Altered mismatch response of inferior parietal lobule in amnestic mild cognitive impairment: A magnetoencephalographic study

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Abstract

Background: Mismatch negativity (MMN) reflects the functional integrity of sensory memory function. With the advantages of independence of individual's focused attention and behavioral cooperation, this neurophysiological signal is particularly suitable for investigating elderly with cognitive decline such as amnestic mild cognitive impairment (aMCI). However, the existing results remain substantially inconsistent whether these patients show deficits of MMN. In order to reconcile the previous disputes, the present study used magnetoencephalography combined with distributed source imaging methods to determine the source-level magnetic mismatch negativity (MMNm) in aMCI.

Methods: A total of 26 healthy controls (HC) and 26 patients with aMCI underwent an auditory oddball paradigm during the MEG recordings. MMNm amplitudes and latencies in the bilateral superior temporal gyrus, inferior frontal gyrus, and inferior parietal lobule (IPL) were compared between HC and aMCI groups. The correlations of MMNm responses with performance of auditory/verbal memory tests were examined. Finally, MMNm and its combination with verbal/auditory memory tests were submitted to receiver operating characteristic (ROC) curve analysis.
Results: Compared to HC, patients with aMCI showed significantly delayed MMNm latencies in the IPL. Among the patients with aMCI, longer MMNm latencies of left IPL were associated with lower scores of Chinese Version Verbal Learning Test (CVVLT). The ROC curve analysis revealed that the combination of MMNm latencies of left IPL and CVVLT scores yielded a moderate accuracy in the discrimination of aMCI from HC at an individual level.

Conclusions: Our data suggest dysfunctional MMNm in patients with aMCI, particularly in the IPL.

**KEYWORDS**
mismatch negativity (MMN), amnestic mild cognitive impairment (aMCI), inferior parietal lobule (IPL), magnetoencephalography (MEG)

## 1 | INTRODUCTION

Mild cognitive impairment (MCI) has been proposed to be an intermediate stage of cognitive dysfunction between normal aging and dementia. Unlike patients with dementia, those with MCI still maintain their independence in most of activities of daily living (ADL) with minimal aids or assistance; however, cognitive deficits are noticeable and detected by neuropsychological assessments (ADL) with minimal aids or assistance; however, cognitive deficits maintain their independence in most of activities of daily living (ADL) with minimal aids or assistance. The concept of MCI is further categorized as amnestic MCI (aMCI) and non-amnestic MCI (naMCI). Clinically, aMCI is characterized as apparent deficits in memory rather than other cognitive functions and is shown to be strongly associated with the development of Alzheimer's disease (AD), the most common type of dementia. Since AD would cause severe ADL dysfunction which in turn increases the health care and economic burdens, the early and accurate diagnosis of aMCI prior to AD is imperative.

Up to the date, the diagnosis of aMCI is based on the clinical criteria. Although some biomarkers, such as beta amyloid or tau levels of cerebrospinal fluid (CSF) and positron emission tomography (PET) imaging with C-labeled Pittsburgh compound-B, have been proposed for their utility in the diagnosis of aMCI due to AD, the existing data do not provide strong evidence for the routine use of these biomarkers in clinical practice. Furthermore, with the fact that PET imaging is expensive and CSF is not easy to collect from each patient with aMCI, the search for other markers is needed. Neurophysiological recordings using electroencephalography (EEG) or magnetoencephalography (MEG) have been demonstrated as promising tools in the AD research and can also be considered suitable for the studies of aMCI. When applying neurophysiological recordings in the studies of neurodegenerative diseases, a task or a signal that is largely independent of the individual’s focused attention, motivation, or behavioral cooperation is a key element for its clinical utility and future application. Mismatch negativity (MMN), or its magnetic counterpart (MMNm), is one of the neurophysiological signals that possess these advantages.

MMN/MMNm is an automatic cortical activity elicited by a passive oddball task, in which a sequence of identical auditory stimuli (standards) is occasionally interrupted by deviant sounds (deviants) differing in any of perceptual characteristics, such as pitch, duration, intensity, or location. The generation of the MMN/MMNm has been interpreted as a pre-attentive cognitive process indexing functional integrity of sensory memory and accuracy in detecting changes. Although the existing literature has shown the deficits of MMN/MMNm in patients with AD, the results in aMCI are substantially inconsistent. There are only five studies so far investigating the auditory MMN in patients with aMCI/MCI. Mowszowski et al. used tone duration as deviants and found that compared to healthy controls (HC), patients with MCI exhibited reduced MMN amplitudes. Similar finding of reduced MMN amplitudes in patients with aMCI was also reported by Lindin and colleagues, who used tone frequency as deviants. However, Ji and colleagues, using frequency deviants as well, found defects of MMN latencies, rather than MMN amplitudes, in patients with MCI as compared with HC. In contrast to aforementioned three studies, two studies reported no declined or even improved MMN responses in patients with MCI as compared with HC. As a whole, it is difficult to draw a precise conclusion regarding the MMN in aMCI/MCI.

One of the major causes leading to extremely controversial results is attributed to the mixture of patient characteristics. For example, Mowszowski et al. and Tsolaki et al. recruited both aMCI and naMCI in their studies. The second one is related to the different task instructions among the studies. MMN is conventionally obtained through a passive oddball paradigm, while Tsolaki et al. used an active oddball task in which the subjects were asked to respond to infrequent targets. Finally, all the existing studies investigated MMN by means of EEG, whose signals are potentially distorted by different tissues (e.g., brain, CSF, and skull). Also, due to the limited spatial resolution, the brain activities recorded from the scalp electrodes provide little information of the source activation of MMN.
aimed to use a whole-head MEG, which has a spatial resolution with a millimeter scale and a temporal resolution with a millisecond scale, to examine the spatiotemporal dynamics of MMNm activities in patients with aMCI.

The specific goals of this study were three-fold. Firstly, based on the selected regions of interest (ROIs), we attempted to determine whether, at a group level, MMNm amplitudes and latencies at the cortical level would be reduced in the patients with aMCI versus HC group. Secondly, we sought to examine whether the MMNm in the ROIs, which exhibited significant between-group differences (if detected), would show significant associations with cognitive performance related to auditory/verbal memory tests, including Chinese Version Verbal Learning Test (CVVLT) and Logical Memory A of the Wechsler Memory Scale, and Digit Span Backward. Finally, we used the MMNm activity and its combination with auditory/verbal memory tests to examine the discrimination accuracy between HC and aMCI at an individual level.

2 | METHODS

2.1 | Participants

This study included 26 patients with aMCI (11 males, mean age = 71.96 ± 1.88 years) from the memory clinics at Taipei Veterans General Hospital. Clinical diagnosis of aMCI was made by the neurologist (PNW) based on clinical criteria. The patients had episodic memory impairment (Chinese Version Verbal Learning Test (CVVLT) below 1.5 standard deviation of the norm data) along with normal functioning in ADL. MRI and laboratory examinations were used to rule out stroke, severe white matter diseases, and tumors. They also self-reported no hearing impairment, and normal or corrected-to-normal vision.

The Institutional Review Board of Taipei Veterans General Hospital (Taipei, Taiwan) approved this research project. Written informed consent was obtained from each subject after a complete explanation of the study procedure.

2.2 | Neuropsychological assessments

Each subject was evaluated by a standardized battery of neuropsychological assessments, including MMSE, CVVLT, Logical Memory A of the Wechsler Memory Scale, Rey-Osterrieth Complex Figure Test, Verbal Fluency Test, Boston Naming Test, Digit Span Forward, Digit Span Backward (DSB), and Trail Making Test (Table 1).

Based on that the MMNm reflects functional integrity of auditory sensory memory and the patients with aMCI exhibit impairments in memory function, we specifically examined the following auditory/verbal memory tests in relation to MMNm:

1. CVVLT: Nine two-character nouns were spoken to the subject to measure total (learning over 4 trials) and delayed recall scores.
2. LM: a brief story was spoken to the subject to measure immediate and delayed recall memory function.
3. DSB: a series of digits were spoken to the subject to measure the auditory working memory.

2.3 | MEG recordings

The subjects were presented with an auditory oddball paradigm consisting of 85% standard stimuli (1000 Hz, 70 dB, 100 ms) and 15% deviant stimuli (900 Hz, 70 dB, 100 ms) in a pseudo-random order in which two deviants were separated by at least one standard. The interstimulus interval was 1000 ms. During the whole experiment, the subjects were asked to watch a silent movie with subtitles and ignore the auditory stimuli.

The neuromagnetic responses to standards and deviants were recorded by a whole-head 306-channel MEG system (Elekta-Neuromag), consisting of 102 magnetometers and 204 gradiometer. The online sampling rate and bandpass filter were set at 1000 Hz and 0.1–200 Hz, respectively. In addition to three anatomical landmarks and four head position indicators, further ~100 head points were uniformly digitized on the head surface with a 3D digitizer. Electrooculography (EOG) and electrocardiography (ECG) were used to monitor the eye blinks and cardiac artifacts. The mean numbers of deviants did not significantly differ between HC (121.73 ± 3.84) and aMCI (116.04 ± 2.93) groups (p = 0.245).

2.4 | MEG data analysis

The MEG raw data were pre-processed by MaxFilter to suppress external and internal interference and by signal space projections (SSP) to correct the trials contaminated by eye and cardiac artifacts. The artifact-free standards and deviants were separately epoched into 500 ms, including a 100-ms pre-stimulus baseline. The offline bandpass filter was set at 0.1–30 Hz. In an attempt to achieve an equivalent signal-to-noise between standards and deviants, the number of standards was randomly selected to match the number of deviants. The MMNm was measured as a difference waveform obtained by subtracting neuromagnetic responses to standards from those to deviants. The time window of MMNm was defined as 150–300 ms after the stimulus onset.

An overlapping-sphere method was used to resolve the forward problem. The cortically constrained source imaging was subsequently performed by means of depth-weighted minimum norm estimate.
TABLE 1 Demographic data and neuropsychological measures (mean ± SEM)

|                          | HC (n = 26) | aMCI (n = 26) | p values |
|--------------------------|------------|---------------|----------|
| Sex (male/female)        | 9/17       | 11/15         | 0.10     |
| Age                      | 65.81 ± 1.45 | 71.96 ± 1.88 | 0.10     |
| Race                     | Chinese    | Chinese       | —        |
| Medication               | 1 BZD      | 3 BZD         |          |
|                          |            | 2 SSRIs       |          |
| MMSE                     | 29.04 ± 0.20 | 28.35 ± 0.24 | 0.03*    |
| CVVLT_Total              | 30.92 ± 0.66 | 25.65 ± 0.81 | <0.001*  |
| CVVLT_Delayed            | 8.27 ± 0.19 | 6.35 ± 0.30  | <0.001*  |
| LM_Immediate             | 15.27 ± 0.62 | 10.58 ± 0.75 | <0.001*  |
| LM_Delayed               | 14.19 ± 0.73 | 8.23 ± 0.78  | <0.001*  |
| CFT_Copy                 | 32.8 ± 0.50 | 31.54 ± 0.66 | 0.13     |
| CFT_Immediate            | 24.77 ± 1.23 | 19.10 ± 1.48 | 0.01*    |
| CFT_Delayed              | 24.35 ± 1.32 | 17.73 ± 1.43 | <0.001*  |
| Verbal fluency           | 18.89 ± 0.88 | 15.46 ± 0.97 | 0.01*    |
| BNT_Semantic             | 26.69 ± 0.49 | 26.88 ± 0.52 | 0.80     |
| BNT_Semantic cued        | 0.50 ± 0.15 | 0.23 ± 0.10  | 0.14     |
| BNT_Phonemic cued        | 1.85 ± 0.27 | 1.46 ± 0.32  | 0.36     |
| Digit Span Forward       | 8.31 ± 0.23 | 8.04 ± 0.22  | 0.40     |
| Digit Span Backward      | 5.73 ± 0.28 | 4.62 ± 0.25  | 0.01*    |
| Trail Making Test A (sec)| 18.54 ± 3.29 | 13.50 ± 0.75 | 0.24     |
| Trail Making Test B (sec)| 36.0 ± 5.23 | 47.62 ± 5.35 | 0.13     |

Abbreviations: aMCI, amnestic mild cognitive impairment; BNT, Boston Naming Test; BZD, benzodiazepines; CFT, Rey-Osterrieth Complex Figure Test; CVVLT, Chinese Version Verbal Learning Test; HC, healthy control; LM, Logical Memory A of the Wechsler Memory Scale; MMSE, Mini-Mental State Examination; SEM, standard error of the mean; SSRIs, selective serotonin reuptake inhibitors.

*p < 0.05.

The MME over a set of ~15,000 dipoles distributed on the cortex. The individual's MME map was then rescaled to fit the predefined head points, with the default parameter settings in the brainstorm software. The MME maps of MMNm from each group were averaged onto the ICBM152 brain template for further analysis.

The existing literature and our previous works suggest that neural generators of MMNm include superior temporal gyrus (STG), inferior frontal gyrus (IFG), and inferior parietal lobule (IPL). Therefore, we identified 6 ROIs on the Desikan-Killiany cortical atlas installed in the Brainstorm software: (1) left STG (SCS coordinate = [15, 59, 40], vertex number = 290, area = 47.81 cm²); (2) right STG (SCS coordinate = [23, −59, 37], vertex number = 257, area = 43.98 cm²); (3) left IFG (SCS coordinate = [40, 56, 60], vertex number = 139, area = 20.90 cm²); (4) right IFG (SCS coordinate = [43, −57, 62], vertex number = 118, area = 17.05 cm²); (5) left IPL (SCS coordinate = [−42, 50, 79], vertex number = 351, area = 52.71 cm²); and (6) right IPL (SCS coordinate = [−36, −50, 82], vertex number = 421, area = 61.33 cm²). The ROI identification on the Desikan-Killiany brain template has been reported in other studies.

The MNE magnitude of each dipole (i.e., vertex) was normalized in relation to its fluctuations over 100-ms, yielding a z-score map. The peak amplitudes (z-score) and peak latencies (ms) of MMNm were derived from each ROI.

2.5 Statistical analysis

All the data were presented as mean ± one standard error of the mean (SEM), and p values less than 0.05 were considered as statistically significant. The numerical data were normally distributed as verified by the Kolmogorov-Smirnov tests (Z < 0.9999, p > 0.271). Between-group differences of demographic and neuropsychological data were compared using independent two-sample t-tests or chi-square tests as appropriate. Two-way mixed ANOVAs, with group (HC and aMCI) as a between-subject factor and hemisphere (left and right) as a within-subject factor, were applied to compare MMNm amplitudes and latencies in each identified ROI. Furthermore, age and gender were entered as covariate variables. Greenhouse-Geisser epsilon correction was applied when the assumption of sphericity was violated. Partial eta squared was used to estimate the effect size.

Based on the ROIs with significant between-group differences, partial correlations, with age and gender as covariates, were used to determine the associations between MMNm responses and scores of auditory/verbal memory tests (i.e., CVVLT_Total, CVVLT_Delayed, LM_Immediate, LM_Delayed, DSB) among the patients with aMCI. The significance was further adjusted for multiple comparisons by means of Bonferroni approach.

Finally, based on the significant between-group differences of MMNm responses and significant correlational data, MMNm and its combination with verbal/auditory memory tests were submitted to receiver operating characteristic (ROC) curve analysis. For the area under the curve (AUC), an AUC between 0.5 and 0.7 was considered less accurate, an AUC between 0.7 and 0.9 was considered moderately accurate, and an AUC above 0.9 was considered very accurate.

3 RESULTS

Figure 1 displays the grand-averaged sensor waveforms of MMNm in HC (n = 26) and aMCI (n = 26) groups. The results of MNE source reconstruction reveal cortical activation of temporal, frontal, and parietal cortices between 100 and 300 ms. Based on the identified ROIs, we performed the two-way mixed ANOVAs to investigate the between-group differences of MMNm amplitudes and latencies (Figure 2). Compared to HC, patients with aMCI demonstrated significant prolongation of MMNm latencies in the left IPL (F = 4.893, p = 0.032, two-tailed, partial eta squared = 0.093).
Magnetic mismatch negativity (MMNm) is the difference in neuromagnetic responses to standard and deviant auditory stimuli. The grand-averaged butterfly plots of the sensor waveforms are illustrated for healthy control (HC, n = 26) and amnestic mild cognitive impairment (aMCI, n = 26) groups. The spatiotemporal dynamics of the MMNm reconstructed by the depth-weighted minimum norm estimate (MNE) were obtained via the average of cortical responses across every 50-ms time frame from 100 to 300 ms.
Since significant between-group differences of MMNm latencies were detected in the IPL, it was interesting to further examine whether MMNm latencies in the left and right IPL were associated with the performance of auditory/verbal memory as assessed by CVVLT_Total, CVVLT_Delayed, LM_Immediate, LM_Delayed, and DSB. The correlational results showed that in the left IPL (Figure 3), delayed MMNm latencies were significantly associated with lower scores of CVVLT_Total (partial $r = -0.536$, adjusted $p = 0.035$, two-tailed) among the patients with aMCI. No other significant results were found after the Bonferroni corrections (CVVLT_Delayed: $r = -0.422$, adjusted $p = 0.20$; LM_Immediate: $r = -0.377$, adjusted $p = 0.345$; LM_Delayed: $r = -0.143$, adjusted $p = 1.0$; DSB: $r = -0.081$, adjusted $p = 1.0$).

Given that MMNm latencies of the left IPL and CVVLT_Total showed the most significant results at a group level, we further applied the ROC curve analysis to determine whether the MMNm latency of left IPL or its combination with CVVLT_Total could discriminate aMCI patients from HC at an individual level. The AUC of MMNm latencies of the left IPL was 0.689 (sensitivity = 76.9%, specificity = 61.5%, $p = 0.020$), considered less accurate (Figure 4). It was notable that the MMNm latencies of the left IPL together with CVVLT_Total reached a moderate accuracy in the discrimination aMCI from HC (AUC = 0.842, sensitivity = 80.8%, specificity = 69.2%, $p < 0.001$).

4 | DISCUSSION

The present study used MEG recordings and MNE imaging methods to compared the source-level MMNm responses between HC and aMCI groups. Our results yielded three major findings. Firstly, compared to HC, patients with aMCI exhibited delayed MMNm latency in the IPL. Secondly, MMNm latencies of the left IPL were significantly associated with the performance of memory function measured by Chinese Version Verbal Learning Test. Finally, the ROC curve analysis showed that combining MMNm latencies of the left IPL and CVVLT could accurately discriminate aMCI from HC at an individual level.

Up to the date, the existing 5 MMN studies in aMCI/MCI all applied EEG recordings and analyzed MMN activities on the surface electrodes. Unfortunately, the results were quite inconsistent. Our present MEG study analyzed tone-elicited MMNm activities at a cortical level revealed that MMNm latencies were significantly delayed in the IPL, in consistent with the previous studies. However, unlike other studies showing attenuated MMNm amplitudes in aMCI/MCI,29,30 we did not find significant between-group differences of MMNm amplitudes in any of identified ROIs. One plausible reason to account for this discrepancy was that patients with aMCI and naMCI were mixed in some of the studies. Another interpretation was related to different task design (e.g., tone deviants
vs. novelty deviants, passive oddball vs. active oddball). For example, Lindin and colleagues reported a reduced MMN amplitude in patients with aMCI versus HC, and such a deficit was attributed to novelty deviants rather than tone deviants. Similarly, another study showed that the novelty-elicited MMN was found to be shortened in the patients with aMCI; the tone-elicited MMN amplitudes or latencies did not significantly differ between HC and aMCI groups.

In terms of task instruction, all the studies used passive oddball paradigm except for that Tsolaki and colleagues carried out an active task in which the subjects were asked to make a response to target tones. Notably, we found that MMNm latencies of the left IPL were significantly correlated with the performance of CVVLT. Previous studies have reported significant associations of MMN responses with attention, working memory, planning, and verbal learning and memory in the healthy adults. Here, we further indicated that more delayed MMNm latencies, particularly in the left IPL, were associated with worse performance of verbal learning tests among the patients with aMCI. Mounting evidence from structural and functional studies has shown that the left inferior parietal area is related to auditory working memory and episodic memory. For example, lesion studies have shown that the left IPL is a key region for the storage of verbal short-term memory. Compared to HC, gray matter atrophy of the IPL has been well documented in patients with aMCI. It should be noted that the one of the promising diagnostic values for distinguishing aMCI from HC was the gray matter volume of left IPL (left supramarginal gyrus in their article). Other studies by means of neuro-modulation technique further provided empirical evidence to shed lights on the role of left IPL in the processing of verbal short-term storage and recall. For example, it has been shown that repetitive transcranial magnetic stimulation (rTMS) on left IPL disrupted the subjects’ performance on episodic memory retrieval. Similarly, rTMS on the left or right IPL (i.e., close to the intraparietal sulcus in their article) led to significant deterioration of performance in verbal working memory. Taken together, our current data extended the previous knowledge to reveal that patients with aMCI showed an apparent deficit of pre-attentive change detection in the left IPL, and such a deficit furtherer had a detrimental influence on the verbal learning test.

Our ROC curve analysis revealed that MMNm latency of the left IPL was not an acceptable indicator for the discrimination of aMCI from HC (AUC = 0.769). However, the combination of MMNm and CVVLT largely improved the diagnostic power (AUC = 0.842, sensitivity = 80.8%, specificity = 69.2%) to achieve a moderate accuracy. A previous study using a visual oddball task has shown that P300 latency could serve as an excellent indicator for the discrimination between HC and MCI (AUC = 0.97), with the sensitivity of 80% and specificity of 100%. Despite such a high accuracy, it should be noted that P300 should be obtained through the cooperation of the subjects including sustained attention and motivation, which were usually poor in the patients with neurodegenerative disorders. From the clinical perspective, a pre-attentive/automatic indicator with a satisfactory accuracy is much more expected since it can not only suit for the cross-investigation but also for the monitoring of the disease progression such as from aMCI to AD. Thus, it merits further research using pre-attentive signals, resting-state brain activities, or the combination of these parameters to perfectly separate the aMCI from HC at an individual level.

The present study had several limitations. Firstly, the paradigm we used here was traditional version without a precise control for

![FIGURE 3](image-url)  
**FIGURE 3** Significant association between MMNm latencies of the left inferior parietal lobule and total scores of Chinese Version Verbal Learning Test (CVVLT_Total) among the patients with amnestic mild cognitive impairment was found (p value was adjusted by Bonferroni approach).

![FIGURE 4](image-url)  
**FIGURE 4** Receiver operator characteristic (ROC) curve analysis of MMNm latency of the left inferior parietal lobule (IPL) and its combination with total scores of Chinese Version Verbal Learning Test (CVVLT_Total).
the physical properties of the auditory stimuli. For example, the different magnitudes of refractoriness between standards (85%) and deviants (15%) might cause the non-memory-based N100/N100m to contaminated the memory-based MMN/MMNm.

Over the past decades, a controlled block along with the oddball paradigm has been designed to successfully address this issue. However, in terms of future clinical application, we considered that the traditional oddball paradigm would be easier to operate and the recording time would be short. Secondly, we could not entirely preclude the effects of medicine (e.g., benzodiazepines) on the MMNm responses though these patients were instructed to refrain from taking their medication 24 h prior to MEG recordings. Finally, we did not carefully control the hearing threshold from each subject. However, it has been evident that there was no age-related difference of hearing threshold at the frequency of 1000 Hz. Considering that the tone frequencies we used in the present study were 1000 and 900 Hz, we reasoned that all the participants could successfully encode the auditory stimuli for the basic processing. Furthermore, since both of the HC and aMCI groups were composed of older adults and there was no significant difference of age, thus our sample was considered homogeneous in terms of auditory acuity.

In conclusion, we found that patients with aMCI showed MMNm prolongation selectively in the IPL compared with HC, and such aberration was associated with the performance of auditory/verbal memory (i.e., CVVLT). Our results also indicated that the combination of MMNm latencies of left IPL with CVVLT could adequately discriminate patients with aMCI from HC at an individual level.

ACKNOWLEDGMENTS

This work was supported by Chang Gung Memorial Hospital (CMRPD1K0061), Healthy Aging Research Center, Chang Gung University from the Featured Areas Research Center Program within the Framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan (EMRPD1K0431), Ministry of Science and Technology (MOST-105-2628-B-182-004-MY3, MOST-108-2628-B-182-002, MOST-109-2628-B-182-012), Taiwan.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

CHC and PNW conceived and designed the work and acquired the data. PYC, HYH, YPC, and CHC analyzed the data. PYC, HYH, YPC, RN, and PNW participated in the discussion and provided the comments. PYC, HYH, and CHC wrote the paper. All of the authors have read and approved the manuscript.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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REFERENCES

1. Petersen RC, Caraccio B, Brayne C, Gauthier S, Jelic V, Fratigioni L. Mild cognitive impairment: a concept in evolution. J Intern Med. 2014;275(3):214-228.
2. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001;58(12):1985-1992.
3. Chen HF, Huang LL, Li HY, et al. Microstructural disruption of the right inferior fronto-occipital and inferior longitudinal fuscius contributes to WMH-related cognitive impairment. CNS Neurosci Ther. 2020;26(5):576-588.
4. Kandiah N, Ong PA, Yuda T, et al. Treatment of dementia and mild cognitive impairment with or without cerebrovascular disease: expert consensus on the use of Ginkgo biloba extract, Egb 761(R)). CNS Neurosci Ther. 2019;25(2):288-298.
5. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004;256(3):183-194.
6. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement. 2011;7(3):270-279.
7. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement. 2011;7(3):280-292.
8. Zhang S, Smailagic N, Hyde C, et al. (11)C-PIB-PET for the early diagnosis of Alzheimer’s disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev. 2014;(7):CD010386.
9. Ritchie C, Smailagic N, Noel-Storr AH, Ukoumunne O, Ladds EC, Martin S. CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer’s disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev. 2017;3(3):CD010803.
10. Zhou C, Guan X-J, Guo T, et al. Progressive brain atrophy in Parkinson’s disease patients who convert to mild cognitive impairment. CNS Neurosci Ther. 2020;26(1):117-125.
11. Babiloni C, Blinowska K, Bonanni L, et al. What electrophysiology tells us about Alzheimer’s disease: a window into the synchronization and connectivity of brain neurons. Neurobiol Aging. 2020;85:58-73.
12. Engels M, van der Flier WM, Stam CJ, Hillebrand A, Scheltens PH, van Straaten ECW. Alzheimer’s disease: the state of the art tells us about Alzheimer’s disease: a window into the synchronization and connectivity of brain neurons. Clin Neurophysiol. 2017;128(8):1426-1437.
13. Rossini PM, Di Iorio R, Vecchio F, et al. Early diagnosis of Alzheimer’s disease: the role of biomarkers including advanced EEG signal analysis. Report from the IFCN-sponsored panel of experts. Clin Neurophysiol. 2020;131(6):1287-1310.
14. Chen TC, Hsieh MH, Lin YT, Chan PS, Cheng CH. Mismatch negativity to different deviant changes in autism spectrum disorders: a meta-analysis. Clin Neurophysiol. 2020;131(3):766-777.
15. Cheng CH, Hsu WY, Lin YY. Effects of physiological aging on mismatch negativity: a meta-analysis. Int J Psychophysiol. 2013;90(2):165-171.
16. Näätänen R, Kujala T, Escera C, et al. The mismatch negativity (MMN)-a unique window to disturbed central auditory processing in ageing and different clinical conditions. Clin Neurophysiol. 2012;123(3):424-458.
17. Naatanen R, Paavilainen P, Rinne T, Alho K. The mismatch negativity (MMN) in basic research of central auditory processing: a review. Clin Neurophysiol. 2007;118(12):2544-2590.
18. Yang SH, Wang PN, Cheng CH. Altered auditory repetition suppression and MMNm in relation to cognitive tests in older adults. Biol Psychol. 2019;146: 107725.
19. Cheng CH, Hsu SC, Liu CY. Dysfunctional frontal activation of mismatch negativity in panic disorder: a magnetoencephalographic study. J Affect Disord. 2021;280(Pt A):211-218.

20. Bartha-Doering L, Deuster D, Giordano V, am Zehnhoff-Dinnesen A, Dobel C. A systematic review of the mismatch negativity as an index for auditory sensory memory: from basic research to clinical and developmental perspectives. Psychophysiology. 2015;52(9):1115-1130.

21. Escera C, Malmierca MS. The auditory novelty system: an attempt to integrate human and animal research. Psychophysiology. 2014;51(2):111-123.

22. Naatanen R, Kujala T, Winkler I. Auditory processing that leads to conscious perception: a unique window to central auditory processing opened by the mismatch negativity and related responses. Psychophysiology. 2011;48(1):4-22.

23. Idrizbegovic E, Hederstierna C, Rosenhall U. Mismatch negativity and ear laterality in Alzheimer's disease and in mild cognitive impairment. J Alzheimers Dis. 2016;53(4):1405-1410.

24. Jiang S, Yan C, Qiao Z, et al. Mismatch negativity as a potential neurobiological marker of early-stage Alzheimer disease and vascular dementia. Neurosci Lett. 2017;647:26-31.

25. Papadaniil CD, Kosmidou VE, Tsolaki A, Tsolaki M, Kompatsiaris IY, Hadjileontiadis LJ. Cognitive MMN and P300 in mild cognitive impairment and Alzheimer’s disease: a high density EEG-3D vector field tomography approach. Brain Res. 2016;1648(Pt A):425-433.

26. Pekkonen E, Jousmaki V, Kononen M, Reinikainen K, Partanen J. Mismatch negativity latency and ear laterality in Alzheimer’s disease and in mild cognitive impairment. J Alzheimers Dis. 2014;51(2):111-123.

27. Gao L, Chen J, Gu L, et al. Effects of gender and apolipoprotein E on novelty MMN and P3a in healthy elderly and amnestic mild cognitive impairment. Front Aging Neurosci. 2018;10:256.

28. Ji LL, Zhang YY, Zhang L, He B, Lu GH. Mismatch negativity latency as a biomarker of amnestic mild cognitive impairment in Chinese rural elders. Front Aging Neurosci. 2015;7:22.

29. Lindin M, Correa K, Zurron M, Diaz F. Mismatch negativity (MMN) amplitude as a biomarker of sensory memory deficit in amnestic mild cognitive impairment. Front Aging Neurosci. 2013;5:79.

30. Mowszowski L, Hermens DF, Diamond K, et al. Reduced mismatch negativity in mild cognitive impairment: associations with neuropsychological performance. J Alzheimers Dis. 2012;30(1):209-219.

31. Tsolaki AC, Kosmidou V, Kompatsiaris IY, et al. Brain source localization of MMN and P300 ERPs in mild cognitive impairment and Alzheimer’s disease: a high-density EEG approach. Neurobiol Aging. 2017;55:190-201.

32. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999;56(3):303-308.

33. Wang PN, Chou KH, Chang NJ, et al. Callosal degeneration topographically correlated with cognitive function in amnestic mild cognitive impairment and Alzheimer’s disease dementia. Hum Brain Mapp. 2014;35(4):1529-1543.

34. Chang CC, Kramer JH, Lin KN, et al. Validating the Chinese version of the Verbal Learning Test for screening Alzheimer’s disease. J Int Neuropsychol Soc. 2010;16(2):244-251.

35. Cheng CH, Hsiao FJ, Hsieh YW, Wang PN. Dysfunction of inferior parietal lobe during sensory gating in patients with amnestic mild cognitive impairment. Front Aging Neurosci. 2020;12:39.

36. Muangpaisan W, Intalapaporn S, Assantachai P. Digit span and verbal fluency tests in patients with mild cognitive impairment and normal subjects in Thai-community. J Med Assoc Thai. 2010;93(2):224-230.

37. Taulu S, Kajola M, Simola J. Suppression of interference and artifacts by the signal space separation method. Brain Topogr. 2004;16(4):269-275.

38. Taulu S, Simola J. Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. Phys Med Biol. 2006;51(7):1759-1768.

39. Tesche CD, Uusitalo MA, Ilmoniemi RJ, Huotilainen M, Kajola M, Salonen O. Signal-space projections of MEG data characterize both distributed and well-localized neuronal sources. Electroencephalogr Clin Neurophysiol. 1995;95(3):189-200.

40. Uusitalo MA, Ilmoniemi RJ. Signal-space projection method for separating MEG or EEG into components. Med Biol Eng Comput. 1997;35(2):135-140.

41. Hamalainen MS, Ilmoniemi RJ. Interpreting magnetic fields of the brain: minimum norm estimates. Med Biol Eng Comput. 1994;32(1):35-42.

42. Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM. Brainstorm: a user-friendly application for MEG/EEG analysis. Comput Intell Neurosci. 2011;2011:879716.

43. Opitz B, Rinne T, Mechlinger A, von Cramon DY, Schroger E. Differential contribution of frontal and temporal cortices to auditory change detection: fMRI and ERP results. Neuroimage. 2002;15(1):167-174.

44. Tse CY, Penney TB. On the functional role of temporal and frontal cortex activation in passive detection of auditory deviance. Neuroimage. 2008;41(4):1462-1470.

45. Cheng CH, Baillet S, Hsiao FJ, Lin YY. Effects of aging on neuro-magnetic mismatch responses to pitch changes. Neurosci Lett. 2013;544:20-24.

46. Ono K, Matsuhashi M, Mima T, Fukuyama H, Altmann CF. Effects of regularity on the processing of sound omission in a tone sequence in musicians and non-musicians. Eur J Neurosci. 2013;38(5):2786-2792.

47. Yokosawa K, Kimura K, Takase R, Murakami Y, Boasen J. Functional decline of the precuneus associated with mild cognitive impairment: magnetoencephalographic observations. PLoS One. 2020;15(9):e0239577.

48. Cheng CH, Chang CC, Chao YP, Lu H, Peng SW, Wang PN. Altered mismatch response precedes gray matter atrophy in subjective cognitive decline. Psychophysiology. 2021;58:e13820.

49. Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic for diagnostic tests. Prev Vet Med. 2000;45(1-2):23-41.

50. Todd J, Myers R, Pirillo R, Drysdale K. Neuropsychological correlates of auditory perceptual inference: a mismatch negativity (MMN) study. Brain Res. 2010;1310:113-123.

51. Bonetti L, Haumann NT, Brattico E, et al. Auditory sensory memory and working memory skills: association between frontal MMN and performance scores. Brain Res. 2018;1700:86-98.

52. Foster SM, Kisley MA, Davis HP, Diede NT, Campbell AM, Davalos DB. Cognitive function predicts neural activity associated with pre-attentive temporal processing. Neuropsychologia. 2013;51(2):211-219.

53. Henson RN, Burgess N, Frith CD. Recoding, storage, rehearsal and grouping in verbal short-term memory: an fMRI study. Neuropsychologia. 2000;38(4):426-440.

54. Paulesu E, Frith CD, Frackowiak RS. The neural correlates of the verbal component of working memory. Nature. 1993;362(6418):342-345.

55. Risse GL, Rubens AB, Jordan LS. Disturbances of long-term memory in aphasic patients. A comparison of anterior and posterior lesions. Brain. 1984;107(Pt 2):605-617.

56. Vallar G, Di Betta AM, Silveri MC. The phonological short-term store-rehearsal system: patterns of impairment and neural correlates. Neuropsychologia. 1999;37(6):795-812.

57. Bell-McGinty S, Lopez OL, Meltzer CC, et al. Differential cortical correlates of auditory perceptual inference: a mismatch negativity (MMN) study. Brain Res. 2010;1310:113-123.
59. Oishi A, Yamasaki T, Tsuru A, Minohara M, Tobimatsu S. Decreased gray matter volume of right inferior parietal lobule is associated with severity of mental disorientation in patients with mild cognitive impairment. *Front Neurol*. 2018;9:1086.

60. Sestieri C, Capotosto P, Tosoni A, Luca Romani G, Corbetta M. Interference with episodic memory retrieval following transcranial stimulation of the inferior but not the superior parietal lobule. *Neuropsychologia*. 2013;51(5):900-906.

61. Mottaghy FM, Doring T, Muller-Gartner HW, Topper R, Krause BJ. Bilateral parieto-frontal network for verbal working memory: an interference approach using repetitive transcranial magnetic stimulation (rTMS). *Eur J Neurosci*. 2002;16(8):1627-1632.

62. Parra MA, Ascencio LL, Urquina HF, Manes F, Ibanez AM. P300 and neuropsychological assessment in mild cognitive impairment and Alzheimer dementia. *Front Neurol*. 2012;3:172.

63. Sun HH, Lin MY, Nouchi R, Wang PN, Cheng CH. Neuromagnetic evidence of abnormal automatic inhibitory function in subjective memory complaint. *Eur J Neurosci*. 2021;53:3350-3361.

64. García-Alba J, Ramírez-Toraño F, Esteba-Castillo S, et al. Neuropsychological and neurophysiological characterization of mild cognitive impairment and Alzheimer’s disease in Down syndrome. *Neurobiol Aging*. 2019;84:70-79.

65. Shigihara Y, Hoshi H, Poza J, Rodríguez-González V, Gómez C, Kanzawa T. Predicting the outcome of non-pharmacological treatment for patients with dementia-related mild cognitive impairment. *Aging*. 2020;12(23):24101-24116.

66. Jacobsen T, Schroger E. Is there pre-attentive memory-based comparison of pitch? *Psychophysiology*. 2001;38(4):723-727.

67. Jacobsen T, Schroger E. Measuring duration mismatch negativity. *Clin Neurophysiol*. 2003;114(6):1133-1143.

68. Opitz B, Schroger E, von Cramon DY. Sensory and cognitive mechanisms for preattentive change detection in auditory cortex. *Eur J Neurosci*. 2005;21(2):531-535.

69. Horvath J, Czigler I, Birkas E, Winkler I, Gervai J. Age-related differences in distraction and reorientation in an auditory task. *Neurobiol Aging*. 2009;30(7):1157-1172.

How to cite this article: Chen P-Y, Hsu H-Y, Chao Y-P, Nouchi R, Wang P-N, Cheng C-H. Altered mismatch response of inferior parietal lobule in amnestic mild cognitive impairment: A magnetoencephalographic study. *CNS Neurosci Ther*. 2021;27:1136–1145. [https://doi.org/10.1111/cns.13691](https://doi.org/10.1111/cns.13691)