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Value of Visual Perception, Special Visual Phenomena, and Visual Memory Disorders in Early Diagnosis of Alzheimer's Disease

DOCTORAL DISSERTATION

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ABBREVIATIONS

AChEI	–	Acetylcholinesterase Inhibitor
AD	–	Alzheimer’s Disease
ADAS-Cog	–	Alzheimer’s Disease Assessment Scale-Cognitive Subscale
ADI	–	Alzheimer’s Disease International
ANOVA	–	Analysis of Variance
AUC	–	Area Under the Curve
A β	–	Amyloid-beta
CDR	–	Clinical Dementia Rating Scale
CDR-SB	–	Clinical Dementia Rating Sum of Boxes
CDR-TS	–	Clinical Dementia Rating Total Score
CG	–	Control Group
CI	–	Confidence Interval
CSF	–	Cerebrospinal Fluid
GDS	–	Geriatric Depression Scale
HIS	–	Hachinski Ischemic Score
IQR	–	Interquartile Range
MCI	–	Mild Cognitive Impairment
MD	–	Mild Dementia
ME	–	McCollough Effect
MMSE	–	Mini-Mental State Examination
MRI	–	Magnetic Resonance Imaging
NIA-AA	–	National Institute on Aging-Alzheimer’s Association
PEBL	–	Psychology Experiment Building Language
PET	–	Positron Emission Tomography
ROC	–	Receiver Operating Characteristic
VOSP	–	The Visual Object and Space Perception Battery
WE	–	Watercolor Effect

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LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. **Sutnikiene V**, Audronyte E, Pakulaite-Kazliene G, Kaubrys G. Color Memory as a Diagnostic Test for Mild Cognitive Impairment and Early Stage of Alzheimer's Disease. *Front. Neurol.* 2025;16:1589335. Published 27 May 2025. doi:10.3389/fneur.2025.1589335
- II. **Sutnikiene V**, Pakulaite-Kazliene G, Audronyte E, Kuzmickaite J, Kaubrys G. McCollough and Watercolor Effects: Visual Illusions that Fade in Early Alzheimer's Disease. *Med Sci Monit.* 2025;31:e950194. Published 22 Nov 2025. doi:10.12659/MSM.950194.
- III. **Sutnikiene V**, Pakulaite-Kazliene G, Audronyte E, Kuzmickaite J, Kaubrys G. Time/Movement Estimation and Mental Rotation Tasks as Early Cognitive Markers in Alzheimer's Disease. *Brain Behav.* Published 19 Nov 2025;15(11):e71077. doi:10.1002/brb3.71077.
- IV. **Sutnikiene V**, Audronyte E, Pakulaite-Kazliene G, Kaubrys G. Silhouettes, number location, and cube analysis tests from the VOSP battery reveal visual object and space perception deficits in early Alzheimer's disease. *Sci Rep.* 2026;16(1):3217. Published 21 Dec 2025. doi:10.1038/s41598-025-33126-z.

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PREAMBLE

The doctoral dissertation is submitted for defense as a set of research articles, and some parts have been quoted verbatim from previously published articles listed at the end of the dissertation.

The dissertation consists of several interconnected parts.

First, we examined color recognition memory in patients with early Alzheimer's disease and cognitively normal older adults and evaluated its potential as a diagnostic tool. Second, we analyzed the McCollough and Watercolor Effects in patients with early Alzheimer's disease and cognitively healthy older adults and evaluated the influence of acetylcholinesterase inhibitors in the mild dementia stage of Alzheimer's disease. We evaluated time/movement estimation and mental rotation tasks as diagnostic tests for early Alzheimer's disease using freely available tests from the Psychology Experiment Building Language (PEBL) battery. Finally, we evaluated object and space perception as diagnostic tools for the early detection of Alzheimer's disease and assessed their diagnostic properties and relationships with other cognitive test results.

1. INTRODUCTION

1.1. Research Problem and Relevance of the Study

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60–80% of cases, and is characterized by progressive neurodegeneration and cognitive decline (1,2). According to data from the Framingham Heart Study, the lifetime risk of Alzheimer's dementia at age 45 is 20% for women and 10% for men, indicating that 1 in 5 women and 1 in 10 men of this age could eventually develop AD (3). Nonetheless, according to estimates from the Alzheimer's Disease International (ADI), approximately 75% of individuals with dementia worldwide remain undiagnosed, and as many as 85% do not receive post-diagnostic support services (4). The pathological processes of AD begin many years before individuals exhibit any symptoms (4). Patients with AD who survive from 70 to 80 years of age typically experience the severe stage of the disease for approximately 40% of that decade (5). The period from the onset of AD neuropathological changes to the severe stage presents a critical window for early identification, enabling patients and medical professionals to mitigate risks and manage the condition, including utilizing recent advancements in AD diagnostic tools and therapeutic interventions (6).

Recent discoveries of disease-modifying treatments have been associated with a growing need to develop tools for detection of AD at the earliest clinically determinable stage. However, an audit of memory services in England revealed that less than 2% of patients underwent molecular confirmation of their disease using cerebrospinal fluid biomarkers (7). Moreover, the 2024 ADI report found that over 90% of caregivers and respondents from the public were more inclined to seek a diagnosis if a treatment that could modify the course of the disease was accessible (8). The lack of a valid and reliable cognitive test with minimal influence from language differences which is comparable across multinational and multilingual populations is a concern, and the use of digital language-neutral cognitive evaluations is encouraged (4).

Fundamental aspects of visual perception include light perception, sensitivity to contrast, orientation of stimuli, visual acuity, and the ability to detect form, color, movement, and depth (9,10). Visual alterations emerge early in the progression of AD and may serve as potential non-invasive markers of AD-related neurodegeneration (11). AD-related neuropathological lesions have been identified throughout the visual system, including the retina, resulting in various signs and symptoms (11-13). Visual issues reported in AD

include abnormalities in contrast sensitivity, visual field deficits, abnormalities in eye movements related to fixation and saccades, and abnormalities in visual functions which lead to impaired reading ability, challenges in recognizing objects and shapes, and locating items in one's environment (11-15). Furthermore, the progression from normal cognitive function to mild cognitive impairment (MCI) is linked to decreased visual acuity, thereby suggesting that the impact of vision impairment is greatest during the early stages of cognitive decline (16). According to recent studies, worsening contrast sensitivity over time is associated with a higher likelihood of incident dementia (17). Visual recognition memory impairment also occurs early in the course of MCI (18). One of the 10 signs of AD in the 2024 Alzheimer's Association Report was difficulty in understanding visual images and spatial relationships. As a result, patients with AD experience difficulties in estimating distances and perceiving colors and contrasts, which can lead to challenges while driving (2). Color vision and memory are potential markers as well; however, these visual functions are not usually analyzed. Thus, information about their association with the degree of cognitive impairment remains limited.

The gradual integration of visual data into the visual association cortex occurs through two principal pathways: the ventral stream, which identifies 'what' is seen, and the dorsal stream, which determines 'where' the objects are located in space (19). The rationale for utilizing visual perception and visuospatial tests for early AD detection is based on structural and functional changes in the parietal and temporal lobes early in the disease course (20,21). Memon et al. recently reported a connection between visual function and changes in AD biomarkers (22). Visual perceptual ability and its deterioration in AD warrant particular attention, given the considerable adverse effects on the quality of life of patients (23). However, neuropsychological tests evaluating overall cognition are predominantly verbal, with visual perception comprising only a minor component of the evaluation (24).

Illusions are often described as occurrences that create a discrepancy between what we perceive and our understanding of reality (25). Moreover, visual illusions can serve as valuable instruments for contemplating the reliability and thoroughness of vision, and therefore, for gaining insight into the neural processes involved in the perception of visual information (25,26). Gaining an understanding of how low-level and high-level vision contribute to the experience of visual illusions can shed light on pathological alterations in the visual system (25,26). For instance, the origin of color after-effects has been traced to the retina (27). Several studies have demonstrated that cortical filling-in can induce an afterimage (28,29). Furthermore, neurons in the

primary visual cortex play a role in the orientation-contingent color after-effect, known as the McCollough effect (ME) (30,31). However, data regarding how pathological changes in the early stages of AD influence the perception of visual illusions of induced color are limited.

The identification of subtle cognitive impairment or preserved cognitive function in older adults is highly dependent on the sensitivity and specificity of the assessment tools employed (32). In the domain of neuropsychological assessment, computerized evaluations offer a rapid and efficient means of appraising cognitive function (33). Computers facilitate standardized instruction delivery across multiple languages and support the collection of large volumes of objective data while minimizing experimenter-related errors (32,33). Compared with the traditional paper-and-pencil methods, computerized assessments can be seamlessly integrated into neuroimaging settings and considerably reduce the manual effort attributed to scoring, analysis, and longitudinal monitoring of cognitive performance (33,34).

An increasing number of computerized cognitive assessments are currently commercially available and can be self-administered at home (34). Nonetheless, the cost of extensively researched validated test batteries may limit their accessibility in primary care settings and among researchers in developing countries (35).

Numerous studies have indicated that patients with AD experience difficulties in motion processing and visuospatial disorientation, implicating dysfunction in the posterior parietal regions of the dorsal visual pathway (36,37). The dorsal stream hypothesis of AD is further supported by consistent findings of parietal atrophy and reduced activity in the parietal lobe of affected individuals (36,37). Consequently, tasks assessing temporal judgment and motion perception may serve as valuable diagnostic tools for AD's early detection.

Despite extensive research on cognitive impairments in AD, particularly regarding memory decline and executive dysfunction, distortions in temporal judgment and motion perception in early AD have so far received comparatively little attention (38). Temporal processing and memory impairments are commonly associated with hippocampal dysfunction. Emerging evidence highlights the hippocampus as essential for differentiating time intervals, organizing temporal sequences, and encoding the flow of time (39,40). However, most studies to date have focused on verbal time-estimation tasks, with a limited investigation into alternative paradigms, such as time reproduction or bisection tasks (38).

Despite these findings, the application of visual perception testing in clinical practice remains infrequent. To facilitate the integration of visual

function evaluation into routine practice, further data on specific visual perception tests and their diagnostic properties are required.

This doctoral dissertation is based on four published research articles. Its overarching aim is to assess visual perception impairments in early-stage AD, ascertain their diagnostic efficacy in identifying patients with early-stage AD, and investigate the distinctions between visual and other cognitive changes in patients with AD. **Paper I** analyzes color recognition memory in patients with early AD and cognitively normal older adults and evaluates its potential as a diagnostic tool. **Paper II** analyzes the McCollough and Watercolor Effects in patients with early AD and cognitively healthy older adults and evaluates the influence of acetylcholinesterase inhibitors in the mild dementia stage of AD. **Paper III** analyzes time/movement estimation and mental rotation tasks as diagnostic tests for early AD using freely available tests from the PEBL battery. **Paper IV** evaluates object and space perception as diagnostic tools for the early detection of AD and assesses their diagnostic properties and relationships with other cognitive test results.

1.2. Research Aim

This research aimed to evaluate the value of visual perception, special visual phenomena, and visual memory disorders for the early diagnosis of AD, determine their diagnostic properties, and identify the differences between visual perception and other cognitive functions.

1.3. Research Objectives

1. To evaluate color memory and its diagnostic properties in early-stage AD (**Paper I**).
2. To examine the ME and WE among individuals diagnosed with early AD, as well as to evaluate the influence of acetylcholinesterase inhibitors in the mild dementia stage of AD (**Paper II**).
3. To compare impairments in computerized time/movement estimation and mental rotation with other cognitive impairments and explore their additional value in diagnosing early-stage AD (**Paper III**).
4. To evaluate visual object and space perception and its diagnostic properties in early-stage AD (**Paper IV**).

1.4. Scientific Novelty

Research on the diagnostic potential of color memory tests remains limited due to the infrequent evaluation of color vision and memory. In this research, color recognition memory was assessed alongside a comparison with verbal memory. For the first time, the perceptions of ME and WE were evaluated in participants with early AD, providing insights into the functional alterations of the visual system and ongoing neurodegeneration. Additionally, computerized time/movement estimation and mental rotation tests were included to explore their potential value in diagnosing early-stage AD. Visual object and space perception were evaluated in individuals with mild cognitive impairment (MCI) due to AD as an additional diagnostic tool for the early detection of AD.

1.5. Practical Value of the Study

Early-stage AD diagnosis is becoming a healthcare priority because of the need to reliably identify patients eligible to participate in clinical trials and, in the near future, for disease-modifying treatment. The introduction of simple and accessible diagnostic methods for visual function and visual perception in clinical practice could improve the diagnostic process.

Despite previous research reporting visual changes in patients with early AD, these findings are not commonly integrated into clinical practice. The current study addresses the issues limiting the wider application of visual perception testing, specifically through the use of a color memory task and straightforward digital, language-neutral cognitive evaluations, such as the time/movement estimation task.

1.6. Defended Statements

1. Color memory is impaired in early-stage AD, and color recognition memory has good diagnostic properties for differentiating patients with early-stage AD from cognitively healthy individuals (based on **Paper I**).
2. Perceptions of ME and WE offer insights into the functional alterations in the visual system and ongoing neurodegeneration (based on **Paper II**).
3. The time/movement estimation and mental rotation tasks from the Psychology Experiment Building Language (PEBL) test battery are suitable for identifying early cognitive impairment in AD (based on **Paper III**).
4. Visual object and space perception are impaired in early-stage AD and are suitable as additional tools for the early diagnosis of AD (based on **Paper IV**).

2. LITERATURE REVIEW

2.1. Color Perception and Color Memory

Cholinergic loss is one of the most prominent components of AD neuropathology (41). The nucleus basalis of Meynert contains acetylcholine-producing neurons which are essential for regulating various aspects of visual perception (42). In the visual perception pathway, the ventral stream, which involves interactions among visual areas V1, V2, and V4, plays a crucial role in recognizing and identifying shapes and colors. This pathway projects to regions of the inferior and medial temporal lobe, the latter of which is responsible for encoding long-term memories (19). Therefore, impairment of color perception and memory may be promising as potential non-invasive functional markers of early AD.

Recent studies provide growing evidence that color perception can aid in distinguishing AD from other forms of dementia (43-45). Usually, only one aspect of visual perception is analyzed, such as color vision or color discrimination, with limited information regarding color memory, color recognition, and long-term memory retention in AD. This could be because of color vision and memory assessments being challenging to incorporate into clinical practice due to the complexity of evaluating responses, and the tools required. On the grounds of using the Ishihara test, Arnaoutoglou et al. concluded that color perception differentiates AD from vascular dementia (43). The color recognition tasks require information about the color hue that was seen, and its comparison with the hue that was presented. This leads to widespread cortical activation (46). The impairment of cortical activation may represent early changes in AD (41,45).

2.2. McCollough and Watercolor Effects

ME is a visual after-effect that causes white-aligned gratings to appear as if they are colored (30,31). Initially, 2 perpendicular white gratings seem devoid of color; induction is conducted by alternately displaying colored gratings, usually green and red, as these colors are known to produce the most significant effect, for a duration of 5 to 15 min. Following adaptation, the white patterns exhibit a subtle hue that is complementary to the color of the induction grating with the same orientation (47). Notably, the effect has been observed to persist for several days and may even extend over months, thereby significantly constraining the potential underlying mechanisms (48). Gratings with different orientations appear to have colors; nonetheless, this effect

diminishes almost linearly as the orientation difference from the induction gratings increases, disappearing entirely at about 45° (48). The extended exposure to green vertical stripes tires out those neurons which are sensitive to green vertical patterns, while looking at red horizontal stripes has the opposite effect (30,31). Consequently, observing white vertical and horizontal stripes leads to excessive activation of vertical-red and horizontal-green neurons that have not adapted, resulting in the perception of red and green stripes, respectively. Neurons that are selective to orientation are not present in the retina; they exist solely in the cortex. Therefore, ME likely entails the specific adaptation of cortical neurons, responsive to both orientation and color (49,50). Over 3 decades ago, research by Savoy et al. demonstrated that the ME perception of 5 patients with AD had strength and duration similar to that of the control group (50). However, several neuropharmacological studies have indicated that the cholinergic limbic system plays a role in initiating and extinguishing ME (51). Therefore, whether the use of acetylcholinesterase inhibitors (AChEI) would change the perception of ME remains unclear.

The second example of an induced color visual illusion is the watercolor effect (WE) (52). Researchers have extensively investigated the effect of contextual elements on the perception of surface color through a variety of visual phenomena (53,54). The concept of Pinna et al. on the WE is based on the observation that surface color perception is affected by distant outlines, a phenomenon known as filling-in (52). Studies have shown that the way we perceive the color of surfaces is influenced by both the characteristics of the surfaces themselves and of the surrounding context, such as the presence of distant edges. This influence is termed 'edge-dependent' or 'induced' color (26,52-54). In WE, the hue of the inner edge of a pair of distant, colored outlines changes the look of an interior area that is physically identical to the background, making it appear as a consistent, desaturated color. The WE covers a visual angle that is too broad to be accounted for by the diffusion of light within the eye (26,52). According to recent studies of neural circuits involved in the perception of WE, the dorsal stream of the visual pathway plays a role by modulating feedback to area V1 (the primary visual cortex) and exerts a cross-stream effect on the ventral regions (55). This implies that the local and contextual factors that affect color perception activate separate neural networks (55). Early alterations in AD may be indicated by the disruption of cortical activation within these networks (21).

The rationale for utilizing induced color visual illusions as an evaluation of visual perception in early AD is based on structural and functional changes in the parietal and temporal lobes and the cholinergic system early in the disease course (20,21).

2.3. Computerized Time/Movement Estimation and Mental Rotation Tasks

The Time–Wall task is a nonverbal assessment designed to evaluate temporal judgment, motion perception, and decision-making abilities (35,56). Its original purpose was to measure an individual's ability to predict the time required for a target to move vertically at a constant speed over a specified distance. This task engages cognitive processes involved in both motion perception and temporal judgment (35,56,57). The association between temporal judgment and memory decline in AD is believed to involve the hippocampus, a brain region essential for both functions and particularly vulnerable to AD-related pathology (38).

The mental rotation task is employed to evaluate visuospatial abilities. Recent studies have shown its applicability in patients with mild cognitive impairment (MCI) and AD, particularly in evaluating non-amnestic symptoms (35,58). The task involves mentally transforming the visuospatial features of an image until it matches a target without any physical movement. Performance is measured based on the response accuracy and time, which increases with the rotation angle, reflecting greater difficulty as the angles become larger (35,58,59). Lineweaver et al. found that patients with early AD tend to perform poorly on mental rotation tasks, potentially due to pathological changes in the parietal and temporal lobe association cortices, which impair spatial processing (60).

2.4. Visual Object and Space Perception

The *Visual Object and Space Perception Battery* (VOSP) serves as a common assessment tool for evaluating higher visual processing and consists of eight tests: four for visual object perception (incomplete letters, silhouettes, object decisions, and progressive silhouettes) and four for visual space perception (dot counting, position discrimination, number location, and cube analysis) (61). The VOSP is easy to administer and is a paper-based battery that does not rely on language skills or motor abilities (61). However, implementing the complete set of tasks is time-intensive, and, typically, only a few or single tests are employed. Notably, object perception VOSP test results should be interpreted with caution, especially for Test 3 (object decision), as individuals with low visual acuity have an increased likelihood of scoring below the cutoff point owing to their visual limitations (62). Quental et al. emphasized that the VOSP battery is a highly effective instrument for identifying visuospatial impairments in patients with mild dementia (MD) due to AD, with minimal interference from other cognitive

domains (63). According to this study, the silhouettes test demonstrated the most favorable diagnostic properties among object perception tests, with an area under the curve of 0.86, whereas other object perception tests scored below 0.80 (63). Additionally, the number location and cube analysis tests demonstrated the highest diagnostic accuracy in spatial perception assessments (63). In our research, we selected VOSP tests that have also been identified in recent studies as potential measures for predicting the progression from MCI to AD or for predicting the pathological diagnosis of AD (64-66). Nevertheless, limited information exists regarding its diagnostic properties in differentiating mild cognitive impairment (MCI) due to AD from cognitively normal older adults. These data would be valuable for disease-modifying treatment studies and clinical practice.

3. RESEARCH DESIGN AND METHODS

3.1. Ethical Approval

The study adhered to the 1975 Helsinki Declaration guidelines and was approved by the Vilnius Regional Bioethics Committee (Approval Number 2022/1-1405-877).

All participants were informed of the study procedures and agreed to participate in the study. All study participants provided informed consent in writing prior to their involvement in the research.

3.2. Participants

The research involved three distinct groups: 28 individuals diagnosed with MD, 27 with amnesic *Mild Cognitive Impairment* (MCI), and 26 older adults with normal cognitive function (*Control Group* (CG)) (**Papers II-IV**). In **Paper I**, there were 27, 25, and 25 participants, respectively. Those in the CG reported no cognitive issues, had a total *Clinical Dementia Rating Total Score* (CDR-TS) of 0, and showed no neurological abnormalities. Participants with MCI met the clinical and cognitive standards for MCI due to AD, as outlined by the *National Institute on Aging-Alzheimer's Association* (NIA-AA) (67), and were given a CDR-TS of 0.5. The MD group met the NIA-AA criteria for probable AD (68) and had a CDR-TS of 1.

The study participants were recruited from the Memory Clinic at Vilnius University Hospital, Santaros Klinikos. A cognitive neurologist identified probable AD using established criteria (68), which was further corroborated by noticeable cognitive deterioration, suggesting an active pathological process. The participants underwent structural magnetic resonance imaging (MRI) on a 1.5-T scanner, which was performed as a standard clinical practice when diagnosing AD based on regulations by the Ministry of Health of the Republic of Lithuania. *Cerebrospinal Fluid* (CSF) biomarker analysis was not performed within the framework of this study owing to its exploratory nature. Among the 28 patients diagnosed with MD, seven (25%) had medical records showing positive AD CSF biomarkers, aligned with the 2018 NIA-AA research framework for diagnosing AD (69) (**Papers II-IV**). In **Paper I**, a subset of patients with AD (6/27, or 22%) had medical records containing information about positive AD CSF biomarker status.

The diagnosis of amnesic MCI due to AD was determined through clinical and cognitive criteria, ruling out vascular, traumatic, and other medical causes of cognitive decline, and was supported by documented evidence of ongoing

cognitive deterioration (67). Structural MRI revealed neuronal damage in all MCI cases, with positive AD CSF biomarkers identified in eight out of 27 participants (30%), confirming the AD diagnosis according to the 2018 research framework (69) (**Papers II-IV**). In **Paper I**, for a subset of patients with MCI (7/25, or 28%), medical records contained information about the positive AD CSF biomarker status, thus confirming the AD diagnosis.

Participants with central nervous system disorders were excluded from this study, except those with MCI and MD. Exclusion criteria encompassed cerebrovascular diseases, as evidenced by a Hachinski Ischemic Score of ≥ 4 ; individuals with a history of head injury; and those with major psychiatric disorders (Geriatric Depression Scale score > 9). Additionally, individuals with vision and hearing impairments that affect cognitive testing; known early onset color vision deficiencies; significant eye conditions such as glaucoma, cataracts, diabetic retinopathy, and age-related macular degeneration; those diagnosed with or showing symptoms of major cardiovascular, liver, or metabolic disorders; those with substance abuse issues; and those using psychotropic medications were excluded. Individuals were eligible for inclusion in the study if they were either new to treatment or had been consistently taking a stable dose of an acetylcholinesterase inhibitor for at least 3 months.

3.3. Assessment of Demographic, Cognitive Characteristics, and Color Vision

Demographic data, such as age, sex, the duration of AD symptoms, and medical history, were collected from each participant.

The *Mini-Mental State Examination* (MMSE) was used to evaluate the overall cognitive abilities. MMSE is a brief screening examination designed to detect cognitive impairment and evaluate its severity. It assesses various cognitive functions such as orientation, registration, attention and calculation, recall, language, and visual-spatial abilities. The highest possible score is 30 points.

The *Clinical Dementia Rating Scale* (CDR) is a clinical instrument that is used to assess cognition and daily functioning. It is a semi-structured interview with the patient and an informant (family member or caregiver), which assesses six domains: 1) memory, 2) orientation, 3) judgment and problem solving, 4) community affairs, 5) home and hobbies, and 6) personal care. According to the CDR Total Scores, AD stages are defined as unimpaired cognition (CDR-TS = 0), MCI due to AD (CDR-TS = 0.5), mild AD dementia (CDR-TS = 1). The *Clinical Dementia Rating Sum of Boxes* (CDR-SB) scale

was utilized to evaluate the level of functional impairment and cognitive decline.

In addition, the participants undertook the *AD Assessment Scale–Cognitive Subscale* (ADAS–Cog) 13 for a comprehensive cognitive evaluation. This evaluation covers a range of cognitive areas, such as following commands, constructional praxis, recalling words after a delay, naming, ideational praxis, orientation, recognizing words, remembering test instructions, understanding spoken language, difficulty in finding words, spoken language ability, and number cancellation. Scores on the ADAS–Cog 13 range from 0–85, with higher scores indicating more severe cognitive impairments.

The paper-based 2021 edition of the 24-plate Ishihara test was utilized to assess color vision. The Ishihara Color Vision Test consists of pseudoisochromatic plates designed to detect red–green color vision deficiencies, specifically protan and deutan types. The results are determined by comparing the number of plates correctly identified with the expected outcomes for individuals with normal and deficient color vision. Plates 1–15 were displayed, and the number of mistakes was recorded, allowing for up to two errors.

3.4. Assessment of Color Recognition Memory

Color recognition memory was evaluated by using a 12-color kit displayed on a computer screen. The personal computer monitor parameters were set to factory defaults. The computer monitor was warmed for at least 30 min, and the target luminance value was 120 cd/m² (for a moderately lit room). Monitor parameters were checked by using simple visual/eye-based monitor calibration images from the Lagom LCD test, and a color recognition task was developed by using *Microsoft PowerPoint*. The color memory recognition task was divided into three parts: stimulus presentation and delayed recognition after 5 min and 30 min. Four initial stimulus colors were randomly selected and presented on a grid background for 5 s each, with an interstimulus interval of 5 s to reduce the impact of the color's after-effect. The participants were instructed to memorize the colors since they would be asked to identify the ones that they had seen. Hues were selected by using the RGB (red–green–blue) color model, which is commonly used to represent and display images on electronic systems (such as computers). In this model, the red, green, and blue colors are combined in various proportions to produce other colors. Each pair of colors in the RGB scale differed by at least 64 units in the red, green, or blue range (0–255). The 12 colors used were categorized by using basic color names: red, green, blue, yellow, orange, brown, pink, violet, black,

white, gray, and light blue (with separate categorical names in some languages like Lithuanian, Greek, Italian, and Russian). The RGB values were as follows: red (255, 0, 0), green (0, 255, 0), blue (0, 0, 255), yellow (255, 255, 0), orange (255, 128, 0), brown (128, 64, 0), pink (255, 125, 192), violet (192, 0, 255), light blue (128, 192, 255), black (0, 0, 0), white (255, 255, 255), and gray (128, 128, 128). The participants were not asked to name the colors, but, instead, to memorize them for later identification.

In the delayed recognition task, 5 min after stimulus presentation, the participants were required to recognize which of the eight randomly presented colors (four initial stimulus colors and four randomly selected colors from the 12-color kit) they had previously seen.

After 30 min, the participants were asked to identify which of the eight presented colors they had previously seen (four initial stimulus colors and four new colors from the 12-color kit that had not been used in the previous delayed recognition task) (**Figure 1**).

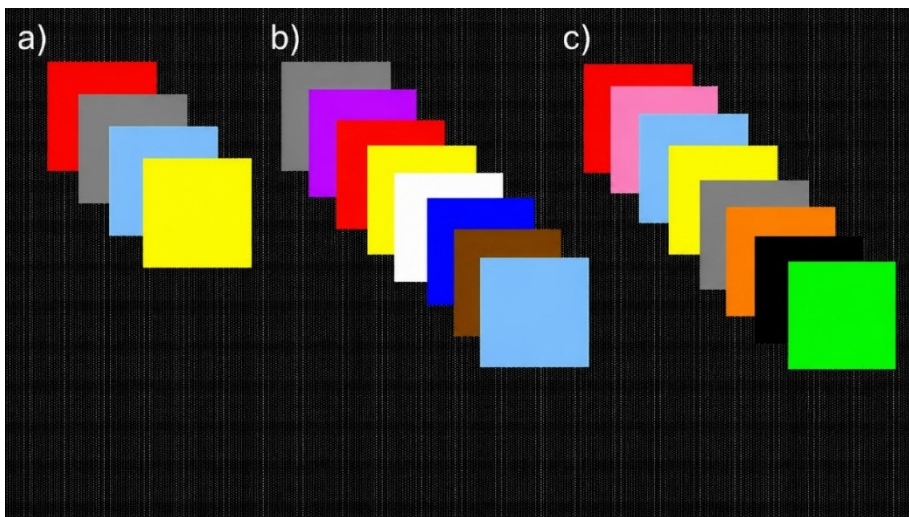


Figure 1. Color recognition memory task, stimuli colors

(a) Four initial stimulus colors were randomly selected and displayed on the computer screen for 5 s, each with an interstimulus interval of 5 s. Color memory was evaluated by color recognition after 5 min and 30 min by using the four initial stimuli and four new colors from kits (b,c).

3.5. Assessment of the McCollough and Watercolor Effects

3.5.1. Apparatus for ME and WE Presentation

Visual stimuli were displayed on a 24-inch LCD monitor with a resolution of 1920×1200 pixels and a refresh rate of 59.95 Hz within a dimly illuminated environment. In both experiments, the participants spent 5 min acclimating to the dim room, which was illuminated by a ‘natural daylight’ bulb, before starting the experiment. The computer monitor’s settings were configured to their original factory specifications. Moreover, the monitor settings were verified by using basic visual calibration images from the Lagom LCD test, and the WE and ME were created by using *Microsoft PowerPoint*. A chin-and-forehead rest was used to minimize head movement and fix the gaze distance to maintain a stable eye-to-screen distance of 70 cm.

3.5.2. Testing Procedure for the McCollough Effect

As shown in Figure 2, the ME was divided into 3 phases: testing before induction, induction, and testing after induction. In the baseline phase, the participants were tasked with evaluating the entire test display. None of the participants reported perceiving colors other than black or white in the test pattern before adaptation. In the induction phase, the ME stimuli were displayed on a monitor with dimensions of 31×31 cm and subtended at a visual angle of 25° . The adaptation stimulus was changed after 10 s, with the 2 stimuli alternating for a total of 5 min. We used 2 grating orientation sets: vertical green (RGB: 0, 255, 0) and black (RGB: 0, 0, 0), and horizontal red (RGB: 255, 0, 0) and black (RGB: 0, 0, 0), with a spatial frequency of 1.42 cycles per degree. After induction, a 1-min rest period followed, during which, the participants waited with their eyes closed to avoid possible retinal after-effects. In the testing after the induction phase, the participants were shown a test display of 4 combinations of cardinal (horizontal and vertical) and oblique (45° and 135°) white-black gratings. The same cycles/degrees and visual angles were used for the induction and achromatic gratings during the testing phase. Oblique gratings fail to generate an after-effect independently because the participants were not previously exposed to the oblique orientation; therefore, the participants should correctly identify slightly red-white or green-white lines in the vertical or horizontal gratings (6 red and 6 green). To ensure objectivity in the results, the participants were asked to evaluate whether the white lines appeared completely white. If the participants accurately identified lines as slightly red or green in the vertical or horizontal

gratings, it was recorded as a correct response, with a maximum of 6 red and 6 green lines correctly identified when the ME was perceived. The number of correctly identified squares with complementary colors was evaluated (**Figure 2**).

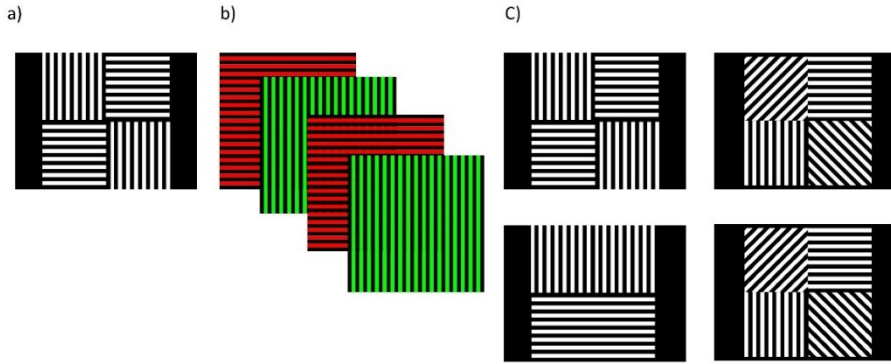


Figure 2. Procedure of testing the McCollough effect

The 3 phases of testing the McCollough Effect: **(A)** testing before induction, **(B)** induction for 5 min, and **(C)** testing after induction. ME was evaluated by reporting the chromatic changes in 6 vertical and 6 horizontal black-and-white line patterns. *Created by using Microsoft Paint, version 6.3 (Microsoft Corporation, Redmond, WA, USA) and Microsoft PowerPoint, Microsoft Office Professional Plus 2016, version 16.0.18827.20102 (Microsoft Corporation, Redmond, WA, USA).*

3.5.3. Testing Procedure for the Watercolor Effect

The first stimulus included 4 large squares, each containing smaller squares at their center, with 2 conditions: 2 squares where WE was visible between 2 orange lines extending from the inner part of the larger square to the outer part of the smaller square, and 2 squares where WE was visible within a smaller square. The second stimulus featured a large rectangle with 2 smaller rectangles inside, where the WE was visible between 2 orange lines extending from the inner part of the larger square to the outer parts of the smaller squares (**Figure 3**). The outer contour was dark purple (RGB: 165, 80, 226 for a; RGB: 154, 126, 216 for b), and the inner contour was light orange (RGB: 255, 207, 37) to optimize a strong color illusion. Each stimulus featured one or more objects set against a white background (RGB: 255, 255, 255). The edges of the WE stimuli were either wavy or had a scalloped design. This shortened the

distance between certain points along the inside of the shape, which helped strengthen the illusion (52). The border contour thickness is approximately 6 arcminutes (6') of the visual angle. To evaluate the perceived extent of color spreading, the participants were asked to identify sections of the figure that appeared completely white or colored. If the participants reported that there was no color outside the lines when WE was induced, it was evaluated as an indication that WE was not observed.

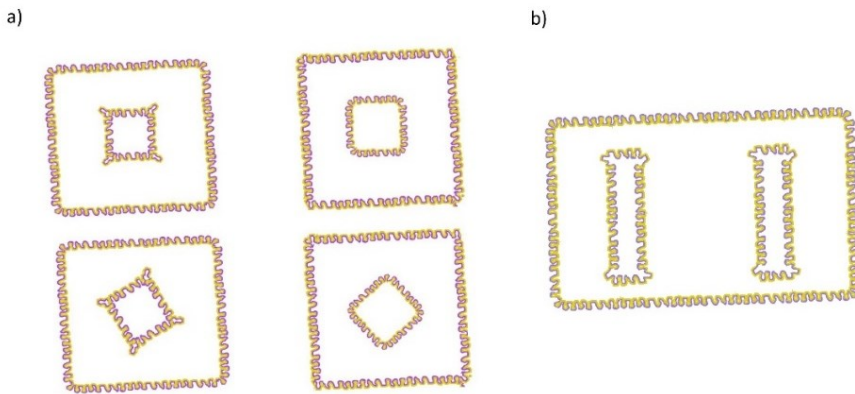


Figure 3. Watercolor effect test images

The revised version of the watercolor illusion was based on the original concept of Pinna et al. (52), adapted under CC BY-NC-SA 3.0. Purple undulated contours adjacent to orange ones are perceived as evenly colored by a light veil of orange tint spreading from the orange contours (coloration effect); (A) 4 large squares, each containing smaller squares at their center, with 2 conditions: 2 squares where WE was visible between 2 orange lines, extending from the inner part of the larger square to the outer part of the smaller square, and 2 squares where WE was visible within a smaller square; (B) a large rectangle with 2 smaller rectangles inside, where WE was visible between the 2 orange lines, extending from the inner part of the larger square to the outer parts of the smaller squares. *Created by using Microsoft Paint, version 6.3 (Microsoft Corporation, Redmond, WA, USA) and Microsoft PowerPoint, Microsoft Office Professional Plus 2016, version 16.0.18827.20102 (Microsoft Corporation, Redmond, WA, USA).*

3.6. Assessment of PEBL Battery Tests: Time–Wall and Mental Rotation Tasks

The Time–Wall task is a time/movement estimation exercise in which a moving object disappears behind a wall, and participants must judge when it will reach a visible gap, assuming constant speed throughout the trial. After descending two-thirds of its trajectory, the target moves behind a wall and consequently becomes obscured from view (**Figure 4**). This task was adapted from the Unified Tri-Services Cognitive Performance Assessment Battery (Systems Research Laboratories Inc., Dayton, Ohio, USA) (70). The participants were instructed to press the space bar at the moment they believed the target aligned with a notch at the bottom of the screen. The task comprised 20 trials, each lasting between 2 and 10 s.

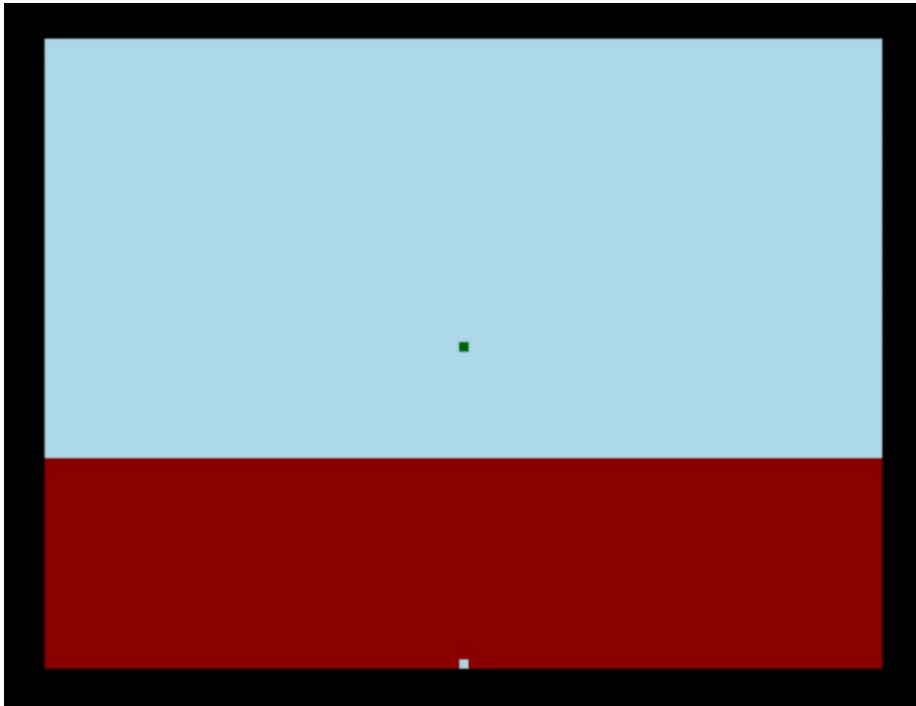


Figure 4. Illustration of the Time–Wall task. Participants estimate when a moving object (a green square), traveling at a constant speed, will reach a gap (the white square at the bottom) after becoming obscured by a red wall.

The average error time across trials was used to evaluate each participant's precision in time perception. Response inaccuracy was calculated as the percentage difference between the *Response Time* (RT) and *Target Time* (TT) by using the formula:

$$(RT - TT)/TT \times 100.$$

Additionally, the percentage of late responses was computed to further characterize the temporal estimation performance.

The mental rotation task is a two-dimensional adaptation of the classical test introduced by Shepard (59,71). The participants were instructed to press either the 'D' or 'S' key on the keyboard to indicate whether a pair of red shapes displayed on a gray screen was mirrored on the screen's plane (mirror condition). The shapes were rotated relative to each other at angles of 0°, 45°, 90°, 135°, and 180° (angle conditions). The pairs consisted of a familiar shape (an L shape) and an unfamiliar shape (a bolt) (**Figure 5**). The task was modified and included six practice trials and 32 experimental trials, each with a maximum duration of 45 s, resulting in a total task duration of up to 30 min. Correct responses and reaction times were recorded for each trial.

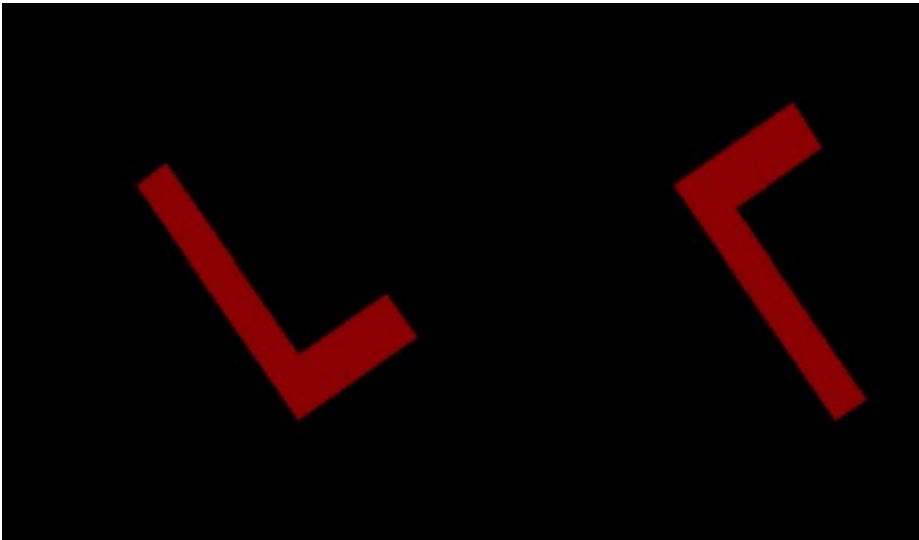


Figure 5. Example of mirror images is depicted. Participants are required to determine whether two figures on the screen's plane are identical or mirror images, with the figures rotated relative to each other

3.7. Assessment of VOSP Battery Tests: Silhouettes, Number Location, and Cube Analysis

Silhouettes: Black shadows of animals and inanimate objects from unusual angles were shown to the participants. The test consisted of 15 silhouettes of animals and 15 silhouettes of inanimate objects. The participants may name, mimic, gesture, or describe the object. The test boards were organized from the easiest to the most challenging, and the examination was discontinued after five mistakes. To establish the threshold scores, we implemented all boards even when the participant made more than five errors (maximum score: 30).

Number location: This test consists of 10 boards, each featuring two vertically aligned squares. The upper square displayed a random arrangement of numbers ranging from 1 to 9. The lower square contains a black dot that corresponds to the location of a specific number. The participants were required to identify the number aligned with the position of the black dot. One point was awarded for each correct identification, with a total of ten boards presented (maximum score: 10).

Cube analysis: Each board displayed a configuration of solid objects. The participants were required to determine the total number of cubes on each board, including those that were not visible. A series of ten boards was presented, with the complexity increasing progressively from one board to the next (maximum score=10).

3.8. Statistical Analysis

Statistical analysis was performed by using the *IBM SPSS Statistics* version 26.0.

To establish adequate study power, we calculated the required number of subjects by using *G_Power* for Windows version 3.1. Power (1-beta) was set at 0.85, the level of significance at the level of $p < 0.05$, one-way, and the effect size was set at 0.4, as one expected to find large effect sizes (f). The Kruskal–Wallis test required a minimum of 72 participants.

The Shapiro–Wilk test was used to assess data normality. Differences in categorical variables between groups were analyzed by using two-tailed chi-square and Fisher’s exact tests. Differences between two groups of non-normally distributed numerical variables were analyzed by using the Mann–Whitney U test. Comparisons between the three groups of numerical variables were performed by using one-way analysis of variance (ANOVA) for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables. Relationships between variables were assessed by using Spearman’s rank correlation coefficient. Linear regression models adjusted for

age, education, and sex were applied to predict the continuous dependent variables. Multinomial logistic regression was used to investigate the relationship between the independent variables and their classification into three groups. Diagnostic test performance was evaluated by using receiver operating characteristic curve analysis. The optimal threshold for each test was determined by maximizing Youden's J statistic ($J = \text{sensitivity} + \text{specificity} - 1$). A p -value of 0.05 was set as the threshold for statistical significance.

4. RESULTS

4.1. Demographic, Clinical, and Cognitive Characteristics

The demographic, clinical, and cognitive characteristics of the participants are presented in **Table 1**.

The analysis revealed no statistically significant differences in the sex distribution among the three groups ($p > 0.05$). Similarly, no statistically significant differences were found in age, educational background, depressive symptoms, or Hachinski ischemia scores ($p > 0.05$). However, statistically significant differences were observed in the cognitive test scores across all three groups ($p < 0.05$). The Ishihara test results differed significantly between the CG and MD groups, and the use of AChEI differed significantly among the CG and MD and the MCI and MD groups. Table 1 presents a detailed summary of the demographic and clinical characteristics as well as the cognitive test and color vision performance of the study participants.

Table 1. Overview of participant characteristics

	CG (n = 26)	MCI (n = 27)	MD (n = 28)	Statistic (χ^2 [2]/H(2), p)
Female (%)	12 (46%)	19 (70%)	18 (64%)	3.09, 0.21
Age	73 (9)	75 (11)	77 (9)	4.63, 0.10
Years of education	16 (1)	15 (4)	15 (3)	4.37, 0.11
GDS	4 (2)	5 (1)	4 (2)	1.40, 0.50
HIS	1 (1)	1 (1)	1 (1)	1.84, 0.40
MMSE*	29 (1)	25 (3)	22 (2)	72.02, < 0.001
ADAS–Cog 13*	12.5 (5.67)	22 (7.66)	31 (7.5)	74.26, < 0.001
CDR-SB*	0 (0)	1.5 (1)	4.5 (0.5)	53.07, < 0.001
Ishihara test, number of errors**	0 (0)	0 (2)	1 (3)	11.75, 0.003
Use of acetylcholinesterase inhibitors (%)***	0	1 (3.7%)	10 (35.71%)	18.02, < 0.001

Note. Unless otherwise specified, the data are shown as medians and interquartile ranges.

Statistical significance is set at $p < 0.05$.

* Three groups differ statistically significantly.

** CG and MD differ statistically significantly.

*** CG and MD, and MCI and MD differ statistically significantly.

Abbreviations in use:

MD, mild dementia; MCI, mild cognitive impairment; CG, control group; GDS, Geriatric Depression Scale; HIS, Hachinski Ischemic Score; ADAS–Cog 13= Alzheimer’s Disease Assessment Scale–Cognitive Subscale 13; CDR-SB, Clinical Dementia Rating Sum of Boxes; MMSE, Mini-Mental State Examination.

4.2. Verbal Memory Assessment

Verbal memory performance was assessed in **paper I** by the number of words not recalled out of 10 after 5 and 30 minutes. The total medians (Interquartile Range (IQR)) of the error score of words not recalled for the CG, MCI, and MD groups are 9 (3), 15 (5), and 16.67 (2.165), respectively. The Kruskal–Wallis test indicated a statistically significant difference ($H[2]=36.18, p < 0.001$). *Post-hoc* analysis revealed significant differences between each pair of groups (all $p < 0.001$). Medians (IQR) of verbal memory errors after 5 minutes for the three groups were 4 (1.34) for CG, 6 (1.67) for MCI, and 7 (1.5) for MD. The Kruskal–Wallis test indicated a statistically significant difference ($H[2]=29.32, p < 0.001$). *Post-hoc* analysis revealed significant differences between each pair of groups (all $p < 0.001$). Medians (IQR) of verbal memory errors after 30 minutes were 5 (2), 9 (4), and 10 (0) for the CG, MCI, and MD groups, respectively. The Kruskal–Wallis test indicated a statistically significant difference ($H[2]=36.13, p < 0.001$). *Post hoc* analysis revealed significant differences between each pair of groups (all $p < 0.001$).

4.3. Color Recognition Memory

4.3.1. Color Recognition Memory Assessment

Medians (IQR) of the color recognition total error scores for CG, MCI and MD were 2 (2), 4 (2), and 5 (3), respectively; the Kruskal–Wallis test indicated a significant difference ($H[2]=34.36, p < 0.001$). *Post-hoc* analysis revealed statistically significant differences between CG and MCI ($p < 0.001$), MCI and MD ($p = 0.007$), and CG and MD ($p < 0.001$). The total error score for each color in three groups is provided in Supplementary Table 1 of Paper I.

Color memory task scores after 5 min were evaluated across the three groups, and the medians (IQR) were found to be 0 (2), 1 (2), and 3 (2) for CG, MCI, and MD, respectively; Kruskal–Wallis $H(2) = 31.11, p < 0.001$; *post-hoc* examination revealed statistically significant differences between the groups: CG vs. MCI, $p = 0.002$; MCI vs. MD, $p = 0.002$; CG vs. MD, $p < 0.001$.

Color memory task scores after 30 min were evaluated across the three groups, and the medians (IQR) for CG, MCI and MD were 1 (2), 2 (2), and 3 (1), respectively; Kruskal–Wallis $H(2) = 34.36, p < 0.001$; *post-hoc* analysis revealed significant differences between the two groups: CG vs. MCI, $p = 0.001$; CG vs. MD, $p < 0.001$, but no significant differences were observed between MCI and MD, $p = 0.15$.

Among all participants, the total error scores for color memory were strongly correlated with the MMSE results (Spearman's rho: -0.647 ; $p < 0.001$) and moderately correlated with CDR-SB (Spearman's rho = 0.593 ; $p < 0.001$), ADAS-Cog 13 (Spearman's rho = 0.568 ; $p < 0.001$), and verbal memory (Spearman's rho = 0.492 ; $p < 0.001$).

When examining separate groups, no notable associations were found between the performance on color memory tasks and cognitive test scores, participant age, or education.

The multiple linear regression showed statistical significance in the adjusted model with MMSE ($R^2 = 0.378$, $F = 10.23$, $\beta = -0.668$, $p < 0.001$), ADAS-Cog 13 ($R^2 = 0.274$, $F = 6.74$, $\beta = 0.588$, $p < 0.001$), and CDR-SB ($R^2 = 0.324$, $F = 8.3$, $\beta = 0.616$, $p < 0.001$).

In all of the models, the color memory scores were not significantly influenced by other variables such as age, sex, education level, and Ishihara test results ($p > 0.05$).

4.3.2. Diagnostic Characteristics of Color Recognition Memory in Comparison with Verbal Memory

To differentiate between CG and AD (MCI or MD) using the color and verbal memory error scores, an analysis using the receiver operating characteristic curves (ROC) was conducted. ROC curves of delayed word recall and color recognition after 5 and 30 min, as well as the total error score, showed no significant differences between the verbal and color memory tasks in distinguishing the participant groups. The total error score for both tasks demonstrated robust diagnostic properties in differentiating CG from pathology (MCI and MD), with an identical AUC of 0.88. In distinguishing the CG from the MCI, the total error scores in the color and verbal memory tasks achieved AUCs of 0.81 and 0.8, respectively. The ROC curves of delayed word recall after 5 min and 30 min, the total score of recall (count of words not recalled), delayed color recognition after 5 min and 30 min, and the total color memory error score with comparisons among all groups are presented in **Figures 6-8**.

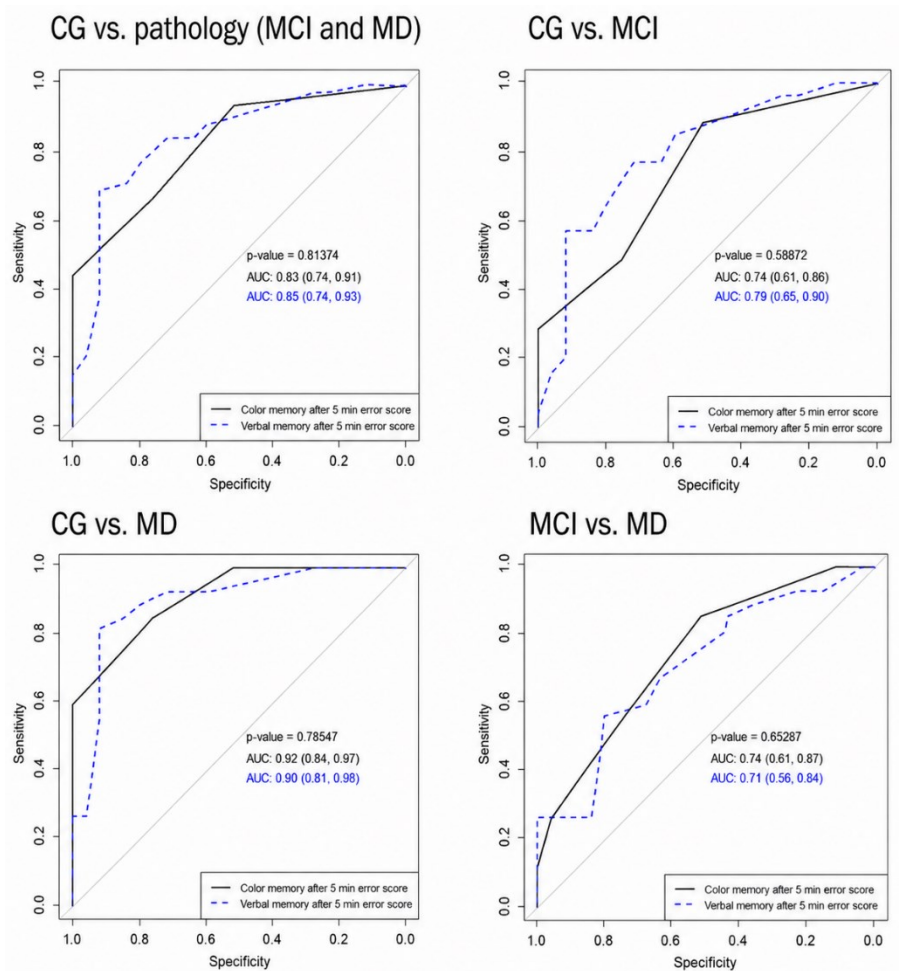


Figure 6. Comparisons of areas under the ROC curves (AUC) in delayed word recall and color recognition after 5 min in the verbal and color memory tasks in distinguishing between participant groups

Note. The solid lines represent color memory and dashed lines represent verbal memory test results. Abbreviations in use: MD, mild dementia; MCI, mild cognitive impairment; CG, control group

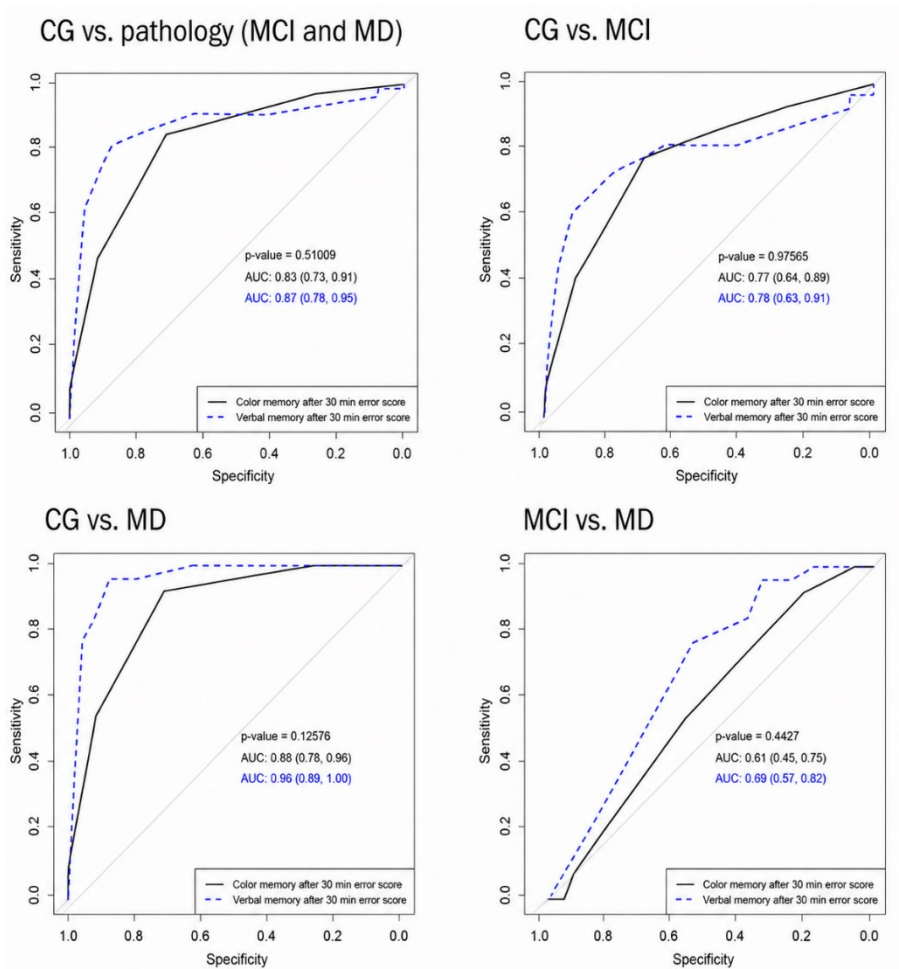


Figure 7. Comparisons of areas under the ROC curves (AUC) in delayed word recall and color recognition after 30 min in verbal and color memory tasks in distinguishing between participant groups

Note. Solid lines represent color memory and dashed lines represent verbal memory test results. Abbreviations in use: MD, mild dementia; MCI, mild cognitive impairment; CG, control group

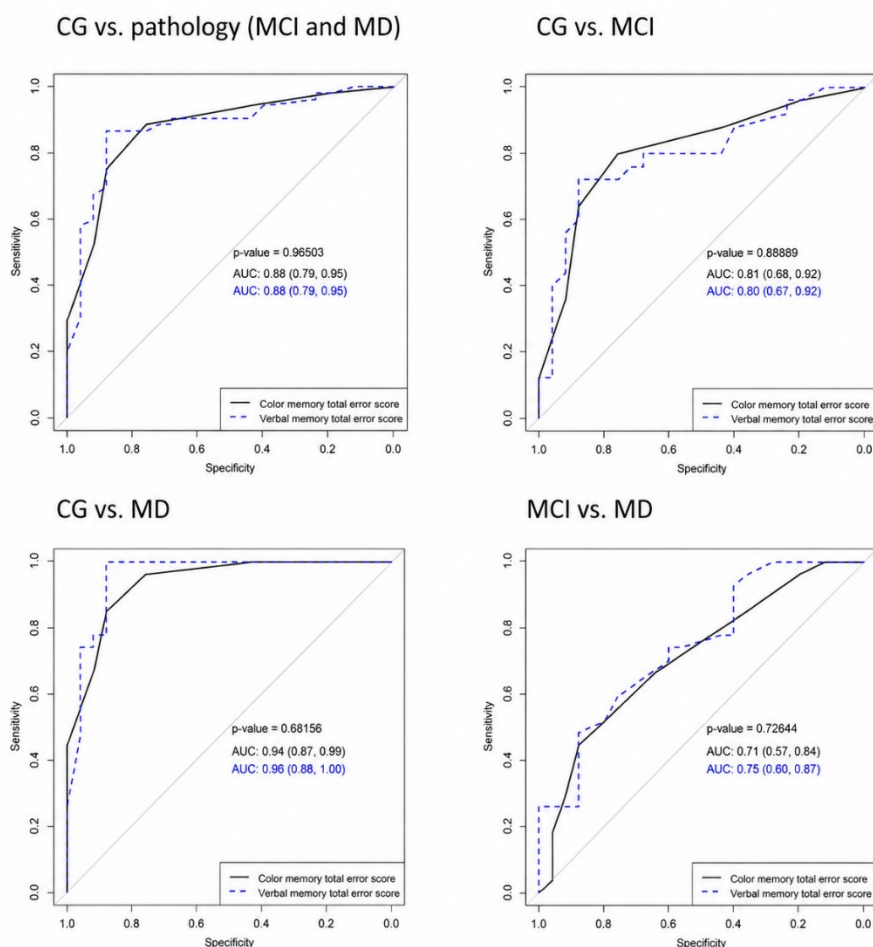


Figure 8. Comparisons of areas under the ROC curves (AUC) in the total error score in color and verbal memory tasks in distinguishing between participant groups

Note. Solid lines represent color memory and dashed lines represent verbal memory test results. Abbreviations in use: MD, mild dementia; MCI, mild cognitive impairment; CG, control group

To distinguish participants with AD (MCI or MD) from CG, a cut-off score of ≥ 3 errors in total error score of color memory task was established as indicative of AD. A cut-off score of ≥ 6 errors was established to differentiate patients with MD from those with MCI (with a score of 6 or above considered to be indicative of MD). The diagnostic properties of these thresholds were evaluated, and the data are presented in **Table 2**.

Table 2. Diagnostic properties of the total error score of the color memory task in differentiating between participants with AD and CG

	CG vs. pathology (MCI and MD), cut-off ≥ 3 errors	CG vs. MCI, cut-off ≥ 3 errors	CG vs. MD, cut-off ≥ 3 errors	MCI vs. MD, cut-off ≥ 6 errors
Sensitivity	88.46% (76.56–95.65%)	80% (59.30–93.17%)	96.3% (81.03–99.91%)	44.44% (25.48–64.67%)
Specificity	76% (54.87–90.64%)	76% (54.87–90.64%)	76% (54.87–90.64%)	88% (68.78–97.45%)
Negative predictive value	76% (59.11–87.40%)	79.17% (62.73–89.56%)	95% (73.27–99.25%)	59.46% (50.4–67.92%)
Positive predictive value	88.46% (79.12–93.94%)	76.92% (61.76–87.31%)	81.25% (68.24–89.73%)	80% (56.07–92.61%)
Overall diagnostic accuracy	84.42% (74.36–91.68%)	78% (64.04–88.47%)	86.54% (74.21–94.41%)	65.38% (50.91–78.03%)

Note. The data are presented as percentage and 95% confidence interval. Abbreviations in use: MD, mild dementia; MCI, mild cognitive impairment; CG, control group

To examine the association between the independent variables and classification into the three groups, a multinomial logistic regression analysis was conducted.

Initially, a model was developed using age, education, sex, and ADAS-Cog 13 score as predictor variables. Addition of the predictor variables enhanced the model's fit to the data, improving upon the initial model that contained only the intercept ($X^2 = 85.881, p < 0.001$; Nagelkerke $R^2 = 0.756$). The overall percentage of accurately categorized cases using this model was 77.9% (96% CG, 64% MCI, and 74.1% MD cases correctly categorized), with the ADAS-Cog 13 score being the strongest and most significant predictor ($X^2 = 76.074, p < 0.001$).

When word recall after 30 min was incorporated into this model, the expanded model's diagnostic accuracy remained similar, and the word recall after 30 min was not a significant predictor ($X^2 = 85.86, p < 0.001$; Nagelkerke $R^2 = 0.77$). The ADAS-Cog 13 score remained a significant predictor ($X^2 = 39.29, p < 0.001$). The overall percentage of cases that were accurately categorized by using this model was 75.3% (92% CG, 64% MCI, and 74.1% MD cases).

Furthermore, color recognition after 30 min was added to the initial model, and the expanded model showed a significant improvement in fit over a null

model ($X^2 = 101.23, p < 0.001$; Nagelkerke $R^2 = 0.823$). This model accurately categorized 83.1% of the cases (96% CG, 72% MCI, and 81.5% MD cases were correctly classified). Both ADAS-Cog 13 and color recognition after 30 min were significant predictors, with X^2 values of 62.47 and 15.35, respectively, ($p < 0.001$).

Finally, when the color memory total error scores were added to the initial model, the expanded model (including age, education, sex, ADAS-Cog 13 scores, and the color memory total error scores) also showed a significant improvement in fit over a null model ($X^2 = 117.176, p < 0.001$; Nagelkerke $R^2 = 0.880$). This model accurately categorized 84.4% of the cases (100% CG, 76% MCI, and 77.8% MD cases). Both ADAS-Cog 13 and the color memory scores were strong and significant predictors, with X^2 values of 63.88 and 31.30, respectively, ($p < 0.001$).

4.4. McCollough and Watercolor Effects

4.4.1. McCollough Effect

ME was perceived as white lines tinted green or red: 25 out of 26 in CG (96.15%), 24 out of 27 in MCI (88.89%), and 17 out of 28 in the MD group (60.71%) ($X^2 = 12.69, p = 0.002$). The majority of the participants in all groups perceived white vertical lines as red, with the median (interquartile range) as follows: CG, 5 (5.25); MCI, 5 (5); MD, 4 (6); and Kruskal–Wallis $H = 0.834$ ($p = 0.659$). Significant differences were observed in perceiving white horizontal lines as green (median [interquartile range]: CG, 3.5 [6]; MCI, 0 [2]; MD, 0 [0]; Kruskal–Wallis $H = 10.27, p = 0.006$, with a medium effect size of $\epsilon^2 = 0.11$) (**Figure 9**). *Post-hoc* analysis revealed significant differences between the CG and MD ($p = 0.002$) but not between the CG and MCI ($p = 0.033$ [not significant after Bonferroni correction for multiple comparisons]), or between MCI and MD ($p = 0.283$). The estimated *post-hoc* power, calculated by using an ANOVA-based approximation from η^2 , was 0.86.

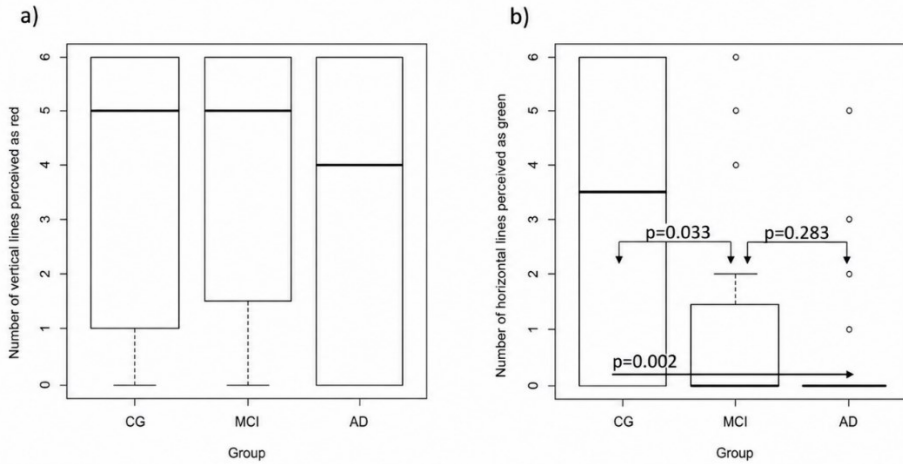


Figure 9. Differences in the McCollough effect between the three groups

a) Number of vertical lines perceived as red in the three groups (no significant differences were observed; $p > 0.05$); b) number of horizontal lines perceived as green in the three groups. Abbreviations in use: AD, mild dementia; MCI, mild cognitive impairment; CG, control group

Lines represent medians; boxes represent interquartile ranges; and error bars represent the minimum and maximum scores.

In the MD group, there were no significant differences between patients taking and not taking AChEI in the perception of ME ($X^2 = 0.749$, $p = 0.387$). No statistically significant differences were observed in the perception of white vertical lines as red or white horizontal lines as green, as indicated by the Mann–Whitney U test results ($p = 0.654$ and $p = 0.524$, respectively).

In the study population, the perception of white horizontal lines as green demonstrated a weak correlation with the MMSE results (Spearman's $\rho = 0.354$; $p = 0.001$), CDR-SB scores (Spearman's $\rho = -0.357$; $p = 0.001$), and ADAS–Cog 13 scores (Spearman's $\rho = -0.336$; $p = 0.002$). No significant correlations were observed with age, education, or the Ishihara test results.

Multiple linear regression models were used to determine whether demographic data, the Ishihara score, and cognitive test results significantly predicted seeing green lines. It was statistically significant in the adjusted model for MMSE ($R^2 = 0.12$, $F = 3.17$, $\beta = 0.318$, $p < 0.001$), ADAS–Cog 13 ($R^2 = 0.101$, $F = 2.8$, $\beta = -0.116$, $p = 0.001$), and CDR-SB ($R^2 = 0.086$, $F = 2.5$, $\beta = -0.432$, $p = 0.002$). In all models, ME was not significantly affected by factors like sex, age, education, and Ishihara results ($p > 0.05$).

4.4.2. Watercolor Effect

All participants in the CG, 25/27 (92.59%), and 22/28 (78.57%) participants in the MCI, and MD groups, respectively, reported seeing WE (Fisher's exact test 6.66, $p = 0.024$). There were significant differences between the CG and MD groups (Fisher's exact test: 6.27, $p = 0.024$).

When WE was not perceived, the participants made a significantly higher number of errors in the Ishihara test. Specifically, the median (interquartile range) of errors was 2.5 (5) when the participants reported not perceiving the WE, compared to 0 (1) when WE was perceived (Kruskal–Wallis $H = 9.29$, $p = 0.002$, with a medium effect size $\varepsilon^2 = 0.09$) (**Figure 10**). The estimated *post-hoc* power, calculated by using an ANOVA-based approximation from η^2 , was 0.83.

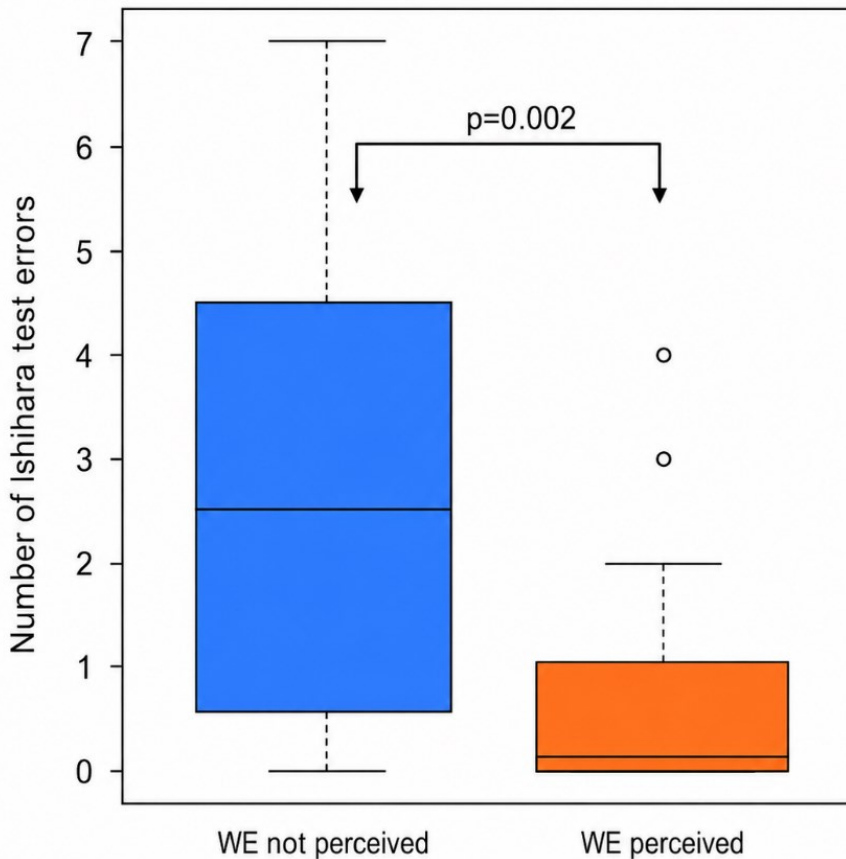


Figure 10. Ishihara test results in accordance with whether the Watercolor effect was perceived

The WE was not perceived when the participants exhibited a significantly higher number of errors on the Ishihara test. The lines represent medians; boxes represent interquartile ranges; and error bars represent the minimum and maximum scores.

In the MD group, there were no significant differences in the perception of WE between the patients taking AChEI and those not taking them (Fisher's exact test 0.19, $p = 1$).

The results of cognitive assessments and color vision were significant predictors of WE in binary logistic regression models, which were adjusted for sex, age, and education: the model with ADAS-Cog13 ($B = -0.158$, Wald = 4.7, $p = 0.03$, Nagelkerke $R^2 = 0.261$); model with CDR-SB ($B = -0.569$, Wald = 5.09, $p = 0.024$, Nagelkerke $R^2 = 0.265$); model with MMSE ($B = 0.342$, Wald = 3.89, $p = 0.049$, Nagelkerke $R^2 = 0.225$), and the model with the Ishihara test ($B = -0.893$, Wald = 8.13, $p = 0.004$, Nagelkerke $R^2 = 0.375$).

4.5. PEBL Battery Tests: Time–Wall and Mental Rotation Tasks

4.5.1. Time–Wall Task

Statistically significant differences were observed in the Time–Wall task inaccuracy scores [medians and interquartile ranges: CG = 11.46 (9), MCI = 19.43 (10.49), MD = 22.82 (14.35); $H(2) = 34.74$; $p < 0.001$], with the CG exhibiting lower scores than did both the MCI and MD cohorts. No statistically significant differences were found between the MCI and MD cohorts ($p = 0.106$).

The percentages of late responses are presented as medians and interquartile ranges: CG = 10 (18.75), MCI = 20 (22), and MD = 25 (23) [$H(2) = 7.3$; $p = 0.026$]. Statistically significant differences were observed between the CG and MD cohorts ($p = 0.01$); however, no statistically significant differences were found between the CG and MCI cohorts ($p = 0.153$), or between the MD and MCI cohorts ($p = 0.143$).

In the study population, Time–Wall task inaccuracy scores were strongly correlated with the MMSE results (Spearman's $\rho = -0.628$; $p < 0.001$) and moderately correlated with CDR-SB (Spearman's $\rho = 0.568$; $p < 0.001$) and ADAS–Cog 13 (Spearman's $\rho = 0.594$; $p < 0.001$) scores. A weak correlation with education (Spearman's $\rho = -0.314$; $p = 0.004$), and no notable correlation with age were found (Spearman's $\rho = 0.17$; $p = 0.129$).

Multiple linear regression models, including age, sex, education, and cognitive test scores, as independent variables, were used to determine their predictive values for the Time–Wall task inaccuracy scores. Statistical significance was observed in the following models: MMSE [$R^2 = 0.345$, $F =$

11.52, $\beta = -0.577$, $p < 0.001$]; ADAS-Cog 13 ($R^2 = 0.321$, $F = 10.46$, $\beta = 0.577$, $p < 0.001$), and CDR-SB ($R^2 = 0.262$, $F = 8.09$, $\beta = 0.498$, $p < 0.001$).

4.5.2. Diagnostic Characteristics of the Time–Wall Task

The efficacy of the Time–Wall task inaccuracy scores in distinguishing the participants with early AD from those in the CG was assessed by using the ROC curve analysis. The ROC curve analysis revealed strong diagnostic capabilities for differentiating between the CG and AD pathology (MCI and MD), with an area under the curve (AUC) of 0.9. Similarly, differentiation between the CG and MCI cohorts resulted in an AUC of 0.86. **Figure 11** illustrates the ROC curves used to evaluate the Time–Wall task performance.

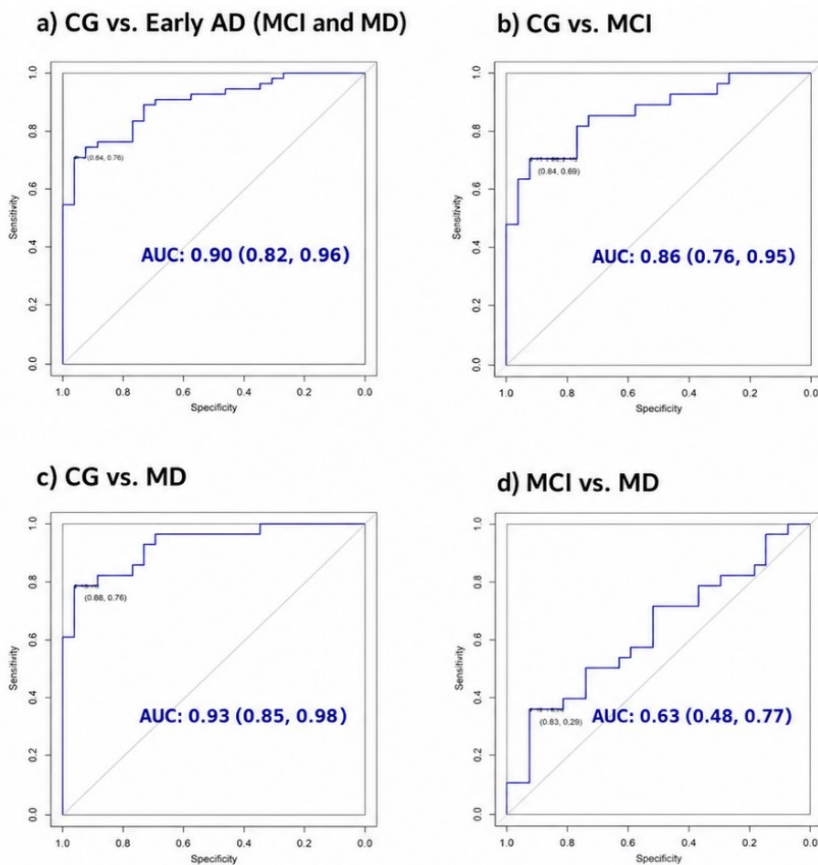


Figure 11. Time–Wall task performance: differentiating between the participants with Alzheimer’s disease and those in the CG

Abbreviations in use: AD = Alzheimer’s disease; CG = control group; MD = mild dementia; MCI = mild cognitive impairment.

A threshold of ≥ 18.35 for the Time–Wall task inaccuracies was selected to indicate AD. By applying this threshold to distinguish the participants with AD (MCI and MD) from the participants in the CG, the Time–Wall task demonstrated a sensitivity of 70.91% (95% CI: 57.1–82.37) and specificity of 96.15% (95% CI: 80.36–99.9%). **Table 3** provides a comprehensive overview of the diagnostic characteristics of the Time–Wall task for differentiating between the participants with AD and those in the CG.

Table 3. Time–Wall task performance: distinguishing participants with Alzheimer’s disease (AD) and control group (CG) members

	CG vs. early AD (MCI and MD): cut-off ≥ 18.35	CG vs. MCI: cut-off ≥ 15.08	CG vs. MD: cut-off ≥ 16.28	MCI vs. MD: cut- off ≥ 21.67
Sensitivity	70.91% (57.1–82.37%)	77.78% (57.74–91.38%)	82.14% (63.11–93.94%)	57.14% (37.18–75.54%)
Specificity	96.15% (80.36–99.9%)	76.92% (56.35–91.03%)	88.46% (69.85–97.55%)	59.26% (38.80%–77.61%)
Negative predictive value	60.98% (50.66–70.39%)	76.92% (61.48–87.44%)	82.14% (67.25–91.15%)	57.14% (43.97–69.37%)
Positive predictive value	97.5% (84.99–99.63%)	77.78% (62.78–87.90%)	88.46% (72.28–95.75%)	59.26% (45.46–71.73%)
Overall diagnostic accuracy	79.01% (68.54–87.27%)	77.36% (63.79–87.72%)	85.19% (72.88–93.38%)	58.18% (44.11–71.35%)

Note. Data are presented as percentages and 95% confidence intervals.

Abbreviations in use: CG, control group; MD, mild dementia; MCI, mild cognitive impairment.

Multinomial logistic regression was conducted to examine the correlation between the predictor variables and cohort membership across three categories: CG, MCI, and MD. A model was first developed that incorporated age, education, sex, and ADAS–Cog 13 scores as predictor variables. This model showed a better fit when compared with a model with only the intercept ($X^2 = 87.85$, $p < 0.001$; Nagelkerke $R^2 = 0.745$). The model achieved an overall classification accuracy of 76.5%, with correct classification rates of 92.3%, 66.7%, and 71.4% for CG, MCI, and MD, respectively. The ADAS–Cog 13 score was identified as the most robust and statistically significant predictor ($X^2 = 78.20$, $p < 0.001$).

The Time–Wall task scores were included in the initial model. The model comprising age, education, sex, ADAS–Cog 13 scores, and Time–Wall task inaccuracy scores showed a marked improvement in fit over the null model ($X^2 = 96.69$, $p < 0.001$; Nagelkerke $R^2 = 0.784$). The model achieved an

overall classification accuracy of 75.3%, with correct classification rates of 92.3%, 59.3%, and 75% for CG, MCI, and MD, respectively. ADAS–Cog 13 and Time–Wall task inaccuracy scores were statistically significant predictors ($X^2 = 49.41, p < 0.001$; $X^2 = 9.24, p = 0.01$, respectively).

4.5.3. Mental Rotation Task

The mental rotation task accuracy scores differed statistically significantly among the cohorts [medians and interquartile ranges: CG = 26.5 (4), MCI = 22 (9), and MD = 21.5 (9); $p = 0.001$]. *Post-hoc* comparisons revealed statistically significant differences between the CG and both MCI ($p = 0.007$) and MD cohorts ($p < 0.001$), yet not between the MCI and MD cohorts ($p = 0.094$). Moreover, the response times varied statistically significantly among the cohorts [$H(2) = 15.12, p = 0.001$; medians and interquartile ranges: CG = 6309.7 (4531.4); MCI = 12 684.5 (7974.7); and MD = 11 657.3 (7053)].

Analysis of the CG, MCI, and MD cohorts revealed no statistically significant differences in the accuracy scores or between the response time and sex. Regarding the CG, the accuracy scores were similar between males [27.5 (5)] and females [25.5 (3)] ($p = 0.494$), and the response times did not differ statistically significantly [males = 6017.9 (6908.1); females = 7235.9 (2957.9); $p = 0.374$]. Regarding the MCI cohort, the accuracy scores were comparable between males [23 (13)] and females [22 (7)] ($p = 0.897$), while the response times showed no statistically significant difference [males = 6975.6 (8787.4); females = 13 080.6 (5720.0); $p = 0.051$]. The accuracy scores for the MD cohort revealed no statistically significant sex differences [males = 22.5 (7); females = 18.5 (10); $p = 0.072$]. Similarly, the response times did not differ statistically significantly between males [9507.6 (8206.0)] and females [12508.1 (9802.4)] ($p = 0.08$).

In this study population, the accuracy scores regarding the mental rotation task revealed a moderate correlation with MMSE (Spearman's $\rho = 0.472$; $p < 0.001$) and the ADAS–Cog 13 scores (Spearman's $\rho = -0.407$; $p < 0.001$), and a weak correlation was found with CDR-SB (Spearman's $\rho = -0.372$; $p = 0.001$), age (Spearman's $\rho = -0.247$; $p = 0.026$), and education (Spearman's $\rho = 0.238$; $p = 0.033$). Moreover, the mental rotation task response times were moderately correlated with the MMSE scores (Spearman's $\rho = -0.405$; $p < 0.001$). Weaker correlations were observed with the ADAS–Cog 13 (Spearman's $\rho = 0.386$; $p = 0.001$) and CDR-SB scores (Spearman's $\rho = 0.277$; $p = 0.015$). No notable correlation was found between mental times and age or education.

Multiple linear regression models were used to assess the predictive value of age, sex, education, and cognitive test scores as independent variables for the mental rotation task accuracy scores. Statistically significant results were observed for the following models: MMSE ($R^2 = 0.265$, $F = 8.22$, $\beta = 0.438$, $p < 0.001$), ADAS-Cog 13 ($R^2 = 0.178$, $F = 5.32$, $\beta = -0.334$, $p = 0.001$), and CDR-SB ($R^2 = 0.177$, $F = 5.3$, $\beta = -0.32$, $p = 0.001$).

4.5.4. Diagnostic Characteristics of the Mental Rotation Task

The ability of the mental rotation task accuracy scores to differentiate the participants with early AD from cognitively healthy controls was evaluated by using the ROC curve analysis. The task demonstrated moderate diagnostic accuracy in distinguishing the participants in the CG from those with AD (MCI and MD), with an AUC of 0.75. Similarly, differentiation between the CG and MCI cohorts yielded an AUC of 0.71. ROC curves illustrating task performance are presented in **Figure 12**.

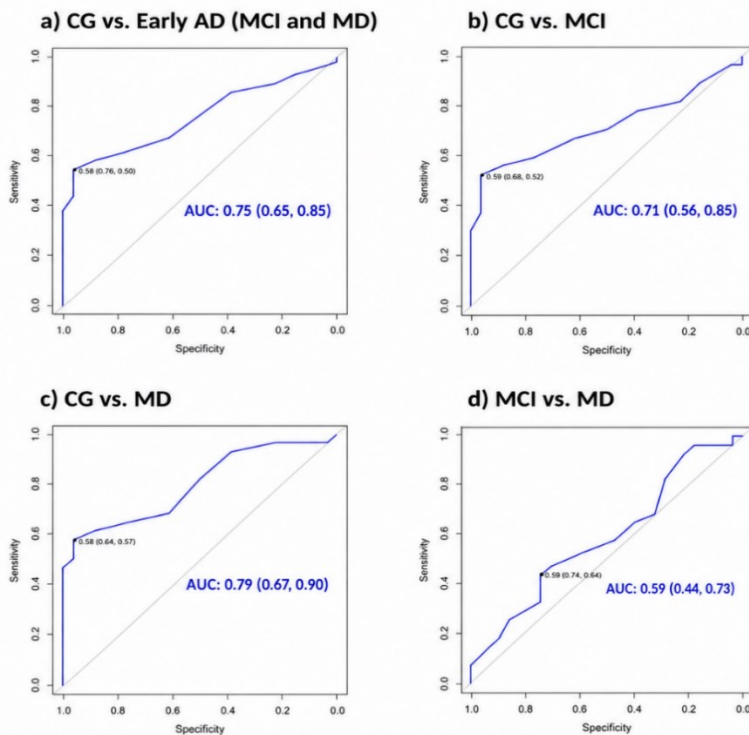


Figure 12. Mental rotation task performance: differentiating between participants with Alzheimer's disease (AD) and cognitively healthy controls

Abbreviations in use: AD, Alzheimer's disease; CG, control group; MD, mild dementia; MCI, mild cognitive impairment

A threshold score of ≤ 22 was selected to indicate AD. By using this cut-off to distinguish participants with AD (MCI and MD) from cognitively healthy controls, the mental rotation task yielded a sensitivity of 54.55% (95% CI: 40.55–68.03) and specificity of 96.15% (95% CI: 80.36–99.9%). **Table 4** presents a comprehensive overview of the diagnostic performance of the mental rotation task in differentiating the participants with AD from those in the CG.

Table 4. Mental rotation task performance: differentiating between participants with Alzheimer’s disease (AD) and cognitively healthy controls

	CG vs. early AD (MCI and MD): cut-off ≤ 22	CG vs. MCI: cut-off ≤ 22	CG vs. MD: cut-off ≤ 22	MCI vs. MD: cut- off ≤ 19
Sensitivity	54.55% (40.55–68.03%)	51.85% (31.95–71.33%)	57.14% (37.18–75.54%)	42.86% (24.4–62.82%)
Specificity	96.15% (80.36–99.9%)	96.15% (80.36–99.9%)	96.15% (80.36–99.9%)	74.07% (53.72–88.89%)
Negative predictive value	50% (42.57–57.43%)	65.79% (56.34–74.13%)	67.57% (57.43–76.29%)	55.56% (45.82–64.88%)
Positive predictive value	96.77% (81.22–99.52%)	93.33% (66.44–99%)	94.12% (69.51–99.12%)	63.16% (44.31–78.7%)
Overall diagnostic accuracy	67.9% (56.6–77.85%)	73.58% (59.67–84.74%)	75.93% (62.36–86.51%)	58.18% (44.11–71.35%)

Note. Data are presented as percentages and 95% confidence intervals.

Abbreviations in use: AD, Alzheimer’s disease; CG, control group; MCI, mild cognitive impairment; MD, mild dementia

The accuracy score and the response time for the mental rotation task were included in the initial model. The model, which incorporated age, education, sex, the ADAS–Cog 13 scores, the mental rotation task accuracy scores, and the response time, showed a marked improvement in fit over the null model ($X^2 = 93.72$, $p < 0.001$; Nagelkerke $R^2 = 0.771$). The model achieved an overall classification accuracy of 75.3%, by virtue of correctly classifying 88.5%, 63%, and 75% of the CG and MCI and MD cohorts, respectively. ADAS–Cog 13 was the only statistically significant predictor ($X^2 = 64.01$, $p < 0.001$).

4.6. Object and Space Perception

4.6.1. Object Perception: Silhouettes

One-way analysis of variance (ANOVA) revealed significant differences in the silhouettes test scores (mean and standard deviation: CG, 18.77 ± 5.64 ; MCI, 13.44 ± 4.85 ; MD, 12.07 ± 4.06 ; $F = 14.06$, $p < 0.001$). *Post-hoc* testing indicated significant differences between the CG and MCI groups as well as the CG and MD groups ($p < 0.001$ for both). However, no significant differences were observed between the MCI and MD groups ($p = 0.90$).

The silhouettes test consists of two components: the identification of 15 animals and 15 inanimate objects. Both components demonstrated statistically significant differences between the CG and MCI groups as well as the CG and MD groups. However, no significant differences were observed between the MCI and MD groups (one-way ANOVA for naming animals: $F = 11.49$, $p < 0.001$; CG vs. MCI, $p = 0.002$; CG vs. MD, $p < 0.001$; and MCI vs. MD, $p = 1$; one-way ANOVA for naming inanimate objects: $F = 9.65$, $p < 0.001$; CG vs. MCI, $p = 0.004$; CG vs. MD, $p < 0.001$; and MCI vs. MD, $p = 1$).

In the sample comprising all participants, the silhouettes test scores demonstrated a moderate correlation with mini-mental state examination (MMSE) (Spearman's rho: 0.477 ; $p < 0.001$), clinical dementia rating–sum of boxes (CDR-SB) (Spearman's rho: -0.437 ; $p < 0.001$), the 13-item version of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13) (Spearman's rho: -0.479 ; $p < 0.001$), and age (Spearman's rho: -0.404 ; $p < 0.001$), while a weak correlation was observed with education (Spearman's rho: 0.295 ; $p = 0.007$).

Multiple linear regression models were employed to assess whether the silhouettes test scores could be predicted by using cognitive test results. These models incorporated cognitive test scores (MMSE, CDR-SB, and ADAS-Cog 13) and were adjusted for sex, age, and education.

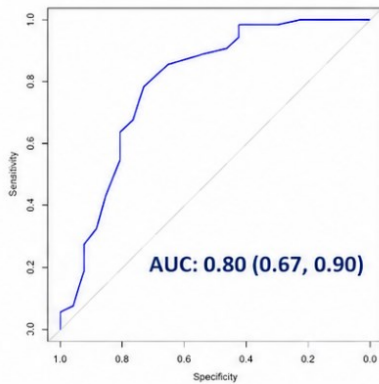
The adjusted models demonstrated statistical significance in the multiple linear regression analysis for MMSE ($R^2 = 0.489$, $F = 20.12$, $\beta = 0.381$, $p < 0.001$), ADAS-Cog 13 ($R^2 = 0.492$, $F = 20.38$, $\beta = -0.4$, $p < 0.001$), and CDR-SB ($R^2 = 0.444$, $F = 16.99$, $\beta = -0.316$, $p < 0.001$).

4.6.2. Diagnostic Characteristics of the Silhouettes Task

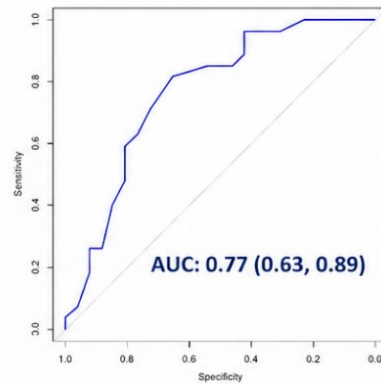
To assess the effectiveness of silhouettes test scores in distinguishing between the CG and patients with AD, including those with MCI or MD, as well as patients with MCI and MD, *Receiver Operating Characteristic* (ROC)

curve analysis was conducted. The ROC curves illustrating the silhouettes test performance for differentiating between the participant groups are shown in **Figure 13**.

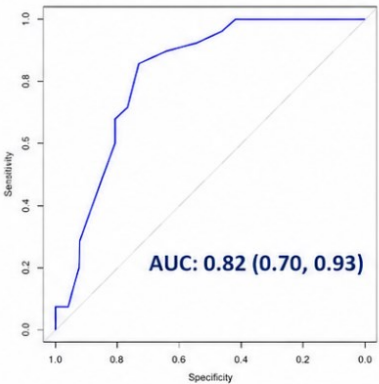
a) CG vs. Early AD (MCI and MD)



b) CG vs. MCI



c) CG vs. MD



d) MCI vs. MD

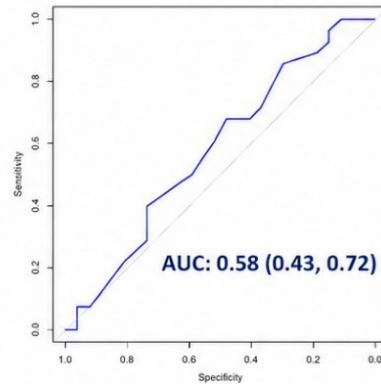


Figure 13. Performance of the Silhouettes test in differentiating between participants with AD and the CG

Abbreviations in use: AD, Alzheimer's disease; CG, control group; MD, mild dementia; MCI, mild cognitive impairment.

A threshold score ≤ 16 on the silhouettes test was established as an indicator of AD. When applied to distinguish AD patients (including those with MCI or MD due to AD) from the CG participants, the silhouettes test demonstrated a sensitivity of 78.18% (95% CI: 64.99–88.19) and specificity

of 73.08% (95% CI: 52.21–88.43%). Furthermore, the test yielded a negative predictive value of 61.29% (95% CI: 47.69–73.33%) and positive predictive value of 86% (95% CI: 76.26–92.16%). The overall accuracy of diagnosis was 76.54% (95% CI: 65.82–85.25%). All cut-off scores and diagnostic properties of the silhouettes test for comparisons between the diagnostic groups are presented in **Table 5**.

Table 5. Diagnostic properties of the silhouettes test for differentiating between participants with AD and CG

	CG vs. early AD (MCI and MD), cut-off ≤ 16	CG vs. MCI, cut-off ≤ 16	CG vs. MD, cut-off ≤ 16	MCI vs. MD, cut-off ≤ 13
Sensitivity	78.18% (64.99–88.19%)	70.37% (49.82–86.25%)	85.71% (67.33–95.97%)	67.86% (47.65–84.12%)
Specificity	73.08% (52.21–88.43%)	73.08% (52.21–88.43%)	73.08% (52.21–88.43%)	48.15% (28.67–68.05%)
Negative predictive value	61.29% (47.69–73.33%)	70.37% (55.94–81.63%)	82.61% (65.05–92.38%)	59.09% (42.61–73.75%)
Positive predictive value	86% (76.26–92.16%)	73.08% (57.92–84.26%)	77.42% (64.13–86.80%)	57.58% (46.54–67.9%)
Overall diagnostic accuracy	76.54% (65.82–85.25%)	71.7% (57.65–83.21%)	79.63% (66.47– 89.37%)	58.18% (44.11–71.35%)

Note. Data are presented as percentage and 95% confidence interval.

Abbreviations in use: AD, Alzheimer’s disease; MD, mild dementia; MCI, mild cognitive impairment; CG, control group

To examine the influence of the predictor variables on group classification (CG, MCI, and MD), a multinomial logistic regression analysis was conducted. Initially, a model incorporating sex, age, education, and ADAS-Cog 13 scores as predictors was developed. The inclusion of these variables significantly enhanced the fit of the model compared to the intercept-only model ($X^2 = 87.79$, $p < 0.001$; Nagelkerke $R^2 = 0.744$). This model accurately classified 76.5% of the cases overall, with correct classification rates of 92.3% for CG, 66.7% for MCI, and 71.4% for MD. Among the predictors, the ADAS-Cog 13 score emerged as the most robust and statistically significant alternative ($X^2 = 78.83$, $p < 0.001$).

A second model incorporating sex, age, education, the ADAS-Cog 13 scores, and the silhouettes test scores demonstrated a notable enhancement in fit compared to a null model ($X^2 = 88.30$, $p < 0.001$; Nagelkerke $R^2 = 0.747$). This model accurately classified 76.4% of the cases overall, with specific

accuracies of 92.3% for CG, 63% for MCI, and 75% for MD. Within this model, ADAS-Cog 13 emerged as a robust and statistically significant predictor ($X^2 = 61.77$, $p < 0.001$), whereas the silhouettes test was not a significant predictor ($X^2 = 0.465$, $p = 0.793$).

4.6.3. Space Perception: Number Location

Significant differences were observed in the number location test scores across the three groups. The median and interquartile ranges were as follows: CG, 9.5 (2); MCI, 8 (3); and MD, 6 (6). A Kruskal-Wallis test ($p < 0.001$) and the subsequent *post-hoc* analysis revealed statistically significant differences between all group pairs: CG versus MCI ($p = 0.007$), MCI versus MD ($p = 0.007$), and CG versus MD ($p < 0.001$).

A moderate correlation was observed between the number location test scores and the performance on the MMSE (Spearman's rho: 0.573; $p < 0.001$), CDR-SB (Spearman's rho: -0.5; $p < 0.001$), and ADAS-Cog 13 (Spearman's rho: -0.467; $p < 0.001$). No significant correlations were observed with age and education.

Multiple linear regression models were employed to assess whether the number location test scores could be predicted by using the cognitive test results. These models incorporated the cognitive test scores (MMSE, CDR-SB, and ADAS-Cog 13), and were adjusted for sex, age, and education.

The adjusted models demonstrated statistical significance in the multiple linear regression analysis with MMSE ($R^2 = 0.384$, $F = 13.47$, $\beta = 0.483$, $p < 0.001$), ADAS-Cog 13 ($R^2 = 0.288$, $F = 9.08$, $\beta = -0.383$, $p < 0.001$), and CDR-SB ($R^2 = 0.364$, $F = 12.46$, $\beta = -0.46$, $p < 0.001$).

4.6.4. Diagnostic Characteristics of the Number Location Task

To assess the effectiveness of the number location test score in distinguishing between the CG and patients with AD, including those with MCI or MD, as well as patients with MCI and MD, ROC curve analysis was conducted. The ROC curves illustrating the number location test performance for differentiating the participant groups are shown in **Figure 14**.

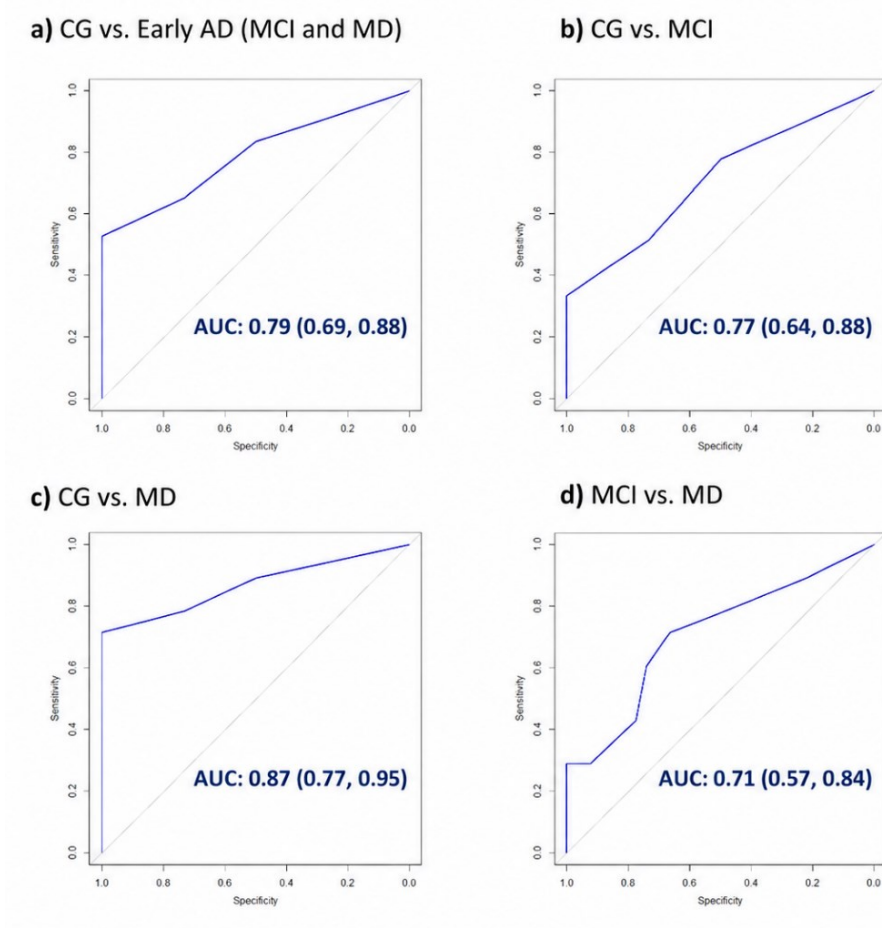


Figure 14. Performance of the number location test in differentiating between participants with AD and the CG

Abbreviations in use: AD, Alzheimer's disease; CG, control group; MD, mild dementia; MCI, mild cognitive impairment

A threshold score ≤ 8 on the number location test was established to indicate AD. When applied to distinguish patients with AD (including those with MCI or MD due to AD) from the CG participants, the number location test demonstrated a sensitivity of 65.45% (95% CI: 51.42–77.76) and specificity of 73.08% (95% CI: 52.21–88.43%). Furthermore, the test yielded a negative predictive value of 50% (95% CI: 39.36–60.64%) and a positive predictive value of 83.72% (95% CI: 72.63–90.88%). The overall accuracy of diagnosis was 67.9% (95% CI: 56.60–77.85%). All cut-off scores and diagnostic properties of the number location test for comparisons between the diagnostic groups are presented in **Table 6**.

Table 6. Diagnostic properties of the number location test for differentiating between participants with AD and CG

	CG vs. early AD (MCI and MD), cut-off ≤ 8	CG vs. MCI, cut-off ≤ 8	CG vs. MD, cut-off ≤ 8	MCI vs. MD, cut-off ≤ 7
Sensitivity	65.45% (51.42–77.76%)	51.65% (31.95–71.33%)	78.57% (59.05–91.7%)	71.43% (51.33–86.78%)
Specificity	73.08% (52.21–88.43%)	73.08% (52.21–88.43%)	73.08% (52.21–88.43%)	66.67% (46.04–83.48%)
Negative predictive value	50% (39.36–60.64%)	59.38% (48.1–69.75%)	73.08% (52.21–88.43%)	69.23% (54.18–81.07%)
Positive predictive value	83.72% (72.63–90.88%)	66.67% (49.07–80.59%)	75.86% (61.84–85.9%)	68.97% (55.38–79.92%)
Overall diagnostic accuracy	67.9% (56.6–77.85%)	62.29% (47.89–75.21%)	75.93% (62.36–86.51%)	69.09% (55.19–80.86%)

Note. Data are presented as percentage and 95% confidence interval.

Abbreviations in use: AD, Alzheimer's disease; MD, mild dementia; MCI, mild cognitive impairment; CG, control group

To examine the influence of the predictor variables on the group classification (CG, MCI, and MD), a multinomial logistic regression analysis was conducted. Initially, a model incorporating sex, age, education, and the ADAS-Cog 13 scores as predictors was developed. Inclusion of these variables significantly enhanced the fit of the model compared to the intercept-only model ($X^2 = 87.79$, $p < 0.001$; Nagelkerke $R^2 = 0.744$). This model accurately classified 76.5% of the cases overall, with correct classification rates of 92.3% for CG, 66.7% for MCI, and 71.4% for MD. Among the predictors, the ADAS-Cog 13 score emerged as the most robust and statistically significant option ($X^2 = 78.83$, $p < 0.001$).

A second model incorporating sex, age, education, the ADAS-Cog 13 scores, and the number location test scores demonstrated a notable enhancement in fit compared to a null model ($X^2 = 104.76$, $p < 0.001$; Nagelkerke $R^2 = 0.816$). This model accurately classified 80.2% of the cases overall, with specific accuracies of 92.3% for CG, 70.4% for MCI, and 78.6% for MD. Within this model, the ADAS-Cog 13 and number location tests were statistically significant predictors ($X^2 = 68.22$, $p < 0.001$; $X^2 = 16.97$, $p < 0.001$, respectively).

4.6.5. Space Perception: Cube Analysis

The cube analysis test scores differed significantly between the groups (medians and interquartile ranges: CG, 10 (1); MCI, 8 (3); MD, 7 (5); Kruskal–Wallis $p < 0.001$). *Post-hoc* analysis revealed significant differences between CG vs. MCI and CG vs. MD, $p < 0.001$, but not between MCI vs. MD, $p = 0.094$.

The cube analysis scores moderately correlated with MMSE (Spearman's $\rho = 0.579$; $p < 0.001$), CDR-SB (Spearman's $\rho = -0.489$; $p < 0.001$), ADAS-Cog 13 (Spearman's $\rho = -0.521$; $p < 0.001$), while a weak correlation was observed with age (Spearman's $\rho = -0.337$; $p = 0.002$), and education (Spearman's $\rho = 0.346$; $p = 0.002$).

Multiple linear regression models were employed to assess whether the cube analysis test scores could be predicted by using the cognitive test results. These models incorporated the cognitive test scores (MMSE, CDR-SB, and ADAS-Cog 13) and were adjusted for sex, age, and education.

The adjusted models demonstrated statistical significance in the multiple linear regression analysis with MMSE ($R^2 = 0.376$, $F = 13.03$, $\beta = 0.471$, $p < 0.001$), ADAS-Cog 13 ($R^2 = 0.29$, $F = 9.16$, $\beta = -0.382$, $p < 0.001$), and CDR-SB ($R^2 = 0.296$, $F = 9.4$, $\beta = -0.376$, $p < 0.001$).

4.6.6. Diagnostic Characteristics of the Cube Analysis Task

To assess the effectiveness of the cube analysis test score in distinguishing between the CG and patients with AD, including those with MCI or MD, as well as patients with MCI and MD, ROC curve analysis was conducted. The ROC curves illustrating the cube analysis test performance for differentiating the participant groups are shown in **Figure 15**.

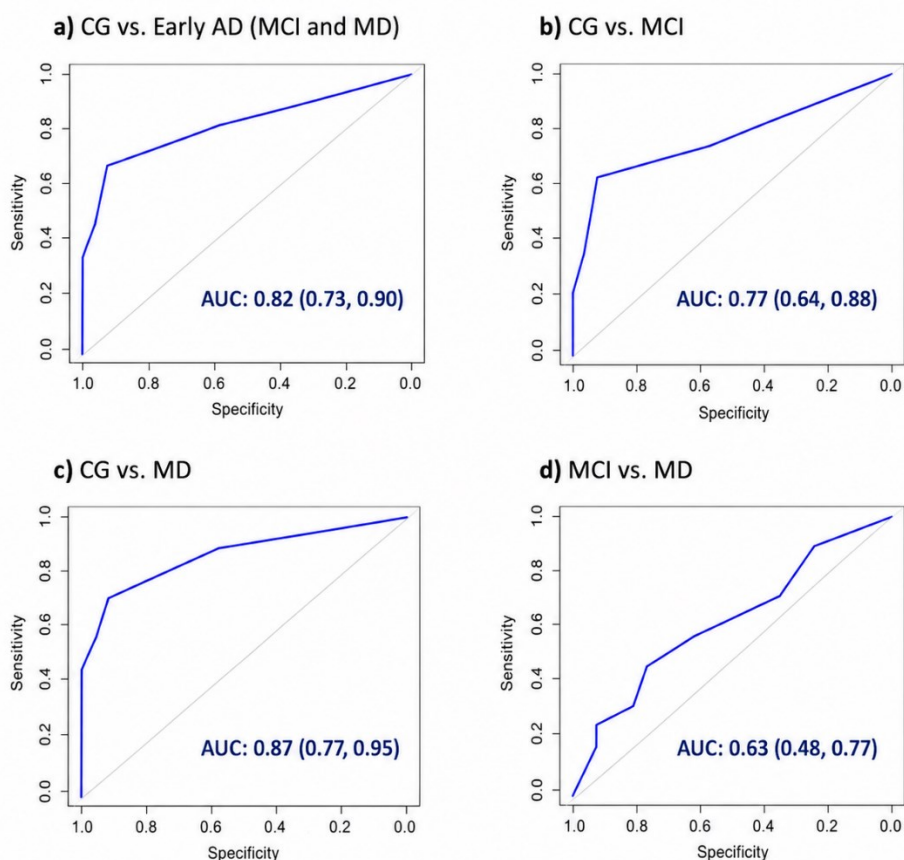


Figure 15. Performance of cube analysis test in differentiating between participants with AD and the CG

Abbreviations in use: AD, Alzheimer's disease; CG, control group; MD, mild dementia; MCI, mild cognitive impairment

A threshold score ≤ 8 on the cube analysis test was established to indicate AD. When applied to distinguish patients with AD (including those with MCI or MD due to AD) from CG participants, the test demonstrated a sensitivity of 67.27% (95% CI: 53.29–79.32%) and a specificity of 92.31% (95% CI: 74.87–99.05%). Furthermore, the test yielded a negative predictive value of 57.14% (95% CI: 47.32–66.43%) and a positive predictive value of 94.87% (95% CI: 82.83–98.61%). The overall accuracy of diagnosis was 75.31% (95% CI: 64.47–84.22%). All cut-off scores and diagnostic properties of the cube analysis test for comparisons between the diagnostic groups are presented in **Table 7**.

Table 7. Diagnostic properties of the cube analysis test for differentiating between participants with AD and CG

	CG vs. early AD (MCI and MD), cut-off ≤ 8	CG vs. MCI, cut-off ≤ 8	CG vs. MD, cut-off ≤ 8	MCI vs. MD, cut-off ≤ 7
Sensitivity	67.27% (53.29–79.32%)	62.96% (42.37–80.60%)	71.43% (51.33–86.78%)	57.14% (37.18–75.54%)
Specificity	92.31% (74.87–99.05%)	92.31% (74.87–99.05%)	92.31% (74.87–99.05%)	62.96% (42.37–80.6%)
Negative predictive value	57.14% (47.32–66.43%)	70.59% (59.18–79.89%)	75.00% (62.31–84.48%)	58.62% (45.81–70.36%)
Positive predictive value	94.87% (82.83–98.61%)	89.47% (68.51–97.08%)	90.91% (72.12–97.48%)	61.54% (47.07–74.22%)
Overall diagnostic accuracy	75.31% (64.47–84.22%)	77.36% (63.79–87.72%)	81.48% (68.57–90.75%)	60% (45.91–72.98%)

Note. Data are presented as percentage and 95% confidence interval.

Abbreviations in use: AD, Alzheimer's disease; MD, mild dementia; MCI, mild cognitive impairment; CG, control group

To examine the influence of predictor variables on the group classification (CG, MCI, and MD), a multinomial logistic regression analysis was conducted. Initially, a model incorporating sex, age, education, and the ADAS-Cog 13 scores as predictors was developed. The inclusion of these variables significantly enhanced the fit of the model compared to the intercept-only model ($X^2 = 87.79$, $p < 0.001$; Nagelkerke $R^2 = 0.744$). This model accurately classified 76.5% of the cases overall, with correct classification rates of 92.3% for CG, 66.7% for MCI, and 71.4% for MD. Among the predictors, the ADAS-Cog 13 score emerged as the most robust and statistically significant option ($X^2 = 78.83$, $p < 0.001$).

A second model incorporating sex, age, education, the ADAS-Cog 13 scores, and the cube analysis test scores demonstrated a notable enhancement in fit compared to a null model ($X^2 = 94.08$, $p < 0.001$; Nagelkerke $R^2 = 0.773$). This model accurately classified 80.2% of the cases overall, with specific accuracies of 92.3% for CG, 70.4% for MCI, and 78.6% for MD. Within this model, ADAS-Cog 13 and cube analysis test were statistically significant predictors ($X^2 = 59.93$, $p < 0.001$; $X^2 = 6.29$, $p = 0.043$, respectively).

5. DISCUSSION

Consistent with previous studies, visual perceptual dysfunction is considered an early indication of MCI due to AD and the progression to AD (11,72,73). The aspects that showed diagnostic potential in our study were color memory, time/movement estimation, as well as object and spatial perception. The perception of visual illusions and the execution of mental rotation tasks offer valuable insights into functional changes associated with early-stage AD.

In the current study, our findings revealed that color recognition memory is impaired in the early stages of AD and is more pronounced in the mild dementia stages. Significant differences in color recognition memory were observed between the CG and the MCI group, thus emphasizing the usefulness of color memory evaluation in the early stages of AD. The color recognition task is a memory task that relies on hippocampus integrity, a region known to be implicated in AD (74). The ventral stream of the visual perception pathway is responsible for color identification and recognition (19). According to recent studies, better visual recognition is associated with the memory of the categorical features of a visual scene aiding in discriminating between the targets and lures. During a visual recognition task, activation with categorical representations in the precuneus, inferior temporal cortex, and superior occipital cortex improved scene memory (75). Relying solely on verbal memory tasks to evaluate the cognitive function may lead to the overlooking of visual memory deficits. Incorporating visual memory tasks for cognitive evaluations may be useful in improving the diagnostic process. Oltra-Cucarella et al. emphasized that, although verbal amnesic MCI was the most prevalent form, a substantial number of the participants exhibited either visual-only amnesic MCI or a combination of visual and verbal amnesic MCI. The likelihood of developing AD was equivalent in individuals with visual amnesic or verbal amnesic MCI alone, and higher in those with combined amnesic MCI (76). Squarzoni et al. concluded that the visual compared to verbal episodic memory scores correlated most significantly with the presence of amyloid-beta ($A\beta$), as measured by positron emission tomography (PET) scans (77). As reported by Cecchini et al., the short-term memory binding test, which evaluates the capacity to retain the integration of surface features such as shapes and colors, has shown sensitivity to indicators of AD pathology, and that it may function as a cognitive marker within the AD continuum (78). Contrary to our study findings, Meyer et al. concluded that episodic recognition memory, based on the incidental learning of visual associations, is largely preserved in comparison with recall in cases of

amnesic MCI and mild AD (79,80). The stimuli utilized in this study comprised 24 line drawings, thus indicating that our research may provide novel insights into the similarity between color recognition memory and verbal recall memory in early AD, and that color recognition memory may be more impaired than object recognition memory. Our findings underscore the necessity of incorporating both verbal and visual memory evaluations into neuropsychological examinations to identify amnesic MCI with greater precision.

The color recognition task scores demonstrated a significant and strong correlation with the MMSE results, and a moderate correlation with the ADAS-Cog 13 and CDR-SB scores. A linear regression analysis significantly predicted the total error scores for color memory using these three tests. Factors such as age, sex, and education did not have a substantial impact on the color memory scores. These results confirm that color memory impairment is associated with the pathological processes of AD rather than other factors known to influence visual perception such as age (11-14). This study also supports the finding that AD-related neuropathological lesions described from the retina to all parts of the visual system affect the visual function (11-13).

Recent studies have used color discrimination tasks to differentiate AD from other dementias (43-45). Unger et al. used a color vision task (Farnsworth D-15 color vision test) to distinguish AD from dementia with Lewy bodies, and found that color vision impairment could be utilized as a diagnostic tool to differentiate dementia with Lewy bodies from AD. However, a significant proportion (20%) of patients with AD have color vision impairment. Furthermore, lower cognitive test scores and visuospatial or executive function subscores were associated with color vision impairment in patients with dementia and Lewy bodies, thus suggesting that this impairment is more closely related to a cognitive decline in the later stages of the disease (45). Our study's findings indicate that the Ishihara color vision test results revealed significant differences between the MD and CG groups. However, no significant differences were detected between the CG and MCI groups, or between the MCI and MD groups. These results suggest that alterations in color vision may be attributed to progressive neurodegeneration (81).

Research on the diagnostic potential of color memory tests remains limited because evaluations of color vision and memory are infrequent. This study revealed that the color recognition memory task effectively distinguished the participants with early AD from cognitively normal older adults (AUC = 0.88) and those with prodromal AD from cognitively normal older adults (AUC = 0.81). Additionally, the incorporation of the color memory scores into multinomial logistic regression models resulted in a notable improvement in

the overall classification accuracy. This enhancement led to an increase in the three-group classification accuracy from 77.9 to 84.4%, representing a 6.5-percentage-point improvement. Notably, the precise identification of MCI showed considerable improvement, increasing from 64 to 76%, representing a 12-percentage-point enhancement in precision. Identifying MCI is particularly difficult in primary care settings. According to the 2024-dated World Alzheimer Report (4,8), approximately 80% of the population, and more concerning, 65% of medical professionals erroneously perceive dementia as a normal part of aging. This misconception can delay an early detection and timely access to necessary treatment and assistance (7). Color memory testing may be beneficial in enhancing the diagnostic accuracy, particularly when distinguishing between MCI due to AD from age-related changes.

Although the color memory task showed satisfactory diagnostic performance in differentiating the participants with an early AD from older adults with normal cognition, its ability to differentiate among MCI and mild dementia due to AD was suboptimal. One explanation for these results is that color memory impairment most likely occurs early in the disease course. These changes are evident even in the early stages of AD, thereby reducing their effectiveness in tracking the disease progression. This finding aligns with those of Ritchie et al., who found that middle-aged individuals whose parents had been diagnosed with dementia showed lower-than-expected scores on the visual memory tests, whereas their performance in the verbal memory assessments remained normal (82).

In the present study, we also assessed the visual illusions of induced color, specifically the ME and WE, in individuals with a diagnosis of early AD and those who were cognitively normal. The perceptions of ME and WE were more impaired in the MD group than in the CG and MCI groups. Moreover, the use of AChEI did not influence the perception of ME or WE in the mild dementia stage of AD. We conclude that the visual illusions of induced colors are more severely compromised in mild AD, which may provide insight into changes in visual perception.

Our study showed that ME was significantly impaired during the MD stage of AD. While no significant differences were identified among the 3 groups in the perception of white vertical lines as red, notable differences were observed in the perception of white horizontal lines as green. During ME induction, a specific orientation, such as horizontal, is consistently paired with a particular color, such as red, for several minutes. This process results in a shift of the 'neutral point' for red toward the over-represented end of the red color continuum in the presence of horizontal orientations (30,31). Over the past 3

decades, considerable discourse has emerged in the literature regarding the potential nature of these underlying mechanisms. Initially, Skowbo et al. proposed that the rapid decay of the ME induced by achromatic gratings supports the hypothesis that the ME is predicated upon an adaptation process (83). Additionally, the rapid decline of the ME can be explained as the fading-away of a conditioned response (83). There is significant debate surrounding whether the ME originates in early visual areas (84,85). While some studies support the hypothesis that the effect begins in V1, a considerable number of studies oppose this perspective (86,87). Functional MRI studies have observed alterations in activity across several brain regions, concluding that the ME is generated through top-down processing originating from the frontal cortex and other areas (86). Furthermore, the ventral occipital cortex (V4 alpha) was significantly activated in association with ME (87). The strength of the ME has been demonstrated to have an inverse relationship with acetylcholine (51). It is notably enhanced by the administration of scopolamine, an anticholinergic, and diminished by physostigmine, a cholinergic, when these substances are given prior to exposure to ME stimuli (51). However, there is a lack of comprehensive data on ME among patients with early AD and those who are on AChEI. Our study shows that AChEI does not significantly affect ME and provides the insight that ME is diminished in the MD stage of early AD, especially in terms of the after-effect of red horizontal gratings. The reason for the stronger after-effect of green vertical gratings is debatable. Marino et al. suggested that this explanation lies in the concept of natural entities, which involves the activation of neurons that are simultaneously responsive to the color green and the vertical orientation. This might be because the variability in their activation is lower than that of other modality-specific channels (88). Our study findings may diverge from those of Savoy et al., as previous evaluations of ME in individuals with AD have analyzed the red and green after-effects collectively, whereas our approach involved a separate comparison of the red and green after-effects (50). In contrast to WE, ME was not significantly affected by the results of the Ishihara test, thus indicating that the underlying mechanisms responsible for the production of induced colors differed. The results of the cognitive assessments significantly predicted the perception of the white horizontal lines as green, with lower scores indicating diminished or absent ME. The present findings further corroborate the hypothesis that ME is influenced by changes in early AD, particularly in relation to the color orientation after-effect, which is characterized by more variable activation (red horizontal). These results offer valuable insights into the alterations in visual perception associated with AD.

The WE effect was influenced by the outcomes of the Ishihara test, demonstrating that, when the WE effect was not perceived, there was a significantly higher incidence of errors in the Ishihara test. Recent studies have used color discrimination tasks to distinguish AD from other forms of dementia, revealing that a substantial proportion (20%) of patients with AD exhibit color vision impairment (44,45). Moreover, lower scores on cognitive assessments and subscores related to visuospatial or executive functions are associated with color vision impairment (45). The findings of our study reveal that the results of the WE and Ishihara color vision tests showed significant differences only between the CG and MD groups. These results align with those of Vidal et al., who attributed alterations in color vision to progressive neurodegeneration rather than to individuals exhibiting only signs of A β deposition in the brain (81). As previously reported, Gerardin et al. suggest that the induction of WE involves the modulation of area V1 by the dorsal stream of the visual pathway, which subsequently influences the ventral regions (55). Consequently, WE may serve as a functional indicator of neurodegenerative changes in these areas, but it is not specific to very early AD changes, such as A β deposition in the brain.

In the current study, computerized time/movement estimation (Time–Wall) and mental rotation tasks were evaluated as potential diagnostic tools for early AD. The Time–Wall task demonstrated strong diagnostic performance, with AUC values of 0.9 for distinguishing cognitively healthy controls from the participants with early AD (MCI and MD) and 0.86 for differentiating the CG from the MCI cohort alone. Conversely, the performance of the mental rotation task was more modest, with AUC values of 0.75 for distinguishing the participants in the CG from those with early AD and 0.71 for differentiating the CG from the MCI cohort.

This study's findings indicated that the Time–Wall task performance was already impaired at the MCI stage, with no marked differences observed between the MCI and MD cohorts. In our study population, the median inaccuracy in the CG was 11.46%. In comparison, Piper et al. have reported an average inaccuracy of $12.3\% \pm 0.8\%$ across all age cohorts, with a general tendency to respond too early (35). Notably, their study found no evidence of a performance decline among older adults (35). These results suggest that the general reduction in processing speed, which is typically associated with aging, may confer a slight advantage in this simple decision-making task, which contrasts with findings from other executive function tests (35).

Our study found that inaccuracy scores of the Time–Wall task were strongly correlated with cognitive assessment outcomes; these scores also showed a weak correlation with the educational background, and no

perceptible correlation with age. Furthermore, the Time–Wall task accuracy score emerged as a major predictor in the multinomial logistic regression model used to classify the participants into the CG and MCI and MD cohorts. Therefore, these findings highlight the robust diagnostic potential of the Time–Wall task for early AD, with minimal influence from demographic factors, such as age.

According to Porter et al., the processing of complex motions, which are dynamic, moving stimuli, is more susceptible to deterioration than that of complex static forms, possibly due to its greater reliance on extensive neural connections, which are considerably affected by AD pathology (89). Moreover, distinguishing AD from normal aging might be more effectively achieved through complex motion detection rather than when focusing on directionality (36,90). To better understand the differences in temporal judgment in AD, further research is required to evaluate a broad range of timing tasks, such as the Time–Wall task, which incorporates both time and motion processing.

Performance of the mental rotation task, as measured by the accuracy scores and response times, demonstrated notable differences between the CG and those with MCI or MD. No marked differences were observed between the MCI and MD cohorts. The diagnostic accuracy of mental rotation was lower than expected, and the inclusion of the mental rotation task resulted in a multinomial logistic regression model that did not improve cohort classification. According to Suzuki et al., the mental rotation task with a 180° rotating angle was able to distinguish MCI cases from their controls with 80.0% accuracy (58).

Several factors may explain the limited diagnostic potential of this task. Most notably, constraints on the length and complexity of mental rotation tasks, particularly for older adults and patients with AD, necessitate accounting for fatigue, which can negatively affect performance during extended tasks across all population groups (91). In our study, the participants completed six practice trials and 32 experimental trials involving mental rotation. The average task duration was 5–10 min for CG and 10–20 min for MCI and MD, with a time limit of 30 min. By contrast, the original mental rotation task within the PEBL battery comprised 128 trials, and the task duration in the study by Langner et al. was approximately 4 h 30 min (59). Second, according to Yassa et al., asymptomatic individuals at risk for familial late-onset AD exhibit more extensive neural activity than healthy individuals during mental rotation tasks. This infers that a genetic predisposition to AD is associated with altered brain function, marked by an increased activation in the parietal cortex, particularly in the prefrontal regions, potentially reflecting

a compensatory network (92). These results indicate that the diagnostic accuracy of the mental rotation task in distinguishing between cognitively healthy individuals and those with pathology may be influenced by compensatory mechanisms in the frontal lobe regions that are not yet affected by AD (92).

While studies have frequently shown that males outperform females on spatial ability tests, our study found no distinct differences in sex when independently analyzing the cohorts (93). Furthermore, the mental rotation task performance exhibited a weak correlation with age and educational attainment, thus suggesting a minimal impact of demographic variables. These findings highlight the need for a more comprehensive evaluation of mental rotation tasks so that to better capture the compensatory brain network function.

Our study demonstrated that the VOSP battery tests (silhouettes, number location, and cube analysis) are appropriate additional tools for an early diagnosis of AD. These three tests demonstrated similar diagnostic potential in differentiating MCI from the CG (area under the curve (AUC) = 0.77 for all). In contrast, the cube analysis test exhibited the highest diagnostic accuracy in distinguishing the CG from MCI and MD diagnostic groups (AUC silhouettes = 0.80, number location = 0.79, and cube analysis = 0.82). The findings of this study indicate that performance on the silhouettes test is impaired at the MCI stage, with no significant differences observed between the MCI and MD groups. Compared with the study by Quental et al., the cut-off score for differentiating the CG from early AD was identical in the silhouettes test, and our diagnostic accuracy results fell within the confidence interval range (63). A longitudinal study by Eckerström et al. evaluating the conversion of MCI or subjective cognitive decline to dementia using CSF biomarkers and cognitive testing showed that the silhouettes test results were significantly worse in the A β aggregation (A), tau aggregation (T), and neurodegeneration (N) positive (A + T + N+) groups than in the group with negative biomarkers (A-T-N-) at baseline evaluation (94). In our study, a moderate negative correlation was observed between age and performance on the silhouettes test, and a weak or no correlation between demographic data and the number location or cube analysis tests. In a study by Herrera-Guzmán et al., the educational level was a significant predictor of performance in a population with the normal cognitive function for silhouettes and object decision tests (95). Multinomial logistic regression analysis, incorporating demographic data, the ADAS-Cog 13 scores, and the silhouettes test results, accurately classified 76.4% of the cases; however, the silhouettes test was not a significant predictor in this model. The specific accuracies showed poor

performance in classifying MCI (92.3% for CG, 63% for MCI, and 75% for MD). Consequently, this test is influenced by demographic characteristics and object perception impairment occurs early in the course of AD. Performance on the number location task differed significantly across the three groups, thereby suggesting its potential utility for the very early diagnosis of AD. In this study, lower cut-off scores in the number location and cube analysis tests were used to differentiate the CG from early AD (MCI and MD) compared to the study by Quental et al. (63). A cut-off value ≤ 8 was selected to indicate early AD, whereas Quental et al. reported a cut-off score of 9 for distinguishing the CG from MD in both tasks (63). Incorporation of the number location or cube analysis task results into a multinomial regression model with age, education, sex, and the ADAS-Cog 13 scores improved correctly classified CG, MCI, and MD cases from 76.5% to 80.2% (specific accuracies: 92.3% for CG, 70.4% for MCI, and 78.6% for MD). Both space perception tests improved the diagnostic accuracy of the models. As previously mentioned, cube analysis provided the best AUC results, differentiating the CG from early AD, and improved the group classification. This test stands out among spatial tests because of its unique requirement for three-dimensional perception despite being presented as a two-dimensional image. In addition, it involves the detection of hidden cubes, which must be deduced rather than observed directly (62). In the human brain, the parieto-occipital junction is responsible for stereoscopic processing, which is crucial for spatial reasoning (96). In addition to our finding that the number location and cube analysis tests enhance the diagnostic accuracy in amnesic early AD, evidence demonstrates their substantial efficacy in diagnosing early atypical presentations of AD (66,73,97). Recent studies with pathological confirmation of the diagnosis provide evidence that atypical AD variants with prominent visual agnosia (posterior cortical atrophy) and motor AD variant (corticobasal syndrome) can be clinically diagnosed by using VOSP tests (66,73,97). Boyd et al. reported that, in a clinicopathological investigation of individuals with corticobasal syndrome, poor performance on incomplete letters and all spatial VOSP tests correlated with an increased likelihood of an underlying AD pathology, with cube analysis emerging as the most effective option (sensitivity: 100%; specificity: 77%) (66).

This study has a few limitations. Firstly, our results were limited by the cross-sectional study design; future longitudinal studies are needed to assess the progression of visual perception impairment during the course of AD. Secondly, cerebrospinal fluid biomarker analysis was conducted for a small proportion of participants with MCI and MD, and PET scans were not performed. Incorporation of these methods would have offered valuable

insights into how changes in color memory relate to the accumulation of brain A β and the deterioration of neurons. Thirdly, the appearance of colors on a computer screen usually differs across devices due to variation in display settings. To minimize the effects of this limitation, we used distinct colors, each varying by approximately 25% in the red, blue, or green components of the RGB scale. It is well established that ocular conditions such as glaucoma, diabetic retinopathy, and macular degeneration can impact color vision even in their initial stages (98-101). Although all participants in this study had documented prior eye examinations, a recent ophthalmological assessment was not conducted. Consequently, it is not possible to ascertain whether the included patients had ophthalmological conditions that could introduce a selection bias at the time of recruitment. Finally, despite the observed significant differences, the small sample size may limit the generalizability of our findings. A larger sample size is necessary to confirm these results.

6. CONCLUSIONS

1. The test results for color recognition memory showed significant differences between older adults with normal cognition and those with early AD, highlighting its potential in the early diagnosis of AD. Color memory testing has good diagnostic characteristics and can be an easy-to-execute, reliable, and non-invasive diagnostic test for early AD.
2. Significant differences in ME and WE were observed between the participants with the normal cognitive function and those in the early stages of AD. This finding offers insight into the functional alterations of the visual system, suggesting that diminished or absent ME and WE may serve as indicators of ongoing neurodegeneration. The ME after-effect of the red horizontal lines might represent early AD changes, which may aid in a more advanced understanding of visual perception in AD.
3. The computerized Time–Wall task is an efficient clinical assessment tool, enabling a quick evaluation of temporal judgment and motion perception in early AD. Age did not influence the performance of the Time–Wall task. The mental rotation task requires further evaluation, as it may offer insights into compensatory brain network functions.
4. The VOSP serves as an inexpensive and efficient clinical assessment instrument, allowing easy and fast evaluation of visuoperceptual function in early AD. We recommend using silhouettes and space perception tasks (number location and cube analysis) to improve early AD diagnosis.

7. FUTURE PERSPECTIVES/PRACTICAL RECOMMENDATIONS

This doctoral dissertation establishes that visual perception impairments appear early in patients with Alzheimer's disease (AD). Tests assessing color recognition memory, visual object and space perception, as well as computerized evaluations of time and movement estimation, demonstrated strong diagnostic capabilities for identifying early-stage AD. Consequently, incorporating these tests into standard clinical practice is advisable. Testing for visual perception and color memory could act as dependable, non-invasive, and cost-effective indicators to enhance the diagnostic process, particularly in primary care settings. To validate the promising results of this study, further research with larger sample sizes is necessary. Additionally, future research should incorporate cerebrospinal fluid, positron emission tomography, and other biomarkers to ensure the highest diagnostic accuracy, and to explore the relationship between these biomarkers and changes in visual perception.

SUMMARY IN LITHUANIAN

SANTRUMPOS

AChEI	–	acetilcholinesterazės inhibitoriai
ADAS-Cog	–	Alzheimerio ligos vertinimo skalės kognityvinė subskalė
ADI	–	tarptautinė organizacija <i>Alzheimer's Disease International</i>
AE	–	akvarelės efektas (angl. <i>Watercolor effect</i>)
AL	–	Alzheimerio liga
ANOVA	–	dispersinė analizė
AUC	–	plotas po ROC kreive
A β	–	beta amiloidas
CDR	–	klinikinė demencijos vertinimo skalė
CDR-SB	–	klinikinės demencijos vertinimo skalės langelių suma
CDR-TS	–	klinikinės demencijos vertinimo skalės bendras įvertis
CG	–	kontrolinė grupė
GDS	–	geriatrinė depresijos skalė
HII	–	Hačinskio išemijos indeksas
IQR	–	tarpkvartilinis intervalas
LKS	–	lengvas kognityvinis sutrikimas
MCI	–	lengvo kognityvinio sutrikimo grupė
MD	–	lengvos demencijos grupė
ME	–	McCollough efektas
MMSE	–	mini protinės būklės tyrimas
MRT	–	magnetinio rezonanso tomografija
NIA-AA	–	angl. <i>National Institute on Aging-Alzheimer's Association</i>
PEBL	–	angl. <i>Psychology Experiment Building Language</i>
PET	–	pozitronų emisijos tomografija
PI	–	patikimumo intervalas
ROC kreivė	–	ROC (angl. <i>Receiver operating characteristic</i>) kreivė
VOSP	–	angl. <i>Visual Object and Space Perception Battery</i>

MOKSLINIŲ PUBLIKACIJŲ SĄRAŠAS

Ši daktaro disertacija parengta keturių mokslinių publikacijų pagrindu. Mokslinės publikacijos tolesniame tekste žymimos nurodytais romėniškais skaitmenimis:

- I. **Sutnikiene V**, Audronyte E, Pakulaite-Kazliene G, Kaubrys G. Color memory as a diagnostic test for mild cognitive impairment and early stage of Alzheimer's disease. *Front Neurol* 2025; 16: 1589335. Published 27 May 2025. DOI: 10.3389/fneur.2025.1589335.
- II. **Sutnikiene V**, Pakulaite-Kazliene G, Audronyte E, Kuzmickaite J, Kaubrys G. McCollough and watercolor effects: Visual illusions that fade in early Alzheimer's disease. *Med Sci Monit* 2025; 31: e950194. Published 22 Nov 2025. DOI: 10.12659/MSM.950194.
- III. **Sutnikiene V**, Pakulaite-Kazliene G, Audronyte E, Kuzmickaite J, Kaubrys G. Time/movement estimation and mental rotation tasks as early cognitive markers in Alzheimer's disease. *Brain Behav* 2025; 15(11): e71077. Published 19 Nov 2025. DOI: 10.1002/brb3.71077.
- IV. **Sutnikiene V**, Audronyte E, Pakulaite-Kazliene G, Kaubrys G. Silhouettes, number location, and cube analysis tests from the VOSP battery reveal visual object and space perception deficits in early Alzheimer's disease. *Sci Rep* 2026; 16(1): 3217. Published 21 Dec 2025. DOI: 10.1038/s41598-025-33126-z.

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PREAMBULĖ

Ši daktaro disertacija teikiama ginti kaip mokslinių straipsnių rinkinys. Kai kurios jos dalys pažodžiui cituojamos iš anksčiau publikuotų straipsnių, pateiktų disertacijos pabaigoje.

Disertaciją sudaro kelios tarpusavyje susijusios dalys.

Visų pirma, ištirta ankstyvosiomis Alzheimerio ligos stadijomis sergančių tiriamųjų spalvų atpažinimo atmintis ir įvertintos šios užduoties diagnostinės savybės. Antra, išanalizuoti McCollough ir akvarelės (angl. *Watercolor*) efektai, esant ankstyvosios Alzheimerio ligos stadijoms, ir įvertinta acetilcholinesterazės inhibitorių įtaka šiems efektams suvokti sergant lengvos stadijos Alzheimerio liga. Trečia, įvertintos laiko ir judesio vertinimo bei mintinės rotacijos užduotys kaip diagnostiniai testai ankstyvosioms Alzheimerio ligos stadijoms nustatyti, naudojant atvirosios prieigos PEBL (angl. *Psychology Experiment Building Language*) testų bateriją. Galiausiai įvertintas objektų ir erdvės suvokimas kaip diagnostinis įrankis ankstyvajai Alzheimerio ligos stadijai diagnozuoti bei išanalizuotos jo diagnostinės savybės ir sąsajos su kitų kognityvinių testų rezultatais.

1. ĮVADAS

1.1. Tiriamoji problema ir jos aktualumas

Alzheimerio liga (AL) yra dažniausia demencijos priežastis, sudaranti 60–80 proc. visų demencijos atvejų, sukelianti progresuojančius neurodegeneracinius procesus ir pažinimo funkcijų blogėjimą [1, 2]. AL patologiniai procesai prasideda daug metų iki klinikinių simptomų pasireiškimo [4]. Laikotarpis nuo neuropatologinių AL pokyčių pradžios iki sunkesnių ligos stadijų yra kritinis ankstyvajai diagnostikai, leidžiantis pacientams ir sveikatos priežiūros specialistams mažinti riziką ir valdyti ligą, pasitelkiant naujausius AL diagnostikos ir gydymo pasiekimus [6].

Pastaraisiais metais atrasti ligą modifikuojantys gydymo metodai didina poreikį kurti priemones, leidžiančias nustatyti AL kuo ankstesnėje kliniškai atpažįstamoje stadijoje. 2024 m. organizacijos „Alzheimer’s Disease International“ (ADI) ataskaita parodė, kad daugiau negu 90 proc. globėjų ir visuomenės apklausos dalyvių būtų labiau linkę kreiptis dėl diagnozės nustatymo, jei būtų prieinamas ligos eigą modifikuojantis gydymas [8]. Patikimo ir validuoto kognityvinio testo, kuris būtų minimaliai veikiamas kalbos skirtumų ir tinkamas taikyti daugiakalbėse bei daugiakultūrese populiacijose, trūkumas išlieka aktuali problema, todėl skatinama naudoti skaitmeninius, kalbos atžvilgiu neutralius kognityvinius testus [4].

Pagrindiniai regimojo suvokimo aspektai apima šviesos suvokimą, jautrumą kontrastui, stimulų orientaciją, regėjimo aštrumą bei gebėjimą atpažinti formą, spalvą, judesį ir gylį [9, 10]. Regos funkcijų pakitimai pasireiškia ankstyvosiose AL stadijose ir gali būti potencialūs neinvaziniai AL sukeltos neurodegeneracijos žymenys [11]. Neuropatologinių AL pokyčių nustatyta visoje regos sistemoje, įskaitant tinklainę, todėl pasireiškia įvairūs vizualiniai simptomai ir požymiai [11–13]. Sergant AL, pasireiškia jautrumo kontrastui sutrikimai, regos lauko defektai, fiksacijos ir sakadinių akių judesių sutrikimai bei kiti regos funkcijų pakitimai, lemiantys skaitymo, objektų ir formų atpažinimo bei orientacijos aplinkoje sunkumus [11–15]. Be to, yra duomenų, jog regėjimo aštrumo mažėjimas susijęs su perėjimu iš normalaus kognityvinio funkcionavimo būklės į lengvą kognityvinį sutrikimą (LKS), o tai rodo, kad regos sutrikimų poveikis yra didžiausias ankstyvosiose kognityvinių funkcijų sutrikimo stadijose [16]. Vizualinės atpažinimo atminties sutrikimai taip pat pasireiškia ankstyvosiose LKS stadijose [18]. 2024 m. Alzheimerio asociacijos ataskaitoje vienu iš dešimties pagrindinių AL požymių įvardyti sunkumai suprasti vaizdinius ir erdvinius ryšius, dėl kurių AL sergantys pacientai patiria atstumo vertinimo bei spalvų ir kontrasto

suvokimo sunkumų, galinčių apsunkinti vairavimą [2]. Spalvinis matymas ir spalvų atmintis gali būti potencialūs žymenys, tačiau šios funkcijos dažnai nėra tiriamos, todėl jų ryšys su kognityvinio sutrikimo laipsniu išlieka nepakankamai ištirtas.

Regimojo suvokimo ir vizualinių erdvinį testų taikymas ankstyvajai AL diagnostikai grindžiamas ankstyvais struktūriniais ir funkciniais pakitimais momeninėse ir smilkininėse smegenų skiltyse [20, 21]. Naujausi Memono ir bendraautorų [22] tyrimai parodė ryšį tarp regimojo suvokimo funkcijų ir AL biožymenų pokyčių. Šie sutrikimai ir jų progresavimas sergant AL daro didelę įtaką pacientų gyvenimo kokybei, tačiau dauguma neuropsichologinių testų yra verbaliniai, o regimojo suvokimo vertinimas sudaro tik nedidelę bendro neuropsichologinio vertinimo dalį [23, 24].

Iliuzijos dažnai apibūdinamos kaip reiškiniai, sukeliantys neatitikimą tarp to, ką suvokiame, ir realybės supratimo [25]. Regimosios iliuzijos gali būti vertingi įrankiai, padedantys suprasti regėjimo patikimumą ir išsamumą bei suteikiantys įžvalgų apie procesus, susijusius su regimosios informacijos suvokimu [25, 26]. Supratimas, kaip paprastesni optiniai ir aukštesniųjų žievinių funkcijų procesai prisideda prie regimųjų iliuzijų patyrimo, gali padėti atskleisti patologinius regos sistemos pokyčius [25, 26]. Pavyzdžiui, spalvinių povaizdžių kilmė siejama su tinklaine [27]. Keletas tyrimų parodė, kad žievinio „užpildymo“ procesai gali sukelti povaizdžius [28, 29]. Pirminės regimosios žievės neuronai dalyvauja nuo orientacijos priklausančio spalvinio povaizdžio, vadinamo McCollough efektu (ME), susidaryme [30, 31]. Vis dėlto yra nedaug duomenų, kaip patologiniai pokyčiai ankstyvosiose AL stadijose veikia indukuotų spalvinių iliuzijų suvokimą.

Lengvo kognityvinio sutrikimo arba išsaugotų kognityvinių funkcijų nustatymas vyresnio amžiaus asmenims labai priklauso nuo naudojamų vertinimo priemonių jautrumo ir specifiškumo [32]. Neuropsichologinio vertinimo srityje kompiuterizuoti testai yra greitas ir efektyvus būdas įvertinti kognityvines funkcijas [33]. Kompiuteriai leidžia standartizuotai pateikti instrukcijas įvairiomis kalbomis ir sudaro sąlygas surinkti didelius objektyvių duomenų kiekius, taip sumažinant tyrėjo klaidų tikimybę [32, 33]. Palyginti su tradiciniais popieriniais testais, kompiuterizuoti testai gali būti lengvai integruojami atliekant neurovaizdinimo tyrimus ir gerokai sumažina tyrėjo darbo sąnaudas vertinant, analizuojant rezultatus bei vykdant ilgalaikę kognityvinės būklės stebėseną [33, 34].

Tyrimų duomenimis, AL sergantys pacientai patiria judesio ir vizualinio erdvinio suvokimo sutrikimų, siejamų su užpakalinėse momeninėse srityse esančių dorsalinių regos takų disfunkcija [36, 37]. Užduotys, vertinančios laiko ir judesio suvokimą, gali būti vertingi diagnostiniai įrankiai ankstyvajai

AL diagnostikai. Nepaisant gausių tyrimų apie kognityvinius sutrikimus sergant AL, ypač apie atminties silpnėjimą ir vykdomųjų funkcijų sutrikimus, duomenų apie laiko vertinimo ir judesio suvokimo pakitimus ankstyvosiose AL stadijose vis dar yra nedaug [38]. Laiko suvokimo ir atminties sutrikimai dažnai siejami su hipokampo disfunkcija. Naujausi duomenys rodo, kad hipokampus yra svarbus skiriant laiko intervalus, struktūruojant laiko sekas ir koduojant laiko tėkmę [39, 40]. Dauguma iki šiol atliktų tyrimų daugiausia rėmėsi verbalinėmis laiko vertinimo užduotimis, o alternatyvios paradigmos, pavyzdžiui, laiko atkartojimo ar laiko padalijimo į du intervalus užduotys, tiriamos retai [38].

Sukaupti duomenys rodo, kad regimojo suvokimo testai turi diagnostinį potencialą, tačiau klinikinėje praktikoje jie vis dar taikomi retai. Siekiant palengvinti vizualinių funkcijų vertinimo integraciją į klinikinę praktiką, reikalingi papildomi duomenys apie konkrečius regimojo suvokimo testus ir jų diagnostines savybes.

Ši daktaro disertacija parengta keturių publikuotų mokslinių straipsnių pagrindu. Bendras jos tikslas – įvertinti regimojo suvokimo sutrikimus ankstyvosiose AL stadijose, nustatyti jų diagnostinę vertę ankstyvajai AL stadijai diagnozuoti ir ištirti regimojo suvokimo bei kitų kognityvinių pokyčių skirtumus sergant AL. **I straipsnyje** analizuojama ankstyvosios stadijos AL sergančių pacientų ir kognityviškai sveikų vyresnio amžiaus asmenų spalvų atpažinimo atmintis bei vertinamas jos diagnostinis potencialas. **II straipsnyje** tiriami ankstyvąja AL stadija sergančių pacientų ir kognityviškai sveikų vyresnio amžiaus asmenų McCollough ir akvarelės efektai (AE) bei vertinama acetilcholinesterazės inhibitorių įtaka sergant lengvos demencijos stadijos AL. **III straipsnyje** analizuojamos laiko ir judesio vertinimo bei mintinės rotacijos užduotys kaip diagnostiniai testai ankstyvosios stadijos AL diagnozuoti, naudojant atvirosios prieigos PEBL baterijos testus. **IV straipsnyje** vertinamas objektų ir erdvės suvokimas kaip diagnostinis įrankis ankstyvosioms AL stadijoms diagnozuoti bei analizuojamos jo diagnostinės savybės ir sąsajos su kitų kognityvinių testų rezultatais.

1.2. Tyrimo tikslas

Įvertinti regimojo suvokimo, specialiųjų regos fenomenų ir vizualinės atminties sutrikimų reikšmę ankstyvajai AL diagnostikai, nustatyti jų diagnostines savybes bei išanalizuoti regimojo suvokimo ir kitų kognityvinių funkcijų skirtumus.

1.3. Tyrimo uždaviniai

1. Įvertinti spalvų atmintį ir jos diagnostines savybes ankstyvosiose Alzheimerio ligos stadijose (**I straipsnis**).
2. Ištirti McCollough ir akvarelės efektus sergant ankstyvosiomis AL stadijomis bei įvertinti acetilcholinesterazės inhibitorių įtaką lengvos demencijos stadijoje (**II straipsnis**).
3. Palyginti kompiuterizuotų laiko ir judesio vertinimo bei mintinės rotacijos užduočių sutrikimus su kitais kognityviniais sutrikimais ir įvertinti jų papildomą diagnostinę vertę ankstyvajai AL diagnostikai (**III straipsnis**).
4. Įvertinti objektų ir erdvės vizualinį suvokimą bei jo diagnostines savybes ankstyvosiose AL stadijose (**IV straipsnis**).

1.4. Mokslinis naujumas

Spalvų atminties testų diagnostinis potencialas ankstyvosiose AL stadijose ištirtas nepakankamai, nes spalvinis matymas ir spalvinė atmintis vertinami retai. Disertacijoje pristatomame tyrime spalvų atpažinimo atmintis buvo vertinama ir lyginama su verbaline atmintimi. Pirmą kartą tirtas ankstyvąja AL stadija sergančių asmenų McCollough ir akvarelės efektų suvokimas, o gauti rezultatai suteikė naujų įžvalgų apie regos sistemos funkcinius pokyčius ir vykstančią neurodegeneraciją. Be to, į tyrimą įtrauktos kompiuterizuotos laiko ir judesio vertinimo bei mintinės rotacijos užduotys, siekiant nustatyti jų galimą diagnostinę vertę ankstyvosiose AL stadijose. Asmenų, sergančių lengvu kognityviniu sutrikimu, išsivysčiusiu dėl AL, regimasis objektų ir erdvės suvokimas vertintas kaip papildoma ankstyvosios AL stadijos diagnostikos priemonė.

1.5. Praktinė tyrimo vertė

Ankstyvosios AL stadijos diagnostika tampa vis svarbesnė sveikatos priežiūros sistemoje, nes būtina patikimai atrinkti pacientus klinikiniam tyrimams ir klinikinėje praktikoje pradedamam taikyti ligą modifikuojančiam gydymui. Paprastų ir lengvai prieinamų regimųjų funkcijų bei regimojo suvokimo vertinimo metodų diegimas klinikinėje praktikoje galėtų pagerinti diagnostikos procesą.

Tyrimai rodo vizualinių procesų ir regimojo suvokimo pokyčius ankstyvosiose AL stadijose, tačiau šios žinios klinikinėje praktikoje taikomos retai. Disertacijoje pristatomu tyrimu siekiama spręsti problemas, ribojančias platesnį regimojo suvokimo testų taikymą, pasitelkiant spalvų atminties

užduotis ir paprastus skaitmeninius, kalbos atžvilgiu neutralius kognityvinius testus, pavyzdžiui, laiko ir judesio vertinimo užduotis.

1.6. Ginamieji teiginiai

1. Spalvinė atmintis yra sutrikusi ankstyvosiose AL stadijose, o spalvų atpažinimo atminties testai pasižymi geromis diagnostinėmis savybėmis, atskiriant ankstyvąją AL stadiją sergančius pacientus nuo kognityviškai sveikų asmenų (**I straipsnis**).
2. Ankstyvąją AL stadiją sergančių asmenų McCollough ir akvarelės efektų suvokimas suteikia naujų įžvalgų apie regos sistemos funkcinius pokyčius ir vykstančią neurodegeneraciją (**II straipsnis**).
3. Laiko ir judesio vertinimo bei mintinės rotacijos užduotys iš PEBL (angl. *Psychology Experiment Building Language*) testų baterijos yra tinkamos ankstyviems kognityviniams sutrikimams, sukeltiems AL, nustatyti (**III straipsnis**).
4. Regimasis objektų ir erdvės suvokimas yra sutrikęs ankstyvosiose AL stadijose ir gali būti taikomas kaip papildomas ankstyvosios AL diagnostikos įrankis (**IV straipsnis**).

2. METODAI

2.1. Leidimas moksliniam darbui atlikti

Tyrimas atliktas laikantis Helsinkio deklaracijos principų. Jam atlikti gautas Vilniaus regioninio biomedicininio tyrimų etikos komiteto leidimas (Nr. 2022/1-1405-877).

Visi tyrimo dalyviai buvo supažindinti su tyrimo procedūromis ir sutiko dalyvauti tyrime. Prieš dalyvaudami tyrime visi pasirašė informuoto asmens sutikimo formą.

2.2. Tiriamieji

Tyrime dalyvavo 81 tiriamasis. Jie suskirstyti į tris grupes: 28 asmenys, sergantys lengva demencija dėl AL (MD grupė), 27 asmenys, sergantys amnestiniu lengvu kognityviniu sutrikimu dėl AL (MCI grupė), ir 26 kognityviškai sveiki vyresnio amžiaus asmenys (kontrolinė grupė, CG) (**II–IV straipsniai**). **I straipsnyje** aprašomame tyrime atitinkamai dalyvavo 27, 25 ir 25 asmenys; visi jie dalyvavo ir II–IV straipsniuose aprašomuose tyrimuose.

Kontrolinės grupės dalyviai neturėjo kognityvinių nusiskundimų, jų Klinikinės demencijos vertinimo skalės bendrasis įvertis (angl. *Clinical Dementia Rating Total Score*, CDR-TS) – 0, neurologinių pakitimų nenustatyta. MCI grupės dalyviai atitiko NIA-AA (angl. *National Institute on Aging-Alzheimer's Association*) [67] klinikinius ir kognityvinius lengvo kognityvinio sutrikimo dėl AL kriterijus, jų CDR-TS įvertis – 0,5. Lengva demencija dėl AL sergantys dalyviai atitiko NIA-AA [68] tikėtinos AL diagnostinius kriterijus, jų CDR-TS įvertis – 1.

Tiriamieji konsultuoti Vilniaus universiteto ligoninės Santaros klinikų Alzheimerio ligos kabinete. Tikėtiną AL diagnozę nustatė gydytojas specialistas, remdamasis pripažintais diagnostiniais kriterijais [68] ir progresuojančio kognityvinio blogėjimo požymiais. Visiems MCI ir MD grupių dalyviams pagal Lietuvos Respublikos sveikatos apsaugos ministerijos nustatytą tvarką atliktas struktūrinis magnetinio rezonanso tomografijos (MRT) tyrimas kaip įprastinės klinikinės praktikos dalis diagnozuojant AL. Smegenų skysčio (CSF) biožymenų analizė šiame tyrime nebuvo atliekama dėl žvalgomojo tyrimo pobūdžio. Iš 28 lengva demencija dėl AL sergančių pacientų 7 (25 %) medicininėje dokumentacijoje buvo nurodyti teigiami AL CSF biožymenys, atitinkantys 2018 m. NIA-AA diagnostinius kriterijus [69] (**II–IV straipsniai**). **I straipsnyje** aprašytame tyrime 6 iš 27 AL sergančių pacientų (22 %) medicininėje dokumentacijoje taip pat buvo nurodyti teigiami AL CSF biožymenys.

Amnestinio LKS dėl AL diagnozė nustatyta remiantis klinikiniais ir kognityviniais kriterijais, atmetus kraujagyslines, traumines ir kitas medicininės kognityvinio blogėjimo priežastis, bei patvirtinta dokumentuotu progresuojančiu kognityvinių funkcijų blogėjimu [67]. Struktūrinis MRT visais LKS atvejais parodė neurodegeneracijos požymius, o 8 iš 27 (30 %) tiriamųjų medicininėje dokumentacijoje nurodyti teigiami AL CSF biožymenys, atitinkantys 2018 m. NIA-AA diagnostinius kriterijus [69] (**II–IV straipsniai**). **I straipsnyje** aprašytame tyrime 7 iš 25 MCI grupės pacientų (28 %) medicininėje dokumentacijoje taip pat nurodyti teigiami AL CSF biožymenys.

Į tyrimą nebuvo įtraukti asmenys, sergantys kitomis centrinės nervų sistemos ligomis, išskyrus LKS ir lengvą demenciją dėl AL. Neįtraukimo kriterijai: smegenų kraujagyslių ligos (Hačinskio išemijos indeksas ($HII \geq 4$), sunki galvos smegenų trauma anamnezėje, sunkūs psichikos sutrikimai (Geriatrinės depresijos skalės (GDS) įvertis >9), regos ar klausos sutrikimai, galintys paveikti kognityvinių testų rezultatus, įgimti ar jaunystėje nustatyti spalvų matymo sutrikimai, reikšmingos akių ligos (glaukoma, katarakta, diabetinė retinopatija, su amžiumi susijusi geltonosios dėmės degeneracija),

sunkios širdies ir kraujagyslių, kepenų ar metabolinės ligos, piktnaudžiavimas psichoaktyviosiomis medžiagomis ir psichotropinių vaistų vartojimas. Dalyviai galėjo būti įtraukti į tyrimą, jei nebuvo pradėję gydymo arba bent 3 mėn. vartojo stabilią acetilcholinesterazės inhibitoriaus dozę.

2.3. Demografinių ir kognityvinių rodiklių bei spalvų matymo įvertinimas

Įvertinti kiekvieno tiriamojo demografiniai duomenys: amžius, lytis, AL simptomų trukmė ir medicininė anamnezė.

Bendrosios kognityvinės funkcijos įvertintos naudojant mini protinės būklės tyrimą (MMSE).

Klinikinės demencijos vertinimo skalė (CDR) naudota kognityvinei būklei ir kasdieniam funkcionavimui įvertinti. Tai pusiau struktūruotas interviu su pacientu ir jo artimuoju (šeimos nariu ar globėju). Pagal CDR bendrąją įvertį nustatytos šios stadijos: normali kognityvinė būklė (CDR-TS = 0, CG), LKS dėl AL (CDR-TS = 0,5, MCI grupė) ir lengva AL demencija (CDR-TS = 1, MD grupė). Funkciniam sutrikimui ir kognityviniam blogėjimui įvertinti taip pat naudota CDR-SB (angl. *Clinical Dementia Rating Sum of Boxes*) skalė.

Išsamesniam kognityvinių funkcijų įvertinimui taikyta Alzheimerio ligos vertinimo skalės kognityvinė subskalė (ADAS-Cog 13). Įvertis svyruoja nuo 0 iki 85 balų. Didesnis balas rodo ryškesnius kognityvinius sutrikimus.

Spalvų matymui įvertinti naudotas 2021 m. leidimo popierinis 24 plokštelių Ishiharos testas, skirtas raudonos ir žalios spalvų matymo sutrikimams nustatyti. Buvo rodomos 1–15 plokštelės, registruojant klaidų skaičių (leidžiama padaryti ne daugiau kaip dvi klaidas).

2.4. Spalvų atpažinimo atminties vertinimas

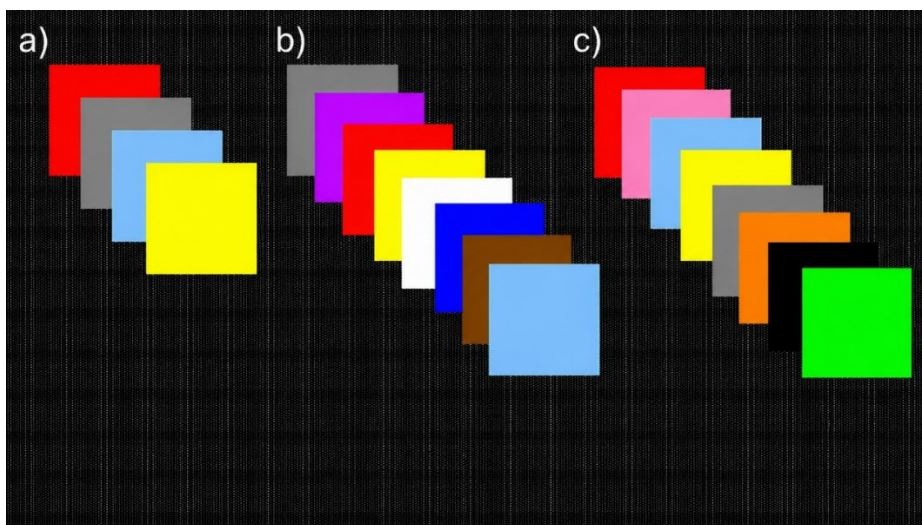
Spalvų atpažinimo atmintis vertinta naudojant kompiuterio ekrane pateikiamą 12 spalvų rinkinį. Asmeninio kompiuterio monitoriaus parametrai nustatyti į gamyklinius nustatymus. Monitorius buvo įjungtas ne trumpiau kaip 30 min., o tikslinis ryškumo lygis nustatytas 120 cd/m² (vidutiniškai apšviestai patalpai).

Spalvų atpažinimo atminties užduotis suskirstyta į tris dalis: stimulo pateikimą ir uždelstą atpažinimą po 5 ir 30 min. Atsitiktine tvarka parinktos keturios pradinės stimulo spalvos, kurios tinklelio fone buvo pateikiamos po 5 s kiekviena, tarp jų darant 5 s tarpstimulinius intervalus, siekiant sumažinti spalvinio poveikio įtaką. Dalyviams nurodyta įsiminti spalvas, nes vėliau jie turės atpažinti tas, kurias jau buvo matę. Atspalviai parinkti naudojant RGB (raudona–žalia–mėlyna) spalvų modelį, plačiai taikomą vaizdams

elektroninėse sistemose atvaizduoti. Kiekviena RGB skalės spalvų pora skyrėsi bent 64 vienetais bent viename iš kanalų (0–255 intervale). Naudotos 12 spalvų suskirstytos pagal kategorinius spalvų pavadinimus: raudona, žalia, mėlyna, geltona, oranžinė, ruda, rožinė, violetinė, juoda, balta, pilka ir žydra (kai kuriose kalbose tai atskira spalvų kategorija). Dalyvių nebuvo prašoma įvardyti spalvų – tik jas įsiminti, kad vėliau galėtų atpažinti.

Po 5 min. uždelsto atpažinimo etape dalyvių buvo prašoma nurodyti, kurias iš aštuonių pateiktų spalvų (keturias pradinės ir keturias atsitiktinai parinktas iš 12 spalvų rinkinio) jie buvo matę anksčiau.

Po 30 min. uždelsto atpažinimo etape dalyvių buvo prašoma atpažinti keturias pradines spalvas iš aštuonių pateiktų spalvų (rodytos keturios pradinės ir keturios naujos spalvos, nenaudotos ankstesniame uždelsto atpažinimo etape) (1 pav.). Išsamus metodų aprašymas pateikiamas I straipsnyje.



1 pav. Spalvų atpažinimo atminties užduotis: spalviniai stimulai

Keturios atsitiktinai atrinktos spalvos kompiuterio ekrane rodomos po 5 s, tarp jų paliekant 5 s intervalus (A). Po 5 min. pateikiamos keturios pradinės ir keturios atsitiktinai parinktos spalvos iš 12 spalvų rinkinio (B). Po 30 min. pateikiamos keturios pradinės ir keturios naujos spalvos (C).

2.5. McCollough ir akvarelės efektų vertinimas

2.5.1. ME ir AE efektų pateikimo aparatūra

Regimieji stimulai buvo pateikiami 24 colių įstrižainės LCD monitoriuje (1920×1200 pikselių raiška, 59,95 Hz atnaujinimo dažnis), pritremdyto

apšvietimo aplinkoje. Galvos judesiams sumažinti naudota smakro ir kaktos atrama, išlaikant 70 cm atstumą iki ekrano.

2.5.2. McCollough efekto įvertinimas

ME tyrimą sudarė trys fazės: testavimas prieš indukciją, indukcija ir testavimas po indukcijos. Pradinėje fazėje dalyviai vertino testinį vaizdą. Prieš adaptaciją nė vienas dalyvis nematė kitų spalvų, tik juodą ar baltą. Indukcijos fazėje naudoti du grotelių orientacijos rinkiniai: vertikalios žalios (RGB 0, 255, 0) ir juodos (0, 0, 0) linijos bei horizontalios raudonos (255, 0, 0) ir juodos (0, 0, 0) linijos. Erdvinis dažnis – 1,42 ciklo laipsniui. Stimulai kaitaliojami kas 10 s, bendra indukcijos trukmė – 5 min. Po indukcijos buvo skiriama 1 min. poilsio užmerktomis akimis, siekiant išvengti tinklainės poveikio.

Testavimo po indukcijos metu buvo pateikiamos keturios achromatinės to paties erdvinio dažnio grotelių kombinacijos (horizontalios, vertikalios, 45° ir 135°). Dalyvių buvo prašoma įvertinti, ar baltos linijos atrodo visiškai baltos. Jei vertikaliose arba horizontaliose linijose jie atpažindavo lengvą rausvą ar žalsvą atspalvį, atsakymas buvo laikomas teisingu (daugiausia 6 rausvos ir 6 žalsvos grotelės).

2.5.3. Akvarelės efekto įvertinimas

Pirmąjį stimulą sudarė keturi dideli kvadratai, kurių kiekvieno centre buvo mažesnis kvadratas. Taikytos dvi sąlygos: dviejuose kvadratuose AE buvo matomas tarp dviejų oranžinių linijų, besitęsiančių nuo didesniojo kvadrato vidinės dalies iki mažesniojo kvadrato išorinės dalies, o kituose dviejuose kvadratuose AE buvo matomas mažesniojo kvadrato viduje. Antrasis stimulus vaizdavo didelį stačiakampį su dviem mažesniais stačiakampiais viduje. Juose AE buvo matomas tarp dviejų oranžinių linijų, besitęsiančių nuo didesniojo stačiakampio vidinės dalies iki mažesniųjų stačiakampių išorinių dalių.

Siekiant įvertinti suvokiamą indukuotos spalvos sklidimo mastą, dalyvių buvo prašoma nurodyti figūros dalis, kurios atrodė visiškai baltos arba nuspalvintos. Jei dalyviai nurodė, kad indukuojant AE už linijų ribų spalvos nebuvo matyti, buvo laikoma, kad AE nepasireiškė. Išsamus metodų aprašymas pateikiamas **II straipsnyje**.

2.6. PEBL testų baterija: *Time–Wall* ir mintinės rotacijos užduotys

Time–Wall yra laiko ir judesio vertinimo užduotis, kurios metu judantis objektas dingsta už sienos, o dalyviai turi nuspręsti, kada jis pasieks matomą

tarpą, darydami prielaidą, kad viso bandymo metu objekto greitis nekinta. Nusileidęs du trečdalius savo trajektorijos, taikinys pasislenka už sienos ir tampa nebematomas. Dalyvių prašoma paspausti tarpo klavišą tuo momentu, kai, jų manymu, taikinys susilygiuoja su kvadratėliu ekrano apačioje. Užduotį sudaro 20 bandymų, kurių kiekvieno trukmė – nuo 2 iki 10 s.

Vidutinė paklaida per visus bandymus naudota kiekvieno dalyvio laiko suvokimo tikslumui įvertinti. Atsako netikslumas apskaičiuotas kaip procentinis skirtumas tarp atsako laiko (RT) ir tikslinio laiko (TT), naudojant formulę:

$$(RT-TT)/TT \times 100.$$

Papildomai apskaičiuotas pavėluotų atsakų procentas, siekiant išsamiau apibūdinti laiko suvokimo gebėjimus.

Mintinės rotacijos užduotis yra dvimatė klasikinio Shepardo testo adaptacija [59, 71]. Dalyvių buvo prašoma paspausti klaviatūros klavišą „D“ arba „S“, nurodant, ar pilkame ekrane pateikta raudonų figūrų pora yra veidrodinis viena kitos atspindys ekrano plokštumoje (veidrodinė sąlyga). Figūros buvo pasuktos 0°, 45°, 90°, 135° ir 180° kampais (kampų sąlygos). Figūrų poras sudarė viena L formos ir viena varžto formos figūra.

Užduotis buvo modifikuota ir apėmė šešis mokomuosius bei 32 eksperimentinius bandymus. Kiekvieno bandymo maksimali trukmė buvo 45 s, todėl bendra užduoties trukmė galėjo siekti iki 30 min. Kiekvieno bandymo metu registruoti teisingi atsakymai ir reakcijos laikas.

Metodai išsamiai aprašyti **III straipsnyje**.

2.7. VOSP baterijos testų vertinimas: siluetai, skaičių vieta ir kubų analizė

Siluetai. Dalyviams buvo pateikiami juodi gyvūnų ir negyvų objektų siluetai, pavaizduoti neįprastais rakursais. Testą sudarė 15 gyvūnų ir 15 negyvų objektų siluetai. Dalyviai galėjo objektą įvardyti, imituoti, parodyti gestu arba apibūdinti (maksimalus balų skaičius – 30).

Skaičių vieta. Testą sudarė 10 lentelių, kurių kiekvienoje buvo pavaizduoti du vertikalčiai išdėstyti kvadratai. Viršutiniame kvadrato pateiktas atsitiktinis skaičių nuo 1 iki 9 išdėstymas. Apatiniame kvadrato pavaizduotas juodas taškas, atitinkantis konkretaus skaičiaus vietą. Dalyvių buvo prašoma nurodyti skaičių, atitinkantį juodo taško padėtį (maksimalus balų skaičius – 10).

Kubų analizė. Kiekvienoje lentelėje buvo pavaizduota erdvinių kūnų konfigūracija. Dalyvių buvo prašoma nustatyti bendrą kiekvienoje lentelėje pavaizduotų kubų skaičių, įskaitant ir tuos, kurių nebuvo galima matyti (maksimalus balų skaičius – 10).

Metodai išsamiai aprašyti **IV straipsnyje**.

2.8. Statistinė analizė

Statistinė analizė atlikta naudojant IBM SPSS Statistics 26.0 programinę įrangą.

Duomenų pasiskirstymo normalumui vertinti taikytas Shapiro ir Wilk testas. Kategorinių kintamųjų skirtumai tarp grupių analizuoti taikant dvipusį chi kvadrato (χ^2) testą ir Fisherio tikslųjį testą. Dviejų grupių nenormaliai pasiskirsčiusių skaitinių kintamųjų skirtumai vertinti naudojant Manno ir Whitney U testą. Trijų grupių skaitiniai kintamieji lyginti taikant vienfaktorinę dispersinę analizę (ANOVA), kai jų pasiskirstymas buvo normalus, bei Kruskalio ir Walliso testą, kai kintamieji buvo pasiskirstę nenormaliai.

Ryšiai tarp kintamųjų vertinti naudojant Spearmano ranginės koreliacijos koeficientą. Siekiant prognozuoti intervalinius priklausomuosius kintamuosius, taikyti tiesinės regresijos modeliai, koreguoti pagal amžių, išsilavinimą ir lytį. Daugiakategorinė logistinė regresija taikyta siekiant iširti ryšį tarp nepriklausomųjų kintamųjų ir tiriamųjų priskyrimo trimis grupėms.

Diagnosticinių testų efektyvumas vertintas naudojant ROC (angl. *Receiver operating characteristic*) kreivių analizę. Optimalus kiekvieno testo slenkstis nustatytas maksimalizuojant Youdeno J statistiką ($J = \text{jautrumas} + \text{specifiškumas} - 1$). Statistinio reikšmingumo riba nustatyta, kai $p < 0,05$.

3. REZULTATAI

3.1. Demografiniai, klinikiniai ir kognityviniai rodikliai

Tiriamųjų demografiniai, klinikiniai ir kognityviniai rodikliai pateikti **1 lentelėje**.

Analizė parodė, kad tarp trijų grupių statistiškai reikšmingų lyties pasiskirstymo skirtumų nenustatyta (χ^2 kriterijus, $p > 0,05$). Taip pat nenustatyta statistiškai reikšmingų išsilavinimo, depresijos simptomų įverčių (GDS) ir HII skalės balų skirtumų (visais atvejais Kruskalio ir Walliso testo $p > 0,05$). Tarp visų trijų grupių nustatyti statistiškai reikšmingi pažinimo funkcijų vertinimo testų rezultatų skirtumai ($p < 0,05$). Ishiharos testo rezultatai statistiškai reikšmingai skyrėsi tarp kognityviškai sveikų tiriamųjų ir lengva demencija dėl AL sergančių pacientų grupių. Be to, acetilcholinesterazės inhibitorių vartojimas statistiškai reikšmingai skyrėsi tarp lengvo kognityvinio sutrikimo dėl AL (MCI) ir lengvos demencijos dėl AL (MD) grupių.

1 lentelė. Tiriamųjų demografiniai ir klinikiniai rodikliai, pažinimo funkcijų ir spalvų matymo vertinimo rezultatai

	CG (n = 26)	MCI (n = 27)	MD (n = 28)	Statistiniai rodikliai ($\chi^2[2]/H(2)$, p)
Moterys (%)	12 (46 %)	19 (70 %)	18 (64 %)	3,09; 0,21
Amžius	73 (9)	75 (11)	77 (9)	4,63; 0,10
Išsilavinimas	16 (1)	15 (4)	15 (3)	4,37; 0,11
GDS	4 (2)	5 (1)	4 (2)	1,40; 0,50
HII	1 (1)	1 (1)	1 (1)	1,84; 0,40
MMSE*	29 (1)	25 (3)	22 (2)	72,02; <0,001
ADAS-Cog 13*	12,5 (5,67)	22 (7,66)	31 (7,5)	74,26; <0,001
CDR-SB*	0 (0)	1,5 (1)	4,5 (0,5)	53,07; <0,001
Ishihara testas, klaidų skaičius**	0 (0)	0 (2)	1 (3)	11,75; 0,003
AChEI vartojimas, n (%)***	0	1 (3,7 %)	10 (35,71 %)	18,02; <0,001

Jei nenurodyta kitaip, duomenys pateikiami kaip medianos ir tarpkvartiliniai intervalai.

Statistinis reikšmingumas nustatytas, kai $p < 0,05$.

* Trys grupės skyrėsi statistiškai reikšmingai.

**Statistiškai reikšmingi skirtumai nustatyti tarp kontrolinės grupės ir lengva demencija dėl AL sergančių pacientų.

*** Statistiškai reikšmingi skirtumai nustatyti tarp kontrolinės grupės ir lengva demencija dėl AL sergančių pacientų bei tarp lengvu kognityviniu sutrikimu dėl AL ir lengva demencija dėl AL sergančių pacientų.

Santrumpos: CG – kontrolinė grupė; MCI – lengvas kognityvinis sutrikimas; MD – lengva demencija; GDS – Geriatriinės depresijos skalė; HII – Hačinskio išemijos indeksas; ADAS-Cog 13 – Alzheimerio ligos vertinimo skalės kognityvinė subskalė (13 punktų versija); CDR-SB – Klinikinės demencijos vertinimo skalės suminis balas (angl. *Sum of Boxes*); MMSE – mini protinės būklės tyrimas.

3.2. Verbalinė ir spalvų atpažinimo atmintis

3.2.1. Verbalinės ir spalvų atpažinimo atminties vertinimas

Verbalinė atmintis **I straipsnyje** vertinta pagal žodžių, neprisimintų po 5 ir po 30 min., skaičių (iš 10). Bendrosios neprisimintų žodžių skaičiaus medianos (tarpkvartiliniai intervalai (IQR)) CG, MCI ir MD grupėse buvo atitinkamai 9 (3), 15 (5) ir 16,67 (2,165). Kruskalio ir Walliso testas parodė statistiškai reikšmingą skirtumą tarp grupių ($H[2] = 36,18$; $p < 0,001$). Post hoc analizė atskleidė statistiškai reikšmingus skirtumus tarp visų trijų grupių ($p < 0,001$).

Spalvų atpažinimo bendro klaidų skaičiaus medianos (IQR) CG, MCI ir MD grupėse buvo atitinkamai 2 (2), 4 (2) ir 5 (3). Kruskalio ir Walliso testas parodė statistiškai reikšmingą skirtumą tarp grupių ($H[2] = 34,36$, $p < 0,001$). Post hoc analizė atskleidė statistiškai reikšmingus skirtumus tarp CG ir MCI ($p < 0,001$), tarp MCI ir MD ($p = 0,007$) bei tarp CG ir MD ($p < 0,001$).

Visų tiriamųjų imtyje bendras spalvų atminties klaidų skaičius stipriai koreliavo su MMSE rezultatais (Spearmano $\rho = -0,647$; $p < 0,001$), vidutiniškai – su CDR-SB (Spearmano $\rho = 0,593$; $p < 0,001$), ADAS-Cog 13 (Spearmano $\rho = 0,568$; $p < 0,001$) ir verbalinės atminties rezultatais (Spearmano $\rho = 0,492$; $p < 0,001$).

Išsami verbalinės ir spalvų atpažinimo atminties bei kognityvinių testų rezultatų koreliacijų analizė pateikta **I straipsnyje**.

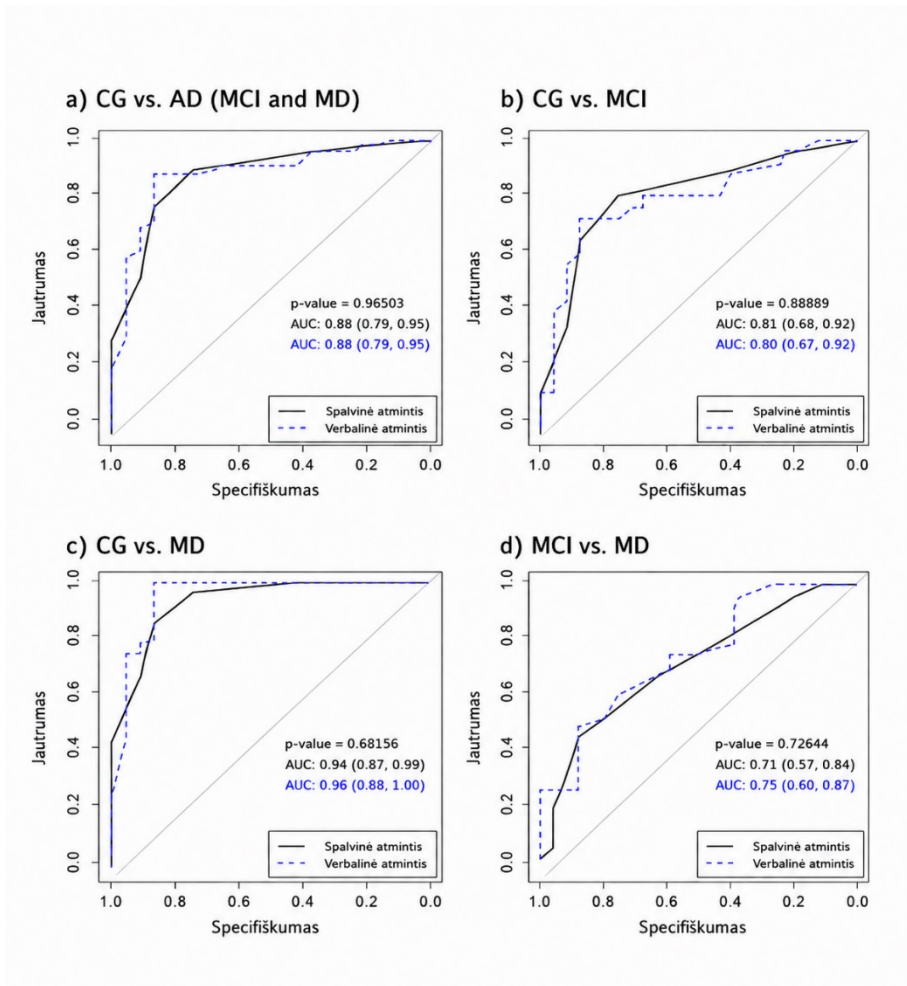
Daugialypė tiesinė regresinė analizė parodė statistškai reikšmingus rezultatus pakoreguotuose modeliuose su MMSE ($R^2 = 0,378$, $F = 10,23$, $\beta = -0,668$, $p < 0,001$), ADAS-Cog 13 ($R^2 = 0,274$, $F = 6,74$, $\beta = 0,588$, $p < 0,001$) ir CDR-SB ($R^2 = 0,324$, $F = 8,30$, $\beta = 0,616$, $p < 0,001$).

Visuose modeliuose spalvų atminties rodikliams statistškai reikšmingos įtakos neturėjo amžius, lytis, išsilavinimas ir Ishiharos testo rezultatai ($p > 0,05$).

3.2.2. Spalvų atpažinimo atminties ir verbalinės atminties diagnostinių savybių palyginimas

Atlikta ROC (angl. *receiver operating characteristic*) kreivių analizė, siekiant įvertinti spalvų atpažinimo atminties testo gebėjimą atskirti kontrolinės grupės tiriamuosius nuo ankstyvąja AL stadija sergančių pacientų (MCI arba MD) pagal spalvų ir verbalinės atminties klaidų skaičių. Uždelsto žodžių atgaminimo ir spalvų atpažinimo po 5 ir 30 min. bei bendro klaidų skaičiaus ROC kreivės neparodė statistškai reikšmingų verbalinės ir spalvų atminties užduočių diagnostinių savybių skirtumų, diferencijuojant tiriamųjų grupes.

Abiejų užduočių bendras klaidų skaičius pasižymėjo geromis diagnostinėmis savybėmis, atskiriant kontrolinės grupės tiriamuosius nuo ankstyvosios AL stadijos grupių tiriamųjų (MCI ir MD): abiem atvejais ploto po kreive (AUC) reikšmė buvo vienoda – 0,88. Diferencijuojant CG ir MCI grupes, spalvų ir verbalinės atminties bendro klaidų skaičiaus AUC buvo atitinkamai 0,81 ir 0,80 (2 pav.).



2 pav. Verbalinės atminties bendro neprisimintų žodžių skaičiaus ir spalvų atminties bendro klaidų skaičiaus ROC kreivės ir AUC, lyginant visas grupes

Santrumpos: AD – Alzheimerio liga; CG – kontrolinė grupė; MCI – lengvas kognityvinis sutrikimas; MD – lengva demencija.

Verbalinės atminties uždelsto žodžių atgaminimo po 5 ir 30 min. bei spalvų atpažinimo po 5 ir 30 min. ROC kreivės, lyginant visas grupes, pateiktos **I straipsnyje**.

Siekiant atskirti ankstyvosios AL stadijos pacientus (MCI arba MD) nuo kontrolinės grupės, nustatyta, kad ≥ 3 bendros spalvų atminties užduoties klaidos būdingos AL. Diferencijuojant MD ir MCI grupes, nustatyta ≥ 6 klaidų riba – 6 ir daugiau klaidų laikyta būdinga MD. Šių ribinių reikšmių diagnostinės savybės įvertintos, o išsamūs duomenys pateikiami **I straipsnyje**.

Siekiant įvertinti ryšį tarp prognostinių kintamųjų ir tiriamųjų priskyrimo trims grupėms (CG, MCI ir MD), taikyta daugiakategorinė logistinė regresija.

Pirmiausia sudarytas modelis, į kurį kaip prediktoriniai kintamieji įtraukti amžius, išsilavinimas, lytis ir ADAS-Cog 13 balas. Įtraukus šiuos prediktorius, modelio atitiktis duomenims pagerėjo, palyginti su pradiniu modeliu, kuriame buvo tik konstanta ($\chi^2 = 85,881$, $p < 0,001$; Nagelkerke $R^2 = 0,756$). Taikant šį modelį, bendras teisingai suklasifikuotų atvejų procentas buvo 77,9 % (teisingai suklasifikuota 96 % CG, 64 % MCI ir 74,1 % MD atvejų), o stipriausias ir statistiškai reikšmingiausias prediktorius buvo ADAS-Cog 13 balas ($\chi^2 = 76,074$, $p < 0,001$).

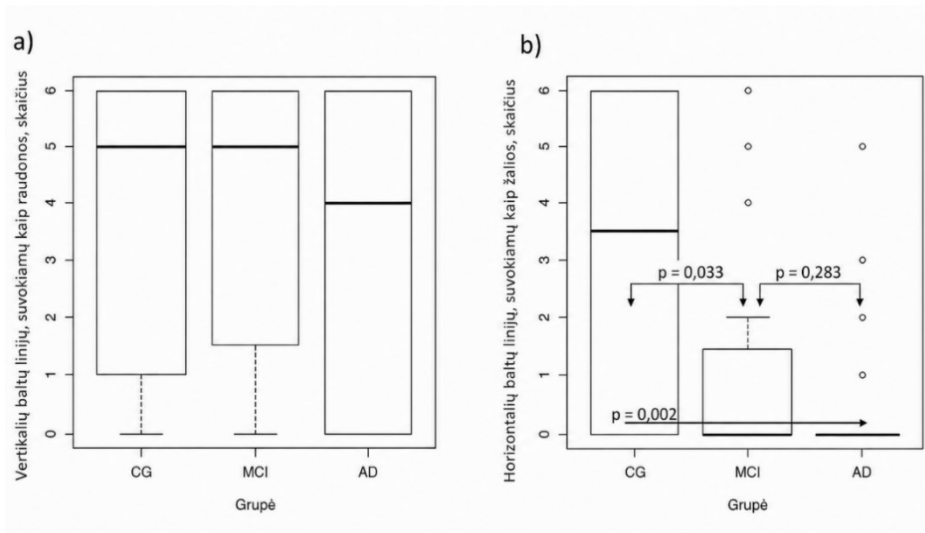
Į pradinį modelį įtraukus bendrą spalvų atminties klaidų skaičių, išplėstinis modelis (apimantis amžių, išsilavinimą, lytį, ADAS-Cog 13 balą ir bendrą spalvų atminties klaidų skaičių) taip pat parodė statistiškai reikšmingai geresnę atitiktį duomenims, palyginti su nuliniu modeliu ($\chi^2 = 117,176$, $p < 0,001$; Nagelkerke $R^2 = 0,880$).

Taikant šį modelį teisingai suklasifikuota 84,4 proc. atvejų (100 % CG, 76 % MCI ir 77,8 % MD atvejų). ADAS-Cog 13 balas ir spalvų atminties rodikliai buvo stiprūs, statistiškai reikšmingi prediktoriai (atitinkamai $\chi^2 = 63,88$ ir $\chi^2 = 31,30$; $p < 0,001$). Išsamūs spalvų atminties po 5 ir 30 min. rezultatai pateikiami **I straipsnyje**.

3.3. McCollough efektas ir akvarelės efektas

3.3.1. McCollough efekto vertinimas

ME buvo suvokiamas kaip baltos linijos su žalsvu arba rausvu atspalviu: 25 iš 26 CG grupės tiriamųjų (96,15 %), 24 iš 27 MCI grupės tiriamųjų (88,89 %) ir 17 iš 28 MD grupės tiriamųjų (60,71 %) ($\chi^2 = 12,69$; $p = 0,002$). Dauguma visų grupių tiriamųjų baltas vertikalias linijas suvokė kaip raudonas; medianos (IQR) buvo tokios: CG – 5 (5,25), MCI – 5 (5), MD – 4 (6); Kruskalio ir Walliso $H = 0,834$ ($p = 0,659$). Statistiškai reikšmingi skirtumai nustatyti suvokiant baltas horizontalias linijas kaip žalias (mediana [IQR]: CG – 3,5 [6], MCI – 0 [2], MD – 0 [0]; Kruskalio ir Walliso $H = 10,27$; $p = 0,006$; vidutinio dydžio efektas $\varepsilon^2 = 0,11$). Post hoc analizė parodė statistiškai reikšmingą skirtumą tarp CG ir MD ($p = 0,002$), tačiau statistiškai reikšmingų skirtumų tarp CG ir MCI ($p = 0,033$; pritaikius Bonferroni korekciją dėl daugybinių palyginimų skirtumas nebuvo statistiškai reikšmingas) ir tarp MCI ir MD ($p = 0,283$) nenustatyta (3 pav.).



3 pav. McCollough efekto suvokimo skirtumai tarp trijų grupių

a) Vertikalių baltų linijų, suvokiamų kaip raudonos, skaičius tarp trijų grupių statistiškai reikšmingai nesiskyrė ($p > 0,05$). b) Horizontalių baltų linijų, suvokiamų kaip žalios, skaičius tarp trijų grupių statistiškai reikšmingai skyrėsi ($p = 0,006$). Santrumpos: AD – lengva demencija; MCI – lengvas kognityvinis sutrikimas; CG – kontrolinė grupė.

MD grupėje nenustatyta statistiškai reikšmingų skirtumų tarp pacientų, vartojančių acetilcholinesterazės inhibitorius ir jų nevartojančių, vertinant ME suvokimą ($\chi^2 = 0,749$, $p = 0,387$). Taip pat, remiantis Manno ir Whitney U testo rezultatais, nenustatyta statistiškai reikšmingų skirtumų vertinant, ar baltos vertikalios linijos buvo suvokiamos kaip raudonos, o baltos horizontalios – kaip žalios (atitinkamai $p = 0,654$ ir $p = 0,524$).

Tiriamosioje populiacijoje baltų horizontalių linijų suvokimas kaip žalių silpnai koreliavo su MMSE rezultatais (Spearmano rho = 0,354; $p = 0,001$), CDR-SB balais (Spearmano rho = -0,357; $p = 0,001$) ir ADAS-Cog 13 balais (Spearmano rho = -0,336; $p = 0,002$). Statistiškai reikšmingų koreliacijų su amžiumi, išsilavinimu ar Ishiharos testo rezultatais nenustatyta.

Daugialypės tiesinės regresinės analizės modeliai taikyti siekiant nustatyti, ar demografiniai rodikliai, Ishiharos testo rezultatai ir kognityvinių testų balai reikšmingai prognozuoja baltų horizontalių linijų suvokimą kaip žalių. Statistiškai reikšmingi rezultatai gauti pakoreguotuose modeliuose su MMSE ($R^2 = 0,12$, $F = 3,17$, $\beta = 0,318$, $p < 0,001$), ADAS-Cog 13 ($R^2 = 0,101$, $F = 2,8$, $\beta = -0,116$, $p = 0,001$) ir CDR-SB ($R^2 = 0,086$, $F = 2,5$, $\beta = -0,432$, $p = 0,002$). Visuose modeliuose lytis, amžius, išsilavinimas ir Ishiharos testo rezultatai statistiškai reikšmingos įtakos ME suvokimui neturėjo ($p > 0,05$).

3.3.2. Akvarelės efekto vertinimas

AE matymą nurodė visi CG grupės tiriamieji: 25 iš 27 (92,59 %) MCI grupėje ir 22 iš 28 (78,57 %) MD grupėje (Fisherio tikslusis kriterijus 6,66, $p = 0,024$). Nustatyti statistiškai reikšmingi skirtumai tarp CG ir MD grupių (Fisherio tikslusis kriterijus 6,27, $p = 0,024$).

Kai AE nebuvo suvokiamas, tiriamieji padarė statistiškai reikšmingai daugiau klaidų Ishiharos teste. Mediana (IQR) siekė 2,5 (5), kai tiriamieji nurodė nematantys AE, ir 0 (1), kai AE buvo suvokiamas (Kruskalio ir Walliso $H = 9,29$, $p = 0,002$; vidutinio dydžio efektas $\epsilon^2 = 0,09$).

MD grupėje AE suvokimas statistiškai reikšmingai nesiskyrė tarp pacientų, vartojančių acetilcholinesterazės inhibitorius ir jų nevartojančių (Fisherio tikslusis kriterijus 0,19, $p = 1$).

Kognityvinių testų ir spalvinio matymo rezultatai buvo statistiškai reikšmingi AE prognozuojantys veiksniai dvejetainės regresijos modeliuose, pakoreguotuose pagal lytį, amžių ir išsilavinimą. Statistiškai reikšmingi buvo modeliai su ADAS-Cog 13 ($B = -0,158$, Wald = 4,7, $p = 0,03$, Nagelkerke $R^2 = 0,261$), CDR-SB ($B = -0,569$, Wald = 5,09, $p = 0,024$, Nagelkerke $R^2 = 0,265$), MMSE ($B = 0,342$, Wald = 3,89, $p = 0,049$, Nagelkerke $R^2 = 0,225$) ir Ishiharos testu ($B = -0,893$, Wald = 8,13, $p = 0,004$, Nagelkerke $R^2 = 0,375$).

3.4. PEBL testų baterija: *Time–Wall* ir mintinės rotacijos užduotys

3.4.1. *Time–Wall* užduoties vertinimas

Nustatyti statistiškai reikšmingi *Time–Wall* užduoties vidutinių paklaidų skirtumai. Medianos ir tarpkvartiliniai intervalai: CG = 11,46 (9), MCI = 19,43 (10,49), MD = 22,82 (14,35) [$H(2) = 34,74$; $p < 0,001$]. CG grupės tiriamieji užduotį atliko tiksliau negu MCI ir MD grupių tiriamieji. Statistiškai reikšmingų skirtumų tarp MCI ir MD grupių nenustatyta ($p = 0,106$).

Vėluojančių atsakų procentinės dalies medianos ir tarpkvartiliniai intervalai: CG = 10 (18,75), MCI = 20 (22), MD = 25 (23) [$H(2) = 7,3$; $p = 0,026$]. Statistiškai reikšmingi skirtumai nustatyti tarp CG ir MD grupių ($p = 0,01$), tačiau reikšmingų skirtumų tarp CG ir MCI ($p = 0,153$) bei tarp MD ir MCI grupių ($p = 0,143$) nenustatyta.

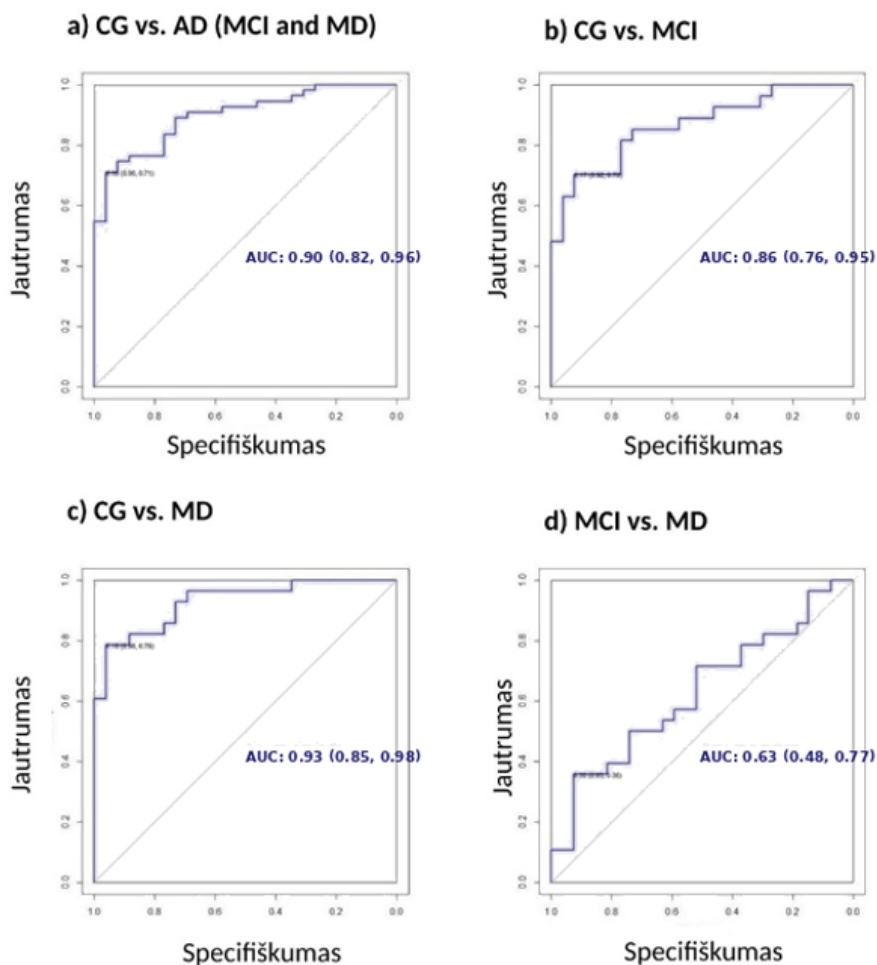
Tiriamojame populiacijoje *Time–Wall* užduoties vidutinė paklaida stipriai koreliavo su MMSE rezultatais (Spearmano $\rho = -0,628$; $p < 0,001$), vidutiniškai – su CDR-SB (Spearmano $\rho = 0,568$; $p < 0,001$) ir ADAS-Cog 13 (Spearmano $\rho = 0,594$; $p < 0,001$) balais, o silpnai – su išsilavinimu

(Spearmano $\rho = -0,314$; $p = 0,004$). Statistiškai reikšmingos koreliacijos su amžiumi nenustatyta (Spearmano $\rho = 0,17$; $p = 0,129$).

Daugialypė tiesinė regresinė analizė, į kurios modelius kaip nepriklausomi kintamieji įtraukti amžius, lytis, išsilavinimas ir kognityvinių testų rezultatai, taikyta siekiant nustatyti jų prognozinę reikšmę *Time–Wall* užduoties vidutinei paklaidai. Statistiškai reikšmingi rezultatai nustatyti modeliuose su MMSE ($R^2 = 0,345$, $F = 11,52$, $\beta = -0,577$, $p < 0,001$), ADAS-Cog 13 ($R^2 = 0,321$, $F = 10,46$, $\beta = 0,577$, $p < 0,001$) ir CDR-SB ($R^2 = 0,262$, $F = 8,09$, $\beta = 0,498$, $p < 0,001$).

3.4.2. *Time–Wall* užduoties diagnostinės savybės

Time–Wall užduoties vidutinių paklaidų gebėjimas atskirti ankstyvąją Alzheimerio ligos stadiją (MCI ir MD) sergančius tiriamuosius nuo CG vertintas taikant ROC kreivės analizę. ROC analizė parodė stiprias diagnostines šios užduoties savybes – ploto po kreive (AUC) reikšmė, diferencijuojant CG ir ankstyvąją Alzheimerio ligos stadiją (MCI ir MD) sergančius tiriamuosius, buvo 0,9. Diferencijuojant CG ir MCI grupes, AUC reikšmė – 0,86. 4 paveiksle pateiktos ROC kreivės, naudotos *Time–Wall* užduoties rezultatams įvertinti.



4 pav. Time–Wall užduoties diagnostinės savybės, diferencijuojant ankstyvąją Alzheimerio ligos stadiją sergančius tiriamuosius ir CG

Santrumpos: AD – Alzheimerio liga; CG – kontrolinė grupė; MCI – lengvas kognityvinis sutrikimas; MD – lengva demencija.

Ankstyvosios AL stadijos tiriamiesiems nustatyti pasirinkta $\geq 18,35$ *Time–Wall* užduoties vidutinių paklaidų riba. Taikant šią ribą, ankstyvąją AL stadiją (MCI ir MD) sergantiems tiriamiesiems atskirti nuo CG, *Time–Wall* užduotis pasižymėjo 70,91 proc. jautrumu (95 % PI: 57,1–82,37) ir 96,15 proc. specifiškumu (95 % PI: 80,36–99,9). **III straipsnyje** pateikta išsami *Time–Wall* užduoties diagnostinių charakteristikų analizė, diferencijuojant ankstyvąją AL stadiją sergančius tiriamuosius ir CG.

Siekiant įvertinti ryšį tarp prediktorinių kintamųjų ir priklausymo grupei (CG, MCI ir MD), atlikta daugiakategorė logistinė regresinė analizė.

Pirmiausia sudarytas modelis, į kurį įtraukti amžius, išsilavinimas, lytis ir ADAS-Cog 13 balai. Šis modelis geriau atitiko duomenis negu modelis, turintis tik konstantą ($\chi^2 = 87,85$, $p < 0,001$; Nagelkerke $R^2 = 0,745$). Bendras klasifikavimo tikslumas siekė 76,5 proc.: teisingai suklasifikuota 92,3 % CG, 66,7 % MCI ir 71,4 % MD atvejų. ADAS-Cog 13 balas buvo stipriausias ir statistiškai reikšmingiausias prediktorius ($\chi^2 = 78,20$, $p < 0,001$).

Į pradinį modelį papildomai įtrauktos *Time–Wall* užduoties vidutinės paklaidos. Modelis, apimantis amžių, išsilavinimą, lytį, ADAS-Cog 13 balus ir *Time–Wall* užduoties vidutinės paklaidas, geriau atitiko duomenis negu nulinis modelis ($\chi^2 = 96,69$, $p < 0,001$; Nagelkerke $R^2 = 0,784$). Bendras klasifikavimo tikslumas siekė 75,3 proc.: teisingai suklasifikuota 92,3 % CG, 59,3 % MCI ir 75 % MD atvejų. ADAS-Cog 13 balai ir *Time–Wall* užduoties vidutinės paklaidos buvo statistiškai reikšmingi prediktoriai (atitinkamai $\chi^2 = 49,41$, $p < 0,001$ ir $\chi^2 = 9,24$, $p = 0,01$).

3.4.3. Mintinės rotacijos užduoties vertinimas

Mintinės rotacijos užduoties tikslumo balai tarp grupių statistiškai reikšmingai skyrėsi. Medianos ir tarpkvartiliniai intervalai: CG = 26,5 (4), MCI = 22 (9), MD = 21,5 (9) ($p = 0,001$). Post hoc palyginimai parodė statistiškai reikšmingus skirtumus tarp CG ir MCI ($p = 0,007$) bei tarp CG ir MD ($p < 0,001$), tačiau reikšmingų skirtumų tarp MCI ir MD grupių nenustatyta ($p = 0,094$). Atsako laikai tarp grupių taip pat statistiškai reikšmingai skyrėsi [$H(2) = 15,12$, $p = 0,001$]. Medianos ir tarpkvartiliniai intervalai: CG = 6309,7 (4531,4), MCI = 12 684,5 (7974,7), MD = 11 657,3 (7053).

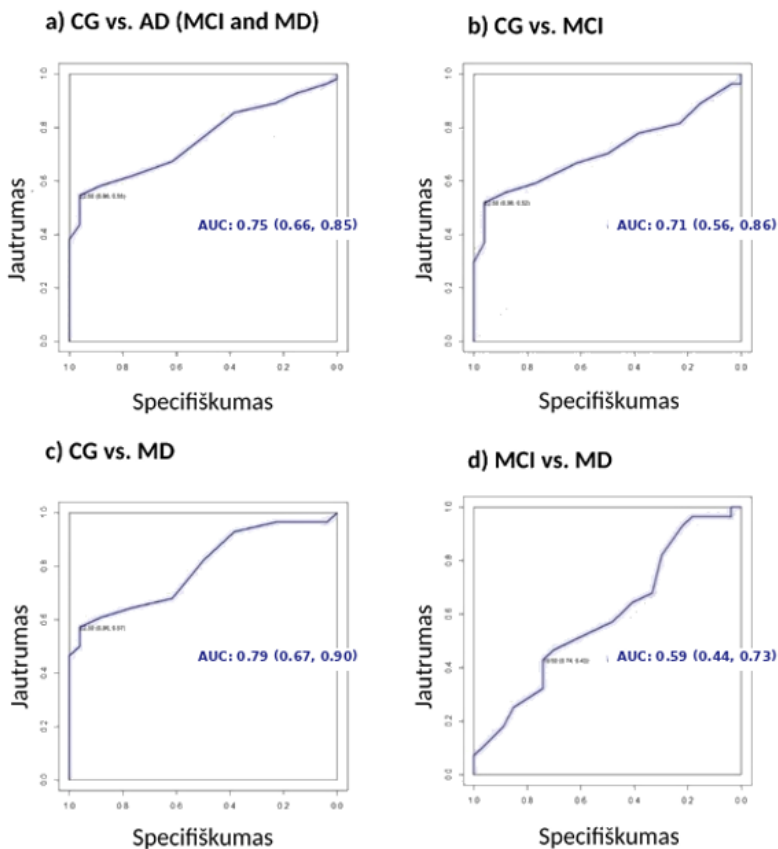
Šioje tiriamojoje populiacijoje mintinės rotacijos užduoties tikslumo balai parodė vidutinio stiprumo koreliaciją su MMSE rezultatais (Spearmano $\rho = 0,472$; $p < 0,001$) ir ADAS-Cog 13 balais (Spearmano $\rho = -0,407$; $p < 0,001$), taip pat silpną koreliaciją su CDR-SB balais (Spearmano $\rho = -0,372$; $p = 0,001$), amžiumi (Spearmano $\rho = -0,247$; $p = 0,026$) ir išsilavinimu (Spearmano $\rho = 0,238$; $p = 0,033$). Mintinės rotacijos užduoties atsako laikai vidutiniškai koreliavo su MMSE balais (Spearmano $\rho = -0,405$; $p < 0,001$). Silpnesnės koreliacijos nustatytos su ADAS-Cog 13 (Spearmano $\rho = 0,386$; $p = 0,001$) ir CDR-SB balais (Spearmano $\rho = 0,277$; $p = 0,015$). Statistiškai reikšmingų koreliacijų su amžiumi ir išsilavinimu nenustatyta.

Daugialypės tiesinės regresijos modeliai taikyti siekiant įvertinti amžiaus, lyties, išsilavinimo ir kognityvinių testų rezultatų, kaip nepriklausomų kintamųjų, prognozinę reikšmę mintinės rotacijos užduoties tikslumo balams. Statistiškai reikšmingi rezultatai nustatyti modeliuose su MMSE ($R^2 = 0,265$,

$F = 8,22$, $\beta = 0,438$, $p < 0,001$), ADAS-Cog 13 ($R^2 = 0,178$, $F = 5,32$, $\beta = -0,334$, $p = 0,001$) ir CDR-SB ($R^2 = 0,177$, $F = 5,3$, $\beta = -0,32$, $p = 0,001$).

3.4.4. Mintinės rotacijos užduoties diagnostinės savybės

Mintinės rotacijos užduoties tikslumo balų gebėjimas diferencijuoti ankstyvąją AL stadiją (MCI ir MD) sergančius tiriamuosius nuo kognityviškai sveikų kontrolinės grupės tiriamųjų vertintas taikant ROC kreivės analizę. Užduotis pasižymėjo vidutiniu diagnostiniu tikslumu atskiriant CG ir ankstyvąją AL stadiją (MCI ir MD) sergančius tiriamuosius; ploto po kreive (AUC) reikšmė – 0,75. Diferencijuojant CG ir MCI grupes, AUC reikšmė – 0,71. Užduoties rezultatų ROC kreivės pateiktos 5 paveiksle.



5 pav. Mintinės rotacijos užduoties diagnostinės savybės, diferencijuojant ankstyvąją AL stadiją sergančius tiriamuosius ir CG

Santrumpos: AD – Alzheimerio liga; CG – kontrolinė grupė; MCI – lengvas kognityvinis sutrikimas; MD – lengva demencija.

Ankstyvąją AL stadiją (MCI ir MD) sergantiems tiriamiesiems atskirti nuo CG pasirinkta ≤ 22 mintinės rotacijos užduoties tikslumo balų riba. Taikant šią ribą, mintinės rotacijos užduotis pasižymėjo 54,55 proc. jautrumu (95 % PI: 40,55–68,03) ir 96,15 proc. specifiškumu (95 % PI: 80,36–99,9).

III straipsnyje pateikta išsami mintinės rotacijos užduoties diagnostinių rodiklių analizė, diferencijuojant ankstyvąją AL stadiją sergančius tiriamuosius ir CG.

Į pradinį modelį įtraukti mintinės rotacijos užduoties tikslumo balai ir atsako laikas. Modelis, apimantis amžių, išsilavinimą, lytį, ADAS-Cog 13 balus, mintinės rotacijos užduoties tikslumo balus ir atsako laiką, parodė reikšmingai geresnę atitiktį, palyginti su nuliniu modeliu ($\chi^2 = 93,72$, $p < 0,001$; Nagelkerke $R^2 = 0,771$). Bendras klasifikavimo tikslumas siekė 75,3 proc.: teisingai suklasifikuota 88,5 % CG, 63 % MCI ir 75 % MD atvejų. Vienintelis statistiškai reikšmingas prediktorius buvo ADAS-Cog 13 ($\chi^2 = 64,01$, $p < 0,001$).

3.5. Objektų ir erdvės suvokimas

3.5.1. Objektų suvokimas: siluetų vertinimas

Vienfaktorinė dispersinė analizė (ANOVA) parodė statistiškai reikšmingus siluetų testo balų skirtumus (vidurkis ir standartinis nuokrypis: CG = $18,77 \pm 5,64$; MCI = $13,44 \pm 4,85$; MD = $12,07 \pm 4,06$; $F = 14,06$, $p < 0,001$). Post hoc analizė atskleidė statistiškai reikšmingus skirtumus tarp CG ir MCI bei tarp CG ir MD grupių (abiem atvejais $p < 0,001$). Statistiškai reikšmingų skirtumų tarp MCI ir MD grupių nenustatyta ($p = 0,90$).

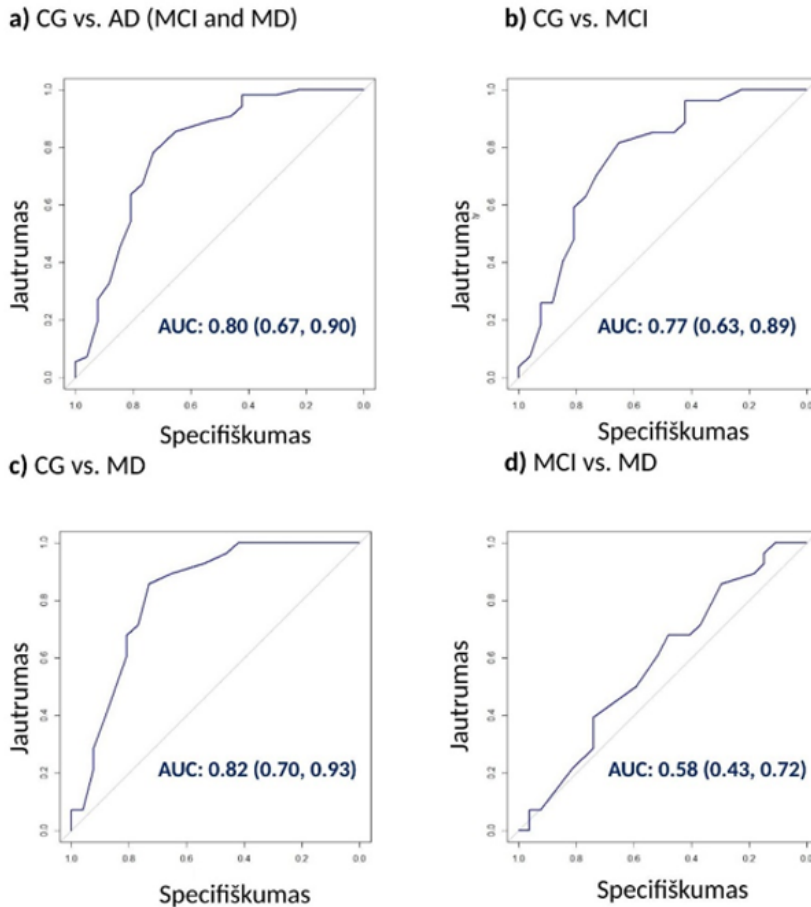
Visų tiriamųjų imtyje siluetų testo balai vidutiniškai koreliavo su MMSE (Spearmano $\rho = 0,477$; $p < 0,001$), CDR-SB (Spearmano $\rho = -0,437$; $p < 0,001$), ADAS-Cog 13 (Spearmano $\rho = -0,479$; $p < 0,001$) balais ir amžiumi (Spearmano $\rho = -0,404$; $p < 0,001$), o silpna koreliacija nustatyta su išsilavinimu (Spearmano $\rho = 0,295$; $p = 0,007$).

Daugialypės tiesinės regresijos modeliai taikyti siekiant įvertinti, ar siluetų testo balus galima prognozuoti pagal kognityvinių testų rezultatus. Į modelius įtraukti kognityvinių testų balai (MMSE, CDR-SB ir ADAS-Cog 13), o modeliai pakoreguoti pagal lytį, amžių ir išsilavinimą.

Statistiškai reikšmingi rezultatai nustatyti pakoreguotuose modeliuose su MMSE ($R^2 = 0,489$, $F = 20,12$, $\beta = 0,381$, $p < 0,001$), ADAS-Cog 13 ($R^2 = 0,492$, $F = 20,38$, $\beta = -0,4$, $p < 0,001$) ir CDR-SB ($R^2 = 0,444$, $F = 16,99$, $\beta = -0,316$, $p < 0,001$).

3.5.2. Siluetų užduoties diagnostinės savybės

Siekiant įvertinti siluetų testo balų diagnostines savybes diferencijuojant ankstyvąją AL stadiją (MCI ar MD) sergančius tiriamuosius ir CG bei atskiriant MCI ir MD grupes, atlikta ROC kreivės analizė. ROC kreivės, iliustruojančios siluetų testo rezultatus diferencijuojant tiriamųjų grupes, pateiktos 6 paveiksle.



6 pav. Siluetų užduoties diagnostinės savybės, diferencijuojant ankstyvąją AL stadiją sergančius tiriamuosius nuo CG

Santrumpos: AD – Alzheimerio liga; CG – kontrolinė grupė; MCI – lengvas kognityvinis sutrikimas; MD – lengva demencija.

Siluetų teste nustatyta ≤ 16 balų riba buvo laikoma ankstyvosios AL stadijos indikatoriumi. Taikant šią ribą ankstyvąją AL stadiją (įskaitant MCI ir MD dėl AL) sergantiems tiriamiesiems atskirti nuo CG, siluetų testas

pasižymėjo 78,18 proc. jautrumu (95 % PI: 64,99–88,19) ir 73,08 proc. specifiskumu (95 % PI: 52,21–88,43). Nustatyta neigiama prognostinė vertė – 61,29 proc. (95 % PI: 47,69–73,33 %). Teigiama prognostinė vertė – 86 proc. (95 % PI: 76,26–92,16 %). Bendras diagnostinis tikslumas siekė 76,54 proc. (95 % PI: 65,82–85,25 %). Visos ribinės reikšmės ir siluetų testo diagnostinės savybės, lyginant diagnostines grupes, pateiktos **IV straipsnyje**.

Siekiant įvertinti prediktorinių kintamųjų įtaką priklausymui grupei (CG, MCI ir MD), atlikta daugiakategorė logistinė regresinė analizė. Iš pradžių sudarytas modelis, į kurį įtraukta lytis, amžius, išsilavinimas ir ADAS-Cog 13 balai. Šių kintamųjų įtraukimas reikšmingai pagerino modelio atitiktį, palyginti su modeliu, turinčiu tik konstantą ($\chi^2 = 87,79$, $p < 0,001$; Nagelkerke $R^2 = 0,744$). Šis modelis teisingai suklasifikavo 76,5 proc. atvejų: 92,3 % CG, 66,7 % MCI ir 71,4 % MD. Iš visų prediktorių ADAS-Cog 13 balas buvo stipriausias ir statistiškai reikšmingiausias ($\chi^2 = 78,83$, $p < 0,001$).

Antrasis modelis, apimantis lytį, amžių, išsilavinimą, ADAS-Cog 13 balus ir siluetų testo balus, parodė šiek tiek geresnę atitiktį, palyginti su nuliniu modeliu ($\chi^2 = 88,30$, $p < 0,001$; Nagelkerke $R^2 = 0,747$). Bendras klasifikavimo tikslumas siekė 76,4 proc.: teisingai suklasifikuota 92,3 % CG, 63 % MCI ir 75 % MD atvejų. Šiame modelyje ADAS-Cog 13 balas išliko stiprus ir statistiškai reikšmingas prediktorius ($\chi^2 = 61,77$, $p < 0,001$), o siluetų testo balai statistiškai reikšmingos prognostinės vertės neturėjo ($\chi^2 = 0,465$, $p = 0,793$).

3.5.3. Erdvės suvokimas: skaičių vietos vertinimas

Nustatyti statistiškai reikšmingi skaičių vietos testo įverčių skirtumai tarp trijų grupių. Medianos ir tarpkvartiliniai intervalai: CG = 9,5 (2), MCI = 8 (3), MD = 6 (6). Kruskalio ir Walliso testas ($p < 0,001$) bei vėlesnė post hoc analizė parodė statistiškai reikšmingus skirtumus tarp visų grupių porų: CG ir MCI ($p = 0,007$), MCI ir MD ($p = 0,007$) bei CG ir MD ($p < 0,001$).

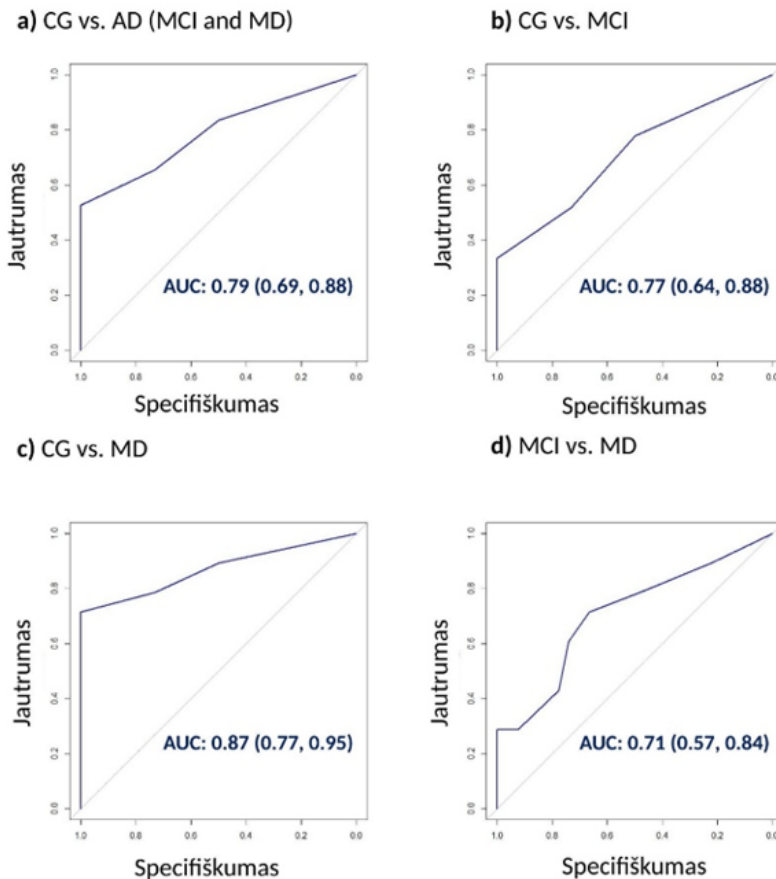
Nustatyta vidutinio stiprumo koreliacija tarp skaičių vietos testo balų ir MMSE rezultatų (Spearmano $\rho = 0,573$; $p < 0,001$), CDR-SB (Spearmano $\rho = -0,5$; $p < 0,001$) bei ADAS-Cog 13 balų (Spearmano $\rho = -0,467$; $p < 0,001$). Statistiškai reikšmingų koreliacijų su amžiumi ir išsilavinimu nenustatyta.

Daugialypės tiesinės regresijos modeliai taikyti siekiant įvertinti, ar skaičių vietos testo balus galima prognozuoti pagal kognityvinių testų rezultatus. Į modelius įtraukti kognityvinių testų balai (MMSE, CDR-SB ir ADAS-Cog 13), o modeliai pakoreguoti pagal lytį, amžių ir išsilavinimą.

Statistiškai reikšmingi rezultatai nustatyti pakoreguotuose modeliuose su MMSE ($R^2 = 0,384$, $F = 13,47$, $\beta = 0,483$, $p < 0,001$), ADAS-Cog 13 ($R^2 = 0,288$, $F = 9,08$, $\beta = -0,383$, $p < 0,001$) ir CDR-SB ($R^2 = 0,364$, $F = 12,46$, $\beta = -0,46$, $p < 0,001$).

3.5.4. Skaičių vietos užduoties diagnostinės savybės

Siekiant įvertinti skaičių vietos testo balų diagnostines savybes diferencijuojant ankstyvąją AL stadiją (įskaitant MCI ir MD) sergančius tiriamuosius ir CG bei atskiriant MCI ir MD grupes, atlikta ROC kreivės analizė. ROC kreivės, iliustruojančios skaičių vietos testo rezultatus diferencijuojant tiriamųjų grupes, pateiktos 7 paveiksle.



7 pav. Skaičių vietos užduoties diagnostinės savybės, diferencijuojant ankstyvąją AL stadiją sergančius tiriamuosius nuo CG

Santrumpos: AD – Alzheimerio liga; CG – kontrolinė grupė; MCI – lengvas kognityvinis sutrikimas; MD – lengva demencija.

Skaičių vietos teste nustatyta ≤ 8 balų riba buvo laikoma ankstyvosios AL stadijos indikatoriumi. Taikant šią ribą ankstyvąją AL stadiją (įskaitant MCI ir MD dėl AL) sergantiems tiriamiesiems atskirti nuo CG, skaičių vietos testas pasižymėjo 65,45 proc. jautrumu (95 % PI: 51,42–77,76) ir 73,08 proc. specifiškumu (95 % PI: 52,21–88,43). Be to, nustatyta neigiama prognostinė vertė – 50 proc. (95 % PI: 39,36–60,64 %) ir teigiama prognostinė vertė – 83,72 proc. (95 % PI: 72,63–90,88 %). Bendras diagnostinis tikslumas siekė 67,9 proc. (95 % PI: 56,60–77,85 %). Visos ribinės reikšmės ir skaičių vietos testo diagnostinės savybės, lyginant diagnostines grupes, pateiktos **IV straipsnyje**.

Daugiakategorės logistinės regresijos modelis, apimantis lytį, amžių, išsilavinimą, ADAS-Cog 13 balus ir skaičių vietos testo balus, parodė reikšmingai geresnę atitiktį, palyginti su nuliniu modeliu ($\chi^2 = 104,76$, $p < 0,001$; Nagelkerke $R^2 = 0,816$). Bendras klasifikavimo tikslumas siekė 80,2 proc.: teisingai suklasifikuota 92,3 % CG, 70,4 % MCI ir 78,6 % MD atvejų. Šiame modelyje tiek ADAS-Cog 13 balai, tiek skaičių vietos testo balai buvo statistiškai reikšmingi prediktoriai (atitinkamai $\chi^2 = 68,22$, $p < 0,001$ ir $\chi^2 = 16,97$, $p < 0,001$).

3.5.5. Erdvės suvokimas: kubų analizės vertinimas

Kubų analizės testo balai tarp grupių statistiškai reikšmingai skyrėsi. Medianos ir tarpkvartiliniai intervalai: CG = 10 (1), MCI = 8 (3), MD = 7 (5); Kruskalio ir Walliso $p < 0,001$. Post hoc analizė parodė statistiškai reikšmingus skirtumus tarp CG ir MCI bei tarp CG ir MD (abiem atvejais $p < 0,001$), tačiau reikšmingų skirtumų tarp MCI ir MD grupių nenustatyta ($p = 0,094$).

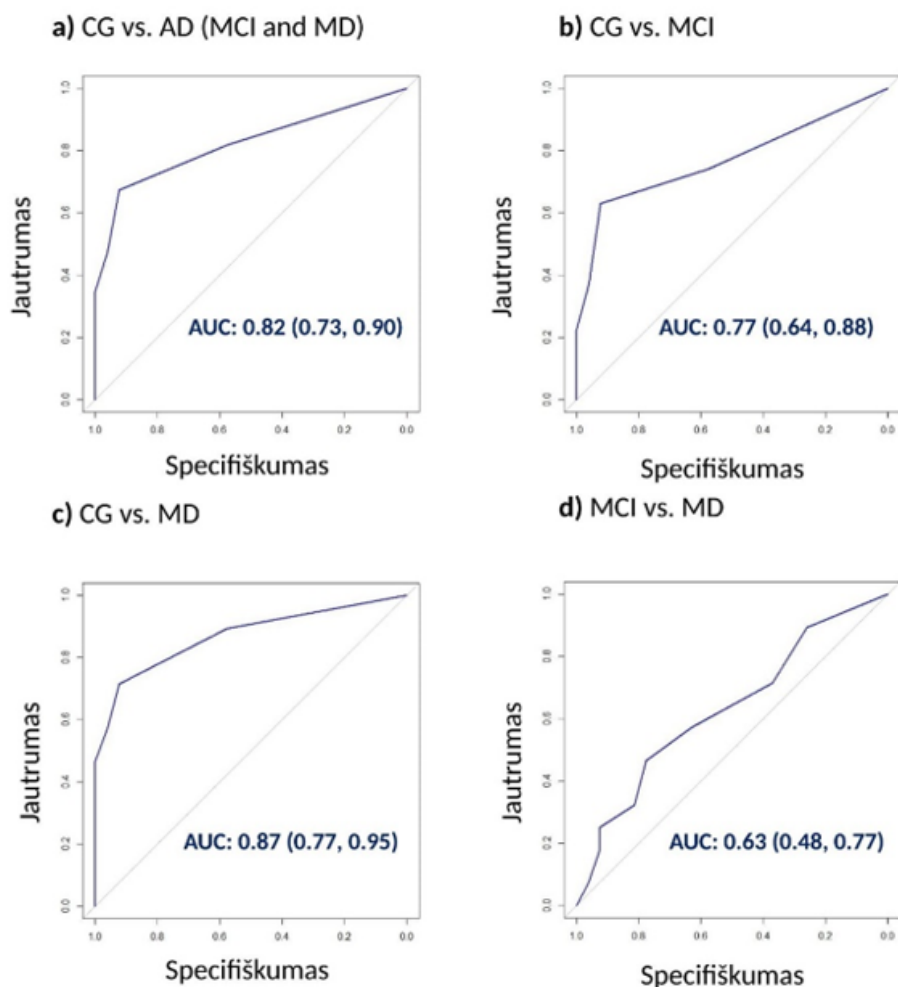
Kubų analizės testo balai vidutiniškai koreliavo su MMSE balais (Spearmano $\rho = 0,579$; $p < 0,001$), CDR-SB balais (Spearmano $\rho = -0,489$; $p < 0,001$) ir ADAS-Cog 13 balais (Spearmano $\rho = -0,521$; $p < 0,001$), o silpna koreliacija nustatyta su amžiumi (Spearmano $\rho = -0,337$; $p = 0,002$) ir išsilavinimu (Spearmano $\rho = 0,346$; $p = 0,002$).

Daugialypės tiesinės regresijos modeliai taikyti siekiant įvertinti, ar kubų analizės testo balus galima prognozuoti pagal kognityvinių testų rezultatus. Į modelius įtraukti kognityvinių testų balai (MMSE, CDR-SB ir ADAS-Cog 13), o modeliai pakoreguoti pagal lytį, amžių ir išsilavinimą.

Statistiškai reikšmingi rezultatai nustatyti pakoreguotuose modeliuose su MMSE ($R^2 = 0,376$, $F = 13,03$, $\beta = 0,471$, $p < 0,001$), ADAS-Cog 13 ($R^2 = 0,29$, $F = 9,16$, $\beta = -0,382$, $p < 0,001$) ir CDR-SB ($R^2 = 0,296$, $F = 9,4$, $\beta = -0,376$, $p < 0,001$).

3.5.6. Kubų analizės diagnostinės savybės

Siekiant įvertinti kubų analizės testo balų diagnostines savybes diferencijuojant ankstyvąją AL stadiją (įskaitant MCI ir MD) sergančius tiriamuosius ir CG bei atskiriant MCI ir MD grupes, atlikta ROC kreivės analizė. ROC kreivės, iliustruojančios kubų analizės testo rezultatus diferencijuojant tiriamųjų grupes, pateiktos 8 paveiksle.



8 pav. Kubų analizės užduoties diagnostinės savybės, diferencijuojant ankstyvąją AL stadiją sergančius tiriamuosius nuo CG

Santrumpos: AD – Alzheimerio liga; CG – kontrolinė grupė; MCI – lengvas kognityvinis sutrikimas; MD – lengva demencija.

Kubų analizės teste nustatyta ≤ 8 balų riba buvo laikoma ankstyvosios AL stadijos indikatoriumi. Taikant šią ribą ankstyvąją AL stadiją (įskaitant MCI ir MD dėl AL) sergantiems tiriamiesiems atskirti nuo CG, testas pasižymėjo 67,27 proc. jautrumu (95 % PI: 53,29–79,32 %) ir 92,31 proc. specifiškumu (95 % PI: 74,87–99,05 %). Be to, nustatyta neigiama prognostinė vertė – 57,14 proc. (95 % PI: 47,32–66,43 %). Teigiama prognostinė vertė – 94,87 proc. (95 % PI: 82,83–98,61 %). Bendras diagnostinis tikslumas siekė 75,31 proc. (95 % PI: 64,47–84,22 %). Visos ribinės reikšmės ir kubų analizės testo diagnostinės savybės, lyginant diagnostines grupes, pateiktos **IV straipsnyje**.

Daugiakategoris logistinės regresijos modelis, apimantis lytį, amžių, išsilavinimą, ADAS-Cog 13 balus ir kubų analizės testo balus, parodė reikšmingai geresnę atitiktį, palyginti su nuliniu modeliu ($\chi^2 = 94,08$, $p < 0,001$; Nagelkerke $R^2 = 0,773$). Bendras klasifikavimo tikslumas siekė 80,2 proc.: teisingai suklasifikuota 92,3 % CG, 70,4 % MCI ir 78,6 % MD atvejų. Šiame modelyje tiek ADAS-Cog 13 balai, tiek kubų analizės testo balai buvo statistiškai reikšmingi prediktoriai (atitinkamai $\chi^2 = 59,93$, $p < 0,001$ ir $\chi^2 = 6,29$, $p = 0,043$).

4. IŠVADOS

1. Ankstyvosiose Alzheimerio ligos stadijose yra sutrikusi spalvų atpažinimo atmintis, o šios užduoties rezultatai pasižymi geromis diagnostinėmis savybėmis. Spalvinės atminties testas gali būti paprasta, patikima, neinvazinė ankstyvosios AL stadijos diagnostinė priemonė.
2. ME ir AE suvokimo skirtumai tarp kognityvinių sutrikimų neturinčių ir ankstyvąją AL stadiją sergančių tiriamųjų rodo funkcinį regimojo suvokimo pokyčius, sergant AL. Susilpnėjęs ar išnykęs ME ir AE matymas gali būti vykstančių neurodegeneracijos procesų žymuo. Raudonų horizontalių linijų ME poveikio susilpnėjimas gali būti nustatomas ankstyvosiose AL stadijose ir padeda geriau suprasti regimojo suvokimo pokyčius, sergant AL.
3. Kompiuterizuota *Time–Wall* užduotis yra efektyvi klinikinė priemonė, padedanti greitai įvertinti laiko ir judesio suvokimo pokyčius, sergant ankstyvosiomis AL stadijomis. Amžius nedaro įtakos *Time–Wall* užduoties tikslumui. Mintinės rotacijos užduoties reikšmė AL diagnostikai turėtų būti vertinama tolesniuose tyrimuose, nes ši užduotis gali padėti įvertinti kompensacinius neuronų tinklus.

4. VOSP baterijos testai yra nebrangi, efektyvi ir greita vizualinių funkcijų vertinimo priemonė ankstyvosiose AL stadijose. Siluetų, skaičių vietos ir kubų analizės testai, kaip papildomos priemonės, gali pagerinti ankstyvosios AL stadijos diagnostiką.

BRIEF INFORMATION ABOUT THE DOCTORAL CANDIDATE

Vaiva Sutnikienė is a medical doctor and neurologist. She was a doctoral student in medicine at Vilnius University from 2019 to 2025. Her research interests include cognitive neurology, early diagnosis of neurodegenerative diseases of the central nervous system, and disorders of visual perception and visual memory in Alzheimer's disease. In 2018, she completed her residency in neurology at Vilnius University. She works at Vilnius University Hospital Santaros Klinikos and at the Clinic of Neurology and Neurosurgery, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University. During her doctoral studies, she investigated early changes in visual perception, visual memory, and specific visual phenomena in Alzheimer's disease, as well as their significance for the early diagnosis of Alzheimer's disease. Four scientific articles have been published in international scientific journals on the topic of her dissertation, and four scientific presentations have been delivered at international scientific conferences.

TRUMPOS ŽINIOS APIE DISERTANTĘ

Vaiva Sutnikienė – medicinos gydytoja neurologė, 2019–2025 m. Vilniaus universiteto medicinos krypties doktorantė. Jos mokslinių interesų sritys apima kognityvinę neurologiją, neurodegeneracinių centrinių nervų sistemos ligų ankstyvąją diagnostiką, regimojo suvokimo ir vizualinės atminties sutrikimus sergant Alzheimerio liga. 2018 m. baigė neurologijos rezidentūrą Vilniaus universitete. Dirba VUL Santaros klinikose ir Vilniaus universiteto Medicinos fakulteto Klinikinės medicinos instituto Neurologijos ir neurochirurgijos klinikoje. Doktorantūros metu tyrė ankstyvuosius regimojo suvokimo, vizualinės atminties ir specialiųjų regos fenomenų pokyčius sergant Alzheimerio liga bei jų reikšmę ankstyvajai Alzheimerio ligos diagnostikai. Disertacijos tema paskelbė keturis mokslinius straipsnius tarptautiniuose mokslo leidiniuose ir pristatė keturis mokslinius pranešimus tarptautinėse mokslinėse konferencijose.

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REFERENCES

- [1] World Health Organization. Global action plan on the public health response to dementia 2017–2025. Geneva: World Health Organization; 2017. Available from: <https://www.who.int/publications/i/item/global-action-plan-on-the-public-health-response-to-dementia-2017---2025>. Accessed December 2, 2024.
- [2] Alzheimer's Association. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2024;20:3708–3821. doi:10.1002/alz.13809.
- [3] Chêne G, Beiser A, Au R, Preis SR, Wolf PA, Dufouil C, et al. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimers Dement*. 2015;11:310–320. doi:10.1016/j.jalz.2013.10.005.
- [4] Gauthier S, Rosa-Neto P, Morais JA, Webster C. World Alzheimer report 2021: journey through the diagnosis of dementia. London: Alzheimer's Disease International; 2021.
- [5] Arrighi HM, Neumann PJ, Lieberburg IM, Townsend RJ. Lethality of Alzheimer disease and its impact on nursing home placement. *Alzheimer Dis Assoc Disord*. 2010;24(1):90-95. doi:10.1097/WAD.0b013e31819fe7d1.
- [6] Alzheimer's Disease International. From plan to impact V: WHO Global action plan: the time to act is now. London: Alzheimer's Disease International; 2022.
- [7] Cook L, Souris H, Isaacs J. The 2019 national memory service audit. London: Dementia Clinical Network, NHS England and NHS Improvement (London Region); 2020.
- [8] Evans-Lacko S, Aguzzi E, Read S, Comas-Herrera A, Farina N. World Alzheimer report 2024: global changes in attitudes to dementia. London: Alzheimer's Disease International; 2024.
- [9] Owsley C, Sloane ME. Contrast sensitivity, acuity, and the perception of 'real-world' targets. *Br J Ophthalmol*. 1987;71(10):791-796. doi:10.1136/bjo.71.10.791.
- [10] Livingstone MS, Hubel DH. Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *J Neurosci*. 1987;7(11):3416-3468. doi:10.1523/JNEUROSCI.07-11-03416.1987.
- [11] Chang LYL, Lowe J, Ardiles A, Lim J, Grey AC, Robertson K, et al. Alzheimer's disease in the human eye: clinical tests that identify ocular and visual information processing deficit as biomarkers. *Alzheimers Dement*. 2014;10(2):251-261. doi:10.1016/j.jalz.2013.06.004.
- [12] Iseri PK, Altınış O, Tokay T, Yüksel N. Relationship between cognitive impairment and retinal morphological and visual functional

- abnormalities in Alzheimer disease. *J Neuroophthalmol*. 2006;26(1):18-24. doi:10.1097/01.wno.0000204645.56873.26.
- [13] Marquié M, Castilla-Martí M, Valero S, Martínez J, Sánchez D, Hernández I, et al. Visual impairment in aging and cognitive decline: experience in a memory clinic. *Sci Rep*. 2019;9(1):8698. doi:10.1038/s41598-019-45055-9.
 - [14] Pache M, Smeets CHW, Gasio PF, Savaskan E, Flammer J, Wirz-Justice A, et al. Colour vision deficiencies in Alzheimer's disease. *Age Ageing*. 2003;32(4):422-426. doi:10.1093/ageing/32.4.422.
 - [15] Alegret M, Boada-Rovira M, Vinyes-Junqué G, Valero S, Espinosa A, Hernández I, et al. Detection of visuoperceptual deficits in preclinical and mild Alzheimer's disease. *J Clin Exp Neuropsychol*. 2009;31(7):860-867. doi:10.1080/13803390802595568.
 - [16] Ehrlich JR, Swenor BK, Zhou Y, Langa KM. The longitudinal association of vision impairment with transitions to cognitive impairment and dementia: findings from the Aging, Demographics and Memory Study. *J Gerontol A Biol Sci Med Sci*. 2021;76(12):2187-2193. doi:10.1093/gerona/glab157.
 - [17] Almidani L, Mihailovic A, Varadaraj V, Swenor BK, Ramulu PY. Longitudinal changes in visual acuity and contrast sensitivity and incident dementia. *Am J Ophthalmol*. 2024;266:227-234. doi:10.1016/j.ajo.2024.06.001.
 - [18] Barbeau E, Didic M, Tramon E, Felician O, Joubert S, Sontheimer A, et al. Evaluation of visual recognition memory in MCI patients. *Neurology*. 2004;62(8):1317-1322. doi:10.1212/01.WNL.0000120548.24298.DB.
 - [19] Goodale MA, Milner AD. Separate visual pathways for perception and action. *Trends Neurosci*. 1992;15(1):20-25. doi:10.1016/0166-2236(92)90344-8.
 - [20] Sintini I, Graff-Radford J, Senjem ML, Schwarz CG, Machulda MM, Martin PR, et al. Longitudinal neuroimaging biomarkers differ across Alzheimer's disease phenotypes. *Brain*. 2020;143(7):2281-2294. doi:10.1093/brain/awaa155.
 - [21] Pontecorvo MJ, Devous MD Sr, Kennedy I, Navitsky M, Lu M, Galante N, et al. A multicentre longitudinal study of flortaucipir (18F) in normal ageing, mild cognitive impairment and Alzheimer's disease dementia. *Brain*. 2019;142(6):1723-1735. doi:10.1093/brain/awz090.
 - [22] Memon A, Moore JA, Kang C, Ismail Z, Forkert ND; Alzheimer's Disease Neuroimaging Initiative. Visual functions are associated with

- biomarker changes in Alzheimer's disease. *J Alzheimers Dis.* 2024;99(2):623-637. doi:10.3233/JAD-231084.
- [23] Tyler SL, Maltby J, Paterson KB, Hutchinson CV. Reduced vision-related quality of life in dementia: a preliminary report. *J Alzheimers Dis.* 2022;87(1):239-246. doi:10.3233/JAD-215435.
- [24] Alzola P, Carnero C, Bermejo-Pareja F, Sánchez-Benavides G, Peña-Casanova J, Puertas-Martín V, et al. Neuropsychological assessment for early detection and diagnosis of dementia: current knowledge and new insights. *J Clin Med.* 2024;13(12):3442. doi:10.3390/jcm13123442.
- [25] Shapiro AG, Todorović D, editors. *The Oxford compendium of visual illusions.* New York: Oxford University Press; 2017.
- [26] Pinna B, Porcheddu D, Skilters J. From perceptual organization to visual illusions and back. *Front Hum Neurosci.* 2022;16:960542. doi:10.3389/fnhum.2022.960542.
- [27] Daw NW. Why after-images are not seen in normal circumstances. *Nature.* 1962;196:1143-1145. doi:10.1038/1961143a0.
- [28] Shimojo S, Kamitani Y, Nishida S. Afterimage of perceptually filled-in surface. *Science.* 2001;293(5535):1677-1680. doi:10.1126/science.1060161.
- [29] van Lier R, Vergeer M, Anstis S. Filling-in afterimage colors between the lines. *Curr Biol.* 2009;19(8). doi:10.1016/j.cub.2009.03.010.
- [30] McCollough C. Color adaptation of edge-detectors in the human visual system. *Science.* 1965;149(3688):1115-1116. doi:10.1126/science.149.3688.1115.
- [31] McCollough C. Do McCollough effects provide evidence for global pattern processing? *Percept Psychophys.* 2000;62(2):350-362. doi:10.3758/BF03205555.
- [32] Kessels RPC. Improving precision in neuropsychological assessment: bridging the gap between classic paper-and-pencil tests and paradigms from cognitive neuroscience. *Clin Neuropsychol.* 2019;33(2):357-368. doi:10.1080/13854046.2018.1518489.
- [33] Chan JYC, Kwong JSW, Wong A, Kwok TCY, Tsoi KKF. Comparison of computerized and paper-and-pencil memory tests in detection of mild cognitive impairment and dementia: a systematic review and meta-analysis of diagnostic studies. *J Am Med Dir Assoc.* 2018;19(9):748-756.e5. doi:10.1016/j.jamda.2018.05.010.
- [34] Kochan NA, Heffernan M, Valenzuela M, Sachdev PS, Lam BCP, Fiatarone Singh M, et al. Reliability, validity, and user-experience of remote unsupervised computerized neuropsychological assessments in community-living 55- to 75-year-olds. *J Alzheimers Dis.* 2022;90(4):1629-1645. doi:10.3233/JAD-220665.

- [35] Piper BJ, Mueller ST, Geerken AR, Dixon KL, Kroliczak G, Olsen RHJ, et al. Reliability and validity of neurobehavioral function on the Psychology Experimental Building Language test battery in young adults. *PeerJ*. 2015;3:e1460. doi:10.7717/peerj.1460.
- [36] Liu Y, Feng D, Wang H. Distinct forms of motion sensitivity impairments in Alzheimer's disease. *Sci Rep*. 2019;9(1):12931. doi:10.1038/s41598-019-48942-3.
- [37] Deng Y, Shi L, Lei Y, Liang P, Li K, Chu WCW, et al. Mapping the "what" and "where" visual cortices and their atrophy in Alzheimer's disease: combined activation likelihood estimation with voxel-based morphometry. *Front Hum Neurosci*. 2016;10:333. doi:10.3389/fnhum.2016.00333.
- [38] El Haj M, Kapogiannis D. Time distortions in Alzheimer's disease: a systematic review and theoretical integration. *NPJ Aging Mech Dis*. 2016;2:16016. doi:10.1038/npjamd.2016.16.
- [39] MacDonald CJ, Fortin NJ, Sakata S, Meck WH. Retrospective and prospective views on the role of the hippocampus in interval timing and memory for elapsed time. *Timing Time Percept*. 2014;2(1):51-61. doi:10.1163/22134468-00002020.
- [40] Meck WH, Church RM, Matell MS. Hippocampus, time, and memory: a retrospective analysis. *Behav Neurosci*. 2013;127(5):642-654. doi:10.1037/a0034201.
- [41] Hampel H, Mesulam MM, Cuello AC, Farlow MR, Giacobini E, Grossberg GT, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain*. 2018;141(7):1917-1933. doi:10.1093/brain/awyl32.
- [42] Goard M, Dan Y. Basal forebrain activation enhances cortical coding of natural scenes. *Nat Neurosci*. 2009;12(11):1444-1449. doi:10.1038/nn.2402.
- [43] Arnaoutoglou NA, Arnaoutoglou M, Nemtsas P, Costa V, Baloyannis SJ, Ebmeier KP. Color perception differentiates Alzheimer's disease (AD) from vascular dementia (VaD) patients. *Int Psychogeriatr*. 2017;29(8):1355-1361. doi:10.1017/S1041610217000096.
- [44] Flanigan PM, Khosravi MA, Leverenz JB, Tousi B. Color vision impairment differentiates Alzheimer dementia from dementia with Lewy bodies. *J Geriatr Psychiatry Neurol*. 2018;31(2):97-102. doi:10.1177/0891988718767579.
- [45] Unger RH, Flanigan PM, Khosravi M, Leverenz JB, Tousi B. Clinical and imaging characteristics associated with color vision impairment in Lewy body disease. *J Alzheimers Dis*. 2019;72(4):1233-1240. doi:10.3233/JAD-190727.

- [46] Zeki S, Marini L. Three cortical stages of colour processing in the human brain. *Brain*. 1998;121(9):1669-1685. doi:10.1093/brain/121.9.1669.
- [47] Spigler G. Neural modelling of the McCollough effect in color vision [master's thesis]. Edinburgh: University of Edinburgh, School of Informatics; 2014.
- [48] Vul E, Krizay E, MacLeod DIA. The McCollough effect reflects permanent and transient adaptation in early visual cortex. *J Vis*. 2008;8(12):4.1-4.12. doi:10.1167/8.12.4.
- [49] Johnson EN, Hawken MJ, Shapley R. The orientation selectivity of color-responsive neurons in macaque V1. *J Neurosci*. 2008;28(32):8096-8106. doi:10.1523/JNEUROSCI.1404-08.2008.
- [50] Savoy RL, Gabrieli JD. Normal McCollough effect in Alzheimer's disease and global amnesia. *Percept Psychophys*. 1991;49(5):448-455. doi:10.3758/BF03212178.
- [51] Byth W, McMahon D, King DJ. Cholinergic agents and the McCollough effect. *Perception*. 2000;29(4):461-480. doi:10.1068/p2892.
- [52] Pinna B, Brelstaff G, Spillmann L. Surface color from boundaries: a new 'watercolor' illusion. *Vision Res*. 2001;41(20):2669-2676. doi:10.1016/S0042-6989(01)00105-5.
- [53] Komatsu H. The neural mechanisms of perceptual filling-in. *Nat Rev Neurosci*. 2006;7(3):220-231. doi:10.1038/nrn1869.
- [54] Kim J, Francis G. Color selection, color capture, and afterimage filling-in. *J Vis*. 2011;11(3):23. doi:10.1167/11.3.23.
- [55] Gerardin P, Dojat M, Knoblauch K, Devinck F. Effects of background and contour luminance on the hue and brightness of the watercolor effect. *Vision Res*. 2018;144:9-19. doi:10.1016/j.visres.2018.01.003.
- [56] The PEBL Project. PEBL [Internet]. The PEBL Project; 2019 [cited 2025 May 10]. Available from: <https://pebl.sourceforge.net>
- [57] Kim T, Jounghani AR, Gozdas E, Hosseini SMH. Cortical neurite microstructural correlates of time perception in healthy older adults. *Heliyon*. 2024;10(12):e32534. doi:10.1016/j.heliyon.2024.e32534.
- [58] Suzuki A, Shinozaki J, Yazawa S, Ueki Y, Matsukawa N, Shimohama S, et al. Establishing a new screening system for mild cognitive impairment and Alzheimer's disease with mental rotation tasks that evaluate visuospatial function. *J Alzheimers Dis*. 2018;61(4):1653-1665. doi:10.3233/JAD-170801.
- [59] Langner R, Scharnowski F, Ionta S, Salmon CEG, Piper BJ, Pamplona GSP. Evaluation of the reliability and validity of computerized tests of attention. *PLoS One*. 2023;18(1):e0281196. doi:10.1371/journal.pone.0281196.

- [60] Lineweaver TT, Salmon DP, Bondi MW, Corey-Bloom J. Differential effects of Alzheimer's disease and Huntington's disease on the performance of mental rotation. *J Int Neuropsychol Soc.* 2005;11(1):30-39. doi:10.1017/S1355617705050034.
- [61] Warrington EK, James M. *The Visual Object and Space Perception Battery*. Bury St Edmunds: Thames Valley Test Company; 1991.
- [62] de Haan GA, Tucha O, Heutink J. Effects of low visual acuity on neuropsychological test scores: a simulation study. *Clin Neuropsychol.* 2020;34(1):140-157. doi:10.1080/13854046.2019.1596315.
- [63] Quental NBM, Brucki SMD, Bueno OFA. Visuospatial function in early Alzheimer's disease: the use of the Visual Object and Space Perception (VOSP) battery. *PLoS One.* 2013;8(7):e68398. doi:10.1371/journal.pone.0068398.
- [64] Belleville S, Fouquet C, Hudon C, Zomahoun HTV, Croteau J; Consortium for the Early Identification of Alzheimer's Disease-Quebec. Neuropsychological measures that predict progression from mild cognitive impairment to Alzheimer's type dementia in older adults: a systematic review and meta-analysis. *Neuropsychol Rev.* 2017;27(4):328-353. doi:10.1007/s11065-017-9361-5.
- [65] Eckerström C, Olsson E, Bjerke M, Malmgren H, Edman Å, Wallin A, et al. A combination of neuropsychological, neuroimaging, and cerebrospinal fluid markers predicts conversion from mild cognitive impairment to dementia. *J Alzheimers Dis.* 2013;36(3):421-431. doi:10.3233/JAD-122440.
- [66] Boyd CD, Tierney M, Wassermann EM, Spina S, Oblak AL, Ghetti B, et al. Visuoperception test predicts pathologic diagnosis of Alzheimer disease in corticobasal syndrome. *Neurology.* 2014;83(6):510-519. doi:10.1212/WNL.0000000000000667.
- [67] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008.
- [68] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005.
- [69] Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: toward a biological definition

- of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018.
- [70] Sam N. Unified tri-service cognitive performance assessment battery (UTCPAB) [Internet]. In: *Psychology Dictionary*. 2013 [cited 2025 Apr 15]. Available from: <https://psychologydictionary.org/unified-tri-service-cognitive-performance-assessment-battery-utcpab/>
- [71] Shepard RN, Metzler J. Mental rotation of three-dimensional objects. *Science*. 1971;171(3972):701-703. doi:10.1126/science.171.3972.701.
- [72] Yamasaki T, Horie S, Muranaka H, Kaseda Y, Mimori Y, Tobimatsu S. Relevance of in vivo neurophysiological biomarkers for mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis*. 2012;31 Suppl 3:S137–S154. doi:10.3233/JAD-2012-112093.
- [73] Salimi S, Irish M, Foxe D, Hodges JR, Piguet O, Burrell JR. Can visuospatial measures improve the diagnosis of Alzheimer's disease? *Alzheimers Dement (Amst)*. 2018;10:66-74. doi:10.1016/j.dadm.2017.10.004.
- [74] Mayes A, Montaldi D, Migo E. Associative memory and the medial temporal lobes. *Trends Cogn Sci*. 2007;11(3):126-135. doi:10.1016/j.tics.2006.12.003.
- [75] Morales-Torres R, Wing EA, Deng L, Davis SW, Cabeza R. Visual recognition memory of scenes is driven by categorical, not sensory, visual representations. *J Neurosci*. 2024;44(21):e1479232024. doi:10.1523/JNEUROSCI.1479-23.2024.
- [76] Oltra-Cucarella J, Sánchez-SanSegundo M, Lipnicki DM, Crawford JD, Lipton RB, Katz MJ, et al. Visual memory tests enhance the identification of amnesic MCI cases at greater risk of Alzheimer's disease. *Int Psychogeriatr*. 2019;31(7):997-1006. doi:10.1017/S104161021800145X.
- [77] Squarzoni P, Faria DP, Yassuda MS, Porto FHG, Coutinho AM, Costa NAD, et al. Relationship between PET-assessed amyloid burden and visual and verbal episodic memory performance in elderly subjects. *J Alzheimers Dis*. 2020;78(1):229-244. doi:10.3233/JAD-200758.
- [78] Cecchini MA, Yassuda MS, Squarzoni P, Coutinho AM, de Paula FD, Duran FLS, et al. Deficits in short-term memory binding are detectable in individuals with brain amyloid deposition in the absence of overt neurodegeneration in the Alzheimer's disease continuum. *Brain Cogn*. 2021;152:105749. doi:10.1016/j.bandc.2021.105749.
- [79] Meyer SRA, Boelaarts L, Lindeboom J, De Jonghe JFM, Ponds R. Episodic recognition memory based on incidental learning of visual associations is largely preserved compared to recall in amnesic mild cognitive impairment and mild Alzheimer's disease. *Appl Neuropsychol Adult*. 2022;29(1):23-31. doi:10.1080/23279095.2019.1703705.

- [80] Meyer SRA, De Jonghe JFM, Schmand B, Ponds RWHM. Visual associations to retrieve episodic memory across healthy elderly, mild cognitive impairment, and patients with Alzheimer's disease. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2019;26(3):447-462. doi:10.1080/13825585.2018.1475002.
- [81] Vidal KSM, Decleva D, Barboni MTS, Nagy BV, de Menezes PAH, Aher A, et al. The association between acquired color deficiency and PET imaging of neurodegeneration in mild cognitive impairment and Alzheimer disease. *Invest Ophthalmol Vis Sci*. 2022;63(5):20. doi:10.1167/iov.63.5.20.
- [82] Ritchie K, Carrière I, Su L, O'Brien JT, Lovestone S, Wells K, et al. The midlife cognitive profiles of adults at high risk of late-onset Alzheimer's disease: the PREVENT study. *Alzheimers Dement*. 2017;13(10):1089-1097. doi:10.1016/j.jalz.2017.02.008.
- [83] Skowbo D, Gentry T, Timney B, Morant RB. The McCollough effect: influence of several kinds of visual stimulation on decay rate. *Percept Psychophys*. 1974;16(1):47-49. doi:10.3758/BF03203248.
- [84] Humphrey GK, James TW, Gati JS, Menon RS, Goodale MA. Perception of the McCollough effect correlates with activity in extrastriate cortex: a functional magnetic resonance imaging study. *Psychol Sci*. 1999;10(5):444-448. doi:10.1111/1467-9280.00184.
- [85] Grossberg S, Hwang S, Mingolla E. Thalamocortical dynamics of the McCollough effect: boundary-surface alignment through perceptual learning. *Vision Res*. 2002;42(10):1259-1286. doi:10.1016/S0042-6989(02)00055-X.
- [86] Vul E, MacLeod DIA. Contingent aftereffects distinguish conscious and preconscious color processing. *Nat Neurosci*. 2006;9(7):873-874. doi:10.1038/nn1723.
- [87] Humphrey GK, Goodale MA. Probing unconscious visual processing with the McCollough effect. *Conscious Cogn*. 1998;7(3):494-519. doi:10.1006/ccog.1998.0369.
- [88] Marino BFM, Borghi AM, Gemmi L, Cacciari C, Riggio L. Neural adaptation effects in conceptual processing. *Behav Sci (Basel)*. 2015;5(3):353-371. doi:10.3390/bs5030353.
- [89] Porter G, Wattam-Bell J, Bayer A, Haworth J, Braddick O, Atkinson J, et al. Different trajectories of decline for global form and global motion processing in aging, mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging*. 2017;56:17-24. doi:10.1016/j.neurobiolaging.2017.03.004.

- [90] Wu SZ, Masurkar AV, Balcer LJ. Afferent and efferent visual markers of Alzheimer's disease: a review and update in early stage disease. *Front Aging Neurosci.* 2020;12:572337. doi:10.3389/fnagi.2020.572337.
- [91] Ren P, Anderson AJ, McDermott K, Baran TM, Lin F. Cognitive fatigue and cortical-striatal network in old age. *Aging (Albany NY).* 2019;11(8):2312-2326. doi:10.18632/aging.101915.
- [92] Yassa MA, Verduzco G, Cristinzio C, Bassett SS. Altered fMRI activation during mental rotation in those at genetic risk for Alzheimer disease. *Neurology.* 2008;70(20):1898-1904. doi:10.1212/01.wnl.0000312288.45119.d1.
- [93] Wei W, Chen C, Dong Q, Zhou X. Sex differences in gray matter volume of the right anterior hippocampus explain sex differences in three-dimensional mental rotation. *Front Hum Neurosci.* 2016;10:580. doi:10.3389/fnhum.2016.00580.
- [94] Eckerström C, Svensson J, Kettunen P, Jonsson M, Eckerström M. Evaluation of the ATN model in a longitudinal memory clinic sample with different underlying disorders. *Alzheimers Dement (Amst).* 2021;13(1):e12031. doi:10.1002/dad2.12031.
- [95] Herrera-Guzmán I, Peña-Casanova J, Lara JP, Gudayol-Ferré E, Böhm P. Influence of age, sex, and education on the Visual Object and Space Perception Battery (VOSP) in a healthy normal elderly population. *Clin Neuropsychol.* 2004;18(3):385-394. doi:10.1080/1385404049052421.
- [96] Tsao DY, Vanduffel W, Sasaki Y, Fize D, Knutsen TA, Mandeville JB, et al. Stereopsis activates V3A and caudal intraparietal areas in macaques and humans. *Neuron.* 2003;39(3):555-568. doi:10.1016/S0896-6273(03)00459-8.
- [97] North C, Desai R, Saunders R, Suárez-González A, Bamiou D, Costafreda SG, et al. Neuropsychological deficits in Posterior Cortical Atrophy and typical Alzheimer's disease: a meta-analytic review. *Cortex.* 2021;143:223-236. doi:10.1016/j.cortex.2021.07.011.
- [98] Declewa D, Vidal KS, Kreuz AC, de Menezes PAHL, Ventura DF. Alterations of color vision and pupillary light responses in age-related macular degeneration. *Front Aging Neurosci.* 2023;14:933453. doi:10.3389/fnagi.2022.933453.
- [99] Duque-Chica GL, Gracitelli CPB, Moura ALA, Nagy BV, Vidal KS, Paranhos A Jr, et al. Inner and outer retinal contributions to pupillary light response: correlation to functional and morphologic parameters in glaucoma. *J Glaucoma.* 2018;27(8):723-732. doi:10.1097/IJG.0000000000001003.
- [100] Feitosa-Santana C, Oiwa NN, Paramei GV, Bimler D, Costa MF, Lago M, et al. Color space distortions in patients with type 2 diabetes mellitus. *Vis Neurosci.* 2006;23(3-4):663-668. doi:10.1017/S0952523806233546.

- [101] Gella L, Raman R, Kulothungan V, Pal SS, Ganesan S, Srinivasan S, et al. Color vision abnormalities in type II diabetes: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study II report no 2. *Indian J Ophthalmol.* 2017;65(10):989-994. doi:10.4103/ijo.IJO_601_16.

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Color memory as a diagnostic test for mild cognitive impairment and early stage of Alzheimer's disease

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Background: Color vision and memory are potential markers of Alzheimer's disease (AD); however, information regarding their changes in early AD remains limited.

Objective: The aim of this study was to evaluate color recognition memory in mild cognitive impairment (MCI), early Alzheimer's disease (AD), and older adults with normal cognition, as well as to assess its diagnostic properties.

Methods: We included 27 participants with mild dementia (MD), 25 with MCI, and 25 older adults with normal cognition who served as the control group (CG). Participants completed the Mini-Mental Status Examination (MMSE), the Clinical Dementia Rating (CDR), and the Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13) for cognitive assessment; delayed word recall (after 30 min), the Ishihara test, and a color recognition memory test were also administered. The color recognition memory test was performed using a basic 12-color kit displayed on a computer screen. Color recognition was evaluated after 5 and 30 min using four initial stimuli and four new colors from the 12-color kit. Participants were required to recognize which of the eight randomly presented colors they had previously seen.

Results: Significant differences were observed in the total error scores for color recognition memory among the three groups. Medians (interquartile range) for CG, MCI, and MD groups were 2 (2), 4 (2), and 5 (3) respectively. A Kruskal-Wallis test returned a significant p -value ($p < 0.001$); *post-hoc* analysis of group pairs was then conducted for CG and MCI ($p < 0.001$), MCI and MD ($p = 0.007$), and CG and MD ($p < 0.001$). Using demographic information and ADAS-Cog 13 scores as predictors, a multinomial logistic regression model accurately categorized 77.9% of cases (96% of CG, 64% of MCI, and 74.1% of MD cases). Adding the color memory total error score to the model improved accuracy to 84.4% (100% of CG, 76% of MCI, and 77.8% of MD cases).

Conclusion: Color recognition memory test results differed significantly between participants with normal cognition and those with MCI and early AD. Therefore, it may help in the early diagnosis of AD as a simple, non-invasive diagnostic marker.

KEYWORDS

Alzheimer's disease, color memory, color recognition memory, color vision, mild cognitive impairment

1 Introduction

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60–80% of cases, and causes progressive neurodegeneration and cognitive decline (1, 2). According to data from the Framingham Heart Study, the lifetime risk of Alzheimer's dementia at age 45 is 20% for women and 10% for men, indicating that 1 in 5 women and 1 in 10 men of this age could eventually develop AD (3). Nonetheless, according to estimates from the Alzheimer's Disease International, approximately 75% of individuals with dementia worldwide remain undiagnosed, and as many as 85% do not receive post-diagnostic support services (4).

Recent discoveries of disease-modifying treatments have been associated with a growing need to develop tools for detection of AD at the earliest clinically determinable stage. However, an audit of memory services in England revealed that less than 2% of patients underwent molecular confirmation of their disease using cerebrospinal fluid biomarkers (5). Moreover, the 2024 Alzheimer's disease International report found that over 90% of caregivers and respondents from the public were more inclined to seek a diagnosis if a treatment that could modify the course of the disease was accessible (6). The lack of a valid and reliable cognitive test with minimal influence from language differences which is comparable across multinational and multilingual populations is a concern, and using digital language-neutral cognitive evaluations is encouraged (4).

Visual alterations emerge early in the progression of AD and may serve as potential noninvasive markers of AD-related neurodegeneration (7). AD-related neuropathological lesions have been identified throughout the visual system, including the retina, resulting in various signs and symptoms (7–9). Visual issues reported in AD include abnormalities in contrast sensitivity, visual field deficits, abnormalities in eye movements related to fixation and saccades, and abnormalities in visual functions which lead to impaired reading ability, challenges in recognizing objects and shapes, and locating items in one's environment (7–11). Furthermore, the progression from normal cognitive function to mild cognitive impairment (MCI) is linked to decreased visual acuity, suggesting that the impact of vision impairment is greatest during the early stages of cognitive decline (12). According to recent studies, worsening contrast sensitivity over time is associated with a higher likelihood of incident dementia (13). Visual recognition memory impairment also occurs early in the course of MCI (14). One of the 10 signs of AD in the 2024 Alzheimer's Association Report was difficulty in understanding visual images and spatial relationships. As a result, patients with AD experience difficulties in estimating distances and perceiving colors and contrasts, which can lead to challenges while driving (2). Color vision and memory are potential markers as well; however, these visual functions are not usually analyzed. Thus, information about their association with the degree of cognitive impairment remains limited.

Cholinergic loss is one of the most prominent components of AD neuropathology (15). The nucleus basalis of Meynert contains acetylcholine-producing neurons which are essential for regulating various aspects of visual perception (16). In the visual perception pathway, the ventral stream, which involves interactions among visual areas V1, V2, and V4, plays a crucial role in recognizing and identifying shapes and colors. This pathway projects to regions of the inferior and medial temporal lobe, the latter of which is responsible for encoding long-term memories (17). Therefore, impairment of

color perception and memory may be promising as potential non-invasive functional markers of early AD.

Recent studies provide growing evidence that color perception can aid in distinguishing AD from other forms of dementia (18–20). Usually, only one aspect of visual perception is analyzed, such as color vision or color discrimination, with limited information regarding color memory, color recognition, and long-term memory retention in AD. This could be because color vision and memory assessments are challenging to incorporate into clinical practice due to the complexity of evaluating responses, and the tools required. Using the Ishihara test, Arnaoutoglou et al. concluded that color perception differentiates AD from vascular dementia (18). The color recognition tasks require information about the color hue that was seen, and its comparison with the hue that was presented. This leads to widespread cortical activation (21). The impairment of cortical activation may represent early changes in AD (15, 20).

This study aimed to examine color recognition memory in patients with early AD and cognitively normal older adults, as well as to evaluate its potential as a diagnostic tool. We hypothesized that the ability to recognize colors is compromised in MCI and early AD, which could effectively distinguish participants with AD from those who were cognitively healthy.

2 Materials and methods

2.1 Participants

The study included three groups; 27 subjects diagnosed with mild dementia due to Alzheimer's disease (MD), 25 subjects with amnesic mild cognitive impairment (MCI), and 25 cognitively healthy older adults who served as the control group (CG).

Participants diagnosed with MD met the criteria for probable AD as outlined by the National Institute on Aging and Alzheimer's Association (NIA/AA) (22) and scored 1 on the Clinical Dementia Rating Total Score (CDR-TS). Subjects in the MCI group met the NIA/AA criteria for clinical MCI attributed to AD (23), and scored a CDR-TS of 0.5. Cognitively healthy older adults in the CG exhibited no cognitive complaints, scored 0 on the CDR-TS and displayed no signs of neurological disorders.

Participants were recruited from the Memory Clinic at Vilnius University Hospital, Santaros Klinikos. Using established criteria, a specialist in cognitive neurology determined a probable AD diagnosis, which was validated by the observed progression of cognitive deterioration indicative of an ongoing pathological process (22). For a subset of patients with AD (6/27, or 22%), medical records contained information about positive AD cerebrospinal fluid (CSF) biomarker status, which confirmed the AD diagnosis according to the 2018 NIA-AA (National Institute on Aging and Alzheimer's Association) (NIA-AA) research framework (24). MCI due to AD was identified by implementing clinical and cognitive criteria, and the underlying cause of MCI was found to align with the AD pathophysiological process (23). This diagnostic approach involved excluding vascular, traumatic, and medical factors contributing to cognitive decline and documenting progressive cognitive deterioration over time (23). Biomarker analysis suggested a moderate probability that participants' MCI was linked to AD, as structural magnetic resonance imaging (MRI) exhibited indications of neuronal damage. For a subset of

patients with MCI (7/25, or 28%), medical records contained information about positive AD CSF biomarker status, confirming the AD diagnosis (24). Due to the exploratory nature of our study, CSF biomarker analysis was not performed within the framework of this study.

This study excluded individuals with neurological conditions affecting the central nervous system (except for MCI and MD); cerebrovascular disorders (indicated by a Hachinski Ischemic Score of 4 or higher); prior head injury; major psychiatric conditions (e.g., schizophrenia, delirium, psychosis, or depression with a Geriatric Depression Scale score exceeding 9); vision and hearing disorders impairing cognitive testing; known color vision impairment from a young age; significant ophthalmologic conditions (glaucoma, cataract, diabetic retinopathy, age-related macular degeneration); diagnosed or symptomatic significant cardiovascular, hepatic, or metabolic disorders; substance abuse; and use of psychotropic drugs. The study adhered to the 1975 Helsinki Declaration guidelines and was approved by the Vilnius Regional Bioethics Committee (Approval Number 2022/1-1405-877). All study participants provided informed consent in writing prior to their involvement in the research.

2.2 Assessments of cognitive function and color vision

The Mini-Mental State Examination (MMSE) was used to assess overall cognitive function. For a more comprehensive cognitive evaluation, participants completed the 13-item version of the Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13). This assessment encompasses various cognitive domains, including word recall after 5 minutes, commands, constructional praxis, delayed word recall, naming, ideational praxis, orientation, word recognition, remembering test instructions, comprehension of spoken language, word-finding difficulty, spoken language ability, and number cancellation. The ADAS-Cog 13 employs a scoring system ranging from 0 to 85, with higher scores indicating impaired cognitive function. The Clinical Dementia Rating Sum of Boxes (CDR-SB) scale was used to assess the extent of cognitive decline and functional impairment. Color vision was assessed using a paper-based version of the Ishihara test. Plates 1–15 from the 2021 edition of the 24-plate Ishihara test were presented and the number of errors was recorded. According to the test instructions, plates 1–15 determine the normality of color vision. Color vision was considered normal if 13 or more plates were read correctly (two or fewer errors).

2.3 Assessment of color recognition memory

Color recognition memory was evaluated using a 12-color kit displayed on a computer screen. The personal computer monitor parameters were set to factory default. The computer monitor was warmed for at least 30 min and the target luminance value was 120 cd/m² (for a moderately lit room). Monitor parameters were checked using simple visual/eye-based monitor calibration images from Lagom LCD test, and a color recognition task was developed using the Microsoft PowerPoint. The color memory recognition task was divided into three parts: stimulus presentation and delayed recognition

after 5 and 30 min. Four initial stimulus colors were randomly selected and presented on a grid background for 5 s each, with an interstimulus interval of 5 s to reduce the impact of the color's after-effect. Participants were instructed to memorize the colors since they would be asked to identify the ones that they had seen. Hues were selected using the RGB (red-green-blue) color model, which is commonly used to represent and display images on electronic systems (such as computers). In this model, the red, green, and blue colors are combined in various proportions to produce other colors. Each pair of colors in the RGB scale differed by at least 64 units in the red, green, or blue range (0–255). The 12 colors used were categorized using basic color names: red, green, blue, yellow, orange, brown, pink, violet, black, white, gray, and light blue (separate categorical names in some languages like Lithuanian, Greek, Italian, and Russian). The RGB values were as follows: red (255, 0, 0), green (0, 255, 0), blue (0, 0, 255), yellow (255, 255, 0), orange (255, 128, 0), brown (128, 64, 0), pink (255, 125, 192), violet (192, 0, 255), light blue (128, 192, 255), black (0, 0, 0), white (255, 255, 255), and gray (128, 128, 128). The participants were not asked to name the colors, but to memorize them for later identification.

In the delayed recognition task, 5 min after stimulus presentation, participants were required to recognize which of the eight randomly presented colors (four initial stimulus colors and four randomly selected colors from the 12-color kit) they had previously seen.

After 30 min, participants were asked to identify which of the eight presented colors they had previously seen (four initial stimulus colors and four new colors from the 12-color kit that had not been used in the previous delayed recognition task) (Figure 1).

2.4 Data analysis

Statistical analysis was performed using the IBM SPSS Statistics version 26.0. To establish adequate study power, we calculated the required number of subjects using G_Power for Windows version 3.1. Power (1-beta) was set at 0.85, the level of significance at the level of $p < 0.05$, one-way, and the effect size was set at 0.4, as expected to find large effect sizes (f). The Kruskal–Wallis test required a minimum of 72 participants. The Shapiro–Wilk test was used to assess data normality. Differences in demographic and clinical data, as well as test results among groups, were examined using Kruskal–Wallis or chi-square tests. In addition, verbal memory performance was assessed by the total medians (IQR) of the error score of words not recalled out of 10 after 5 and 30 min between these groups. Furthermore, the color recognition error scores medians (IQR) after 5 and 30 min for the CG, MCI, and MD were evaluated. Correlations of the total error scores for color memory with cognitive test results and demographic data were calculated using Spearman's rank correlation coefficient. Multiple linear regression models adjusted for age, education, sex, Ishihara test, and cognitive test scores (MMSE, ADAS-Cog-13, and CDR-SB) as independent variables were used to determine whether these factors could significantly predict the total error scores observed in the color memory tasks. The diagnostic characteristics of color recognition memory were assessed and compared with those of verbal memory (based on the ADAS-Cog 13 delayed word recall after 5 and 30 min). The cut-off scores for the total error score of the color memory task were established as indicative of pathology (MCI and MD), MCI, and MD. To examine the association

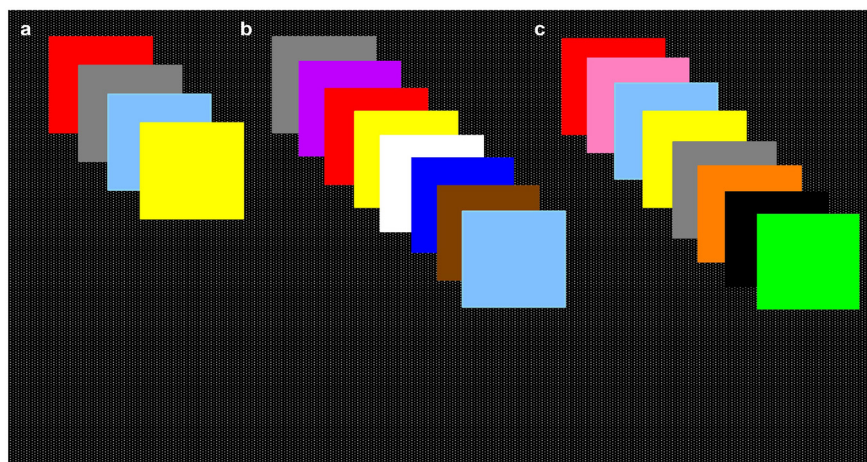


FIGURE 1

Color recognition memory task, stimuli colors. (a) Four initial stimulus colors were randomly selected and displayed on the computer screen for 5 s, each with an inter-stimulus interval of 5 s. Color memory was evaluated by color recognition after 5 and 30 min using the four initial stimuli and four new colors from kits (b,c).

between the independent variables and their classification into three groups, a multinomial logistic regression analysis was conducted. Initially, a model was developed using age, education, sex, and ADAS-Cog 13 score as predictor variables. Second, word recall after 30 min was incorporated into the model. Finally, color recognition after 30 min was added to the initial model. The fit of the model to the data while adding predictor variables and the classification accuracies of the models were calculated. A p -value of 0.05 was set as a baseline of statistical significance and adjusted for multiple comparisons using Bonferroni correction.

3 Results

3.1 Demographic and clinical characteristics

The distribution of sexes was comparable across all three groups, with no statistically significant differences observed (chi-square test, $p > 0.05$). Similarly, the Kruskal–Wallis test revealed no significant differences in educational background, age, Geriatric Depression Scale scores (indicating depressive symptoms), or Hachinski ischemic scores among the groups ($p > 0.05$). The demographic and clinical characteristics of the patients are presented in Table 1.

The Kruskal–Wallis test indicated significant differences in cognitive tests performance across the three groups ($p < 0.05$), as confirmed by the *post-hoc* analysis.

The medians (interquartile ranges [IQR]) of the Ishihara test results (number of errors in 15 plates) for the CG, MCI, and MD groups were 0 (0), 0 (1), 1 (3) respectively; the Kruskal–Wallis test indicated a significant difference ($H[2] = 12.27$, $p = 0.002$). *Post-hoc* analysis also

showed significant differences between MD and CG ($p < 0.001$). However, no significant differences were observed between the CG and MCI, or the MCI and MD groups ($p > 0.05$). Detailed results of the cognitive assessment and color vision are presented in Table 2.

Verbal memory performance was assessed by the number of words not recalled out of 10 after 5 and 30 min. The total medians (IQR) of the error score of words not recalled for the CG, MCI, and MD groups are 9 (3), 15 (5), and 16.67 (2.165) respectively. The Kruskal–Wallis test indicated a statistically significant difference ($H[2] = 36.18$, $p < 0.001$). *Post hoc* analysis revealed significant differences among the three groups ($p < 0.001$). Medians (IQR) of verbal memory errors after 5 min for the three groups were 4 (1.34) for CG, 6 (1.67) for MCI, and 7 (1.5) for MD. The Kruskal–Wallis test indicated a statistically significant difference ($H[2] = 29.32$, $p < 0.001$). *Post hoc* analysis revealed significant differences among the three groups ($p < 0.001$). Medians (IQR) of verbal memory errors after 30 min were 5 (2), 9 (4), and 10 (0) for the CG, MCI, and MD groups, respectively. The Kruskal–Wallis test indicated a statistically significant difference ($H[2] = 36.13$, $p < 0.001$). *Post hoc* analysis revealed significant differences among the three groups ($p < 0.001$).

3.2 Color recognition memory

Medians (IQR) of the color recognition total error scores for CG, MCI and MD were 2 (2), 4 (2), and 5 (3) respectively; the Kruskal–Wallis test indicated a significant difference ($H[2] = 34.36$, $p < 0.001$). *Post-hoc* analysis revealed statistically significant differences between CG and MCI ($p < 0.001$), MCI and MD ($p = 0.007$), and CG and MD ($p < 0.001$). Total error score for each color in three groups is provided in Supplementary Table 1.

TABLE 1 Demographic and clinical characteristics of the participants.

	CG (N = 25)	MCI (N = 25)	MD (N = 27)	Statistics ($\chi^2(2)/H(2)$, p)
Male (%) *	13 (52%)	7 (28%)	10 (37%)	3.09, 0.21
Years of education *	16 (2)	15 (4)	15 (3)	4.06, 0.132
Age *	73 (9)	75 (11)	77 (9)	4.39, 0.111
GDS *	4 (2)	4 (1.5)	4 (2)	1.58, 0.453
HIS *	1 (1)	1 (1)	1 (1)	2.04, 0.36

Unless otherwise indicated, data are expressed as the median along with the interquartile range. * Groups did not differ significantly. MD, mild dementia; MCI, mild cognitive impairment; CG, control group; GDS, Geriatric Depression Scale; HIS, Hachinski Ischemic Score.

TABLE 2 Cognitive tests and color vision results of the participants.

	CG (N = 25)	MCI (N = 25)	MD (N = 27)	Statistics (H(2), p)
MMSE *	29 (1)	25 (2)	22 (2)	68.45, <0.001
ADAS-Cog 13 *	12 (5.5)	22 (7.66)	31 (7.67)	51.4, <0.001
CDR Sum of Boxes *	0 (0)	1.5 (0.8)	4.5 (0.5)	70.63, <0.001
Ishihara test **	0 (0)	0 (1)	1 (3)	12.27, 0.002

The data are expressed as the median along with the interquartile range. * There were significant differences among the three groups. ** There was significant difference only between MD and CG. MD, mild dementia; MCI, mild cognitive impairment; CG, control group.

Color memory task scores after 5 min were evaluated across the three groups, and the medians (IQR) were found to be 0 (2), 1 (2), and 3 (2) for CG, MCI, and MD respectively; Kruskal–Wallis $H(2) = 31.11$, $p < 0.001$; *post-hoc* examination revealed statistically significant differences between the groups: CG vs. MCI, $p = 0.002$; MCI vs. MD, $p = 0.002$; CG vs. MD, $p < 0.001$.

Color memory task scores after 30 min were evaluated across the three groups, and the medians (IQR) for CG, MCI and MD were 1 (2), 2 (2), and 3 (1) respectively; Kruskal–Wallis $H(2) = 34.36$, $p < 0.001$; *post-hoc* analysis revealed significant differences between the two groups: CG vs. MCI, $p = 0.001$; CG vs. MD, $p < 0.001$, but no significant differences were observed between MCI and MD, $p = 0.15$.

Among all participants, the total error scores for color memory were strongly correlated with the MMSE results (Spearman's rho: -0.647 ; $p < 0.001$) and moderately correlated with CDR-SB (Spearman's rho: 0.593 ; $p < 0.001$), ADAS-Cog 13 (Spearman's rho: 0.568 ; $p < 0.001$), and verbal memory (Spearman's rho: 0.492 ; $p < 0.001$).

When examining separate groups, no notable associations were found between the performance on color memory tasks and cognitive test scores, participant age, or education.

The multiple linear regression showed statistical significance in the adjusted model with MMSE ($R^2 = 0.378$, $F = 10.23$, $\beta = -0.668$, $p < 0.001$), ADAS-Cog 13 ($R^2 = 0.274$, $F = 6.74$, $\beta = 0.588$, $p < 0.001$), and CDR-SB ($R^2 = 0.324$, $F = 8.3$, $\beta = 0.616$, $p < 0.001$).

In all of the models, color memory scores were not significantly influenced by other variables such as age, sex, education level, and Ishihara test results ($p > 0.05$).

3.3 Diagnostic characteristics of color recognition memory in comparison with verbal memory

To differentiate between CG and AD (MCI or MD) using color and verbal memory error scores, an analysis using the receiver

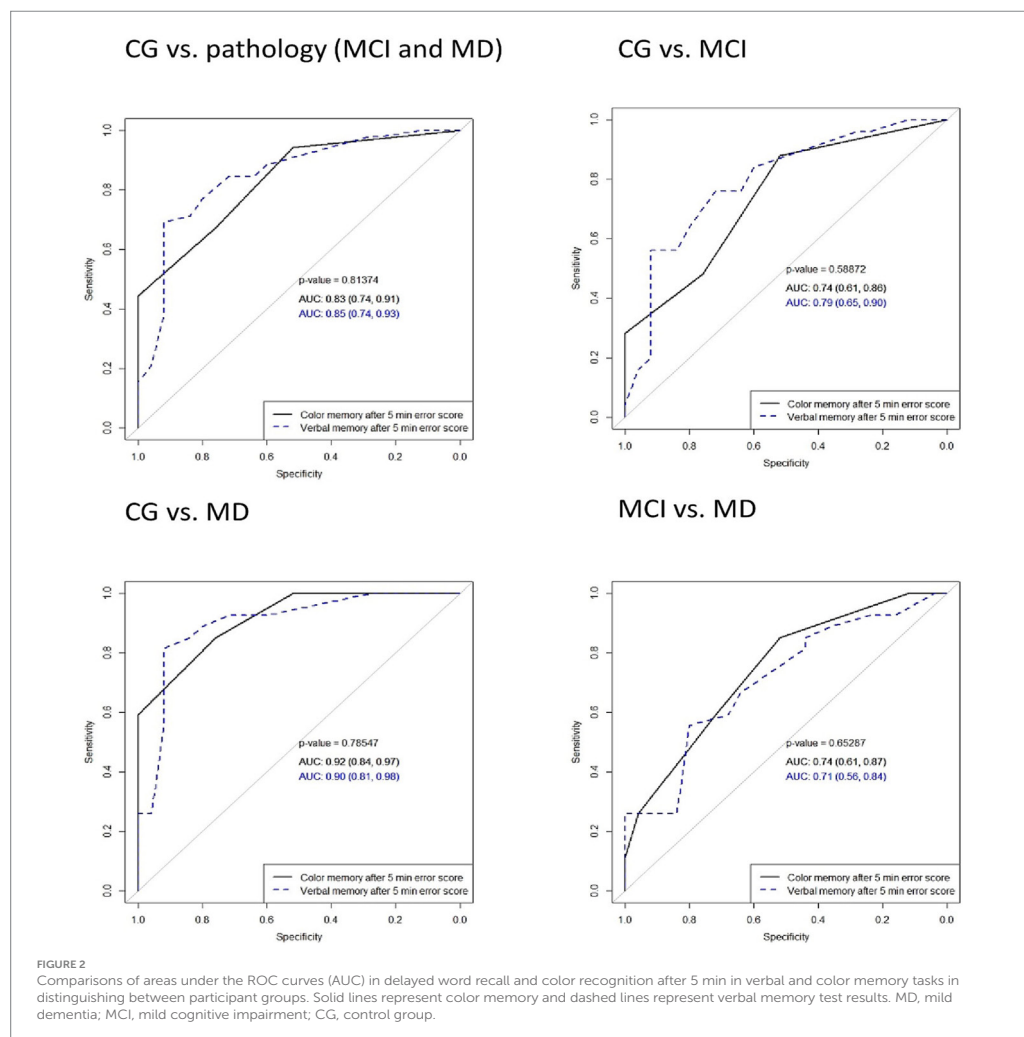
operating characteristic curves (ROC) was conducted. ROC curves of delayed word recall and color recognition after 5 and 30 min, as well as the total error score, showed no significant differences between verbal and color memory tasks in distinguishing the participant groups. The total error score for both tasks demonstrated robust diagnostic properties in differentiating CG from pathology (MCI and MD), with an identical AUC of 0.88. In distinguishing the CG from the MCI, the total error scores in color and verbal memory tasks achieved AUCs of 0.81 and 0.8, respectively. The ROC curves of delayed word recall after 5 min and 30 min, total score of recall (count of words not recalled), delayed color recognition after 5 min and 30 min, and total color memory error score with comparisons among all groups are presented in Figures 2–4.

To distinguish participants with AD (MCI or MD) from CG, a cut-off score of ≥ 3 errors in total error score of color memory task was established as indicative of AD. A cut-off score of ≥ 6 errors was established to differentiate patients with MD from those with MCI (with a score of 6 or above considered to be indicative of MD). The diagnostic properties of these thresholds were evaluated and the data are presented in Table 3.

To examine the association between the independent variables and classification into the three groups, a multinomial logistic regression analysis was conducted.

Initially, a model was developed using age, education, sex, and ADAS-Cog 13 score as predictor variables. Adding predictor variables enhanced the model's fit to the data, improving upon the initial model that contained only the intercept ($X^2 = 85.881$, $p < 0.001$; Nagelkerke $R^2 = 0.756$). The overall percentage of accurately categorized cases using this model was 77.9% (96% CG, 64% MCI, and 74.1% MD cases correctly categorized), with ADAS-Cog 13 score being the strongest and most significant predictor ($X^2 = 76.074$, $p < 0.001$).

When word recall after 30 min was incorporated into this model, the expanded model's diagnostic accuracy remained similar, and word recall after 30 min was not a significant predictor ($X^2 = 85.86$, $p < 0.001$; Nagelkerke $R^2 = 0.777$). ADAS-Cog 13 score remained a significant predictor ($X^2 = 39.29$, $p < 0.001$). The overall percentage of



cases that were accurately categorized using this model was 75.3% (92% CG, 64% MCI, and 74.1% MD cases).

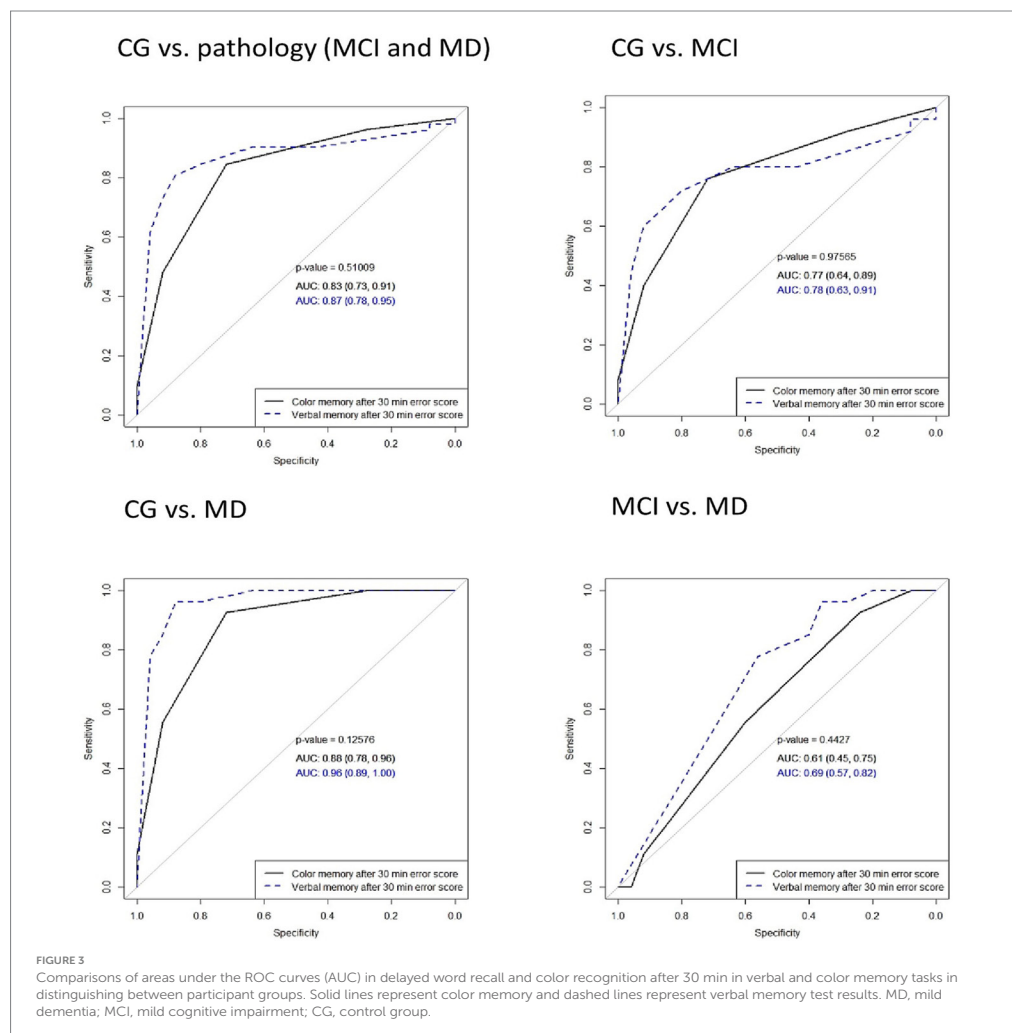
Furthermore, color recognition after 30 min was added to the initial model, and the expanded model showed a significant improvement in fit over a null model ($\chi^2 = 101.23$, $p < 0.001$; Nagelkerke $R^2 = 0.823$). This model accurately categorized 83.1% of the cases (96% CG, 72% MCI, and 81.5% MD cases were correctly classified). Both ADAS-Cog 13 and color recognition after 30 min were significant predictors, with χ^2 values of 62.47 and 15.35, respectively, ($p < 0.001$).

Finally, when the color memory total error scores were added to the initial model, the expanded model (including age, education, sex, ADAS-Cog 13 scores, and color memory total error scores) also

showed a significant improvement in fit over a null model ($\chi^2 = 117.176$, $p < 0.001$; Nagelkerke $R^2 = 0.880$). This model accurately categorized 84.4% of the cases (100% CG, 76% MCI, and 77.8% MD cases). Both ADAS-Cog 13 and color memory scores were strong and significant predictors, with χ^2 values of 63.88 and 31.30, respectively, ($p < 0.001$).

4 Discussion

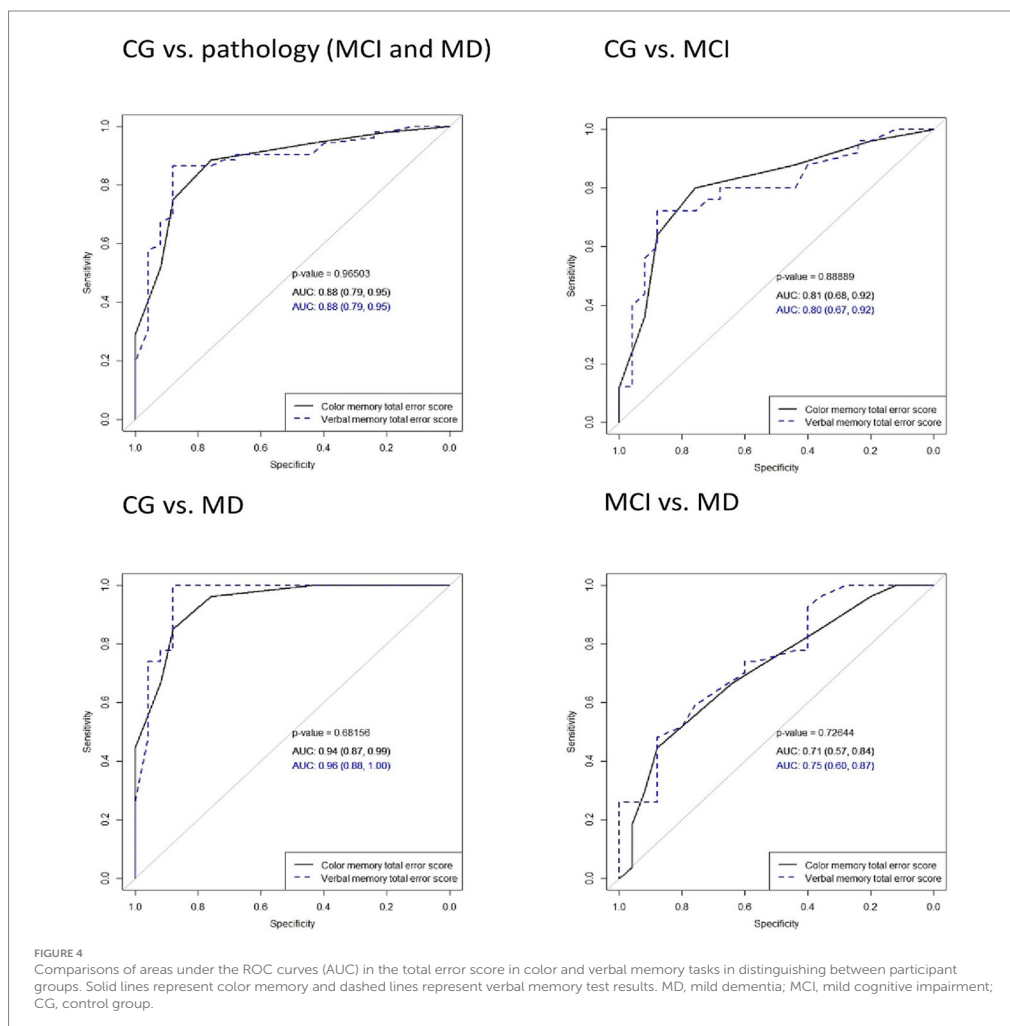
Our findings revealed that color recognition memory is impaired in the early stages of AD and is more pronounced in the mild dementia stages. Consistent with previous studies, visual perceptual dysfunction



is considered an early indication of MCI due to AD and the progression to AD, and the aspects that showed diagnostic potential were perception or memory of figure or structure (7, 25, 26).

In this study, significant differences in color recognition memory were observed between the CG and the MCI group, emphasizing the usefulness of color memory evaluation in the early stages of AD. The color recognition task is a memory task that relies on hippocampus integrity, a region known to be implicated in AD (27). The ventral stream of the visual perception pathway is responsible for color identification and recognition (17). According to recent studies, better visual recognition is associated with the memory of the categorical

features of a visual scene aiding in discriminating between targets and lures. During a visual recognition task, activation with categorical representations in the precuneus, inferior temporal cortex, and superior occipital cortex improved scene memory (28). Relying solely on verbal memory tasks to evaluate cognitive function may lead to the overlooking of visual memory deficits. Incorporating visual memory tasks for cognitive evaluations may be useful in improving the diagnostic process. Oltra-Cucarella et al. emphasized that although verbal amnesic MCI was the most prevalent form, a substantial number of participants exhibited either visual-only amnesic MCI or a combination of visual and verbal amnesic MCI. The likelihood of



developing AD was equivalent in individuals with visual amnesic or verbal amnesic MCI alone, and higher in those with combined amnesic MCI (29). Squarzone et al. concluded that visual compared to verbal episodic memory scores correlated most significantly with the presence of amyloid- β , as measured by positron emission tomography scans (30). As reported by Cecchini et al., the short-term memory binding test, which evaluates the capacity to retain the integration of surface features such as shapes and colors, has shown sensitivity to indicators of AD pathology and may function as a cognitive marker within the AD continuum (31). Contrary to our study findings, Meyer et al. concluded that episodic recognition memory, based on the incidental learning of visual associations, is

largely preserved in comparison with recall in cases of amnesic MCI and mild AD (32, 33). The stimuli utilized in this study comprised 24 line drawings, indicating that our research may provide novel insights into the similarity between color recognition memory and verbal recall memory in early AD, and that color recognition memory may be more impaired than object recognition memory. Our findings underscore the necessity of incorporating both verbal and visual memory evaluations into neuropsychological examinations to identify amnesic MCI with greater precision.

The color recognition task scores demonstrated a significant and strong correlation with the MMSE results, and a moderate correlation with the ADAS-Cog 13 and CDR-SB scores. A linear regression analysis

TABLE 3 Diagnostic properties of the total error score color memory task in differentiating between participants with AD and CG.

	CG vs. pathology (MCI and MD), cut-off ≥3 errors	CG vs. MCI, cut-off ≥3 errors	CG vs. MD, cut-off ≥3 errors	MCI vs. MD, cut-off ≥ 6 errors
Sensitivity	88.46% (76.56–95.65%)	80% (59.30–93.17%)	96.3% (81.03–99.91%)	44.44% (25.48–64.67%)
Specificity	76% (54.87–90.64%)	76% (54.87–90.64%)	76% (54.87–90.64%)	88% (68.78–97.45%)
Negative predictive value	76% (59.11–87.40%)	79.17% (62.73–89.56%)	95% (73.27–99.25%)	59.46% (50.4–67.92%)
Positive predictive value	88.46% (79.12–93.94%)	76.92% (61.76–87.31%)	81.25% (68.24–89.73%)	80% (56.07–92.61%)
Overall diagnostic accuracy	84.42% (74.36–91.68%)	78% (64.04–88.47%)	86.54% (74.21–94.41%)	65.38% (50.91–78.03%)

Data are presented as percentage and 95% confidence interval. MD, mild dementia; MCI, mild cognitive impairment; CG, control group.

significantly predicted the total error scores for color memory using these three tests. Factors such as age, sex, and education did not have a substantial impact on color memory scores. These results confirm that color memory impairment is associated with the pathological processes of AD rather than other factors known to influence visual perception such as age (7–10). This study also supports the finding that AD-related neuropathological lesions described from the retina to all parts of the visual system affect visual function (7–9).

Recent studies have used color discrimination tasks to differentiate AD from other dementias (18–20). Unger et al. used a color vision task (Farnsworth D-15 color vision test) to distinguish AD from dementia with Lewy bodies, and found that color vision impairment could be utilized as a diagnostic tool to differentiate dementia with Lewy bodies from AD. However, a significant proportion (20%) of patients with AD have color vision impairment. Furthermore, lower cognitive test scores and visuospatial or executive function subscores were associated with color vision impairment in patients with dementia and Lewy bodies, suggesting that this impairment is more closely related to cognitive decline in the later stages of the disease (20). Our study's findings indicate that the Ishihara color vision test results revealed significant differences between the MD and CG groups. However, no significant differences were detected between the CG and MCI groups or between the MCI and MD groups. These results suggest that alterations in color vision may be attributed to progressive neurodegeneration (34).

Research on the diagnostic potential of color memory tests remains limited because evaluations of color vision and memory are infrequent. This study revealed that the color recognition memory task effectively distinguished participants with early AD from cognitively normal older adults (AUC = 0.88) and those with prodromal AD from cognitively normal older adults (AUC = 0.81). Additionally, the incorporation of color memory scores into multinomial logistic regression models resulted in a notable improvement in overall classification accuracy. This enhancement led to an increase in the three-group classification accuracy from 77.9 to 84.4%, representing a 6.5% improvement. Notably, the precise identification of MCI showed considerable improvement, increasing from 64 to 76%, representing a 12% enhancement in precision. Identifying MCI is particularly difficult in primary care settings. According to the 2024 World Alzheimer Report (4, 6), approximately 80% of the population, and more concerning, 65% of medical professionals erroneously perceive dementia as a normal part of aging. This misconception can delay early detection and timely access to necessary treatment and assistance (5). Color memory testing may be beneficial in enhancing diagnostic accuracy, particularly when distinguishing between MCI due to AD from age-related changes.

Although the color memory task showed satisfactory diagnostic performance in differentiating participants with early AD from older adults with normal cognition, its ability to differentiate among MCI and mild dementia due to AD was suboptimal. One explanation for these results is that color memory impairment most likely occurs early in the disease course. These changes are evident even in the early stages of AD, thereby reducing their effectiveness in tracking disease progression. This finding aligns with that of Ritchie et al., who found that middle-aged individuals whose parents had been diagnosed with dementia showed lower than expected scores on visual memory tests, whereas their performance in verbal memory assessments remained normal (35).

This study has a few limitations. Firstly, our results were limited by the cross-sectional study design; future longitudinal studies are needed to assess the progression of color memory impairment during the course of AD. Secondly, cerebrospinal fluid biomarker analysis was conducted for a small proportion of participants with MCI and MD, and positron emission tomography scans were not performed. Incorporating these methods would have offered valuable insights into how changes in color memory relate to the accumulation of brain A β and the deterioration of neurons. Thirdly, the appearance of colors on a computer screen usually differs across devices due to variation in display settings. To minimize the effects of this limitation, we used distinct colors, each varying by approximately 25% in the red, blue, or green components of the RGB scale. It is well established that ocular conditions such as glaucoma, diabetic retinopathy, and macular degeneration can impact color vision even in their initial stages (36–39). Although all participants in this study had documented prior eye examinations, a recent ophthalmological assessment was not conducted. Consequently, it is not possible to ascertain whether the included patients had ophthalmological conditions that could introduce a selection bias at the time of recruitment. Finally, despite the observed significant differences, the small sample size may limit the generalizability of our findings. A larger sample size is necessary to confirm our findings.

In conclusion, the test results for color recognition memory showed significant differences between older adults with normal cognition and those with early AD, highlighting its potential in the early diagnosis of AD. Color memory testing has good diagnostic characteristics and can be an easy-to-execute, reliable, and noninvasive diagnostic test for early 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 humans were approved by Vilnius Regional Bioethics Committee (Approval Number 2022/1-1405-877). 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

VS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. EA: Data curation, Formal analysis, Investigation, Writing – review & editing. GP-K: Data curation, Investigation, Writing – review & editing. GK: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing.

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References

1. World Health Organization (2017). Global action plan on the public health response to dementia 2017–2025. Available online at: <https://www.who.int/publications/i/item/global-action-plan-on-the-public-health-response-to-dementia-2017---2025>, (Accessed December 2, 2024).
2. Alzheimer's Association Report. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement.* (2024) 20:3708–821. doi: 10.1002/alz.13809
3. Chêne G, Beiser A, Au R, Preis SR, Wolf PA, Dufouil C, et al. Gender and incidence of dementia in the Framingham heart study from mid-adult life. *Alzheimers Dement.* (2015) 11:310–20. doi: 10.1016/j.jalz.2013.10.005
4. Gauthier S, Rosa-Neto P, Morais JA, Webster C. World Alzheimer report 2021: Journey through the diagnosis of dementia. London, UK: Alzheimer's Disease International (2021).
5. Cook L, Souris H, Isaacs J. The 2019 national memory service audit. London: NHS London Clinical Networks (2019).
6. Evans-Lacko S, Aguzzi E, Read S, et al. World Alzheimer report 2024: Global changes in attitudes to dementia. London, UK: Alzheimer's Disease International (2024).
7. Chang LYL, Lowe J, Ardiles A, Lim J, Grey AC, Robertson K, et al. Alzheimer's disease in the human eye. Clinical tests that identify ocular and visual information processing deficit as biomarkers. *Alzheimers Dement.* (2014) 10:251–61. doi: 10.1016/j.jalz.2013.06.004
8. Iseri PK, Altınas O, Tokay T, Yüksel N. Relationship between cognitive impairment and retinal morphological and visual functional abnormalities in Alzheimer disease. *J Neuroophthalmol.* (2006) 26:18–24. doi: 10.1097/01.wno.0000204645.56873.26
9. Marquie M, Castilla-Martí M, Valero S, Martínez J, Sánchez D, Hernández I, et al. Visual impairment in aging and cognitive decline: experience in a memory clinic. *Sci Rep.* (2019) 9:8698. doi: 10.1038/s41598-019-45055-9
10. Pache M, Smeets CHW, Gasio PF, Savaskan E, Flammer J, Wirz-Justice A, et al. Colour vision deficiencies in Alzheimer's disease. *Age Ageing.* (2003) 32:422–6. doi: 10.1093/ageing/32.4.422
11. Alegret M, Boada-Rovira M, Vinyes-Junqué G, Valero S, Espinosa A, Hernández I, et al. Detection of visuospatial deficits in preclinical and mild Alzheimer's disease. *J Clin Exp Neuropsychol.* (2009) 31:860–7. doi: 10.1080/13803390802595568

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.

Generative AI statement

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2025.1589335/full#supplementary-material>

12. Ehrlich JR, Swenor BK, Zhou Y, Langa KM. The longitudinal association of vision impairment with transitions to cognitive impairment and dementia: findings from the aging, demographics and memory study. *J Gerontol A Biol Sci Med Sci.* (2021) 76:2187–93. doi: 10.1093/geron/ab1157
13. Almidani L, Mihailovic A, Varadaraj V, Swenor BK, Ramulu PY. Longitudinal changes in visual acuity and contrast sensitivity and incident dementia. *Am J Ophthalmol.* (2024) 266:227–34. doi: 10.1016/j.ajo.2024.06.001
14. Barbeau E, Didic M, Tramon E, Felician O, Joubert S, Sontheimer A, et al. Evaluation of visual recognition memory in MCI patients. *Neurology.* (2004) 62:1317–22. doi: 10.1212/01.WNL.0000120548.24298.DB
15. Hampel H, Mesulam MM, Cuello AC, Farlow MR, Giacobini E, Grossberg GT, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain.* (2018) 141:1917–33. doi: 10.1093/brain/awy132
16. Goard M, Dan Y. Basal forebrain activation enhances cortical coding of natural scenes. *Nat Neurosci.* (2009) 12:1444–9. doi: 10.1038/nn.2402
17. Goodale MA, Milner AD. Separate visual pathways for perception and action. *Trends Neurosci.* (1992) 15:20–5. doi: 10.1016/0166-2236(92)90344-8
18. Arnaoutoglou NA, Arnaoutoglou M, Nemtsas P, Costa V, Baloyannis SJ, Ebmeier KP. Color perception differentiates Alzheimer's disease (AD) from vascular dementia (VaD) patients. *Int Psychogeriatr.* (2017) 29:1355–61. doi: 10.1017/S1041610217000096
19. Flanigan PM, Khosravi M, Leverenz JB, Tousei B. Color vision impairment differentiates Alzheimer dementia from dementia with Lewy bodies. *J Geriatr Psychiatry Neurol.* (2018) 31:97–102. doi: 10.1177/0891988718767579
20. Unger RH, Flanigan PM, Khosravi M, Leverenz JB, Tousei B. Clinical and imaging characteristics associated with color vision impairment in lewy body disease. *J Alzheimers Dis.* (2019) 72:1233–40. doi: 10.3233/JAD-190727
21. Zeki S, Marini L. Three cortical stages of colour processing in the human brain. *Brain.* (1998) 121:1669–85. doi: 10.1093/brain/121.9.1669
22. McKhann GM, Knopman DS, Chertkov H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic

guidelines for Alzheimer's disease. *Alzheimers Dement.* (2011) 7:263–9. doi: 10.1016/j.jalz.2011.03.005

23. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* (2011) 7:270–9. doi: 10.1016/j.jalz.2011.03.008

24. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* (2018) 14:535–62. doi: 10.1016/j.jalz.2018.02.018

25. Yamasaki T, Horie S, Muranaka H, Kaseda Y, Mimori Y, Tobimatsu S. Relevance of *in vivo* neurophysiological biomarkers for mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis.* (2012) 31:S137–54. doi: 10.3233/JAD-2012-112093

26. Salimi S, Irish M, Foxe D, Hodges JR, Piguet O, Burrell JR. Can visuospatial measures improve the diagnosis of Alzheimer's disease? *Alzheimers Dement.* (2018) 10:66–74. doi: 10.1016/j.dadm.2017.10.004

27. Mayes A, Montaldi D, Migo E. Associative memory and the medial temporal lobes. *Trends Cogn Sci.* (2007) 11:126–35. doi: 10.1016/j.tics.2006.12.003

28. Morales-Torres R, Wing EA, Deng L, Davis SW, Cabeza R. Visual recognition memory of scenes is driven by categorical, not sensory, visual representations. *J Neurosci.* (2024) 44:e1479232024. doi: 10.1523/JNEUROSCI.1479-23.2024

29. Oltra-Cucarella J, Sánchez-SanSegundo M, Lipnicki DM, Crawford JD, Lipton RB, Katz MJ, et al. Visual memory tests enhance the identification of amnesic MCI cases at greater risk of Alzheimer's disease. *Int Psychogeriatr.* (2019) 31:997–1006. doi: 10.1017/S104161021800145X

30. Squarzoni P, Faria DP, Yassuda MS, Porto FHG, Coutinho AM, Costa NAD, et al. Relationship between PET-assessed amyloid burden and visual and verbal episodic memory performance in elderly subjects. *J Alzheimers Dis.* (2020) 78:229–44. doi: 10.3233/JAD-200758

31. Cecchini MA, Yassuda MS, Squarzoni P, Coutinho AM, de Paula FD, Duran FLS, et al. Deficits in short-term memory binding are detectable in individuals with brain

amyloid deposition in the absence of overt neurodegeneration in the Alzheimer's disease continuum. *Brain Cogn.* (2021) 152:105749. doi: 10.1016/j.bandc.2021.105749

32. Meyer SRA, Boelaerts L, Lindeboom J, De Jonghe JFM, Ponds R. Episodic recognition memory based on incidental learning of visual associations is largely preserved compared to recall in amnesic mild cognitive impairment and mild Alzheimer's disease. *Appl Neuropsychol Adult.* (2019) 29:23–31. doi: 10.1080/23279095.2019.1703705

33. Meyer SRA, De Jonghe JFM, Schmand B, Ponds RWHM. Visual associations to retrieve episodic memory across healthy elderly, mild cognitive impairment, and patients with Alzheimer's disease. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn.* (2019) 26:447–62. doi: 10.1080/13825585.2018.1475002

34. Vidal KS, Decleva D, Barboni MTS, Nagy BV, de Menezes PAH, Aher A, et al. The association between acquired color deficiency and PET imaging of neurodegeneration in mild cognitive impairment and Alzheimer disease. *Invest Ophthalmol Vis Sci.* (2022) 63:20. doi: 10.1167/iov.63.5.20

35. Ritchie K, Carrière I, Su L, O'Brien JT, Lovestone S, Wells K, et al. The midlife cognitive profiles of adults at high risk of late-onset Alzheimer's disease: the PREVENT study. *Alzheimers Dement.* (2017) 13:1089–97. doi: 10.1016/j.jalz.2017.02.008

36. Decleva D, Vidal KS, Kreuz AC, de Menezes PAHL, Ventura DF. Alterations of color vision and pupillary light responses in age-related macular degeneration. *Front Aging Neurosci.* (2023) 14:933453. doi: 10.3389/fnagi.2022.933453

37. Duque-Chica GL, Gracitelli CPB, Moura ALA, Nagy BV, Vidal KS, Paranhos A, et al. Inner and outer retinal contributions to pupillary light response: correlation to functional and morphologic parameters in Glaucoma. *J Glaucoma.* (2018) 27:723–32. doi: 10.1097/IJG.0000000000001003

38. Feitosa-Santana C, Oiwa NN, Paramei GV, Bimler D, Costa MF, Lago M, et al. Color space distortions in patients with type 2 diabetes mellitus. *Vis Neurosci.* (2006) 23:663–8. doi: 10.1017/S0952523806233546

39. Gella L, Raman R, Kulothungan V, Pal SS, Ganesan S, Srinivasan S, et al. Color vision abnormalities in type II diabetes: Sankara Nethralaya diabetic retinopathy epidemiology and molecular genetics study II report no 2. *Indian J Ophthalmol.* (2017) 65:989–94. doi: 10.4103/ijo.IJO_601_16

2nd publication/ 2 publikacija

**McCollough and Watercolor Effects: Visual Illusions that Fade in
Early Alzheimer's Disease.**

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McCollough and Watercolor Effects: Visual Illusions that Fade in Early Alzheimer's Disease

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Background: Visual illusions provide insight into visual perception processes. We examined the McCollough effects (ME) and watercolor effects (WE) in patients with early Alzheimer disease (AD) and cognitively healthy older adults, and evaluated the influence of acetylcholinesterase inhibitors in the AD mild dementia (MD) stage.

Material/Methods: We included 28, 27, and 26 patients with MD, amnesic mild cognitive impairment (MCI), and normal cognition (control group), respectively. Participants completed the CDR, MMSE, ADAS-Cog 13, Ishihara test, and ME and WE evaluations. ME was evaluated by identifying chromatic changes in vertical, horizontal black, and white line patterns. WE was evaluated by identifying white or colored sections.

Results: Regarding ME, white vertical lines appeared red, with no significant differences between groups ($H=0.834$, $P=0.659$). Differences were observed in perception of white horizontal lines as green ($H=10.27$, $P=0.006$). All in the control group, 25 of 27 in MCI group, and 22 of 28 in MD group reported seeing WE (Fisher exact 6.66, $P=0.024$). In binary logistic regression, cognitive tests and Ishihara results predicted perception of WE. Regarding MD, no significant differences were reported between patients taking or not taking acetylcholinesterase inhibitors (chi-square 0.749, $P=0.38$; $P=0.19$, $P=1.00$, respectively).

Conclusions: Perceptions of ME and WE differed significantly between cognitively normal participants and those with early AD, offering insights into the functional alterations of the visual system and ongoing neurodegeneration. The ME after-effect of red horizontal lines might represent very early AD changes, which could aid in a better understanding of AD visual perception.

Keywords: Alzheimer Disease • Cognition Disorders • Illusions • Visual Perception

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Introduction

Alzheimer disease (AD) is the most prevalent form of dementia [1]. Difficulty in comprehending spatial information and visual images has been identified as a sign of AD [1]. Early in the progression of AD, changes in visual perception can be observed and may act as potential non-invasive indicators of neurodegeneration [2,3]. Illusions are often described as occurrences that create a discrepancy between what we perceive and our understanding of reality [4]. Moreover, visual illusions can serve as valuable instruments for contemplating the reliability and thoroughness of vision, and therefore, for gaining insight into the neural processes involved in the perception of visual information [4,5]. Gaining an understanding of how low-level and high-level vision contribute to the experience of visual illusions can shed light on pathological alterations in the visual system [4,5]. For instance, the origin of color after-effects has been traced to the retina [6]. Several studies have demonstrated that cortical filling-in can induce an afterimage [7,8]. Furthermore, neurons in the primary visual cortex play a role in the orientation-contingent color after-effect, known as the McCollough effect (ME) [9,10]. However, data regarding how pathological changes in the early stages of AD influence the perception of visual illusions of induced color is limited.

ME is a visual after-effect that causes white-aligned gratings to appear as if they are colored [9,10]. Initially, 2 perpendicular white gratings seem devoid of color; induction is conducted by alternately displaying colored gratings, usually green and red, as these colors are known to produce the most significant effect, for a duration of 5 to 15 min. Following adaptation, the white patterns exhibit a subtle hue that is complementary to the color of the induction grating with the same orientation [11]. Notably, the effect has been observed to persist for several days and may even extend over months, thereby significantly constraining the potential underlying mechanisms [12]. Gratings with different orientations appear to have colors; nonetheless, this effect diminishes almost linearly as the orientation difference from the induction gratings increases, disappearing entirely at about 45° [12]. The extended exposure to green vertical stripes tires out neurons that are sensitive to green vertical patterns, while looking at red horizontal stripes has the opposite effect [9,10]. Consequently, observing white vertical and horizontal stripes leads to excessive activation of vertical-red and horizontal-green neurons that have not adapted, resulting in the perception of red and green stripes, respectively. Neurons that are selective to orientation are not present in the retina; they exist solely in the cortex. Therefore, ME likely entails the specific adaptation of cortical neurons, responsive to both orientation and color [13,14]. Over 3 decades ago, research by Savoy et al demonstrated that the ME perception of 5 patients with AD had strength and duration similar to that of the control group [14]. However, several

neuropharmacological studies have indicated that the cholinergic limbic system plays a role in initiating and extinguishing ME [15]. Therefore, whether the use of acetylcholinesterase inhibitors would change the perception of ME remains unclear.

The second example of an induced color visual illusion is the watercolor effect (WE) [16]. Researchers have extensively investigated the effect of contextual elements on the perception of surface color through a variety of visual phenomena [17,18]. The concept of Pinna et al on the WE is based on the observation that surface color perception is affected by distant outlines, a phenomenon known as filling-in [16]. Studies have shown that the way we perceive the color of surfaces is influenced by both the characteristics of the surfaces themselves and of the surrounding context, such as the presence of distant edges. This influence is termed edge-dependent or induced color [5,16-18]. In WE, the hue of the inner edge of a pair of distant, colored outlines changes the look of an interior area that is physically identical to the background, making it appear as a consistent, desaturated color. The WE covers a visual angle that is too broad to be accounted for by the diffusion of light within the eye [5,16]. According to recent studies of neural circuits involved in the perception of WE, the dorsal stream of the visual pathway plays a role by modulating feedback to area V1 (the primary visual cortex) and exerts a cross-stream effect on the ventral regions [19]. This implies that the local and contextual factors that affect color perception activate separate neural networks [19]. Early alterations in AD may be indicated by the disruption of cortical activation within these networks [20].

The rationale for utilizing induced color visual illusions as an evaluation of visual perception in early AD is based on structural and functional changes in the parietal and temporal lobes and the cholinergic system early in the disease course [15,21].

In the present study, we aimed to examine the ME and WE of individuals with a diagnosis of early AD and of those who are cognitively normal, as well as to evaluate the influence of acetylcholinesterase inhibitors in the mild dementia stage of AD. We hypothesized that the visual illusions of induced colors are compromised in early AD and could provide insights into the changes in visual perception.

Material and Methods

Ethical Considerations and Informed Consent

The Vilnius Regional Bioethics Committee approved this study on January 11, 2022 (approval number: 2022/1-1405-877). This study adhered to the principles outlined in the Declaration of Helsinki. Before participating in the study and consenting to

the publication of anonymized data, all participants signed written informed consent forms.

Study Design

The research involved 3 distinct groups: 28 individuals with a diagnosis of MD, 27 with amnesic mild cognitive impairment (MCI), and 26 older adults with normal cognitive function, comprising the control group (CG). Those in the CG group reported no cognitive issues, had a total Clinical Dementia Rating total score (CDR-TS) of 0, and showed no neurological abnormalities. Participants with MCI met the clinical and cognitive standards for MCI due to AD, as outlined by the National Institute on Aging–Alzheimer's Association (NIA/AA) [22], and had a CDR-TS of 0.5. The MD group met the NIA/AA criteria for probable AD [23] and had a CDR-TS of 1.

The study participants were recruited from the Memory Clinic at Vilnius University Hospital, Santaros Klinikos. A cognitive neurologist identified probable AD using established criteria [23], which was further corroborated by noticeable cognitive deterioration, suggesting an active pathological process. The participants underwent structural magnetic resonance imaging (MRI), which was performed as a standard clinical practice when diagnosing AD based on regulations by the Ministry of Health of the Republic of Lithuania. Cerebrospinal fluid biomarker analysis was not performed within the framework of this study owing to its exploratory nature. Among the 28 patients with a diagnosis of MD, 7 (25%) had medical records showing positive AD cerebrospinal fluid biomarkers, aligned with the 2018 NIA-AA research framework for diagnosing AD [24].

The diagnosis of amnesic MCI due to AD was determined through clinical and cognitive criteria, ruling out vascular, traumatic, and other medical causes of cognitive decline, and was supported by documented evidence of ongoing cognitive deterioration [22]. Structural MRI revealed neuronal damage in all MCI cases, with positive AD cerebrospinal fluid biomarkers identified in 8 of 27 patients (30%), confirming AD diagnosis according to the 2018 research framework [24].

Participants with central nervous system disorders were excluded from this study, except those with MCI and MD. Exclusion criteria encompassed cerebrovascular diseases, as evidenced by a Hachinski Ischemic Score of ≥ 4 ; individuals with a history of head injury; and those with major psychiatric disorders (Geriatric Depression Scale score >9). Additionally, individuals with vision and hearing impairments that affect cognitive testing; known early-onset color vision deficiencies; significant eye conditions such as glaucoma, cataracts, diabetic retinopathy, and age-related macular degeneration; diagnosis or showing symptoms of major cardiovascular, liver, or metabolic disorders; substance abuse issues; and use of psychotropic

medications were excluded. Individuals were eligible for inclusion in the study if they were either new to treatment or had been consistently taking a stable dose of an acetylcholinesterase inhibitor for at least 3 months.

Assessments of Cognitive Function and Color Vision

The Mini-Mental State Examination (MMSE) was used to evaluate overall cognitive abilities. The MMSE is a brief screening examination designed to detect cognitive impairment and evaluate its severity. It assesses various cognitive functions, such as orientation, registration, attention and calculation, recall, language, and visual-spatial abilities. The highest possible score on the MMSE is 30 points. The CDR is a clinical instrument used to assess cognition and daily functioning. It is a semi-structured interview with the patient and an informant, such as a family member or caregiver, and assesses 6 domains: (1) memory, (2) orientation, (3) judgment and problem solving, (4) community affairs, (5) home and hobbies, and (6) personal care. According to the CDR-TS, AD stages are defined as unimpaired cognition (CDR-TS=0), MCI due to AD (CDR-TS=0.5), mild AD dementia (CDR-TS=1). The CDR Sum of Boxes (CDR-SB) scale was used to evaluate the level of functional impairment and cognitive decline. In addition, participants completed the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) 13 for a comprehensive evaluation of cognition. This evaluation covers a range of cognitive areas, such following commands, constructional praxis, recalling words after a delay, naming, ideational praxis, orientation, recognizing words, remembering test instructions, understanding spoken language, difficulty in finding words, spoken language ability, and number cancellation. Scores on the ADAS-Cog 13 range from 0 to 85, with higher scores indicating more severe cognitive impairments. The paper-based 2021 edition of the 24-plate Ishihara Color Vision Test was used to assess color vision. The Ishihara test consists of pseudoisochromatic plates designed to detect red-green color vision deficiencies, specifically protan and deutan types. The results are determined by comparing the number of plates correctly identified with the expected outcomes for individuals with normal and deficient color vision. Plates 1 to 15 were displayed, and the number of mistakes was recorded, allowing for up to 2 errors.

Apparatus for ME and WE Presentation

Visual stimuli were displayed on a 24-inch LCD monitor with a resolution of 1920×1200 pixels and a refresh rate of 59.95 Hz within a dimly illuminated environment. In both experiments, participants spent 5 min acclimating to the dim room, which was illuminated by a "natural daylight" bulb, before starting the experiment. The computer monitor's settings were configured to their original factory specifications. Moreover, the monitor settings were verified using basic visual calibration

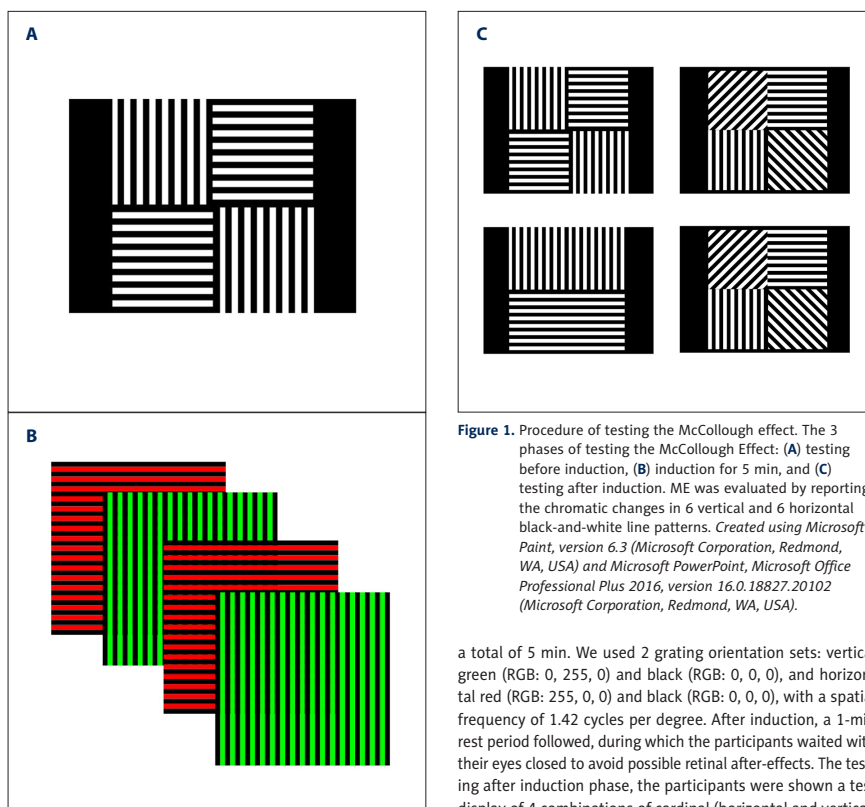


Figure 1. Procedure of testing the McCollough effect. The 3 phases of testing the McCollough Effect: (A) testing before induction, (B) induction for 5 min, and (C) testing after induction. ME was evaluated by reporting the chromatic changes in 6 vertical and 6 horizontal black-and-white line patterns. Created using Microsoft Paint, version 6.3 (Microsoft Corporation, Redmond, WA, USA) and Microsoft PowerPoint, Microsoft Office Professional Plus 2016, version 16.0.18827.20102 (Microsoft Corporation, Redmond, WA, USA).

images from the Lagom LCD test, and the WE and ME were created using Microsoft PowerPoint. A chin-and-forehead rest was used to minimize head movement and fix the gaze distance to maintain a stable eye-to-screen distance of 70 cm.

Testing Procedure for the ME

As shown in **Figure 1**, the ME was divided into 3 phases: testing before induction, induction, and testing after induction. In the baseline phase, the participants were tasked with evaluating the entire test display. None of the participants reported perceiving colors other than black or white in the test pattern before adaptation. In the induction phase, the ME stimuli were displayed on a monitor with dimensions of 31×31 cm and subtended at a visual angle of 25°. The adaptation stimulus was changed after 10 s, with the 2 stimuli alternating for

a total of 5 min. We used 2 grating orientation sets: vertical green (RGB: 0, 255, 0) and black (RGB: 0, 0, 0), and horizontal red (RGB: 255, 0, 0) and black (RGB: 0, 0, 0), with a spatial frequency of 1.42 cycles per degree. After induction, a 1-min rest period followed, during which the participants waited with their eyes closed to avoid possible retinal after-effects. The testing after induction phase, the participants were shown a test display of 4 combinations of cardinal (horizontal and vertical) and oblique (45° and 135°) white-black gratings. The same cycles/degrees and visual angles were used for the induction and achromatic gratings during the testing phase. Oblique gratings fail to generate an after-effect independently because participants were not previously exposed to the oblique orientation; therefore, participants should correctly identify slightly red-white or green-white lines in the vertical or horizontal gratings (6 red and 6 green). To ensure objectivity in the results, participants were asked to evaluate whether the white lines appeared completely white. If participants accurately identified lines as slightly red or green in the vertical or horizontal gratings, it was recorded as a correct response, with a maximum of 6 red and 6 green lines correctly identified when the ME was perceived. The number of correctly identified squares with complementary colors was evaluated.

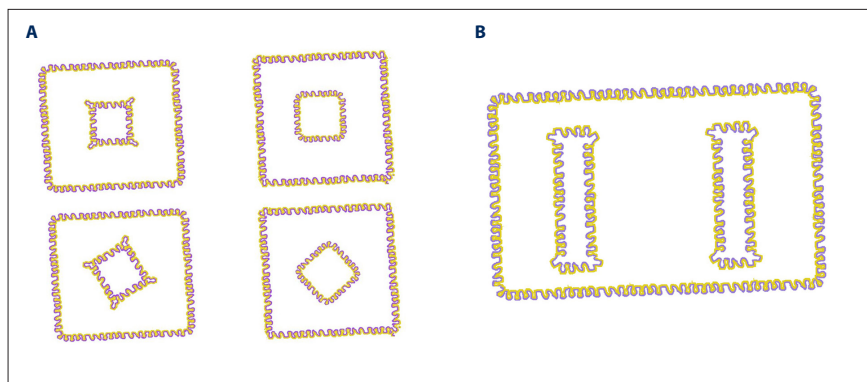


Figure 2. Watercolor effect test images. The revised version of the watercolor illusion based on the original concept of Pinna et al [16], adapted under CC BY-NC-SA 3.0. Purple undulated contours adjacent to orange ones are perceived as evenly colored by a light veil of orange tint spreading from the orange contours (coloration effect); **(A)** 4 large squares, each containing smaller squares at their center, with 2 conditions: 2 squares where WE was visible between 2 orange lines, extending from the inner part of the larger square to the outer part of the smaller square, and 2 squares where WE was visible within a smaller square; **(B)** a large rectangle with 2 smaller rectangles inside, where WE was visible between the 2 orange lines, extending from the inner part of the larger square to the outer parts of the smaller squares. Created using Microsoft Paint, version 6.3 (Microsoft Corporation, Redmond, WA, USA) and Microsoft PowerPoint, Microsoft Office Professional Plus 2016, version 16.0.18827.20102 (Microsoft Corporation, Redmond, WA, USA).

Testing Procedure for the WE

The first stimulus included 4 large squares, each containing smaller squares at their center, with 2 conditions: 2 squares where WE was visible between 2 orange lines extending from the inner part of the larger square to the outer part of the smaller square, and 2 squares where WE was visible within a smaller square. The second stimulus featured a large rectangle with 2 smaller rectangles inside, where the WE was visible between 2 orange lines extending from the inner part of the larger square to the outer parts of the smaller squares (Figure 2). The outer contour was dark purple (RGB: 165, 80, 226 for a; RGB: 154, 126, 216 for b), and the inner contour was light orange (RGB: 255, 207, 37) to optimize a strong color illusion. Each stimulus featured one or more objects set against a white background (RGB: 255, 255, 255). The edges of the WE stimuli were either wavy or had a scalloped design. This shortened the distance between certain points along the inside of the shape, which helped strengthen the illusion [16]. The border contour thickness is approximately 6 arcminutes (6') of the visual angle. To evaluate the perceived extent of color spreading, the participants were asked to identify sections of the figure that appeared completely white or colored. If the participants reported that there was no color outside the lines when WE was induced, it was evaluated as an indication that WE was not observed.

Data Analysis

To achieve sufficient power, the sample size was determined using G*Power for Windows version 3.1 (Heinrich Heine University, Düsseldorf, Germany). We set the power at 0.85 and the significance level at $P < 0.05$ (one-tailed) while expecting a large effect size ($f = 0.4$). The Kruskal-Wallis test revealed that at least 72 participants were required. The Shapiro-Wilk test was used to assess the normality of the data distribution. Differences among groups in demographic and clinical data, in addition to test outcomes, were evaluated using the Kruskal-Wallis or chi-square tests. The Spearman rank correlation coefficient was used to examine correlations between variables. Linear regression models adjusted for demographic factors and Ishihara test results were used to predict the continuous dependent variables. Binary logistic regression models with the cognitive and Ishihara test results were analyzed and adjusted for sex, age, and education. Statistical significance was set at $P < 0.05$. P values for post hoc comparisons were adjusted using the Bonferroni correction. The estimated post hoc power was calculated using ANOVA approximation based on η^2 derived from the H statistic.

Table 1. Overview of participant characteristics.

	CG (n=26)	MCI (n=27)	MD (n=28)	Statistic (χ^2 [2]/H(2), p)
Female (%)*	12 (46%)	19 (70%)	18 (64%)	3.09, 0.21
Age*	73 (9)	75 (11)	77 (9)	4.63, 0.10
Years of education*	16 (1)	15 (4)	15 (3)	4.37, 0.11
GDS*	4 (2)	5 (1)	4 (2)	1.40, 0.50
HIS*	1 (1)	1 (1)	1 (1)	1.84, 0.40
MMSE**	29 (1)	25 (3)	22 (2)	72.02, <0.001
ADAS-Cog 13**	12.5 (5.67)	22 (7.66)	31 (7.5)	74.26, <0.001
CDR-SB**	0 (0)	1.5 (1)	4.5 (0.5)	53.07, <0.001
Ishihara test, number of errors***	0 (0)	0 (2)	1 (3)	11.75, 0.003
Use of acetylcholinesterase inhibitors (%)****	0	1 (3.7%)	10 (35.71%)	18.02, <0.001

Unless otherwise specified, the data are shown as medians and interquartile ranges. Statistical significance is set at $P < 0.05$.

* Groups did not differ significantly; ** Three groups differ statistically significantly; *** CG and MD differ statistically significantly; **** CG and MD, MCI, and MD differ statistically significantly. MD – mild dementia; MCI – mild cognitive impairment; CG – control group; GDS – Geriatric Depression Scale; HIS – Hachinski Ischemic Score; ADAS-Cog 13 – Alzheimer's Disease Assessment Scale-Cognitive Subscale 13; CDR-SB – Clinical Dementia Rating Sum of Boxes; MMSE – Mini-Mental State Examination.

Results

Participant Characteristics

The analysis revealed no statistically significant differences in the sex distribution among the 3 groups ($P > 0.05$). Similarly, no statistically significant differences were found in age, educational background, depressive symptoms, or Hachinski ischemia scores ($P > 0.05$). However, statistically significant differences were observed in the cognitive test scores across all 3 groups ($P < 0.05$). The Ishihara test results differed significantly between the CG and MD groups, and the use of acetylcholinesterase inhibitors differed significantly between the CG and MD groups and the MCI and MD groups. **Table 1** presents a detailed summary of the demographic and clinical characteristics as well as the cognitive test and color vision performance of the study participants.

Results of the ME

ME was perceived as white lines tinted green or red in 25 of 26 in the CG group (96.15%), 24 of 27 in the MCI group (88.89%), and 17 of 28 in the MD group (60.71%) (chi-square test 12.69, $P = 0.002$). Most participants in all groups perceived white vertical lines as red, with median (interquartile range [IQR]), as follows: CG group, 5 [5.25]; MCI-AD group, 5 [5]; and MD-AD group, 4 [6]; Kruskal-Wallis $H = 0.834$ ($P = 0.659$). Significant differences were observed in perceiving white horizontal lines

as green (median [IQR], as follows: CG group, 3.5 [6]; MCI-AD group, 0 [2]; and MD-AD group, 0 [0]; Kruskal-Wallis $H = 10.27$ ($P = 0.006$), with a medium effect size $\eta^2 = 0.11$ (**Figure 3**). Post hoc analysis revealed significant differences between the CG and MD groups ($P = 0.002$) but not between the CG and MCI groups ($P = 0.033$ [not significant after Bonferroni correction for multiple comparisons]) or between the MCI and MD groups ($P = 0.283$). The estimated post hoc power, calculated using an ANOVA-based approximation from η^2 , was 0.86.

In the MD group, there were no significant differences between patients taking and not taking acetylcholinesterase inhibitors in the perception of ME (chi-square test 0.749, $P = 0.387$). No statistically significant differences were observed in the perception of white vertical lines as red or white horizontal lines as green, as indicated by the Mann-Whitney U test results ($P = 0.654$ and $P = 0.524$, respectively).

In the study population, the perception of white horizontal lines as green demonstrated a weak correlation with the MMSE results (Spearman $\rho = 0.354$; $P = 0.001$), CDR-SB scores (Spearman $\rho = -0.357$; $P = 0.001$), and ADAS-Cog 13 scores (Spearman $\rho = -0.336$; $P = 0.002$). No significant correlations were observed with age, education, or the Ishihara test results.

Multiple linear regression models were used to determine whether demographic data, Ishihara scores, and cognitive test results significantly predicted seeing green lines. Results

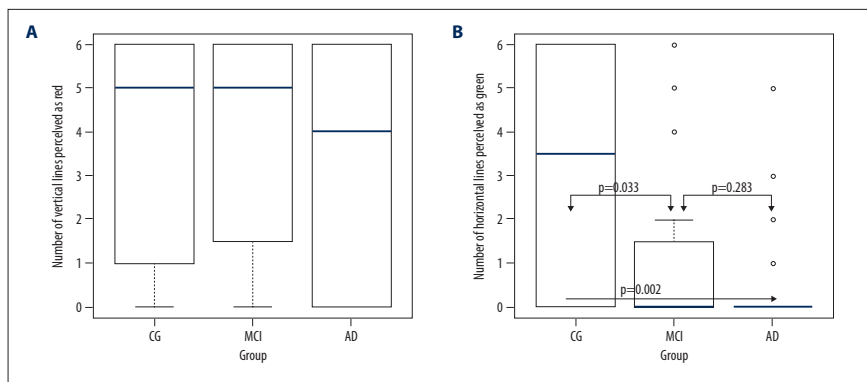


Figure 3. Differences in the McCollough effect between the 3 groups. (A) Number of vertical lines perceived as red in the 3 groups (no significant differences were observed; $P>0.05$); (B) number of horizontal lines perceived as green in the 3 groups. MD – mild dementia; MCI – mild cognitive impairment; CG – control group. Lines represent medians; boxes represent interquartile ranges; and error bars represent the minimum and maximum scores. Created using RStudio, version 1.2.5033 (RStudio, PBC, Boston, MA, USA).

were statistically significant in the adjusted model for the MMSE ($R^2=0.12$, $F=3.17$, $\beta=0.318$, $P<0.001$), ADAS-Cog 13 ($R^2=0.101$, $F=2.8$, $\beta=-0.116$, $P=0.001$), and CDR-SB ($R^2=0.086$, $F=2.5$, $\beta=-0.432$, $P=0.002$). In all models, ME was not significantly affected by factors such as sex, age, education, and Ishihara results ($P>0.05$).

Results of the Watercolor Effect

All participants in the CG group, 25 of 27 (92.59%) in the MCI group, and 22 of 28 (78.57%) in the MD groups reported seeing WE (Fisher exact test 6.66, $P=0.024$). There were significant differences between the CG and MD groups (Fisher exact test: 6.27, $P=0.024$).

When WE was not perceived, participants made a significantly higher number of errors in the Ishihara test. Specifically, the median [IQR] of errors was 2.5 [5] when participants reported not perceiving the WE, compared with 0 [1] when WE was perceived (Kruskal-Wallis $H=9.29$, $P=0.002$, with a medium effect size $\epsilon^2=0.09$) (Figure 4). The estimated post hoc power, calculated using an ANOVA-based approximation from η^2 , was 0.83.

In the MD group, there were no significant differences in the perception of WE between patients taking acetylcholinesterase inhibitors and those not taking them in the perception of WE (Fisher exact test 0.19, $P=1.00$).

The results of cognitive assessments and color vision were significant predictors of WE in binary logistic regression models,

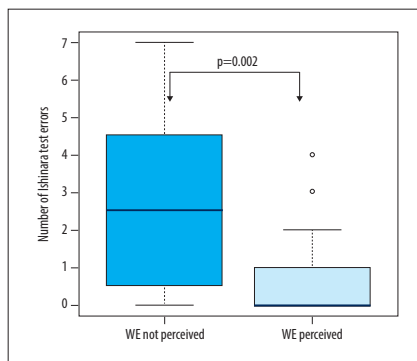


Figure 4. Ishihara test results in accordance with whether the Watercolor effect was perceived. The WE was not perceived when participants exhibited a significantly higher number of errors on the Ishihara test. Lines represent medians; boxes represent interquartile ranges; and error bars represent the minimum and maximum scores. Created using RStudio, version 1.2.5033 (RStudio, PBC, Boston, MA, USA).

which were adjusted for sex, age, and education: model with ADAS-Cog13 ($B=-0.158$, Wald=4.7, $P=0.03$, Nagelkerke $R^2=0.261$); model with CDR-SB ($B=-0.569$, Wald=5.09, $P=0.024$, Nagelkerke $R^2=0.265$); model with MMSE ($B=0.342$, Wald=3.89, $P=0.049$, Nagelkerke $R^2=0.225$), and model with Ishihara test ($B=-0.893$, Wald=8.13, $P=0.004$, Nagelkerke $R^2=0.375$).

Discussion

In the present study, we assessed the visual illusions of induced color, specifically the ME and WE, in individuals with a diagnosis of early AD and those who were cognitively normal. Perceptions of ME and WE were more impaired in the MD group than in the CG and MCI groups. Moreover, the use of acetylcholinesterase inhibitors did not influence the perception of ME or WE in the mild dementia stage of AD. We conclude that the visual illusions of induced colors are more severely compromised in mild AD, which may provide insight into changes in visual perception.

Our study showed that ME was significantly impaired during the MD stage of AD. While no significant differences were identified among the 3 groups in the perception of white vertical lines as red, notable differences were observed in the perception of white horizontal lines as green. During ME induction, a specific orientation, such as horizontal, is consistently paired with a particular color, such as red, for several minutes. This process results in a shift of the “neutral point” for red toward the over-represented end of the red color continuum in the presence of horizontal orientations [9,10]. Over the past 3 decades, considerable discourse has emerged in the literature regarding the potential nature of these underlying mechanisms. Initially, Skowbo et al proposed that the rapid decay of the ME induced by achromatic gratings supports the hypothesis that the ME is predicated upon an adaptation process [25]. Additionally, the rapid decline of the ME can be explained as the fading away of a conditioned response [25]. There is significant debate surrounding whether the ME originates in early visual areas [26,27]. While some studies support the hypothesis that the effect begins in V1, a considerable number of studies oppose this perspective [28,29]. Functional MRI studies have observed alterations in activity across several brain regions, concluding that the ME is generated through top-down processing originating from the frontal cortex and other areas [28]. Furthermore, the ventral occipital cortex (V4 alpha) was significantly activated in association with ME [29]. The strength of the ME has been demonstrated to have an inverse relationship with acetylcholine [20]. It is notably enhanced by the administration of scopolamine, an anti-cholinergic, and diminished by physostigmine, a cholinergic, when these substances are given prior to exposure to ME stimuli [20]. However, there is a lack of comprehensive data on ME among patients with early AD and those who are on acetylcholinesterase inhibitors. Our study shows that acetylcholinesterase inhibitors do not significantly affect ME and provide the insight that ME is diminished in the MD stage of early AD, especially the after-effect of red horizontal gratings. The reason for the stronger after-effect of green vertical gratings is debatable. Marino et al suggested that this explanation lie in the concept of natural entities, which involves the activation of

neurons that are simultaneously responsive to the color green and vertical orientation. This might be because the variability in their activation is lower than that of other modality-specific channels [30]. Our study findings may diverge from those of Savoy et al, as previous evaluations of ME in individuals with AD have analyzed the red and green after-effects collectively, whereas our approach involved a separate comparison of the red and green after-effects [14]. In contrast to WE, ME was not significantly affected by the results of the Ishihara test, indicating that the underlying mechanisms responsible for the production of induced colors differed. The results of the cognitive assessments significantly predicted the perception of the white horizontal lines as green, with lower scores indicating diminished or absent ME. The present findings further corroborate the hypothesis that ME is influenced by changes in early AD, particularly in relation to the color orientation after-effect, which is characterized by more variable activation (red horizontal). These results offer valuable insights into the alterations in visual perception associated with AD.

The WE effect was influenced by the outcomes of the Ishihara test, demonstrating that, when the WE effect was not perceived, there was a significantly higher incidence of errors in the Ishihara test. Recent studies have used color discrimination tasks to distinguish AD from other forms of dementia, revealing that a substantial proportion (20%) of patients with AD exhibit color vision impairment [31,32]. Moreover, lower scores on cognitive assessments and subscores related to visuospatial or executive functions are associated with color vision impairment [32]. The findings of our study reveal that the results of the WE and Ishihara color vision tests showed significant differences only between the CG and MD groups. These results align with those of Vidal et al, who attributed alterations in color vision to progressive neurodegeneration rather than to individuals exhibiting only signs of β -amyloid deposition in the brain [33]. As previously reported, Gerardin et al suggest that the induction of WE involves the modulation of area V1 by the dorsal stream of the visual pathway, which subsequently influences the ventral regions [19]. Consequently, WE may serve as a functional indicator of neurodegenerative changes in these areas, but it is not specific to very early AD changes, such as β -amyloid deposition in the brain.

This study had some limitations. First, it is a cross-sectional study, and additional longitudinal research is necessary to evaluate the perceptions of ME and WE throughout the course of AD. Second, only a limited number of participants underwent cerebrospinal fluid biomarker analysis, and positron emission tomography scans were not used. Incorporating these approaches might have offered significant insights into how alterations in ME and WE relate to the brain β -amyloid deposition and neurodegeneration. Further research on various neurodegenerative diseases, particularly dementia with Lewy bodies, is essential to

enhance the understanding of the visual illusions of induced color, given that prominent symptoms include alterations in visual perception [31,32]. Although all participants had a documented prior ophthalmological evaluation, it was not performed in this study. Therefore, it remains unclear whether any participant had eye conditions that might have an impact on visual function. In conclusion, despite observing significant differences, expanding the sample size is necessary to substantiate our conclusions.

Conclusions

In conclusion, significant differences in ME and WE were observed between participants with normal cognitive function and those in the early stages of AD. This finding offers insight into the functional alterations of the visual system, suggesting that diminished or absent ME and WE can serve as indicators of ongoing neurodegeneration. The ME after-effect of the red

horizontal lines might represent very early AD changes, which may aid in a better understanding of visual perception in AD.

Ethics Approval and Consent to Participate

This study was approved by the Vilnius Regional Bioethics Committee on January 11, 2022 (approval number: 2022/1-1405-877). Moreover, this study was conducted in accordance with the principles of the Declaration of Helsinki and Standards for Reporting Diagnostic Accuracy Studies (STARD) guidelines. All participants provided written informed consent prior to study participation.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

- Lahita R, Kluger J, Drayer DE, et al. 2024 Alzheimer's disease facts and figures. *Alzheimer's Dement.* 2024;20(5):3708-821
- Chang LYL, Lowe J, Ardiles A, et al. Alzheimer's disease in the human eye. Clinical tests that identify ocular and visual information processing deficit as biomarkers. *Alzheimers Dement.* 2014;10(2):251-61
- Marquie M, Castilla-Marti M, Valero S, et al. Visual impairment in aging and cognitive decline: Experience in a Memory Clinic. *Sci Rep.* 2019;9(1):8698
- Shapiro AG, Todorovic D. *The Oxford compendium of visual illusions.* New York, NY: Oxford University Press; 2017
- Pinna B, Porcheddu D, Skilters J. From perceptual organization to visual illusions and back. *Front Hum Neurosci.* 2022;16:960542
- Daw NW. Why afterimages are not seen in normal circumstances. *Nature.* 1962;196:1143-45
- Shimojo S, Kamitani Y, Nishida S. Afterimage of perceptually filled-in surface. *Science.* 2001;293(5535):1677-80
- van Lier R, Vergeer M, Anstis S. Filling-in afterimage colors between the lines. *Curr Biol.* 2009;19(8):R323-R24
- McCollough C. Color adaptation of edge detectors in the human visual system. *Science.* 1965;149(3688):1115-16
- McCollough C. Do McCollough effects provide evidence for global pattern processing? *Percept Psychophys.* 2000;62(2):350-62
- Spingler G. Neural modelling of the McCollough effect in color vision (51360784). Master of Science Cognitive Science (Neural Computation & Neuroinformatics) School of Informatics, University of Edinburgh; 2014
- Vul E, Krizay E, MacLeod DIA. The McCollough effect reflects permanent and transient adaptation in early visual cortex. *J Vis.* 2008;8(12):4.1-12
- Johnson EN, Hawken MJ, Shapley R. The orientation selectivity of color-responsive neurons in macaque V1. *J Neurosci.* 2008;28(32):8096-106
- Savory RL, Gabrieli JD. Normal McCollough effect in Alzheimer's disease and global amnesia. *Percept Psychophys.* 1991;49(5):448-55
- Byth W, McMahon D, King DJ. Cholinergic agents and the McCollough effect. *Perception.* 2000;29(4):461-80
- Pinna B, Brelstaff G, Spillmann L. Surface color from boundaries: A new "watercolor" illusion. *Vision Res.* 2001;41(20):2669-76
- Komatsu H. The neural mechanisms of perceptual filling-in. *Nat Rev Neurosci.* 2006;7(3):220-31
- Kim J, Francis G. Color selection, color capture, and afterimage filling-in. *J Vis.* 2011;11(3):23
- Gerardin P, Dojat M, Knoblauch K, Devinc F. Effects of background and contour luminance on the hue and brightness of the watercolor effect. *Vision Res.* 2018;144:9-19
- Pontecorvo MJ, Devous MD, Kennedy I, et al. A multicentre longitudinal study of flortaucipir (18F) in normal ageing, mild cognitive impairment and Alzheimer's disease dementia. *Brain.* 2019;142(6):1723-35
- Sintini I, Graff-Radford J, Senjem ML, et al. Longitudinal neuroimaging biomarkers differ across Alzheimer's disease phenotypes. *Brain.* 2020;143(7):2281-94
- Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):270-79
- McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):263-69
- Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018;14(4):535-62
- Skowbo D, Gentry T, Timney B, Morant RB. The McCollough effect: Influence of several kinds of visual stimulation on decay rate. *Percept Psychophys.* 1974;16(1):47-49
- Humphrey GK, James TW, Gati JS, et al. Perception of the McCollough effect correlates with activity in extrastriate cortex: A functional magnetic resonance imaging study. *Psychol Sci.* 1999;10(5):444-48
- Grossberg S, Hwang S, Mingolla E. Thalamocortical dynamics of the McCollough effect: Boundary-surface alignment through perceptual learning. *Vision Res.* 2002;42(10):1259-86
- Vul E, MacLeod DIA. Contingent aftereffects distinguish conscious and pre-conscious color processing. *Nat Neurosci.* 2006;9(7):873-74
- Humphrey GK, Goodale MA. Probing unconscious visual processing with the McCollough effect. *Conscious Cogn.* 1998;7(3):494-519
- Marino BFM, Borghi AM, Gemmi L, et al. Neural adaptation effects in conceptual processing. *Behav Sci (Basel).* 2015;5(3):353-71
- Flanigan PM, Khosravi MA, Leverenz JB, Tausi B. Color vision impairment differentiates Alzheimer dementia from dementia with Lewy bodies. *J Geriatr Psychiatry Neurol.* 2018;31(2):97-102
- Unger RH, Flanigan PM, Khosravi M, et al. Clinical and imaging characteristics associated with color vision impairment in lewy body disease. *J Alzheimers Dis.* 2019;72(4):1233-40
- Vidal KSM, Declewa D, Barboni MTS, et al. The association between acquired color deficiency and PET imaging of neurodegeneration in mild cognitive impairment and Alzheimer disease. *Invest Ophthalmol Vis Sci.* 2022;63(5):20

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**Time/Movement Estimation and Mental Rotation Tasks as Early
Cognitive Markers in Alzheimer's Disease.**

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Time/Movement Estimation and Mental Rotation Tasks as Early Cognitive Markers in Alzheimer's Disease

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ABSTRACT

Introduction: Cognitive impairments, including memory decline and executive dysfunction, are well-documented in Alzheimer's disease (AD); however, distortions in temporal judgment, motion perception and mental rotation in the early stages remain underexplored. Existing research has predominantly relied on verbal time-estimation tasks, with a limited investigation into alternative paradigms, such as time reproduction or bisection tasks. This study investigated the diagnostic utility of time-movement estimation and mental rotation tasks from the psychology experiment building language (PEBL) test battery for identifying early cognitive impairment. Moreover, it assessed correlations among task performance, cognitive test scores, and demographic variables.

Methods: This cross-sectional study included 28 patients with mild dementia (MD), 27 with amnesic mild cognitive impairment (MCI), and 26 with normal cognitive function as the control cohort (CC). Participants completed the mini-mental state examination, clinical dementia rating assessments, Alzheimer's disease assessment scale–cognitive subscale 13 (ADAS–Cog 13), and PEBL-based Time–Wall and mental rotation tasks.

Results: Time–Wall task inaccuracy scores exhibited strong diagnostic accuracy in distinguishing between the CC and early AD (MCI and MD), with an AUC of 0.9, and effectively differentiated CC from MCI, with an AUC of 0.86. Conversely, the mental rotation task exhibited weaker diagnostic properties, with AUC values of 0.75 for distinguishing CC from early AD and 0.71 for distinguishing CC from MCI. The multinomial logistic regression model accurately categorized 75.3% of participants (CC = 92.3%, MCI = 59.3%, and MD = 75%), utilizing demographic data and ADAS–Cog 13 and Time–Wall inaccuracy scores as predictors. Both ADAS–Cog 13 and Time–Wall task inaccuracy scores were statistically significant predictors ($X^2 = 49.41$, $p < 0.001$; $X^2 = 9.24$, $p = 0.01$, respectively). Time–Wall task inaccuracy scores did not notably correlate with age.

Conclusions: The Time–Wall task showed strong diagnostic utility in identifying early AD, independent of age. The mental rotation task exhibited low sensitivity and requires further investigation regarding its potential to reflect compensatory brain network functions.

1 | Background

Alzheimer's disease (AD) is the most common cause of dementia, globally affecting over 57 million individuals (WHO 2025)]. Its prevalence increases markedly with age: approximately 13.2% and

33.4% of individuals aged 75–84 years and those aged ≥85 years are affected by AD, respectively (Rajan et al. 2021). The early stages of the disease, frequently accompanied by subtle clinical symptoms, constitute a critical window for intervention and care planning, during which treatment may be most beneficial (Spargo

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et al. 2023). Contemporary biological research frameworks for AD incorporate in vivo biomarkers of β -amyloid and tau, thereby extending the neuropathological definition of the disease to include living individuals (Jack et al. 2024). The identification of subtle cognitive impairment or preserved cognitive function in older adults is highly dependent on the sensitivity and specificity of the assessment tools employed (Kessels 2019).

In the domain of neuropsychological assessment, computerized evaluations offer a rapid and efficient means of appraising cognitive function [6]. Computers facilitate standardized instruction delivery across multiple languages and support the collection of large volumes of objective data while minimizing experimenter-related errors (Kessels 2019; Chan et al. 2018). Compared with traditional paper-and-pencil methods, computerized assessments can be seamlessly integrated into neuroimaging settings and considerably reduce the manual effort attributed to scoring, analysis, and longitudinal monitoring of cognitive performance (Chan et al. 2018; Kochan et al. 2022).

An increasing number of computerized cognitive assessments are currently commercially available and can be self-administered at home (Kochan et al. 2022). Nonetheless, the cost of extensively researched validated test batteries may limit their accessibility in primary care settings and among researchers in developing countries (Piper et al. 2015). By contrast, the psychology experiment building language (PEBL) is freely available for download at <http://pebl.sourceforge.net/> and is accompanied by comprehensive documentation, enabling researchers to customize tests for their specific experimental requirements. The current 2.1 version of the PEBL battery includes approximately 50 assessments, encompassing many widely recognized neuropsychological measures (Piper et al. 2015; The PEBL Project 2019).

The Time-Wall task is a nonverbal assessment designed to evaluate temporal judgment, motion perception, and decision-making abilities (Piper et al. 2015; The PEBL Project 2019). Its original purpose was to measure an individual's ability to predict the time required for a target to move vertically at a constant speed over a specified distance. This task engages cognitive processes involved in both motion perception and temporal judgment (Piper et al. 2015; The PEBL Project 2019; Kim et al. 2024). The association between temporal judgment and memory decline in AD is believed to involve the hippocampus, a brain region essential for both functions and particularly vulnerable to AD-related pathology (El Haj and Kapogiannis 2016).

Numerous studies have indicated that patients with AD experience difficulties in motion processing and visuospatial disorientation, implicating dysfunction in the posterior parietal regions of the dorsal visual pathway (Liu et al. 2019; Deng et al. 2016). The dorsal stream hypothesis of AD is further supported by consistent findings of parietal atrophy and reduced activity in the parietal lobe of affected individuals (Liu et al. 2019; Deng et al. 2016). Consequently, tasks assessing temporal judgment and motion perception may serve as valuable diagnostic tools for AD's early detection.

The mental rotation task is employed to evaluate visuospatial abilities. Recent studies have shown its applicability in patients

with mild cognitive impairment (MCI) and AD, particularly in evaluating non-amnesic symptoms (Piper et al. 2015; Suzuki et al. 2018). The task involves mentally transforming the visuospatial features of an image until it matches a target without any physical movement. Performance is measured based on response accuracy and time, which increases with the rotation angle, reflecting greater difficulty as the angles become larger (Piper et al. 2015; Suzuki et al. 2018; Langner et al. 2023). Lineweaver et al. found that patients with early AD tend to perform poorly on mental rotation tasks, potentially due to pathological changes in the parietal and temporal lobe association cortices, which impair spatial processing (Lineweaver et al. 2005).

Despite extensive research on cognitive impairments in AD, particularly regarding memory decline and executive dysfunction, distortions in temporal judgment and motion perception in early AD have received comparatively little attention (El Haj and Kapogiannis 2016). Temporal processing and memory impairments are commonly associated with hippocampal dysfunction. Emerging evidence highlights the hippocampus as essential for differentiating time intervals, organizing temporal sequences, and encoding the flow of time (MacDonald et al. 2014; Meck et al. 2013). However, most studies to date have focused on verbal time-estimation tasks, with a limited investigation into alternative paradigms, such as time reproduction or bisection tasks (El Haj and Kapogiannis 2016).

Consequently, this study evaluated time-movement estimation and mental rotation tasks as diagnostic tests for early AD using freely available tests from the PEBL battery. Moreover, correlations between cognitive test outcomes and demographic variables were examined.

2 | Methods

2.1 | Ethical Considerations and Informed Consent

This study was approved by the Vilnius Regional Bioethics Committee on January 11, 2022 (approval number: 2022/1-1405-877). Moreover, this study was conducted in accordance with the principles of the Declaration of Helsinki and standards for reporting diagnostic accuracy studies (STARD) guidelines. Written informed consent was obtained from all participants prior to study participation and for the publication of their de-identified data.

2.2 | Study Design

In this cross-sectional study, participants were recruited from the memory clinic at Vilnius University Hospital, Santaros Klinikos. A cognitive neurologist diagnosed probable AD based on established criteria (Albert et al. 2011), further supported by observed cognitive decline, indicating an ongoing pathological process. Of the 28 patients with mild dementia (MD), seven (25%) had medical records with documented positive AD cerebrospinal fluid (CSF) biomarkers, consistent with the 2018 National Institute on Aging and Alzheimer's Association (NIA-AA) research framework for AD diagnosis (Jack et al. 2018). Given the exploratory

nature of our study, the analysis of CSF biomarkers was not conducted within the scope of this research.

The diagnosis of amnesic MCI attributed to AD was established using clinical and cognitive criteria, excluding vascular, traumatic, and other medical etiologies of cognitive decline, and was supported by documented evidence of progressive cognitive deterioration (McKhann et al. 2011). Structural magnetic resonance imaging confirmed neuronal damage in all MCI cases, with positive AD CSF biomarkers documented in eight of 27 participants (30%), confirming an AD diagnosis based on the 2018 research framework (Jack et al. 2018).

Exclusion criteria were as follows: (1) neurological disorders affecting the central nervous system, apart from MCI and MD; (2) cerebrovascular conditions with Hachinski ischemic scores ≥ 4 ; (3) a history of head trauma; (4) major psychiatric disorders, including schizophrenia, delirium, psychosis, or depression (with a geriatric depression scale score > 9); (5) sensory impairments in vision or hearing that could interfere with cognitive assessments; (6) major cardiovascular, hepatic, or metabolic diseases; (7) substance abuse; and (8) the use of psychoactive medications.

The study included three cohorts: 28 participants with MD, 27 with amnesic MCI, and 26 older adults with normal cognitive abilities who served as the control cohort (CC). Participants in the CC reported no cognitive impairments, achieved a clinical dementia rating total score (CDR-TS) of 0, and exhibited no neurological abnormalities. Participants with MCI met the clinical and cognitive criteria for MCI due to AD, as defined by the NIA/AA [17], and were assigned a CDR-TS of 0.5. Participants in the MD cohort fulfilled the NIA/AA criteria for probable AD [18] and had a CDR-TS score of 1.

2.3 | Assessments of Cognitive Function

The mini-mental state examination (MMSE) was employed to assess general cognitive function. The clinical dementia rating sum of boxes (CDR-SB) scale was used to evaluate the severity of functional impairment and cognitive decline. Moreover, participants completed the AD assessment scale–cognitive subscale (ADAS–Cog) 13 for a comprehensive cognitive evaluation. This test includes components such as word recall, following commands, constructional praxis, delayed recall, naming, ideational praxis, orientation, word recognition, remembering test instructions, understanding spoken language, word-finding difficulty, spoken-language ability, and number cancellation. ADAS–Cog 13 scores ranged from 0 to 85, with higher scores indicating greater cognitive impairment.

2.4 | Assessment of PEBL Battery Tests: Time–Wall and Mental Rotation Tasks

The Time–Wall task is a time–movement estimation exercise in which a moving object disappears behind a wall, and participants must judge when it will reach a visible gap, assuming constant speed throughout the trial. After descending two-thirds of its trajectory, the target moves behind a wall and consequently becomes obscured from view (Figure 1). This task was adapted

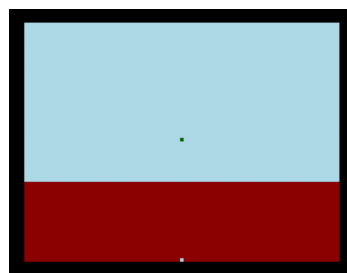


FIGURE 1 | Illustration of the Time–Wall task. Participants estimate when a moving object (green square), traveling at a constant speed, will reach a gap (white square at the bottom) after becoming obscured by a red wall.



FIGURE 2 | Example of mirror images is depicted. Participants are required to determine whether two figures on the screen's plane are identical or mirror images, with the figures rotated relative to each other.

from the Unified Tri-Services Cognitive Performance Assessment Battery (Systems Research Laboratories Inc., Dayton, Ohio, USA) (Sam et al. 2013). Participants were instructed to press the space bar at the moment they believed the target aligned with a notch at the bottom of the screen. The task comprised 20 trials, each lasting between 2 and 10 s.

The average error time across trials was used to evaluate each participant's precision in time perception. Response inaccuracy was calculated as the percentage difference between the response time (RT) and target time (TT) using the formula:

$$(RT - TT) / TT \times 100. \quad (1)$$

Additionally, the percentage of late responses was computed to further characterize temporal estimation performance.

The mental rotation task is a two-dimensional adaptation of the classical test introduced by Shepard (Langner et al. 2023; Shepard and Metzler 1971). Participants were instructed to press either the “D” or “S” key on the keyboard to indicate whether a pair of red shapes displayed on a gray screen was mirrored on the screen's plane (mirror condition). The shapes were rotated relative to each other at angles of 0°, 45°, 90°, 135°, and 180° (angle conditions). The pairs consisted of a familiar shape (an L shape) and an unfamiliar shape (a bolt) (Figure 2). The task was modified and included six practice trials and 32 experimental trials, each with

a maximum duration of 45 s, resulting in a total task duration of up to 30 min. Correct responses and reaction times were recorded for each trial.

2.5 | Data Analysis

To ensure adequate power, we calculated the required sample size using G*Power for Windows version 3.1 (Heinrich Heine University Düsseldorf, Düsseldorf, Germany), setting power at 0.85 and significance at $p < 0.05$ (one-tailed), while anticipating a large effect size ($f = 0.4$). Consequently, the Kruskal–Wallis test indicated that a minimum of 72 participants was required.

The Shapiro–Wilk test was used to assess the normality of data distribution. Differences in demographic, clinical, and test outcome data among cohorts were evaluated using the Kruskal–Wallis or chi-square tests. Spearman's rank correlation coefficient was applied to examine correlations between variables. Linear regression models, adjusted for demographic factors, were subsequently used to predict continuous dependent variables. For each model, we reported the coefficient of determination (R^2) to indicate the proportion of variance explained by the model, the F-statistic (F) to assess overall model significance, and the standardized beta coefficient (β) to reflect the strength and direction of the correlations between predictors and outcomes. Multinomial logistic regression was conducted to examine the correlation between predictor variables and cohort membership across three categories: CC, MCI, and MD. Nagelkerke R^2 was used to assess the explanatory power of logistic regression models. Diagnostic performance was assessed using the receiver operating characteristic (ROC) curve analysis. Statistical significance was set at $p < 0.05$, with Bonferroni correction applied to *post hoc* comparisons.

3 | Results

3.1 | Participant Characteristics

Analysis revealed no statistically significant differences in sex distribution among the three cohorts ($p > 0.05$). Similarly, no statistically significant differences were found in age, educational background, depressive symptoms, or Hachinski ischemic scores ($p > 0.05$). However, statistically significant differences were observed in cognitive test scores across all three cohorts ($p < 0.05$). Table 1 presents a detailed summary of the demographic and clinical characteristics, as well as the cognitive test performances, of the study participants.

3.2 | Time–Wall Task Results

Statistically significant differences were observed in the Time–Wall task inaccuracy scores [medians and interquartile ranges: CC = 11.46 (9), MCI = 19.43 (10.49), MD = 22.82 (14.35); $H(2) = 34.74$; $p < 0.001$], with the CC exhibiting lower scores than did both the MCI and MD cohorts. No statistically significant differences were found between the MCI and MD cohorts ($p = 0.106$).

The percentages of late responses are presented as medians and interquartile ranges: CC = 10 (18.75), MCI = 20 (22), and MD = 25 (23) [$H(2) = 7.3$; $p = 0.026$]. Statistically significant differences were observed between the CC and MD cohorts ($p = 0.01$); however, no statistically significant differences were found between the CC and MCI cohorts ($p = 0.153$) or between the MD and MCI cohorts ($p = 0.143$).

In the study population, Time–Wall task inaccuracy scores were strongly correlated with the MMSE results (Spearman's $\rho = -0.628$; $p < 0.001$) and moderately correlated with CDR–SB (Spearman's $\rho = 0.568$; $p < 0.001$) and ADAS–Cog 13 (Spearman's $\rho = 0.594$; $p < 0.001$) scores. A weak correlation with education (Spearman's $\rho = -0.314$; $p = 0.004$) (Figure S1) and no notable correlation with age were found (Spearman's $\rho = 0.17$; $p = 0.129$).

Multiple linear regression models, including age, sex, education, and cognitive test scores, as independent variables, were used to determine their predictive values for the Time–Wall task inaccuracy scores. Statistical significance was observed in the following models: MMSE [$R^2 = 0.345$, $F = 11.52$, $\beta = -0.577$, $p < 0.001$]; ADAS–Cog 13 ($R^2 = 0.321$, $F = 10.46$, $\beta = 0.577$, $p < 0.001$), and CDR–SB ($R^2 = 0.262$, $F = 8.09$, $\beta = 0.498$, $p < 0.001$).

3.3 | Diagnostic Characteristics of the Time–Wall Task

The efficacy of the Time–Wall task inaccuracy scores in distinguishing participants with early AD from those in the CC was assessed using the ROC curve analysis. The ROC curve analysis revealed strong diagnostic capabilities for differentiating between the CC and early AD (MCI and MD), with an area under the curve (AUC) of 0.9. Similarly, differentiation between the CC and MCI cohorts resulted in an AUC of 0.86. Figure 3 illustrates the ROC curves used to evaluate the Time–Wall task performance.

A threshold of ≥ 18.35 for the Time–Wall task inaccuracies was selected to indicate AD. By applying this threshold to distinguish participants with AD (MCI and MD) from participants in the CC, the Time–Wall task demonstrated a sensitivity of 70.91% (95% CI: 57.1–82.37) and specificity of 96.15% (95% CI: 80.36–99.9%). Table 2 provides a comprehensive overview of the diagnostic characteristics of the Time–Wall task for differentiating between participants with AD and those in the CC.

Multinomial logistic regression was conducted to examine the correlation between predictor variables and cohort membership across three categories: CC, MCI, and MD. A model was first developed that incorporated age, education, sex, and ADAS–Cog 13 scores as predictor variables. This model showed a better fit when compared with a model with only the intercept ($X^2 = 87.85$, $p < 0.001$; Nagelkerke $R^2 = 0.745$). The model achieved an overall classification accuracy of 76.5%, with correct classification rates of 92.3%, 66.7%, and 71.4% for CC, MCI, and MD, respectively. The ADAS–Cog 13 score was identified as the most robust and statistically significant predictor ($X^2 = 78.20$, $p < 0.001$).

The Time–Wall task scores were included in the initial model. The model comprising age, education, sex, ADAS–Cog 13 scores, and

TABLE 1 | Overview of participant characteristics.

	CC (n = 26)	MCI (n = 27)	MD (n = 28)	Statistic (χ^2 [2]/H(2), p)
Female (%) [*]	12 (46%)	19 (70%)	18 (64%)	3.09, 0.21
Age [*]	73 (9)	75 (11)	77 (9)	4.63, 0.10
Years of education [*]	16 (1)	15 (4)	15 (3)	4.37, 0.11
GD [*]	4 (2)	5 (1)	4 (2)	1.40, 0.50
HIS [*]	1 (1)	1 (1)	1 (1)	1.84, 0.40
MMSE ^{**}	29 (1)	25 (3)	22 (2)	72.02, < 0.001
ADAS-Cog 13 ^{**}	12.5 (5.67)	22 (7.66)	31 (7.5)	74.26, < 0.001
CDR-SB ^{**}	0 (0)	1.5 (1)	4.5 (0.5)	53.07, < 0.001

Unless otherwise specified, the data are shown as medians and interquartile ranges.
Statistical significance is set at $p < 0.05$.
Abbreviations: ADAS-Cog 13 = Alzheimer's disease assessment scale-cognitive subscale 13; CC = control cohort; CDR-SB = clinical dementia rating sum of boxes; GDS = geriatric depression scale; HIS = Hachinski ischemic score; MCI = mild cognitive impairment; MD = mild dementia; MMSE = mini-mental state examination.
^{*}Cohorts do not differ statistically significantly.
^{**}Three cohorts differ statistically significantly.

TABLE 2 | Time-Wall task performance: Distinguishing participants with Alzheimer's disease (AD) and control cohort (CC) members.

	CC vs. early AD (MCI and MD): cut-off ≥ 18.35	CC vs. MCI: cut-off ≥ 15.08	CC vs. MD: cut-off ≥ 16.28	MCI vs. MD: cut-off ≥ 21.67
Sensitivity	70.91% (57.1–82.37%)	77.78% (57.74–91.38%)	82.14% (63.11–93.94%)	57.14% (37.18–75.54%)
Specificity	96.15% (80.36–99.9%)	76.92% (56.35–91.03%)	88.46% (69.85–97.55%)	59.26% (38.80–77.61%)
Negative predictive value	60.98% (50.66–70.39%)	76.92% (61.48–87.44%)	82.14% (67.25–91.15%)	57.14% (43.97–69.37%)
Positive predictive value	97.5% (84.99–99.63%)	77.78% (62.78–87.90%)	88.46% (72.28–95.75%)	59.26% (45.46–71.73%)
Overall diagnostic accuracy	79.01% (68.54–87.27%)	77.36% (63.79–87.72%)	85.19% (72.88–93.38%)	58.18% (44.11–71.35%)

Data are presented as percentages and 95% confidence intervals.
Abbreviations: MCI = mild cognitive impairment; MD = mild dementia.

Time-Wall task inaccuracy scores showed a marked improvement in fit over the null model ($X^2 = 96.69$, $p < 0.001$; Nagelkerke $R^2 = 0.784$). The model achieved an overall classification accuracy of 75.3%, with correct classification rates of 92.3%, 59.3%, and 75% for CC, MCI, and MD, respectively. ADAS-Cog 13 and Time-Wall task inaccuracy scores were statistically significant predictors ($X^2 = 49.41$, $p < 0.001$; $X^2 = 9.24$, $p = 0.01$, respectively).

3.4 | Mental Rotation Task

Mental rotation task accuracy scores differed statistically significantly among the cohorts [medians and interquartile ranges: CC = 26.5 (4), MCI = 22 (9), and MD = 21.5 (9); $p = 0.001$]. *Post hoc* comparisons revealed statistically significant differences between the CC and both MCI ($p = 0.007$) and MD cohorts ($p < 0.001$), yet not between the MCI and MD cohorts ($p = 0.094$). Moreover, response times varied statistically significantly among the cohorts

[$H(2) = 15.12$, $p = 0.001$; medians and interquartile ranges: CC = 6309.7 ms (4531.4); MCI = 12 684.5 ms (7974.7); and MD = 11 657.3 ms (7053)].

Analysis of the CC, MCI, and MD cohorts revealed no statistically significant differences in accuracy scores or between the response time and sex. Regarding the CC, accuracy scores were similar between males [27.5 (5)] and females [25.5 (3)] ($p = 0.494$), and response times did not differ statistically significantly [males = 6017.9 (6908.05); females = 7235.88 (2957.87); $p = 0.374$]. Regarding the MCI cohort, accuracy scores were comparable between males [23 (13)] and females [22 (7)] ($p = 0.897$), while response times showed no statistically significant difference [males = 6975.6 (8787.42); females = 13080.63 (5720.03); $p = 0.051$]. Accuracy scores for the MD cohort revealed showed no statistically significant sex differences [males = 22.5 (7); females = 18.5 (10); $p = 0.072$]. Similarly, response times did not differ statistically significantly between males [9507.59 (8206.03)] and females [12508.13 (9802.41)] ($p = 0.08$).

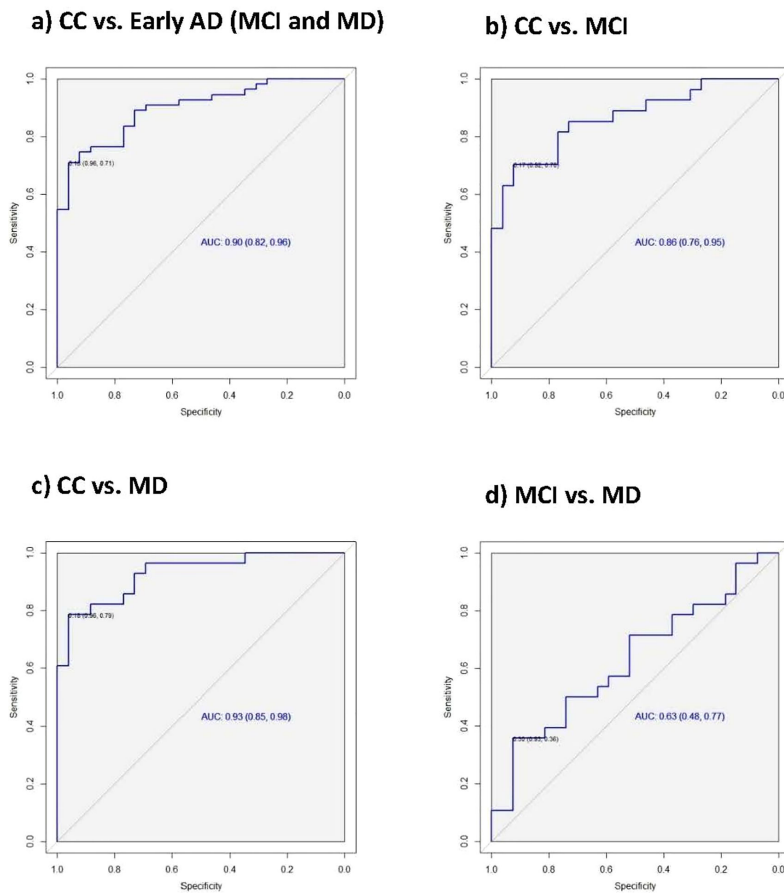


FIGURE 3 | Time-Wall task performance: differentiating between participants with Alzheimer's disease and those in the CC. Abbreviations: CC = control cohort; MD = mild dementia; MCI = mild cognitive impairment.

In this study population, accuracy scores regarding the mental rotation task revealed a moderate correlation with MMSE (Spearman's $\rho = 0.472$; $p < 0.001$) and ADAS-Cog 13 scores (Spearman's $\rho = -0.407$; $p < 0.001$), and a weak correlation with CDR-SB (Spearman's $\rho = -0.372$; $p = 0.001$), age (Spearman's $\rho = -0.247$; $p = 0.026$), and education (Spearman's $\rho = 0.238$; $p = 0.033$). Moreover, mental rotation task response times were moderately correlated with MMSE scores (Spearman's $\rho = -0.405$; $p < 0.001$). Weaker correlations were observed with ADAS-Cog 13 (Spearman's $\rho = 0.386$; $p = 0.001$) and CDR-SB scores (Spearman's $\rho = 0.277$; $p = 0.015$). No notable correlation was found between age (Spearman's $\rho = 0.19$; $p = 0.09$) and the educational level (Spearman's $\rho = 0.20$; $p = 0.06$) (Figure S2).

Multiple linear regression models were used to assess the predictive value of age, sex, education, and cognitive test scores as

independent variables for mental rotation task accuracy scores. Statistically significant results were observed for the following models: MMSE ($R^2 = 0.265$, $F = 8.22$, $\beta = 0.438$, $p < 0.001$), ADAS-Cog 13 ($R^2 = 0.178$, $F = 5.32$, $\beta = 0.334$, $p = 0.001$), and CDR-SB ($R^2 = 0.177$, $F = 5.3$, $\beta = -0.32$, $p = 0.001$).

3.5 | Diagnostic Characteristics of the Mental Rotation Task

The ability of mental rotation task accuracy scores to differentiate participants with early AD from cognitively healthy controls was evaluated using the ROC curve analysis. The task demonstrated moderate diagnostic accuracy in distinguishing participants in the CC from those with AD (MCI and MD), with an AUC of 0.75. Similarly, differentiation between the CC and MCI cohorts

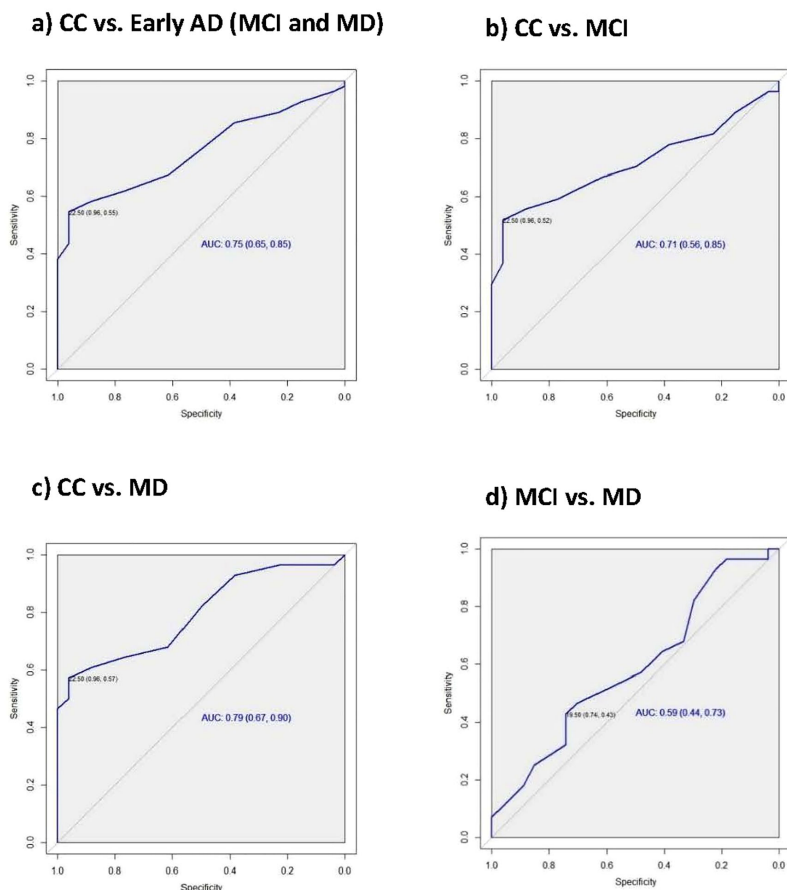


FIGURE 4 | Mental rotation task performance: differentiating between participants with Alzheimer's disease (AD) and cognitively healthy controls. Abbreviations: MD = mild dementia; MCI = mild cognitive impairment; CC = control cohort.

yielded an AUC of 0.71. ROC curves illustrating task performance are presented in Figure 4.

A threshold score of ≤ 22 was selected to indicate AD. Using this cutoff to distinguish participants with AD (MCI and MD) from cognitively healthy controls, the mental rotation task yielded a sensitivity of 54.55% (95% CI: 40.55–68.03) and specificity of 96.15% (95% CI: 80.36–99.9%). Table 3 presents a comprehensive overview of the diagnostic performance of the mental rotation task in differentiating participants with AD from those in the CC.

The accuracy score and response time for the mental rotation task were included in the initial model. The model, which incorporated age, education, sex, ADAS–Cog 13 scores, mental rotation task accuracy scores, and response time, showed a marked improvement in fit over the null model ($X^2 = 93.72$, p

< 0.001 ; Nagelkerke $R^2 = 0.771$). The model achieved an overall classification accuracy of 75.3%, correctly classifying 88.5%, 63%, and 75% of the CC and MCI and MD cohorts, respectively. ADAS–Cog 13 was the only statistically significant predictor ($X^2 = 64.01$, $p < 0.001$).

4 | Discussion

In this study, computerized time–movement estimation (Time–Wall) and mental rotation tasks were evaluated as potential diagnostic tools for early AD. The Time–Wall task demonstrated strong diagnostic performance, with AUC values of 0.9 for distinguishing cognitively healthy controls from participants with early AD (MCI and MD) and 0.86 for differentiating the CC from the MCI cohort alone. Conversely, the performance of the

TABLE 3 | Mental rotation task performance: Differentiating between participants with Alzheimer's disease (AD) and cognitively healthy controls.

	CC vs. early AD (MCI and MD): cut-off ≤ 22	CC vs. MCI: cut-off ≤ 22	CC vs. MD: cut-off ≤ 22	MCI vs. MD: cut-off ≤ 19
Sensitivity	54.55% (40.55–68.03)	51.85% (31.95–71.33%)	57.14% (37.18–75.54%)	42.86% (24.4–662.82%)
Specificity	96.15% (80.36–99.9%)	96.15% (80.36–99.9%)	96.15% (80.36–99.9%)	74.07% (53.72–88.89%)
Negative predictive value	50% (42.57–57.43%)	65.79% (56.34–74.13%)	67.57% (57.43–76.29%)	55.56% (45.82–64.88%)
Positive predictive value	96.77% (81.22–99.52%)	93.33% (66.44–99%)	94.12% (69.51–99.12%)	63.16% (44.31–78.7%)
Overall diagnostic accuracy	67.9% (56.6–77.85%)	73.58% (59.67–84.74%)	75.93% (62.36–86.51%)	58.18% (44.11–71.35%)

Data are presented as percentages and 95% confidence intervals.
Abbreviations: CC = control cohort; MCI = mild cognitive impairment; MD = mild dementia.

mental rotation task was more modest, with AUC values of 0.75 for distinguishing participants in the CC from those with early AD and 0.71 for differentiating the CC from the MCI cohort. Table 4 presents a comparison of Time–Wall and mental rotation administration time and performance with existing cognitive screening tools, differentiating between participants with AD and cognitively healthy controls.

This study's findings indicated that the Time–Wall task performance was already impaired at the MCI stage, with no marked differences observed between the MCI and MD cohorts. In our study population, the median inaccuracy in the CC was 11.46%. In comparison, Piper et al. have reported an average inaccuracy of $12.3\% \pm 0.8\%$ across all age cohorts, with a general tendency to respond too early (Piper et al. 2015). Notably, their study found no evidence of performance decline among older adults [8]. These results suggest that the general reduction in processing speed typically associated with aging may confer a slight advantage in this simple decision-making task, which contrasts with findings from other executive function tests (Piper et al. 2015).

Our study found that inaccuracy scores of the Time–Wall task were strongly correlated with cognitive assessment outcomes, showed a weak correlation with educational background, and no perceptible correlation with age. Furthermore, the Time–Wall task accuracy score emerged as a major predictor in the multinomial logistic regression model used to classify participants into the CC and MCI and MD cohorts. Therefore, these findings highlight the robust diagnostic potential of the Time–Wall task for early AD, with minimal influence from demographic factors, such as age.

While numerous studies have examined cognitive impairments in AD, particularly memory loss and executive dysfunction, relatively few have investigated distortions in temporal judgment and motion perception associated with early AD (El Haj and Kapogiannis 2016). Timing and memory deficits are commonly associated with hippocampal dysfunction. Research emphasizes the role of the hippocampus in distinguishing durations, representing temporal sequences, and encoding the passage of time (MacDonald et al. 2014; Meck et al. 2013). Most existing studies have relied on verbal time-estimation tasks, with only a few exploring time reproduction or bisection tasks (El Haj and Kapogiannis 2016; Schaffner et al. 2022; Pai et al. 2021).

According to Porter et al., the processing of complex motions, which are dynamic, moving stimuli, is more susceptible to deterioration than that of complex static forms, possibly due to its greater reliance on extensive neural connections, which are considerably affected by AD pathology (Porter et al. 2017). Moreover, distinguishing AD from normal aging might be more effectively achieved through complex motion detection rather than focusing on directionality (Liu et al. 2019; Wu et al. 2020). To better understand the differences in temporal judgment in AD, further research is required to evaluate a broad range of timing tasks, such as the Time–Wall task, which incorporates both time and motion processing.

Performance of the mental rotation task, as measured by accuracy scores and response times, demonstrated notable differences between the CC and those with MCI or MD. No marked

TABLE 4 | Comparison of Time–Wall and mental rotation administration time and performance with existing cognitive screening tools, differentiating between participants with Alzheimer's disease (AD) and cognitively healthy controls.

Cognitive assessment tool	Administration time	CC vs. MD	CC vs. MCI
MMSE	10–15 min	Sensitivity 81% (78%–84%) Specificity 89% (87%–91%) (Tsoi et al. 2015)	Sensitivity 89.2% (85.4–92.4%) Specificity 45.1% (39.2–51.1%) (Mitchell et al. 2009)
MoCA*	10–15 min	Sensitivity 91% (84%–95%) Specificity 81% (71%–88%) (Tsoi et al. 2015)	Sensitivity 89% (84%–92%) Specificity 75% (62%–85%) (Tsoi et al. 2015)
ADAS-Cog	30–45 min	Sensitivity 92.2% (88.2–95.5%) Specificity 90.7% (88.8–92.5%) (Wang et al. 2023)	Sensitivity 86.9% (80.0–92.9%) Specificity 83.5% (80.3–86.6%) (Wang et al. 2023)
Time–Wall task	3–5 min	Sensitivity 82.14% (63.11–93.94%) Specificity 88.46% (69.85–97.55%)	Sensitivity 77.78% (57.74–91.38%) Specificity 76.92% (56.35–91.03%)
Mental rotation task**	5–20 min (time limit 30 min)	Sensitivity 57.14% (37.18–75.54%) Specificity 96.15% (80.36–99.9%)	Sensitivity 51.85% (31.95–71.33%) Specificity 96.15% (80.36–99.9%)

Data are presented as percentages and 95% confidence intervals.
Abbreviations: ADAS–Cog = Alzheimer's disease assessment scale–cognitive subscale; CC = control cohort; MCI = mild cognitive impairment; MD = mild dementia; MMSE = mini-mental state examination; MoCA = Montreal cognitive assessment.

*Not performed in this study.

**The PEBL mental rotation task was modified and included six practice trials and 32 experimental trials.

differences were observed between the MCI and MD cohorts. The diagnostic accuracy of mental rotation was lower than expected, and the inclusion of the mental rotation task resulted in a multinomial logistic regression model that did not improve cohort classification. According to Suzuki et al., the mental rotation task with a 180° rotating angle was able to distinguish MCI cases from their controls with 80.0% accuracy (Suzuki et al. 2018).

Several factors may explain the limited diagnostic potential of this task. Most notably, constraints on the length and complexity of mental rotation tasks, particularly for older adults and patients with AD, necessitate accounting for fatigue, which can negatively affect performance during extended tasks across all population groups (Ren et al. 2019). In our study, participants completed six practice trials and 32 experimental trials involving mental rotation. The average task duration was 5–10 min for CC and 10–20 min for MCI and MD, with a time limit of 30 min. By contrast, the original mental rotation task within the PEBL battery comprised 128 trials, and the task duration in the study by Langner et al. was approximately 4 h 30 min (Langner et al. 2023). Second, according to Yassa et al., asymptomatic individuals at risk for familial late-onset AD exhibit more extensive neural activity than healthy individuals during mental rotation tasks. This infers that a genetic predisposition to AD is associated with altered brain function, marked by increased activation in the parietal cortex, particularly in the prefrontal regions, potentially reflecting a compensatory network (Yassa et al. 2008). These results indicate that the diagnostic accuracy of the mental rotation task in distinguishing between cognitively healthy individuals and those with pathology may be influenced by compensatory

mechanisms in frontal lobe regions that are not yet affected by AD (Yassa et al. 2008).

While studies have frequently shown that males outperform females on spatial ability tests, our study found no distinct differences in sex when independently analyzing the cohorts (Wei et al. 2016). Furthermore, the mental rotation task performance exhibited a weak correlation with age and educational attainment, suggesting a minimal impact of demographic variables. These findings highlight the need for a more comprehensive evaluation of mental rotation tasks to better capture compensatory brain network function.

This study had several limitations. First, CSF biomarker data were available for only a small number of participants due to the invasive nature of the procedure, and positron emission tomography biomarkers were not used. Including CSF biomarkers for all participants would have enabled the exclusion of MCI caused by dementia with Lewy bodies. This condition can be challenging to differentiate from MCI due to AD when relying on cognitive tests focused on motion perception or mental rotation. Nevertheless, none of the participants met the 2017 revised criteria for the clinical diagnosis of dementia with Lewy bodies (McKeith et al. 2017). Second, the sample size was adequate to demonstrate notable changes; however, additional studies with larger sample sizes would be advantageous for validating these findings. Third, the cross-sectional design of the study limited the ability to draw definitive conclusions regarding AD progression. Despite the promising results of this study, longitudinal studies are necessary to establish the effectiveness of the Time–Wall and mental rotation tests as reliable assessment tools.

The strengths of this study included the ability to distinguish temporal judgment and motion perception from language skills using the computerized PEBL test. This approach enhanced our understanding of early AD-related changes and demonstrated strong diagnostic accuracy.

5 | Conclusions

The Time-Wall task is a freely available and efficient clinical assessment tool, enabling a quick and straightforward evaluation of temporal judgment and motion perception in early AD. We recommend incorporating the Time-Wall task as an additional tool to enhance the early diagnosis of AD. Notably, age did not influence the performance of this task. The mental rotation task exhibited low sensitivity and requires further evaluation, as it may offer insights into compensatory brain network functions. Combining multiple diagnostic tools, including temporal judgment and motion perception assessments, could provide the most accurate and timely AD diagnosis.

Author Contributions

VS is responsible for the conceptualization of the manuscript; in addition to conducting investigations, formal analyses, and data curation. GP-K and EA contributed to data curation; in addition to conceptualization of, reviewing, and editing the manuscript. JK contributed to data curation; reviewing, and editing the manuscript. GK provided supervision and contributed to formal analysis, in addition to conceptualization of, reviewing, and editing the manuscript. All authors read and approved the final manuscript.

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Ethics Statement

This study was approved by the Vilnius Regional Bioethics Committee on January 11, 2022 (Approval Number: 2022/1-1405-877). Moreover, this study was conducted in accordance with the principles of the Declaration of Helsinki and Standards for Reporting Diagnostic Accuracy Studies (STARD) guidelines. All participants provided written informed consent prior to study participation.

Consent

All participants provided written informed consent prior to study participation for publication of their de-identified data.

Conflicts of Interest

The authors declare that they have no competing interests.

Funding

The authors have nothing to report.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Peer Review

The peer review history for this article is available at <https://doi.org/10.1002/brb3.71077>.

References

- Albert, M. S., S. T. DeKosky, D. Dickson, et al. 2011. "The Diagnosis of Mild Cognitive Impairment Due to Alzheimer's Disease: Recommendations From the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease." *Alzheimer's & Dementia* 7: 270–279.
- Chan, J. Y., J. S. Kwong, A. Wong, T. C. Kwok, and K. K. Tsoi. 2018. "Comparison of Computerized and Paper-and-Pencil Memory Tests in Detection of Mild Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis of Diagnostic Studies." *Journal of the American Medical Directors Association* 19: 748–756.
- Deng, Y., L. Shi, Y. Lei, et al. 2016. "Mapping the "What" and "Where" Visual Cortices and Their Atrophy in Alzheimer's Disease: Combined Activation Likelihood Estimation With Voxel-Based Morphometry." *Frontiers in Human Neuroscience* 10: 333.
- El Haj, M., and D. Kapogiannis. 2016. "Time Distortions in Alzheimer's Disease: A Systematic Review and Theoretical Integration." *NPJ Aging and Mechanisms of Disease* 2: 1–5.
- Jack, C. R. Jr., S. J. Andrews, and T. G. Beach, et al. 2024. "Revised Criteria for the Diagnosis and Staging of Alzheimer's Disease." *Nature Medicine* 30: 2121–2124.
- Jack, C. R., Jr., D. A. Bennett, and K. Blennow, et al. 2018. "NIA-AA Research Framework: Toward a Biological Definition of Alzheimer's Disease." *Alzheimer's & Dementia* 14: 535–562.
- Kessels, R. P. 2019. "Improving Precision in Neuropsychological Assessment: Bridging the Gap Between Classic Paper-and-Pencil Tests and Paradigms From Cognitive Neuroscience." *The Clinical Neuropsychologist* 33: 357–368.
- Kim, T., A. R. Jounghani, E. Gozdas, and S. H. Hosseini. 2024. "Cortical Neurite Microstructural Correlates of Time Perception in Healthy Older Adults." *Heliyon* 10, no. 12: e32534. <https://doi.org/10.1016/j.heliyon.2024.e32534>.
- Kochan, N. A., M. Heffernan, M. Valenzuela, et al. 2022. "Reliability, Validity, and User-Experience of Remote Unsupervised Computerized Neuropsychological Assessments in Community-Living 55- to 75-Year-Olds." *Journal of Alzheimer's Disease* 90: 1629–1645.
- Langner, R., F. Scharnowski, S. Ionta, C. E. G. Salmon, B. J. Piper, and G. S. Pamplona. 2023. "Evaluation of the Reliability and Validity of Computerized Tests of Attention." *PLoS ONE* 18: e0281196.
- Lineweaver, T. T., D. P. Salmon, M. W. Bondi, and J. Corey-Bloom. 2005. "Differential Effects of Alzheimer's Disease and Huntington's Disease on the Performance of Mental Rotation." *Journal of the International Neuropsychological Society* 11: 30–39.
- Liu, Y., D. Feng, and H. Wang. 2019. "Distinct forms of motion sensitivity impairments in Alzheimer's disease." *Scientific Reports* 9: 12931.
- MacDonald, C. J., N. J. Fortin, S. Sakata, and W. H. Meck. 2014. "Retrospective and Prospective Views on the Role of the Hippocampus in Interval Timing and Memory for Elapsed Time." *Timing & Time Perception* 2: 51–61.
- McKeith, I. G., B. F. Boeve, D. W. Dickson, et al. 2017. "Diagnosis and Management of Dementia With Lewy Bodies: Fourth Consensus Report of the DLB Consortium." *Neurology* 89: 88–100.
- McKhann, G. M., D. S. Knopman, and H. Chertkow, et al. 2011. "The Diagnosis of Dementia Due to Alzheimer's Disease: Recommendations From the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease." *Alzheimer's & Dementia* 7: 263–269.

- Meck, W. H., R. M. Church, and M. S. Matell. 2013. "Hippocampus, Time, and Memory—A Retrospective Analysis." *Behavioral Neuroscience* 127: 642.
- Mitchell, A. J. 2009. "A Meta-Analysis of the Accuracy of the Mini-Mental State Examination in the Detection of Dementia and Mild Cognitive Impairment." *Journal of Psychiatric Research* 43, no. 4: 411–431.
- Pai, M. C., C. J. Yang, and S. Y. Fan. 2021. "Time Perception in Prodromal Alzheimer's Dementia and in Prodromal Dementia With Lewy Bodies." *Frontiers in Psychiatry* 12: 728344.
- Piper, B. J., S. T. Mueller, A. R. Geerken, et al. 2015. "Reliability and Validity of Neurobehavioral Function on the Psychology Experimental Building Language Test Battery in Young Adults." *PeerJ* 3: e1460.
- Porter, G., J. Wattam-Bell, A. Bayer, et al. 2017. "Different Trajectories of Decline for Global Form and Global Motion Processing in Aging, Mild Cognitive Impairment and Alzheimer's Disease." *Neurobiology of Aging* 56: 17–24.
- Rajan, K. B., J. Weuve, L. L. Barnes, E. A. McAninch, R. S. Wilson, and D. A. Evans. 2021. "Population Estimate of People With Clinical Alzheimer's Disease and Mild Cognitive Impairment in the United States (2020–2060)." *Alzheimer's & Dementia* 17: 1966–1975.
- Ren, P., A. J. Anderson, K. McDermott, T. M. Baran, and F. Lin. 2019. "Cognitive Fatigue and Cortical-Striatal Network in Old Age." *Aging* 11: 2312.
- Sam, N. 2013. "Unified Tri-Service Cognitive Performance Assessment Battery (UTCPAB)." *Psychology Dictionary*. Accessed April 15, 2025. <https://psychologydictionary.org/unified-tri-service-cognitive-performance-assessment-battery-utcpab/>.
- Schaffner, E., M. Sandoz, C. Grisot, N. Auclair-Ouellet, and M. Fossard. 2022. "Mental Time Travel and Time Reference Difficulties in Alzheimer's Disease: Are They Related? A Systematic Review." *Frontiers in Psychology* 13: 858001.
- Shepard, R. N., and J. Metzler. 1971. "Mental Rotation of Three-Dimensional Objects." *Science* 171: 701–703.
- Spargo, D., R. Zur, P. J. Lin, P. Synnott, E. Klein, and A. Hartry. 2023. "Estimating Prevalence of Early Symptomatic Alzheimer's Disease in the United States." *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* 15: e12497.
- Suzuki, A., J. Shinozaki, S. Yazawa, et al. 2018. "Establishing a New Screening System for Mild Cognitive Impairment and Alzheimer's Disease With Mental Rotation Tasks that Evaluate Visuospatial Function." *Journal of Alzheimer's Disease* 61: 1653–1665.
- The PEBL Project. 2019. "PEBL." <https://pebl.sourceforge.net>. Accessed May 10, 2025.
- Tsoi, K. K. F., J. Y. C. Chan, H. W. Hirai, S. Y. S. Wong, and T. C. Y. Kwok. 2015. "Cognitive Tests to Detect Dementia: A Systematic Review and Meta-Analysis." *JAMA Internal Medicine* 175, no. 9: 1450–1458.
- Wang, X., F. Li, J. Tian, and Y. Zhang. 2023. "Bayesian Estimation for the Accuracy of Three Neuropsychological Tests in Detecting Alzheimer's Disease and Mild Cognitive Impairment: A Retrospective Analysis of the ADNI Database." *European Journal of Medical Research* 28: 427.
- Wei, W., C. Chen, Q. Dong, and X. Zhou. 2016. "Sex Differences in Gray Matter Volume of the Right Anterior Hippocampus Explain Sex Differences in Three-Dimensional Mental Rotation." *Frontiers in Human Neuroscience* 10: 580.
- World Health Organization. 2025. Dementia: Key Facts. <https://www.who.int/news-room/fact-sheets/detail/dementia>.
- Wu, S. Z., A. V. Masurkar, and L. J. Balcer. 2020. "Afferent and Efferent Visual Markers of Alzheimer's Disease: A Review and Update in Early Stage Disease." *Frontiers in Aging Neuroscience* 12: 572337.
- Yassa, M. A., G. Verduzco, C. Cristinzio, and S. S. Bassett. 2008. "Altered fMRI Activation During Mental Rotation in Those at Genetic Risk for Alzheimer Disease." *Neurology* 70: 1898–1904.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Abbreviations: CC = control cohort; MD = mild dementia; MCI = mild cognitive impairment. Abbreviations: CC = control cohort; MD = mild dementia; MCI = mild cognitive impairment.

4th publication/ 4 publikacija

Silhouettes, number location, and cube analysis tests from the VOSP battery reveal visual object and space perception deficits in early Alzheimer's disease.

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OPEN Silhouettes, number Location, and cube analysis tests from the VOSP battery reveal visual object and space perception deficits in early Alzheimer's disease

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The Visual Object and Space Perception Battery (VOSP) is a widely used tool for evaluating higher visual processing. However, limited information exists regarding its diagnostic utility in differentiating mild cognitive impairment (MCI) and mild dementia (MD) due to Alzheimer's disease (AD) from cognitively normal older adults (CG). This study aimed to evaluate VOSP tests for object perception (silhouettes) and space perception (number location and cube analysis) as diagnostic tools for the early detection of AD. This study included 81 participants (28 with MD, 27 with MCI, and 26 in the CG). Our findings indicate that performance on the silhouettes, number location, and cube analysis tests showed good diagnostic properties in distinguishing CG from individuals with MCI or MD: AUC = 0.8, 0.79, and 0.82, respectively. Incorporating number location or cube analysis results into a multinomial regression model that included sex, age, education, and ADAS-Cog 13 scores improved correctly classified CG, MCI, and MD cases (from 76.5% to 80.2%). These results confirm that silhouettes, number location, and cube analysis tasks are suitable as additional tools for early diagnosis of AD, and space perception tasks improve diagnostic accuracy.

Keywords Alzheimer's disease, Cube analysis, Mild cognitive impairment, Number location, Silhouettes, VOSP

The pathological processes of Alzheimer's disease (AD) begin many years before individuals exhibit any symptoms¹. Patients with AD who survive from 70 to 80 years of age typically experience the severe stage of the disease for approximately 40% of that decade². The period from the onset of AD neuropathological changes to the severe stage presents a critical window for early identification, enabling patients and medical professionals to mitigate risks and manage the condition, including utilizing recent advancements in AD diagnostic tools and therapeutic interventions³.

According to the National Memory Service Audit in England, the use of in vivo indicators of AD-related brain abnormalities (such as cerebrospinal fluid (CSF) analysis) remains limited, and the actual number of patients referred for these investigations in the audit was very low⁴. Disclosing AD biomarker results to patients without clinical evaluation and proper counseling can be detrimental⁵. The Revised criteria for the diagnosis and staging of AD, released in 2024 by the Alzheimer's Association Workgroup, do not endorse the routine clinical assessment of AD-related biomarkers in asymptomatic individuals. Such evaluations are currently recommended only within the framework of observational or interventional studies⁶.

Cognitive testing remains essential; however, no single cognitive test is ideal for detecting the earliest stages of AD. Recent studies have provided growing evidence that visual perception is a promising noninvasive marker^{7,8}. Fundamental aspects of visual perception include light perception, sensitivity to contrast, orientation of stimuli, visual acuity, and the ability to detect form, color, movement, and depth^{9,10}. The gradual integration of visual data into the visual association cortex occurs through two principal pathways: the ventral stream, which identifies "what" is seen, and the dorsal stream, which determines "where" objects are located in space¹¹. The rationale for utilizing visual perception and visuospatial tests for early AD detection is based on structural and functional changes in the parietal and temporal lobes early in the disease course^{12,13}. Memon et al. recently

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	CG (N = 26)	MCI (N = 27)	MD (N = 28)	Statistics ($\chi^2(2)/H(2), p$)
Female (%) ^a	12 (46%)	19 (70%)	18 (64%)	3.09, 0.21
Age ^a	73 (9)	75 (11)	77 (9)	4.63, 0.10
Years of education ^a	16 (1)	15 (4)	15 (3)	4.37, 0.11
GDS ^a	4 (2)	5 (1)	4 (2)	1.40, 0.50
HIS ^a	1 (1)	1 (1)	1 (1)	1.84, 0.40

Table 1. Demographic and clinical data of the participants. The data are represented as median and interquartile range, except where otherwise noted. ^aGroups did not differ significantly. MD, mild dementia; MCI, mild cognitive impairment; CG, control group; GDS, Geriatric Depression Scale; HIS, Hachinski Ischemic Score.

	CG (N = 26)	MCI (N = 27)	MD (N = 28)	Statistics (H(2), p)
MMSE ^a	29 (1)	25 (3)	22 (2)	72.02, <0.001
ADAS-Cog 13 ^a	12.5 (5.67)	22 (7.66)	31 (7.5)	74.26, <0.001
CDR-SB ^a	0 (0)	1.5 (1)	4.5 (0.5)	53.07, <0.001

Table 2. Cognitive tests results of the participants. The data are represented as median and interquartile range. ^aAll three groups differed significantly. MD, mild dementia; MCI, mild cognitive impairment; CG, control group.

reported a connection between visual function and changes in AD biomarkers¹⁴. Visual perceptive ability and its deterioration in AD warrant particular attention, given the considerable adverse effects on the quality of life of patients¹⁵. However, neuropsychological tests evaluating overall cognition are predominantly verbal, with visual perception comprising only a minor component of the evaluation¹⁶.

The Visual Object and Space Perception Battery (VOSP) serves as a common assessment tool for evaluating higher visual processing and consists of eight tests: four for visual object perception (incomplete letters, silhouettes, object decisions, and progressive silhouettes) and four for visual space perception (dot counting, position discrimination, number location, and cube analysis)¹⁷. The VOSP is easy to administer and is a paper-based battery that does not rely on language skills or motor abilities¹⁷. However, implementing the complete set of tasks is time-intensive, and typically, only a few or single tests are employed. Notably, object perception VOSP test results should be interpreted with caution, especially for Test 3 (object decision), as individuals with low visual acuity have an increased likelihood of scoring below the cutoff point owing to their visual limitations¹⁸. Quental et al. emphasized that the VOSP battery is a highly effective instrument for identifying visuospatial impairments in patients with mild dementia (MD) due to AD, with minimal interference from other cognitive domains¹⁹. According to this study, the silhouettes test demonstrated the most favorable diagnostic properties among object perception tests, with an area under the curve of 0.859, whereas other object perception tests scored below 0.8¹⁹. Additionally, the number location and cube analysis tests demonstrated the highest diagnostic accuracy in spatial perception assessments¹⁹. In our research, we selected VOSP tests that have also been identified in recent studies as potential measures for predicting the progression from MCI to AD or for predicting the pathological diagnosis of AD^{20–22}. Nevertheless, limited information exists regarding its diagnostic properties in differentiating mild cognitive impairment (MCI) due to AD from cognitively normal older adults. These data would be valuable for disease-modifying treatment studies and clinical practice.

This study aimed to evaluate the VOSP tests for object (silhouettes) and space (number location, and cube analysis) perceptions as diagnostic tools for the early detection of AD. In addition, we assessed their diagnostic properties and relationships with other cognitive test results.

Results

The analysis revealed no statistically significant differences in sex distribution between the three groups (chi-squared test, $p > 0.05$). Similarly, no significant differences were observed in educational background, age, depressive symptoms (as measured by the Geriatric Depression Scale), or Hachinski ischemic scores (Kruskal-Wallis $p > 0.05$). A comprehensive summary of the demographic and clinical data of the study participants is presented in Table 1.

Significant differences were observed in cognitive test results between the three groups (Kruskal-Wallis $p < 0.05$). The results of the cognitive tests are presented in Table 2.

Object perception: silhouettes

One-way analysis of variance (ANOVA) revealed significant differences in silhouettes test scores (mean and standard deviation: CG, 18.77 ± 5.64 ; MCI, 13.44 ± 4.85 ; MD, 12.07 ± 4.06 ; $F = 14.06$, $p < 0.001$). Post-hoc testing indicated significant differences between the CG and MCI groups as well as the CG and MD groups ($p < 0.001$ for both). However, no significant differences were observed between the MCI and MD groups ($p = 0.90$).

The silhouettes test consists of two components: the identification of 15 animals and 15 inanimate objects. Both components demonstrated statistically significant differences between the CG and MCI groups as well as the CG and MD groups. However, no significant differences were observed between the MCI and MD groups (one-way ANOVA for naming animals: $F = 11.49$, $p < 0.001$; CG vs. MCI, $p = 0.002$; CG vs. MD, $p < 0.001$; and MCI vs. MD, $p = 1$; one-way ANOVA for naming inanimate objects: $F = 9.65$, $p < 0.001$; CG vs. MCI, $p = 0.004$; CG vs. MD, $p < 0.001$; and MCI vs. MD, $p = 1$).

In the sample comprising all participants, silhouettes test scores demonstrated a moderate correlation with mini-mental state examination (MMSE) (Spearman's rho: 0.477; $p < 0.001$), clinical dementia rating-sum of boxes (CDR-SB) (Spearman's rho: -0.437; $p < 0.001$), The 13-item version of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13) (Spearman's rho: -0.479; $p < 0.001$), and age (Spearman's rho: -0.404; $p < 0.001$), while a weak correlation was observed with education (Spearman's rho: 0.295; $p = 0.007$).

Multiple linear regression models were employed to assess whether silhouettes test scores could be predicted using cognitive test results. These models incorporated cognitive test scores (MMSE, CDR-SB, and ADAS-Cog 13) and were adjusted for sex, age, and education.

The adjusted models demonstrated statistical significance in the multiple linear regression analysis for MMSE ($R^2 = 0.489$, $F = 20.12$, $\beta = 0.381$, $p < 0.001$), ADAS-Cog 13 ($R^2 = 0.492$, $F = 20.38$, $\beta = -0.4$, $p < 0.001$), and CDR-SB ($R^2 = 0.444$, $F = 16.99$, $\beta = -0.316$, $p < 0.001$).

To assess the effectiveness of silhouettes test scores in distinguishing between the CG and patients with AD, including those with MCI or MD, as well as patients with MCI and MD, receiver operating characteristic (ROC) curve analysis was conducted. The ROC curves illustrating the silhouettes test performance for differentiating between participant groups are shown in Fig. 1.

A threshold score ≤ 16 on the silhouettes test was established as an indicator of AD (sensitivity 78%, specificity 73%, maximum Youden's $J = 0.51$). When applied to distinguish AD patients (including those with MCI or MD

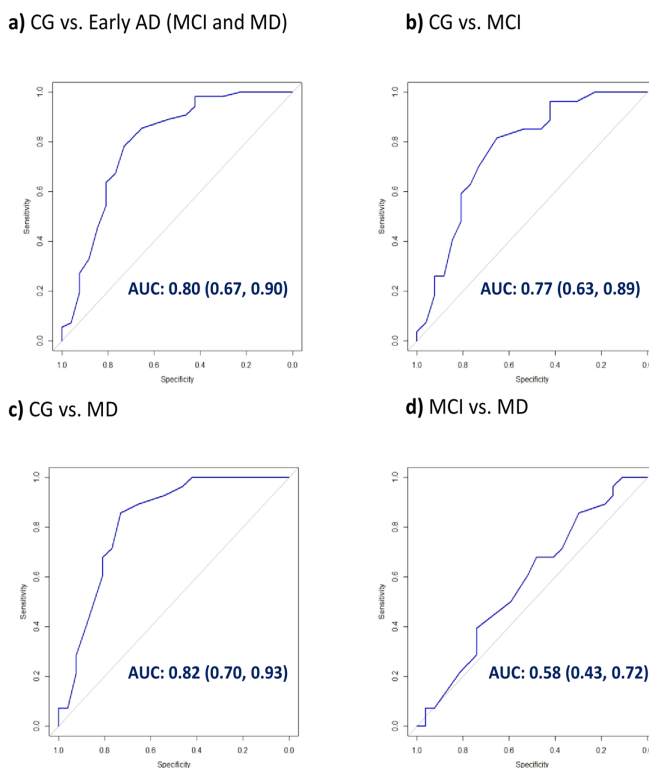


Fig. 1. Performance of the silhouettes test in differentiating between participants with AD from the CG. AD, Alzheimer's disease; CG, control group; MD, mild dementia; MCI, mild cognitive impairment.

due to AD) from CG participants, the silhouettes test demonstrated a sensitivity of 78.18% (95% CI: 64.99–88.19) and specificity of 73.08% (95% CI: 52.21–88.43%). Furthermore, the test yielded a negative predictive value of 61.29% (95% CI: 47.69–73.33%) and positive predictive value of 86% (95% CI: 76.26–92.16%). The overall accuracy of diagnosis was 76.54% (95% CI: 65.82–85.25%). A threshold score ≤ 13 on the silhouettes test was established for differentiating MCI from MD (sensitivity 68%, specificity 48%, maximum Youden's $J = 0.16$). All cutoff scores and diagnostic properties of the silhouettes test for comparisons between the diagnostic groups are presented in Table 3.

To examine the influence of predictor variables on group classification (CG, MCI, and MD), a multinomial logistic regression analysis was conducted. Initially, a model incorporating sex, age, education, and ADAS-Cog 13 scores as predictors was developed. The inclusion of these variables significantly enhanced the fit of the model compared to the intercept-only model ($X^2 = 87.79$, $p < 0.001$; Nagelkerke $R^2 = 0.744$). This model accurately classified 76.5% of cases overall, with correct classification rates of 92.3% for CG, 66.7% for MCI, and 71.4% for MD. Among the predictors, the ADAS-Cog 13 score emerged as the most robust and statistically significant ($X^2 = 78.83$, $p < 0.001$).

A second model incorporating sex, age, education, ADAS-Cog 13 scores, and silhouettes test scores demonstrated a notable enhancement in fit compared to a null model ($X^2 = 88.30$, $p < 0.001$; Nagelkerke $R^2 = 0.747$). This model accurately classified 76.4% of cases overall, with specific accuracies of 92.3% for CG, 63% for MCI, and 75% for MD. Within this model, ADAS-Cog 13 emerged as a robust and statistically significant predictor ($X^2 = 61.77$; $p < 0.001$), whereas the silhouettes test was not a significant predictor ($X^2 = 0.465$; $p = 0.793$).

Space perception: number location

Significant differences were observed in the number location test scores across the three groups. The median and interquartile ranges were as follows: CG, 9.5 (2); MCI, 8 (3); and MD, 6 (6). A Kruskal-Wallis test ($p < 0.001$) and subsequent post hoc analysis revealed statistically significant differences between all group pairs: CG versus MCI ($p = 0.007$), MCI versus MD ($p = 0.007$), and CG versus MD ($p < 0.001$).

A moderate correlation was observed between number location test scores and performance on the MMSE (Spearman's rho: 0.573; $p < 0.001$), CDR-SB (Spearman's rho: -0.5; $p < 0.001$), and ADAS-Cog 13 (Spearman's rho: -0.467; $p < 0.001$). No significant correlations were observed with age and education.

Multiple linear regression models were employed to assess whether silhouettes test scores could be predicted using cognitive test results. These models incorporated cognitive test scores (MMSE, CDR-SB, and ADAS-Cog 13) and were adjusted for sex, age, and education.

The adjusted models demonstrated statistical significance in the multiple linear regression analysis with MMSE ($R^2 = 0.384$, $F = 13.47$, $\beta = 0.483$, $p < 0.001$), ADAS-Cog 13 ($R^2 = 0.288$, $F = 9.08$, $\beta = -0.383$, $p < 0.001$), and CDR-SB ($R^2 = 0.364$, $F = 12.46$, $\beta = -0.46$, $p < 0.001$).

To assess the effectiveness of the number location test score in distinguishing between the CG and patients with AD, including those with MCI or MD, as well as patients with MCI and MD, ROC curve analysis was conducted. The ROC curves illustrating the number location test performance for differentiating participant groups are shown in Fig. 2.

A threshold score ≤ 8 on the number location test was established to indicate AD (sensitivity 65%, specificity 73%, maximum Youden's $J = 0.39$). When applied to distinguish patients with AD (including those with MCI or MD due to AD) from CG participants, the number location test demonstrated a sensitivity of 65.45% (95% CI: 51.42–77.76) and specificity of 73.08% (95% CI: 52.21–88.43%). Furthermore, the test yielded a negative predictive value of 50% (95% CI: 39.36–60.64%) and positive predictive value of 83.72% (95% CI: 72.63–90.88%). The overall accuracy of diagnosis was 67.9% (95% CI: 56.60–77.85%). A threshold score ≤ 7 on the number location test was established for differentiating MCI from MD (sensitivity 71%, specificity 67%, maximum Youden's $J = 0.38$). All cut-off scores and diagnostic properties of the number location test for comparisons between the diagnostic groups are presented in Table 4.

To examine the influence of predictor variables on group classification (CG, MCI, and MD), a multinomial logistic regression analysis was conducted. Initially, a model incorporating sex, age, education, and ADAS-Cog 13 scores as predictors was developed. Including these variables significantly enhanced the fit of the model

	CG vs. early AD (MCI and MD), cut-off ≤ 16	CG vs. MCI, cut-off ≤ 16	CG vs. MD, cut-off ≤ 16	MCI vs. MD, cut-off ≤ 13
Sensitivity	78.18% (64.99–88.19%)	70.37% (49.82–86.25%)	85.71% (67.33–95.97%)	67.86% (47.65–84.12%)
Specificity	73.08% (52.21–88.43%)	73.08% (52.21–88.43%)	73.08% (52.21–88.43%)	48.15% (28.67–68.05%)
Negative predictive value	61.29% (47.69–73.33%)	70.37% (55.94–81.63%)	82.61% (65.05–92.38%)	59.09% (42.61–73.75%)
Positive predictive value	86% (76.26–92.16%)	73.08% (57.92–84.26%)	77.42% (64.13–86.80%)	57.58% (46.54–67.9%)
Overall diagnostic accuracy	76.54% (65.82–85.25%)	71.7% (57.65–83.21%)	79.63% (66.47–89.37%)	58.18% (44.11–71.35%)

Table 3. Diagnostic properties of the silhouettes test for differentiating between participants with AD and CG. Data are presented as percentage and 95% confidence interval. MD, mild dementia; MCI, mild cognitive impairment; CG, control group.

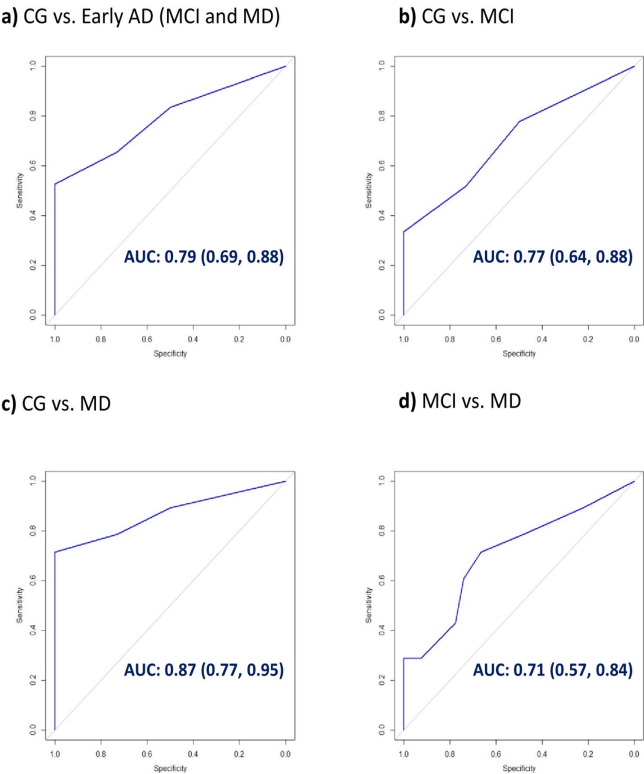


Fig. 2. Performance of the number location test in differentiating between participants with AD from the CG. AD, Alzheimer's disease; CG, control group; MD, mild dementia; MCI, mild cognitive impairment.

	CG vs. early AD (MCI and MD), cut-off ≤ 8	CG vs. MCI, cut-off ≤ 8	CG vs. MD, cut-off ≤ 8	MCI vs. MD, cut-off ≤ 7
Sensitivity	65.45% (51.42–77.76)	51.65% (31.95–71.33%)	78.57% (59.05–91.7%)	71.43% (51.33–86.78%)
Specificity	73.08% (52.21–88.43%)	73.08% (52.21–88.43%)	73.08% (52.21–88.43%)	66.67% (46.04–83.48%)
Negative predictive value	50% (39.36–60.64%)	59.38% (48.1–69.75%)	73.08% (52.21–88.43%)	69.23% (54.18–81.07%)
Positive predictive value	83.72% (72.63–90.88%)	66.67% (49.07–80.59%)	75.86% (61.84–85.9%)	68.97% (55.38–79.92%)
Overall diagnostic accuracy	67.9% (56.6–77.85%)	62.29% (47.89–75.21%)	75.93% (62.36–86.51%)	69.09% (55.19–80.86%)

Table 4. Diagnostic properties of the number location test for differentiating between participants with AD and CG. Data are presented as percentage and 95% confidence interval. MD, mild dementia; MCI, mild cognitive impairment; CG, control group.

compared to the intercept-only model ($X^2=87.79$, $p<0.001$; Nagelkerke $R^2=0.744$). This model accurately classified 76.5% of cases overall, with correct classification rates of 92.3% for CG, 66.7% for MCI, and 71.4% for MD. Among the predictors, the ADAS-Cog 13 score emerged as the most robust and statistically significant ($X^2=78.83$, $p<0.001$).

A second model incorporating sex, age, education, ADAS-Cog 13 scores, and number location test scores demonstrated a notable enhancement in fit compared to a null model ($X^2=104.76$, $p<0.001$; Nagelkerke $R^2=0.816$). This model accurately classified 80.2% of cases overall, with specific accuracies of 92.3% for CG, 70.4% for MCI, and 78.6% for MD. Within this model, ADAS-Cog 13 and number location tests were statistically significant predictors ($X^2 68.22$, $p<0.001$; $X^2 16.97$, $p<0.001$, respectively).

Space perception: cube analysis

The cube analysis test scores differed significantly between the groups (medians and interquartile ranges: CG, 10 (1); MCI, 8 (3); MD 7 (5); Kruskal–Wallis $p<0.001$). Post-hoc analysis revealed significant differences between CG vs. MCI and CG vs. MD, $p<0.001$, but not between MCI vs. MD, $p=0.094$).

The cube analysis scores moderately correlated with MMSE (Spearman's rho: 0.579; $p<0.001$), CDR-SB (Spearman's rho: -0.489; $p<0.001$), ADAS-Cog 13 (Spearman's rho: -0.521; $p<0.001$), while a weak correlation was observed with age (Spearman's rho: -0.337; $p=0.002$), and education (Spearman's rho: 0.346; $p=0.002$).

Multiple linear regression models were employed to assess whether cube analysis test scores could be predicted using cognitive test results. These models incorporated cognitive test scores (MMSE, CDR-SB, and ADAS-Cog 13) and were adjusted for sex, age, and education.

The adjusted models demonstrated statistical significance in the multiple linear regression analysis with MMSE ($R^2=0.376$, $F=13.03$, $\beta=0.471$, $p<0.001$), ADAS-Cog 13 ($R^2=0.29$, $F=9.16$, $\beta=-0.382$, $p<0.001$), and CDR-SB ($R^2=0.296$, $F=9.4$, $\beta=-0.376$, $p<0.001$).

To assess the effectiveness of the cube analysis test score in distinguishing between the CG and patients with AD, including those with MCI or MD, as well as patients with MCI and MD, ROC curve analysis was conducted. The ROC curves illustrating the cube analysis test performance for differentiating participant groups are shown in Fig. 3.

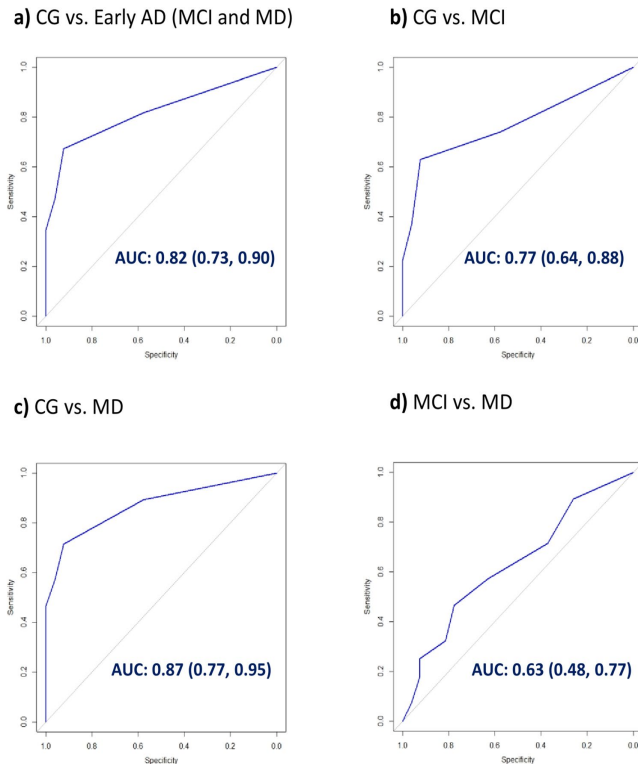


Fig. 3. Performance of cube analysis test in differentiating between participants with AD from the CG. AD, Alzheimer's disease; CG, control group; MD, mild dementia; MCI, mild cognitive impairment.

	CG vs. early AD (MCI and MD), cut-off ≤ 8	CG vs. MCI, cut-off ≤ 8	CG vs. MD, cut-off ≤ 8	MCI vs. MD, cut-off ≤ 7
Sensitivity	67.27% (53.29–79.32%)	62.96% (42.37–80.60%)	71.43% (51.33–86.78%)	57.14% (37.18–75.54%)
Specificity	92.31% (74.87–99.05%)	92.31% (74.87–99.05%)	92.31% (74.87–99.05%)	62.96% (42.37–80.6%)
Negative predictive value	57.14% (47.32–66.43%)	70.59% (59.18–79.89%)	75.00% (62.31–84.48%)	58.62% (45.81–70.36%)
Positive predictive value	94.87% (82.83–98.61%)	89.47% (68.51–97.08%)	90.91% (72.12–97.48%)	61.54% (47.07–74.22%)
Overall diagnostic accuracy	75.31% (64.47–84.22%)	77.36% (63.79–87.72%)	81.48% (68.57–90.75%)	60% (45.91–72.98%)

Table 5. Diagnostic properties of the cube analysis test for differentiating between participants with AD and CG. Data are presented as percentage and 95% confidence interval. MD, mild dementia; MCI, mild cognitive impairment; CG, control group.

A threshold score ≤ 8 on the cube analysis test was established to indicate AD (sensitivity 67%, specificity 92%, maximum Youden's $J=0.59$). When applied to distinguish patients with AD (including those with MCI or MD due to AD) from CG participants, the test demonstrated a sensitivity of 67.27% (95% CI: 53.29–79.32%) and specificity of 92.31% (95% CI: 74.87–99.05%). Furthermore, the test yielded a negative predictive value of 57.14% (95% CI: 47.32–66.43%) and positive predictive value of 94.87% (95% CI: 82.83–98.61%). The overall accuracy of diagnosis was 75.31% (95% CI: 64.47–84.22%). A threshold score ≤ 8 on the cube analysis test was established for differentiating MCI from MD (sensitivity 57%, specificity 63%, maximum Youden's $J=0.2$). All cut-off scores and diagnostic properties of the cube analysis test for comparisons between the diagnostic groups are presented in Table 5.

To examine the influence of predictor variables on group classification (CG, MCI, and MD), a multinomial logistic regression analysis was conducted. Initially, a model incorporating sex, age, education, and ADAS-Cog 13 scores as predictors was developed. The inclusion of these variables significantly enhanced the fit of the model compared to the intercept-only model ($X^2=87.79$, $p<0.001$; Nagelkerke $R^2=0.744$). This model accurately classified 76.5% of cases overall, with correct classification rates of 92.3% for CG, 66.7% for MCI, and 71.4% for MD. Among the predictors, the ADAS-Cog 13 score emerged as the most robust and statistically significant ($X^2=78.83$, $p<0.001$).

A second model incorporating sex, age, education, ADAS-Cog 13 scores, and cube analysis test scores demonstrated a notable enhancement in fit compared to a null model ($X^2=94.08$, $p<0.001$; Nagelkerke $R^2=0.773$). This model accurately classified 80.2% of cases overall, with specific accuracies of 92.3% for CG, 70.4% for MCI, and 78.6% for MD. Within this model, ADAS-Cog 13 and cube analysis test were statistically significant predictors ($X^2=59.93$, $p<0.001$; $X^2=6.29$, $p=0.043$, respectively).

Discussion

Our study demonstrated that the VOSP battery tests (silhouettes, number location, and cube analysis) are appropriate additional tools for early diagnosis of AD. These three tests demonstrated similar diagnostic potential in differentiating MCI from CG (area under the curve (AUC)=0.77 for all). In contrast, the cube analysis test exhibited the highest diagnostic accuracy in distinguishing CG from MCI and MD diagnostic groups (AUC silhouettes=0.8, number location=0.79, and cube analysis=0.82).

The findings of this study indicate that performance on the silhouettes test is impaired at the MCI stage, with no significant differences observed between the MCI and MD groups. Compared with the study by Quental et al., the cutoff score for differentiating CG from early AD was identical in the silhouettes test, and our diagnostic accuracy results fell within the confidence interval range¹⁹. A longitudinal study by Eckerström et al. evaluating the conversion of MCI or subjective cognitive decline to dementia using CSF biomarkers and cognitive testing showed that silhouettes test results were significantly worse in the amyloid beta aggregation (A), tau aggregation (T), and neurodegeneration (N) positive (A + T + N+) groups than in the group with negative biomarkers (A-T-N-) at baseline evaluation²³. In our study, a moderate negative correlation was observed between age and performance on the silhouette test, and a weak or no correlation between demographic data and number location or cube analysis tests. In a study by Herrera-Guzmán et al., educational level was a significant predictor of performance in a population with normal cognitive function for silhouettes and object decision tests²⁴. Multinomial logistic regression analysis, incorporating demographic data, ADAS-Cog 13 scores, and silhouettes test results, accurately classified 76.4% of cases; however, the silhouettes test was not a significant predictor in this model. The specific accuracies showed poor performance in classifying MCI (92.3% for CG, 63% for MCI, and 75% for MD). Consequently, this test is influenced by demographic characteristics and object perception impairment occurs early in the course of AD.

Performance on the number location task differed significantly across the three groups, suggesting its potential utility for the very early diagnosis of AD. In this study, lower cut-off scores in number location and cube analysis tests were used to differentiate CG from early AD (MCI and MD) compared to the study by Quental et al.¹⁹. A cutoff value ≤ 8 was selected to indicate early AD, whereas Quental et al. reported a cutoff score of 9 for distinguishing CG from MD in both tasks¹⁹. Incorporating number location or cube analysis task results into a multinomial regression model with age, education, sex, and ADAS-Cog 13 scores improved

correctly classified CG, MCI, and MD cases from 76.5% to 80.2% (specific accuracies: 92.3% for CG, 70.4% for MCI, and 78.6% for MD). Both space perception tests improved the diagnostic accuracy of the models. As previously mentioned, cube analysis provided the best AUC results, differentiating CG from early AD, and improved group classification. This test stands out among spatial tests because of its unique requirement for three-dimensional perception despite being presented as a two-dimensional image. In addition, it involves the detection of hidden cubes, which must be deduced rather than observed directly¹⁷. In the human brain, the parieto-occipital junction is responsible for stereoscopic processing, which is crucial for spatial reasoning²⁵.

In addition to our finding that the number location and cube analysis tests enhance diagnostic accuracy in amnesic early AD, evidence demonstrates their substantial efficacy in diagnosing early atypical presentations of AD^{22,26,27}. Recent studies with pathological confirmation of the diagnosis provide evidence that atypical AD variants with prominent visual agnosia (posterior cortical atrophy) and motor AD variant (corticobasal syndrome) can be clinically diagnosed using VOSP tests^{22,26,27}. Boyd et al. reported that, in a clinicopathological investigation of individuals with corticobasal syndrome, poor performance on incomplete letters and all spatial VOSP tests correlated with an increased likelihood of underlying AD pathology, with cube analysis emerging as the most effective (sensitivity: 100%; specificity: 77%)²².

This study had a few limitations. First, CSF biomarker analysis was not performed within the framework of this study owing to its exploratory nature. Medical records with CSF biomarker data were available for only a limited number of patients because of the invasiveness and cost of the procedure, and positron emission tomography biomarkers were not used. Using CSF biomarkers for all participants would have excluded MCI due to dementia with Lewy bodies, which may be challenging to differentiate from MCI due to AD with cognitive testing using visual perceptual function tests. However, none of the participants fulfilled the 2017 revised criteria for the clinical diagnosis of dementia with Lewy bodies²⁸. In addition, while the study's sample size was adequate to demonstrate significant changes, additional research involving a larger group of participants would be beneficial in validating these results. Moreover, the study's cross-sectional design restricts its capacity to draw conclusive inferences regarding the progression of AD. Despite the promising outcomes of this study, longitudinal investigations are necessary to confirm the effectiveness of silhouettes, number location, and cube analysis tests as valuable assessment tools. The strengths of this study include the separation of visuospatial perception from language and motor abilities using VOSP, which provides a better understanding of early AD-related changes and improved diagnostic accuracy.

In conclusion, the VOSP serves as an inexpensive and efficient clinical assessment instrument, allowing easy and fast evaluation of visuospatial function in early AD. We recommend using silhouettes and space perception tasks (number location and cube analysis) as additional tools to improve early AD diagnosis. Combining multiple diagnostic tools, including verbal cognitive, visual object, and space perception tests (number location, and cube analysis), may provide the most accurate and early diagnosis of AD.

Methods

Participants

This study included three groups: 28 participants diagnosed with MD due to AD, 27 with amnesic MCI, and 26 cognitively normal older adults who served as the CG.

Individuals diagnosed with MD met the National Institute on Aging and Alzheimer's Association (NIA/AA) criteria for probable AD²⁹ and scored 1 on the clinical dementia rating total score (CDR-TS). Those classified as having MCI met the NIA/AA clinical and cognitive criteria for MCI due to AD³⁰ and received a CDR-TS of 0.5. Cognitively healthy older adults in the CG reported no cognitive issues, scored 0 on the CDR-TS, and showed no neurological abnormalities.

The study participants were recruited from the Memory Clinic of the Vilnius University Hospital, Santaros Klinikos. A cognitive neurologist diagnosed probable AD based on criteria for probable AD dementia with increased certainty²⁹, supported by the observed progression of cognitive decline, suggesting an ongoing and active pathological process²⁹. For a subset of patients with MD (7/28 (25%)), medical records included positive AD CSF biomarker status, confirming AD diagnosis according to the 2018 NIA-AA research framework³¹. The diagnosis of MCI due to AD was established by applying clinical and cognitive criteria, with its etiology determined to be consistent with the pathophysiological process of AD³⁰. This diagnosis involved ruling out vascular, traumatic, and medical causes of amnesic MCI along with documented longitudinal cognitive deterioration³⁰. The biomarkers indicated an intermediate likelihood of MCI due to AD, as structural MRI revealed signs of neuronal injury (medial temporal lobe atrophy) in all cases. Medical records with positive AD CSF biomarker status were available for a subset of patients with MCI (8/27 (30%)), confirming AD diagnosis³¹.

The exclusion criteria included neurological disorders affecting the central nervous system (except for MCI and MD); cerebrovascular issues (indicated by a Hachinski Ischemic Score ≥ 4); history of head injury; major psychiatric conditions (such as schizophrenia, delirium, psychosis, or depression with a Geriatric Depression Scale score exceeding 9); vision and hearing disorders impairing cognitive testing; diagnosis or any symptoms of substantial cardiovascular, hepatic, or metabolic disorders; drug or alcohol abuse; and use of psychoactive medications. The study was conducted in accordance with the Declaration of Helsinki (1975) and approved by the Vilnius Regional Bioethics Committee (Approval Number 2022/1-1405-877). All participants provided written informed consent before participating in the study.

Assessments of cognitive function

The MMSE test was used to evaluate overall cognition. The ADAS-Cog 13 was administered to the participants for detailed cognitive evaluation. The ADAS-Cog 13 includes word recall, commands, constructional praxis, delayed word recall, naming, ideational praxis, orientation, word recognition, remembering test instructions, comprehension of spoken language, word-finding difficulty, spoken language ability, and number cancellation.

ADAS-Cog 13 scores ranged from 0 to 85. The Clinical Dementia Rating Sum of Boxes (CDR-SB) scale was used to assess the extent of functional impairment and cognitive decline.

Assessment of VOSP battery tests: silhouettes, number location, and cube analysis

Silhouettes: Black shadows of animals and inanimate objects from unusual angles were shown to the participants. The test consisted of 15 silhouettes of animals and 15 silhouettes of inanimate objects. Participants may name, mimic, gesture, or describe the object. The test boards were organized from the easiest to the most challenging, and the examination was discontinued after five mistakes. To establish the threshold scores, we implemented all boards even when the participant made > five errors (maximum score: 30).

Number location: This test consists of 10 boards, each featuring two vertically aligned squares. The upper square displayed a random arrangement of numbers ranging from 1 to 9. The lower square contains a black dot that corresponds to the location of a specific number. The participants were required to identify the number aligned with the position of the black dot. One point was awarded for each correct identification, with a total of ten boards presented (maximum score: 10).

Cube analysis: Each board displayed a configuration of solid objects. Participants were required to determine the total number of cubes on each board, including those that were not visible. A series of ten boards was presented, with the complexity increasing progressively from one board to the next. (maximum score = 10).

Data analysis

The Shapiro–Wilk test was used to evaluate whether the data followed a normal distribution. Group differences in demographic and clinical data, as well as test results were analyzed using one-way ANOVA, Kruskal–Wallis, or chi-square tests. Spearman's rank correlation coefficient was used to evaluate the associations between the variables. Subsequently, linear regression models, adjusted for demographic data, were used to predict continuous dependent variables. Multinomial logistic regression was employed to examine the association between independent variables and classification into the three groups. Diagnostic test performance was evaluated using ROC curve analysis. The optimal threshold for each test was determined by maximizing Youden's J statistic ($J = \text{sensitivity} + \text{specificity} - 1$). Statistical significance was set at $p < 0.05$.

Data availability

The datasets used and analyzed in this study are available from the corresponding author upon reasonable request.

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References

- Gauthier, S., Rosa-Neto, P., Morais, J. A. & Webster, C. World Alzheimer Report 2021: Journey through the Diagnosis of Dementia (Alzheimer's Disease Int., London, England, (2021)).
- Arrighi, H. M., Neumann, P. J., Lieberburg, I. M. & Townsend, R. J. Lethality of alzheimer disease and its impact on nursing home placement. *Alzheimer Dis. Assoc. Disord.* **24**, 90–95 (2010).
- Alzheimer's Disease International. *From Plan To Impact V: WHO Global Action Plan: the time To Act Is now* (Alzheimer's Disease Int., 2022).
- Cook, L., Souris, H. & Isaacs, J. The 2019 National memory service audit. *NHS England* (2020). Epub 2020 Apr 8 (<https://www.england.nhs.uk/london/wp-content/uploads/sites/8/2020/04/The-2019-national-memory-service-audit.pdf> [cited 5 Jan 2025]).
- Shaughnessy, L. W. & Weintraub, S. The role of neuropsychological assessment in the evaluation of patients with cognitive-behavioral change due to suspected alzheimer's disease and other causes of cognitive impairment and dementia. *Alzheimers Dement.* **21**, e14363 (2025). Epub 2024 Dec 28.
- Jack, C. R. et al. Revised criteria for diagnosis and staging of alzheimer's disease: alzheimer's association workgroup. *Alzheimers Dement.* **20**, 5143–5169 (2024).
- Chang, L. Y. L. et al. Alzheimer's disease in the human eye. Clinical tests that identify ocular and visual information processing deficit as biomarkers. *Alzheimers Dement.* **10**, 251–261 (2014).
- Marquie, M. et al. Visual impairment in aging and cognitive decline: experience in a memory clinic. *Sci. Rep.* **9**, 8698 (2019).
- Owsley, C. & Sloane, M. E. Contrast sensitivity, acuity, and the perception of 'real-world' targets. *Br. J. Ophthalmol.* **71**, 791–796 (1987).
- Livingstone, M. S. & Hubel, D. H. Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *J. Neurosci.* **7**, 3416–3468 (1987).
- Goodale, M. A. & Milner, A. D. Separate visual pathways for perception and action. *Trends Neurosci.* **15**, 20–25 (1992).
- Sintini, I. et al. Longitudinal neuroimaging biomarkers differ across alzheimer's disease phenotypes. *Brain* **143**, 2281–2294 (2020).
- Pontecorvo, M. J. et al. A multicentre longitudinal study of flortaucipir (18F) in normal ageing, mild cognitive impairment and alzheimer's disease dementia. *Brain* **142**, 1723–1735 (2019).
- Memon, A. et al. Visual functions are associated with biomarker changes in alzheimer's disease. *J. Alzheimers Dis.* **99**, 623–637 (2024).
- Tyler, S. L., Maltby, J., Paterson, K. B. & Hutchinson, C. V. Reduced vision-related quality of life in dementia: A preliminary report. *J. Alzheimers Dis.* **87**, 239–246 (2022).
- Alzola, P. et al. Neuropsychological assessment for early detection and diagnosis of dementia: current knowledge and new insights. *J. Clin. Med.* **13**, 3442 (2024).
- Warrington, E. K. & James, M. *The Visual Object and Space Perception Battery*, (1991).
- de Haan, G. A., Tucha, O. & Heutink, J. Effects of low visual acuity on neuropsychological test scores: A simulation study. *Clin. Neuropsychol.* **34**, 140–157 (2020).
- Quental, N. B. M., Brucki, S. M. D. & Bueno, O. F. A. Visuospatial function in early alzheimer's disease—The use of the visual object and space perception (VOSP) battery. *PLOS One.* **8**, e68398 (2013).
- Belleville, S. et al. Neuropsychological Measures that Predict Progression from Mild Cognitive Impairment to Alzheimer's type dementia in Older Adults: A Systematic Review and Meta-Analysis. *Neuropsychol Rev* **27**, 328–353 (2017).

21. Eckerström, C. et al. A combination of neuropsychological, neuroimaging, and cerebrospinal fluid markers predicts conversion from mild cognitive impairment to dementia. *J. Alzheimers Dis.* **36**, 421–431 (2013).
22. Boyd, C. D. et al. Visuospatial perception test predicts pathologic diagnosis of alzheimer disease in corticobasal syndrome. *Neurology* **83**, 510–519 (2014). Epub. PMID: 24991033, PMCID: PMC4142003.
23. Eckerström, C., Svensson, J., Kettunen, P., Jonsson, M. & Eckerström, M. Evaluation of the ATN model in a longitudinal memory clinic sample with different underlying disorders. *Alzheimers Dement. (Amst)*. **13**, e12031 (2021).
24. Herrera-Guzmán, I., Peña-Casanova, J., Lara, J. P., Gudayol-Ferré, E. & Böhm, P. Influence of age, sex, and education on the visual object and space perception battery (VOSP) in a healthy normal elderly population. *Clin. Neuropsychol.* **18**, 385–394 (2004).
25. Tsao, D. Y. et al. Stereopsis activates V3A and caudal intraparietal areas in macaques and humans. *Neuron* **39**, 555–568 (2003).
26. Salimi, S. et al. Can visuospatial measures improve the diagnosis of alzheimer's disease? *Alzheimers Dement. (Amst)*. **10**, 66–74 (2018).
27. North, C. et al. Neuropsychological deficits in posterior cortical atrophy and typical alzheimer's disease: A meta-analytic review. *Cortex* **143**, 223–236 (2021). ISSN 0010-9452.
28. McKeith, I. G. et al. Diagnosis and management of dementia with lewy bodies: fourth consensus report of the DLB consortium. *Neurology* **89**, 88–100 (2017).
29. McKhann, G. M. et al. The diagnosis of dementia due to alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for alzheimer's disease. *Alzheimers Dement.* **7**, 263–269 (2011).
30. Albert, M. S. et al. The diagnosis of mild cognitive impairment due to alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for alzheimer's disease. *Alzheimers Dement.* **7**, 270–279 (2011).
31. Jack, C. R. Jr. et al. NIA-AA research framework: toward a biological definition of alzheimer's disease. *Alzheimers Dement.* **14**, 535–562 (2018).

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Author contributions

V.S. and G. K. conceived and designed the study. V.S., E.A., and G.P.-K. collected the data. V.S., E.A. and G.P.-K. analyzed the data. V. S. and G. K. prepared the manuscript. E.A. and G.P.-K. revised the manuscript. All the authors have approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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LIST OF PUBLICATIONS NOT INCLUDED IN THE THESIS

1. Audronytė E, Sutnikienė V, Kaubrys G. Demencija sergančių pacientų priežiūros rekomendacijos COVID-19 pandemijos metu = Dementia care recommendations during the COVID 19 pandemic. Neurologijos seminarai. 2020;24(84):136-137. doi:10.29014/ns.2020.19.
2. Audronyte E, Pakulaite-Kazliene G, Sutnikiene V, Kaubrys G. Properties of odor identification testing in screening for early stage Alzheimer's disease. Sci Rep. 2023;13(1):6075. Published 2023 Apr 13. doi:10.1038/s41598-023-32878-w.
3. Audronyte E, Pakulaite-Kazliene G, Sutnikiene V, Kaubrys G. Odor Discrimination as a Marker of Early Alzheimer's Disease. J Alzheimers Dis. 2023;94(3):1169-1178. Published 2023 Aug 1. doi:10.3233/JAD230077.
4. Audronyte E, Sutnikiene V, Pakulaite-Kazliene G, Kaubrys G. Brief Test of Olfactory Dysfunction Based on Diagnostic Features of Specific Odors in Early Stage Alzheimer Disease. Med Sci Monit. 2023;29:e940363. Published 2023 May 27. doi:10.12659/MSM.940363.
5. Audronyte E, Sutnikiene V, Pakulaite-Kazliene G, Kaubrys G. Olfactory memory in mild cognitive impairment and Alzheimer's disease. Front. Neurol. 2023;14:1165594. Published 2023 June 02. doi:10.3389/fneur.2023.1165594.

LIST OF PRESENTATIONS

1. “Mental rotation in early Alzheimer’s disease.” Poster presentation at the *10th Baltic Congress of Neurology*, Tallinn, Estonia, 28–30 April 2022.
2. “Movement estimation task in early Alzheimer’s disease.” Oral presentation at the *5th International Conference of Evolutionary Medicine*, Vilnius, Lithuania, 24–27 August 2022.
3. “Color memory in mild cognitive impairment and Alzheimer’s disease.” Virtual poster presentation at the *10th Congress of the European Academy of Neurology*, Helsinki, Finland, 29 June–2 July 2024.
4. “Watercolor and McCollough effects: visual illusions that fade in early Alzheimer’s disease.” Virtual poster presentation at the *11th Congress of the European Academy of Neurology*, Helsinki, Finland, 21–24 June 2025.

NOTES

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