in the opposite direction.

Concerning the available literature, a commonly used parameter in saccade-related paradigms is the *saccade latency*, which is the reaction time between the appearance of the target and the initiation of the orienting saccade. According to the results presented by Chehrehnegar et al. (2019), the reaction time was longer among

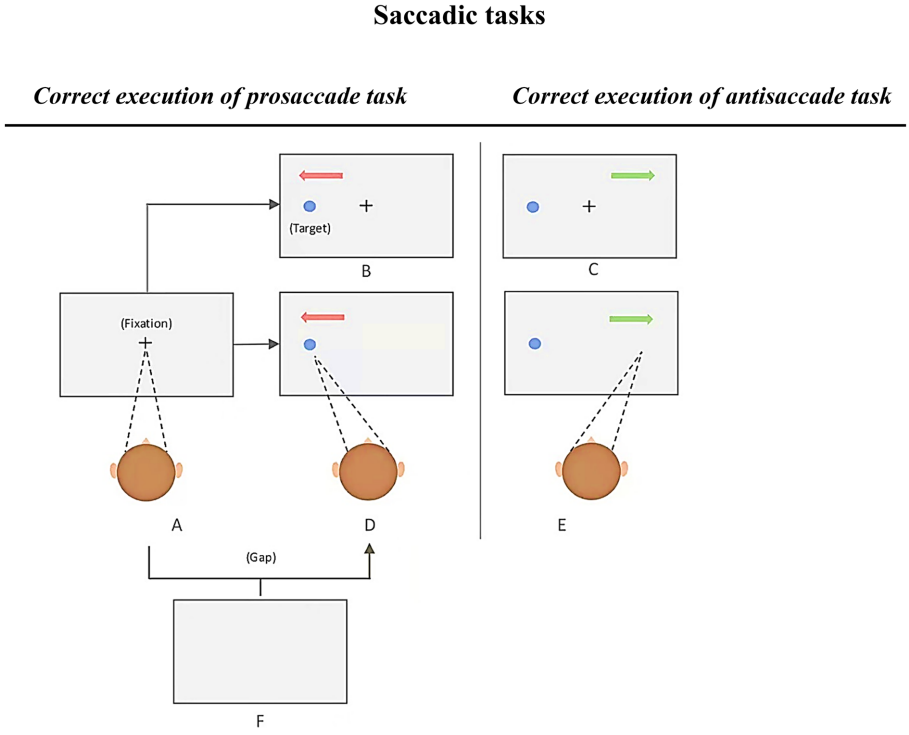

FIGURE 3
Various conditions of the prosaccade and antisaccade tasks, adapted from Si et al., 2022. Each trial begins with a presentation of a fixation cross at the center of the screen. Participants are required to fixate on it and to make a prosaccade or antisaccade (depending on the task's instruction). Immediate prosaccade: A-D; Immediate antisaccade: A-E; Gap prosaccade: A-F-D; Gap antisaccade: A-F-E; Overlap prosaccade: A-B; Overlap antisaccade: A-C.

participants with aMCI and AD when compared to healthy controls (HCs). The general increase in time of processing speed relates to increased motor and sensory processing times, which could be related to AD signatures in cortical regions. The observation of differences in saccadic reaction times between aMCI and HCs (Chehrehnegar et al., 2019) aligns with the suggestion that subjects with aMCI can be portrayed to be at an intermediate level of performance between HCs and patients with AD (Wilcockson et al., 2019; Pereira et al., 2020).

By examining another commonly used eye-movement parameter, the accuracy of a saccade (*saccade gain*), Chehrehnegar and colleagues identified this metric as the most sensitive measure to distinguish between individuals with aMCI and HCs (AS gap task, area under the curve [AUC] = 0.7; PS gap task, AUC = 0.63; AS overlap task, AUC = 0.73; the only paradigm that did not show any differences between aMCI and normal elderly was the overlap PS task). Moreover, since saccade gain was strongly correlated with neuropsychological measures, it has been speculated that this parameter could be of significant use to identify subtle executive deficits in the aMCI population. Thus, Chehrehnegar and colleagues highlighted that combining the antisaccade task with commonly used neuropsychological batteries may result in an improved sensitivity; for example, the use of the Addenbrookes Cognitive Examination in combination with the first gain parameter from the AS task resulted in an improved sensitivity index of 0.97.

Previous scientific contributions supported the notion that the AS task may be an additional prognostic tool that can differentiate the manifestations of preclinical cognitive decline. However, many of these studies referred to comparisons between patients with AD and healthy control groups. Therefore, further investigations that reveal saccadic impairments among elderlies with a higher risk for dementia due to AD (aMCI) would provide compelling support for the validity of the saccadic tasks as an early diagnostic marker.

With this objective in mind, in 2022 Chehrehnegar and colleagues performed another study that aimed to further investigate the possibility of distinguishing between HCs and participants with aMCI and AD. Several saccade parameters (including saccade amplitude and reaction time, error rates, omissions, and uncorrected saccades) were measured to clarify whether these biological markers are sensitive enough to clearly distinguish between healthy aging controls and cognitively impaired groups (MCI and AD). As in previous work, AS and PS tasks with *gap* and *overlap* conditions were implemented (Chehrehnegar et al., 2019). Notably, the researchers emphasized that after looking in the wrong direction, patients with aMCI had extreme difficulty in correcting their eye positions. Hence, when compared to HCs, the gaze behavior of the aMCI group was characterized by a greater number of errors and more saccade omissions (Chehrehnegar et al., 2022).

To elaborate more on the errors on the antisaccade task, they are most prevalent when the participants move their gaze toward the displayed target rather than away from it (also called the *error prosaccade*). The situation when participants make an error but quickly correct it, by looking away from the presented stimulus, is referred to as a self-corrected error. In a manner similar to patients with AD, older adults with MCI are prone to not correct committed errors due to alterations in the self-monitoring and correction

network, which recruits the prefrontal cortex and anterior cingulate region. This result aligns with error monitoring and impairment of inhibitory control demonstrated by Wilcockson et al. (2019). They observed that the percentage of uncorrected AS errors of patients with AD and the amnestic variant of MCI was not only similar but also higher than subjects with naMCI and HC. Furthermore, in a more recent study, another independent research group noted greater failure to self-correct made mistakes among adults with aMCI, generating a high proportion of erroneous saccades (Opwonya et al., 2022b). Thus, an elevated error rate and abnormally high number of uncorrected saccades can be regarded as future markers for the early detection of aMCI (Peltsch et al., 2014) and mild AD (Opwonya et al., 2022a,b). On another note, in contrast to a previous report (Chehrehnegar et al., 2019), the follow-up study by Chehrehnegar and colleagues showed that the time to initiate saccades did not differ between subjects with aMCI and the HC group (Chehrehnegar et al., 2022). Given that saccadic reaction time may not be disrupted during the early stages of cognitive decline, the potential use of this particular gaze parameter remains debatable.

Although the clinical significance of saccadic eye movement impairments in MCI remains to be fully elucidated, researchers continue to search for alternative paradigms for discriminating between subtypes and assessing cognitive functioning among adults. A recent study performed by Koçoğlu and colleagues outlined differences in saccadic eye movements between the subtypes of MCI and HCs. While performing recordings of horizontal and vertical antisaccades, it was reported that, in comparison to HCs, patients with aMCI have a higher percentage of "express" saccades (defined as visually driven short latency saccades with response times falling between 80 and 120 milliseconds). Moreover, following the horizontal and vertical AS paradigm, the researchers reported a strong association between saccadic reaction time and participants' cognitive status. The saccadic reaction time of corrected errors in the aMCI ($p = 0.001$) and naMCI ($p = 0.038$) groups were significantly longer than those in the HC group (Koçoğlu et al., 2021).

Next, following the context of alternative paradigms, it would be prudent to briefly mention the predictive saccades (PreS) task in which participants are instructed to direct their gaze in expectation of the emergence of a target in a particular spot with a fixed temporal frequency. Notably, in relation to current knowledge, this task has not been employed in research concerning the differentiation between MCI subtypes despite the notion that it could be used to reflect patients' decreased ability to efficiently keep a representation of the target's location in working memory (Noiret et al., 2018). In the context of patients with AD, it has been reported that they can predict a follow-up target, however, their anticipated saccades are more scattered around the target's location (for a study on the PreS task and attentional control in AD see Mosimann et al., 2005; Noiret et al., 2018).

To conclude this section, the results of the presented studies identify SEM as liable biomarkers to early detect individuals at high risk of AD (Chehrehnegar et al., 2019, 2022; Wilcockson et al., 2019; Koçoğlu et al., 2021; Opwonya et al., 2022b). However, the available scientific literature is inconclusive about whether SEM tasks are useful to spot significant differences in gaze behavior between the MCI subgroups. While examining saccade metrics could be beneficial for guiding interventions aimed at treating older adults who are at a greater risk of developing MCI, more extensive studies with larger sample sizes are needed to confirm the clinical significance of SEM impairments in MCI (Koçoğlu et al., 2021). Similarly, longitudinal investigations are essential to (i) understand age-related cognitive changes and (ii) draw more definitive conclusions about the early detection of the transition from normal/healthy aging to MCI. Concurrently, by citing an interesting statement from the work of Everling and Fisher, one would like to assess whether it is essential to exclusively focus on saccadic tests: "*Despite a high sensitivity of the antisaccade task, its specificity for a disease or the location of the involved brain structure may be low* (…) (Everling and Fischer, 1998)." Therefore, besides SEM tasks, are there any other paradigms that are more suitable for differentiating between cognitively unimpaired and MCI populations? With this question in mind, the reader is invited to the next section of this review, dedicated to cognitively informative paradigms that may be of use in the future design of cognitive assessment tests.

6.2. Cognitively informative paradigms indicate eye movement impairments in MCI

As elucidated in the previous section, performing antisaccade tasks requires subjects to execute a goal-directed saccade in the opposite direction while suppressing the reflexive gaze towards the suddenly appearing stimuli. The antisaccade task has been considered a sensitive protocol to investigate inhibitory control and draw a line between HC and clinical populations, including individuals with AD and those suffering from MCI (Chehrehnegar et al., 2022). At the same time, it is hampered by low specificity. Abnormal gaze parameters such as an increased error rate have also been reported in the context of other disorders (Si et al., 2022). In the context of schizophrenia research, for example, the antisaccade task generates the most frequently observed volitional saccade abnormality (Levy et al., 2010).

Another limitation to consider is that antisaccadic eye movements have been reported as unnatural (Godijn and Kramer, 2007) and "*artificial by nature*" (Readman et al., 2021). To investigate how clinical populations approach daily life tasks, new research questions should require examination of paradigms that provide context-related exploratory eye movements in addition to the quantification of fixations and saccades (Readman et al., 2021; Wolf and Ueda, 2021; Wolf et al., 2021a). Also, the application of ecologically valid studies resembling real-life situations is surprisingly inadequate; hence, extensive investigations in lab-based and ecologically valid settings need to be conducted and reported in equally accessible publications.

Although the effectiveness of using eye-tracking technology to recognize individuals with MCI appears promising, in the past 5 years few research groups have implemented cognitively informative tasks. The following section is dedicated to studies that follow cognitively informative paradigms in order to differentiate between adults with MCI, AD, and HC, where (i) eye-movements represent an index for memory (for example, using the Visual Paired-Comparison task or Visuospatial Memory Eye-Tracking task), or visual attention and processing speed (King Devick test), and (ii) participants are challenged with a real-life situation (face recognition).

6.2.1. Visual paired-comparison task

The human ability to identify, process, and ascribe greater attentional resources (attention bias) to novel stimuli is essential for exploring new opportunities and consequently adapting to changing environments (Eizenman et al., 2019). Therefore, the Visual Paired-Comparison (VPC) task offers the opportunity to provide complementary support to traditional composites for detecting early cognitive changes. In essence, the VPC task is an eye-tracking-based paradigm of particular interest due to its scientifically established method for detecting memory dysfunction in humans from infancy through adulthood (Pascalis et al., 1998; Manns et al., 2000; Crutcher et al., 2009; Zola et al., 2013). Furthermore, it has been shown that the VPC task reliably detects early signs of cognitive decline in older adults (Bott et al., 2017; Haque et al., 2019). In essence, a 30-min task quantifies how the participant splits attention between familiar and novel visual stimuli, with a familiarization phase preceding a testing phase.

In a study performed by Bott et al. (2018), subjects were presented with pairs of identical visual stimuli for 5 s (familiarization phase). Moreover, to assess immediate as well as delayed recognition memory, the test phase followed a delay of either 2 s or 2 min. During the testing phase, viewers were presented with additional pairs of visual stimuli, including one from the familiarization phase (familiar image) and one novel stimulus. Novelty preference (NP) defined the percentage of time the viewer spent looking at an unknown image compared with the image from the familiarization phase (thus, the ratio of time produces the NP score). A higher NP score represents a better declarative memory function, whereas a lower score indicates impaired function (Fantz, 1964; Fagan, 1970; Crutcher et al., 2009; Bott et al., 2018).

Individuals with MCI or AD have impaired declarative memory for previously viewed images and tend to spend an equal amount of time gazing at both novel and previously viewed (familiar) images. Conversely, individuals with normal cognitive function spend more time viewing novel images (photos not previously shown). Subsequently, one can assume that healthy older adults should not have notably lower scores on VPC tasks than younger individuals, as recognition memory remains stable with healthy cognitive aging (Danckert and Craik, 2013). On the other hand, individuals with MCI, AD, or even those who may have preclinical changes in cognition would be expected to score lower than unimpaired individuals (Bott et al., 2017, 2018; Gills et al., 2019).

Notably, performance on a 30-min VPC task demonstrated convergent validity between the eye-tracking test and cognitive composites that serve as preclinical AD indices, such as the Preclinical Alzheimer's Cognitive Composite and NIH Toolbox for the Assessment of Neurological Behavior and Function Cognition Battery (NIHTB-CB). Exploring the influence of the used eye-tracker on task performance has been also underlined as a necessity, since it may impact the future application strategy (Bott et al., 2018). Indeed, the VPC test has been used in combination with commercial eye-trackers, which are capable of split-second monitoring of one's gaze behavior, capturing an abundance of gaze metrics. However, it is essential to mention that high-quality equipment may be expensive and/or only available in research facilities, limiting the scalability of the clinical assessment. Therefore, Bott and colleagues underlined that an alternative and validated eye-tracking system needs to be proposed for feasible and widespread use.

A number of previous studies focused primarily on data obtained from commercial eye trackers. Notably, the investigation by Bott and colleagues presents modest-to-moderate correlations between VPC task performance using device-embedded cameras and scores on gold-standard cognitive composites. Device-embedded cameras offer a reliable and valid way to accurately assess VPC performance. Furthermore, since the strength of these relationships does not differ between types of camera devices, several researcher groups postulate that the ubiquity of cameras on most standard smart devices represents a scalable technique that is highly suitable for collecting population-level data (Bott et al., 2017, 2018; Gills et al., 2019). Correspondingly, with the growing number of smartphone and internet users (recent estimates indicate that there are over 5.44 billion smartphone users worldwide, equating to 68% of the world's total population), positive developments pave the way toward improved healthcare in developing countries (Vashist et al., 2014). Scientists performing longitudinal studies on the early detection of MCI may consider cost-effective, remote eye-tracking options that empower personalized healthcare (Valliappan et al., 2020). Yet, above all, the next-generation digital diagnostic assessments must be thoroughly evaluated to guarantee their ethical, responsible, and professional use (Ahmed et al., 2015; Kasper et al., 2020; Kröger et al., 2020). While the enormous potential of nascent technologies should be acknowledged, an omnipresent use of eye-trackers will raise privacy concerns not only because gaze data may be collected and shared in non-transparent ways, but also because such data can contain a wealth of sensitive information about the viewer (for potential inferences that can be drawn from eye-tracking data refer to Kröger et al., 2020).

6.2.2. The brief 5-min VPC test

Before proceeding to the detailed concept of the brief VPC test, it is worth mentioning that the VPC 30 falls into the category of passive paradigms, which means that participants complete the test without explicit instructions on where they are supposed to look. Accordingly, the test's integrity depends on the user not knowing what the test is measuring. Therefore, it has been speculated that utilizing a shorter paradigm, in which participants are given specific instructions beforehand, would improve the user experience and increase the scalability of the assessment (Gills et al., 2019). A shorter and more active version of the VPC test has thus been established.

In the brief 5-min VPC test, before the testing phase begins, participants are instructed to focus their gaze on the new image (novel stimulus). While this quick test has been previously validated to evaluate declarative memory function among healthy individuals, it remains unknown whether this test accurately discriminates between cognitively healthy and cognitively impaired older adults. Therefore, Gills and colleagues aimed to determine the ability of the eye-movement metrics obtained from the 5-min VPC test (*via* a factory-installed web camera) in distinguishing between cognitively normal and cognitively impaired adults (Gills et al., 2021). Their results demonstrated the brief VPC task to be a helpful screening tool for cognitive impairment that can be used to accurately assess memory function. Besides noteworthy correlations with the MoCA, the brief VPC task is characterized by significant correlations with individual NIHTB-CB tasks measuring inhibitory control and attention, processing speed, and visual episodic memory. Moreover, the researchers could successfully discriminate between cognitively impaired and cognitively normal individuals irrespective of age.

Finally, the brief version gives a premise of high test–retest reliability (Gills et al., 2021).

Another independent study, which aimed to assess differences in gaze behavior between healthy elderly individuals and patients with MCI, has been conducted by Nie et al. (2020). In line with previous investigations, the research group assessed the NP score in the VPC eye-tracking task and concluded that this parameter is a simple and non-invasive diagnostic biomarker of MCI. The NP score accurately distinguishes patients with MCI from cognitively normal subjects. Notably, when assessing the NP after either a 2-s or 2-min delay, AUC analysis showed that an NP score of 0.605 in the 2-min-delay condition effectively differentiated participants with MCI from HCs. Echoing previous findings (Crutcher et al., 2009), Nie and colleagues reported that novelty preference differs significantly between HCs and participants with MCI when the delay period is 2 min but not 2 s. Moreover, this difference remained significant at two-week follow-up. In conclusion, the method achieved a specificity of 72% and sensitivity of 53% (Nie et al., 2020). Furthermore, nine participants with poor novelty preference scores (whose novelty preference score fell below the 0.605 cut-off point at the initial testing) showed significant decline in cognition during 1-year follow-up (Nie et al., 2020).

Due to the lack of objective indicators and boundaries between MCI and cognitively healthy elderly individuals, distinguishing between these groups can be more challenging than diagnosing dementia (Seligman and Giovannetti, 2015; Nie et al., 2020). Nevertheless, with cognitive examinations increasing in popularity (Gills et al., 2021), VPC paradigms unfold valuable screening tools for assessing and tracking cognitive status over time. In addition, the short VPC task is clinically valuable despite not being widely available. Combined with near-infrared eye-tracking apparatus or device-embedded cameras, VPC tasks may identify seemingly cognitively healthy subjects in whom MCI is underdiagnosed. The brief VPC has been reported to be well-tolerated by participants due to the shorter testing times (the test requires only 5–10 min to complete, including calibration). To conclude this section, investigations in the memory recognition domain open new perspectives to study cognitive disturbances in clinical populations (refer to the take-home notes in Figure 4). Despite the fact that further longitudinal clinical studies are needed, novelty preference scores have surfaced as an easily accessible physiological marker for MCI (Crutcher et al., 2009; Bott et al., 2017; Gills et al., 2019).

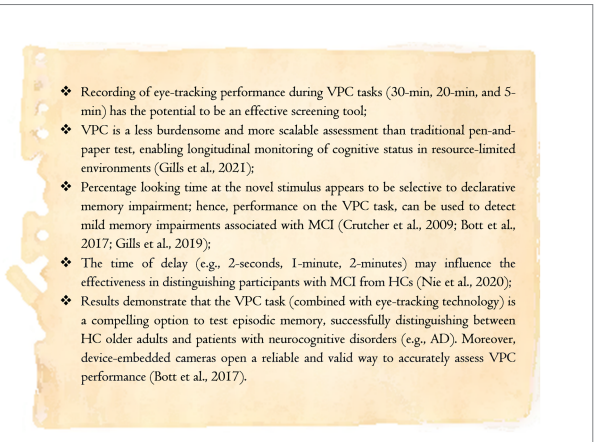

FIGURE 4
Take-home messages for the section dedicated to the Visual Paired-Comparison test (own elaboration based on reports from Bott et al., 2017; Gills et al., 2019, 2021; Nie et al., 2020).

6.2.3. Visuospatial memory eye-tracking task: a screening tool for cognitive impairment and AD status

Since pathological changes in AD develop years before the onset of clinical symptoms, the preclinical AD period has generated considerable interest in detecting subtle memory impairments (Dubois et al., 2016; Parnetti et al., 2019). Therefore, Haque and colleagues sought to develop an easily administered, enjoyable, and sensitive paradigm for passively assessing mild memory deficits at an early stage of the disease course. In particular, the authors followed the suggestion that visuospatial memory paradigms are sensitive indicators of hippocampal-dependent memory function decline (Small et al., 2000; Yassa et al., 2011; Reagh et al., 2016; Hampstead et al., 2018) and, therefore, may serve as an early indicator of memory impairment in AD.

Previously, paradigms that investigated eye movements as an index of memory retrieval requested participants to view a set of images (encoding phase) and their manipulated (or not) versions (objects added, removed, or moved; Ryan et al., 2000; Smith and Squire, 2008). Notably, regarding the repeated images, it has been reported that participants spend more time viewing the manipulated regions compared to the unchanged regions. These results suggest that eye movements rather than explicit memory judgments are suitable for assessing visuospatial memory and evaluating its performance among healthy controls and memory-impaired subjects. Furthermore, more recent studies support the use of eye movements as an indicator of memory dysfunction (Crutcher et al., 2009; Hannula et al., 2012; Zola et al., 2013; Pathman and Ghetti, 2015; Pavisic et al., 2021).

Hence, building on these scientific contributions, Haque and colleagues developed the Visuospatial Memory Eye-Tracking Task (VisMET), during which participants perform a memory paradigm that relies solely on participant's eye movements (Figure 5). During the encoding phase, participants are instructed to "enjoy" viewing a set of naturalistic images. It is crucial to note that VisMET requires memory for a complex set of associations between objects and locations and is assessed passively using eye movements rather than requiring explicit memory judgments. Participants are not informed that they have been given a memory task. In the recognition phase, participants view a modified version of the same set of images with either an item removed (*removed condition*) from the photo or an item added to the image (*added condition*). Importantly, to minimize the impact of one's eye movements from the central fixation cross of the calibration screen preceding each image, the authors reported modifications being applied to noncentral locations only.

The amount of time viewing the manipulated regions of interest, compared to unchanged regions of the images, can be used to measure memory of either a previously viewed object and location (removed condition) or a new object and location (added condition; Figure 5). Moreover, Haque and colleagues speculated whether obtained performance score could be used as a screening tool for identifying MCI and AD states. Therefore, the 4-min paradigm has been primarily administered to 296 control and memory-impaired participants (MCI or AD) with the aim to compare visuospatial memory performance in healthy aging and at different stages of AD. When training the models

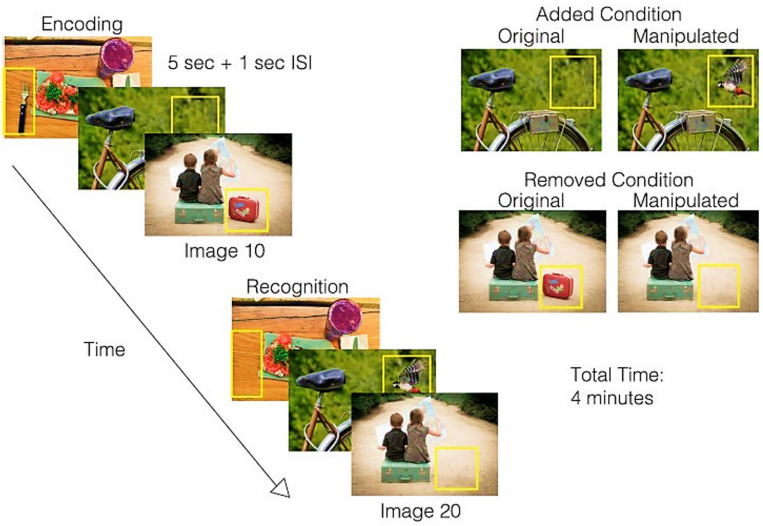

FIGURE 5
Schematic of the visuospatial memory eye-tracking task with a brief explanation (figure of the paradigm taken from Haque et al., 2019). Participants are asked to view a set of images for 5 s (with a 1 s interstimulus interval during the encoding phase). During the recognition phase, participants view the same set of realistic images with either one item removed (removed condition) or one item added (added condition). The manipulated regions (indicated by the yellow box just for an explanatory reason) are used to quantify memory performance. The final test consists of the presentation of two sets of 10 original and manipulated pairs (seven with removed condition and three with added condition) with a delay of 1 min between the original and manipulated presentations. The entire task takes 4 min.

to predict cognitive impairment (MoCA ≤23), the researchers found that VisMET performance was able to achieve an AUC of 0.85 compared to an AUC of 0.71 and 0.56 when using age and education, respectively. This model was able to achieve a sensitivity of 0.83 and specificity of 0.74, using a cutoff probability of 0.64. To further evaluate VisMET, researchers aimed to determine the sensitivity of VisMET performance in predicting disease status, where the output of the model was the diagnostic classification of healthy control, MCI, or AD. By training a logistic regression classifier with the same three features as before, memory performance predicted MCI/AD status with an AUC of 0.85 compared to 0.73 and 0.58 when using age and education alone. Notably, after taking into account all of the features, the achieved sensitivity and specificity were 0.85 and 0.75 respectively, with a cut-off probability of 0.63 (Haque et al., 2019).

In conclusion, Haque and colleagues raised a number of important results, including that memory performance on the VisMET task is (1) different between healthy and MCI/AD participants, and (2) dependent on the difficulty in interpretation of the original and manipulated images. In relation to the latter aspect, since difficulty can be manipulated, it may allow VisMET to be sensitive across a broad range of memory abilities. Furthermore, VisMET performance has been reported to be age-dependent. The group of people aged 50–59 years performed better on the memory task than those aged 60–69 and 70+ years. Moreover, the percentage of critical regions viewed by the 50–59 years age group differed statistically when compared to the 60–69 years ($p < 0.001$, unpaired t-test) and the 70+ years age groups ($p < 0.01$, unpaired t-test). Concurrently, there was no difference in performance between the age groups 60–69 and 70+ years. Finally, a multivariate model of memory performance on the task predicted cognitive impairment and AD status with high sensitivity and identified a subpopulation of healthy controls with relatively weak performance on the task.

Following these promising results, to enable efficient and widespread administration of the VisMET task Haque and colleagues developed a mobile version of the memory paradigm. VisMET has been delivered on iPad devices to assess cognitive status in a population of 250 individuals (Haque et al., 2021). The authors used a transfer learning approach to train a deep neural network to track participants' gaze behavior. In conclusion, mild-to-severe cognitive impairment was identifiable with a test accuracy of 70%; furthermore, by enforcing a minimal calibration error of 2 cm, an accuracy of 76% was achieved. It is important to mention that this result has been reported to be equivalent to the accuracy obtained using commercial eye-tracking hardware. Overall, these data demonstrate a mobile VisMET version that can estimate the presence of cognitive impairment (Haque et al., 2021). With the widespread use of smart devices as a non-pharmacological intervention (Astell et al., 2019), future advancements in technology combined with eye-tracking may offer new opportunities for detecting the onset of an abnormal aging process (Bott et al., 2018; Boyd et al., 2021) as well as visual impairments linked to other disorders (Wolf and Ueda, 2021; Wolf et al., 2021a) on a worldwide level.

6.2.4. King Devick test

Due to cognitive deficits in information processing, memory, and visual learning, a commonly used instrument to measure information processing speed is the King Devick (KD) test, which has been reported to be sensitive in detecting performance change in clinical

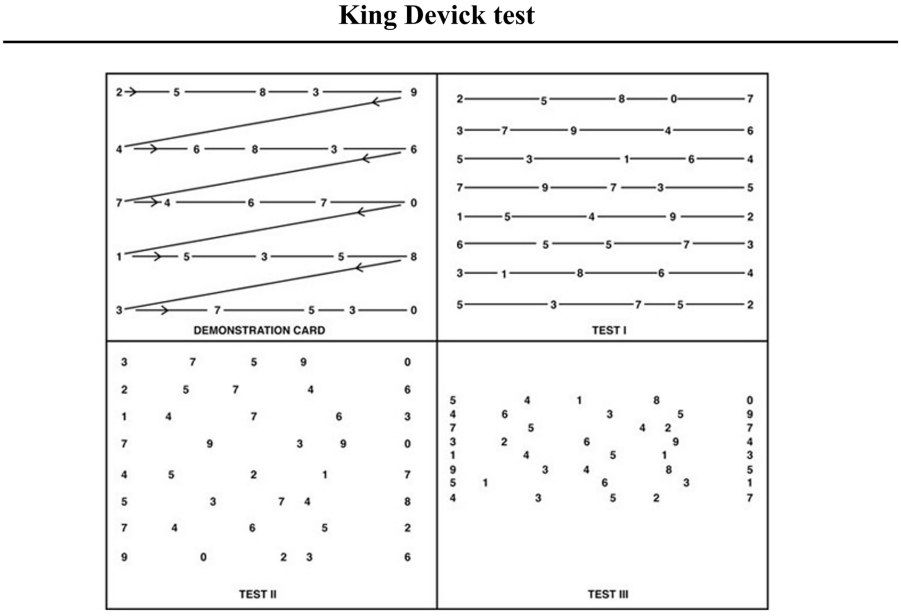

FIGURE 6
Schematic view of the King Devick test with a brief explanation (figure obtained from Leong et al., 2015). Each test card displays 40 digits in five rows, with the spacing between each number varying between rows and across rows. Notably, the visual demands of the test cards increase as the test progresses. The first test card has straight lines connecting the numbers that aid visual scanning. In the second test card, the lines connecting the numbers are missing. The final test card is made up of numbers with no connecting lines and with the spacing between the rows truncated.

populations. It comprises a simple visual-verbal task that requires precise saccades and intersaccadic fixations. Previous research has shown the KD test's performance to be correlated with the Symbol Digit Modalities Test (SDMT) as well as MoCA scores.

In short, the KD test is a 1–2-min, rapid number naming test, often used to assist cognitive impairment in multiple sclerosis or after concussion (Galetta et al., 2015; Gold et al., 2021). Notably, it also has clinical utility in other conditions such as Parkinson's disease and AD. This visual scanning test requires participants to read numbers out loud as quickly as possible. Commonly, there is one demonstration card at the beginning, followed by 3 test cards that become progressively more difficult due to changes in spacing and vertical crowding of the numbers (Figure 6). Each card increases visual demands and allows interference from other rows as the participant reads across the page. Scores are generated based on the total time taken to complete the test. A higher score indicates worse performance where aged-normed T-Scores ≤40 are classified as borderline or impaired.

As previously mentioned, impaired eye movements may be an early indicator of AD (Molitor et al., 2015; Kahana Levy et al., 2018; Hannonen et al., 2022; Opwonya et al., 2022b) with saccadic eye movement impairments being one of the most commonly documented forms of oculomotor dysfunction among patients with AD (Fernández et al., 2013; Chang et al., 2014; Galetta et al., 2017). Additional studies have also demonstrated that patients with aMCI exhibit abnormal saccades resembling mild AD (Peltsch et al., 2014; Wilcockson et al., 2019). These findings raise the possibility that testing goal-directed eye movements may have strong utility in the detection of cognitive impairment (Readman et al., 2021). Since the KD test requires participants to perform precise, horizontal eye movements coupled with a rapid number naming task, it's score may provide an early indicator of an overall cognitive impairment, where impaired individuals are expected to have a greater number of errors and take more time to complete the number naming task (Lin et al., 2014). In short, the KD test score is the total time required (in seconds) to complete three test cards, where higher scores reflect worse performance (Lin et al., 2014; Galetta et al., 2017; Gold et al., 2021).

The first research group to test the utility of the KD in AD was Galetta et al. (2017). The sample included 135 HCs and 71 cognitively impaired patients (MCI = 39, AD = 32), AUCs generated from logistic regression models revealed that the KD test can distinguish controls from cognitively impaired subjects (MCI AUC = 0.71; AD AUC = 0.74). KD time scores between 48–52 s were associated with high sensitivity (>90.0%) and negative predictive values (>85.0%) for each diagnostic group. The research group concluded that the KD test is a simple and effective screening tool to detect cognitive impairment associated with AD in an efficient time frame (Galetta et al., 2017). Moreover, worse performance on the KD test may capture distinct pathological changes related to AD that affect saccadic oculomotor function. Nevertheless, these preliminary results await further validation through empirical testing.

Recently, the KD test has been used to examine whether obtained gaze metrics (saccadic duration and amplitude) can differentiate cognitively healthy control groups from subjects with minor changes on cognitive tests or those diagnosed with mild AD (Hannonen et al., 2022). Hannonen and colleagues recruited 57 non-demented participants and 21 patients with mild AD (Hannonen et al., 2022). All subjects underwent neurological examination, including the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological test battery (CERAD-NB) and a Clinical Dementia Rating interview. Furthermore, the

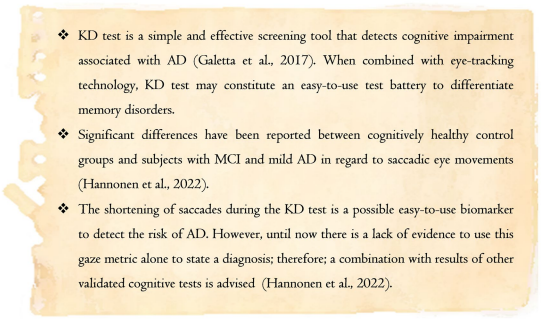

FIGURE 7
Take-home-messages for the section dedicated to the King Devick test (own elaboration based on scientific works by Galetta et al., 2017; Hannonen et al., 2022).

non-demented participants were divided into two groups, namely control (normal CERAD subtests, mean MMSE = 28) and objective MCI (decline in at least one CERAD memory score, mean MMSE = 27). The research group found significant differences between the three groups (control, objective MCI, and AD) in regard to the mean saccade amplitude (3.58, 3.33, and 3.21 ms, respectively, $p < 0.03$) and duration (27.1, 25.3, and 24.8 ms, respectively, $p < 0.05$). Furthermore, the KD error scores of AD patients differed significantly ($p < 0.01$) from the other groups (Hannonen et al., 2022).

Overall, the results from KD testing provided the scientific community with some practical insights regarding future practices related to eye-tracking technologies (refer to the take-home notes in Figure 7; Galetta et al., 2017; Hannonen et al., 2022). The previously reported notion of eye-tracking technology adding value to the screening process in MCI has been unanimously supported. Moreover, the convenience of portable eye-tracking devices for future use in primary health care memory clinics has been highlighted (Hannonen et al., 2022). However, considering the accuracy of the KD test as a screening tool and large in-group variances among participants, neither saccadic duration nor saccadic amplitude alone can faultlessly classify cognitively unimpaired individuals. For now, it is advised to use these two parameters in combination with other screening tools (Hannonen et al., 2022).

6.2.5. Visual impairments in face processing tasks

Eye-tracking represents a category of interdisciplinary research that successfully combines with various tasks. It can also evaluate human gaze behavior in association with numerous stimuli categories, such as geometrical figures, illusions, and pictures of computerized human faces (Simion and Shimojo, 2006; Prats et al., 2010; Borji et al., 2013; Gidlöf et al., 2013; Spinks and Mortimer, 2015; Vriens et al., 2020; Wolf and Ueda, 2021). Yet, the use of abstract stimuli may reduce the ecological validity of a neuropsychological study, defined by Sbordone and Long in 1996 as "*the functional and predictive relationship between the patient's performance on a set of neuropsychological tests and the patient's behavior in a variety of real-world settings (e.g., at home, work, school, and community)*" (p. 16; Sbordone, 1996; Diaz-Orueta et al., 2022). Hence, few research groups opt to use realistic stimuli to investigate visual processing among adults with MCI.

For example, Kawagoe and colleagues requested study participants (aMCI and HCs) to judge whether two images (faces or houses) were the same or different (*perception study*). In the follow-up task, the participants were asked to indicate which of the two images, if any, had been presented previously (*short-term memory study*). The results showed that, when judging whether the images were the same or different, HCs spent more time visually inspecting the eye and nose. Notably, this effect was not observed among older adults with aMCI, who looked longer at the mouth area. When judging whether an image had been previously presented, the observed fixation pattern of facial landmarks did not differ between groups (HC and aMCI), yet patients with aMCI showed a decline in memory for faces but not for houses (Kawagoe et al., 2017).

In 2018, McCade and colleagues introduced a novel eye-tracking paradigm to investigate if deficits in emotion recognition are evident among individuals with MCI. For that reason, the research group used naturalistic stimuli in the form of emotional faces (NimStem Set of Facial Expressions) to introduce recruited participants (18 HC, 18 patients with naMCI, and 14 patients with aMCI) to a free visual search paradigm. Although older adults with aMCI were less accurate on emotion recognition than HC and naMCI, no significant difference in mean fixation durations on eye, mouth, and peripheral facial regions was reported. Gaze behavior analysis revealed all participants showing a preference for the eye region. Interestingly, while visually exploring disgusted and angry faces, fixation time on the eye region was significantly shorter for all groups (McCade et al., 2018). In comparison to HC and naMCI, participants with aMCI were less accurate in recognizing the emotion of all categories of presented facial stimuli (McCade et al., 2018). The result of poorer performance in emotion recognition among individuals with aMCI has been replicated in another independent study introducing a computer-based emotion recognition test for older adults (HC = 69; AD = 84; and aMCI = 59), where the processing speed score from the Affect-GRADIOR test has been reported to slightly improve the predictive power of the MMSE (García-Casal et al., 2019; for an excellent review on emotion recognition and processing in MCI patients refer to Morellini et al., 2022).

In summary, forming conclusions regarding the efficacy of face processing paradigms as an early diagnostic tool is limited due to the shortage and high variability of currently available scientific literature (Readman et al., 2021). Nevertheless, the inclusion of naturalistic stimuli and tasks that mimic instrumental activities of daily living such as face recognition or social conversation is of great interest (Kim et al., 2019; Miyake et al., 2020; Sayma et al., 2020; Oliveira et al., 2021; Otake-Matsuura et al., 2021). By transforming the available protocols into real life scenarios, ecologically valid results can be generated (Tarnanas et al., 2013; Sonkusare et al., 2019). Moreover, the adaptation of naturalistic stimuli in neuroscience continues to promise exciting new applications integrating ecologically valid paradigms with VR protocols (Kim et al., 2019; Sonkusare et al., 2019; Sayma et al., 2020; Oliveira et al., 2021; Readman et al., 2021; Lee et al., 2022).

6.3. Combination of eye-movement tests

To commence this section, the authors would like to quote a pertinent observation made by Arolt and colleagues that, although

made in relation to schizophrenia research, is highly relevant to the investigation of cognitive deficits among other clinical entities. *"It has to be kept in mind that each of the mentioned deficits is nonspecific, but can occur in a variety of brain diseases. With regard to the literature on eye movement dysfunction in schizophrenia, it is obvious that not by one single task, but possibly by their combination, eye movements might serve as a biologically based diagnostic tool, in addition to psychopathology"* (Arolt et al., 1998). In the mentioned citation, Arolt strongly emphasizes that a single task may not serve as a reliable diagnostic tool. A similar conclusion shapes the direction of recent projects related to MCI and AD research, where a combination of gaze metrics obtained from multiple tasks may increase the classification accuracy to distinguish patients from HC (Oyama et al., 2019), as well as characterize MCI subtypes.

Since it has consistently been demonstrated that eye movements differ between individuals with AD and healthy controls, and that performance might be associated with attentional factors, two independent research groups employed a series of paradigms to match the following requirements: (i) reproductivity, (ii) inclusion of scientifically recognized tasks, and (iii) implementation of attention-demanding components (including working memory, attention and calculation tasks, and visual working memory tasks) that are suspected to help differentiate the groups (Oyama et al., 2019; Tadokoro et al., 2021).

6.3.1. Novel methods for the rapid assessment of cognitive impairment

To assess cognitive function supported by eye-tracking technology, Oyama and colleagues developed a novel cognitive assessment tool. The cognitive function of HC ($n = 27$), MCI participants ($n = 26$), and patients with dementia ($n = 27$) were assessed (mean MMSE scores were 28.7, 25.7, and 16.0, respectively). Moreover, a subset of participants underwent cognitive assessments such as the ADAS-Cog, Frontal Assessment Battery (FAB), and Clinical Dementia Rating where patients with MCI and dementia performed significantly worse than healthy older adults. According to the methodology, all participants were asked to view a series of short movies and pictures displayed on a screen. Since the total assessment time was approximately 3 min, the screening tool has been reported as practical and brief (Oyama et al., 2019).

A series of 10 short movies and pictures, each designed to assess specific neurological domains, were used in this rapid assessment test. In each task the target image (correct answer) and non-target images (distractors) were presented on a monitor. The subjects were instructed to identify and focus their gaze on the correct answer (see Figure 8 for a schematic view of the paradigm). The idea behind it is simple and straightforward, a region of interest (ROI) was set on the correct answer (target image), and the percentage fixation duration on the ROI was used to calculate the cognitive score. Importantly, valid gaze detection data (not the total exposure duration) was used to determine the cognitive score, considering loss in data due to blinking or looking outside the monitor area. In result, the assessed cognitive scores showed a strong positive correlation with MMSE scores ($p < 0.00001$), and correlated well with scores from the ADAS-Cog, FAB, and Clinical Dementia Rating, showing an outstanding diagnostic performance in detecting patients with dementia (Oyama et al., 2019).

In 2021, Tadokoro and colleagues examined the utility of an eye-tracking test resembling that presented by Oyama et al. (2019). During each procedure, 10 tasks were displayed one-by-one for a

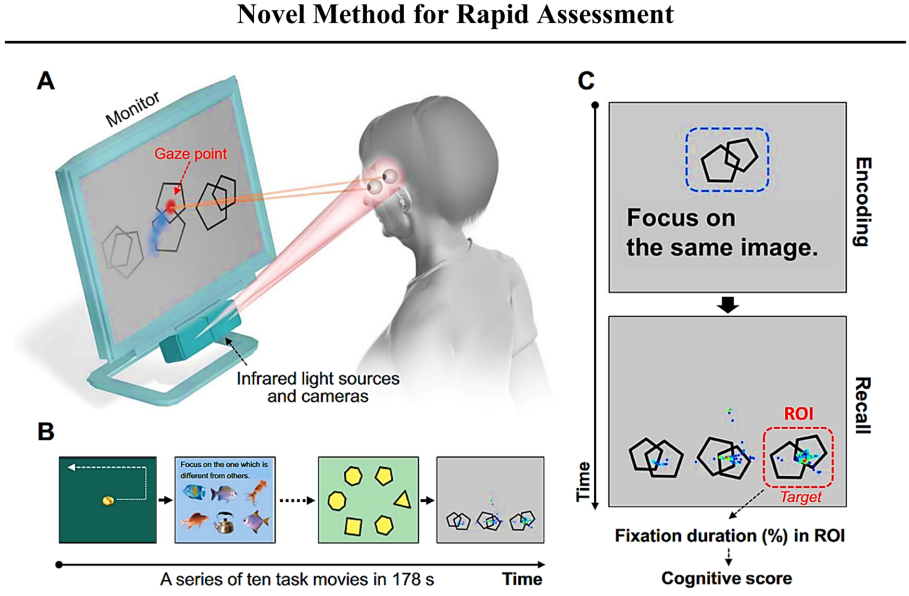

FIGURE 8
Schematic view of the Rapid Assessment of Cognitive Impairment Test, obtained with permission from Oyama et al. (2019). **(A)** Rapid cognitive assessment using an eye-tracking technology and ten task movies. **(B)** The subject views a series of tasks and pictures (for a total of 178 s), which assess smooth pursuit eye movement, deductive reasoning, visuospatial function, and working memory. **(C)** An example (Task 4) of the visual working memory task (pattern matching). The participant is asked to look at target image (here: a combination of a circle and a triangle) for 10 s (encoding) in order to correctly recall the object later on. The fixation duration within the region of interest (ROI) of the target object is used to calculate the cognitive score. For full details of the procedure kindly refer to the supplementary information in Oyama et al. (2019).

total of 3 min on the computer monitor. Again, as in the pipeline presented by Oyama et al., 2019, each subject was required to look at the monitor while the eye-tracking device recorded their gaze points through infrared light cameras. Several ROIs were set, representing the locations of correct answers, incorrect answers, and the explanatory text for each task (specifically for tasks: #1-b, #3, #5, #6, #7, #9, and #10). Total score and subscale scores of delayed recall, working memory, judgement, and visuospatial function (range 0–100; higher means better) were automatically calculated (Tadokoro et al., 2021). In addition, Tadokoro and colleagues evaluated cognitive function of healthy controls ($n = 52$) *via* MMSE, alongside patients with MCI ($n = 52$) and AD ($n = 70$). It was reported that eye tracking scores declined significantly in individuals with MCI ($p < 0.01$ vs. HCs) and AD ($p < 0.01$ vs. HCs, $p < 0.01$ vs. MCI), and correlated well with the MMSE score ($p < 0.05$). Notably, the total score was an average of only four tasks as, according to the article, gaze metrics obtained in tasks #2 [moving coin video], #4 [free viewing of a static landscape photograph], and #8 [an animation of a falling water drop] were not used to calculate the total score.

AUC values were calculated from the ROC curve as an indicator of diagnostic value. In addition to the goal-directed tasks (to select a correct answer: #1-b, #3, #5, and #7), the moving coin task (#2) also showed a high AUC. These results align with previous reports on impaired smooth pursuit in AD. Notably, some of the goal-directed tasks (task numbers #6, #9, and #10) did not effectively distinguish between HCs, MCI, and AD; the authors pointed at the low difficulty level as a possible reason. Therefore, in order to keep the screening procedure as time restricted as possible, Tadokoro and colleagues suggested to omit ineffective tasks (#4, #6, #8, #9, and #10) while implementing their paradigm into future screening applications (Tadokoro et al., 2021).

Interestingly, the landscape photograph task (landscape photograph displayed without instructions, see task #4 in Figure 9) has been reported to fail in exerting a good diagnostic power (Tadokoro et al., 2021); suggesting the possibility that the landscape scene was too simple and/or of low interest to the viewers. Indeed, previous scientific reports mentioned eye-movement impairments among AD patients while looking at naturalistic pictures. However, such observation refers primarily to the diminished curiosity aspect (Przybyszewski et al., 2023). Another point for emphasis is the specific protocol of the free-viewing task, which requires participants to freely view a given scene without explicit instructions (such as *a photograph of a bench in a park*). Such choice of procedure removed the requirement for any potential influences that could dictate where participants should direct their gaze (Tadokoro et al., 2021). Nonetheless, keeping the assignment simple and instruction-less makes it difficult to conclude whether a task is assessing a specific cognitive domain or whether participants' abilities (or impairments) influence their performance on a task. Goal-directed free-viewing paradigms, on the other hand, have the potential to robustly identify cognitive impairment in preclinical stages (Manns et al., 2000; Dragan et al., 2017; Readman et al., 2021). Hence, although the presented studies (Oyama et al., 2019; Tadokoro et al., 2021) demonstrate practical eye-tracking tests for grading the cognitive state of older adults, their scientific conclusions clearly show a direction for further improvements (for example, modifying/replacing some blocks). Finally, in order to transform valuable observations related to atypical gaze patterns into applicable cognitive scoring tests, it is essential to carry out longitudinal studies in laboratory- and home-based settings,

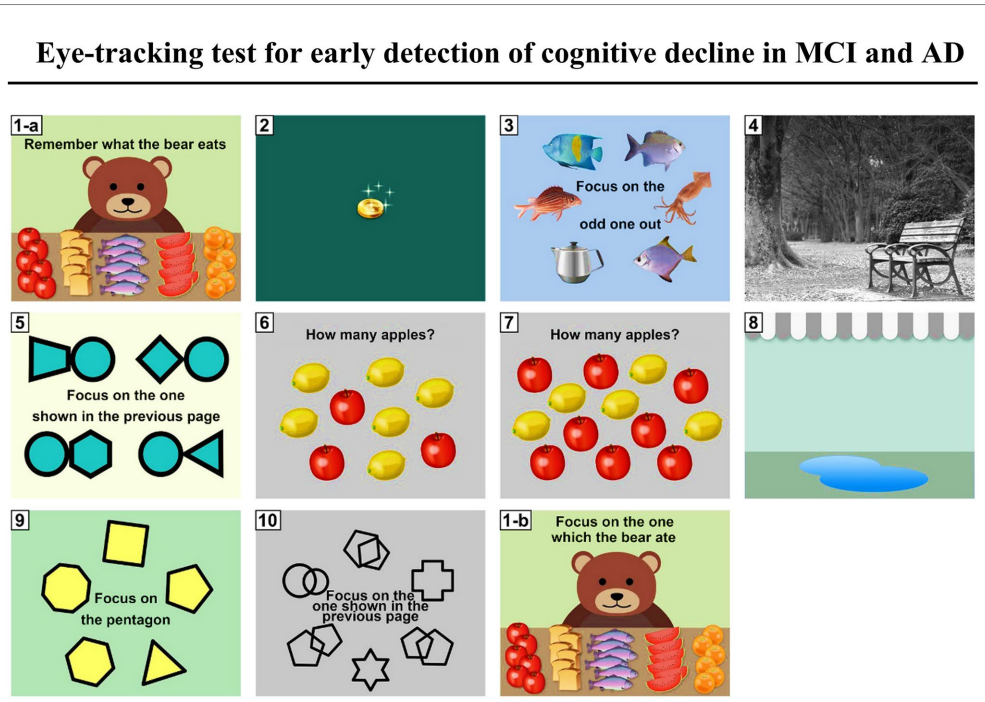

FIGURE 9
Eye tracking test for the early detection of cognitive decline in mild cognitive impairment and Alzheimer's disease, obtained with permission from Tadokoro et al. (2021). Representative images of all 10 tasks with English instructions, which were initially given in Japanese. For full details of the instructions, see Tadokoro et al. (2021).

and report the results in equally accessible publications (Sbordone, 1996; Tarnanas et al., 2013; Sun et al., 2022).

7. Discussion

7.1. ... on addressing eye-tracking-based screening

Until now, the exact mechanisms of how and why various forms of dementia develop remain unclear. Disappointing results of clinical trials for putative new treatments for AD combined with growing evidence of a decade-long preclinical stage of AD have led the scientific community to develop screening tools with high sensitivity and specificity as well as preventive countermeasures (Tarnanas et al., 2013; Galetta et al., 2017; Palsetia et al., 2018; Rutkowski et al., 2020; Thabtah et al., 2020; Lee et al., 2022). Undoubtedly, the accurate prediction of which older adults will progress to develop AD would mark a breakthrough by maintaining their independence (Langa and Burke, 2019). Since, in the context of AD, it is desirable to reach a diagnosis before the disease has progressed to involve massive neuronal loss in the brain, identification of the intermediate phase plays an important role in early intervention, prevention, and treatment (Ataollahi Eshkoor et al., 2015). Hence, it is imperative to develop user-friendly cognitive scoring tools that would aid clinicians to accurately identify and classify a neurodegenerative condition as early as possible (Marandi and Gazerani, 2019; Alber et al., 2020; Majeed et al., 2021; Klyucherev et al., 2022).

A growing body of evidence suggests that gaze metrics are useful in the screening of individuals at risk of diseases, including AD, Parkinson's, Autism spectrum disorder, and nystagmus syndrome (Rosengren et al., 2020; Kong et al., 2022; Sun et al., 2022). Further investigations of specific eye movement biomarkers and neuropsychological criteria that precisely separate MCI subtypes (aMCI and naMCI) may assist in the forecasting of dementia progression. Along the same line, a better understanding of MCI subtypes could facilitate the development of targeted prevention strategies and offer a more effective approach for testing the efficacy of future therapeutic interventions (Busse et al., 2006; Csukly et al., 2016; Wright and O'Connor, 2018; Clark et al., 2019).

Future eye-tracking-based experiments may address the challenges and aim to expand the knowledge of differential diagnostics. While it remains speculative if gaze metrics will ever be used as a standalone diagnostic criterion (Clark et al., 2019), experimental paradigms that take into account one's eye-movement behavior (Rodrigue et al., 2018; Clark et al., 2019; Wolf et al., 2021a) have appeared to shorten screening procedures and improve diagnostic accuracy (Lagun et al., 2011; Zola et al., 2013; Lauermann et al., 2017; Ehrlich et al., 2022). Yet thought-provoking is the fact that although visual and oculomotor problems are prevalent among older adults, and gaze recordings may support clustering various clinical problems, *eye-tracking* technology is somehow excluded from routine screening investigations (Tsitsi et al., 2021) and remains in the academic dimension only (Wolf et al., 2021a). Furthermore, despite available reports on improved eye care going hand-in-hand with an improved dementia prevention strategy, information about visual impairments is not used to shape public health policy nor research priorities of dementia risk factors (Ehrlich et al., 2022; The Lancet Regional Health – Europe, 2022). An increase in awareness about the diagnostic value of one's gaze and knowledge in interpretations of gaze behavior abnormalities is crucial (Cañigueral et al., 2019; Holmqvist et al., 2022); especially, that routine eye-movement-based cognitive assessments, which provide a quantitative and objective method to aid diagnoses in older adults, are technically feasible (Galetta et al., 2017; Oyama et al., 2019; Dickens and Ramaesh, 2020; Tadokoro et al., 2021).

Monitoring potential changes in the performance of eye-movement tests may facilitate the identification of older adults who are at risk of developing AD, becoming a valuable tool for primary health care clinics (Molitor et al., 2015; Holden et al., 2018; Wilcockson et al., 2019; Pereira et al., 2020; Lehtola et al., 2022). It has been reported that such recordings could be performed in eye care clinics equipped with cost-effective eye trackers (Rosen, 2004; Dickens and Ramaesh, 2020) or at home *via* devices with built-in cameras such as smartphones or tablets. Following the dramatic increase in the use of consumer electronics by aging adults, digital approaches that leverage the capacities of mobile devices and internet connectivity represent a promising direction for detecting MCI in non-clinical environments. To support this concept, mobile versions of several tests have been reported to demonstrate a high capability of estimating the presence of cognitive impairment (Bott et al., 2017; Sabbagh et al., 2020a; Haque et al., 2021). Hence, it is becoming increasingly possible to detect visual impairments associated with neurodegenerative disorders on a global level. Paving the way for computer-based diagnosis and prognosis, eye tracking facilitates the automation of medical decision support. Such a multimodal approach would increase the range of screening possibilities for older adults, although proposed assays need to be adequately validated and linked to healthcare systems with equity.

The authors of this review echo the conclusions of previous works that the static image of the eye can provide the scientific community with information regarding physiological changes in the brain. However, the pathological changes in the retina are difficult to associate with a singular disease. On a dynamic scale, however, eye movements can provide valuable hints to understand one's cognitive functioning and narrow the possible diagnostic options. Unveiling pathological brain changes associated with AD is a challenging task, especially considering that people do not show symptoms of *dementia* until late into the disease course. The support of eye-tracking technology opens the possibility of getting closer to the invisible part of neuronal connections, overcoming limitations related to self-reported methodologies (Connors et al., 2016; Bell et al., 2018). Therefore, eye-trackers are powerful precision instruments ready to accelerate the transition toward a non-invasive and accessible screening procedure for MCI. As outlined in this review, eye-tracking technology can be useful in detecting early signs of decline in combination with experimental paradigms investigating cognitive function including memory loss and difficulties with attention and processing speed.

Eye-movement-based cognitive scoring is an area of active research and development, with ongoing studies aiming to refine and improve the accuracy and reliability of used tools. Experimental paradigms described in this work provide a promising direction for gaze parameters serving as potential biomarkers to assess symptoms of cognitive decline, with the ultimate goal of indicating the preclinical stages of AD (Crutcher et al., 2009; Zola et al., 2013). However, due to methodological differences in applied paradigms, selection of subjects,

choice of the apparatus, and length of follow-up in longitudinal studies, discrepancies between results of the studies may occur.

Of particular importance is the assessment of methodological frameworks and transparent reporting. Notably, while implementing pro- and antisaccade tasks, one should consider that disparity in carried-out conditions (gap or overlap) may account for ambiguity in the findings and, as a direct consequence, the selection of parameters relevant in distinguishing between MCI subtypes, AD patients, and HC. The "gap" effect, for instance, may account for a change in participants' saccade latencies (Polden et al., 2020) and, as a result, yield conflicting findings. Moreover, difficulty in disengaging attention from the fixation dot presented in the center of the screen would account for slowing down in prosaccade task.

Regarding the instruction-less paradigm methodology, such protocols can be useful in assessing the cognitive capacities of older adults, especially those who have problems with language comprehension. The absence of an explicit instruction may remove any influences that would dictate where participants should direct their gaze. On the other hand, it has been suggested that an increased level of complexity of goal-directed eye movement tasks may be required to robustly identify preclinical stages of cognitive impairment.

Eye-tracking-based cognitive screening tools being investigated and replicated across various populations is another crucial aspect to be addressed. Since demographic and ethnic differences have been identified as influencing eye movement patterns, it is important to take these factors into account when interpreting gaze behavior data. As an illustrative example, we use two studies (Kawagoe et al., 2017; McCade et al., 2018) that both used photographs of human faces in their experimental protocols. While Kawagoe and colleagues observed face-specific abnormalities in scanning behavior in the aMCI group, McCade and colleagues reported comparable face scanning behavior among all three groups (aMCI, naMCI, and HCs). In addition, given that facial processing deficits may appear in various clinical populations (including AD, aMC, depressive disorder, and schizophrenia), it may seem challenging to differentiate between different clinical entities while following a face recognition task. In order to differentiate between healthy aging adults and patients suffering from disorders, scrupulous comparison of clinical subtypes across various populations is important. Reports of such studies may support the choice of the most promising set of gaze metrics as future biomarkers for AD-related MCI, increasing the opportunities for early intervention.

In 2020, Lehtola and colleagues investigated whether computer-based eye-tracking analysis of the KD test could differentiate patients with idiopathic normal pressure hydrocephalus (iNPH; a progressive neurodegenerative disease with characteristic symptoms of gait disturbance, cognitive decline, and urinary incontinence) from cognitively unimpaired adults and individuals with AD. The research group followed previous statements that the combination of eye-tracking technology and the KD test constitute an easy-to-use test battery to differentiate disorders characterized by memory impairments (Galetta et al., 2017; Hannonen et al., 2022). However, although the tested parameters (total time used for the reading test, number of errors, durations of fixation and saccade, and saccade amplitudes) significantly differed between the AD group and the cognitively unimpaired group, no significant differences between the patients with iNPH and AD group were detected. Accordingly, extensive investigations are needed to test the possibility of gaze metrics to distinguish AD from other disorders or diseases. In this regard, machine learning methods could analyze scores from a combination of psychological and eye movement tests to predict the trajectory of an individual's AD progression (Haque et al., 2021; Thabtah et al., 2022a).

7.2. ... on innovation as integral part of the MCI screening process

In recent years, several research groups showed that deep-learning models combined with eye-tracking technology have good performance in identifying neurological diseases. For example, Chaabouni and colleagues developed a deep-learning architecture to predict the visual attention model of patients with dementia and reached a predictive accuracy of 99.27% (Chaabouni et al., 2017). Furthermore, Biondi and colleagues developed a deep-learning approach to differentiate between the reading behavior of patients with AD and healthy controls. Notably, their presented model had 89.78% accuracy for identifying the cognitively impaired AD group (Biondi et al., 2018). Therefore, it should not pass unnoticed that insights on gaze parameters such as fixations, saccades, and regions/areas of interest provide valuable information for developing eye-tracking-based cognitive tests (Bott et al., 2017; Gills et al., 2019; Oyama et al., 2019; Tadokoro et al., 2021). However, the lack of large-scale eye-tracking datasets is a limiting factor for using deep-learning models for the recognition or classification of AD-related MCI based on eye movement data. Therefore, it is important for the scientific community to establish access to such databases in order to advance the development of machine-learning and deep-learning-based models for identifying cognitive function impairment with higher sensitivity (Fabrizio et al., 2021; Haque et al., 2021; Miltiadous et al., 2021; Rutkowski et al., 2021; Rizzo et al., 2022; Sun et al., 2022). While remarkable advancements are occurring in the field of digital health sector (Dagum, 2018; Kourtis et al., 2019; Topol, 2019; Khan and Javaid, 2021), the challenge is for healthcare system leaders to stay abreast of the latest findings and information about gaze metrics as an emerging option for cognitive screening. Therefore, this systematic review should provide a comprehensive overview of the latest evidence-based knowledge and establish a basis for further advancements.

7.3. Limitations

A limitation of any review is the possibility that relevant studies may have not been identified due to the selection of databases and search strings used. In order to reduce the likelihood of omitting relevant papers, reference lists of all studies included in this work were additionally screened. Following the aim to provide a quality review on future biological markers for AD, it is important to underline that the authors focused primarily on paradigms that compared visual information processes between older adults with aMCI and their age-matched control group. Notably, while the review covers various paradigms, the number of representative studies is limited. This observation should be considered by interdisciplinary research groups when proposing follow-up and/or alternative paradigms for assessing cognitive functioning among older adults.

7.4. Conclusion

The findings of this systematic review have indicated that eye-tracking-based paradigms may ameliorate the screening limitations of traditional cognitive assessments and contribute to early AD detection. However, before widespread clinical adoption, longitudinal investigations in lab-based and ecologically valid settings are necessary to translate the findings relating to abnormal gaze behavior.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AW, KT, and MO-M made the conceptualization and methodology. AW and KT have done identification and screening of the scientific reports. AW done the draft preparation, revisions, and editing. MO-M and SU provided expertise in the field and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prefrontal event-related potential markers in association with mild cognitive impairment

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Background: Alzheimer's disease (AD) is among the leading contributors of dementia globally with approximately 60–70% of its cases. Current research is focused on the mild cognitive impairment (MCI), which is associated with cognitive decline but does not disrupt routine activities. Event-related potential (ERP) research is essential in screening patients with MCI. Low-density channel electroencephalography (EEG) is frequently used due to its convenience, portability, and affordability, making it suitable for resource-constrained environments. Despite extensive research on neural biomarkers for cognitive impairment, there is a considerable gap in understanding the effects on early stages of cognitive processes, particularly when combining physiological and cognitive markers using portable devices. The present study aimed to examine cognitive shortfalls and behavioral changes in patients with MCI using prefrontal selective attention ERP recorded from a prefrontal two-channel EEG device.

Methods: We assessed cognitive decline using the Mini-Mental State Examination (MMSE) and the Seoul Neuropsychological Screening Battery (SNSB). We administered auditory selective attention tasks to 598 elderly participants, including those with MCI (160) and cognitively normal (CN) individuals (407). We conducted statistical analyses such as independent t-tests, Pearson's correlations, and univariate and multiple logistic regression analyses to assess group differences and associations between neuropsychological tests, ERP measures, behavioral measures, and MCI prevalence.

Results: Our findings revealed that patients with MCI demonstrated slower information-processing abilities, and exhibited poorer task execution, characterized by reduced accuracy, increased errors, and higher variability in response time, compared to CN adults. Multiple logistic regression analyses confirmed the association between some ERP and behavioral measures with MCI prevalence, independent of demographic and neuropsychological factors. A relationship was observed between neuropsychological scores, ERP, and behavioral measures.

Discussion: The slower information processing abilities, and poor task execution in the MCI group compared to the CN individuals suggests flawed neurological changes and reduced attentional maintenance during cognitive processing, respectively. Hence, the utilization of portable EEG devices to capture prefrontal selective attention ERPs, in combination with behavioral assessments, holds promise for the identification of mild cognitive deficits and neural alterations in individuals with MCI. This approach could potentially augment the traditional neuropsychological tests during clinical screening for MCI.

KEYWORDS

Alzheimer's disease, mild cognitive impairment, event-related potential, electroencephalography, cognitive function, behavioral measure, screening tool

1. Introduction

Dementia, with an estimated morbidity of 55 million and a yearly incidence of approximately 10 million is a prominent contributor of death and incapacity among the elderly population globally (WHO, 2022). The leading contributor of dementia is Alzheimer's disease (AD), with approximately 60–70% of its cases (WHO, 2022). With an expected rise in the prevalence and related social costs of AD in the period between 2030 and 2050, current scientific and clinical research on AD prioritizes early detection of the intermediate stage between cognitively normal aging, mild cognitive impairment (MCI), and dementia (Dubois et al., 2007; Mantzavinos and Alexiou, 2017).

Mild cognitive impairment is a syndrome pronounced by cognitive decline which is higher than anticipated for a person's age and level of education, without disrupting routine life activities (Gauthier et al., 2006). It could be an early indication of various degenerative, vascular, psychiatric, and medical disorders, with a potential to advance into degenerative conditions like AD dementia, frontotemporal dementia (FTD), and dementia with Lewy bodies (DLB). Furthermore, it might manifest as a symptom within non-degenerative conditions like vascular cognitive impairment (VCI), major depressive disorder, generalized anxiety disorders, uncompensated heart failure, and poorly managed diabetes mellitus (Petersen, 2016). Its further categorized into amnestic MCI (aMCI) if memory domain is affected or non-amnestic MCI (naMCI) if other cognitive domains are impaired. The quantity of impacted domains plays a crucial role in assessing the magnitude of underlying brain pathology, the disease's impact, and the probability of transitioning to dementia. The yearly rate of progression from MCI to dementia fluctuates between 8 and 15% (Petersen, 2016) and its prevalence in persons ≥60 years is estimated to be between 15 and 20%, making it a rampant condition clinicians encounter (Gauthier et al., 2006).

This has attracted profound research interests as it's crucial to promptly diagnose and treat individuals with a high risk of developing dementia prior to the emergence of substantial structural deficits. These individuals are suitable for therapeutic intervention (Missonnier et al., 2005). Furthermore, detecting individuals with increased risk of dementia is crucial in stopping disease progression, enabling the adoption of preventive healthcare, and easing potential emotional and financial pressures for both patients and caregivers. At present, patients with MCI and dementia are identified through assessment of cognitive function using neuropsychological tests. The Mini-Mental State Examination (MMSE) (Dick et al., 1984) is among the most extensively accessible and conveniently administered neuropsychological screening tests by primary care practitioners (Langa and Levine, 2014).

In South Korea, the Seoul Neuropsychological Screening Battery (SNSB) is a widely used comprehensive neuropsychological evaluation tool that provides scores in cognitive domains such as attention, memory, frontal/executive function, language, and visuospatial skills (Ryu and Yang, 2023). It provides key information for the evaluation of early cognitive decline, analysis of cognitive decline patterns, judgment of dementia severity, and differential diagnosis of dementia (Ryu and Yang, 2023). The complete administration of SNSB-II (the present version of SNSB) approximately takes 1 h and 45 min to 2 h. When exclusively conducting cognitive function tests, the duration is reduced to about 1 h to 1 h and 15 min (Ryu and Yang, 2023). This long duration renders the test impractical for patients with diminished attention spans and does not provide the global cognitive function (GCF) score, a valuable metric for continuous patient monitoring (Ahn et al., 2010).

Degenerative cognitive impairment is marked by a decline in several cognitive processes involving sensation, perception, cognition, and recognition, which precede higher-level cognitive functions (Perry and Hodges, 1999; Morrison et al., 2018). It's often accompanied by the neurological alterations in the cerebral cortex and limbic system leading to deficits in learning, memory, language, and visuospatial skills (Corey-Bloom, 2002; Murman, 2015). While extensive research has been devoted to discovering the neural biomarkers responsible for cognitive impairment (Paitel et al., 2021), there is a considerable gap in understanding their effects on the early stages of cognitive processes, particularly when examining the combination of physiological and cognitive markers in a larger participant pool using a portable measurement device.

Using sensory or oddball event-related potential (ERP) paradigms, features that indicate impairments in cognitive processes have been studied (Nessler et al., 2007; Lai et al., 2010). Synchronized with an event, such as the start of a stimulus or the performance of a manual response (Kappenman and Luck, 2012), ERPs allow for the observation of a sequence of cognitive processes that unfold prior to the delivery of sensory information to the peripheral nervous system, persisting even after a behavioral response is executed (Woodman, 2010). In addition, they are more effective due to being readily accessible, cost-effectiveness, and high temporal specificity in contrast with other neuroimaging modalities (Paitel et al., 2021). The P300 ERP component signifies the cognitive processes associated with allocating attention and engaging working memory (Polich, 2007). It's an expression of the central nervous system's (CNS) activity involved in processing novel information while actively updating memory representations (Polich and Kok, 1995). Disparities in P300 observed during a simple stimulus discrimination task can reliably reflect individual variations in cognitive processing proficiency and swiftness (Polich and Kok, 1995), making it valuable for cognitive evaluation to identify and track the onset and progression of neurogenerative diseases (Medvidovic et al., 2013).

Recently, several studies have shown that EEG or ERP measures can be utilized to differentiate patients with MCI from cognitively normal persons or those with other cognitive impairments. For instance, Chapman et al. (2011) used the ERP obtained in the perceptual or cognitive paradigm to predict individuals with MCI who would later develop AD, using discriminant analysis with cross-validation accuracies of 70–78%. Ganapathi et al. (2022) obtained an area under the curve (AUC) of 0.72, differentiating between subjective cognitive impairment (SCI) and MCI. Bennys et al. (2007) observed

significantly prolonged N200 and P300 latencies in patients with AD when compared to those with MCI or controls. Studies by Frodl et al. (2002) and Golob et al. (2002, 2007, 2009) provided more evidence suggesting a compromised P300 in individuals with MCI. However, some studies reported no differences in P300 measurements of amplitude (Papaliagkas et al., 2008; Lai et al., 2010; Cid-Fernández et al., 2014) and latency (Frodl et al., 2002; Papadaniil et al., 2016; Tsolaki et al., 2017; Cintra et al., 2018) between the CN and patients with MCI.

To enhance the early detection of MCI, there is a critical need for a diagnostic tool that is easily accessible, objective, and user-friendly, suitable for both clinical and non-clinical settings. Recent advancements in EEG technology have created the potential to develop a portable, cost-effective, and widely accessible EEG tool for MCI screening in primary care and outpatient settings (Doan et al., 2021; Smith, 2022). For instance, Khatun et al. (2019) achieved an accuracy of 87.9% in detecting MCI using a Support Vector Machine (SVM) with auditory ERPs obtained from a single-channel EEG device positioned at Fpz. Additionally, Choi et al. (2019) devised a regression model that exhibited a strong correlation of 0.757 in predicting MMSE scores in the elderly, utilizing resting-state prefrontal EEG data from a 2-channel EEG device (Fp1 and Fp2, per the 10-20 system). In a similar setup to Choi et al. (2019), Doan et al. (2021) achieved an Area Under the Receiver Operating Characteristic (AUROC) of 89.1% when distinguishing patients with Alzheimer's Disease (AD) from healthy individuals, employing selective attention auditory ERPs.

This study aimed to assess the effectiveness of a portable EEG system in detecting MCI, with a specific focus on an auditory oddball task that elicits memory and attention ERPs, such as P300. By analyzing the ERP components related to selective attention, higher cognitive functions believed to be impaired in patients with MCI can be understood. We hypothesized that MCI-related neurological changes might impact ERP measures (Woodman, 2010), resulting in decreased task performance and ERP alterations in components associated with the oddball task in contrast to cognitively normal (CN) individuals of matching age. Furthermore, we anticipated a correlation between neuropsychological scores and both ERP and task-based behavioral measures.

2. Materials and methods

2.1. Participants

The present study included 598 participants, recruited between October 2019 and December 2020 at the Gwangju Alzheimer's Disease and Related Dementia (GARD) center (Gwangju City, South Korea). We excluded 264 participants from the analysis because they were neither CN nor had MCI [$n = 31$], did not respond to target stimuli or had extreme errors compared to correct responses in the behavioral measures [$n = 19$], and had incomplete neuropsychological information [$n = 2$]. In addition, visual assessment was conducted by two experts, to identify a prominent P300 peak in the averaged ERPs. This criterion was used for participant inclusion, resulting in the exclusion of participants who did not display a discernible peak in the oddball ERP trace when compared to the standard ERP trace within the 300-600 ms time window [$n = 212$] (Supplementary Figure S2). This exclusion criterion was implemented in order to use the differential ERP method (Levi-Aharoni et al., 2020). This method is applicable when the data demonstrate two dependable time zero-crossing points, namely T1 and T2, between the oddball ERP and standard ERP.

The study participants were divided into two groups of similar ages: CN individuals and those diagnosed with MCI. This grouping was carried out as per the methodology described by Opwonya et al. (2022) which states, "All participants were examined through a clinical interview, which included assessment of the clinical dementia rating (CDR). The CN participants had a CDR score of 0. They had normal cognitive function with no evidence of brain atrophy, white matter changes, multiple lacunae, infarction, or other focal brain lesions on magnetic resonance imaging (MRI) scans. Participants with MCI met the Petersen criteria (Petersen, 2004) and had a CDR score of 0.5. Their neuropsychological test z scores were below −1.5 on at least one of five domain tests according to age, education, and sex-specific norms."

The CN group had 239 participants (99 men and 140 women), with mean age ± standard deviation of 72.17 ± 5.72 years; the MCI group had 95 participants (42 men and 53 women), with mean age ± standard deviation of 74.13 ± 6.27 years (Table 1).

Every participant gave written informed consent, and the study received approval from the Institutional Review Board of Chonnam National University Hospital (IRB No. CNUH-2019-279).

2.2. Neuropsychological battery

In the present study, the latest version of the SNSB (SNSB II) was used to assess the cognitive function of the participants (Kang et al., 1997, 2003). Comprised of five cognitive domain scores—attention, language, memory, visuospatial, and frontal/executive functions—the SNSB II serves as a prominent neuropsychological screening battery in South Korea, usually employed to assess cognitive function in patients with MCI and dementia. We additionally employed the Korean Mini-Mental State Examination (K-MMSE) as the primary screening tool.

2.3. ERP recording

Event-related potentials were recorded using NeuroNicle FX2 (LAXTHA, Daejeon, South Korea) based on the 10-20 International system using 2 prefrontal monopolar scalp electrodes placed on Fp1 and Fp2 with a reference on the right earlobe. Additional details of our EEG/ERP experiments, as quoted below, were drawn from our earlier studies by Choi et al. (2019), Doan et al. (2021): "In addition, a bandstop filter was set between 55 and 65 Hz. All the EEG electrode contact impedances were maintained below 10 kΩ. The data were digitized in continuous recording mode at a sampling frequency of 250 Hz and 15-bit resolution. To eliminate muscle and eye movement artifacts and monitor sleepiness in the participants, qualified operators inspected the individuals and EEG traces during the recording. The operator guided the participants to remain comfortably seated with their eyes closed and alerted them whenever signs of behavioral or EEG drowsiness were detected. The EEG signals from the participants were acquired while they remained seated in an upright position under three sequential conditions: (1) spontaneous brain activity to establish background EEG signals in a resting state for 5 min

TABLE 1 Demographic characteristics and neuropsychological test domain scores.

Characteristic	CN, $N = 239^1$	MCI, $N = 95^1$	T-statistic	Value of p^2
Demographic characteristics				
Age	72.17 (5.72)	74.13 (6.27)	−2.747	**0.006**
Sex			0.217	0.6
Female	140/239 (59%)	53/95 (56%)		
Male	99/239 (41%)	42/95 (44%)		
EDUYR	10.58 (4.37)	9.40 (4.78)	2.165	**0.031**
Neuropsychological test domain scores				
MMSE	27.62 (1.91)	26.04 (2.54)	6.192	**<0.001**
Attention	9.49 (2.21)	8.38 (1.90)	4.292	**<0.001**
Language	0.21 (0.25)	−0.13 (0.49)	8.251	**<0.001**
Visuospatial	0.52 (0.37)	0.00 (0.88)	7.541	**<0.001**
Memory	0.32 (0.59)	−0.55 (0.67)	11.621	**<0.001**
Frontal	0.22 (0.55)	−0.42 (0.71)	8.940	**<0.001**

[1]Mean (SD); n/N (%); [2]Two Sample t-test; Pearson's Chi-squared test; significant features (value of $p \leq 0.05$) are bolded.

(resting-state EEG), (2) sensory-evoked potentials for 8 min, and (3) a selective attention task to acquire the corresponding ERPs for 5 min. To elicit selective-attention ERP, we adopted an active auditory oddball task presenting 64 rare random target stimuli of 2,000 Hz (1/5 ratio) and 256 standard auditory stimuli of 750 Hz (4/5 ratio)."

In this study, only selective attentional ERPs were considered. Prior to the commencement of the experiment, all participants underwent evaluations of their auditory hearing acuity for both the rare tone (2,000 Hz) and the standard tone (750 Hz). Furthermore, participants were assessed for their capacity to distinguish between these tones (using earphones set at a uniform volume level of 70 dB). During the ERP experiment, participants were instructed to press a response key when they recognized the target stimuli. Recordings were made while participants kept their eyes closed in a soundproof room with regular illumination, ensuring a controlled environment for data collection.

2.4. Data pre-processing and feature extraction

The EEG data were analyzed using custom scripts written in *Python (version 3.8.16)*. The features extracted for the present study are described in Supplementary Table S1 and illustrated in Supplementary Figure S2.

2.4.1. ERP measures

The EEG data for the two prefrontal channels (Fp1 and Fp2) were averaged to obtain EEG data from which subsequent pre-processing and feature extraction were performed. We extracted time epochs from −200 to 800 ms with respect to the presentation of stimuli from each of the correct trials (only the trials in which the standard stimuli were not responded to, and the target stimuli were responded to). The average standard and target ERPs were calculated by averaging the ERPs extracted from the EEG data for each participant's stimuli. Each of the derived ERP traces (standard and target) was then baseline-corrected relative to a −200 to 0 ms period, and a moving average filter of order nine was applied to the final ERP traces. To isolate the ERP components, we derived the difference in ERP trace by subtracting the standard ERP trace from the target ERP trace, which was used to generate ERP variables (Levi-Aharoni et al., 2020) and 300-600 ms after stimulus onset was considered as the ERP time window.

The ERP measures extracted encompass various parameters, including Peak Amplitude (AMP), Latency (LAT), 50% Fractional Area Latency (FAL), onset zero-crossing point (T1), late zero-crossing point (T2), Area Under the Curve (AUC), the difference between T1 and T2 (T2T1), the difference between FAL and T1 (FALT1), and the difference between T2 and FAL (T2FAL).

2.4.2. Behavioral measures

We also extracted features related to the behaviors of the participants during the ERP experiment. These include the number of incorrect or committed error responses (NI), error to correct ratio, i.e., ratio of all errors (incorrect and omitted error responses) to the correct responses (ER), response accuracy (ACC), weighted error percentile (WER), mean response time (RT), and variability in response time (RTSD), as measured by the standard deviation of the response times (Supplementary Table S1).

2.5. Statistical analysis

The statistical analyses were carried out using *R Studio (version 2022.07.2+576)*, running on *R (version 4.1.3)* for Windows, including packages *gtsummary (version 1.6.1)*, *ggplot2 (version 3.4.0)* and *corrplot (version 0.92)* (Wickham, 2016; Sjoberg et al., 2021; Wei and Simko, 2021; R Core Team, 2022) with a significance level of $\alpha = 0.05$ for all tests. Independent sample t-tests were performed using Student's t-test for continuous variables, and chi-squared tests were used for categorical variables. Univariate and multiple logistic regression analyses were performed to calculate the odds ratios associated with MCI for each ERP and behavioral measure while controlling for covariates such as age, sex, and years of education. The MMSE score was incorporated as an extra covariate to assess the

independent relationship between ERPs, behavioral variables, and MCI. In addition, Pearson's correlations were examined separately to understand the relationships between the neuropsychological domains and both attentional ERP and behavioral variables in the MCI and CN groups.

3. Results

3.1. Participant characteristics

The demographic information and neuropsychological characteristics of the participants considered for analysis in the present study are listed in Table 1.

The number of participants with MCI and CN was 95 and 239, respectively. The patients with MCI comprised 56% women and 44% men while the CN group comprised 59% women and 41% men. Patients with MCI were older than CN individuals, with mean age ± standard deviation of 74.13 ± 6.27 and 72.17 ± 5.72 years ($p = 0.006$) respectively. Furthermore, the patients with MCI had less years of education [9.40 ± 4.78] than CN individuals [10.58 ± 4.37] ($p = 0.031$). As expected, the patients with MCI had lower MMSE scores than CN individuals, with 26.04 ± 2.54 and 27.62 ± 1.91 score ($p < 0.001$) respectively. Overall, patients with MCI had lower MMSE scores and higher mean age than CN (Opwonya et al., 2022).

Patients with MCI had lower scores in all the SNSB II domains; attention [8.38 ± 1.90], language [−0.13 ± 0.49], visuospatial [0.00 ± 0.88], memory [−0.55 ± 0.67], and frontal [−0.42 ± 0.71] compared to CN individuals [9.49 ± 2.21, 0.21 ± 0.25, 0.52 ± 0.37, 0.32 ± 0.59, and 0.22 ± 0.55] ($p < 0.001$) respectively.

There were no statistically significant differences between the CN and MCI in sex.

3.2. ERP measures

Patients with MCI showed a significantly larger AUC of the P300 duration [$t = -2.13$, $p = 0.034$] and an early onset zero-crossing time point (T1) [$t = 2.38$, $p = 0.018$] compared to the CN individuals, while exhibiting a higher difference between the onset zero-crossing time point and the 50% fractional area latency (FALT1) [$t = -3.08$, $p = 0.002$], the difference between the 50% fractional area latency and the late zero-crossing time point (T2FAL) [$t = -2.25$, $p = 0.025$], and the duration of the P300; the difference between the late and onset zero-crossing time points (T2T1) [$t = -3.30$, $p = 0.001$]. However, there were no significant differences in the distribution of peak amplitude (AMP), peak latency (LAT), late zero-crossing time point (T2), or 50% fractional area latency (FAL) among participants in either group (Figure 1A and Table 2).

3.3. Behavioral measures

Compared to the CN individuals, patients with MCI exhibited significantly more incorrect responses (NI) [$t = -3.49$, $p < 0.001$], a higher

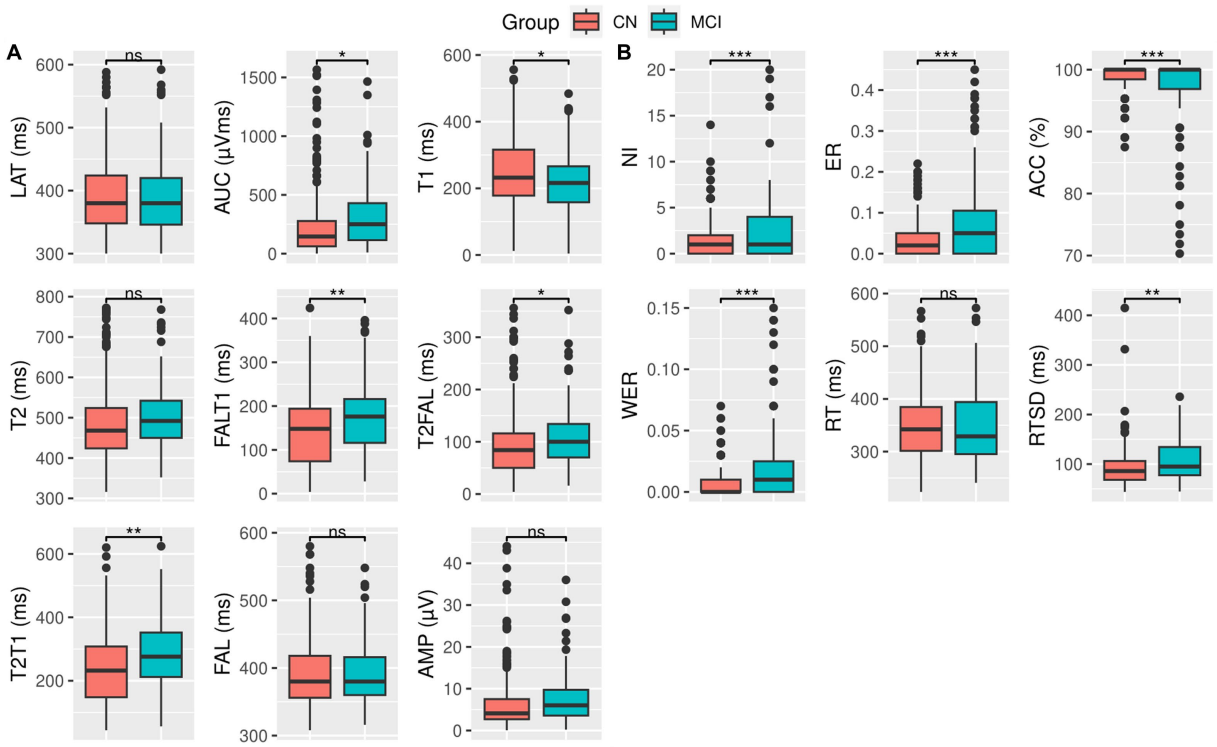

FIGURE 1
Box plot and *t*-test for **(A)** ERP variables and **(B)** behavioral measures for CN (red) and MCI (green) groups. Significance levels are denoted as follows: *** for $p < 0.001$, ** for $p < 0.01$, * for $p \leq 0.05$, and ns for not significant. Detailed statistical scores and value of *p*s can be found in Table 2.

TABLE 2 Participant's ERP and behavioral measures.

Characteristic	CN, $N = 239^1$	MCI, $N = 95^1$	T-statistic	Value of p^2
ERP measures				
FAL	390.88 (53.42)	392.21 (49.52)	−0.21	0.8
AUC	245.88 (297.27)	321.52 (281.66)	−2.13	**0.034**
AMP	6.58 (7.12)	7.99 (6.80)	−1.65	0.10
LAT	388.35 (62.41)	393.35 (63.52)	−0.66	0.5
T1	247.21 (101.51)	218.32 (96.81)	2.38	**0.018**
T2	484.75 (98.34)	503.66 (91.35)	−1.62	0.11
FALT1	143.67 (79.94)	173.89 (82.99)	−3.08	**0.002**
T2FAL	93.87 (65.18)	111.45 (62.10)	−2.25	**0.025**
T2T1	237.54 (119.41)	285.35 (119.62)	−3.30	**0.001**
Behavioral measures				
NI	1.52 (2.19)	2.71 (3.96)	−3.49	**<0.001**
ER	0.04 (0.05)	0.09 (0.12)	−5.82	**<0.001**
ACC	98.80 (2.23)	96.30 (7.02)	4.92	**<0.001**
WER	0.01 (0.01)	0.02 (0.04)	−5.47	**<0.001**
RT	347.80 (64.15)	348.80 (75.60)	−0.12	>0.9
RTSD	92.76 (39.96)	106.89 (40.72)	−2.90	**0.004**

[1]Mean (SD); [2]Two Sample t-test; Significant variables (value of $p \leq 0.05$) are bolded.

ratio of error to correct responses (ER) [$t = -5.82$, $p < 0.001$], a greater response time variability (RTSD) [t = −2.90, $p = 0.004$], and higher weighted error percentile (WER) [$t = -5.47$, $p < 0.001$]. In addition, they showed a reduced response accuracy (ACC) [$t = 4.92$, $p < 0.001$].

However, the distribution of response time (RT) was similar between the two groups (Figure 1B and Table 2).

3.4. Logistic regression

Table 3 presents the odd ratios for ERP and behavioral measures for the risk of MCI.

3.4.1. ERP measures

In the unadjusted model, the odds ratios and corresponding 95% confidence intervals for the following variables were notably distinct from 1, indicating a potential association with the risk of MCI: AUC [OR = 1.27, $p = 0.039$], T1 [OR = 0.74, $p = 0.017$], FALT1 [OR = 1.45, $p = 0.002$], T2FAL [OR = 1.29, $p = 0.026$], and T2T1 [OR = 1.48, $p = 0.001$]. However, AMP, T2, LAT, and FAL did not show any significant risk of MCI.

After adjusting for the demographic characteristics of sex, age, and years of education, the second model showed that T1 [OR = 0.74, $p = 0.019$], FALT1 [OR = 1.42, $p = 0.005$], and T2T1 [OR = 1.44, $p = 0.004$] remained predictors for MCI. This confirmed their independence from demographic characteristics as predictors for MCI.

Further adjusting the second model with MMSE scores, FALT1 [OR = 1.33, $p = 0.029$] and T2T1 [OR = 1.36, $p = 0.019$] remained as predictors for MCI. An increase of 1 ms in the FALT1 and T2T1 levels increased the risk of MCI by 33 and 36%, respectively. This confirmed the true independence of FAT1 and T2T1 from both demographic characteristics and MMSE scores as predictors for MCI.

3.4.2. Behavioral measures

The unadjusted model revealed that several behavioral measures had odds ratios and corresponding 95% confidence intervals notably distinct from 1, suggesting a risk of MCI. These measures included the NI [OR = 1.47, $p < 0.001$], ER [OR = 1.92, $p < 0.001$], ACC [OR = 0.57, $p < 0.001$], WER [OR = 1.87, $p < 0.001$], and RTSD [OR = 1.39, $p = 0.005$]. However, RT did not result in a significant risk for MCI.

After adjusting for the demographic characteristics of sex, age, and years of education, the second model showed that NI [OR = 1.43, $p = 0.002$], ER [OR = 1.83, $p < 0.001$], ACC [OR = 0.59, $p < 0.001$], WER [OR = 1.80, $p < 0.001$], and RTSD [OR = 1.31, $p = 0.027$] were predictors for MCI, confirming their independence from the influence of demographic characteristics.

Further adjusting the second model for MMSE score, revealed that NI [OR = 1.42, $p = 0.004$], ER [OR = 1.72, $p < 0.001$], ACC [OR = 0.63, $p = 0.001$], and WER [OR = 1.69, $p < 0.001$] persisted as predictors for MCI. Therefore, a unit increase in NI, ER, and WER increased the risk of MCI by 42, 72, and 69%, respectively. However, a unit decrease in the ACC increased the risk of MCI by 37%. However, RTSD is no longer considered a predictor for MCI.

3.5. Correlation

To identify significant relationships between ERP, behavioral and neuropsychological measures (MMSE and SNSB II domain scores) in each participant group (CN and MCI), we calculated Pearson correlation coefficients while controlling for the effects of demographic characteristics of age, sex, and years of education (Figure 2).

3.5.1. ERP measures and neuropsychological test scores

Among CN individuals, no significant correlations were observed between ERP variables and the neuropsychological tests.

TABLE 3 Estimated OR and 95% CI for ERP and behavioral measures derived from LR models.

Variables	Model 1			Model 2			Model 3		
	OR[1]	95% CI[2]	Value of *p*	OR[1]	95% CI[2]	Value of *p*	OR[1]	95% CI[2]	Value of *p*
ERP measures									
FAL	1.03	0.81, 1.30	0.83	0.99	0.78, 1.26	0.97	0.98	0.75, 1.25	0.85
AUC	1.27	1.01, 1.59	**0.039**	1.25	0.99, 1.58	0.060	1.17	0.92, 1.49	0.20
AMP	1.21	0.96, 1.51	0.11	1.20	0.95, 1.52	0.12	1.14	0.89, 1.45	0.28
LAT	1.08	0.85, 1.37	0.51	1.06	0.83, 1.34	0.65	1.06	0.82, 1.36	0.66
T1	0.74	0.57, 0.95	**0.017**	0.74	0.57, 0.95	**0.019**	0.78	0.59, 1.01	0.059
T2	1.21	0.96, 1.53	0.11	1.16	0.91, 1.47	0.24	1.13	0.88, 1.45	0.33
FALT1	1.45	1.14, 1.85	**0.002**	1.42	1.11, 1.83	**0.005**	1.33	1.03, 1.73	**0.029**
T2FAL	1.29	1.03, 1.63	**0.028**	1.24	0.98, 1.57	0.071	1.22	0.95, 1.56	0.11
T2T1	1.48	1.17, 1.90	**0.001**	1.44	1.12, 1.85	**0.004**	1.36	1.05, 1.77	**0.019**
Behavioral measures									
NI	1.47	1.17, 1.90	**<0.001**	1.43	1.14, 1.85	**0.002**	1.42	1.12, 1.83	**0.004**
ER	1.92	1.49, 2.55	**<0.001**	1.83	1.42, 2.43	**<0.001**	1.72	1.33, 2.30	**<0.001**
ACC	0.57	0.42, 0.73	**<0.001**	0.59	0.43, 0.76	**<0.001**	0.63	0.46, 0.84	**0.001**
WER	1.87	1.45, 2.51	**<0.001**	1.80	1.39, 2.41	**<0.001**	1.69	1.28, 2.31	**<0.001**
RT	1.01	0.80, 1.28	0.90	1.00	0.78, 1.28	0.99	0.98	0.76, 1.27	0.90
RTSD	1.39	1.10, 1.79	**0.005**	1.31	1.03, 1.70	**0.027**	1.23	0.96, 1.59	0.10

[1]OR, odds ratio; [2]CI, confidence interval; LR, logistic regression; Model 1: the unadjusted LR model; Model 2: LR model adjusted for demographic characteristics of age, sex and years of education; Model 3: LR model adjusted for demographic characteristics and the MMSE score. Significant variables (value of $p \leq 0.05$) are bolded.

For patients with MCI, we found a significant negative correlation between the frontal/executive function and T1 [$r = -0.28$, $p = 0.01$], and a positive correlation between the frontal and FALT1 [$r = 0.26$, $p = 0.01$]. However, no correlations were observed between the remaining ERP variables and neuropsychological tests.

3.5.2. Behavioral measures and neuropsychological test scores

The CN participants displayed statistically significant negative correlations between frontal and various behavioral measures of task performance. Specifically, negative correlations were found between the frontal and the ER [$r = -0.14$, $p = 0.03$], WER [$r = -0.16$, $p = 0.02$], and RTSD [$r = -0.18$, $p = 0.01$], and between language and ACC [$r = -0.14$, $p = 0.03$].

However, there were significant positive correlations between the frontal and ACC [$r = 0.17$, $p = 0.01$] and between language and WER [$r = 0.14$, $p = 0.03$]. Notably, no significant correlations were found between behavioral measures and any of the MMSE, and the neuropsychological domains of attention, visuospatial function, and memory in CN individuals.

In patients with MCI, significant negative correlations were found between the MMSE and WER [$r = -0.23$, $p = 0.03$], MMSE and RTSD [$r = -0.21$, $p = 0.04$], language and ER [$r = -0.30$, $p < 0.001$], language and WER [$r = -0.26$, $p = 0.01$], language and RTSD [$r = -0.22$, $p = 0.03$], memory and RT [$r = -0.21$, $p = 0.04$], frontal and NI [$r = -0.22$, $p = 0.03$], frontal and ER [$r = -0.37$, $p < 0.001$], frontal and WER [$r = -0.36$, $p < 0.001$], and frontal and RTSD [$r = -0.50$, $p < 0.001$]. Furthermore, there were significant positive correlations between the MMSE and ACC [$r = 0.25$, $p = 0.01$], language and ACC [$r = 0.26$, $p = 0.01$], and frontal and ACC [$r = 0.34$, $p < 0.001$].

Behavioral measures showed no significant correlation with the neuropsychological domains of attention, visuospatial function, and memory in patients with MCI.

4. Discussion

This study examined the use of selective attention prefrontal ERP and task-related behavioral measures as possible biomarkers for identifying MCI using a portable EEG system. We analyzed the differences in ERP and task-related behavioral measures between individuals with MCI and CN individuals using an auditory oddball paradigm. Furthermore, we investigated the correlation between neuropsychological tests commonly used in MCI screening and both ERP and behavioral measures.

The ERP analysis indicated that patients with MCI displayed an elevated AUC and early T1, while demonstrating slower P300 timings of FALT1, T2FAL, and T2T1, compared to CN individuals. However, there were no notable differences in AMP, T2, LAT, or FAL between the two groups. After accounting for demographic factors of age, sex, and years of education, the T1, FALT1, and T2T1 ERP measures still showed a significant association with MCI. Even after additional consideration of the MMSE score, FALT1 and T2T1 retained their ability to differentiate between individuals with MCI and CN among the previously identified significant ERP variables. This suggests the true influence of ERP measures of FALT1 and T2T1 as possible predictors for MCI, independent of demographic characteristics and neuropsychological tests.

Specifically, we did not observe any significant difference in the amplitude between the two groups, although the MCI group had larger amplitudes than the CN group. This was similar with prior studies (Papaliagkas et al., 2008; Lai et al., 2010; Cid-Fernández et al., 2014) that reported no difference in P300 amplitudes between patients with MCI and CN individuals. These results indicate that both groups comparably mobilized the attentional resources needed for stimuli categorization and updating the context in working memory (Gironell et al., 2005). These results could be attributed to several factors. First, it is possible that patients with MCI compensate for cognitive deficits

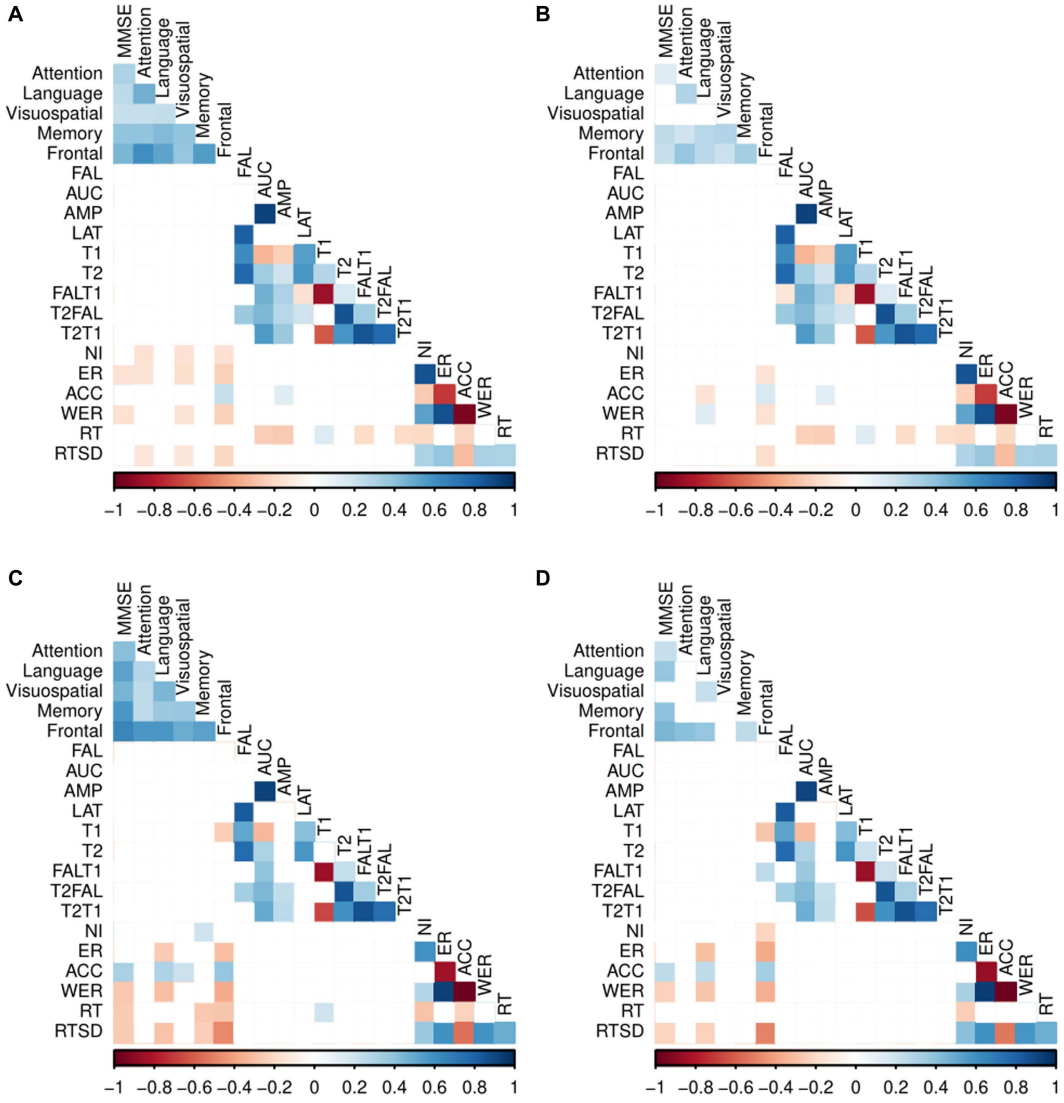

FIGURE 2
Pearson correlation coefficients between the two group's ERP, behavioral measures, and neuropsychological measures. **(A)** Correlation between the ERP, behavioral measures, and neuropsychological tests in CN. **(B)** Partial correlations between the ERP, behavioral measures and neuropsychological tests in CN adjusted for age, sex and years of education. **(C)** Correlation between the ERP, behavioral measures, and neuropsychological tests in MCI. **(D)** Partial correlation between the ERP, behavioral measures and neuropsychological tests in MCI adjusted for age, sex and years of education. Exact partial correlation scores and value of *ps* are presented in Supplementary Tables S2, S3; Blank (white colored cells) represents no significant correlation between the variables.

by recruiting additional neural resources (Scheller et al., 2014), leading to increased mobilization of attentional resources needed for stimulus categorization and context updating in working memory; (Gironell et al., 2005) thus, demonstrating analogous performance to CN individuals. Second, differences in the ERP tasks used or variations among studies that employed similar auditory oddball tasks and discrepancies in the inclusion criteria for the MCI group [owing to the heterogeneity of the MCI patients (Petersen, 2004; Delano-Wood et al., 2009)] may have contributed to the discrepancies in the results of most of the other studies.

Next, we did not observe any statistically significant differences in the P300 latency measures of LAT and FAL between MCI and CN groups. This result suggests that the cognitive decline observed in our MCI group did not influence the duration required for the assessment and categorization of auditory target stimuli within working memory. This agrees with prior studies (Frodl et al., 2002; Papadaniil et al., 2016; Tsolaki et al., 2017; Cintra et al., 2018) that used the auditory oddball task and found no significant differences in the latency between the MCI and CN groups. Evidence has shown that the P300 peak latencies are more accurate in the prodromal phase when patients are typically younger than 70 years (Bennys et al., 2007). This could be a reason for our findings, as the participants in the present study were generally older (mean age, 73.15 years) and it's possible that the increased neural degeneration associated with aging could render oddball tasks excessively demanding on cognitive resources, potentially making it challenging to attain a consistent distinction between patients and cognitively normal individuals (Howe et al., 2014).

In contrast to the behavior of P300 amplitude or latencies, in the novel difference measures, we observed that patients with MCI had lengthened P300 timings for T2T1, FALT1 and T2FAL, and a shorter T1 duration compared to the CN individuals. T2T1, the difference in the zero-crossing time points of the P300 component suggests its duration and can be an index of cognitive processing time. The prolonged FALT1, T2FAL, and T2T1 in patients with MCI compared to the CN individuals indicated that the CN group possessed faster information processing and decision-making abilities than the MCI group. This delay within the MCI group during the task implies a need for extra time to process information, hinting at a possible impairment in cognitive ability (van Deursen et al., 2009) and a possible neocortical dysfunction, which predicts further cognitive decline (Lai et al., 2010). T1 represents the time point extracted from the isolated P300 component using a differential wave approach (Vogel et al., 1998; Luck et al., 2009) where the P300 trace deviates from the baseline (Kiesel et al., 2008). Short T1 duration suggests an early onset of P300, indicating that information processing may commence earlier in the MCI group than in the CN group. Once adjustments were made for demographic measures of sex, age, and education level, T1, FALT1, and T2T1 continued to exhibit noteworthy associations as predictors for MCI. Despite further adjustment for MMSE score, FALT1 and T2T1 remained significant predictors for MCI. This suggests that FALT1 and T2T1 are independent features for MCI screening and can be used in place or as supplements to the MMSE score.

Similarly, we found a significantly larger AUC in patients with MCI than in CN individuals. The AUC quantifies the overall pattern of the P300 waveform, providing insights into the level of cognitive processing across a temporal span (Kim et al., 2013). Reiterating this understanding with respect to the AUC results, suggests that patients with MCI perform more processing and use more effort and attentional resources to complete the same task than CN individuals. MCI refers to a state of cognitive impairment, primarily impacting memory and other cognitive domains, and an increased ERP AUC in patients with MCI compared to healthy individuals could also reflect altered cognitive processing. This suggests that patients with MCI may compensate for cognitive deficits by recruiting additional neural resources or exhibiting hyperactivation in certain brain regions (Scheller et al., 2014). Nonetheless, upon accounting for demographic measures of age, sex, and education level, the significance of the AUC diminished, suggesting that these factors might have exerted considerable influence on the extent of cognitive processing over time within the MCI group.

In the analysis of task-related behavioral measures, patients with MCI demonstrated significantly increased RTSD, NI, ER, and WER compared to CN individuals. Additionally, the MCI group showed reduced accuracy (ACC) in the task. The elevated RTSD in MCI patients indicates an underlying functional integrity that could potentially serve as a differentiator between MCI and CN individuals, suggesting RTSD's sensitivity to cognitive decline, pathological load, and neurological dysfunction (Strauss et al., 2007; McLaughlin et al., 2010). It is likely that RTSD might be more pronounced in the presence of early stage and advanced dementia, further supported by previous studies that investigated response time variability in MCI or AD (Gorus et al., 2008; Burton et al., 2009; Bielak et al., 2010; Phillips et al., 2013). Furthermore, the increased error-related measures (NI, ER, and WER) in MCI patients suggest a decline in the capacity to sustain attention and manage actions while engaging in cognitive task processing (Vecchio and Määttä, 2011). This could imply impairments in the brain's ability to filter irrelevant information and allocate attention efficiently to relevant stimuli, leading to heightened distractibility and difficulty in accurately identifying target stimuli in an ERP task, resulting in more incorrect responses (Lorenzo-López et al., 2016). These findings are consistent with prior studies that reported a higher frequency of errors in MCI patients compared to CN individuals (Cid-Fernández et al., 2014; Zurrón et al., 2018). Notably, the statistical significance of RTSD, NI, ER, WER, and ACC as predictors for MCI remained intact, even after adjusting for age, sex, and education level, indicating their robust predictive power independent of these demographic factors. Additionally, after further adjustment for the MMSE score, the significance of NI, ER, WER, and ACC as predictors for MCI persisted, underscoring their true influence as independent predictors for MCI.

This study also investigated the correlation between neuropsychological measures and both ERP and behavioral measures. We controlled for demographic characteristics to ensure that any correlations observed between neuropsychological measures and both ERP and behavioral measures were not confounded by demographic factors of age, sex, and years of education. Certain correlations seemed to be linked to demographic factors, as their impact diminished upon controlling for these factors. In the MCI group, we found negative and positive correlations between the frontal function and the T1 and FALT1, respectively (Figure 2).

We observed mild-to-moderate correlations between the behavioral measurements and neuropsychological scores. Particularly, we found significant negative correlations between the NI and frontal/executive function in patients with MCI but not in the CN individuals. Furthermore, we observed polarized correlations within the language domain when analyzing both ACC and WER in both groups. In the CN group, we found negative correlations between language and ACC, while in the MCI group, we observed the opposite, with language showing a positive correlation with ACC. In contrast, the CN group displayed positive correlations between language and WER, whereas the MCI group demonstrated the reverse pattern. Moreover, we found significant negative correlations between the frontal and both the ER and WER in both groups. This implies that more errors during a task could indicate reduced executive function, which is a manifestation of age-related cognitive decline. This suggests that neurodegeneration taking place in the brain regions responsible for advanced cognitive functions and task execution advances laterally (Opwonya et al., 2022). Additionally, negative correlations between RTSD and frontal domain scores were observed in both groups. In addition, there were significant negative correlations between MMSE and RTSD and between language and both the ER and RTSD in the MCI group but not in the CN group. This implies that the higher the RTSD, the lower the MMSE and language function scores. These negative correlations suggest a link between onset cognitive decline and lapses in attention (Datta et al., 2007). Lastly, there was a significant positive correlation between the frontal and the ACC in both groups. This indicates that the higher the accuracy, the greater the executive function performance.

The ERP and behavioral measures capable of discriminating MCI independently from neuropsychological screening tests such as the MMSE will be good replacements or complements for the MMSE,

owing to certain constraints of screening tools like the MMSE which include limitations stemming from language or educational differences, the potential for a learning effect, and reduced sensitivity in the early stages of cognitive decline (Scazufca et al., 2009; Carnero-Pardo, 2014). These studies (Chapman et al., 2007, 2011; Cecchi et al., 2015; Stuckenschneider et al., 2020; Doan et al., 2021; Ganapathi et al., 2022) developed diagnostic systems based on EEG/ERP measurements, so some of the relevant features identified in our work can be used to improve MCI or early AD screening models.

This study had several limitations. First, the generalizability of our findings may be limited, as we examined ERP measures only in ethnically Korean participants. Second, the MCI participants were not categorized into amnestic or non-amnestic phenotypes because of their smaller number compared to the healthy participants. This heterogeneity of patients with MCI may have contributed to discrepancies in the results (Petersen, 2004; Delano-Wood et al., 2009). Third, we deployed a rigorous exclusion criterion by eliminating participants who did not have a P300 ERP component onset or late zero-crossing points. This methodological drawback resulted in the exclusion of a significant number of participants. Fourth, because our results were based on a single EEG recording, there's a potential for the cognitive function of patients with MCI to evolve over time, which could involve either a return to normal function or progression to other conditions. Thus, further investigation into the longitudinal changes of ERP measures is desirable to validate our results. It is also necessary to conduct prospective studies aimed at establishing the clinical implications and significance of the ERP measures utilized in the current study.

In conclusion, our study aimed to demonstrate the potential of prefrontal ERP measures from a portable EEG device for distinguishing patients with MCI from CN individuals. We provided a comprehensive description of these ERP measures and examined their relationships with neuropsychological tests commonly used in MCI screening. Our findings showed that patients with MCI demonstrated slower information processing abilities, initiated information processing earlier and exhibited poor task execution than CN. Logistic regression analysis for MCI prediction showed that some ERP and behavioral measures remained statistically significant even after adjusting for demographic characteristics and neuropsychological test scores, providing further evidence that ERP and behavioral measures could serve as valuable complements to neuropsychological tests for screening mild cognitive deficits. In future studies, there are possible areas to explore. First, it is important to validate our findings by broadening the study to encompass a more diverse ethnic population. Furthermore, there is need to establish links between the identified ERP measures and neurodegeneration biomarkers, as well as functional or structural neuroimaging data. Moreover, in the pursuit of enhancing predictive models for MCI, inclusion of these ERP measures, either independently or in combination with other non-invasive techniques like eye-tracking measurements could be considered.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Institutional Review Board of Chonnam National University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JE: Conceptualization, Data curation, Formal analysis, Investigation, Software, Validation, Writing – original draft, Writing – review & editing, Methodology. WK: Data curation, Formal analysis, Writing – review & editing, Methodology, Writing – original draft. KK: Data curation, Methodology, Project administration, Writing – review & editing. KL: Methodology, Writing – review & editing, Data curation. JK: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing, Data curation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1273008/full#supplementary-material

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Predicting mild cognitive impairment among Chinese older adults: a longitudinal study based on long short-term memory networks and machine learning

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Background: Mild cognitive impairment (MCI) is a transitory yet reversible stage of dementia. Systematic, scientific and population-wide early screening system for MCI is lacking. This study aimed to construct prediction models using longitudinal data to identify potential MCI patients and explore its critical features among Chinese older adults.

Methods: A total of 2,128 participants were selected from wave 5–8 of Chinese Longitudinal Healthy Longevity Study. Cognitive function was measured using the Chinese version of Mini-Mental State Examination. Long- short-term memory (LSTM) and three machine learning techniques, including 8 sociodemographic features and 12 health behavior and health status features, were used to predict individual risk of MCI in the next year. Performances of prediction models were evaluated through receiver operating curve and decision curve analysis. The importance of predictors in prediction models were explored using Shapley Additive explanation (SHAP) model.

Results: The area under the curve values of three models were around 0.90 and decision curve analysis indicated that the net benefit of XGboost and Random Forest were approximate when threshold is lower than 0.8. SHAP models showed that age, education, respiratory disease, gastrointestinal ulcer and self-rated health are the five most important predictors of MCI.

Conclusion: This screening method of MCI, combining LSTM and machine learning, successfully predicted the risk of MCI using longitudinal datasets, and enables health care providers to implement early intervention to delay the process from MCI to dementia, reducing the incidence and treatment cost of dementia ultimately.

KEYWORDS

mild cognitive impairment, machine learning (ML), LSTM (long short-term memory networks), prediction model, China

1. Introduction

With an increasing older adult population worldwide, geriatric health concerns cannot be ignored. Aging results in declining physical and cognitive functions, leading to a high risk of disability and death (Klimova et al., 2017). Distinguishing between pathological and normal cognitive decline, generally referred to as dementia or cognitive impairment, remains challenging. As an inevitable human phenomenon, aging is a significant factor in deteriorating cognitive function. With a global increase in life expectancy, older adults have an increased likelihood of developing dementia and cognitive impairment. The World Health Organization (WHO) stated that >55 million older adults had a diagnosis of dementia in 2021, with >139 million older adults estimated to be diagnosed with dementia in 2050 worldwide. In 2019, the annual cost of dementia-related treatment exceeded US $1.3 trillion (World Health Organization, 2021). China has the greatest population of people with dementia, comprising 25% of the global population. Aggregate expenditure on dementia in China reached US $195 billion in 2019 (Jia et al., 2020b; Mattap et al., 2022).

With no reversal therapies available, prevention of dementia remains a priority. Mild cognitive impairment (MCI), a risk factor for dementia, is considered a transitional stage between normal cognitive function and dementia, where there is objective cognitive decline but with a capacity to live independently. However, approximately 10–20% of older adults aged ≥65 years with MCI are diagnosed with dementia after 1 year (Langa and Levine, 2014). Delaying the progression of MCI to dementia is currently the most effective approach, as diverse treatments for MCI have proven to be effective and less costly (Langa and Levine, 2014; Anderson, 2019; Huang et al., 2022), with early identification and intervention in high-risk groups shown to prevent dementia onset in 40% of such cases.

Currently, screening techniques and questionnaires for MCI are limited. On account of the fact that neurodegenerative disease starts to develop many years before the symptoms are observed, while applying MCI screening to the population with normal cognitive function, imaging examinations, and fluid biomarkers can detect the neurodegenerative and pathological changes most accurately. Imaging techniques, such as magnetic resonance imaging (MRI), positron emission computed tomography (PET), and single photon emission computed tomography (SPECT), are capable of showing the tiny changes in brain structure, blood flow, metabolism, and neurotransmitters in patients with MCI. Nevertheless, due to the rarity and inaccessibility of these techniques for the general public, they cannot be used as a common screening tool for MCI (Dunne et al., 2021), with limited coverage in terms of MCI questionnaires [Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA)] that generally require a significant investment in manpower and their training. Therefore, an effective, systematic, and convenient MCI screening method to identify high-risk older adults in the general population is urgently needed. Effective screening could be conducive to targeted interventions for those at high risk of MCI. One study reported significant changes through implementing appropriate early intervention for potential patients in England, namely, an 8.5% decrease in the incidence of dementia and a reduction in dementia-related expenditure of approximately $180 million (Mukadam et al., 2020). Owing to the irreversible nature of dementia, treatment for patients with dementia places considerable financial and psychological pressure on families and caregivers (Chiao et al., 2015). Given the significant negative effects of dementia, it is critical to identify high-risk individuals at an early stage.

Some studies have adopted multiple perspectives to identify risk factors in people with MCI. A national cross-sectional study in China that comprised 46,011 older adults showed that MCI was associated with sociodemographic characteristics, including age, sex, parental history, education level, residence, and marital status (Jia et al., 2020a). Several cohort studies have shown a causal relationship between health status and behaviors that contribute to MCI. Chronic diseases, such as hypertension, stroke, and diabetes as well as harmful lifestyle behaviors, such as smoking and alcohol consumption, significantly increase the risk of MCI, while regular physical exercise, tea/coffee consumption, and playing Mahjong can prevent cognitive impairment (Kivipelto et al., 2018; Kakutani et al., 2019; Zhang et al., 2020, 2022). Owing to limitations in conventional regression methods in terms of collinearity potentially affecting predictors, some studies have applied machine learning based on imaging data or biomarkers to further determine whether an individual has MCI and to explore key features of MCI (Mirzaei et al., 2016; Wang et al., 2022; Alamro et al., 2023). However, most machine learning studies have only used single-wave panel data, and neurodegenerative disorders have a natural history of progression, thus ignoring the dynamic and longitudinal nature of these diseases, such that early identification and intervention could be sufficient.

Consequently, to address those deficiencies in previous studies, we used long short-term memory networks (LSTMs) in this study to capture the interdependence of predictors in longitudinal data. In combination with machine learning, it is possible to generate a model that can forecast the likelihood of conversion to MCI after several years. This model facilitates convenient and efficient screening for MCI and identification of risk groups for targeted intervention procedures. LSTMs are a form of recurrent neural network that address long-term dependencies and gaps between significant events in sequential data. Compared to traditional times series analysis like the Autoregressive Integrated Moving Average model (ARIMA), LSTMs models generally generate better outcomes in nonlinear and volatile time series data (Lou et al., 2022; Liu X. D. et al., 2023) despite the complexity of model interpretations and the long duration of model training. LSTMs were originally introduced into medically relevant applications to forecast the incidence and prevalence of diseases with considerable success during the COVID-19 pandemic (Borges and Nascimento, 2022; Gautam, 2022; Liu X. D. et al., 2023). Simultaneously, several studies have shown the feasibility of using LSTMs prediction in relation to individual characteristics in machine learning techniques to predict depression in older adults through applying longitudinal sequence data (Su et al., 2020; Lin et al., 2022).

No previous studies have used multiple sequence data waves to predict potential MCI in older Chinese adults. On the basis of the traits that LSTMs could effectively capture the temporal dependencies and trends of individual characters in longitudinal data from multiple data waves, and the capability that machine learning could extract important variables with significant trends related to MCI, therefore, this study assumes that the combination of LSTMs and machine learning could successfully identify the older adults at high risk for MCI and indicate instructions of implementing early interventions to prevent dementia.

2. Materials and methods

2.1. Data source and samples

The data used in this study were Waves 5–8 (2008, 2011, 2014, 2018) of the Chinese Longitudinal Healthy Longevity Survey (CLHLS), a secondary data series collected by the Center for Healthy Aging and Development and the China Mainland Information Group, Peking University, since 1998 (Center for Healthy Aging and Development Studies. The Chinese Longitudinal Healthy Longevity Survey (CLHLS)-Longitudinal Data, 1998–2018). Respondents in the CLHLS among the selected waves were randomly sampled from approximately half of the counties and city districts of China's 23 mainland provinces. The CLHLS questionnaire includes a wide range of instruments, such as the Mini-Mental State Examination (MMSE), the Center for Epidemiologic Studies Depression Scale, and the Self-Rating Anxiety Scale. Previous studies have confirmed that the design of questionnaire and quality of datasets are excellent (Gu, 2008; Zeng, 2012).

The Wave 5 questionnaire of the CLHLS was used to obtain baseline characteristics of the older adults, including 2,334 home-based interviewees who continuously responded until Wave 8. After excluding respondents lacking answers or records for cognition measurement, that is, the MMSE questionnaire in this study, and respondents who had been diagnosed with dementia in Waves 5–7 based on the their MMSE scores, 2,128 eligible participants were included in the ultimate data preprocessing and statistical analysis.

2.2. Assessment of MCI and outcome variables

The MMSE has been widely applied to screen for cognitive dysfunction among older adults. In the CLHLS questionnaires, the MMSE was modified into a Chinese version, including 24 items within six dimensions: five items for orientation (five points in total), one for naming (seven points in total, one point for naming each kind of food), three for registration (three points in total), five for attention and calculation (five points in total), three for recall (three points in total), and seven for language (seven points in total). The final cognitive function score was the sum of the scores of the six dimensions, with a possible total of 30 points.

In this study, due to the age distribution of participants (age range, 70–80 years, 31.72%; age ≥ 80 years, 68.28%), MCI was defined as an MMSE score < 18 in this study (patients with MCI = 1; normal participants = 0) (An and Liu, 2016; Gao et al., 2017).

2.3. Predictors

We considered three levels of individual characteristics to fit the LSTMs and machine learning models from Waves 5–8, namely (Supplementary Table 1), (i) sociodemographic characteristics, such as age, sex, geographical area, education level, marital status, residence, income level, and living status; (ii) health behavior factors, including active smoking, alcohol consumption, exercise, self-rated health [SRH], and sleep quality; and (iii) health status factors, such as a history of hypertension, diabetes, cardiopathy, stroke, chronic respiratory disease, cancer, or gastrointestinal ulcer.

2.4. Processing of missing values

In order to reduce the probability of bias during the imputation procedure, variables with >20% information were abandoned to guarantee good performance (Jakobsen et al., 2017). The ultimate predictors included from CLHLS Waves 5–7 were imputed utilizing a MICE package in R studio 4.2.3 software, applying multivariate iterative random forest ("RF" method) imputation algorithms with five iterations to produce datasets with the least variance compared with datasets being imputed before.

2.5. Statistical analysis

Statistical analyses were performed using Keras package (version 2.6.0) software for deep learning and Scikit-Learn package (version 1.1.2) for machine learning in Python (version 3.9) software. We randomly partitioned the data into three disjoint sets: training, testing, and validation, with proportions of 60, 20, and 20%, respectively. Details about hyperparameters of LSTMs and parameters of three machine learning models were listed in Supplementary Tables 2, 3.

2.5.1. The multivariate LSTMs models

Machine learning techniques are generally applied to panel data from a cross-sectional perspective, but are not able to capture features with time sensitivity. To forecast the development of predictors and explore potential outcomes, recurrent neural networks (RNNs) are used to capture the inputs of predictors from specific time periods and transfer information to subsequent time periods through combining the interdependence among predictors. However, traditional RNNs cannot cope with gradient vanishing and gradient exploding in long-term dependency issues owing to their simple neuron structure, whereas LSTMs can successfully handle these disadvantages in RNNs through the use of "forget gate" and the sigmoid function in each LSTMs unit. The LSTMs model has been validated as a powerful and precise model for forecasting time-series data in longitudinal studies. As shown in Figure 1, time-sensitivity predictors in CLHLS Waves 5–6 were randomly split such that 70% of the samples were used to train the LSTMs model to forecast the values of the predictors in Wave 7, and the remaining 30% of the samples were used to test our LSTMs model. The model was then fitted to CLHLS Waves 6–7 to forecast predictors in Wave 8, combining invariable features such as age, sex, education level, and geographical area that did not need to be predicted over time to constitute a new dataset.

2.5.2. Synthetic minority oversampling technique

Imbalanced data were a challenge for machine learning as the proportion of older adults with MCI was only 16.92% in this study. A common issue is that models tend to be biased toward the majority class, resulting in suboptimal performance. To address this problem, we applied the synthetic minority oversampling technique (SMOTE). SMOTE creates synthetic samples from the existing minority class

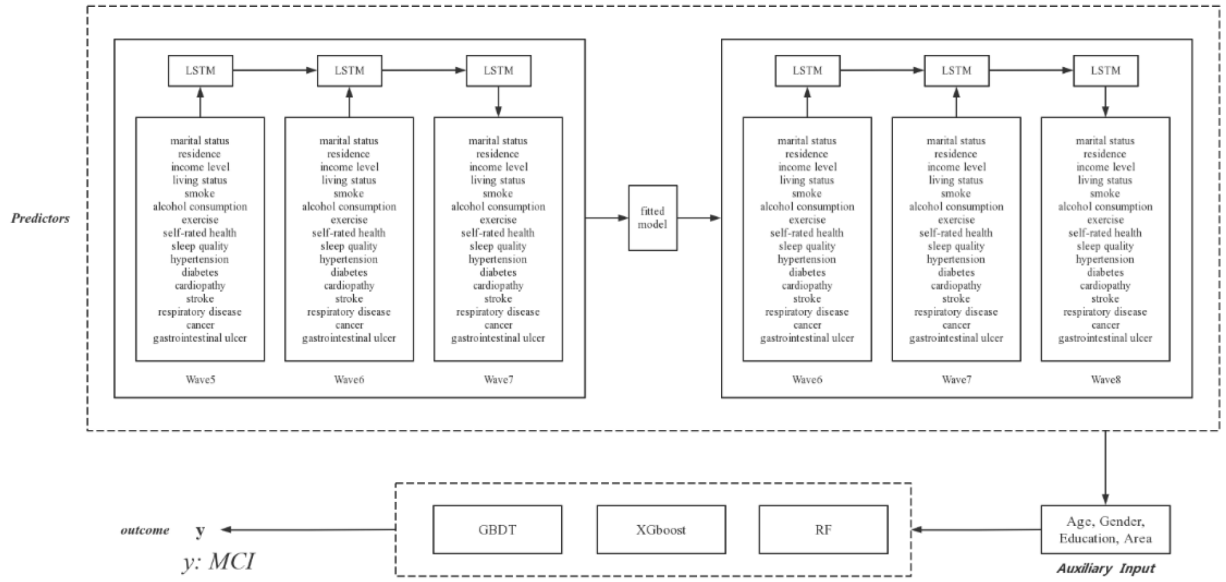

FIGURE 1
The predictors of the LSTMs model for older adults with MCI from CLHLS wave 5 to wave 8.

through interpolation from its nearest neighbors, thereby increasing the number of minority samples in the datasets.

2.5.3. Gradient boosting decision tree (GBDT)

The GBDT is an ensemble machine learning approach for classification and regression based on the CART algorithm. The GBDT improves prediction accuracy through gradually improving estimation using a boosting method. In addition, the GBDT utilizes a nonlinear regression procedure to improve tree accuracy. A series of decision trees was created, which produced a set of weak prediction models and generated loss functions. The final classification model was the weighted sum of all weak prediction models through each round of training.

2.5.4. Extreme gradient boosting

XGBoost is a scalable and efficient implementation of gradient boosting, a popular machine learning technique that combines weak learners (typically decision trees) into a strong ensemble model. XGBoost offers several advantages over other gradient boosting frameworks, such as parallelization, regularization, and missing value handling. In addition, XGBoost can handle encoded categorical variables.

2.5.5. Random Forest algorithm

Random Forest (RF) is a machine learning technique that builds an ensemble of decision trees and aggregates their predictions. RF can handle both classification and regression problems, as well as categorical and numerical features. It also provides measures of feature importance and variable selection. RF introduces randomness in two ways: by bootstrapping the training data for each tree, and by selecting a random subset of features for each split. To analyze the ultimate result, each decision tree was accessed in the final decision to obtain a reliable result. Based on majority selection for all decision trees, each sample was classified into two classes.

2.6. Model assessment

To assess the outcomes of each machine learning model, we calculated the area under the receiver operating characteristic curve (ROC; AUC) and sensitivity (equation 1), specificity (equation 2), accuracy (equation 3), and balanced accuracy (equation 4). True positives and true negatives indicate older adults who were correctly identified as patients with MCI or the normal cognitive function group, respectively; false positives and false negatives indicate older adults who were inaccurately identified as patients with MCI or the normal cognitive function group, respectively. Each machine learning model could predict the probability of cognitive impairment in older adults. If the probability of an individual was greater than the threshold, then older adults were regarded as patients with MCI, and vice versa. To further evaluate and understand the prediction models, we calculated the net benefit of the machine learning models using decision curve analysis (DCA). This method indicated the proportion of patients who received a correct diagnosis minus the percentage of patients who were misdiagnosed under different threshold values.

$$\text{Sensitivity} = \frac{True\ Positive}{True\ Positive + False\ Negative} \quad (1)$$

$$\text{Specificity} = \frac{True\ Negative}{True\ Negative + False\ Positive} \quad (2)$$

$$\text{Accuracy} = \frac{True\ Negative + True\ Positive}{True\ Negative + True\ Positive + False\ Negative + False\ Positive} \quad (3)$$

$$\text{Balance accuracy} = \frac{2 * Specificity * Sensitivity}{Specificity + Sensitivity} \quad (4)$$

2.7. SHapley Addictive explanation models

For ensemble machine learning models applied in this study, the processes of their predictions are generally opaque. Unlike the traditional statistical models, it is difficult for people to understand their working mechanisms and certain positive or negative contributions of predictors to the outcomes. To address this problem, post-hoc interpretations of the model output should be proposed for machine learning studies. Based on the individual and joint contributions among players, Shapley values are a way of fairly allocating the payoff of a game in cooperative game theory, which was introduced into machine learning techniques to explain the attribution of each input feature toward the outcome. SHapley Addictive explanation models (SHAP) is able to be used to provide various types of visualized explanations for machine learning models, including global feature importance, feature interaction, and feature dependence. SHAP was performed in Python using shap package (Version 0.42.1) in this study and was used to visualize the importance of each predictor and the association between predictors and MCI quantitatively (Ekanayake et al., 2022).

3. Results

As presented in Table 1, 2,146 older adults in the baseline CLHLS wave of 2008 participated in this study (older adults with MCI, 17.29%). The median age of patients with MCI was 92 years (range, 86–97 years), which was 10 years older than that of older adults with normal cognitive function (82 years, range, 78–88 years). The proportions of older adult males (46.62%) and females (53.38%) were relatively equal, with approximately two-thirds of the participants with MCI being female. Of older adults with MCI, 71.67% were illiterate, and 75.28% were single older adults. Older adults with low or very low-income levels comprised the majority of participants with MCI. The percentage of individuals living alone was higher among those with normal cognitive function than among those with MCI. Only 13.61% of older adults regularly exercised among those with MCI. People with normal cognitive function generally rated their health and sleep quality as better than those with MCI. A higher percentage of older adults in the normal group had a diagnosis of hypertension. A total of 14.17% of older adults with a history of stroke had poorer MMSE scores.

For further descriptive analysis, odds ratios (ORs) for each predictor were evaluated using univariate and multivariate logistic regression analyses. Among sociodemographic variables, the analysis showed that age was a risk factor for MCI (adjusted OR [aOR] 1.123, 95% CI 1.103–1.143). Compared with literate older adults, illiterate older adults had a higher risk of developing MCI (aOR 1.641, 95% CI 1.199–2.247). Older adults with very low income levels had a higher risk of MCI than their wealthier counterparts (aOR 5.673, 95% CI 1.067–30.180). Among health behavior/health status variables, older adults who did not regularly exercise had a high risk of MCI (aOR 2.277, 95% CI 1.596–3.248). Older adults with poor or very poor self-rated health had a higher risk of MCI compared with those who had very good self-rated health (aOR 2.069, 95% CI 1.145–3.740 and aOR 3.874, 95% CI 1.527–9.826, respectively). Moreover, older adults with no history of stroke had a reduced risk of MCI (aOR 0.515, 95% CI 0.347–0.776).

LSTMs model performance is illustrated in Figure 2. The mean squared errors of both the training and validation sets were generally equal (approximately 0.08) after 30 rounds of training, and the inflection points of both sets were close, indicating that the LSTMs model could be utilized to forecast characteristics of older adults three years later. Table 2 and Figure 3A shows the ROC curves and AUC values of the three machine learning models in the testing set (GBDT 0.902, 95% CI 0.879–0.925; XGBoost 0.928, 95% CI 0.908–0.948; and RF 0.938, 95% CI 0.919–0.956). Table 3 and Figure 3B shows the performance of the three models in the validation set. The AUC values of all three machine learning models in the test sets were >0.9. The three machine learning models produced equal results in the validation sets, indicating that they were robust models for classifying patients with MCI and healthy people. XGBoost had the highest and most balanced accuracy and the second-highest sensitivity using 0.3 as a threshold (Table 2), and RF produced the highest sensitivity under this condition. The DCA results (Figure 4) showed that the XGboost and RF models were close, within the range of 0–0.8, and the net benefit values were higher than 0.4 using 0.3 as a threshold.

Figure 5 illustrates the ranking of feature importance in MCI prediction. Age, education, and chronic respiratory disease were the first, second, and third-most important characteristics of older adults when predicting MCI in all three models, respectively. Younger literate older adults with no history of chronic respiratory disease had a lower probability of developing MCI. Self-rated health was also an important feature that presented a direct trend in MCI output. All three SHAP models indicated that having a gastrointestinal ulcer was one of the most important features for predicting potential MCI in patients; however, it did not show a clear tendency in relation to MCI progression.

4. Discussion

To our knowledge, this study is the first to forecast cognitive impairment in older Chinese adults using an LSTMs model and machine learning based on CLHLS Waves 5–8, with predictions that included sociodemographic health behaviors and health status characteristics. In total, 2,128 older adults were included in this study. Our LSTMs model produced robust results in the validation set; thus, it was capable of forecasting the feature values of older adults in the next wave using the SMOTE algorithm and three machine learning approaches that performed well in predicting MCI. Figure 6 depicts the conceptual framework discussed, summarizes the accuracy of the prediction models, presents the results, and presents multiple perspective values.

Regarding model precision, this prediction method combining LSTMs and machine learning can be successfully applied to longitudinal data to capture temporal information, thus improving the accuracy of MCI predictions in older adults (Chae et al., 2018; Wang

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TABLE 1 Predicted characteristics in 2018 and odds ratio of older adults with MCI.

Predictors		All N (%)	MCI N (%)	Normal N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Overall		2,128	360 (16.92)	1,768 (83.08)		
Sociodemographic variables						
Age		83 (78–90)	92 (86–97)	82 (78–88)	**1.136 (1.119, 1.154)*****	**1.123 (1.103, 1.143)*****
Gender	Male	992 (46.62)	117 (32.50)	875 (49.49)	Ref	Ref
	Female	1,136 (53.38)	243 (67.50)	893 (50.51)	**2.035 (1.602, 2.586)*****	1.331 (0.956, 1.854)
Geographical area	Eastern	959 (45.07)	155 (43.06)	804 (45.48)	Ref	Ref
	Central	471 (22.13)	82 (22.78)	389 (22.00)	1.093 (0.815, 1.467)	1.008 (0.712, 1.425)
	Northeastern	87 (4.09)	15 (4.17)	72 (4.07)	1.081 (0.604, 1.934)	1.749 (0.877, 3.489)
	Northwestern	611 (28.71)	108 (30.00)	503 (28.45)	1.114 (0.850, 1.459)	0.843 (0.611, 1.164)
Education	Literate	1,105 (51.93)	102 (28.33)	1,003 (56.73)	Ref	Ref
	Illiterate	1,023 (48.07)	258 (71.67)	765 (43.27)	**3.316 (2.588, 4.249)*****	**1.641 (1.199, 2.247)****
Marital status	Married	933 (43.84)	89 (24.72)	844 (47.74)	Ref	Ref
	Single	1,195 (56.16)	271 (75.28)	924 (52.26)	**2.781 (2.151, 3.596)*****	1.292 (0.931, 1.794)
Residence	City	352 (16.54)	51 (14.17)	301 (17.02)	Ref	Ref
	Town/Rural	1776 (83.46)	309 (85.83)	1,467 (82.98)	1.243 (0.902, 1.714)	0.967 (0.651, 1.436)
Income level	Very high	52 (2.44)	3 (0.83)	49 (2.77)	Ref	Ref
	High	396 (18.61)	41 (11.39)	355 (20.08)	1.886 (0.563, 6.324)	2.306 (0.594, 8.949)
	Fair	1,467 (68.94)	267 (74.17)	1,200 (67.87)	**3.634 (1.124, 11.747)***	3.426 (0.923, 12.725)
	Low	193 (9.07)	42 (11.67)	151 (8.54)	**4.543 (1.348, 15.309)***	3.671 (0.939, 14.350)
	Very low	20 (0.94)	7 (1.94)	13 (0.74)	**8.795 (1.993, 38.802)****	**5.674 (1.067, 30.180)***
Living	With family	1732 (81.39)	309 (85.83)	1,423 (80.49)	Ref	Ref
	Alone	396 (18.61)	51 (14.17)	345 (19.51)	**0.681 (0.495, 0.936)***	**0.589 (0.405, 0.857)****
Health behavior/health status variables						
Smoking	Yes	345 (16.21)	36 (10.00)	309 (17.48)	Ref	Ref
	No	1783 (83.79)	324 (90.00)	1,459 (82.52)	**1.906 (1.322, 2.747)*****	1.086 (0.688, 1.712)
Alcohol consumption	Yes	327 (15.37)	32 (8.89)	295 (16.69)	Ref	Ref
	No	1801 (84.63)	328 (91.11)	1,473 (83.31)	**2.053 (1.398, 3.014)*****	1.390 (0.866, 2.231)
Exercising	Yes	711 (33.41)	49 (13.61)	662 (37.44)	Ref	Ref
	No	1,417 (66.59)	311 (86.39)	1,106 (62.56)	**3.799 (2.769, 5.212)*****	**2.277 (1.596, 3.248)*****
SRH	Very good	258 (12.12)	28 (7.78)	230 (13.01)	Ref	Ref
	Good	744 (34.96)	99 (27.50)	645 (36.48)	1.261 (0.807, 1.969)	1.104 (0.653, 1.868)
	Fair	824 (38.72)	155 (43.06)	669 (37.84)	**1.903 (1.239, 2.924)****	1.562 (0.928, 2.631)
	Bad	262 (12.31)	64 (17.78)	198 (11.20)	**2.655 (1.638, 4.304)*****	**2.069 (1.145, 3.740)***

(Continued)

TABLE 1 (Continued)

Predictors		All N (%)	MCI N (%)	Normal N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
	Very bad	40 (1.88)	14 (3.89)	26 (1.47)	**4.423 (2.071, 9.448)*****	**3.874 (1.527, 9.826)****
Sleep quality	Very good	364 (17.11)	44 (12.22)	320 (18.10)	Ref	Ref
	Good	725 (34.07)	121 (33.61)	604 (34.16)	**1.457 (1.006, 2.111)***	1.309 (0.847, 2.024)
	Fair	704 (33.08)	133 (36.94)	571 (32.30)	**1.694 (1.173, 2.446)****	1.084 (0.698, 1.683)
	Poor	285 (13.39)	47 (13.06)	238 (13.46)	1.436 (0.921, 2.239)	1.012 (0.598, 1.714)
	Very poor	50 (2.35)	15 (4.17)	35 (1.98)	**3.117 (1.576, 6.165)*****	**2.442 (1.083, 5.506)***
Hypertension	Yes	902 (42.39)	122 (33.89)	780 (44.12)	Ref	Ref
	No	1,226 (57.61)	238 (66.11)	988 (55.88)	**1.540 (1.214, 1.953)*****	1.278 (0.959, 1.703)
Diabetes	Yes	177 (8.32)	21 (5.83)	156 (8.82)	Ref	Ref
	No	1951 (91.68)	339 (94.17)	1,612 (91.18)	1.562 (0.976, 2.501)	1.091 (0.630, 1.890)
Cardiopathy	Yes	360 (16.92)	42 (11.67)	318 (17.99)	Ref	Ref
	No	1768 (83.08)	318 (88.33)	1,450 (82.01)	**1.660 (1.177, 2.342)****	**1.565 (1.035, 2.368)***
Stroke	Yes	253 (11.89)	51 (14.17)	202 (11.43)	Ref	Ref
	No	1875 (88.11)	309 (85.83)	1,566 (88.58)	0.782 (0.562, 1.088)	**0.519 (0.347, 0.776)*****
Respiratory disease	Yes	264 (12.41)	53 (14.72)	211 (11.93)	Ref	Ref
	No	1,864 (87.59)	307 (85.28)	1,557 (88.07)	0.785 (0.567, 1.087)	0.716 (0.487, 1.054)
Cancer	Yes	15 (0.71)	2 (0.56)	13 (0.74)	Ref	Ref
	No	2,113 (99.30)	358 (99.44)	1755 (99.27)	1.326 (0.298, 5.901)	0.673 (0.120, 3.783)
Gastrointestinal ulcer	Yes	85 (3.99)	9 (2.50)	76 (4.30)	Ref	Ref
	No	2043 (96.01)	351 (97.50)	1,692 (95.70)	1.752 (0.870, 3.529)	**3.006 (1.314, 6.878)****

Bold font indicates statistical significance (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

et al., 2019; Su et al., 2020). To date, most studies have used LSTMs to forecast the prevalence and incidence rates or temporal trends in medical-related applications (Borges and Nascimento, 2022; Gautam, 2022; Liu X. D. et al., 2023). In addition, LSTMs have shown excellent performance when predicting high-dimensional data such as air and water pollution (Kim et al., 2022; Middya and Roy, 2022). Thus, building on previous LSTMs applications, some studies have used LSTMs to detect early health deterioration in individual clinical data (da Silva et al., 2021). Furthermore, the utilization of LSTMs to forecast individual features, followed by machine learning to construct predictive models, has been shown to be useful in disease prediction; for example, in the prediction of depression (Su et al., 2020; Lin et al., 2022) and in glaucoma assessment (Dixit et al., 2021). To date, no studies have utilized LSTMs and machine learning to establish a prediction model for MCI and explore its risk factors. Compared to the previous two prediction models using CLHLS, this study revealed relatively high accuracy and robustness with the AUCs of 0.902 to 0.938 for the test set and high sensitivity and specificity, and from 0.890 to 0.914 for the validation test. One longitudinal study proposed to use The Growth Mixed Model (GMM) and machine learning combination to forecast the MMSE trajectory of older adults. Due to the time effect bias for the application of constant baseline individual character in forecasting models, the AUCs of their models ranged from 0.51 to 0.66 in eight machine learning techniques (Wu et al., 2022). The other study utilized sociodemographic and life behavioral features of Chinese older adults to construct prediction models, achieving an accuracy of 0.7540 and the AUC of 0.8269 at maximum (Wang et al., 2022). To conclude, the outcomes of LSTMs and machine learning framework demonstrates the feasibility and effectiveness of the study hypothesis.

Three decision tree-based models (GBDT, XGBoost, and RF) were used with SHAP to interpret individual predictions. Age, education level, chronic respiratory disease, gastrointestinal ulcers, and self-rated health were identified as the five most important predictors in this study. Age and education level have been reported in previous studies to be important predictors of MCI (Chun et al., 2022; Liu H. et al., 2023). Physiological decline in cognitive function is inevitable as people age (Langa and Levine, 2014) and age is a major predictor of MCI. Lower educational levels have been shown to be significantly associated with cognitive decline, and education in later life may also contribute to improved cognitive function (Peeters et al., 2020). According to our results, older adults with a

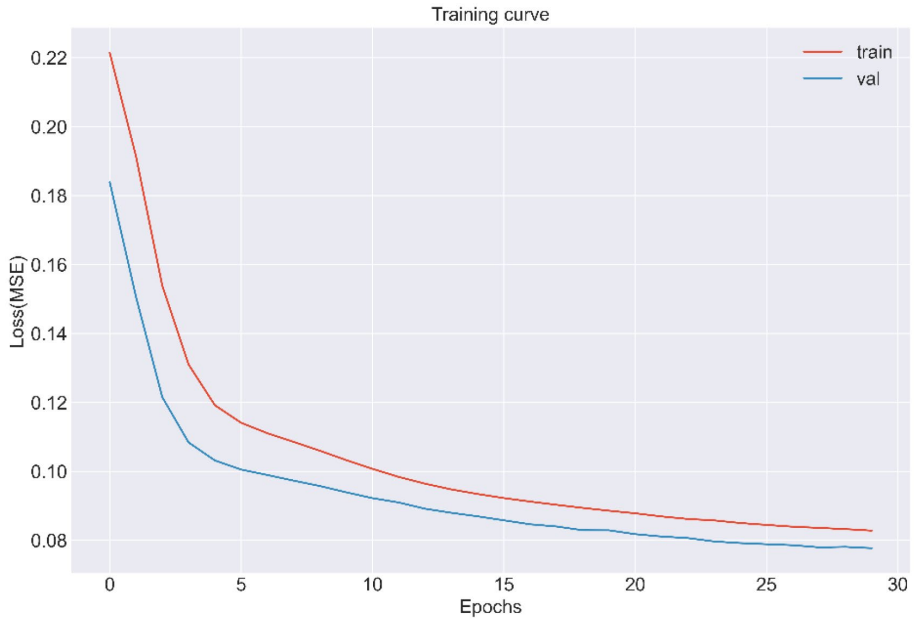

FIGURE 2
The training and validation curve of LSTMs from CLHLS wave5 to wave 7 (MSE, Mean squared error).

formal education performed well in terms of MMSE scores. The other three features were not found to be strong predictors in other studies; however, they have all been shown to be closely associated with MCI. Older adults with no history of chronic respiratory disease are less likely to develop MCI. Common chronic respiratory diseases, such as chronic obstructive pulmonary disease and obstructive sleep apnea-hypopnea syndrome, lead to perennial hypoxia and hypercarbia (Olaithe et al., 2018), causing damage to brain functions, including language, execution, and attention. Ultimately, cognitive function continues to decline under these pathological conditions. Gastrointestinal ulcers did not show a clear trend in Figure 5, whereas changes in metabolic substances in the gastrointestinal tract under pathological conditions are reported to impair brain function via the gut-brain axis (Zeng et al., 2022). Moreover, a healthy gastrointestinal tract can guard against cognitive decline and mitigate neuroinflammation (Xiang et al., 2022); hence, this result needs to be verified in another study. The SHAP analysis illustrated a positive correlation between self-rated health and MCI; that is, good self-rated health may represent good cognitive function and vice versa, which is consistent with previous cohort studies (Bond et al., 2006).

MCI prediction models could provide references for clinical practice and bring broad benefits to society; however, they still need adjustment and practice to meet the standards for real-world application. When applied for MCI screening, the most appropriate prediction model requires striking a balance between sensitivity and specificity to achieve high precision and cost-effectiveness. Consequently, it is critical to determine the threshold for identifying patients with MCI and conducting further interventions. As shown in Figure 4, the XGBoost prediction model had the greatest net benefit and balanced accuracy when the threshold probability was <0.6. When the threshold probability was 0.3, RF had the highest sensitivity and identifies most patients with MCI with relatively low cost-effectiveness owing to the proportion of misdiagnoses. Determining the ultimate thresholds require constant evaluation and collaboration between governments and healthcare providers to obtain optimal clinical, economic, and social outcomes.

Ongoing application of this approach and cooperation can be viewed from three perspectives: the nation (macro), healthcare providers (medium), and individuals (micro). As a macro-regulator, the government should enhance the utilization of big data and incorporate prediction models into various healthcare provider and public Internet platforms. This screening method could promote population health and reduce the disease burden. Various healthcare providers can select different thresholds in terms of specific medical conditions and testing technologies and change their criteria according to local prevalence and incidence. As psychiatric hospitals are generally equipped with adequate medical resources, the threshold for machine learning models could be relatively low to achieve suitable resource allocation. Once MCI predictive models become more sophisticated with continuous training and with more individual information available, such as risk genes or biomarkers, the threshold can be adjusted to pursue relatively high cost-effectiveness. In terms of the micro perspective, the general public could benefit through becoming more aware of their own and their families' risk of MCI through the application of this prediction model, avoiding additional examinations and ameliorating individual MCI risk.

This study contributes to the prevention of MCI and dementia. First, the combination of an LSTMs model and machine learning could precisely identify patients with MCI and their critical features several years earlier. Age, literacy level, chronic respiratory disease, gastrointestinal ulcers, and self-rated health were good predictors of MCI. Second, MCI prediction models have substantial clinical,

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TABLE 2 Performance of machine learning models in test set of predicting MCI among Chinese older adults.

Model	AUC	Thresholds	TP/TN/FP/FN	Sensitivity (%)	Specificity (%)	Accuracy (%)	Balanced accuracy (%)
GBDT	0.902 (0.879, 0.925)	0.3	335/255/90/27	92.54 (89.84, 95.25)	73.91 (69.28, 78.55)	83.45 (80.71, 86.19)	85.13 (82.65, 87.62)
		0.4	325/270/75/37	89.78 (86.66, 92.90)	78.26 (73.91, 82.61)	84.16 (81.47, 86.85)	85.30 (82.79, 87.82)
		0.5	313/278/67/49	86.46 (82.94, 89.99)	80.58 (76.41, 84.75)	83.59 (80.86, 86.32)	84.37 (81.75, 86.98)
		0.6	303/286/59/59	83.70 (79.90, 87.51)	82.90 (78.93, 86.87)	83.31 (80.56, 86.06)	83.70 (81.01, 86.39)
		0.7	287/296/49/75	79.28 (75.11, 83.46)	85.80 (82.11, 89.48)	82.46 (79.66, 85.26)	82.23 (79.40, 85.07)
XGboost	0.928 (0.908, 0.948)	0.3	336/267/78/26	92.82 (90.16, 95.48)	77.39 (72.98, 81.81)	85.29 (82.68, 87.90)	86.60 (84.20, 88.99)
		0.4	332/277/68/30	91.71 (88.87, 94.55)	80.29 (76.09, 84.49)	86.14 (83.59, 88.69)	87.14 (84.76, 89.52)
		0.5	329/286/59/33	90.88 (87.92, 93.85)	82.90 (78.93, 86.87)	86.99 (84.51, 89.47)	87.73 (85.39, 90.08)
		0.6	321/292/53/41	88.67 (85.41, 91.94)	84.64 (80.83, 88.44)	86.70 (84.20, 89.21)	87.23 (84.82, 89.64)
		0.7	315/301/44/47	87.02 (83.55, 90.48)	87.25 (83.73, 90.77)	87.13 (84.66, 89.60)	87.38 (84.95, 89.80)
RF	0.938 (0.919, 0.956)	0.3	349/212/133/13	96.41 (94.49, 98.33)	61.45 (56.31, 66.59)	79.35 (76.37, 82.33)	82.70 (80.15, 85.25)
		0.4	340/260/85/22	93.92 (91.46, 96.38)	75.36 (70.82, 79.91)	84.87 (82.22, 87.51)	86.40 (84.01, 88.80)
		0.5	317/292/53/45	87.57 (84.17, 90.97)	84.64 (80.83, 88.44)	86.14 (83.59, 88.69)	86.61 (84.15, 89.08)
		0.6	300/313/32/62	82.87 (78.99, 86.75)	90.72 (87.66, 93.79)	86.70 (84.20, 89.21)	86.46 (83.91, 89.00)
		0.7	247/327/18/115	68.23 (63.44, 73.03)	94.78 (92.44, 97.13)	81.19 (78.31, 84.07)	78.79 (75.59, 81.99)

GBDT, Gradient boosting decision tree; XGboost, Extreme gradient boosting; RF, Random Forest; AUC, Area Under the Curve; TP, True Positives; TN, True Negatives; FP, False Positives; FN, False Negatives.

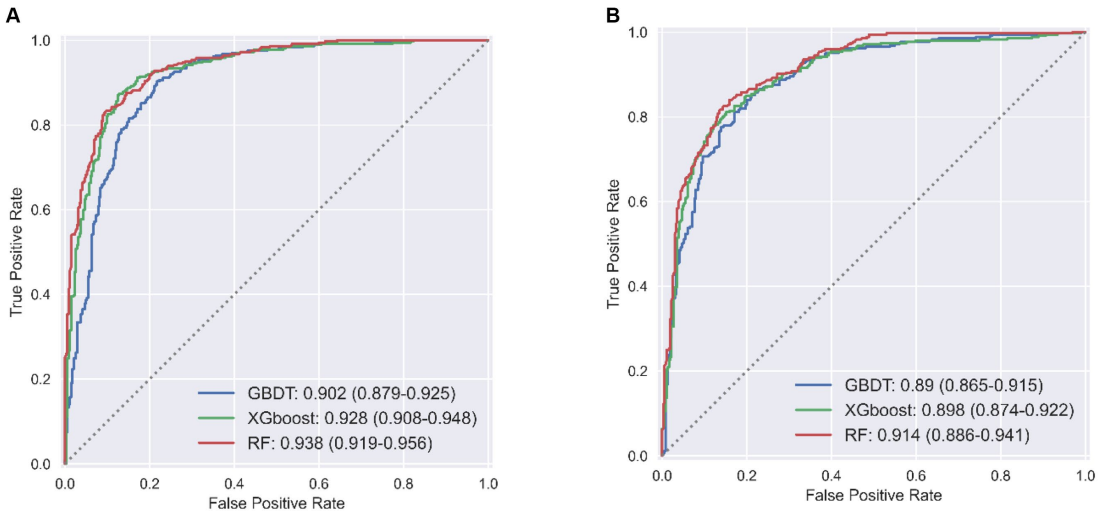

FIGURE 3
Performance of machine learning models in test set **(A)** and validation set **(B)**.

TABLE 3 Performance of machine learning models in validation set of predicting MCI among Chinese older adults.

Model	AUC	TP/TN/FP/FN	Sensitivity (%)	Specificity (%)	Accuracy (%)	Balanced accuracy (%)
GBDT	0.890 (0.865, 0.915)	304/266/98/40	88.37 (84.98, 91.76)	73.08 (68.52, 77.63)	80.51 (77.71, 83.54)	81.50 (78.72, 84.29)
		300/273/91/44	87.21 (83.68, 90.74)	75.00 (70.55, 79.45)	80.93 (78.16, 83.94)	81.63 (78.83, 84.43)
		297/282/82/47	86.34 (82.71, 89.97)	77.47 (73.18, 81.76)	81.78 (79.06, 84.73)	82.16 (79.37, 84.95)
		292/289/75/52	84.88 (81.10, 88.67)	79.40 (75.24, 83.55)	82.06 (79.36, 85.00)	82.14 (79.32, 84.95)
		284/302/62/60	82.56 (78.55, 86.57)	82.97 (79.11, 86.83)	82.77 (80.11, 85.66)	82.32 (79.47, 85.17)
XGboost	0.898 (0.874, 0.922)	309/251/113/35	89.83 (86.63, 93.02)	68.96 (64.20, 73.71)	79.10 (76.10, 82.09)	80.68 (77.88, 83.47)
		301/269/95/43	87.50 (84.01, 90.99)	73.90 (69.39, 78.41)	80.51 (77.71, 83.54)	81.35 (78.55, 84.16)
		295/282/82/49	85.76 (82.06, 89.45)	77.47 (73.18, 81.76)	81.50 (78.76, 84.47)	81.83 (79.02, 84.65)
		282/295/69/62	81.98 (77.91, 86.04)	81.04 (77.02, 85.07)	81.50 (78.76, 84.47)	81.15 (78.24, 84.06)
		271/302/62/73	78.78 (74.46, 83.10)	82.97 (79.11, 86.83)	80.93 (78.16, 83.94)	80.06 (77.05, 83.07)
RF	0.914 (0.886, 0.941)	329/226/138/15	95.64 (93.48, 97.80)	62.09 (57.10, 67.07)	78.39 (75.36, 81.42)	81.13 (78.44, 83.83)
		310/261/103/34	90.12 (86.96, 93.27)	71.70 (67.08, 76.33)	80.65 (77.74, 83.56)	81.90 (79.16, 84.64)
		290/303/61/54	84.30 (80.46, 88.15)	83.24 (79.40, 87.08)	83.76 (81.04, 86.47)	83.45 (80.69, 86.22)
		269/318/46/75	78.20 (73.83, 82.56)	87.36 (83.95, 90.78)	82.91 (80.14, 85.68)	81.64 (78.68, 84.59)
		233/339/25/111	67.73 (62.79, 72.67)	93.13 (90.53, 95.73)	80.79 (77.89, 83.69)	77.41 (74.07, 80.75)

GBDT, Gradient boosting decision tree; XGboost, Extreme gradient boosting; RF, Random Forest; AUC, Area Under the Curve; TP, True Positives; TN, True Negatives; FP, False Positives; FN, False Negatives.

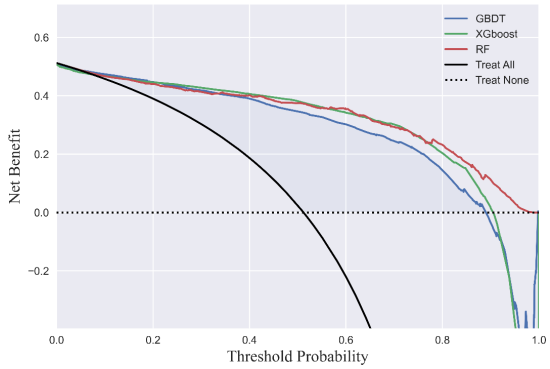

FIGURE 4
Decision curve analysis. The *x*-axis indicates the threshold probability of MCI. The *y*-axis indicates the net benefit.

economic, and social value through optimizing prediction under governmental direction and adjusting thresholds for MCI probability according to the specific needs of different healthcare providers. Finally, this study contributes to the prevention of dementia and MCI and promotes healthy aging.

5. Study limitations

This study had some limitations. First, we examined the robustness of both LSTMs and machine learning models and included four waves of data; however, our findings need to be validated in another cohort. Lacking external validation may affect the performance and adaptability of prediction models in different scenarios, as well as the confidence in the predictive ability of the models. Therefore, future researchers need to use other sources or types of data to validate this method framework and explore possibilities for improvement. Second, most predictors in this study were self-reported, which could have led to information bias. Third, the MMSE has a ceiling effect, meaning that it may not detect subtle changes in cognition that occur during MCI. Furthermore, MMSE scores could be affected by certain individual sociodemographic background factors (Arevalo-Rodriguez et al., 2021; Wu et al., 2022); therefore, MCI evaluations should be more comprehensive and include using Montreal Cognitive Assessment and the Clinical Dementia Rating evaluations, in addition to detecting biomarkers and undertaking imaging examinations for a more accurate clinical diagnosis in future studies. While this study proposes a convenient screening method using accessible individual features for the general public, outcomes obtained using this method are for reference only and cannot replace acknowledged MCI diagnosis standards.

6. Conclusion

This study showed that individual features could be predicted through combining LSTMs and machine learning models. The risk of MCI could be accurately predicted through exploring critical risk factors, such as age, education level, chronic respiratory disease, gastrointestinal ulcer, and self-rated health, in patients with MCI using three SHAP models among older Chinese adults based on four waves of CLHLS datasets. The combination of LSTMs and machine learning models captured

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the interdependence of predictors and generated an effective decision support system for healthcare providers to identify patients at high risk of MCI. With macro-direction undertaken at a governmental level, this screening method can continue to be optimized to obtain better thresholds for MCI screening. Our study findings may offer healthcare providers MCI screening support to implement early interventions to delay the progression from MCI to dementia, increase test availability among the population, and reduce incidence rates and treatment costs, ultimately contributing to healthy aging.

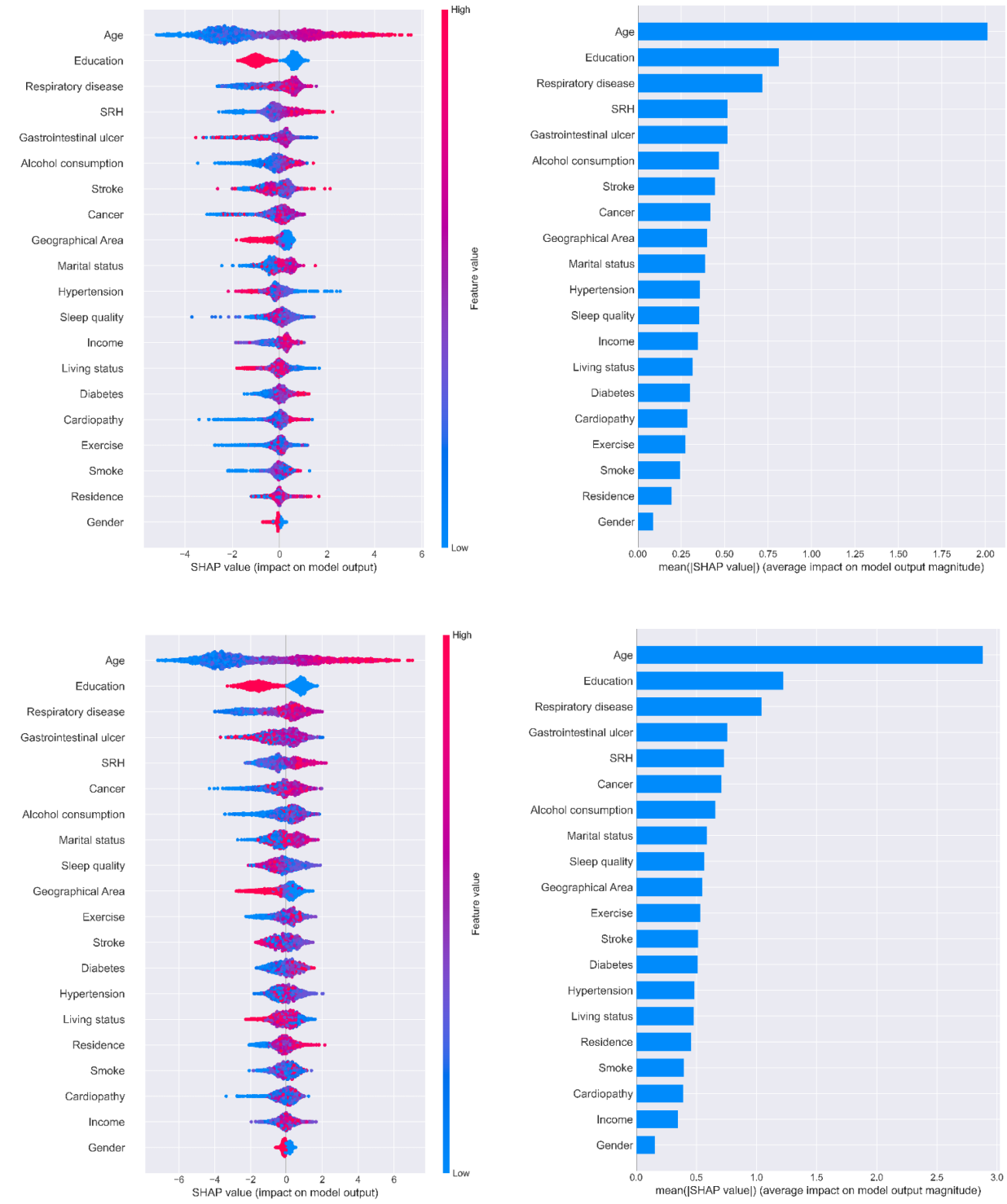

FIGURE 5 (Continued)

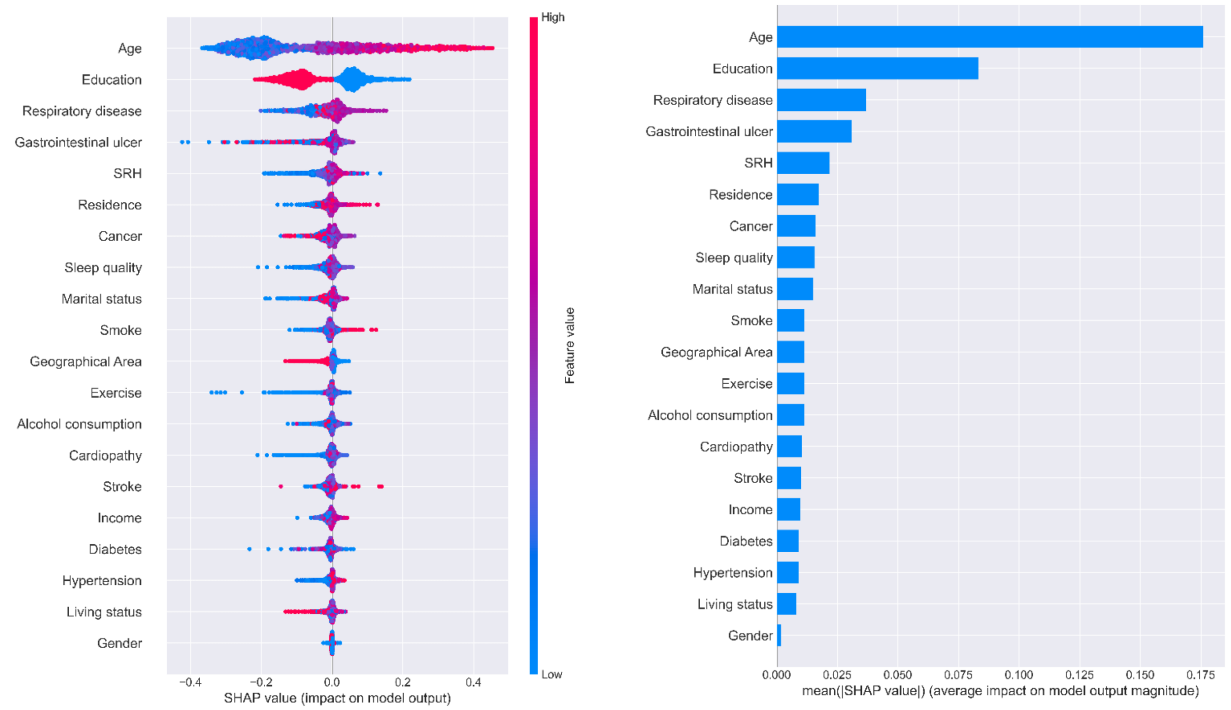

FIGURE 5
Importance of predictors analysis by SHAP model. SHAP (SHapley Additive exPlanation) values are ranked by value of a feature to the predictions made by the GBDT/XGboost/RF.

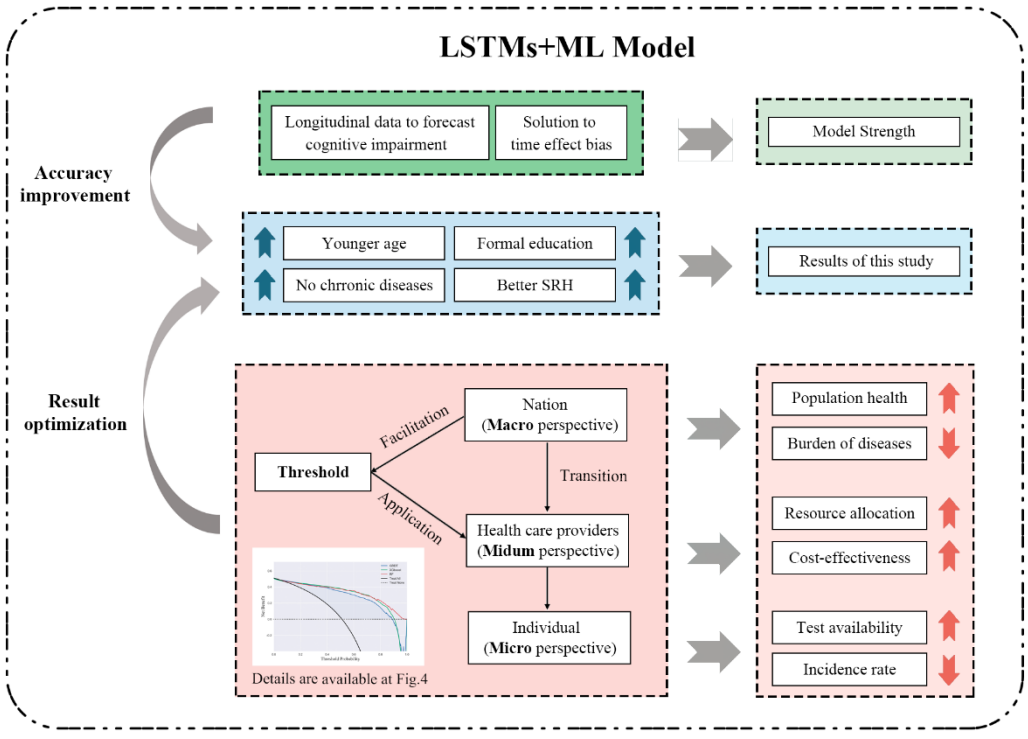

FIGURE 6
Conceptual framework of discussion in this study.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

YH: Conceptualization, Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization. ZH: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. QY: Validation, Writing – review & editing, Methodology, Software. HJ: Methodology, Software, Writing – review & editing, Data curation. TX: Writing – review & editing. YF: Writing – review & editing, Visualization. YZ: Writing – review & editing, Formal analysis. XZ: Writing – review & editing, Funding acquisition, Resources. CC: Funding acquisition, Resources, Writing – review & editing, Conceptualization, Investigation, Project administration, Supervision, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1283243/full#supplementary-material

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Spoken discourse in episodic autobiographical and verbal short-term memory in Chinese people with dementia: the roles of global coherence and informativeness

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Introduction: Memory and discourse production are closely related in healthy populations. A few studies in people with amnestic mild cognitive impairment and people with dementia (PWD) suggested similar links, although empirical evidence is insufficient to inform emerging intervention design and natural language processing research. Fine-grained discourse assessment is needed to understand their complex relationship in PWD.

Methods: Spoken samples from 104 PWD were elicited using personal narrative and sequential picture description and assessed using Main Concept Analysis and other content-based analytic methods. Discourse and memory performance data were analyzed in bivariate correlation and linear multiple regression models to determine the relationship between discourse production and episodic autobiographical memory and verbal short-term memory (vSTM).

Results: Global coherence was a significant predictor of episodic autobiographical memory, explaining over half of the variance. Both episodic autobiographical memory and vSTM were positively correlated with global coherence and informativeness, and negatively with empty speech indices.

Discussion: Coherence in personal narrative may be supported by episodic autobiographical memory and vice versa, suggesting potential mechanism of interventions targeting personhood through conversation. Indices of global coherence, informativeness, and empty speech can be used as markers of memory functions in PWD.

KEYWORDS

dementia, spoken discourse, personal narratives, sequential picture description, episodic autobiographical memory, verbal short-term memory, global coherence, informativeness

1. Introduction

Memory impairments underlie a range of cognitive and functional deficits in people with dementia (PWD). Impairment in episodic memory is the clinical hallmark for Alzheimer's disease (AD) and other types of dementia (Arlt, 2013; Economou et al., 2016). More specifically, autobiographical memory decline is linked to sense of self and identity (Caddell and Clare, 2010; El Haj et al., 2015), with PWD demonstrating impoverished self-representation (Ben Malek et al., 2019). Reduced details in autobiographical memory can also be noted in very early dementia before episodic memory impairments can be detected using standardized memory tests (Lindsay et al., 2021). Episodic autobiographical memory is the memory for specific events from one's own past. Greater richness in episodic autobiographical memory supports better subjective re-experiencing of the past, including emotions and thoughts (Irish et al., 2018) (for a review, see Allen et al., 2018). On the other hand, deficits in verbal short-term memory (vSTM), the ability to actively maintain verbal information mentally for brief periods, have also been widely reported (Ober et al., 1985; Caramelli et al., 1998).

Episodic autobiographical memory and vSTM are related to language deficits in PWD. There has been an increasing interest in natural language processing and spontaneous speech in dementia (Lindsay et al., 2021), with researchers looking into their use as early markers (Luz et al., 2021). Language deficits can present at various levels in dementia, including word-finding, sentence comprehension, and discourse cohesion (Kempler and Goral, 2008). Previous studies in dementia mostly focused on syntactic or more 'basic' units in language, such as lexico-semantic changes (Szatloczki et al., 2015). In dementia, unlike aphasia or other brain conditions, language deficits caused by a focal brain damage is rare (Kempler and Goral, 2008). Discourse is a language unit whose organization supersedes any single words or sentences (Olness, 2006). It provides a multidimensional evaluation of various linguistic levels of spoken output (Filiou et al., 2019). Some studies have suggested that discourse production involves higher cognitive demands, it is more sensitive than other linguistic assessments, such as naming and verbal fluency, in distinguishing PWD from controls (e.g., Caramelli et al., 1998). In particular, memory plays a vital role in producing discourse (Caramelli et al., 1998; Dijkstra et al., 2004). Episodic memory is responsible for the retrieval of past information, especially in producing personal narratives (Caspari and Parkinson, 2000; Beltrami et al., 2018). vSTM, on the other hand, is required to store verbal information temporarily to continue the flow of spoken discourse (Brandão et al., 2009). On the other hand, Mueller et al. (2018), for example, provided a discussion of the pros and cons of using connected speech tasks, and cited at least one study that noted no advantage of picture description over naming and verbal fluency. Moreover, Gordon and Kindred (2011) explained that speakers have the option of selecting alternative words to compensate for word-retrieval impairments when producing a discourse, with a higher degree of flexibility to achieve coherence and cohesion. It, therefore, remains unclear whether discourse is a more sensitive task to reflect cognitive impairments.

The detailed relationship between memory and discourse remains elusive. Studies conducted in populations with neuro-communicative disorders have found the following: in traumatic brain injury, working memory (WM) was found to be correlated with syntactic complexities (Youse and Coelho, 2005) while vSTM was linked to informativeness and global coherence (Galetto et al., 2013); in aphasia, WM was associated with global coherence in story retell (Cahana-Amitay and Jenkins, 2018), but no such an association was observed in personal narratives (Rogalski et al., 2010). Limited research conducted in mild cognitive impairment (MCI) or dementia suggested that episodic memory is correlated positively with global coherence in autobiographical narratives in MCI (Seixas-Lima et al., 2020), and WM negatively correlated with the use of nominal references and pronouns in narratives and picture descriptions, respectively (Almor et al., 1999; March et al., 2009). Methodological variations likely contributed to the inconclusive findings, especially with the use of varied discourse tasks including narratives and picture descriptions (Hill et al., 2018). It is also worth highlighting that in cognitively healthy older adults, decline in performance on spoken oral discourse through story telling was found to significantly correlate with that of cognitive measures in memory and attention (Wright et al., 2011).

The above-mentioned studies were done predominantly in English speakers, although Chinese populations are the major drive in the continued growth in global dementia prevalence (Alzheimer's Disease International, 2013), with 9.5 million PWD currently residing in Hong Kong, Taiwan, and China (Wu et al., 2018). The relationship between language and memory may differ between English and Cantonese due to several factors, including the cultural background (Gutchess and Indeck, 2009), and linguistic structure and cognitive processes involved in using each language (Pennington and Ellis, 2000). In other words, with regard to language-memory relationships, results from studies in English might not be representative of those in Cantonese; this forms a strong argument for language diversity in studies on this issue. A handful of research has been done in Cantonese-speaking people with traumatic brain injury, revealing the positive correlation between attention, executive functions, visuo-spatial skills, and syntactic complexities (Kong et al., 2020; Lau et al., 2022). To our knowledge, no study has examined the relationship between memory and discourse production in native Cantonese-speaking PWD.

In this study, the relationship between memory and discourse production in Cantonese-speaking PWD is investigated, using discourse produced in both personal narrative and picture description. Our aim is to examine if discourse can be utilized clinically to inform methods of diagnosing dementia. Specifically, based on the High Level Language Hypothesis (Galetto et al., 2013), macrolinguistic deficits could be attributed to impaired conceptual organization of a narrative; it was therefore hypothesized that (1) there would be a positive association between episodic memory and global coherence of personal narrative. In addition, organizing a discourse requires a person to temporarily move forward or backward between mental sets, a crucial component in vSTM; it was therefore hypothesized that (2) vSTM would be correlated with informativeness of discourse production and empty speech. Moreover, which discourse measure(s) would best predict(s) memory deficits was explored.

2. Methods

2.1. Participants and discourse samples

Discourse samples were collected from 119 participants at baseline from a pilot study to investigate virtual delivery of

non-pharmacological interventions to community-dwelling families living with dementia during COVID lockdown. Inclusion criteria of the study were a diagnosis of mild/moderate dementia as indicated in the referral and/or medical documentation and able to provide a joint consent with a family carer; exclusion criteria were inability to communicate and participate in interviews and intervention via a tablet computer, and severe visual or hearing impairment. Participants were users of local social programs (including community dementia care, aged care, and housing service users) recruited from service units in Hong Kong. After data screening, personal narratives of 49 participants and picture descriptions of 15 participants were excluded because of one of the following three problems: total words fewer than 40 [as transcripts of this length did not contain sufficient amount of content for a valid linguistic analysis (Saffran et al., 1989; Kong, 2022)], lack of discourse samples produced, or incomplete discourse task. A final 70 personal narratives and 104 picture description samples were included from 104 participants (see Table 1 for their demographic characteristics). *T*-test results indicated that the subgroup of 70 and the original group of 104 participants were not significantly different in terms of age [t (172) = 0.614, p = 0.423] and education [t (172) = −0.409, p = 0.434]. Chi-square results also revealed the two group were not significantly different in dementia severity [χ^2 (2,174) = 0.415, p = 0.981].

2.2. Procedures

Discourse samples were collected by trained researchers following the Cantonese Aphasia Bank protocol (Kong and Law, 2019). For the personal narrative discourse, participants were asked a probing question "Tell me about the most joyful event in your life." If there were no responses, general prompts (e.g., "how about traveling, or family events?") were provided. For sequential picture description, they were asked to describe a sequential picture set (story of buying ice-cream) following the Main Concept Analysis (MCA) protocol (Kong, 2016), with proven sensitivity in distinguishing PWD from people with aphasia and controls (Kong et al., 2016). Participants were asked to tell a story portrayed in four picture cards pre-arranged in the correct order. If no relevant response was obtained, general prompts (e.g., "what is happening here?") were provided. This sequential picture description elicited verbal output of temporally and causally related sequence of activities (Kong, 2022). The discourse samples were transcribed orthographically and then divided into T-units, defined as an independent clause with or without a subordinate clause (March et al., 2009; see Supplementary Table S1 for special cases of segmentation of T-units in Cantonese), for analysis.

Participants were assessed for their cognitive performance by trained researchers using the Hong Kong Montreal Cognitive Assessment (HK-MoCA) 5-min Protocol (Wong et al., 2015) and a

TABLE 1 Demographic characteristics of participants (total n = 104).

	Number of participants (%)	
Characteristics	N = 104	Subgroup of n = 70 with personal narratives
Age		
60–69	6 (5.7%)	4 (5.7%)
70–79	27 (26.0%)	20 (28.6%)
80–89	59 (56.7%)	46 (65.7%)
90 or above	12 (11.5%)	6 (8.6%)
All	104 (100%); 81.8 ± 7.5, 63–98*	70 (100%); 81.1 ± 6.9, 64–97*
Gender		
Male	38 (36.5%)	28 (40%)
Female	66 (63.5%)	42 (60%)
Years of education		
0–3	38 (36.5%)	25 (35.7%)
4–6	27 (26.0%)	15 (21.4%)
7–9	8 (7.7%)	7 (10%)
10 or above	25 (24.0%)	19 (27.1%)
Unknown	6 (5.8%)	4 (5.7%)
All	104 (100%); 6.17 ± 5.1, 0–19*	70 (100%); 6.52 ± 5.4, 0–19*
Severity of dementia		
Suspected	10 (9.5%)	8 (11.4%)
Mild	47 (44.8%)	31 (44.3%)
Mild-to-moderate	12 (11.4%)	8 (11.4%)
Moderate	29 (27.6%)	19 (27.1%)
Unknown	7 (6.7%)	4 (5.7%)

*Data are presented in Mean ± SD, range.

Cantonese version of the Oxford Cognitive Screen-Plus (OCS-Plus; Demeyere et al., 2021). Demographic characteristics including age, gender, education, and dementia severity were collected through interviews with carers.

2.3. Measures

Memory measures. Episodic autobiographic memory was assessed following the protocol of Seixas-Lima et al. (2020). Each T-unit in a personal narrative was classified as episodic if it reflected re-experiencing of events specific to time and place, including happenings, spatial, temporal, and perceptual information and internal states, i.e., thoughts of feelings (Levine et al., 2002). The number of episodic details was tallied and divided by the number of T-units in the same narrative to compute the score of episodic memory. vSTM was assessed using the HK-MoCA, which generates immediate recall, delayed recall, delayed cued recall, and total recall scores, and OCS-Plus (Demeyere et al., 2021), which generates delayed recall, recognition recall, and total recall scores. A vSTM composite score was also computed for the seven measures from HK-MoCA and OCS-Plus. The raw scores of each measure were converted into Z-scores, and a weighted mean of these Z-scores was calculated, forming the final composite score.

Discourse measures. Global coherence, the linkage between the main topic and contents of individual utterances of the discourse (Wright et al., 2014), was assessed using a 4-point rating scale (Seixas-Lima et al., 2020). Each T-unit was rated from 0 to 3, based on the degree of propositional information relevant to the main topic. An average score was computed to represent global coherence for each sample (see Supplementary Tables 2 for specific scoring criteria).

Informativeness was evaluated using (a) MCA, (b) information rating of the Cantonese version of Western Aphasia Battery (CAB; Yiu, 1992), and (c) indices of empty speech. MCA measures presence and completeness of information in a discourse (Kong, 2022). For (a) MCA, six indices, including accurate and complete, accurate but incomplete, inaccurate, and absent concepts, overall main concept score, and 'accurate and complete' concepts per minute (Kong, 2009), were calculated for sequential picture description; MCA was not applied for personal narrative as the subjective nature of personal narrative precluded objective assessment of information accuracy and completeness. For (b) information rating of CAB, originally developed to assess connected speech in picture description, it was used to subjectively assess the informativeness of discourse production, with reference to number of correctly named items. For (c) empty speech, a main characteristic of PWD, it refers to reduced informative content and lack of references in connected speech (Nicholas et al., 1985). We applied six indices (see Supplementary Table S3 for details) to both personal narrative and picture description: percentage of pronouns adopted from Almor et al. (1999); and pronouns without antecedents, deictic terms, repetitions, empty phrases, and comments derived from Nicholas et al. (1985). For the last four indices, raw counts were divided by the number of T-units in each discourse sample to obtain a ratio.

2.4. Inter- and intra-rater reliability

A second independent examiner, who was a speech-language pathologist trainee (i.e., similar to the second author, or first examiner, in terms of background/experience) and received training on calculating the measures, reviewed 10 personal narratives and 15 picture descriptions (15% of samples) that were randomly selected. The same set of samples were reviewed by the second author two months after initial analyses. The inter-rater and intra-rater reliability were measured using Intraclass Correlation Coefficient. Both reliability measures were high overall, with most ICC results reaching levels of good to excellent (Koo and Li, 2016; see Supplementary Table S4). A discrepancy was only found in inter-rater reliability for indices 'accurate but incomplete' and 'inaccurate' concepts, where 'accurate but incomplete' was rated as 'inaccurate', and 'inaccurate' was rated as 'absent'; this was similar to previous report of decreased reliability when more than one incomplete or inaccurate concept was present in a PWD's description (Kong et al., 2016).

2.5. Statistical analysis

Since the data were not normally distributed, a non-parametric test of Spearman's Rank was conducted to explore the correlations between memory and discourse measures. An adjustment of significance level was done using Bonferroni's method due to multiple comparisons of memory measures (0.05/3 or 0.0167). Since the number of variables under consideration was large, a forward stepwise analysis was utilized in SPSS (George and Mallery, 2019), with the vSTM composite score and episodic memory score being the dependent variables, and all discourse measures as independent variables in the regression model. Given the range of age and education, these variables were included in the regression analyses. This forward selection started with a null model (with no predictors) and proceeds to add variables one at a time, and so unlike backward selection, it does not have to consider the full model that which would include all the predictors.

3. Results

The descriptive statistics of all memory and discourse measures can be found in Supplementary Table S5. Tables 2, 3 summarize the correlations between various memory and discourse measures in the personal narrative and picture description tasks, respectively.

3.1. Exploratory correlational analysis

In the personal narrative task, global coherence positively correlated with episodic autobiographical memory, HK-MoCA cued delayed and total recall, OCS-Plus delayed and total recall. Among all, episodic autobiographical memory and global coherence yielded the highest correlation coefficient ($r = 0.772$, $p < 0.001$). For empty speech indices, use of repetitions negatively correlated with HK-MoCA immediate recall ($r = 0.296$, $p < 0.0167$).

For the sequential picture description task, global coherence significantly correlated with episodic memory ($r = 0.478$, $p < 0.001$) and vSTM measures in HK-MoCA (e.g., cued delay recall: $r = 0.366$, $p < 0.001$) and OCS-Plus (e.g., delayed recall: $r = 0.281$, $p < 0.01$). Negative correlations were found between memory and all empty speech indices (except for percentage of pronouns), although these correlations were relatively weak, with most of the Spearman $r < 0.30$. Significant

TABLE 2 Correlation between memory and discourse measures in personal narratives.

		Global coherence	Use of pronoun (%)	Deictic term	Repetition	Pronouns without antecedent (%)	Empty phrase	Comment
Episodic autobiographical memory		**0.772*****	−0.071	−0.159	0.004	−0.217	−0.221	−0.221
HK-MoCA	Immediate recall	0.125	0.092	−0.094	**−0.296***	−0.080	0.037	0.201
	Delayed recall	0.092	0.163	−0.100	−0.010	−0.098	0.057	0.120
	Cued delayed recall	**0.363****	−0.039	−0.004	0.013	−0.200	0.013	0.001
	Total recall	0.282	0.021	0.029	−0.017	−0.174	0.066	0.036
	Total score	**0.332****	0.042	−0.018	−0.126	−0.108	−0.032	0.055
OCS-Plus	Delayed recall	0.293	−0.035	−0.014	0.032	−0.056	0.108	0.138
	Recognition recall	0.085	−0.014	−0.070	0.058	−0.160	−0.254	−0.146
	Total recall	0.237	−0.027	−0.065	0.086	−0.163	−0.139	−0.022

The significant correlations were bolded. *$p < 0.0167$; **$p < 0.01$; ***$p < 0.001$.

TABLE 3 Correlations between memory and discourse measures in picture descriptions.

		Global coherence	Use of pronoun (%)	Deictic term	Repetition	Pronouns without antecedent (%)	Empty phrase	Comment	MC score	CAB info.
Episodic autobiographical memory		**0.478*****	0.109	0.208	−0.076	−0.253	−0.009	**−0.356****	**0.454*****	**0.501****
HK-MoCA	Immediate recall	0.129	−0.081	−0.031	−0.133	−0.177	−0.208	−0.104	0.125	0.139
	Delayed recall	0.107	0.033	−0.011	−0.128	0.069	−0.107	−0.038	0.152	0.197
	Cued delayed recall	**0.366*****	−0.169	−0.221	−0.178	−0.134	**−0.285****	−0.156	**0.416*****	**0.437*****
	Total recall	**0.306****	−0.129	−0.170	−0.178	−0.061	**−0.262****	−0.110	**0.348*****	**0.393*****
	Total score	**0.361*****	−0.058	−0.095	**−0.295****	−0.077	**−0.297****	−0.109	**0.443*****	**0.481*****
OCS	Delayed recall	**0.281****	−0.119	−0.129	−0.151	0.008	0.025	−0.065	**0.337*****	**0.293****
	Recognition recall	**0.283****	−0.050	−0.030	−0.172	−0.189	−0.158	−0.100	0.218	**0.259****
	Total recall	**0.382*****	−0.101	−0.085	**−0.238***	−0.128	−0.113	−0.106	**0.352*****	**0.358*****

MC score, main concept score; CAB info. = Cantonese Aphasia Battery information rating. The significant correlations were bolded.
*$p < 0.0167$; **$p < 0.01$, ***$p < 0.001$.

correlations were found between most memory tests and the MC score. Information rating of CAB also positively correlated with all memory measures, except for immediate and delayed recall in HK-MoCA.

3.2. Regression analysis

All discourse measures were entered against episodic autobiographical memory and vSTM composite score (Tables 4, 5). For the model of episodic autobiographical memory, global coherence of both genres and use of deictic terms in picture description were significant predictors, accounting for a total variance of 70.0% [$F(3,64) = 47.499$, $p < 0.001$]. It is worth noting that global coherence in personal narrative alone accounted for 61% variance of episodic autobiographical memory. For the model of vSTM composite score, the regression analysis was significant [$F(1,67) = 19.273$, $p < 0.001$], with information rating of CAB being the only discourse predictor of vSTM. It accounted for 48.4% of the total variance. The variables of age and education did not yield any significant contributions to the regression models.

4. Discussion

This study provided, to our knowledge, the first evidence of the close relationship between discourse performance and memory in

TABLE 4 Stepwise regression of episodic autobiographical memory as dependent variable.

Predictor	*B*	SE B	*β*	*t*	*p*
Step 1					
Constant	−0.005	0.078		−0.062	0.951
PN GCR	0.323	0.032	0.789	10.205	< 0.001
Step 2					
Constant	−0.084	0.080		−1.045	0.300
PN GCR	0.325	0.030	0.794	10.762	< 0.001
SPD deictic terms	0.171	0.064	0.199	2.691	0.009
Step 3					
Constant	−0.144	0.079		−1.826	0.073
PN GCR	0.282	0.033	0.690	8.666	< 0.001
SPD deictic terms	0.213	0.062	0.248	3.426	0.001
SPD GCR	0.086	0.031	0.226	2.771	0.007

PN GCR = global coherence of personal narratives; SPD = sequential picture description.
Adjusted $R^2 = 0.617$ for step 1 ($p < 0.001$); $\Delta R^2 = 0.663$ for step 2 ($p < 0.05$); $\Delta R^2 = 0.685$ for step 3 ($p < 0.05$).

TABLE 5 Stepwise regression of vSTM composite score as dependent variable.

Predictor	*B*	SE B	*β*	*t*	*p*
Step 1					
Constant	−0.796	0.201		−3.965	< 0.001
CAB information	0.129	0.029	0.484	4.390	< 0.001

CAB, Cantonese Aphasia Battery.
Adjusted $R^2 = 0.234$ for step 1 ($p < 0.001$).

a sizable Chinese sample of PWD with standardized discourse measures. We noted a particularly strong positive relationship between episodic autobiographical global coherence, which echoed an earlier study in people with MCI (Seixas-Lima et al., 2020). These findings showed an important role of discourse as part of the clinical presentation in neurocognitive disorders that affect global cognition, through its association with episodic memory and vSTM.

Our finding that global coherence is correlated with vSTM measures is in line with previous studies (Brandão et al., 2009; Kim et al., 2019). The relationship between informativeness in picture description (as reflected by the main concept performance) and vSTM confirmed previous reports in AD and traumatic brain injury (Brandão et al., 2009; Galetto et al., 2013). It can be interpreted based on reports investigating neural correlates of vSTM and language production. Overlapping areas of activation (left inferior frontal and left posterior temporal areas) between vSTM and language production have been widely reported (Melrose et al., 2009; Peters et al., 2009; Koenigs et al., 2011). The association between informativeness in picture description and episodic memory observed in this study is interesting: as visual stimuli were provided, we expected minimal involvement of episodic memory in the picture description task. A plausible explanation is the relationship between long-term memory, the representational basis of vSTM (Cameron et al., 2005), and vSTM. When vSTM is engaged, long-term memory is activated to help with the maintenance of semantically related information. Better long-term memory capacity, including episodic memory, could help enhance vSTM during discourse production.

The negative correlation between empty speech (i.e., deictic terms, repetitions, empty phrases) and vSTM is worth noting. Although PWD have been shown to produced significantly more deictic terms, repetitions, and empty phrases than controls (Kong et al., 2016), no quantitative studies examining their relationships with vSTM have been reported. Empty speech in PWD was suggested to stem from both linguistic and cognitive disturbances, such as memory and attention (Carlomagno et al., 2005; Kong et al., 2016). Our finding can be understood based on two key theories of vSTM, output interference and response suppression, which suggest that recalling of an item interferes with the uncalled ones that needs to be suppressed, otherwise it would continue to be activated (Lewandowsky, 2008). As empty speech in PWD is often manifested by occurrence of deictic terms, repetitions, and empty phrases, deficits in vSTM would further reinforce these frequently activated items (which would be overused in discourse). However, it should also be noted that although the association were statistically significant, these correlations were relatively weak. This might be related to the uneven distribution of severity level of PWD. More than half of our participants (65.7%) had a severity of mild-to-moderate or below, while only around a quarter of them (27.6%) was diagnosed with moderate dementia. Previous studies showed that empty speech was more likely to manifest in middle or late stage of dementia (March et al., 2009; Forbes-McKay et al., 2013; Kong et al., 2016). Therefore, the memory impairment of our participants might not be severe enough for empty speech to manifest.

The finding that global coherence is the best predictor of episodic autobiographical global coherence in personal narrative is

significant yet unsurprising, considering the essential functions of episodic memory in recalling specific time, location, and thoughts (El Haj et al., 2015) to maintain a coherent personal narrative. While both episodic autobiographical memory and semantic autobiographical memory (i.e., "personal semantics" or semantic knowledge about oneself, see Conway, 2005) changes are clinical hallmarks in dementia, with a recent study showing their higher sensitivity over standard neurocognitive tests in cognitively unimpaired people with increased genetic risk (APOE4 carriers) (Grilli et al., 2021), episodic autobiographic memory is possibly a more important marker and intervention target: its differential impairment is linked to underlying disease pathology in different dementia types including AD and frontotemporal dementia (Irish et al., 2011). Its role in supporting re-experiencing of the past (Irish et al., 2018) is theoretically central to interventions targeting personhood in dementia, such as cognitive stimulation therapy (CST) and reminiscence therapy. These interventions typically involve conversations on autobiographical topics; their mechanisms of action on cognitive outcome are unclear, although in CST the cognitive enhancement effects (Woods et al., 2012) may be linked to language use (Spector et al., 2010; Lobbia et al., 2019) and brain networks responsible for episodic memory retrieval and mental self-representation (Liu et al., 2021). Our finding that global coherence explained over half of the variance in episodic autobiographic memory provided further insight into how conversations revolving around personal experience may be associated with episodic memory and a cohesive sense of self over time (Strikwerda-Brown et al., 2019) as an intervention target in dementia. Potential strategies may include spaced retrieval and post-sentential training, to support PWD's memory loading in spoken discourse production (Brush and Camp, 1998).

Information rating of CAB was the only significant predictor of vSTM in our regression analysis. This rating scale was originally designed for people with aphasia instead of PWD (Yiu, 1992). Since it is an overall scoring of relevant content, including any naming and descriptions, one may argue that this scale has a broader scope of scoring than other content-based measures, such as MCA, which might explain why it could be more sensitive in predicting vSTM. This study offers preliminary evidence that information rating might be clinically useful in understanding discourse production in PWD. Future studies might focus on how to adjust the scoring criteria of the rating so it can be better adapted for PWD.

Our overall findings are in line with previous literature which demonstrated a close relationship between global coherence and memory measures (Drummond et al., 2015; Kim et al., 2019). In addition, the close link between deictic elements of a language (which contain limited meaning in sentences) and memory seemed to also help the formation of utterances to a particular time, place, speaker, or discourse context (Brewer and Harris, 1974). The current study in a Chinese sample adds to a growing literature of speakers of different languages (Fleming and Harris, 2008; March et al., 2009; Kim et al., 2019), including Western studies showing significant associations between working memory and discourse measures (Almor et al., 1999; Youse and Coelho, 2005; Cahana-Amitay and Jenkins, 2018). It contributes to the knowledge base supporting the emerging research methods of natural language processing and automated speech analysis in dementia, which is increasingly noted with its potential link to clinician observations (Yeung et al., 2021). This being said, however, the potential values of discourse measures as markers of memory ability needs to be further evaluated, as our cross-sectional findings are essentially preliminary. From the present findings, it may be difficult to see how the discourse measures (which are indirectly and sometimes weakly related to the memory measures, not to mention being more labor-intensive to collect and process) can provide an advantage over the memory measures themselves. We argue that discourse measures and other memory measures in dementia are likely complementary: discourse data are in general easier to conduct (simple training not requiring specific qualifications; less intimidating among older people with lower education/cognitive impairment to engage in a chat than a test; can be easier conducted remotely) but more challenging to rate, although the rapid development in machine learning (e.g., see Lindsay et al., 2021) suggests this challenge may be temporary. As a potential screening tool for people with suspected dementia, the ease of data collection is particularly important, considering the many barriers (e.g., stigma and fear) currently exist in dementia help-seeking. In future studies, apart from the cognitive screening tools (HK-MoCA and OCS-Plus) used in this study, more refined cognitive tests and other functional outcomes should be included in longitudinal studies to understand its performance as a simple memory marker and potential predictor of illness severity in dementia.

Finally, there were several limitations in the present investigation. First, the length of the included narrative samples was relatively short. The mean length of narrative and picture description samples was 70 and 80 characters, respectively. Although there was no reported word recommendation on Cantonese discourse samples, previous studies recognized the problems of insufficient length of discourse samples, resulting in insignificant findings of correlation analysis (Mueller et al., 2018). This might explain some of the insignificant correlations observed in the personal narrative task. For English-speaking PWD, it has been suggested a mean length of 100 words for discourse samples (Fraser et al., 2016) might act as a reference for future studies. Second, due to a lack of participants with middle or late stage of dementia, the current discourse samples cannot fully represent discourse produced with the cognitive deficits in later stages of dementia. Lastly, due to the cross-sectional nature of this study, no direction of the relationship can be inferred. One may also argue that the CAB information rating scale might contain a confound as it includes autobiographical questions, making it difficult to draw a clear conclusion about the relative importance of the predictors. This study nevertheless provided detailed discourse measures for identifying important markers/intervention targets for understanding the link between episodic autobiographical memory, vSTM, and various discourse measures. Future longitudinal or experimental research can examine the direction of relationships to inform prediction model and intervention design.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving humans were approved by the Human Research Ethics Committee of The University of Hong Kong. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AK and RC contributed to the conception and design of the study, and wrote the first draft of the manuscript. GW, JC, and RD contributed to the conception of the study and were responsible for data collection. AS contributed to the conception of the study. JC has gone through the official certification process of HK-MoCA and obtained appropriate permission the copyright holders of HK-MoCA to use this scale. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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Diagnosis of Alzheimer's disease via resting-state EEG: integration of spectrum, complexity, and synchronization signal features

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Background: Alzheimer's disease (AD) is the most common neurogenerative disorder, making up 70% of total dementia cases with a prevalence of more than 55 million people. Electroencephalogram (EEG) has become a suitable, accurate, and highly sensitive biomarker for the identification and diagnosis of AD.

Methods: In this study, a public database of EEG resting state-closed eye recordings containing 36 AD subjects and 29 normal subjects was used. And then, three types of signal features of resting-state EEG, i.e., spectrum, complexity, and synchronization, were performed by applying various signal processing and statistical methods, to obtain a total of 18 features for each signal epoch. Next, the supervised machine learning classification algorithms of decision trees, random forests, and support vector machine (SVM) were compared in categorizing processed EEG signal features of AD and normal cases with leave-one-person-out cross-validation.

Results: The results showed that compared to normal cases, the major change in EEG characteristics in AD cases was an EEG slowing, a reduced complexity, and a decrease in synchrony. The proposed methodology achieved a relatively high classification accuracy of 95.65, 95.86, and 88.54% between AD and normal cases for decision trees, random forests, and SVM, respectively, showing that the integration of spectrum, complexity, and synchronization features for EEG signals can enhance the performance of identifying AD and normal subjects.

Conclusion: This study recommended the integration of EEG features of spectrum, complexity, and synchronization for aiding the diagnosis of AD.

KEYWORDS

Alzheimer's disease (AD), electroencephalogram (EEG), spectrum, complexity, synchronization, supervised machine learning

Introduction

According to the World Health Organization (WHO), more than 55 million individuals currently live with dementia, a number projected to increase to 78 million by 2030 and a staggering 139 million by 2050 (WHO, 2021). Alzheimer's disease (AD), a neurological disorder, constitutes the predominant form of dementia, accounting for approximately 70% of cases in the world (Blennow et al., 2006). AD mainly occurs in people aged 65 and older, with its incidence rate notably escalating as age advances (McKhann et al., 1984). Due to the high prevalence of AD and its effect on economic cost, WHO has issued a call to prioritize dementia on global health agendas to heighten awareness, enhance early diagnosis, and offer improved care and support to individuals affected by dementia (Subedi and Sapkota, 2019).

Diagnosis of AD, and in particular early diagnosis is essential due to several reasons (Brookmeyer et al., 2007; Dauwels et al., 2010; Galimberti and Scarpini, 2011): (1) it gives patients a warning effect; (2) symptoms-delaying medications are most effective at an early stage of the disease; (3) effective management of psychiatric symptoms, such as depression or psychosis, holds the potential to alleviate the societal burden and associated costs; (4) preventive therapies may be developed to raise the chance of treating the AD. Thus far, diagnosing AD typically involves a comprehensive approach that combines extensive testing and the systematic elimination of alternative potential causes. Psychological assessments, e.g., mini-mental state examinations (MMSE; Folstein et al., 1975) and Montreal cognitive assessment (MoCA; Nasreddine et al., 2005), blood tests (Moretti, 2015), cerebrospinal fluid (CSF; Jack et al., 2011), and emerging imaging techniques are being employed to diagnose AD (Weiner, 2009).

In recent decades, neuroimaging tools, e.g., magnetic resonance imaging (MRI; Dickerson and Wolk, 2011), positron emission tomography (PET; Risacher et al., 2021), and computed tomography (CT; Imabayashi et al., 2013), have been extensively employed to investigate the underlying causes of AD and to enhance the precision of its diagnosis. However, patients receive a diagnosis based on the present spatial resolution of these neuroimaging techniques, often after notable neurodegeneration has occurred. Additionally, these advanced neuroimaging methods come with considerable expenses, demand time-intensive investment, and necessitate experts for their proper intervention.

Electroencephalogram (EEG), an alternative approach that offers greater ease and convenience, has been used as a biomarker in AD diagnosis, due to its low cost, wide availability, high resolution, and high efficiency (Cassani et al., 2018). By measuring the brain's electrical activity, EEG can detect anomalies in brain waves associated with specific disorders (Noachtar and Rémi, 2009; Kemp et al., 2010; Zheng et al., 2019). Given that EEG signals can reflect functional alterations in the cerebral cortex, EEG-based biomarkers hold the potential to evaluate neuronal degeneration caused by AD progression even before the manifestation of behavioral symptoms (Miltiadous et al., 2021). EEG offers many perspectives from recorded signals, including frequency, dynamic alterations, and source imaging. Previous studies have proven these three typical effects, i.e., diffuse slowing, reduced complexity, and decreased synchronization, of AD patients on resting-state EEG signals compared to normal subjects (Cassani et al., 2018). Firstly, diffuse slowing of brain activity refers to a phenomenon where the power of higher EEG frequency bands (e.g., alpha, beta, and gamma bands) decreases, while the power of lower EEG frequency bands (e.g., delta and theta bands) increases (Jeong, 2004; Garn et al., 2015). Secondly, reduced complexity means the complexity of the brain's electrical activity decreases in AD patients when compared to healthy individuals (Schätz et al., 2013; Şeker et al., 2021). Thirdly, decreased synchronization manifests as a decline in connectivity between different cortical regions in many AD patients (Koenig et al., 2005; Wen et al., 2015).

After extracting the EEG features by signal processing methods, using the machine learning techniques, e.g., decision trees algorithm, K-nearest neighbors (kNN), regularized linear discriminant analysis (RLDA), and support vector machine (SVM), these features can be automatically analyzed to classify the normal and abnormal (Fiscon et al., 2018; Safi and Safi, 2021). However, the automatic identification of AD through the utilization of machine learning and EEG readings is currently in its early stages and lacks research about the effect on diagnosis performance from the integration of various types of EEG features (Dauwels et al., 2010).

On this basis, this study aimed to explore the EEG characteristics of AD patients and then develop a new diagnostic approach for AD with various types of EEG signal features and supervised machine learning classification methods based on a big public database. First, according to previous studies, the EEG signal features of spectrum, complexity, and synchronization, of AD and normal subjects were obtained. Then, combined with the machine learning algorithms of SVM, decision trees, and random forest, the classification results between AD and normal subjects were acquired by leave-one-person-out cross-validation.

Methods

Database description

The public database containing the resting-state EEG recordings from 36 AD patients (aged 66.4 ± 7.9 years, 24 females) and 29 healthy controls (CN; aged 67.9 ± 5.4 years, 11 females) was used in this study (Miltiadous et al., 2023). No other dementia-related comorbidities have been reported in AD patients. The cognitive and neuropsychological assessment was conducted using the MMSE (Creavin et al., 2016). MMSE score ranges from 0 to 30, where a lower score indicates a more severe cognitive decline. The MMSE for the AD group was 17.75 ± 4.5 and for the CN group was 30.

EEG Recordings were collected from 19 scalp electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2) along with 2 reference electrodes (A1 and A2), conforming to the 10–20 international system (Homan et al., 1987). Each recording adhered to the established clinical protocol with participants having their eyes closed. Each recording lasted approximately 13.5 min for the AD group (min = 5.1, max = 21.3), and 13.8 min for the CN group (min = 12.5, max = 16.5). The sampling rate was 500 Hz.

Signal preprocessing

Firstly, the signals were re-referenced to A1-A2. Secondly, the Butterworth band-pass filter within the frequency range of 0.5 to 45 Hz was employed to eliminate artifacts. Thirdly, the independent component analysis (ICA) method was performed to cancel irrelevant noise. Finally, the automatic artifact reject technique, artifact subspace

reconstruction (ASR), in the EEGLAB toolbox (Delorme and Makeig, 2004), was used to exclude segments of data exceeding the conservative 0.5-s window standard deviation threshold of 17, considered as the maximum acceptable limit.

Feature extraction

In this study, the EEG signals were first extracted to 4-s epochs with a 50% overlap, forming the foundational dataset population, which was subsequently employed for classification with being labeled as AD or CN. Then, three types of signal features of resting-state EEG, i.e., spectrum, complexity, and synchronization, were extracted for each epoch.

Spectrum metrics

For time-domain metrics, the mean, variance, and interquartile range (IQR) were chosen as the features (Miltiadous et al., 2021). For a data segment x_j with length N, the mean metric $\bar{x}$, estimating the central tendency of a probability distribution for a variable, can be defined by:

$$\bar{x} = \frac{1}{N}\sum_{j=1}^{N} x_j$$

The variance metric Var, representing the width of data around its central value, can be defined by:

$$Var = \frac{1}{N-1}\sum_{j=1}^{N}\left(x_j - \bar{x}\right)^2$$

The IQR, the difference between Q_1 and Q_3, referred to 25th percentile (lower) and 75th percentile (upper), respectively, can be calculated by:

$$IQR = Q_3 - Q_1$$

For the frequency-domain metrics, firstly, the power spectral density (PSD) method was used for each 4-s epoch. Next, the PSD for the whole frequency range of 0.5–45 Hz can be also calculated. Then, the five basic EEG rhythms (namely delta of 0.5–4 Hz, theta of 4–8 Hz, alpha of 8–13 Hz, beta of 13–25 Hz, and gamma of 25–45 Hz) were obtained. Finally, to normalized processing, the relative band power (RBP) of each EEG rhythm was obtained by Miltiadous et al., (2023):

$$RBP_i = \frac{\text{Energy}_i}{\sum \text{Energy}_i}, i = \delta,\theta,\alpha,\beta,\gamma$$

Complexity metrics

Entropy measures typically quantify the degree of complexity and predictability of a signal (Coifman and Wickerhauser, 1992). In this study, the approximate entropy (ApEn), permutation entropy (PermEn), multiscale entropy (MSE), and sample entropy (SamplEn) were used to describe the complexity of the entire frequency spectrum.

ApEn is a non-linear method that can be utilized for quantifying the irregularity of a time series, which can be defined by:

$$\text{ApEn}\left(m,r,N\right) = -\left[\varphi^{m+1}\left(\mathrm{r}\right) - \varphi^{m}\left(\mathrm{r}\right)\right]$$

$$\text{where}\varphi^{m}\left(\mathrm{r}\right) = \sum_{k=1}^{N-m+1}\frac{\ln c_r^m\left(k\right)}{N-m+1}, \text{and} c_r^m\left(k\right) = \frac{\text{count}\left[d\left(k,l\right)\le r\right]}{N-m+1}$$

is a correlation integer estimated by the distance $d\left(k,l\right)$ between the vectors $u\left(k\right) = \left[x\left(k\right), x\left(k+1\right),\ldots, x\left(k+m-1\right)\right]$ and $u\left(l\right)$. In this study, the pattern length $m = 1$ and the similarity factor $r = 0.2$ times the standard deviation of the time series (Burioka et al., 2005; Abásolo et al., 2009).

PermEn is a complexity measure of ordinal patterns for arbitrary, noisy, and large signals, which can be defined by:

$$\text{PermEn} = -\int p\left(\pi\right)\log p\left(\pi\right)$$

where π represents all the permutations of order n, which corresponds to the number of embedding dimensions. $p\left(\pi\right)$ represents the probability associated with ordinal patterns π, indicating the relative frequency of ordinal patterns π (Bandt and Pompe, 2002). In this study, n was set as 3 (Tzimourta et al., 2019).

SamplEn is similar to ApEn but it excludes the assessment of self-similar patterns, which can be described by:

$$\text{SamplEn}\left(m,r,N\right) = -\ln\frac{\varphi^{m}\left(\mathrm{r}\right)}{\varphi^{m+1}\left(\mathrm{r}\right)}$$

$$\text{where}\,\varphi^{m}\left(\mathrm{r}\right) = \sum_{i=1}^{N-m+1}\frac{\ln c_r^m\left(i\right)}{N-m+1}, \text{and}\, c_r^m\left(i\right) = \frac{\text{count}\left[d\left(i,j\right)\le r\right]_{i\ne j}}{N-m+1}$$

estimated the distance $d\left(k,l\right)$ between the vectors $u\left(k\right) = \left[x\left(k\right), x\left(k+1\right),\ldots, x\left(k+m-1\right)\right]$ and $u\left(l\right)$. Among them, $m = 2$ and $r = 0.15$ (Yang et al., 2013).

As a modification of SamplEn for the scaled signal, MSE introduces a range for multiple time scales denoted as τ, employed to create a coarse-grained version of the original time series, and each element of the coarse-grained signal can be calculated by:

$$y_j^{(\tau)} = \frac{1}{\tau}\sum_{k=(j-1)\tau+1}^{j\tau} x_k, 1 \le j \le N/\tau$$

In our experiments, $m = 2, r = 0.15$, and $\tau = 5$, which was consistent with previous studies (Costa et al., 2005; Yang et al., 2013).

Synchronization metrics

Based largely on graph theory, recent developments in the analysis of signal synchronization have been rapidly developed (Liu et al., 2017). In this study, the four metrics of clustering coefficient, characteristic path length, efficiency, and small-worldness were used

to describe the signal synchronization from complex brain network features (Bullmore and Sporns, 2009).

The clustering coefficient measures the number of connections among the immediate neighbors of a node, expressed as a proportion of the maximum number of possible connections (Demuru et al., 2020). The clustering coefficient C_i of node i can be defined by:

$$C_i = \frac{2e_i}{k_i \cdot (k_i - 1)}$$

where e_i represents the number of edges in the neighborhood of node i, and k_i representing the degree of node i is a basic feature of the number of connections that node i makes to other nodes.

The characteristic path length L is the minimum number of edges required to traverse from one node to another, which can be defined by Gaal et al. (2010):

$$L = \frac{1}{N \cdot (N-1)} \sum_{i,j \in V, i \neq j} l_{ij}$$

where N represents the number of all nodes, and l_{ij} represents the minimum path length between notes i and j.Efficiency E_{global} exhibits an inverse relationship with path length, yet it is more straightforward to employ for estimating topological distances between elements of disconnected graphs, which can be defined by Buchel et al. (2021):

$$E_{global} = \frac{1}{N \cdot (N-1)} \sum_{i,j \in V, i \neq j} \frac{1}{l_i}$$

The 'small-world' property is characterized by a combination of elevated local clustering among nodes within a network and abbreviated paths that establish global connections across the network. Small-worldness σ is thus determined by the ratio of the clustering coefficient to the path length (Liu et al., 2017):

$$\sigma = \frac{\gamma}{\delta}$$

where γ represents the standardized clustering coefficients, defined by the ratio of the clustering coefficient to the random network's clustering coefficient, and δ represents the standardized characteristic path length, established as the ratio of characteristic path length to the random network's characteristic path length.

Classification algorithm

According to previous studies (Fiscon et al., 2018; Miltiadous et al., 2021; Safi and Safi, 2021), the supervised learning classification methods of decision trees, random forests, and SVM were used as the classifiers. For each algorithm, the leave-one-person-out cross-validation was used as the testing method (Miltiadous et al., 2021), where all epochs from a specific subject are designated as the test set, while the remaining epochs collectively form the training set. Then, the indexes of accuracy, sensitivity, and specificity were calculated, respectively, according to the following equations (Baratloo et al., 2015):

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN}$$

$$\text{Sensitivity} = \frac{TP}{TP + FN}$$

$$\text{Specificity} = \frac{TN}{TN + FP}$$

where the variables TP, FP, TN, and FN represent true positive, false positive, true negative, and false negative, respectively.

Results

Signal characteristics

To further analyze the spectrum characteristics of the signal, Figure 1 shows examples of the frequency-domain and time-frequency-domain analyses of resting-state EEG for CN and AD subjects. As shown in the frequency-domain spectrum and time-frequency-domain analysis of Figures 1A,B, there was some difference in the frequency spectrum EEG signals between CN and AD subjects, e.g., an increase in the delta rhythms in AD subjects.

Subsequently, the brain network analysis of resting-state EEG for CN and AD subjects was analyzed. As shown in Figure 2A, the correlation matrix between all pairs of electrodes was generated, indicating a decreasing correlation in AD subjects compared to CN subjects. As shown in Figure 2B, the analysis of the brain network gave clearer connectivity between all pairs of electrodes, showing that there was a decrease in brain network connectivity in AD subjects compared to CN subjects, indicating the decreased EEG synchrony in AD patients under rest conditions.

Signal features

For more statistical analysis of EEG signals between CN and AD subjects, the EEG data was first extracted to 4 s epochs with 50% overlap after being preprocessed for each subject, generating 14,515 epochs labeled AD from 36 AD subjects and 12,011 epochs labeled CN from 29 CN subjects. According to the difference between signal characteristics described above, the signal features of time-domain, frequency-domain, complexity, and synchronization were obtained for each epoch. Moreover, the mean and SD of these signal features are shown in Figure 3, and subsequently, their difference between AD and CN individuals was assessed by independent samples t-test.

For time-domain metrics, the mean, variance, and IQR demonstrated a little upward trend for AD subjects ($p < 0.001$, respectively). For frequency-domain metrics, the low-frequency bands of delta and theta showed a slight increase ($p < 0.05$, respectively), the high-frequency band of beta showed a slight decrease ($p < 0.05$), and the high-frequency bands of alpha and gamma showed a decreasing but insignificant trend, indicating that the major changes in the diagnosis of AD were the attenuated power in higher frequency bands (alpha, beta, and gamma) and increased power in

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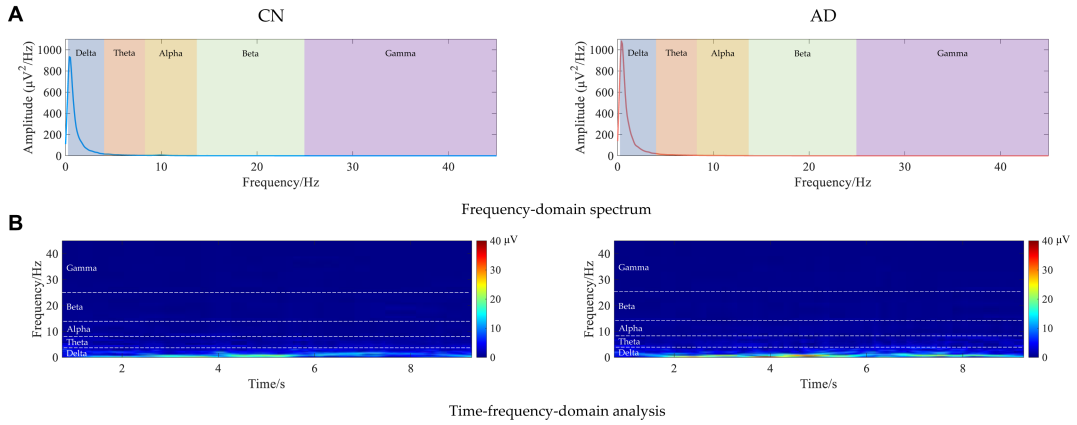

FIGURE 1
Examples of the frequency-domain and time-frequency-domain analyses of resting-state EEG for CN and AD subjects. **(A)** Frequency-domain spectrum. **(B)** Time-frequency-domain analysis.

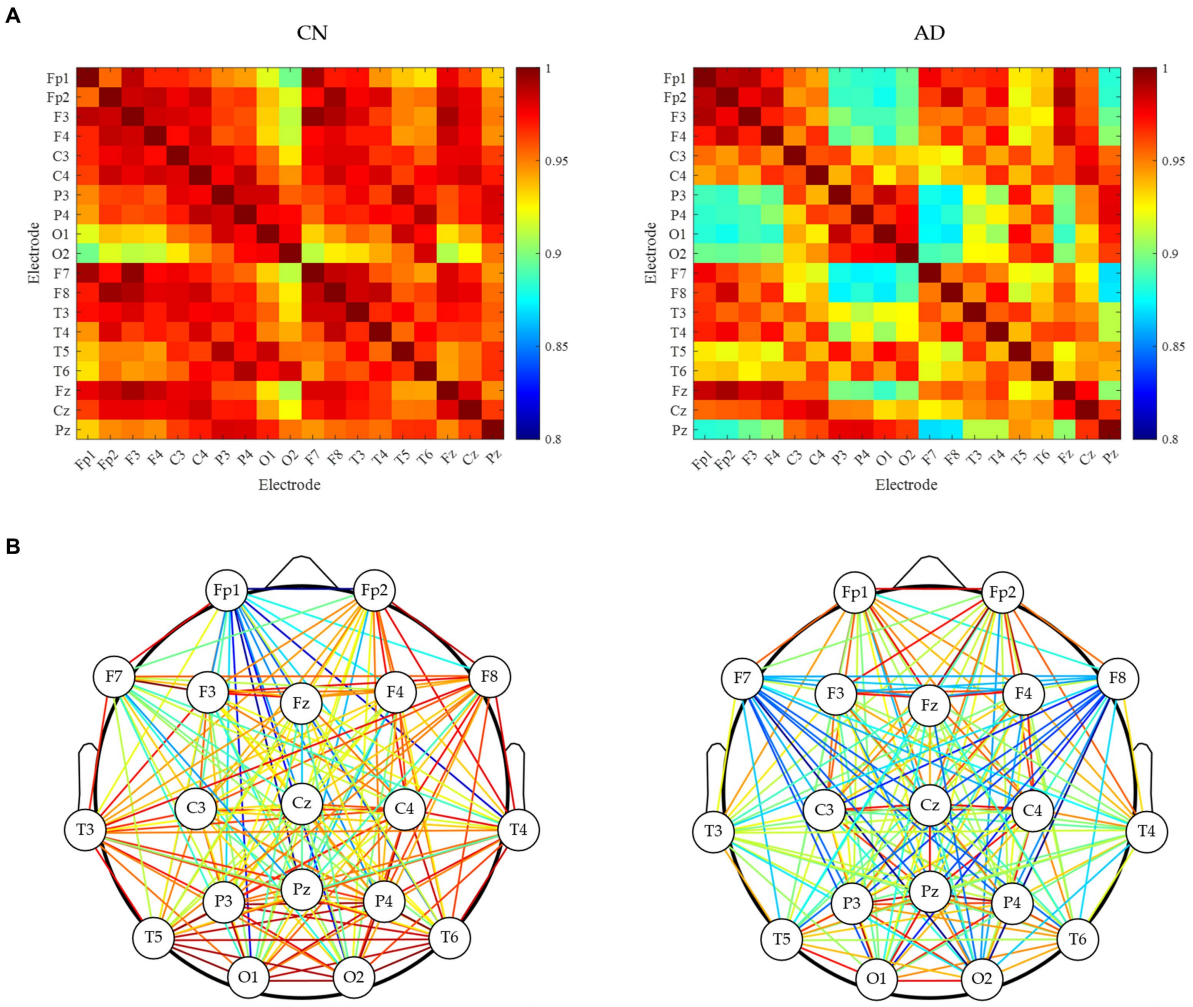

FIGURE 2
Brain network analysis of resting-state EEG for CN and AD subjects. **(A)** Correlation matrix between each electrode. **(B)** brain network connectivity.

lower bands (delta and theta), that is AD caused EEG signals to slow down. For complexity metrics, the entropies of PermEn, SamplEn, and MSE presented a low value in AD subjects ($p < 0.001$, respectively), revealing that EEG signals of AD showed reduced complexity and seemed to be regular. For synchronization metrics, the features of clustering coefficient and small-worldness demonstrated a decreasing

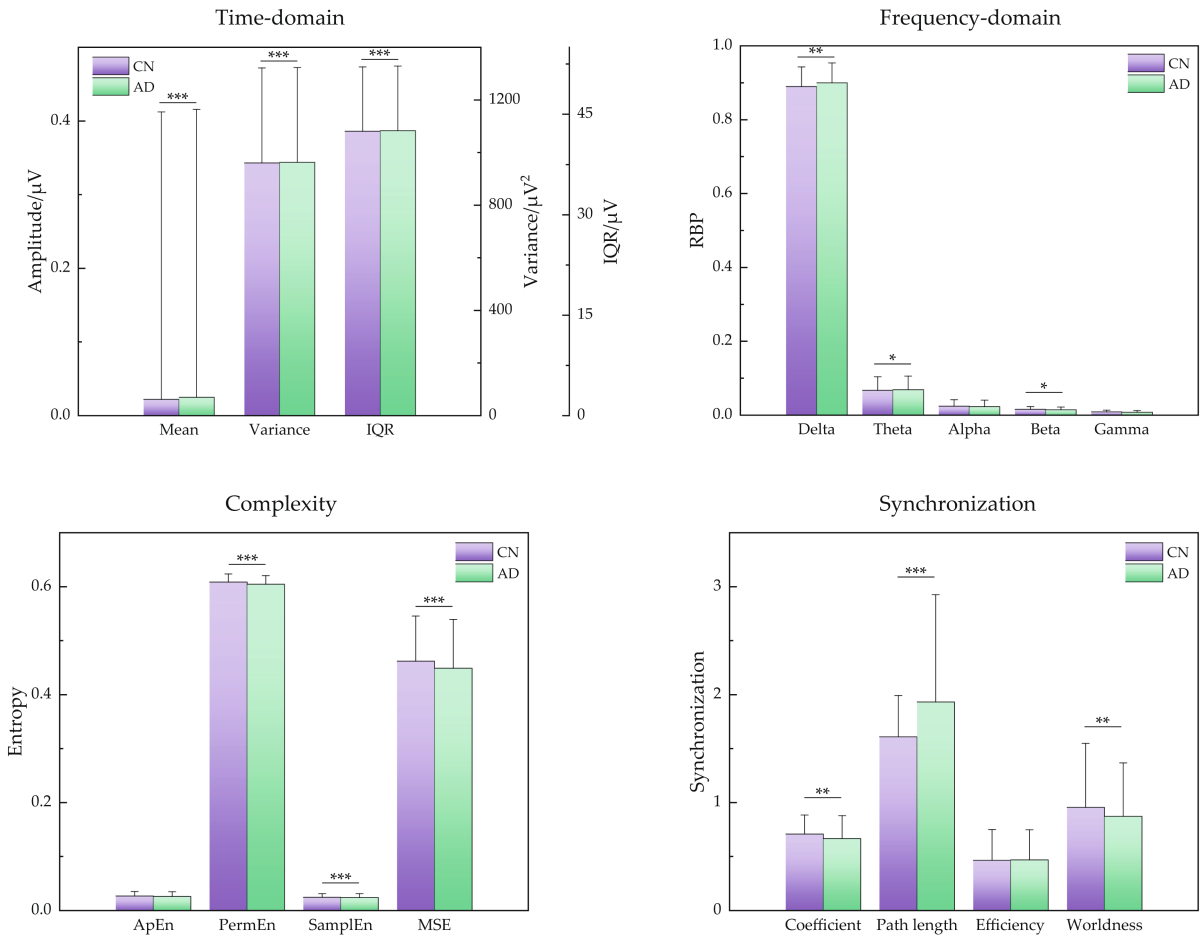

FIGURE 3
Signal features of time-domain, frequency-domain, signal complexity, and signal synchronization for CN and AD individuals. Statistics were assessed by independent samples t-test. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

TABLE 1 Accuracy, sensitivity, and specificity results of three classification algorithms with leave-one-person-out cross-validation.

	Accuracy	Sensitivity	Specificity
Decision tree	95.65%	95.91%	95.35%
Random forest	95.86%	96.41%	97.40%
SVM	88.54%	94.72%	81.23%

tendency ($p < 0.01$, respectively) and characteristic path length demonstrated an increasing tendency ($p < 0.001$), showing decreased EEG synchrony in AD patients.

Classification results

Using these EEG signal features, three classification algorithms of decision trees, random forests, and SVM were carried out to identify the AD and CN groups by the leave-one-person-out cross-validation. Table 1 presents the accuracy, sensitivity, and specificity results of three classification algorithms, showing that the random forest achieved the highest classification performance with an accuracy of 95.86%, and SVM performed the lowest accuracy of 88.54%.

Discussion

The presented study underscores the potential of integrating signal features from spectrum, complexity, and synchronization domains of resting-state EEG for enhancing the diagnosis of AD. This study achieved a higher classification accuracy performance of 95.86% for AD and CN subjects based on resting-state EEG, compared to previous studies using the same dataset with a classification accuracy of 77.01% (Miltiadous et al., 2023), showing the combination of these three types of EEG signal features can enhance the classification performance. Besides, in contrast to other studies, e.g., the classification accuracy of 78.50% (Miltiadous et al., 2021) and 83.30% (Fiscon et al., 2018), our study also showed a better performance.

By capturing diverse aspects of neural dysfunction, this integration of spectrum, complexity, and synchronization signal features may offer a more holistic understanding of the underlying pathology. Several key factors have been studied and explored in the pathological causes of AD, e.g., plaques composed of amyloid β, and tangles composed of hyperphosphorylated tau (Scheltens et al., 2021).

According to the signal features shown in Figure 3, first, the power spectrum shifted from higher frequency components (alpha, beta, and gamma) toward lower frequency components (delta and theta), which may be related to loss of cholinergic innervations in AD patients (Cassani et al., 2018). Second, a decrease in the complexity of the brain's electrical activity has been noted in AD patients. This phenomenon is potentially attributed to extensive neuronal loss and diminished connectivity in cortical regions, resulting in simpler EEG dynamics (Czigler et al., 2008). Third, reduced synchrony was also presented in AD patients, which can potentially be attributed to a functional disconnection within the neocortex, e.g., anatomical disconnections among different cortical regions in combination (Dauwels et al., 2010).

As for the validation method, this study adopted the leave-one-person-out cross-validation method. In contrast to k-fold cross-validation, which employs samples from the same participant in both training and test sets, the leave-one-person-out cross-validation method offers a more realistic validation strategy since no same-subject epochs were in both the training and the test set at the same time (Häfner et al., 2012; Isler et al., 2015).

Some limitations should also be paid attention in this study. First of all, this study only focused on the classification of AD and CN subjects. However, the severity of AD may affect EEG performance, and the severity, e.g., mild, moderate, and serious (Cassani et al., 2018), may also be classified in future studies. Next, the signal processing and feature extraction methods can also be further expanded. For example, the synchronization metrics may also be obtained by Granger causality (Babiloni et al., 2016), phase coherence (McBride et al., 2013), and state space synchrony (Wang et al., 2016), except for the mentioned methods in this study. Then, the features were obtained by averaging EEG signals across the whole recorded electrodes. Nevertheless, the cause of AD may arise from specific brain regions with variable effects on each channel's EEG signals, and the average approach may not be very appropriate. Some techniques, e.g., EEG topographic map (Zheng et al., 2020), physiological cognition (Ranchet et al., 2017), and partial brain networks (Schöll, 2022), may be further carried out in future studies.

Based on prior research, researchers have computed an array of statistical characteristics from EEG recordings, e.g., cohesion (Lindau et al., 2003), wavelet analysis (Fiscon et al., 2018), and Hjorth parameters (Safi and Safi, 2021), which were subsequently employed to train their classification models. Moreover, in some studies, the basic EEG rhythms were further divided (Nishida et al., 2011). For example, the rhythm alpha was found as α1 (8–10 Hz) and α2 (10–12 Hz), and the rhythm beta was divided into β1 (12.5–18 Hz), β2 (18.5–21 Hz), and β3 (21.5–30 Hz) (Caso et al., 2012). Hence, in future studies, further division of EEG rhythms may be used in the frequency-domain metrics and entropies.

Another point the authors would like to mention was that the regional distribution of the brain of these features corresponding to AD was not always consistent for each EEG rhythm and each subject (Knyazeva et al., 2010; Tzimourta et al., 2019). Hence, future studies may focus on the detailed distribution of EEG to find the EEG source localization for AD pathogenesis, and then combine EEG signaling manifestations with causes of AD formation to achieve early detection of AD (Aghajani et al., 2013). Furthermore, the deep learning methods based on large databases can also be explored in future work to realize end-to-end prediction (Khojaste-Sarakhsi et al., 2022).

Conclusion

The proposed integrated approach of three types of EEG signal features demonstrated promising results in differentiating AD patients from healthy controls. The fusion of spectrum, complexity, and synchronization features exhibited improved diagnostic accuracy compared to using individual features alone. This suggests that the combination of multi-domain features of EEG signals provides a more comprehensive representation of the neurophysiological changes associated with AD. This study recommended the integration of EEG features of spectrum, complexity, and synchronization for aiding the diagnosis of AD.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Scientific and Ethics Committee of AHEPA University Hospital, Aristotle University of Thessaloniki. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XZ: Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. BW: Investigation, Writing – original draft. HL: Data curation, Writing – review & editing. WW: Validation, Writing – original draft. JS: Methodology, Project administration, Writing – original draft. WF: Project administration, Writing – original draft. RJ: Funding acquisition, Writing – original draft. YH: Formal analysis, Writing – review & editing. CJ: Conceptualization, Writing – review & editing. XW: Funding–acquisition, Project administration, Visualization, Writing – review & editing. SC: Conceptualization, Data curation, Resources, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Chromatic pupillometry for evaluating melanopsin retinal ganglion cell function in Alzheimer's disease and other neurodegenerative disorders: a review

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The evaluation of pupillary light reflex (PLR) by chromatic pupillometry may provide a unique insight into specific photoreceptor functions. Chromatic pupillometry refers to evaluating PLR to different wavelengths and intensities of light in order to differentiate outer/inner retinal photoreceptor contributions to the PLR. Different protocols have been tested and are now established to assess *in-vivo* PLR contribution mediated by melanopsin retinal ganglion cells (mRGCs). These intrinsically photosensitive photoreceptors modulate the non-image-forming functions of the eye, which are mainly the circadian photoentrainment and PLR, via projections to the hypothalamic suprachiasmatic and olivary pretectal nucleus, respectively. In this context, chromatic pupillometry has been used as an alternative and non-invasive tool to evaluate the mRGC system in several clinical settings, including hereditary optic neuropathies, glaucoma, and neurodegenerative disorders such as Parkinson's disease (PD), idiopathic/isolated rapid eye movement sleep behavior disorder (iRBD), and Alzheimer's disease (AD). The purpose of this article is to review the key steps of chromatic pupillometry protocols for studying *in-vivo* mRGC-system functionality and provide the main findings of this technique in the research setting on neurodegeneration. mRGC-dependent pupillary responses are short-wavelength sensitive, have a higher threshold of activation, and are much slower and sustained compared with rod- and cone-mediated responses, driving the tonic component of the PLR during exposure to high-irradiance and continuous light stimulus. Thus, mRGCs contribute mainly to the tonic component of the post-illumination pupil response (PIPR) to bright blue light flash that persists after light stimulation is switched off. Given the role of mRGCs in circadian photoentrainment, the use of chromatic pupillometry to perform a functional evaluation of mRGcs may be proposed as an early biomarker of mRGC-dysfunction in neurodegenerative disorders characterized by circadian and/or sleep dysfunction such as AD, PD, and its prodromal phase iRBD. The evaluation by chromatic pupillometry of mRGC-system functionality may lay the groundwork for a new, easily accessible biomarker that can be exploited also as the starting point for future longitudinal cohort studies aimed at stratifying the risk of conversion in these disorders.

KEYWORDS

chromatic pupillometry, melanopsin retinal ganglion cells, Alzheimer's disease, pupil, post-illumination pupil response, neurodegeneration

1 Introduction

Over the last decades, the pupil has been considered a window into brain functions for a wide range of clinical settings, including neurodegenerative disorders (Hall and Chilcott, 2018). More specifically, the evaluation of pupil size and dynamics to light stimulation, i.e., pupillary light reflex (PLR), by chromatic pupillometry may provide a unique insight into specific photoreceptor functions (Park et al., 2011; Hall and Chilcott, 2018).

The pupil has a large dynamic range and is controlled by the antagonistic actions of the iris sphincter and dilator muscles, which are innervated by the parasympathetic and sympathetic nervous systems, respectively (Hall and Chilcott, 2018). Average pupil diameter is influenced by factors such as age, sex, iris color, retinal and/or optic nerve health, and optical media clarity, but the most powerful determinant of pupil size is the ambient light level (Hall and Chilcott, 2018).

The term PLR refers to a reflex that controls the constriction and subsequent dilation of the pupil in response to changes in light intensity, and its dynamics follow a pattern composed of four phases (response latency, maximum constriction, pupil escape, and recovery) that can be influenced by the duration, intensity and spectral composition of the light (Hall and Chilcott, 2018). In addition to these PLR dynamic phases, during light stimulation, which is mainly driven by rods and cones, it can be also recognized a slow and sustained component (Park et al., 2011; Adhikari et al., 2016; Joyce et al., 2016) named post-illumination pupil response (PIPR) (Berson et al., 2002; Park et al., 2011). The PIPR is mainly dependent on melanopsin retinal ganglion cells (mRGCs) (Kardon et al., 2009; Park et al., 2011; Adhikari et al., 2015), a class of retinal ganglion cells (RGCs) expressing the photopigment melanopsin, which are intrinsically photosensitive and project to the olivary pretectal nucleus (OPN), the pupillomotor center (Berson et al., 2002; Hattar et al., 2002). Differently, the early sustained PIPR depends on the contributions of both outer and inner retinal photoreceptors (Adhikari et al., 2016; Hall and Chilcott, 2018). Considering that rods, cones, and mRGCs play different roles in mediating the PLR (McDougal and Gamlin, 2010; Rukmini et al., 2019), light stimuli can be designed to preferentially stimulate each photoreceptor class, thus providing a readout of their function (Kardon et al., 2009; Park and McAnany, 2015).

Melanopsin RGCs belong to the most recently identified cell type in the ganglion cell layer of the mammalian retina (Do and Yau, 2010; Hannibal et al., 2017) and represent the third photoreceptor of the eye. These intrinsically photosensitive photoreceptors modulate the non-image-forming functions of the eye, which are mainly the circadian photoentrainment and PLR, via projections to the hypothalamic suprachiasmatic and OPN, respectively (Hattar et al., 2002).

These cells are characterized by a unique property, which is the capability of firing without fatigue in response to continuous stimulation (La Morgia et al., 2018), consistent with their intrinsic activation (Berson et al., 2002; Hattar et al., 2002). In particular, the PIPR magnitude measured after 1.7 s (s) from offset of the light stimulus is considered a specific measure of mRGC function (Adhikari et al., 2015, 2016). In this context, chromatic pupillometry has been used to evaluate this cellular system in several clinical settings, including blinding disorders such as hereditary optic neuropathies (Kawasaki et al., 2010; Moura et al., 2013; Kawasaki et al., 2014; Munch et al., 2015; Nissen et al., 2015; Ba-Ali and Lund-Andersen, 2017; Loo et al., 2017), glaucoma (Kankipati et al., 2011; Rukmini et al., 2015; Kelbsch et al., 2016; Najjar et al., 2018, 2023) and neurodegenerative disorders such as Parkinson's disease (PD) (Joyce et al., 2018; Feigl et al., 2020; Tabashum et al., 2021; Gaynes et al., 2022), idiopathic/isolated rapid eye movement sleep behavior disorder (iRBD) (La Morgia et al., 2022; Steiner et al., 2022), and Alzheimer's disease (AD) (Oh et al., 2019; Romagnoli et al., 2020; La Morgia et al., 2023).

The purpose of this article is to briefly review the key steps of chromatic pupillometry protocols for studying *in-vivo* mRGC system functionality and provide the main findings of this technique in the research setting on neurodegeneration.

1.1 Search criteria

A PubMed literature search was conducted to identify the human studies available in the literature about chromatic pupillometry in Alzheimer's disease. In order to provide a comparison with other neurodegenerative disorders, studies on chromatic pupillometry in Parkinson's disease and isolated REM behavior disorder, were also included in the review. Conversely, works regarding achromatic pupillometry in these pathologies were excluded. The methodology used for the literature search consisted of a thorough search in PubMed including the following keywords, isolated and in combination: "melanopsin," "pupillometry," "chromatic pupillometry," "pupil," "Alzheimer," "Parkinson," and "REM behavior disorder."

2 Key steps of a chromatic pupillometry protocol for *in-vivo* mRGC system evaluation

Chromatic pupillometry (also termed color pupillometry or selective wavelength pupillometry) refers to the evaluation of pupillary response to different wavelengths and intensities of light in order to differentiate outer and inner retinal photoreceptor-dependent contributions to the pupillary light reflex (PLR) (Rukmini et al., 2019). Different protocols, using different light paradigms and experimental settings of stimulation, have been tested and are now established to assess *in-vivo* PLR contribution mediated by melanopsin retinal ganglion cells (mRGCs) (Park et al., 2011; Adhikari et al., 2015; Chougule et al., 2019; Kelbsch et al., 2019; Rukmini et al., 2019).

Melanopsin-dependent pupillary responses are short-wavelength sensitive, have a higher threshold of activation, and are much slower and sustained compared with rod- and cone-mediated responses, dominating the tonic component of the PLR during exposure to high-irradiance and continuous light stimulus (Rukmini et al., 2019). Indeed, mRGCs contribute mainly to the tonic component of the post-illumination pupil response (PIPR) to bright blue light flash that persists after light stimulation is switched off (Adhikari et al., 2015). Given the role of mRGCs in circadian photoentrainment, the use of chromatic pupillometry to perform a functional evaluation of mRGcs may be proposed as an early biomarker of mRGC dysfunction in neurodegenerative disorders characterized by circadian and/or sleep dysfunction such as Alzheimer's disease (AD), Parkinson's disease (PD), and its prodromal stage, idiopathic/isolated rapid eye movement sleep behavior disorder (iRBD) (Wu and Swaab, 2007; Oosterman et al., 2009; Doppler et al., 2017; Ortuno-Lizaran et al., 2018). Specifically, chromatic pupillometry protocols aimed at detecting mRGC function can be categorized as those using short-duration light stimuli (e.g., light flashes or pulses) or those using continuously presented light stimuli (e.g., >30 s) (Rukmini et al., 2019).

One of these established standardized protocols takes about 30 min after a 10-min period of dark adaptation and implies a series of short-duration light (1 s) exposures (470 nm blue/640 nm red light) to assess the rod- (Figure 1A), melanopsin- (Figure 1B), and cone- (Figure 1C) PLR contribution (Park et al., 2011). In our clinic, we routinely adopted this protocol for research purposes in patients affected by different neurodegenerative disorders to ensure as much as possible compliance of these patients given its use of a short-duration stimulus (Figures 1A–C). Details of this protocol are fully described elsewhere (Park et al., 2011), but here we provide the main methodological steps:

1. Monocular recording of the dominant eye (contralateral one covered with a patch);
2. 10 min of dark adaption to naturally dilate the eye prior to chromatic pupillometry testing;
3. Colored light stimuli presentation by using a Ganzfeld ColorDome full-field stimulator (Espion V6, ColorDome Desktop Ganzfeld; Diagnosys LLC, Lowell, MA, United States) with an integrated pupillometer. In particular, mRGC contribution to the PLR was specifically assessed employing high-intensity photopically matched red and blue stimuli (450 cd/m^2) presented in the dark. Specifically, stimuli consisted of long wavelength (red, dominant wavelength of 620–645 nm; mid = 632 nm) and short wavelength (blue, dominant wavelength of 460–485 nm; mid = 472 nm) light flashes of 1 s (s) duration. The integrated pupillometer system measured the pupil diameter at a 100 Hz sampling frequency. The interstimulus interval (ISI) was 30 s for the red stimulus and 70 s for the blue one. All recordings were completed in the same order with the red stimulus followed by the blue. Each stimulus was presented three times consecutively and the individual responses were obtained by their average recording.
4. Data quality control and analysis.

Since the eye-tracking systems may vary considerably in their sampling rate, precision, and noise susceptibility, as well as in the way they mark missing data, it is important to inspect the signals and efficacy of the preprocessing pipeline prior to analyzing the pupil size data. Indiscriminate inclusion of all available data or the use of non-robust outlier rejection methods may result in unnecessarily contaminated datasets, which could lead to incorrect interpretations of the collected data (Kret and Sjak-Shie, 2019). Briefly, the

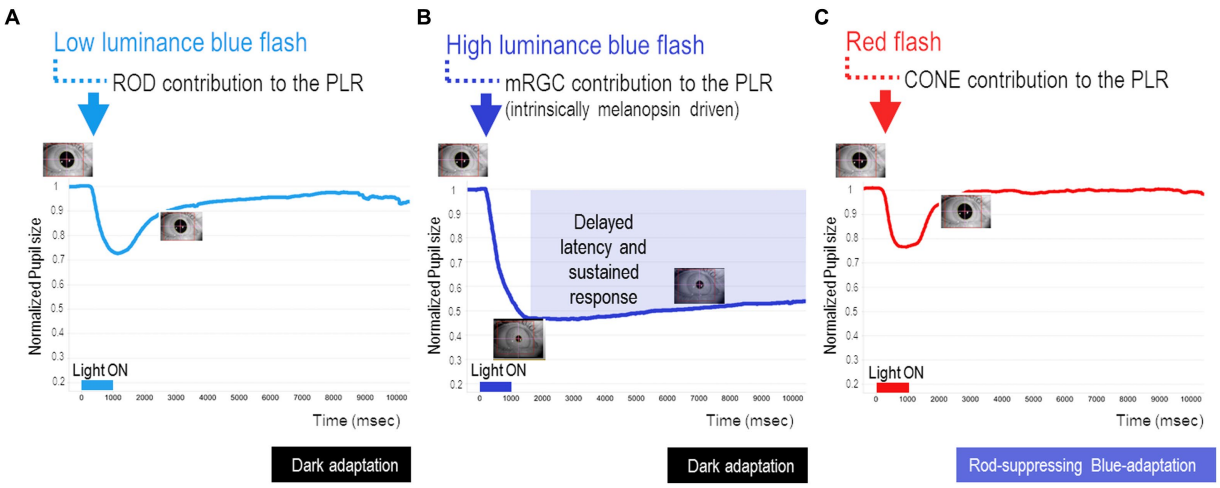

FIGURE 1
Key steps of chromatic pupillometry protocol for assessing retinal photoreceptor contributions to the human pupil light reflex (PLR). For our routine experimental research setting, we considered the following conditions, as previously reported (Park et al., 2011): **(A)** Rod-condition: low luminance (0.001 cd/m^2) blue light flash presented in the dark. **(B)** Melanopsin-condition: photopically matched red and blue light flashes (450 cd/m^2) presented in the dark. **(C)** Cone-condition: red light flash (10 cd/m^2) presented on the rod-suppressing blue adapting field (6 cd/m^2). Stimuli consisted of short wavelength (blue, dominant wavelength of 460–485 nm; mid = 472 nm) and long wavelength (red, dominant wavelength of 620–645 nm; mid = 632 nm) light flashes of 1 s (s) duration. The integrated pupillometer system measured the pupil diameter at a 100 Hz sampling frequency. The interstimulus interval (ISI) was 20 s for the rod- and cone-conditions (for both red and blue stimuli), while for the melanopsin condition, ISI was 30 s for the red stimulus and 70 s for the blue one. All recordings were completed in the same order with the red stimulus followed by the blue. For all three conditions, each stimulus was presented three times consecutively and the individual responses were obtained by their average recording.

preprocessing pipeline (Kret and Sjak-Shie, 2019) can be broken down into:

(I) Preparing the raw eye-tracker output;

(II) Filtering the raw data: by doing so, we are able to identify three types of often occurring invalid pupil size samples (Kret and Sjak-Shie, 2019), namely, dilation speed outliers and edge artifacts, trend-line deviation outliers, and temporally isolated samples.

(III) Upsampling and smoothing the valid samples;

(IV) Splitting the data into the relevant segments and analyzing each segment individually.

In particular, our approach to pupil data preprocessing was to apply a median filter to remove the background noise and the noise given by the eye blink artifacts. Then, we proceeded with the baseline correction (i.e., analyzing changes in pupil size relative to a baseline period), which improves statistical power by taking into account random fluctuations in pupil size over time and controls for individual differences in pupil diameter (Mathot et al., 2018; Kelbsch et al., 2019) (Figures 2A,B). In this regard, we usually normalized the filtered pupil traces by the median pupil size during the 2 s in darkness preceding each light stimulus onset (Figure 2B). First, the median pupil size during the 2 s in darkness just before light exposure was taken as baseline pupil size, then all pupil sizes were divided by this baseline diameter and this was done separately for each trial (normalized pupil size = pupil size/baseline).

3 Chromatic pupillometry mRGC system metrics and their interpretation

Pupillary light reflex (PLR) can be used as an alternative and non-invasive tool to evaluate photoreceptor retinal functions (Maynard et al., 2015).

There are different metrics that could be used to quantify the contribution of rods and cones on human PLR as well as of the melanopsin retinal ganglion cells (mRGCs) (Adhikari et al., 2015). In particular, rod/cone metrics are categorized under the name of "PLR metrics" since they are calculated during the transient pupil constriction being elicited during the light stimulation under the corresponding protocol conditions, while the established marker of direct, intrinsic melanopsin activity is the post-illumination pupil response (PIPR), the sustained pupil-constriction after light offset (Dacey et al., 2005; Wong, 2012; Adhikari et al., 2015).

The PLR signal is quite robust, and metrics could be directly derived from raw data. However, the noise intrinsic to any electrophysiological recording suggests deriving PLR/PIPR metrics not only from raw data but also fitting the collected pupil data to a predefined model (linear, logarithmic, or exponential), and using the related parameters to extract the salient metrics.

We summarize our recently published chromatic pupillometry metrics (La Morgia et al., 2023) as indirect and direct measures of mRGC contribution to the PLR (Table 1 and Figure 3). Generally speaking, the PLR entity and its dynamics could be measured by two approaches. One approach is to quantify the PLR starting from real data resulting from the chromatic pupillometry experiment by calculating parameters such as peak amplitude, contraction onset timing, average slope, and PIPR (Figures 3A,B,D). On the other hand, we may also adopt an approach based on best-fitting (the process of fitting experimental data to a specific mathematical model whose parameters are optimized) to obtain parameter estimates as the global rate constant of an exponential function (Figures 3C,E).

To describe in detail these chromatic pupillometry outcomes, peak amplitude (the maximum pupil constriction entity) was defined as the difference between the normalized baseline and the minimum normalized PLR around 700–1,500 milliseconds (msec) from the light-stimulus onset (Figure 3A), and the contraction onset timing was defined as the time taken to start pupil constriction from light-stimulus onset (Figure 3B). Considering these two PLR metrics, a

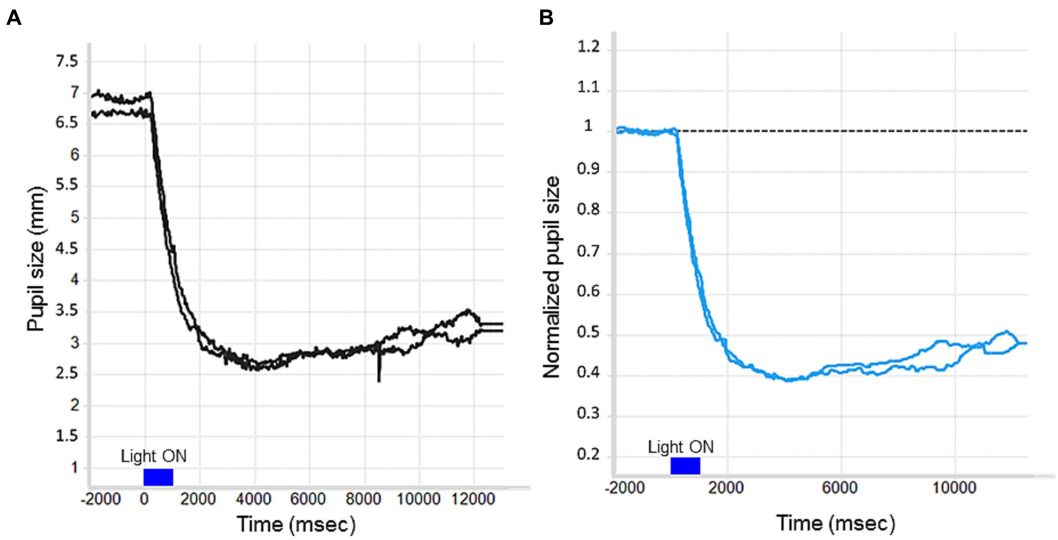

FIGURE 2
The effect of baseline correction on a raw PLR trace. **(A)** No baseline correction. **(B)** Divisive baseline correction: The Y-axis reflects proportional pupil size change relative to the baseline period.

TABLE 1 Description and definition of the proposed PLR and PIPR metrics.

Metrics	Definition
PLR metrics	
Peak amplitude	Difference between the normalized baseline and the minimum normalized PLR after light-stimulus onset
Contraction onset timing	Time taken to start pupil constriction from the light-stimulus onset
Average slope	$\frac{Peak\ amplitude}{Contraction\ peak\ timing - Contraction\ onset\ timing}$
Constriction velocity	By negative exponential fitting of the constriction phase of the PLR curve in the form: $y(t) = A - B \times e^{-\gg \times t}$ where A is a constant, » is the constriction velocity (global rate constant), and t is time in msec
PIPR metric	
PIPR	Difference between the normalized baseline and the median normalized PLR measured over a 5–7 s time interval from the light-stimulus offset
Early AUC	Area under the curve over 5–7 s time interval from the light-stimulus offset
Redilation velocity	The global rate constant of the exponential fitted mRGC sustained response curve during the redilation phase

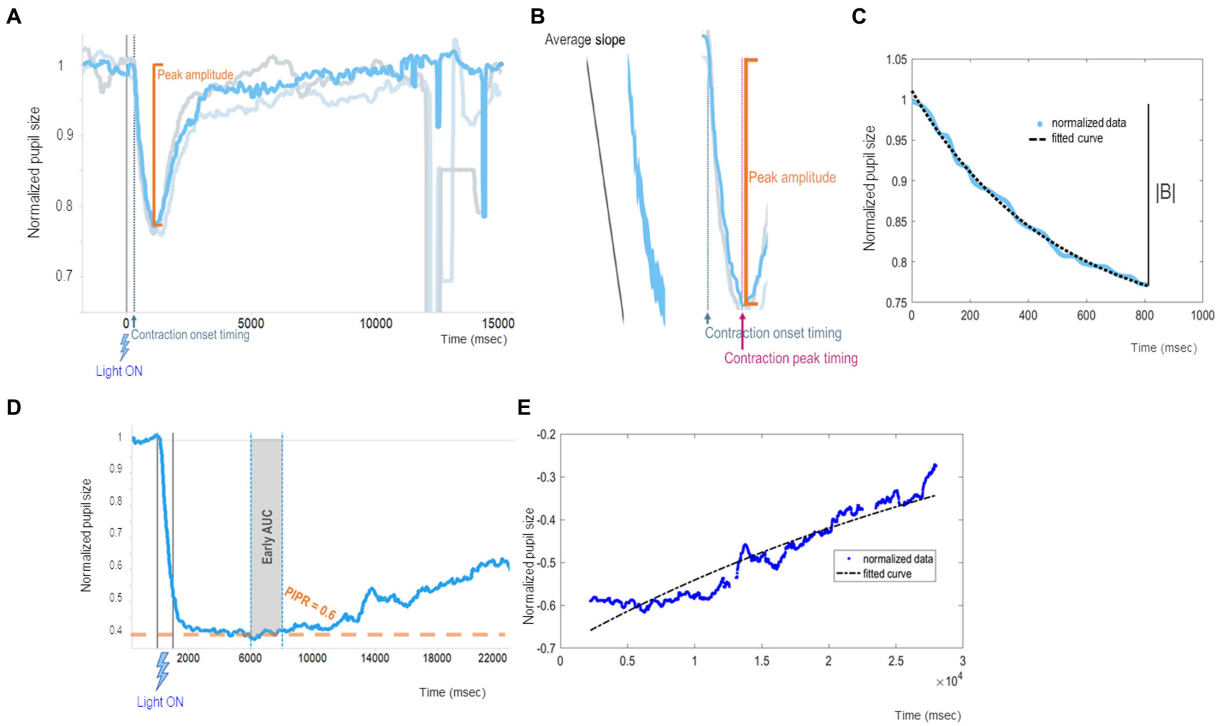

FIGURE 3
Example of chromatic pupillometry data analysis mRGC system metrics. **(A–C)** show examples of PLR metrics that mainly concern the onset of pupil contraction (which has a timing t1 and an amplitude y1 equal to the baseline) and its maximum constriction (which has a timing t2 and an amplitude y2, too) from which it is possible to calculate other metrics such as contraction onset timing (t1), contraction duration (t2-t1), peak amplitude [equal to the contraction amplitude (y2-y1)], and average slopes (y2-y1)/(t2-t1). In particular: **(A)** shows peak amplitude (or transient peak amplitude), which is defined as the difference between the normalized baseline and the minimum normalized PLR after light-stimulus onset (pupil maximum constriction); **(B)** shows an example of normalized PLR trace (azure line) and the contraction onset timing (latency relative to the stimulus delivery needed for the pupil to start constriction) and average slope (computed as the ratio between the peak amplitude and the duration of the contraction) parameters; **(C)** shows an example of a fitted PLR curve (black curve) by using the negative exponential model $y(t) = A - B \times e^{-\gg \times t}$ where A is a constant, » is the constriction velocity (global rate constant), and t is time in msec. **(D,E)** show examples of PIPR metrics evaluating mRGC sustained response entity and its dynamics: **(D)** shows an example of normalized PLR trace (azure line) with PIPR and early AUC (in gray shadow) parameters, where PIPR is calculated as the difference between the normalized baseline and the median normalized PLR measured over a 5–7 s time interval from the stimulus offset. **(E)** shows an example of an exponential modeled curve (black curve) during the mRGC-sustained response (redilation phase).

larger PLR would be the one with a higher value of peak amplitude and a smaller value of contraction onset timing. In addition, we can calculate the average slope as the ratio between the aforementioned peak amplitude and time between the contraction peak timing and the contraction onset timing, as a metric indicative of the pupil constriction velocity (Figure 3B).

As an alternative to the univariate analysis, we can fit the contraction phase to a negative exponential model $y(t) = A - B \times e^{-\lambda \times t}$, where $A - B$ represents the initial value obtained when setting time (t) to 0. In turn, the asymptote reached at an infinite time is A, thus B represents the ideal extent of the contraction in case of an infinite stimulation. Then, λ is the time constant of the exponential curve, i.e., a parameter reflecting the speed of the pupil contraction. Figure 3 recapitulates all the abovementioned parameters with graphical examples.

Moreover, there are several metrics to quantify mRGC intrinsic sustained response, starting from real data as well as based on exponential best-fitting (Adhikari et al., 2015). Based on our previous publications (Romagnoli et al., 2020; La Morgia et al., 2023), the parameters for assessing mRGC sustained response produced by 1 s (s) bright blue light-flash could be the so-called PIPR, early area under curve (AUC) and redilation velocity (Figures 3D,E). PIPR parameter was defined as the difference between the normalized baseline and the median normalized PLR measured over a 5 to 7 s time interval from the light-stimulus offset. A specular metric to PIPR was the AUC estimated early in relation to the same time interval. By respecting these metrics, a larger mRGC sustained response corresponds to larger values of 5–7 s PIPR and early AUC. Mirroring the above case, the dynamics of intrinsic mRGC activity could be estimated via exponential fitting of the pupil redilation phase with the estimation of the exponential coefficient of the best-fitted curve. A larger mRGC sustained response would be defined by higher values of PIPR and early AUC, and by smaller values of redilation velocity as indexed by the time constant of the exponential curve.

4 The potential of chromatic pupillometry technique in the setting of AD research

Chromatic pupillometry has been proposed as a tool to specifically evaluate melanopsin retinal ganglion cell (mRGC) dysfunction in some neurodegenerative disorders, particularly in Alzheimer's disease (AD), as in AD the presence of retinal ganglion cell (RGC) loss has been already documented (Hinton et al., 1986; Curcio and Drucker, 1993) as well as the occurrence of abnormal circadian photoentrainment (La Morgia et al., 2017).

A great deal of studies are available on animal models and these are characterized by circadian and sleep dysfunction even in the early phases of the disease (Uddin et al., 2020). Based on this, an early mRGC dysfunction or loss, which has been already demonstrated in *post-mortem* AD retinas in humans (La Morgia et al., 2016), may be envisaged as a contributor to the circadian and sleep dysregulation in these patients (La Morgia et al., 2017).

AD is the most frequent cause of dementia, characterized by abnormal accumulation of misfolded amyloid-ß (Aß) protein and hyperphosphorylated tau in the brain. Cognitive impairment and memory loss are the most prominent features of the disease, nevertheless, visual and sleep disturbances are frequently reported from the disease's early phases (Uddin et al., 2020). Besides the pathological involvement of the visual cortex, histological hallmarks of AD in the form of amyloid extracellular plaques have also been demonstrated in the eye, especially in the inner retina, in *post-mortem* tissues from patients with AD (Koronyo et al., 2017). The resulting degeneration of RGCs with macular and optic nerve thinning was also confirmed by several *in-vivo* studies with optic coherence tomography (OCT) (Chen et al., 2023). These studies demonstrated a retinal nerve fiber layer (RNFL) thinning mostly in the superior and inferior sectors of the optic nerve, suggesting a preferential loss of the magnocellular component of the optic nerve in AD (Chan et al., 2019). Interestingly, the presence of amyloid pathology has also been demonstrated within the mRGCs in *post-mortem* AD human retinas, as well as the presence of morphological alterations in the surviving mRGCs, such as dendrite varicosities and reduced arborization (La Morgia et al., 2016). This suggests that an early mRGC dysfunction or loss may contribute to the circadian and sleep dysregulation frequently observed in these patients.

The current recommendations for AD diagnosis include tau/amyloid cerebrospinal fluid (CSF) and positron emission tomography (PET) imaging (Dubois et al., 2021), but there is a still unmet need for easily accessible and objective biomarkers either for biological definition of AD and its prodromal phase, the amnestic mild cognitive impairment (aMCI), as well as for stratifying the risk of conversion from aMCI to AD. To improve diagnostic capabilities for AD and aMCI, the diagnostic workup should include laboratory- and/or instrumental-measured early biomarkers; however, the routine use of biomarkers in the clinical setting is not yet recommended for both conceptual and evidence-based reasons (Dubois et al., 2021). In this framework, considering the role of mRGCs in circadian photoentrainment, the use of chromatic pupillometry to perform a functional evaluation of mRGcs may be a potential biomarker of mRGC dysfunction and, thus, of circadian dysfunction in both AD and aMCI.

Besides chromatic pupillometry, non-chromatic pupillometry was variably used in patients with AD, not specifically addressing the mRCG contribution to the pupillary light reflex (PLR) but mainly the cholinergic/parasympathetic dysfunction typical of AD. The results obtained have highlighted significant changes in terms of latency, amplitude, maximum constriction velocity, and acceleration in patients with AD, but did not find any significant difference in PLR in preclinical AD compared with controls (Chougule et al., 2019). Interestingly, Granholm and others studied pupillary diameter during a cognitive task, as a psycho-physiological biomarker of early risk for mild cognitive impairment (MCI) or AD, suggesting that pupillary changes may underlie subtle cognitive abnormalities that can help differentiate between MCI subtypes and identify subjects at risk of AD (Granholm et al., 2017).

mRGC investigation in humans, in particular at early disease stage (Hannibal et al., 2004; La Morgia et al., 2010; Esquiva et al., 2017; Hannibal et al., 2017; Ortuno-Lizaran et al., 2018; Esquiva and Hannibal, 2019; La Morgia et al., 2023), remains challenging due to objective difficulties of *in-vivo* mRGC system exploration and high variability in terms of technical protocols. A few studies that utilized chromatic pupillometry have been carried out on both AD and pre-symptomatic patients in recent years (Table 2). Oh et al. focused on the contribution of mRGC to PLR using intense (2.3 log cd/m^2) red (620 nm) and blue (450 nm) light stimuli. PLR assessment was coupled with actigraphic recordings of the sleep–wake cycle in a group of 10 pre-symptomatic AD patients, defined as cognitively healthy but with abnormal Aβ42/tau CSF ratio compared to 10 healthy controls (Oh et al., 2019). Comparative analysis failed to disclose any significant

TABLE 2 Summary of studies on chromatic pupillometry in Alzheimer's disease and in synucleinopathies.

Study reference	Clinical focus	Light paradigm	Main findings
Oh et al. (2019)	• Pre-symptomatic AD ($n = 10$) • Controls ($n = 10$)	• Red (620 nm) and blue (450 nm) light stimuli • Intensity 2.3 log cd/m^2 • Duration 1 s	No significant differences between groups, higher variability of sustained PLR to blue light in pre-symptomatic AD compared to control
Romagnoli et al. (2020)	• Mild–moderate AD ($n = 26$) • Controls ($n = 26$)	• Red (632 nm) and blue (472 nm) light stimuli: -Rod-condition: blue light, low intensity 0.001 cd/m^2-Melanopsin-condition: red and blue light flashes, high intensity 450 cd/m^2 • Cone-condition: red light (10 cd/m^2) against blue adapting field (6 cd/m^2) • Duration 1 s	Significant difference in rod-mediated transient peak amplitude in the AD group compared to controls Higher variability of PIPR in the AD group, despite not being statistically significant
La Morgia et al. (2023)	• Mild–moderate AD ($n = 29$) • Controls ($n = 26$)	Same as Romagnoli et al., 2020	AD patients (rod-condition): significantly delayed onset of transient PLR response, lower average slope, and also a significantly reduced |B| indicative of a lower exponential decay
Kawasaki et al. (2020)	• Early AD ($n = 16$) • Controls ($n = 16$)	• 2 blue (470 nm) light stimuli, intensity 1.75 and 2.23 log cd/m^2 (0 log = 1 cd/m^2) • 5 red (633 nm) light stimuli, intensity 0, 0.5, 1, 1.5 and 2.6 log cd/m^2 (0 log = 1 cd/m^2) • Duration 1 s	Significantly smaller baseline pupil size in the AD group and no significant difference in pupillary response to all red/blue lights
Joyce et al. (2018)	• PD ($n = 17$) • Controls ($n = 12$)	• Blue (465 nm) and red (638 nm) light stimuli • Irradiance 15.1 log photons.cm^{-2}.s^{-1} • Duration: pulsed (8 s rectangular) or phasic (12 s, 0.5 Hz sinusoidal)	Reduced PIPR amplitude for both pulsed and phasic blue stimulation in patients with PD compared to controls
Feigl et al. (2020)	• PD ($n = 30$) • Controls ($n = 29$)	• Blue (460 nm), green (519 nm) and red (630 nm) light stimuli • Irradiance 15.5 log.quanta.cm^{-2}.s^{-1}	Reduced PIPR to blue and green stimuli in patients with PD compared to controls Correlation between lower PIPR amplitudes with poor sleep quality and decreased RNFL thickness
Tabashum et al. (2021)	• PD ($n = 19$) • Controls ($n = 10$)	• Blue (470 nm) and red (610 nm) light stimuli • High energy 30 µW and low energy 8 µW • Duration 5 s	Significant difference in net PIPR and net PIPR% in patients with PD compared to controls
Gaynes et al. (2022)	• PD ($n = 17$) • Controls ($n = 9$) • Parkinsonism ($n = 2$)	• Blue (470 nm) and red (640 nm) light stimuli • Irradiance 8 and 30 µW·cm^{-2}·nm^{-1} • Duration 5 s	Altered PIPR with blue high irradiance stimuli in patients with PD Abnormal pupil latency at both blue and red stimuli in patients with PD
Steiner et al. (2022)	• iRBD ($n = 69$)	• Blue light pulses (465 nm) • Intensity 56 cd/m^2 • Duration 1 s	Significantly reduced PIPR in iRBD patients with mild neurocognitive disorder compared with patients with iRBD only Significant correlation of PIPR with cognitive performance, more pronounced in patients with lower dopamine-transporter density
La Morgia et al. (2022)	• iRBD ($n = 16$) • Controls ($n = 16$)	Same as Romagnoli et al., 2020	Higher baseline pupil diameter and decreased rod-mediated peak amplitude in patients with iRBD compared to controls Decreased rod-mediated peak amplitude in patients with iRBD with evidence of p-α-syn deposition at skin biopsy No difference in mRGC-mediated PIPR between groups Correlation of the rod-mediated peak amplitude with REM atonia index

AD, Alzheimer's disease; PD, Parkinson's disease; iRBD, isolated REM sleep Behavior Disorder; PLR, pupillary light response; PIPR, post-illumination pupil response; RNFL, retinal nerve fiber layer; mRGCs, melanopsin retinal ganglion cells; p-α-syn, phosphorylated-α-synuclein.

difference in both pupillometric and actigraphic results in patients compared to controls. Nevertheless, higher variability of sustained pupillary response to blue light and in the circadian rhythm was observed in pre-symptomatic AD patients compared to controls, suggesting that a change in mRGC function may be present even before clinical symptoms become evident.

Our group applied the above-described chromatic pupillometry protocol to assess separately the contribution of rods, cones, and mRGCs to the pupillary response in 26 AD patients in the mild–moderate stage compared to 26 controls (Romagnoli et al., 2020). A higher variability of post-illumination pupil response (PIPR) was observed in the AD group, despite not being significantly different from controls. Conversely, a significant difference in rod-mediated transient peak amplitude was observed in AD, suggesting that in early stages, the AD pathology may affect primarily the mRGC dendrites before involving the cell body, thus confirming the aforementioned histological findings (La Morgia et al., 2016).

In order to perform a multimodal investigation of the mRGC system, those patients were further evaluated with OCT, actigraphy recording of the sleep–wake cycle, and brain functional MRI (fMRI) with visual and cognitive stimulation, and compared to controls (La Morgia et al., 2023). The fMRI visual stimulation consisted of periods of illumination with blue or red light (50 s) alternated with darkness (20 to 30 s). The visual paradigm was also combined with cognitive stimulation during fMRI (consisting of an auditory task) to evaluate sustained attention and the effects of the interaction between light stimulation and cognitive task. The OCT analysis failed to show significant differences between AD and controls except for a thinner inferotemporal sector at the ganglion cell layer level corresponding to the superonasal sector of the optic nerve in AD compared to controls. Overall, pupillometry results confirmed the lack of significant differences under the mRGC condition, despite a significantly delayed onset with a lower average slope and reduced amplitude of the transient PLR under rod-condition in the AD group. Actigraphy recording, even if not significantly different, showed higher variability for circadian measures in patients with AD compared to controls. Under the fMRI visual paradigm, patients with AD showed a reduced occipital cortex activation to blue light compared to red light, while, under the visual-cognitive paradigm, the same patients showed a tendency toward an improvement of the cognitive performances under blue light stimulation, even if not statistically significant. Overall, these multimodal findings confirm once again that mRGC dysfunction is central in AD since its early stages, but the progression of this process, from dendropathy to cell death, may be variable among patients (La Morgia et al., 2023).

Finally, Kawasaki et al. performed a pilot sub-study from a prospective study on biomarkers in the early stages of AD, using chromatic pupillometry under photopic conditions to assess primarily cones and melanopsin-mediated pupillary responses. In the study, 16 early AD subjects were compared with 16 controls, showing significantly smaller baseline pupil size, while pupillary responses were not significantly altered, nor correlated with MMSE score, MRI hippocampal volume, or CSF biomarkers. Nevertheless, a trend between absolute hippocampal volume and the blue light PIPR was noted, suggesting that, despite mRCG dysfunction not being detectable with pupillometry in early stages, the PIPR may be an indirect marker of hippocampal atrophy in AD (Kawasaki et al., 2020).

5 Chromatic pupillometry findings in synucleinopathies

Furthermore, chromatic pupillometry to assess melanopsin retinal ganglion cell (mRGC) function has also been applied to other neurodegenerative disorders, such as Parkinson's disease (PD) and its prodromal stage, idiopathic/isolated rapid eye movement sleep behavior disorder (iRBD) (Joyce et al., 2018; Feigl et al., 2020; Tabashum et al., 2021; Gaynes et al., 2022; La Morgia et al., 2022; Steiner et al., 2022).

PD is a complex neurodegenerative disease caused by α-synuclein deposition in the brain that aggregates in the form of Lewy bodies within the neurons and leads to cellular death. Non-motor symptoms, including olfactory deficit, sleep and circadian disturbances, depressed mood, and cognitive impairments are also frequent and may precede motor symptoms. The etiology underlying sleep and circadian disturbances in PD is not well understood; one hypothesis includes dysregulation of the circadian rhythms due to reduced dopaminergic neurotransmission. Moreover, since mRGCs project to brain areas involved in arousal and sleep regulation, their dysfunction may underpin the circadian and sleep disturbances observed in PD (La Morgia et al., 2017). Interestingly, mRGCs are linked to dopaminergic amacrine cells both pre- and post-synaptically (Hannibal et al., 2017). Dopamine has a role in the light-adaptation process, upregulating melanopsin transcription in mRGCs and increasing their photosensitivity (Sakamoto et al., 2005). Thus, the already demonstrated loss of dopaminergic amacrine cells in PD (Ortuno-Lizaran et al., 2020) is expected to cause a reduction of melanopsin expression with dysfunction or loss of mRGCs, consequently altering their contribution to pupillary light reflex (PLR). We here briefly review the latest works on chromatic pupillometry in PD (Table 2).

Joyce et al. evaluated melanopsin and rod/cone contributions to the pupil response in 17 patients with PD and 12 controls using a chromatic pupillometry protocol with pulsed or phasic short (blue) and long (red) wavelength light stimuli. Pupillary unrest in darkness was also used as a measure of autonomic tone. Patients were furthermore assessed for disease severity (UPDRS, H&Y), cognitive impairment (MMSE), sleep quality (Pittsburgh Sleep Quality Index questionnaire), and peripapillary retinal nerve fiber (RNFL) thickness. Patients with PD showed reduced post-illumination pupil response (PIPR) amplitude for both pulsed and phasic blue stimulation compared to controls, while both groups presented similar pupillary unrest. PIPR amplitudes did not correlate with disease severity, sleep quality, or RNFL thickness. These results suggested that melanopsin' contribution to the pupil response is impaired in early-stage PD without clinically evident ophthalmic abnormalities (Joyce et al., 2018).

Feigl et al. assessed PLR and PIPR using chromatic pupillometry in 30 patients with PD and 29 healthy controls. Subjects also underwent ophthalmic examination including optic coherence tomography (OCT) and assessment of circadian rhythm using actigraphy, dim light melatonin onset, and sleep questionnaires. Patients with PD showed significantly reduced melanopsin-mediated PIPR amplitudes, correlating with poor sleep quality, RNFL thinning, and earlier melatonin onset. This suggests that reduced and irregular inputs to the suprachiasmatic nucleus via dysfunctional mRGCs are responsible for poorer sleep in patients with PD (Feigl et al., 2020).

Tabashum et al. measured pupillary diameter variation of the contralateral eye to red and blue light stimuli using automated tracking with a Kalman filter. In all, 19 PD and 10 control subjects were tested. PIPR (pre-stimulus pupil diameter – post-stimulus pupil diameter) and net PIPR (blue PIPR – red PIPR) were calculated, along with two other measures normalized by the pupil diameter: PIPR%

(PIPR*100/pre-stimulus pupil diameter) and net PIPR% (blue PIPR% – red PIPR%). Statistical analysis showed a significant difference in net PIPR and net PIPR% in patients with PD compared to controls, suggesting that net PIPR can be used as a potential biomarker for PD (Tabashum et al., 2021).

More recently, Gaynes et al. recorded consensual PIPR in the left eye after 5-s pulses of blue and red light stimuli to the right dilated eye. In all, 17 PD subjects, 9 controls, and 2 subjects with parkinsonism presumed to have Lewy body dementia and multiple system atrophy were compared. Subjects with PD variably demonstrated altered PIPR with short-wavelength high irradiance stimuli, consistent with mRGC dysfunction, and abnormal pupil latency at both short- and long-wavelength stimuli, while subjects with parkinsonism did not show any pupillary changes (Gaynes et al., 2022).

iRBD represents the strongest prodromal risk factor for α-synucleinopathies, characterized by loss of muscle atonia during REM sleep, leading to abnormal sleep behaviors ranging from simple muscular twitches to complex, sometimes even violent, limb and body movements. Reduced pupil constriction and dilation have been demonstrated both in patients with RBD and PD in comparison to controls (Perkins et al., 2021), while chromatic pupillometry has been used by only two studies in iRBD (La Morgia et al., 2022; Steiner et al., 2022). Steiner et al. (2022) evaluated the melanopsin-mediated PIPR with cognition (CERAD-plus) in 69 patients with iRBD. PIPR was significantly correlated with cognitive functions, especially executive functioning, and this was more evident in patients with lower dopamine-transporter density. Patients with iRBD with mild neurocognitive disorder showed significantly reduced PIPR compared to those without. PIPR was then proposed as a potential biomarker for cognitive function in iRBD.

In our study, 16 patients with iRBD and 16 controls were tested to compare rod- and cone-mediated PLR and mRGC-contribution (PIPR). Pupillometric results were also correlated with clinical signs, REM atonia index (RAI), DaTscan, and skin deposition of phosphorylated-α-synuclein (La Morgia et al., 2022). Patients with iRBD presented higher baseline pupil diameter and decreased rod-mediated peak amplitude, while mRGC-mediated PIPR did not differ from controls. Interestingly, only patients with iRBD with evidence of phosphorylated-α-synuclein skin deposition presented a reduced peak amplitude (rod-condition) compared to controls. Moreover, the rod-mediated PLR correlated with RAI. These results suggest that PLR rod contribution is impaired in iRBD, probably reflecting early mRGC dendropathy, and that it can be considered as a potential biomarker for the risk of phenoconversion of the disease.

6 Final considerations on chromatic pupillometry in AD and other neurodegenerative disease settings

Chromatic pupillometry studies in the setting of neurodegenerative disorders have been limited to small sample sizes, the cross-sectional nature of the studies' design, and methodological differences (Chougule et al., 2019). Larger longitudinal studies correlating pupillometric measures to circadian function in the prodromal stages of the diseases are needed to highlight the role of this cellular system in circadian dysfunction and prediction of disease severity (Mitolo et al., 2018; La Morgia et al., 2023).

In this context, a properly designed light stimulus is *a conditio sine qua non* for a good-quality study, since only an appropriate chromatic stimulus allows the quantification of the mRGC system functional deficit. Unfortunately, the scientific community active in this research field has not yet reached a consensus on a standardized chromatic pupillometric methodology for the evaluation of mRGC-mediated pupil function, both in terms of experimental setting and data manipulation/analysis pipeline, and this makes the results difficult to compare. Indeed, factors such as normalization of the pupillary response to the baseline pupil diameter, smoothing/filtering modes, or different algorithms used to calculate chromatic pupillometric endpoints may, independently or in combination, influence the magnitude/variability of the results (Mathot et al., 2018; Chougule et al., 2019; Kret and Sjak-Shie, 2019).

Although longitudinal studies are fundamental to show the impact of mRGC system dysfunction as the disease progresses, we suggest that research can continue to benefit also from cross-sectional studies, which would be less affected by their intrinsic limitations if based on age- and disease severity-matched comparison groups (Chougule et al., 2019).

Moreover, the evaluation by chromatic pupillometry of mRGC system functionality may lay the groundwork for a new, easily accessible biomarker that can also be exploited as the starting point for future longitudinal cohort studies aimed at stratifying the risk of conversion of these disorders.

We finally highlight that a large-scale multicentric validation of a chromatic pupillometry protocol is warranted, as this approach may have potential use in clinical trials aimed at correcting circadian/sleep disorders as a secondary preventive action of AD, providing an additional low-cost quantitative mRGC outcome, incorporated into easily testing systems.

Author contributions

MR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. GA: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. PA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing, Visualization. VC: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing, Funding acquisition. CLM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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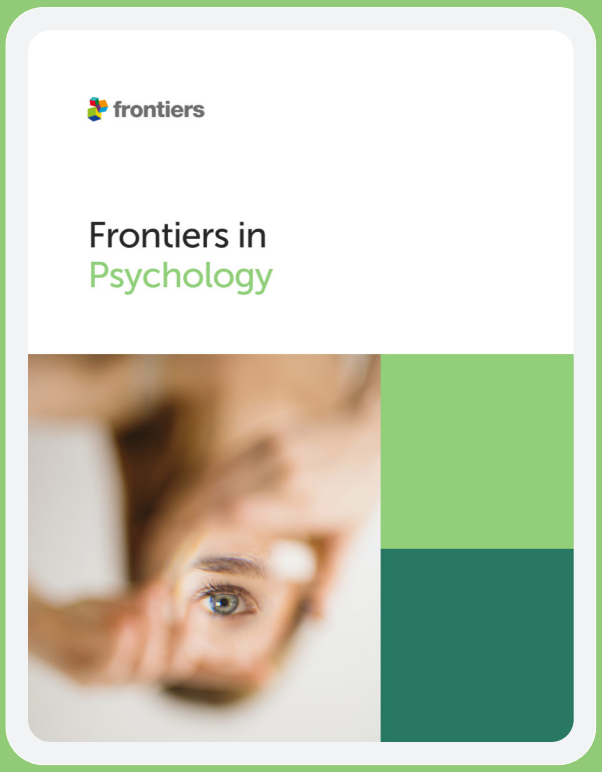

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