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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, amnestic 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

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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 amnestic 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 amnestic 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

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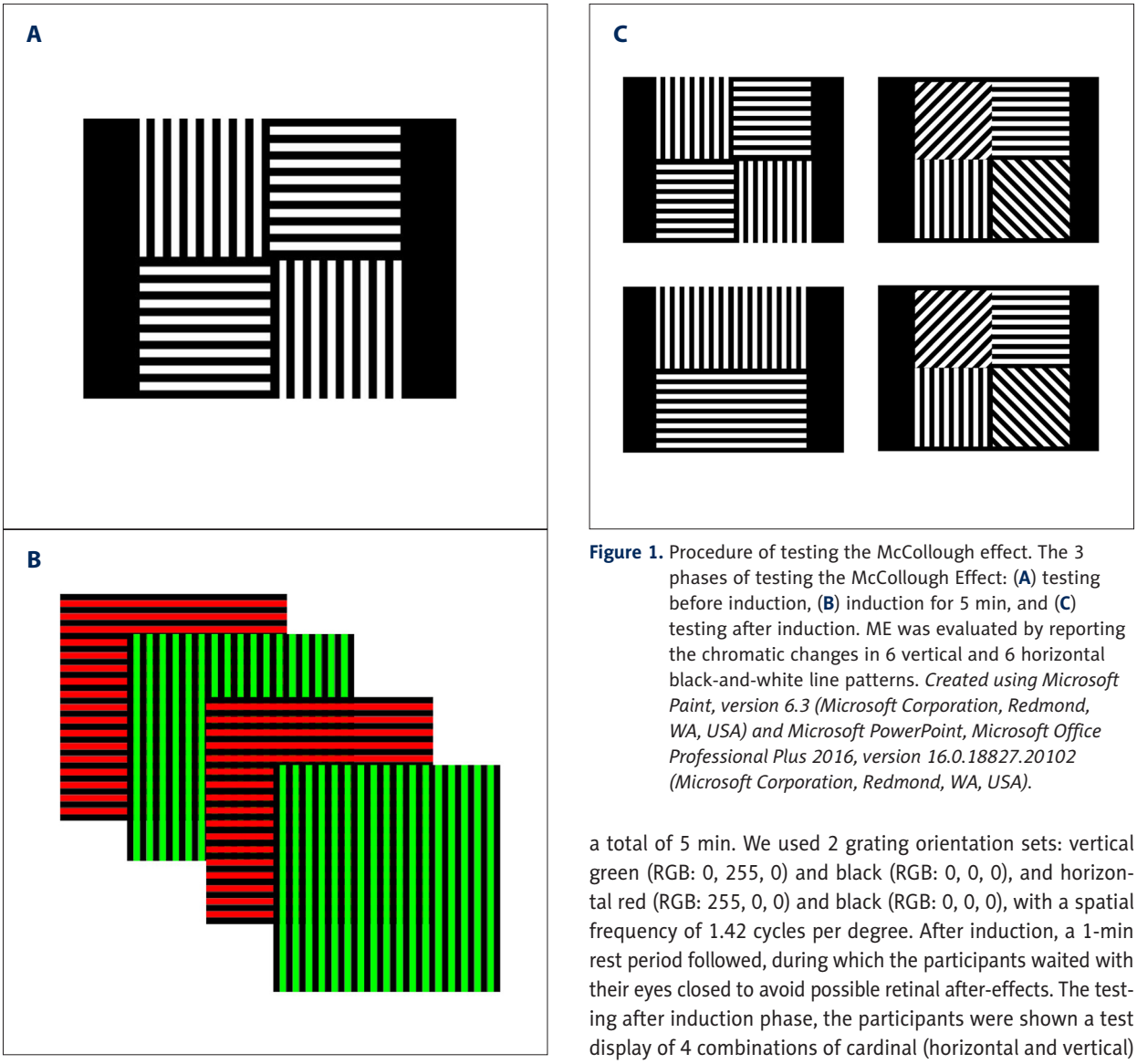

Figure 1. Procedure of testing the McCollough effect. The 3 phases of testing the McCollough Effect: (**A**) testing before induction, (**B**) induction for 5 min, and (**C**) testing after induction. ME was evaluated by reporting the chromatic changes in 6 vertical and 6 horizontal black-and-white line 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 115°) 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.

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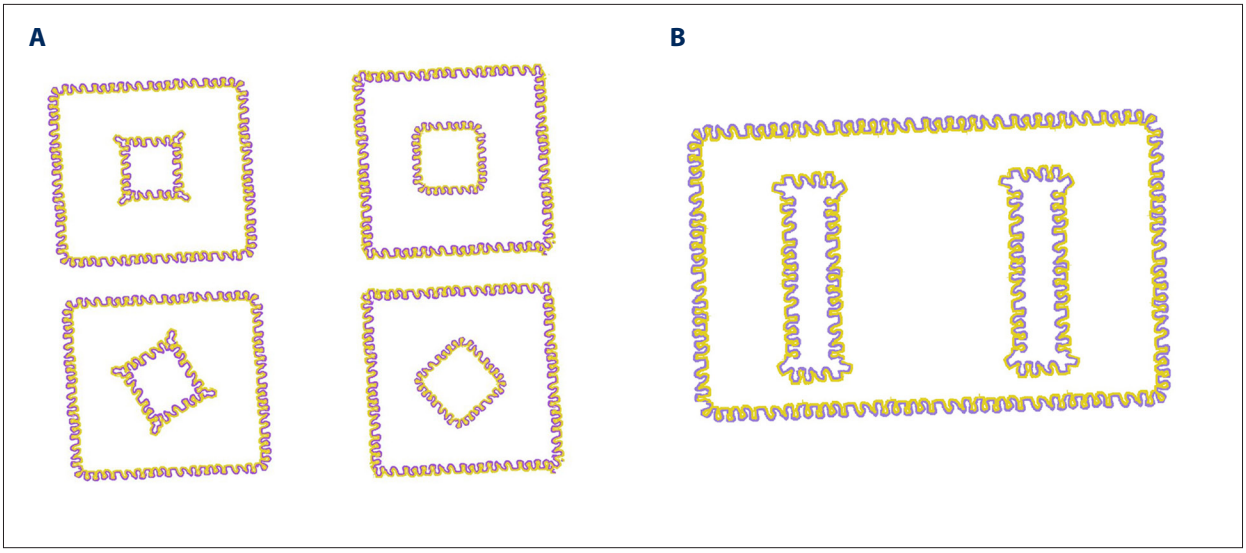

Figure 2. Watercolor effect test images. The revised version of the watercolor illusion based on the original concept of Pinna et al [16], adapted under CC BY-NC-SA 3.0. Purple undulated contours adjacent to orange ones are perceived as evenly colored by a light veil of orange tint spreading from the 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.

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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 $\varepsilon^2=0.11$ (**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

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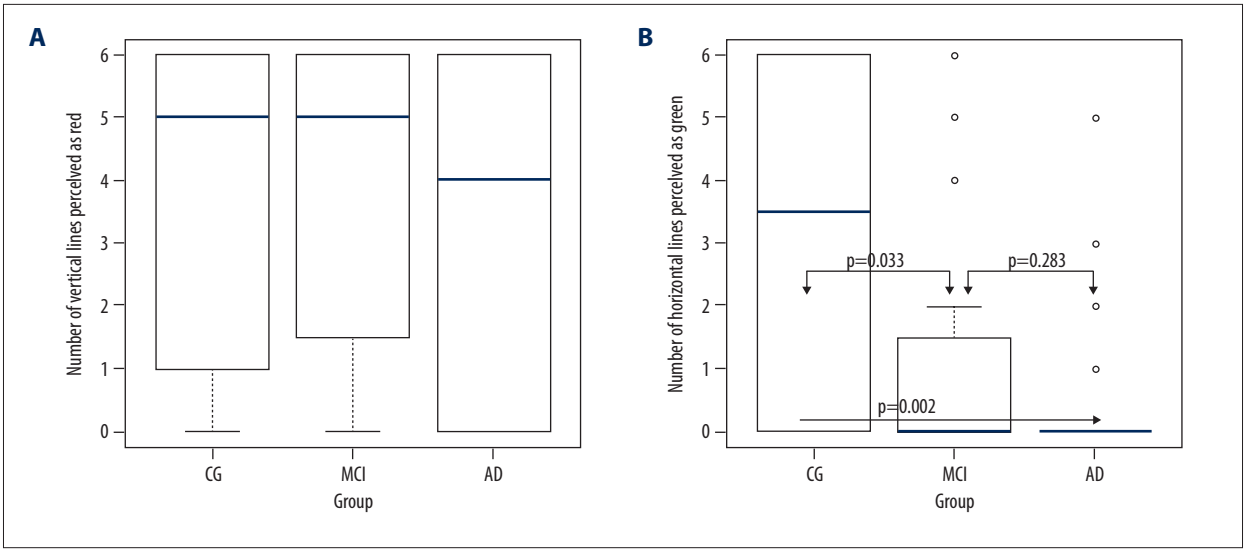

Figure 3. Differences in the McCollough effect between the 3 groups. (**A**) Number of vertical lines perceived as red in the 3 groups (no significant differences were observed; *P*>0.05); (**B**) number of horizontal lines perceived as green in the 3 groups. MD – mild dementia; MCI – mild cognitive 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, β=0.318, *P*<0.001), ADAS-Cog 13 (R^2=0.101, F=2.8, β=-0.116, *P*=0.001), and CDR-SB (R^2=0.086, F=2.5, β=-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 ε^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,

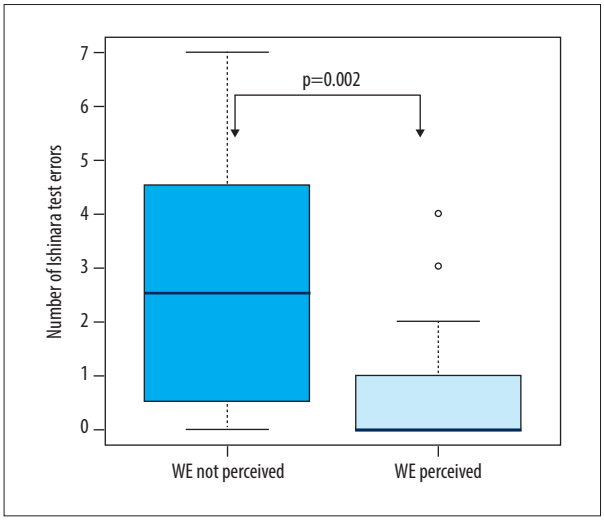

Figure 4. Ishihara test results in accordance with whether the Watercolor effect was perceived. The WE was not perceived when participants exhibited a significantly higher number of errors on the Ishihara test. Lines represent medians; boxes represent interquartile ranges; and error bars represent the 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).

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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

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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.

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