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Artikel Asli/*Original Articles*

Pattern Visual Evoked Potential (VEP) is Unaffected in the Early Stage of Mild Cognitive Impairment

(Visual Evoke Potential (VEP) Tidak Berubah dalam Peringkat Awal Kemerosotan Kognitif Ringan)

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ABSTRACT

The aim of this study was to determine whether pattern-reversal Visual Evoked Potential (PRVEP) is affected in mild cognitive impairment (MCI). Participants aged ≥ 60 years diagnosed as MCI were invited to participate in a study together with a group of controls. PRVEP was measured using A RETI-port/Scan 21 and stimuli of large and small checks sizes, 1° (60 min of arc) and 0.25° (15 min) respectively were used to obtain responses. The amplitude and implicit times of the MCI and control groups were then compared. A total of 18 MCI participants (age 65.7 ± 3.1 years) and 18 controls (65.1 ± 3.8 years) consented to participate in the study. The amplitude and implicit times for the MCI group using the target sizes of 60 min of arc were 9.80 ± 4.06 μV and 108.83 ± 7.63 ms and for 30 min of arc were 11.00 ± 7.44 μV and 123.96 ± 6.18 ms respectively. Consecutively for the control groups the amplitudes and implicit times were 8.96 ± 3.52μV, 105.85 ± 3.60 ms and 11.97± 6.11 μV, 122.57 ± 8.28 ms. PRVEP results did not reveal significant differences in P100-wave amplitude nor implicit time between the two groups under investigation. This study concluded that the visual pathway of MCI participants may be unaffected in the early part of the disease process.

Keywords: Mild cognitive impairment (MCI); pattern-reversal visual evoked potential (PRVEP); elderly; amplitude; implicit times

ABSTRAK

Tujuan kajian ini adalah untuk menentukan sama ada nilai pattern-reversal Visual Evoked Potential (PRVEP) terjejas dalam kemerosotan nilai kognitif ringan (MCI). Peserta berumur ≥ 60 tahun disahkan menghidap MCI telah ditawarkan untuk mengambil bahagian dalam kajian bersama dengan kumpulan kawalan. PRVEP diukur menggunakan A RETI-port/Scan 21 dan rangsangan target saiz besar dan kecil, 1° (60 min arka) dan 0.25° (15 min) masing-masing telah digunakan untuk mendapatkan respons. Amplitud dan masa tersirat bagi MCI dari kumpulan kawalan direkod dan kemudiannya dibandingkan. Seramai 18 peserta MCI (min umur 65.7 ± 3.1 tahun) dan 18 kawalan (65.1 ± 3.8 tahun) bersetuju untuk mengambil bahagian dalam kajian ini. Amplitud dan masa tersirat kumpulan MCI menggunakan saiz sasaran 60 min arka adalah adalah 9.80 ± 4.06 μV dan 108.83 ± 7.63 ms masing-masing dan untuk 30 minit arka, 11.00 ± 7.44 μV dan 123.96 ± 6.18 ms. Turutan dari itu untuk kumpulan kawalan amplitud dan masa pendam ialah 8.96 ± 3.52 μV, 105.85 ± 3.60 ms dan 11.97± 6.11 μV and 122.57 ± 8.28 ms. Keputusan PRVEP tidak menunjukkan perbezaan yang signifikan dalam gelombang amplitud P100 atau masa tersirat antara kedua-dua kumpulan dalam kajian. Kajian ini menyimpulkan bahawa laluan visual peserta MCI mungkin tidak terjejas pada awal proses penyakit ini.

Kata kunci: Kemerosotan kognitif ringan (MCI); pattern-reversal Visual Evoked Potential (PRVEP); warga tua; amplitud; masa pendam

INTRODUCTION

Mild cognitive impairment (MCI) is defined as a transitional phase between normal aging and dementia, characterized by subjective complaint of memory impairment but with normal activity of daily living functioning (Gauthier et al. 2006). The prevalence rate of MCI among those ≥ 65 years of age is 12-18% (Peterson et al. 2007). In Malaysia a study on community based sample of urban multi-ethnic dwelling elderly aged ≥ 60 years from Cheras, Kuala Lumpur, found the prevalence rate of all-type MCI to be 21.1% (Lee et al. 2012). Older adults with MCI represent a target population that is at risk of developing dementia particularly Alzheimer's disease (AD), with reported conversion rate as high as 10-15% annually (Petersen et al. 2001). A Korean study reported a higher rate of conversion at 20.1% (Kim et al. 2011). However, the possibility exists that individuals may remain in this stage of MCI or reverts to normal cognitive function (Fisk et al. 2003; Amieva et al. 2004).

Visual evoked potential (VEP) is a non-invasive recording of electrical signals that occur in the visual

system in response to visual stimulation. The VEP tests reflect functions of the central retina and the visual pathway and provide important information for ocular disease diagnosis and treatment. VEP waveforms can be generated by using different visual stimuli such as line and checkerboard gratings. In abnormal eyes the signals may be smaller in size (reduce amplitudes) and may take longer in transmission which is reflected in the increase in implicit times.

Visual disturbances have been described as one of the initial manifestation of AD especially in the early stage of the disease. Symptoms include problems with reading, blurred vision and vague complaints of poor vision (Cronin-Golomb et al. 1991). Mendez et al. (1990) reported that 43% of AD participants have complex visual complaints. The AD participants were impaired in the visual evaluation of common objects, faces, spatial locations and complex figures. Normal routine ophthalmological examination results often disclosed dysfunctions of retinal ganglion cells as well as the optic nerve. (Danesh et al. 2006, Berisha et al. 2007). However other visual complaints that included abnormal contrast sensitivity (Rizzo et al. 1992) and reduced colour discrimination (Cronin-Golomb 1995) were not accompanied by anatomical changes usually seen during funduscopy, probably because the visual disturbances were caused by neuropathological changes in the visual cortex (Holory & Shepherd 2001, Pelak & Hall 2004). These may well be the cause of visual disturbances in participants in the early stage of AD.

In an attempt to explain the visual symptoms of participants with AD, pathological and neuroimaging studies had been carried on the retina, optic nerve and visual cortex. The results of some studies suggested that in these participants, optic nerve degeneration and loss of retinal cells, specifically disappearance of ganglion cells and their axons was evident (Syed et al. 2005; Danesh-Meyer et al. 2006; Berisha et al. 2007). Other studies suggested these visual complaints were caused by higher level of visual pathway changes within the visual cortex (Pelak & Hall 2004).

PRVEP done on participants at the early stage of AD showed a significant increase in implicit time of the P100 waveform for both the large (1° 4') and small (16') check size stimulus (Krasodomska et al. 2010). However this is in contrast to Katz et al. (1989) and Grayson et al. (1995) who showed normal implicit times of the P100 in AD participants. Grayson et al. (1995) did not detect latency differences using both the flash VEP and pattern reversal VEP. Their results were also supported by Iseri et al. (2006) who also failed to show any significant differences in VEP P100 of their AD participants relative to control.

The findings on effects of VEP on early AD are still controversial since results are contradictory. Available data on effects of VEP on MCI participants is scarce. Since MCI participants exhibit similar clinical features to early AD, it would be interesting to observe whether similar neuropathology changes is observed in the elderly MCI participants with or without subjective complaints of visual disturbances, as changes in the visual cortex could supersede any ocular manifestation. These changes can be examined by comparing the electrophysiology recordings, particularly PRVEP recordings of MCI participants relative to normal elderly participants as controls. Therefore, this study aims to evaluate the bioelectric function of retinal ganglion cells and visual pathway in MCI participants by means of PRVEP.

MATERIALS & METHODS

PARTICIPANTS

A total of 18 Mild Cognitive Impairment (MCI) participants (13 females and 5 males) aged from 60 to 72 years (mean age 65.7 ± 3.1) were invited to participate in the study. They were identified from a previous study that took place at the low cost housing area in Cheras Kuala Lumpur (Lee et al. 2012). The diagnoses were done by a certified psychologist as part of the Kuala Lumpur Ageing Study (KLAS). The diagnosis was performed through a multidisciplinary assessment of factors (nutrition, health, physical function, psychosocial) associated with cognitive decline and impairment through collaboration of experts from various agencies. The MCI participants were compared to a group of controls (2 females and 16 males), aged from 60 to 71 years (mean age 65.1 ± 3.8) who met the normal cognitive function of Malay version of Mini-mental State Examination (MMSE) score of 27 and above. This Malay version of the MMSE has been validated among the local elderly population (Zarina et al. 2007).

Human ethical committee approval was obtained from the Medical Research and Ethics Committee of Universiti Kebangsaan Malaysia (UKM). The experiment protocols adhered to the tenets of the Declaration of Helsinki. All participants were briefed on the study and testing procedure before written consents were obtained.

PARTICIPANTS CRITERIA

The inclusion criteria for MCI participants and their age-matched controls were: best corrected distance visual acuity ≥ 6/9 (Snellen) with refractive error less than ± 4.00 DS and/or ± 2.00 DC (astigmatism), near visual acuity ≥ N8, absence or no previous history of any significant media opacities, retinal disorders and ocular pathologies. The exclusion criteria included having any opacity of the media that reduced vision worse than 6/9 (Snellen), has history of trauma or ocular diseases such as glaucoma and anisocoria greater than 2mm. With regard to systemic diseases often encountered in the elderly such as hypertension and diabetes, participants were excluded if it was more than 5 years duration and funduscopy revealed systemic changes in the retina.

METHODS

There were three stages of this study. The first stage was assessment of cognitive status with MMSE for the controls. Normal participants who met the minimum score of 27 in the Malay version MMSE were accepted. The second stage was optometric examination to identify research participants. All participants chosen had to meet the inclusion and exclusion criteria. The last stage was electrophysiology tests recordings for all research participants done at the Clinic and Electrophysiological Lab, Optometry and Vision Sciences Program, Faculty of Health Sciences, UKM, Kuala Lumpur.

MACHINERY AND SOFTWARE SPECIFICATION

A RETI-port/Scan 21 (serial number 04-99-7003), Roland, Germany was used in this study. The instrument, its accessory and software are calibrated every 6 months to ensure consistency of readings. *Gel-Nuprep* and conductive paste *Paste-Ten20* (D.O. Weaver & Co, USA) were used in preparing participants for VEP recording. The standard protocol for electrophysiology testing followed the guidelines set by the International Society for Clinical Electrophysiology of Vision (ISCEV). For the PRVEP test, stimuli of large and small checks sizes, 1° (60 min of arc) and 0.25° (15 min) respectively were used to obtain PRVEP responses, each at a rate of 3 reversals per second or a frequency of 1.50 Hz.

PARTICIPANT'S PREPARATION AND TEST RECORDING PROCEDURES

Participant's preparation followed ISCEV standard for VEP protocols. Prior to electrode placement, the skin and scalp were cleaned to remove oil and debris using *skin prepping Gel-Nuprep*. Conductive *Paste-Ten20* was used to secure the electrode cup on the scalp and to help ensure good and stable electrical connection between the scalp and electrodes. For PRVEP test, electrodes used were gold disc electrodes (Bradenburg, Germany) of diameter 10 mm. Three electrodes were placed relative to bony landmarks on the scalp along the midline and their placements were in accordance to the International 10/20 system. They were placed at O_z (Active) over the visual cortex, C_z (Ground) and F_z (Reference) on the forehead. To effectively reject unwanted signal noise, the electrode impedances were maintained below 10 kΩ in all cases and were usually below 5 kΩ in most cases. In addition, their impedance differences were controlled to be less than 5 kΩ between electrode sites.

Recordings were performed with the pupils undilated and appropriate refractive error correction in relation to the eye-screen distance was given. A 19" CRT monitor with a black and white reversing checkerboard was presented to participants. In PRVEP test stimuli were presented monocularly to participants while the unstimulated eye was patched tightly using cotton pad securely held with masking tape to prevent light entering the eye. During recording, participants maintained fixation at a cross at the centre of the pattern stimulus. Throughout data recording, participants were advised to remain in relaxed position and refrain from talking to minimise muscle movements and other artefacts. The PRVEP was run twice and the average was calculated. Recordings were first done in the right eye followed by the left eye.

TEST PARAMETERS

For PRVEP the parameter tested included of P100 amplitude and implicit time (60' arc and 15' arc) (Figure 1) for each of the normal and MCI groups. Two consecutive waveforms were recorded in each session and the average readings for each parameter were used in statistical analysis. Manual correction to the automatic curser placement was performed when necessary.

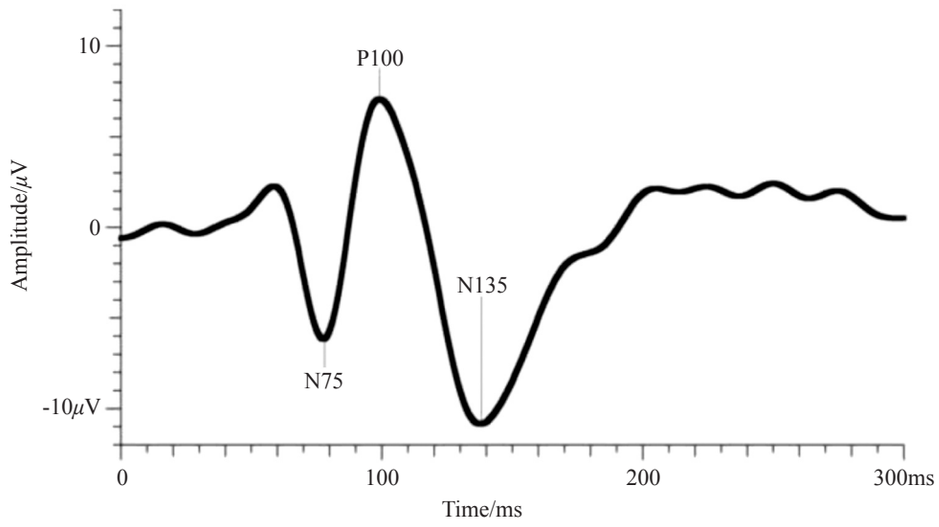

FIGURE 1. A typical waveform component of the PRVEP

STATISTICAL ANALYSIS

PRVEP data was analysed using SPSS statistical software package (Version 20.0; SPSS Inc., Chicago, IL). Parameter results consisted of P100 amplitude and implicit times of the MCI and control groups. Shapiro-Wilks was used to test for normality of data. For normally distributed data ($p > 0.05$) parametric tests were used for statistical analysis. Otherwise non-parametric tests were applied to the same data. Since recordings were done monocularly, correlations between right and left eyes were done. If there was good correlation, reading of only one eye (RE) was used for further analysis. Alpha level of 0.05 will be used as reference and p value < 0.05 considered as statistically significant.

RESULTS

Thirty-six (36) participants comprising of 18 MCI and 18 normal (control) consented to take part in the study. Shapiro-Wilks test showed the data was normally distributed for all parameters ($p > 0.05$) therefore 2-tailed t-test was used to compare results of the MCI and control participants. There was positive correlation between the right and left eyes for all parameters tested ($p = 0.6$-0.9), therefore only the right eye was used for subsequent analysis.

The demography data is presented in Table 1. Amongst the MCI participants there were 5 males and 13 females, whereas in the control group there were 2 females and 16 males. The initial results showed no significant differences between the MCI and control groups with respect to their age and visual acuity. The results also showed no significance differences in amplitude and implicit times of the P100 wave component of the MCI participants compared to its control healthy counterparts. This is true for both the large (60' arc) and small (15' arc) check size stimuli. The results are summarized in Table 2.

TABLE 1. Demography of participants

		MCI	Control	P value
Gender:	Females	13	2	NA
	Males	5	16	NA
Age (Years)		65.7 ± 3.1	65.1 ± 3.8	P = 0.21
VA		0.88 ± 0.23	1.02 ± 0.16	P = 0.91
SE (DS)		+0.67 ± 2.27	+0.40 ± 1.75	P = 0.70

SE = spherical equivalent, VA = Visual Acuity, DS = Dioptre Sphere

TABLE 2. Amplitude and Implicit times of P100 wave component of MCI and control

Parameter	Eyes	MCI (N = 18)		Control (N = 18)		2 tailed t-test between MCI and control
		(mean ± SD)	Range	(mean ± SD)	Range	
P100 amplitude 60' arc (μV)	RE	9.80 ± 4.06	3.14 – 16.20	8.96 ± 3.52	2.81 – 15.55	P = 0.514
P100 implicit time 60' arc (ms)	RE	108.83 ± 7.63	96.85 – 123.00	105.85 ± 3.60	100.10 – 112.40	p = 0.147
P100 amplitude 15' arc (μV)	RE	11.00 ± 7.44	2.20 – 28.60	11.97 ± 6.11	2.63 – 23.64	p = 0.672
P100 implicit time 15' arc (ms)	RE	123.96 ± 6.18	88.95 – 153.25	122.57 ± 8.28	106.00 – 133.15	p = 0.747

RE: Right eye; SD: Standard Deviation

The variations in amplitude and implicit times are displayed in Figure 2 and Figure 3. Only the results from the larger target (60'arc) were depicted that showed no definite trend or pattern in the both the MCI and control groups.

DISCUSSION

In an effort to find whether pattern reversal visual evoked potential is affected in the elderly with MCI, we measured the amplitude and implicit times of 18 elderly diagnosed with MCI and compared the results with 18 normal control. Our result revealed no significant differences of the amplitude and implicit times between the MCI and normal healthy participants. PRVEP represents the function of primary visual cortex and visual pathways. Reduced P100 amplitude can reflect neuronal or axonal loss in the visual system, while an increase in latency of the P100-wave can reflect slowed neural conduction. This result may suggest intact visual pathway in this group of MCI participants.

Sparing of the primary visual cortex in AD participants has also been reported in the literature. Orwin et al. (1986) found normal PRVEP despite increasing latency of the flash VEP in a 58 year-old woman with progressive AD monitored for three and a half years (129 ms in year 1981 to 153ms in year 1984). Rizzo et al. (1992) performed pattern VEP on 25 AD participants (mean age 64.5 ± 8.4 years) of various (mild to severe) stages and compared them with 35 healthy elderly (mean age 65.1 ± 7.2 years) participants. He found no evidence of retino-calcarine abnormality in the neural visual pathways specific in AD participants. They concluded that the visual impairment experienced by some participants with AD primarily resulted from involvement of the visual association cortices rather than from pre-cortical damage, at least before the end stage of the disease. Philpot et al. (2002) who compared PRVEP of normal elderly participants and participants with mild

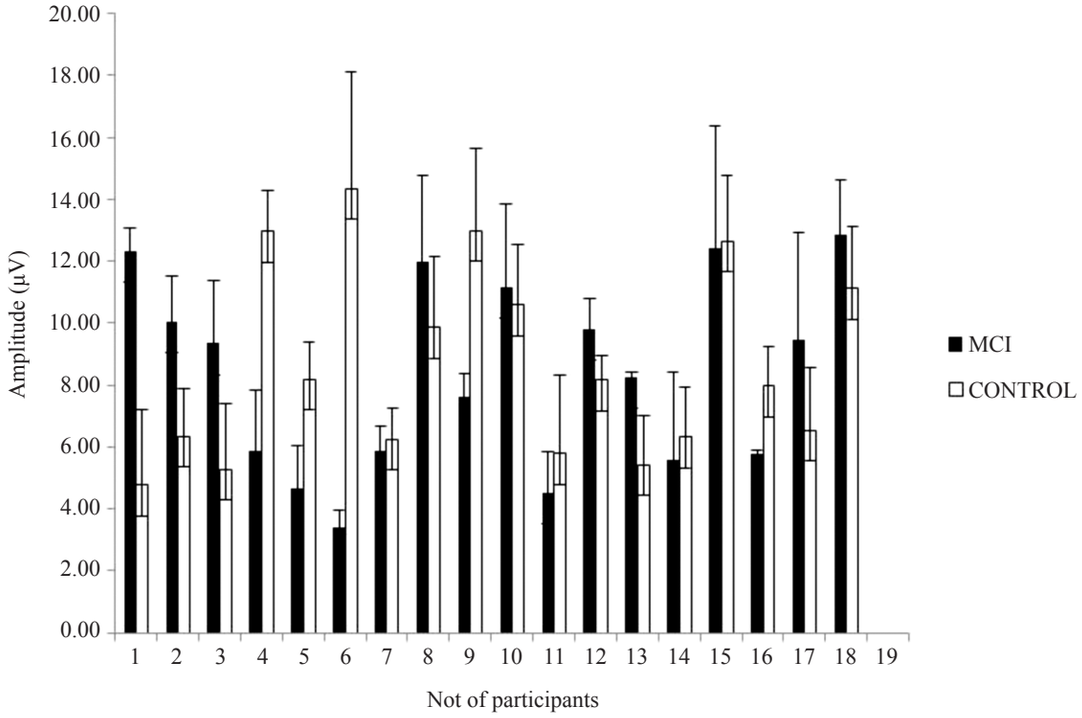

FIGURE 2. Variations in mean amplitude responses between MCI and Control groups

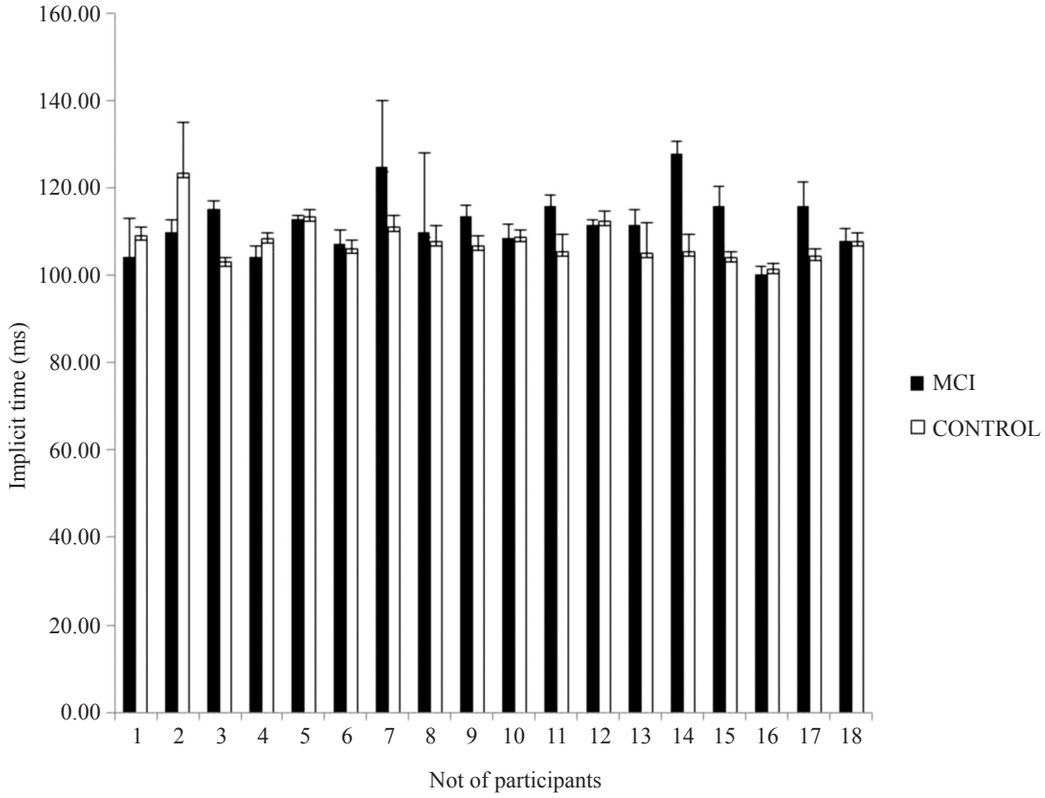

FIGURE 3. Variations in mean implicit times between MCI and Control groups

memory impairment not amounting to dementia observed the P100 component remained relatively unchanged. Kergoat et al. (2002) who compared individuals with dementia of the Alzheimer's type (DAT) and control normal found no attenuation of the VEP amplitude but found a latency delay in VEP in DAT participants. Iseri et al. (2006)

found no abnormalities in VEP values despite significant reduction in parapapillary retinal nerve fibre layer (RNFL), macular thickness and volume in participants with AD. The normal VEP responses in their study suggested that primary cortical region and optic nerve function was normal despite considerable RNFL loss. However Spencer et al. (2014) using the electroencephalographic (EEG) component of the flash VEP found the latency was longer in MCI participants compared to controls.

Several limitations existed in this study. One of them was the unequal number of male and female participants in each group and the obvious difference in gender between groups. Studies have indicated that females give shorter implicit time measurement than male counterpart. However, both Guthkelch et al. (1987) and Gregori et al. (2006) suggested that head size and not gender play a role in influencing VEP readings. Guthkelch et al. (1987) observed the P100 implicit time to correlate highly with head size measurement. Studies that often found a lower implicit time could have consisted of more female participants, as it is generally known that females are of a smaller built-size than males and have smaller head circumference measurement. In this study, the mean implicit time in the MCI group appears to be slightly higher, although not significant, than the control group which is dominated by males. It is not known if the MCI group of female dominants have caused attenuation of the overall P100-wave implicit time parameter. Future studies could take gender into account when measuring VEP.

Another challenge encountered in this study was the much higher variation of P100-wave implicit time seen among the MCI participants, depicted by the standard deviation being as high as double that of control participants. Such variation could be explained by the inclusion of MCI participants of various levels of cognitive impairment. It has been reported that implicit time delay in VEP measurements is associated with extent of cognitive impairment. Most (17 out of 18) of the MCI participants in this study were diagnosed in a larger study carried out 3 years previously. It is unknown if these same participants are still within the early MCI range or have improved cognitively. Studies have shown that cognitive improvement can be catalysed by lifestyle changes either through antioxidant diet (Lee et al. 2011) or physical exercise (Baker et al. 2010).

Another factor that could have contributed to the wide variations in observed implicit times among the MCI participants are probably the criteria used as a cut-off point for MCI classification. Participants recruited for this study was classified as MCI based on MMSE reading of 21 or less. Different cut-off points have been adopted in many studies using the MMSE since there is no clear cut definition of MCI. Instead of employing MMSE 21 cut-off point as in the current study, a narrower cut-off point for MMSE might have been more appropriate to exclude probable-MCI suspects (Razali et al. 2012). Nevertheless this study serves to catalyse more future research in the area of electrophysiology among the MCI sufferers.

All the MCI subjects in this study did not complain of visual problems and funduscopy did not show evidence of external retinal problems. The subjects also have normal pattern ERG but this results on pattern ERG are reported elsewhere. However measurements of nerve fibres thickness of the retina would provide additional data to complement the study. Future study should take into account of some of the limitation mentioned and the different stages of MCI in VEP studies among the elderly.

CONCLUSION

Within the limitation of our study it was found that there was no significant difference in PRVEP of MCI participants as compared to their control healthy counterparts. This may imply that in early MCI the visual pathway and visual cortex may be intact.

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