Neural and Retinal Characteristics in Relation to Working Memory in Older Adults with Mild Cognitive Impairment

Authors: Mabel Ngai Kiu Wong[a], Daniel Wing Leung Lai[b], Henry Ho Lung Chan[c], Bess Yin-Hung Lam [*,d]

*Corresponding author

[a]Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

[b] Department of Social Work, The Hong Kong Baptist University

[c]School of Optometry, The Hong Kong Polytechnic University

[d]Department of Psychiatry, The University of Hong Kong

Email address of corresponding author: bess0127@gmail.com

Address: Department of Psychiatry, The University of Hong Kong, Hong Kong

This is the accepted version of the following article: Mabel N.K. Wong, Daniel W.L. Lai, Henry H.-L. Chan and Bess Y.-H. Lam, "Neural and Retinal Characteristics in Relation to Working Memory in Older Adults with Mild Cognitive Impairment", Current Alzheimer Research 2021; 18(3). The published manuscript is available at EurekaSelect via http://www.eurekaselect.com/10.2174/1567205018666210608114044

Abstract

This study investigated the relationship between neural activities and retinal structures associated with working memory (WM) in older adults with mild cognitive impairment (MCI). Eleven older adults with MCI and 29 healthy controls (60 to 73 years old) were tested. All participants underwent an event-related potential (ERP) recording while performing the two-back memory task. The Optical coherence tomography angiography (OCT-A) was administered to examine the perfusion and vessel density in the retina. Results showed that WM performance in the MCI group was negatively associated with ERP latencies in central parietal regions (CP6 and CP8) (*ps*< 0.05). The left nasal vessel and perfusion densities were negatively correlated with the latencies in these two central parietal regions and positively related to WM performance only in the MCI group (*ps*< 0.05). The findings on WM, central parietal brain activity, and left nasal vessel and perfusion densities in the retina help us gain a better understanding of the neural and retinal underpinnings of WM in relation to MCI.

Keywords: Mild cognitive impairment, retinal perfusion density, retinal vessel density, working memory, event-related potential, cognition

1. Introduction

Mild cognitive impairment (MCI) is a syndrome that occurs in a transition phase between healthy cognitive aging and clinically-based dementia and Alzheimer's Disease (AD) [e.g. 1]. Its prevalence ranges from 3 to 19 percent in general older adult population above 65 years old [2]. Older adults who experience MCI show an increased risk of developing dementia and AD (e.g., 20 to 50% odds ratio) [3] and cognitive deficits are commonly found in MCI [4]. Detecting cognitive decline in people with MCI can in turn prevent further development of AD. Therefore, this study aimed to investigate the neural and retinal characteristics associated with one dimension of cognitive deficits, specifically focusing on working memory (WM) (specifically the learning component instead of retrieval) in older adults with MCI.

Of the different aspects of cognitive deficits found in individuals with AD or MCI, WM is one of the most common [e.g. 5, 6]. According to Baddeley (1992) [7], WM is different from short-term memory, providing the space in the brain system for temporary storage and information manipulation in order to cope with complex cognitive tasks such as language comprehension, learning, and reasoning. With the age effect [8], WM is regarded as an essential process in older adulthood since it is necessary for daily decision making and problem-solving [9]. Previous studies have administered different WM paradigms, including the dual-task [10], global task switching [11], and the *n*-back paradigm [12] to assess WM in younger and older adults. Research has found that young adults demonstrate better WM performance than older adults. For example, Gajewski and Falkenstein (2014) [5] found that healthy older adults reacted more slowly than younger adults in both two-back task and control 0-back task. Lower accuracy was also found in healthy older adults in the two-back task, including missing out and misinterpretation of the target when compared with younger adults. Poor WM performances in older adults might be caused by a decline in bottom-up processing which in turn leads to impaired processing of incoming sensory information [13]. Besides the

age effect, healthy older adults demonstrate better performances in the *n*-back paradigm than older adults with MCI or AD [14, 15]. For example, Fraga et al. (2018) [15] found shorter mean reaction time and higher accuracy across 0-, 1- and 2-bask tasks in healthy older adults when compared with older adults with MCI and AD. These findings revealed the impairment of WM in individuals with MCI and AD. However, the underlying mechanisms of the WM impairment in MCI are yet to be investigated.

Electroencephalography (EEG) studies have reported age-related differences in neural activities underlying the WM process [5, 16]. Specifically, greater P300 amplitudes related to cognitive aging [17] were observed in younger adults especially in the parietal region (PZ, P5, P6), when compared to healthy older adults in the one-back task [18]. Further, reduction of P300 in the centro-parietal and parietal regions was observed in healthy older adults during the *n*-back WM task when compared to younger adults in an ERP study by Gajewski and Falkenstein (2014) [5]. Additionally, Lubitz et al. (2017) [19] found that increased P200 and decreased parietal P300 amplitudes correlated with WM performance in older adults but not younger ones. Similarly, weaker beta and alpha signals, especially in the fronto-central (e.g. C3) and temporal-parietal areas (e.g. TP8), were observed in MCI and AD individuals when compared with healthy older adults [17]. Moreover, lower amplitudes in the parietal regions (PZ, P3, P4) [20] and fronto-centro-parietal regions (e.g., CPz and Pz) [21] were found in those with AD or MCI during WM task. These ERP findings might be explained by the fact that the brain activity in the parietal region is sensitive to the memory load involved in the *n*-back task performances [22] and that P300 was often found to be involved in the age effect in WM performances [e.g. 5]. These findings suggest that individuals with MCI and healthy older adults had differential neural activities in relation to WM. Taking these results together,

a number of brain regions (including fronto-central, temporal-parietal, and central-parietal regions) are significantly associated with WM performances in MCI or AD. Therefore, the present study examined these specific brain regions as the regions of interest (ROIs).

Closely related to neural correlates, retinal characteristics might be potential biomarkers of MCI or AD [e.g. 23-25]. Specifically, retinal and cerebral tissues have common embryological origins and changes in the cerebral structures (e.g. decreased in cerebral blood flow) are reflected by retinal vascular circulation [24]. In individuals with AD or MCI, reduced cerebral blood flow was found when compared to healthy older adults [26], which in turn affected their retinal blood flow in retinal veins [27, 28]. Furthermore the level of cerebral beta-amyloid (Aβ) was also positively associated with the surface area of retinal inclusion bodies together with the chance of clinically diagnosed with AD or MCI [29]. Specifically, a higher level of cerebral Aβ induced the increase in the surface area of retinal inclusion bodies, which showed an increase rate of cognitive decline [30]. Moreover, reduced number of ganglion cells axons in the retina [31] and reduced retinal never fibre layers (RNFL) thickness in the superior quadrant were observed in MCI and AD [27]. These findings reveal that both retinal and cerebral abnormalities found in MCI and AD were closely related. However, whether these abnormalities are associated with WM deficits in MCI or AD requires further investigation.

In recent literature, retinal changes have been significantly correlated with cognitive change in relation to subjective memory impairment in individuals with MCI or AD [32]. Furthermore, degeneration in the optic disc is another sign of AD [33], which results in optic disc cupping, optic disc pallor and neuro-retinal rim thinning [34]. These changes in the optic disc might be associated with cognitive impairment [24]. This growing evidence leads to the hypothesis that abnormal retinal changes might be associated with WM impairment in MCI

and AD. Among the few studies on the relationship between retina and cognitive deficits including WM impairments, Pehlivanoglu et al. (2014) [35] found that the differences in pupillary responses during WM process can be identified in individuals with MCI or AD from healthy individuals. It remains uncertain how retina is related to WM performance. Pupillary responses are driven by the activation in the locus coeruleus (LC), located in the brain stem and found to be the first region in the brain to degenerate at the earliest stage of AD [36]. Furthermore, this brain region is involved in attention, memory, and cognitive control [37], and pupillary responses are related to the amount of cognitive effort needed to process incoming information via the eyes [38]. In particular, since compensatory cognitive effort is required to maintain memory performance, greater pupil dilation has been observed in the individuals with MCI and AD [39], while the opposite result was observed in individuals with severe MCI and AD [35,39]. Moreover, Granholm et al. (2017) [38] found that older adults with MCI exhibited greater dilation in pupil size than those without MCI while doing various neuropsychological tasks, including WM. In addition, their WM performance was poorer than those without MCI. These findings, alongside similar results in other studies [40, 41], suggested that abnormal pupillary characteristics such as retinal structures might indicate WM impairment in MCI. However, further studies are needed to investigate the relationship between neural activities and retinal characteristics in relation to WM in MCI.

The present study took an explorative perspective in examining the relationship between WM performance and the perfusion and vessel densities in the retina, which are both related to WM associated neural correlates in MCI. This study examined the neural and retinal characteristics in relation to WM deficits in MCI. We hypothesized that 1) WM performance measured by the two-back memory task in older adults with MCI would be poorer than those healthy older adults; 2) the latencies in the fronto-central (e.g. FCz), temporal-pa-

rietal (e.g. TP8), and central- parietal regions (e.g. CP6) measured by EEG would be associated with retinal vessel density and perfusion measured by retinal imaging. Additionally, both of them were associated with the WM performances in older adults with MCI.

2. Materials and methods

2.1 Participants

Invitation leaflets were sent to the Institute of Active Aging in the Hong Kong Polytechnic University to recruit community dwelling older adults with different demographic backgrounds. Forty community-dwelling older adults participated in this study on a voluntary basis (M_{age} = 64.60 years, age range = 60 to 73 years, *SD* = 3.84 years). Participants have an average of 12.45 years of education (*SD* = 3.69). Eleven participants were classified as MCI while the rest were healthy controls (*n* = 29), according to the criteria discussed in the next section. The age and years of education of healthy participants were not significantly different from MCI participants (*ps* > 0.05) (Table 1). All participants had normal or corrected-to-normal visual and auditory function. Participants with a history of cognitive impairment (e.g., dementia, head injury, and cerebrovascular disease) were excluded from the study.

2.2 Procedures

Ethical approval was obtained from the Departmental Research Committee of the Hong Kong Polytechnic University. Prior participation in this study, written informed consent was obtained from all participants. Information on participants' age, sex, years of education, and independence in daily activities (personal hygiene and car, locomotion in the home, meal preparation, running errands, housework and finances) of the participants were collected. The IQ of each participant was assessed using the Test of Nonverbal Intelligence - Third Edition (TONI-3) [42]. In addition, all participants' cognitive ability and working memory were assessed by the measures mentioned below. To be classified as the MCI group, a number of criteria pertaining to Chinese individuals with seven or more years of education

were adopted: 1) MoCA score of 24 or below [43]; 2) self-reported independence in daily living activities; and 3) self-reported cognitive decline [44]. The remaining participants who scored 25 or higher on MoCA-HK were categorised as the healthy control group. These diagnostic criteria were adopted from previous studies [45, 46].

Participants in both groups underwent the same procedures for retinal imaging (optical coherence tomography angiography; OCTA) and measurement of neural activity during two-back WM task (electroencephalogram; EEG). EEG neural activity was recorded using the 64-channel Quik-Cap from SynAmps during the two-back memory task with two conditions (practice and experiment). Before the experimental condition, a practice block was run for participants to familiarise with the two-back memory task.

For the retinal imaging, each participant had an assessment on habitual distant visual acuity, intraocular pressure and anterior angles of each eye before pupil dilation. Before the retinal imaging, a registered optometrist placed one drop of Mydrin-P (0.5% Tropicamide + 0.5% Phenylephrine) in each eye for dilated fundus examination. Participants waited for 15 to 20 minutes for the pupils to dilate. Once a registered optometrist confirmed pupil dilation size, participants were directed to a dark room and 6mmx6mm retinal scans of angiography images were captured from both eyes by Optical Coherence Tomography Angiography (Zeiss CIRRUS HD-OCT 5000, Carl Zeiss Meditec, Inc., Dublin, USA). Participants' retinal blood vessel density and perfusion were also measured. Retinal blood vessel density and perfusion density from different regions (including 9 zones from 1-mm centre, 3-mm inner ring with 4 quadrants, and 6-mm outer ring with 4 quadrants) according to the ETDRS grid were analyzed using Zeiss AngioPlex (Carl Zeiss Meditec, Inc., Dublin, USA).

2.3 Measures

2.3.1 Cognitive ability. The Hong Kong version of the Montreal Cognitive Assessment (HK-MoCA) [47] was administered to identify mild cognitive impairment (MCI) in

participants. The HK-MoCA is a short cognitive-screening tool to detect MCI in older adults, with a full score of 30. It covers domains of short-term memory, visuospatial abilities, multiple aspects of executive functions, attention, concentration, working memory, language, orientation to time and place. In Hong Kong Chinese, a high internal consistency ($\alpha = 0.77$) has been found in the HK-MoCA [47].

2.3.2 Working memory. The two-back memory task was used to assess participants' working memory (specifically the learning component instead of retrieval) [48]. The whole task was made up of one practice block with around 30 trials and three experimental blocks with 100 trials each. All stimuli were presented with a STEM-2 programme. Each block began with a 1000 ms fixation cross shown on the screen and each stimulus was shown for 3000 ms on the screen. In each trial, the participants were asked to memorize the first two stimuli shown on the screen. A number between 0 to 9 was then randomly shown to the participants followed by a response time window of 500 ms. During the response time window, participants were instructed to press the number button "1" or "4" to indicate if the stimulus shown was the same as two preceding stimuli. In order to counterbalance the responses from participants, half were instructed to press "1" to indicate that the stimulus matched the two preceding trials and "4" to indicate that the stimulus was different, and vice versa for the other half of participants. A longer reaction time and lower accuracy rate indicated poorer working memory [49].

2.3.3 Electrophysiological recordings. Event-related potentials (ERP) were recorded using EEG during the two-back memory task to measure the corresponding neural activities associated with participants' WM. All ERP data were collected with a 64-channel with 90-mm Ag/AgCl-sintered electrode mounted on the Quik-Cap. Electrode position configuration was predefined according to the SynAmps2 Digital and recorded using a SynAmps RT 64-channel Amplifier that was connected to the Neuroimaging Suite software CURRY Scan 7

Neuroimaging Suite (NeuroScan Labs, Sterling, VA, USA). Four more electrodes were placed at the left and right lateral canthi as well as above and below the left eye to measure the Electro-Oculogram (EOG).

2.3.4 Retinal vessel density and perfusion. Optical coherence tomography angiography (OCTA) was used to measure retinal vessel density (area occupied by vessel lumens after binary reconstruction of images, such as blood vessel density in the nasal area) and perfusion (retinal blood flow rate, such as perfusion in the nasal retinal area) in both eyes of the participants. OCTA is a non-invasive technique using the laser reflectance principle to detect the movement of red blood cells representing blood flow at the back of the eye [50]. It can visualise the blood vessels in the retina down to the capillary level to show structural and blood flow information [e.g. 50, 51]. In comparison with other non-invasive retinal imaging techniques such as Fluorescein angiography (FA) and indocyanine green angiography (ICGA), OCTA provides precise segmentation of different layers in the fundus with angiogram. This technique was reported to identify the retinal vascular pathologies in AD [52].

2.4 Data analysis

All data analyses were interpreted with the significance level at 0.05. The mean accuracy rate and reaction time of all three experimental blocks in the two- back memory tasks were computed. Participants' performance in the two-back task was examined with the independent sample t-test analysis with group (MCI group vs control group) as a between-subject factor. For EEG data analysis, ERP data collected from the fronto-central, temporal-parietal areas, and parietal regions were pre-processed with Neuroimaging Suite software Curry 7. Since P300 is responsible for cognitive aging [17], this latency was extracted from the ERP components of interest for further analysis in this study. These EPR data along with the OCTA data were then exported to IBM SPSS Statistics 24 for further analysis. Specifically,

Pearson's correlation and multiple regression analyses were conducted to examine the relationship of the ERP components of interest (fronto-central, temporal-parietal, and parietal regions), OCTA data (retinal vessel density and perfusion) and WM performance.

3. Results

3.1 Two-back working memory task

The mean reaction time (RT) ($t(38) = 1.87$, $p = 0.07$) and mean accuracy (number of correct responses) ($t(38) = 0.41$, $p = 0.69$) in the two-back memory task were not significantly different between the MCI and healthy control groups.

3.2 Relationship between behavioural and ERP results in relation to WM

Pearson correlation analysis indicated significant relationships between behavioural results and ERP neural activities in relation to two-back WM task. Specifically, in the MCI group, the mean accuracy (number of correct responses) was moderately correlated with the latency in FC1 ($r = 0.62$, $p = 0.04$), CPZ ($r = -0.65$, $p = 0.03$), CP2 ($r = -0.64$, $p = 0.03$), CP4 ($r = -0.77$, $p = 0.01$), CP6 ($r = -0.69$, $p = 0.02$), CP8 ($r = -0.70$, $p = 0.02$), P1 ($r = -0.65$, $p = 0.03$), P4 ($r = -0.62$, $p = 0.04$), P6 ($r = -0.63$, $p = 0.04$), P8 ($r = -0.64$, $p = 0.04$), POZ ($r = -0.64$, $p = 0.04$) and PO6 ($r = -0.60$, $p = 0.05$)* in the MCI group (Table 2). The mean RT for correct responses was also moderately correlated with FP2 ($r = 0.63$, $p = 0.04$) and CP5 ($r = -0.66$, $p = 0.03$) in MCI group (Table 3). These significant relationships were not found in the healthy control group ($ps > 0.05$). [*: C, Central; F, Frontal; P, Parietal; O, Occipital; Z, Midline; Odd number, Left hemisphere; Even number, Right hemisphere.]

3.3. Relationship between WM performances and retinal characteristics

Pearson correlation analysis indicated significant relationships between behavioural results in the two-back WM task and retinal characteristics in the MCI group but not the healthy controls. Specifically, the mean accuracy (number of correct responses) was moderately correlated with left 3mm nasal vessel density ($r = 0.60$, $p = 0.05$), left 3mm superior

vessel density (r = 0.63, p = 0.04), left 3mm superior perfusion density (r = 0.72, p = 0.01), and left 6mm nasal perfusion density (r = 0.62, p = 0.04). Furthermore, no significant correlations between mean accuracy and right 3mm nasal vessel density (r = -0.23, p = 0.23), right 3mm superior vessel density (r = 0.39, p = 0.24), right 3mm superior perfusion density (r = 0.37, p = 0.26), and right 6mm nasal perfusion density (r = -0.02, p = 0.95) were found (Table 2). There were no significant correlations between mean RT during the two-back WM task and retinal characteristics in either group (ps > 0.05).

3.4 Relationship between ERP results in relation to WM and retinal characteristics

Pearson correlation analysis indicated that retinal characteristics (left 3mm nasal vessel density and left 6mm nasal perfusion density) were significantly correlated with ERP neural activities in the MCI group. Left 3mm nasal vessel density was found to moderately correlate to the latency in *FC1 (r = 0.73, p = 0.01), CP6 (r = -0.63, p = 0.04), and CP8 (r = -0.70, p = 0.02; Table 4), and marginally negatively correlate to CP2 (r = -0.60, p = 0.05) in the MCI group. However, right 3mm nasal vessel density did not correlate with any EEG locations of interest in the MCI and healthy control groups (ps > 0.05). Furthermore, left 6mm nasal perfusion density was found to significantly correlate to the latency in CP8 (r = -0.64, p = 0.03; Table 5), and marginally correlated to the one in CP6 (r = -0.59, p = 0.05) in the MCI group. The latencies of the significant EE locations of interest were entered as the independent variables in predicting the retinal characteristics in the multiple linear regression analyses. After controlling for participants' age, multiple linear regression analysis showed that the left 6mm nasal perfusion density was significantly predicted by the latency in CP6 and CP8 ($F_{3,7}$ = 4.24, p = 0.05); and that the left 3mm nasal vessel density was significantly predicted by the latency in CP8, CP6 and FC1 ($F_{4,6}$ = 4.71, p = 0.05). No significant correlations and regression results were found for right 6mm nasal perfusion density, left and right 3mm superior vessel density, left and right 3mm superior perfusion density in either group (ps > 0.05).

[*: C, Central; F, Frontal; P, Parietal; O, Occipital; Z, Midline; Odd number, Left hemisphere; Even number, Right hemisphere.]

4. Discussion

The current study was the first to examine the neural and retinal characteristics in relation to WM in older adults with MCI. Two main findings were observed which were generally consistent with the hypotheses. First, our results showed that WM performances in older adults with MCI were poorer than those in the healthy control group. Second, the relationships between WM performances, the latencies in two specific central parietal regions (CP6 and CP8), and retinal characteristics (left 3mm nasal vessel density and left 6mm nasal perfusion density) were different in those with MCI compared to those in healthy older adults. Specifically, the correlations between WM accuracy and EEG were only found in MCI but not healthy controls while similar differential results were found for the correlation between WM accuracy and retinal density. The differential correlations between WM performance, brain activity in the central parietal regions as well as the left retinal nasal vessel, and perfusion density found in the MCI and healthy individuals informs us about the neural and retinal underpinnings of WM in MCI.

The present findings were consistent with previous studies regarding the two-back WM performances in older adults with MCI [e.g. 14]. In terms of reaction time and accuracy, those with MCI reacted slower and less accurately to the WM stimuli when compared with healthy older adults. Although there was difference between two groups, it was not significant, possibly because the WM task adopted in the present study was different from those in previous studies. Nonetheless, these WM deficits in MCI individuals may be due to impairment in the central executive system of WM (e.g., visuospatial sketchpad) involved in the processing of the incoming information [53].

In terms of the neural underpinnings of WM, latencies in the central parietal, frontal central and parietal regions were negatively associated with WM performance in MCI individuals, which is consistent with prior findings [e.g. 14; 19]. These findings suggest that poorer WM were reflected by higher values of latencies in these brain regions. The relationship between abnormality in these brain regions and WM deficits might be due to the fact that the parietal cortex and prefrontal cortex (PFC) are responsible for WM performance [54-56] and those with MCI and AD are characterised by thinning in the temporo-parietal cortex [57]. Jiang (2005) [58] also reported higher values of EEG power in bilateral parietal lobes during WM tasks among those when compared to healthy older adults. The relationship between abnormality in the central parietal, parietal and frontal central regions and WM deficits in MCI in this study supported the conclusion that WM deficits might be explained by functional abnormality in those brain regions.

In terms of the retinal underpinnings of WM, a number of characteristics were positively related to WM performance, including left 3mm nasal vessel density, left 3mm superior vessel density, left 3mm superior perfusion density, and left 6mm nasal perfusion density. However, left 3mm nasal vessel density and left 6mmm nasal perfusion density were negatively related to latencies in the central parietal regions (specifically CP6 and CP8) only in those with MCI. These findings were consistent with the hypothesis that abnormality in the central parietal region and lower left nasal vessel and perfusion densities might underlie WM deficits in MCI. Specifically, left nasal and perfusion densities decreased with WM performance in MCI, which is consistent with prior research revealing a decrease in retinal vasculature in individuals with MCI and AD who had cognitive dysfunction [59]. In addition, the alteration of the retina such as macular region, retinal vasculature, optic disc, and retinal fiber layer were found in MCI [24, 28] and the decline in those retinal structures was also associated with WM deficits [60]. Furthermore, retinal vasculature that was closely related to the

neural correlates of WM [e.g. 61] was an index of cognitive ability in older adults [62, 63]. Although the literature regarding the present finding is yet to be established, the current findings are in line with previous studies regarding the relationship between retinal and neural characteristics and WM.

With regard to the relationship between WM deficits and associated neural activities and retinal characteristics in older adults with MCI, this is the first study to reveal that left retinal nasal vessel density and nasal perfusion density were both negatively related to the central parietal latencies which can be explained by the common characteristics shared by both [24]. Specifically, retinal structures, such as blood vessel density and perfusion were suggested as indexes of AD because they shared histological, physiological and embryological aspects with the brain [e.g. 24]. Additionally, several layers of neural cells extend to the eye's nerve fibers and vasculature, which suggests that retinal structures reflects neural activities in AD [64]. Furthermore, Jorge, Canário, Quental, Bernardes, and Castelo-Branco (2020) [65] found that retinal thickness was associated with brain cortical thickness in the frontal, parietal and temporal lobes, while den Haan et al. (2018) [66] revealed that parietal cortex atrophy was correlated with retinal thickness in early-onset AD individuals. These findings regarding retinal characteristics and brain regions that contribute to WM suggest that decreased left retinal nasal vessel density and left nasal perfusion density along with central parietal functional abnormality might both underlie WM impairment in MCI. Taking these findings together, it is noteworthy to target both neural and retinal characteristics related to WM while assessing and treating MCI in future studies.

Despite being the first study to investigate the relationship between neural and retinal characteristics and WM deficits in MCI, a number of limitations should be identified. First, because of the relatively small overall sample size, only 11 individuals were categorised as MCI, and the gender effect of WM processing [67] was not examined in the present study.

Future studies with shorter duration of assessments and larger sample sizes should examine if there are gender differences in the retinal and neural underpinnings of WM in MCI. Second, since this is a cross-sectional study, the causal relationship between neural activities, retinal structures and WM performance remains unexamined. A longitudinal design could be adopted in future studies to observe the trajectory of neural and retinal changes, which may inform a better understanding of their relationship with WM deficits in MCI. In addition, participants in the MCI group were only defined with the HK-MoCA but in absence of any biological marker of disease. Future study should include the test of biological marker with beta-amyloid or tau protein and broader neuropsychological battery. Moreover, no correction for multiple comparisons were computed due to the small sample size and each correlation was performed separately from each other. The correlations in the present study were not analysed in one single analysis model. Future study should correct for multiple comparisons if all correlations are to be analysed in one single analysis model. Last but not least, participants had not been evaluated for prodromal AD diagnosis by Aβ/tau PET/CSF and FD6-PET was not obtained to establish the correlates with the topographic retinal findings because of equipment and resources constraint in the present study. This should be addressed in future study for better understanding of prodromal AD diagnosis and topographic retinal findings.

4.1 Conclusion

In conclusion, the novel finding of this study is that brain abnormality (increased central parietal latencies) and reduced retinal densities (retinal left nasal vessel density and left nasal perfusion density) were both associated with WM deficits in MCI individuals while this relationship was not found in the healthy control group. This suggests that WM deficits in MCI might be underpinned by both retinal and neural abnormalities, which in turn leads to the possibility that retinal abnormalities can be a biomarker of MCI or AD. Since WM decline is one MCI marker and the early identification of MCI is of much importance to prevent

or slow down further development of AD, both retinal and neural abnormalities associated with WM deficits can be used as the indexes to detect MCI. Therefore, the current findings have clinical implications, providing knowledge for the development of identification and prevention measures in relation to MCI.

Funding sources

Nil.

Ethics Approval and Consent to Participate

The study was approved by the Departmental Research Committee of the Hong Kong Polytechnic University (Ethic no.: HSEARS20180110001).

Human and Animal Rights

No animals were used in this research. All humans research procedures followed were in accordance with the standards set forth in the Declaration of Helsinki principles of 1975, as revised in 2008 (http://www.wma.net/en/ 20activities/10ethics/10helsinki/).

Conflict of Interest

No conflicts of interest exist.

Acknowledgements

We would like to thank Institute of Active Ageing at Hong Kong Polytechnic University for their support in participant recruitment.

References

[1] Orru, G.; Sampietro, S.; Catanzaro, S.; Girardi, A.; Najjar, M.; Giantin, V.; ... Coin, A. Serial position effect in a free recall task: differences between probable dementia of Alzheimer type (PDAT), vascular (VaD) and mixed etiology dementia (MED). *Arch Gerontol Geriat,* **2009**, *49*, 207-210.

[2] Belleville, S.; Gilbert, B.; Fontaine, F.; Gagnon, L.; Ménard, É.; Gauthier, S. Improvement of episodic memory in persons with mild cognitive impairment and healthy older adults: evidence from a cognitive intervention program. *Dement Geriatr Cogn Disord,* **2006**,*22*, 486-499.

[3] Desikan, R.S.; Cabral, H.J.; Hess, C.P.; Dillon, W.;P.; Glastonbury, C.M.; Weiner, M.W.; ... Fischl, B. Automated MRI measures identify individuals with mild cognitive impairment and Alzheimer's disease. *Brain,* **2009**, *132*, 2048-2057.

[4] Aurtenetxe, S.; García-Pacios, J.; del Río, D.; López, M.E.; Pineda-Pardo, J.A.; Marcos, A., ... Maestú, F. Interference impacts working memory in mild cognitive impairment. *Front Neurosci,* **2016**, *10*, 443.

[5] Gajewski, P.D.; Falkenstein, M. Age-related effects on ERP and oscillatory EEG dynamics in a 2-back task. *J Psychophysiol,* **2014**, *28*, 162-177.

[6] Li, S.C.; Lindenberger, U.; Sikström, S. Aging cognition: From neuromodulation to representation. *Trends Cogn Sci,* **2001**, *5*, 479-486.

[7] Baddeley, A. Working memory. *Science,* **1992**, *255*, 556-559.

[8] Missonnier, P.; Gold, G.; Leonards, U.; Costa-Fazio, L.; Michel, J.P.; Ibáñez, V. Giannakopoulos, P. Aging and working memory: Early deficits in EEG activation of posterior cortical areas. *J Neural Transm Suppl,* **2004**, *111*, 1141-1154.

[9] Nissim, N.R.; O'Shea, A.M.; Bryant, V.; Porges, E.C.; Cohen, R.; Woods, A.J. Frontal structural neural correlates of working memory performance in older adults. *Front Aging Neurosci,* **2017**, *8*, 328.

[10] Hedden, T.; Gabrieli, J.D. Insights into the ageing mind: A view from cognitive neuroscience. *Nat Rev. Neurosci,* **2004**, *5*, 87-96.

[11] Schapkin, S.A.; Gajewski, P.D.; Freude, G. 2014. Age differences in memory-based task switching with and without cues. *J Psychophysiol,* **2014**, *28*, 187-201.

[12] Kirchner, W.K. Age differences in short-term retention of rapidly changing information. *J Exp Psychol Gen*, **1958**, *55*, 352-358.

[13] Delorme, A.; Rousselet, G.A.; Macé, M.J.M.; Fabre-Thorpe, M. Interaction of top-down and bottom-up processing in the fast visual analysis of natural scenes. *Cogn Brain Res,* **2004**, *19*, 103-113.

[14] Fraga, F.J.; Ferreira, L.A.; Falk, T.H.; Johns, E.; Phillips, N.D. In *2017 International Conference on Acoustics, Speech and Signal Processing (ICASSP)*, Proceedings of 2017 ICASSP, New Orleans, LA, US, March 5-9, 2017; Institute of Electrical and Electronics Engineers, US, **2017**; pp. 964-968

[15] Fraga, F.J.; Mamani, G.Q.; Johns, E.; Tavares, G.; Falk, T.H.; Phillips, N.A. Early diagnosis of mild cognitive impairment and Alzheimer's with event-related potentials and event-related desynchronization in N-back working memory tasks. *Comput Meth Prog Bio,* **2018**, *164*, 1-13.

[16] Hou, F.; Liu, C.; Yu, Z.; Xu, X.; Zhang, J.; Peng, C.K.; ... Yang, A. Age-related alterations in electroencephalography connectivity and network topology during n-back working memory task. *Front Hum Neurosci,* **2018**, *12*, 484.

[17] Polich, J. Meta-analysis of P300 normative aging studies. *Psychophysiology,* **1996**, *33*, 334-353.

[18] Saliasi, E.; Geerligs, L.; Lorist, M.M.; Maurits, N.M. The relationship between P3 amplitude and working memory performance differs in young and older adults. *PLoS One,* **2013**, *8*, e63701.

[19] Lubitz, A.F.; Niedeggen, M.; Feser, M. Aging and working memory performance: Electrophysiological correlates of high and low performing elderly. *Neuropsychologia,* **2017**, *106*, 42-51.

[20] Missonnier, P.; Deiber, M.P.; Gold, G.; Herrmann, F.R.; Millet, P.; Michon, A.; ... Giannakopoulos, P. Working memory load-related electroencephalographic parameters can differentiate progressive from stable mild cognitive impairment. *Neuroscience,* **2007**, *150*, 346-356.

[21] Mamani, G.Q.; Fraga, F.J.; Tavares, G.; Johns, E.; Phillips, N.D. In *2017 Healthcare Innovations and Point of Care Technologies (HI-POCT)*, Proceedings of the 2017 HI-POCT, Bethesda, Maryland, USA, 6-8 November, 2017; Institute of Electrical and Electronics Engineers, US, **2017;** pp. 237-240.

[22] Deiber, M.P.; Missonnier, P.; Bertrand, O.; Gold, G.; Fazio-Costa, L.; Ibanez, V.; Giannakopoulos, P. Distinction between perceptual and attentional processing in working memory tasks: a study of phase-locked and induced oscillatory brain dynamics. *J Cognitive Neurosci,* **2007**, *19*, 158-172.

[23] Cabrera DeBuc, D.; Gaca-Wysocka, M.; Grzybowski, A.; Kanclerz, P. Identification of retinal biomarkers in Alzheimer's disease using optical coherence tomography: Recent insights, challenges, and opportunities. *J. Clin. Med*, **2019**, *8*(7), 996.

[24] Ikram, M.K.; Cheung, C.Y.; Wong, T.Y.; Chen, C.P. Retinal pathology as biomarker for cognitive impairment and Alzheimer's disease. *J Neurol, Neurosurgery, and Psychiatry,* **2012**, *83*, 917-922.

[25] Lim, J.K.; Li, Q.X.; He, Z.; Vingrys, A.J.; Wong, V.H.; Currier, N.; ... Nguyen, C.T. The eye as a biomarker for Alzheimer's disease. *Front Neurosci,* **2016**, *10*, 536.

[26] Akkawi, N.M.; Borroni, B.; Agosti, C.; Magoni, M.; Broli, M;, Pezzini, A.; Padovani, A. Volume cerebral blood flow reduction in pre-clinical stage of Alzheimer disease. J *Neurol*, **2005**, *252*, 559-563.

[27] Berisha, F.; Feke, G.T.; Trempe, C.L.; McMeel, J.W.; Schepens, C.L. Retinal abnormalities in early Alzheimer's disease. *Invest Ophth Vis Sci,* **2007**, *48*, 2285-2289.

[28] Feke, G.T.; Hyman, B.T.; Stern, R.A.; Pasquale, L.R. Retinal blood flow in mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement (Amst),* **2015**, *1*, 144-151.

[29] Snyder, P.J.; Johnson, L.N.; Lim, Y.Y.; Santos, C.Y.; Alber, J.; Maruff, P.; Fernández, B. Nonvascular retinal imaging markers of preclinical Alzheimer's disease. *Alzheimers Dement (Amst),* **2016**, *4*, 169-178.

[30] Yeo, J.M.; Waddell, B.; Khan, Z.; Pal, S. A systematic review and meta-analysis of 18F-labeled amyloid imaging in Alzheimer's disease. *Alzheimers Dement (Amst),* **2015**, *1*, 5-13.

[31] Danesh-Meyer, H.V.; Birch, H.; Ku, J.F.; Carroll, S.; Gamble, G. Reduction of optic nerve fibers in patients with Alzheimer disease identified by laser imaging. *Neurology,* **2006**, *67*, 1852-1854.

[32] Cheng, D.L.; Thompson, L.; Snyder, P.J. A Potential Association Between Retinal Changes, Subjective Memory Impairment, and Anxiety in Older Adults at Risk for Alzheimer's Disease: A 27-Month Pilot Study. *Front Aging Neurosci,* **2019**, *11*.

[33] Guo, L.; Duggan, J.; Cordeiro, M.F. Alzheimer's disease and retinal neurodegeneration. *Curr Alzheimer Res,* **2010**, *7*, 3-14.

[34] Zhang, L.; Xu, Y.; Zhu, Y. Relationships between optic nerve damage and the severity of cognitive impairment in patients with mild cognitive impairment and Alzheimer's disease. *Biomed Res,* **2017**, *28*.

[35] Pehlivanoglu, D.; Jain, S.; Ariel, R.; Verhaeghen, P. The ties to unbind: age-related differences in feature (un) binding in working memory for emotional faces. *Front Psychol,* **2014**, *5*, 253.

[36] Braak, H.; Thal, D.R.; Ghebremedhin, E.; Del Tredici, K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropath Exp Neur,* **2011**, *70*, 960-969.

[37] Benarroch, E.E. The locus ceruleus norepinephrine system: Functional organization and potential clinical significance. *Neurology,* **2009**, *73*, 1699-1704.

[38] Granholm, E.L.; Panizzon, M.S.; Elman, J.A.; Jak, A.J.; Hauger, R.L.; Bondi, M.W.; ... Kremen, W.S. Pupillary responses as a biomarker of early risk for Alzheimer's disease. *J Alzheimer's Dis,* **2017**, *56*, 1419-1428.

[39] Van Der Meer, E.; Beyer, R.; Horn, J.; Foth, M.; Bornemann, B.; Ries, J.; ... Wartenburger, I. Resource allocation and fluid intelligence: Insights from pupillometry. *Psychophysiology,* **2010**, *47*, 158-169.

[40] Frost, S.; Kanagasingam, Y.; Sohrabi, H.; Bourgeat, P.; Villemagne, V.; C Rowe, C.; ... L Masters, C. Pupil response biomarkers for early detection and monitoring of Alzheimer's disease. *Curr Alzheimer Res,* **2013**, *10*, 931-939.

[41] Kremen, W.S. Pupillary responses as a biomarker of early risk for Alzheimer's disease. *J Alzheimer's Dis,* **2017**, *56*, 1419-1428.

[42] Brown, L.; Sherbenou, R.J.; Johnsen, S.K. 1997. *Test of Nonverbal Intelligence, Third Edition Examiner's Manual.* Austin, TX: Pro-Ed, **1997**.

[43] Lu, J.; Li, D.; Li, F.; Zhou, A.; Wang, F.; Zuo, X.; ... Jia, J. Montreal cognitive assessment in detecting cognitive impairment in Chinese elderly individuals: a population-based study. *J Geriatr Psych Neur,* **2011**, *24*, 184-190.

[44] Petersen, R.C.; Morris, J.C. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol,* **2005**, *62*, 1160-1163.

[45] Lee, L.P.; Har, A.W.Y.; Ngai, C.H.; Lai, D.W.; Lam, B.Y.H.; Chan, C.C.H. Audiovisual integrative training for augmenting cognitive-motor functions in older adults with mild cognitive impairment. *BMC Geriatr,* **2020**, *20*, 1-5.

[46] Petersen, R.C.; Smith, G.E.; Waring, S.C.; Ivnik, R.J.; Tangalos, E.G.; Kokmen, E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol, 56*, **1999**, 303-308.

[47] Yeung, P.Y.; Wong, L.L.; Chan, C.C.; Leung, J.L.; Yung, C.Y. A validation study of the Hong Kong version of Montreal Cognitive Assessment (HK-MoCA) in Chinese older adults in Hong Kong. *Hong Kong Med J,* **2014**, *20*, 504-510.

[48] Gevins, A.; Smith, M.E.; Le, J.; Leong, H.; Bennett, J.; Martin, N.; ... Whitfield, S. High resolution evoked potential imaging of the cortical dynamics of human working memory. *Electroenceph Clin Neurophysiol,* **1996**, *98*, 327-348.

[49] Deiber, M.P.; Ibañez, V.; Missonnier, P.; Herrmann, F.; Fazio-Costa, L.; Gold, G.; Giannakopoulos, P. Abnormal-induced theta activity supports early directed-attention network deficits in progressive MCI. *Neurobiol Aging,* **2009**, *30*, 1444-1452.

[50] De Carlo, T.E.; Romano, A.; Waheed, N.K.; Duker, J. S. A review of optical coherence tomography angiography (OCTA). *Int J Retin Vitr,* **2015**, *1*, 5.

[51] Suwan, Y.; Geyman, L.S.; Fard, M.A.; Tantraworasin, A.; Chui, T.Y.; Rosen, R.B.; Ritch, R. Peripapillary perfused capillary density in exfoliation syndrome and exfoliation glaucoma versus POAG and healthy controls: an OCTA study. *Asia Pac J Ophthalmol,* **2018**, *7*(2), 84-89.

[52] Bulut, M.; Kurtuluş, F.; Gözkaya, O.; Erol, M.K., Cengiz, A.; Akıdan, M.; Yaman, A. Evaluation of optical coherence tomography angiographic findings in Alzheimer's type dementia. *Br J Ophthalmol,* **2018**, *102*, 233-237.

[53] Kirova, A.M.; Bays, R.B.; Lagalwar, S. Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. *Biomed Res Int,* **2015**, *2015*.

[54] Braver, T.S.; Cohen, J.D.; Nystrom, L.E.; Jonides, J.; Smith, E.E.; Noll, D.C. A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage,* **1997**, *5*, 49-62.

[55] Berryhill, M.E. Insights from neuropsychology: pinpointing the role of the posterior parietal cortex in episodic and working memory. *Front Integr Neurosc,* **2012**, *6*, 31.

[56] Fiez, J.A.; Raife, E.A.; Balota, D.A.; Schwarz, J.P.; Raichle, M.E.; Petersen, S.E. A positron emission tomography study of the short-term maintenance of verbal information. *J Neurosci Res,* **1996**, *16*, 808-822.

[57] Moretti, V.D. Atrophy and lower regional perfusion of temporo-parietal brain areas are correlated with impairment in memory performances and increase of EEG upper alpha power in prodromal Alzheimer's disease. *Am J Neurodegener Dis,* **2015**, *4*, 13-27.

[58] Jiang, Z.Y. Study on EEG power and coherence in patients with mild cognitive impairment during working memory task. *J Zhejiang Univ Sci B,* **2005**, *6*, 1213-1219.

[59] Querques, G.; Borrelli, E.; Sacconi, R.; De Vitis, L.; Leocani, L.; Santangelo, R.; ... Bandello, F. 2019. Functional and morphological changes of the retinal vessels in Alzheimer's disease and mild cognitive impairment. *Sci Rep,* **2019**, *9*, 1-10.

[60] Pham, T.Q.; Kifley, A.; Mitchell, P.; Wang, J.J. Relation of age-related macular degeneration and cognitive impairment in an older population. *Gerontology,* **2006**, *52*, 353-358.

[61] Appaji, A.; Nagendra, B.; Chako, D.M.; Padmanabha, A.; Jacob, A.; Hiremath, C.V.; ... Webers, C. Relation between retinal vascular abnormalities and working memory impairment in patients with schizophrenia and bipolar disorder. *Asian J Psychiatr,* **2020**, *49*, 101942.

[62] Patton, N.; Pattie, A.; MacGillivray, T.; Aslam, T.; Dhillon, B.; Gow, A.; ... Deary, I.J. The association between retinal vascular network geometry and cognitive ability in an elderly population. *Invest Ophth Vis Sci,* **2007**, *48*, 1995-2000.

[63] Williams, M.A.; McGowan, A.J.; Cardwell, C.R.; Cheung, C.Y.; Craig, D.; Passmore, P.; ... McKay, G.J. 2015. Retinal microvascular network attenuation in Alzheimer's disease. *Alzheimers Dement (Amst)*, 1, 229-235.

[64] Patton, N.; Aslam, T.; MacGillivray, T.; Pattie, A.; Deary, I.J.; Dhillon, B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. *J Anat,* **2005**, *206*, 319-348.

[65] Jorge, L.; Canário, N.; Quental, H.; Bernardes, R.; Castelo-Branco, M. Is the Retina a Mirror of the Aging Brain? Aging of Neural Retina Layers and Primary Visual Cortex Across the Lifespan. *Front Aging Neurosci,* **2020**, *11*, 360.

[66] den Haan, J.; Janssen, S.F.; van de Kreeke, J.A.; Scheltens, P.; Verbraak, F.D.; Bouwman, F.H. Retinal thickness correlates with parietal cortical atrophy in early-onset Alzheimer's disease and controls. *Alzheimers Dement (Amst),* **2018**, *10*, 49-55.

[67] Hill, A.C.; Laird, A.R.; Robinson, J.L. Gender differences in working memory networks: A BrainMap meta-analysis. *Biol Psychol,* **2014**, *102*, 18-29.

Table 1. Demographic information of MCI and healthy participants.

	MCI	Healthy controls	All participants	t-test statistics (p-values)
Number of participants	11	29	40	-
Mean age (SD)	64.91 years (3.94)	64.48 years (3.87)	64.69 years (3.84)	$t(38) = -0.31$ (0.76)
Age range	60 to 73 years	60 to 73 years	60 to 73 years	-
Mean MoCA scores (SD)	22.82 (1.17)	26.9 (1.74)	25.78 (2.43)	$t(38) = 7.160$ (0.00**)
Mean years of education (SD)	12.95 years (4.17)	12.45 years (3.64)	12.59 years (3.75)	$t(38) = -0.377$ (0.71)
Mean TONI-3 scores (SD)	18.55 (4.01)	23.72 (8.87)	22.3 (8.13)	$t(38) = 2.535$ (0.02*)
Range of mean income	20,001-25,000 HKD	10,001-15000 HKD	15,001-20,000 HKD	$t(38) = -1.025$ (0.33)

Note: HKD, Hong Kong dollar; MCI, Mild cognitive impairment; MoCA, Montreal Cognitive Assessment; SD, Standard deviation; TONI-3, Test of Nonverbal Intelligence - Third Edition. *$p < 0.05$; **$p < 0.01$.

Table 2a. Correlations between the mean accuracy and EEG latency during the WM task.

EEG locations	Correlation coefficient in MCI participants (p-values)	Correlation coefficient in healthy control participants (p-values)
FP2	0.57 (0.07^)	-0.11 (0.59)
FC1	0.62 (0.04*)	0.15 (0.45)
CPZ	-0.65 (0.03*)	-0.08 (0.70)
CP5	-0.50 (0.12)	0.02 (0.92)
CP2	-0.64 (0.03*)	-0.26 (0.17)
CP4	-0.77 (0.01**)	-0.21 (0.26)
CP6	-0.69 (0.02*)	-0.13 (0.49)
CP8	-0.70 (0.02*)	0.13 (0.49)
P1	-0.65 (0.03*)	0.02 (0.91)
P4	-0.62 (0.04*)	0.02 (0.91)
P6	-0.63 (0.04*)	0.19 (0.34)
P8	-0.64 (0.04*)	0.07 (0.73)
POZ	-0.64 (0.04*)	-0.05 (0.80)
PO6	-0.60 (0.05*)	0.05 (0.82)

Note: *$p <$ 0.05; **p< 0.01. F, Frontal; P, Parietal; O, Occipital; Z, Midline; Odd number, Left hemisphere; Even number, Right hemisphere.

Table 2b. Correlations between the mean accuracy during WM task and retinal density.

Retinal structures	Correlation coefficient in MCI participants (p-values)	Correlation coefficient in healthy control participants (p-values)
Left 3mm nasal vessel density	0.60 (0.05*)	-0.12 (0.55)
Right 3mm nasal vessel density	0.29 (0.39)	-0.23 (0.23)
Left 3mm superior vessel density	0.63 (0.49*)	-0.23 (0.23)
Right 3mm superior vessel density	0.39 (0.24)	-0.16 (0.42)
Left 3mm superior perfusion density	0.72 (0.01*)	-0.26 (0.18)
Right 3mm superior perfusion density	0.37 (0.26)	-0.17 (0.38)
Left 6mm nasal perfusion density	0.62 (0.04*)	0.02 (0.91)

Right 6mm nasal perfusion density	-0.02 (0.95)	-0.15 (0.43)

Note: *$p < 0.05$.

Table 3. Correlations between the mean RT and EEG latency during the WM task.

EEG locations	Correlation coefficient in MCI participants (p-values)	Correlation coefficient in healthy control participants (p-values)
FP2	0.63 (0.04*)	-0.157 (0.42)
FC1	-0.20 (0.55)	-0.01 (0.97)
CPZ	-0.54 (0.09)	-0.07 (0.71)
CP5	-0.66 (0.03*)	0.159 (0.41)
CP2	-0.17 (0.63)	-0.20 (0.30)
CP4	-0.26 (0.43)	-0.09 (0.66)
CP6	-0.18 (0.59)	-0.05 (0.81)
CP8	-0.93 (0.79)	-0.10 (0.59)
P1	-0.45 (0.17)	0.16 (0.41)
P4	-0.19 (0.59)	-0.02 (0.91)
P6	-0.19 (0.57)	0.01 (0.95)

P8	-0.22 (0.52)	-0.07 (0.73)
POZ	-0.48 (0.14)	0.16 (0.40)
PO6	-0.17 (0.62)	0.17 (0.38)

Note: *$p <$ 0.05. F, Frontal; P, Parietal; O, Occipital; Z, Midline; Odd number, Left hemisphere; Even number, Right hemisphere.

Table 4. Correlations between the left 3mm nasal vessel density and the EEG latency.

EEG locations	Correlation coefficient in MCI participants (p-values)	Correlation coefficient in healthy control participants (p-values)
FP2	0.20 (0.56)	0.21 (0.27)
FC1	0.73 (0.01*)	-0.10 (0.60)
CPZ	-0.24 (0.47)	0.20 (0.56)
CP5	-0.22 (0.52)	0.04 (0.85)
CP2	-0.60 (0.05^)	-0.06 (0.74)
CP4	-0.55 (0.08)	-0.15 (0.43)
CP6	-0.63 (0.04*)	-0.13 (0.52)
CP8	-0.67 (0.02*)	-0.13 (0.51)
P1	-0.53 (0.09)	0.05 (0.82)
P4	-0.25 (0.46)	-0.05 (0.80)

P6	-0.33 (0.32)	-0.06 (0.76)
P8	-0.34 (0.30)	0.05 (0.79)
POZ	-0.44 (0.18)	-0.02 (0.90)
PO6	-0.28 (0.41)	0.04 (0.84)

Note: ^$p = 0.07$; *$p < 0.05$. F, Frontal; P, Parietal; O, Occipital; Z, Midline; Odd number, Left hemisphere; Even number, Right hemisphere.

Table 5. Correlations between the left 6mm nasal perfusion density and EEG latency.

EEG locations	Correlation coefficient in MCI participants (p-values)	Correlation coefficient in healthy control participants (p-values)
FP2	0.25 (0.46)	0.04 (0.83)
FC1	0.50 (0.12)	0.09 (0.64)
CPZ	-0.17 (0.61)	0.19 (0.32)
CP5	0.03 (0.93)	0.14 (0.46)
CP2	-0.57 (0.07^)	0.16 (0.40)
CP4	-0.571 (0.07^)	0.11 (0.57)
CP6	-0.59 (0.05*)	0.15 (0.45)
CP8	-0.64 (0.03*)	0.13 (0.50)

P1	-0.28 (0.41)	0.10 (0.59)
P4	-0.46 (0.16)	0.19 (0.33)
P6	-0.53 (0.09)	0.19 (0.33)
P8	-0.51 (0.11)	0.16 (0.40)
POZ	-0.29 (0.40)	-0.02 (0.93)
PO6	-0.51 (0.11)	0.12 (0.53)

Note: ^p = 0.07; *p =< 0.05. F, Frontal; P, Parietal; O, Occipital; Z, Midline; Odd number, Left hemisphere; Even number, Right hemisphere.