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Research article

The changes of central auditory processing function and its electroencephalogram in patients with mild cognitive impairment and early Alzheimer's disease

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ABSTRACT

Background: The aim of this study is to assess the central auditory processing (CAP) function and its electroencephalogram (EEG) in patients with mild cognitive impairment (MCI) and the early stage of Alzheimer's disease (AD).

Methods: In this study, 25 patients with early AD, 22 patients with MCI, and 22 matched healthy controls (HC) were included. After cognitive assessment, binaural processing function was assessed using the staggered spondaic word (SSW) test, and auditory working memory was assessed by auditory n-back paradigm, while EEG was recorded. Patients' behavioral indicators, event-related potentials (ERPs) components, and function connection (FC) were compared between groups and the related factors were analyzed.

Results: The difference of the accuracy of behavioral tests for the three groups of subjects was significant and all the behavioral indicators were positively correlated with cognitive function scores. Intergroup differences in amplitude ($p < 0.05$) and latency ($p < 0.01$) were significant for P3 in the 1-back paradigm. In the SSW test, AD and MCI patients showed reduced connectivity between the left frontal lobe and the whole brain in the δ-band, while in the n-back paradigm, patients with MCI and early AD showed reduced association of frontal leads with central and parietal leads in the δ-band.

Conclusions: Patients with MCI and early AD have reduced CAP functions including binaural processing function and auditory working memory functions. This reduction is significantly associated with reduced cognitive function, and is reflected in different patterns of changes in ERP as well as functional connectivity in the brain.

1. Introduction

More and more researchers have found a close connection between auditory processing and cognitive function. The *Lancet* Commission's 2020 report identified hearing impairment as the greatest modifiable risk factor contributing to dementia [1]. Hearing impairment is generally thought to be caused by both peripheral hearing impairment and reduced central auditory processing (CAP). CAP function refers to a set of processes and mechanisms from the time sound is picked up by the external ear until it is interpreted by the auditory cortex, including components such as sound localization, working memory, attention allocation, and so on [2]. CAP has

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been shown to be strongly associated with Alzheimer's disease (AD) [1,3,4].

Binaural processing function is an important component of CAP. Impaired binaural processing function is present in AD and mild cognitive impairment (MCI), and the related electroencephalograph (EEG) also reflects the changes in neural activity in this process [4]. N-back paradigm is the classical paradigm for assessing working memory function, and auditory working memory and visual working memory belong to different subsystems [5]. Auditory n-back tasks are closely related to CAP. Healthy aging populations showed a significant decreases in the amplitude of event-related potentials (ERPs) compared with young adults in auditory n-back paradigm, which are associated with CAP impaired with age [6]. Less investigators have applied the auditory n-back task to patients on the AD disease spectrum and assessed the changes of their ERPs.

In the present study, based on the theory that CAP and cognitive function are closely related, binaural processing function was evaluated by using the staggered spondaic word test (SSW), and auditory working memory was measured by auditory N-back paradigm in MCI patients and early AD patients. In the meanwhile, EEG was recorded and analyzed by the ERPs and brain functional connection (FC). The aim is to investigate the changes of CAP and its neuroelectrophysiological mechanism in patients with MCI and early AD, so as to provide a basis for early recognition and intervention of AD.

2. Methods

2.1. Participants

The study enrollment period was from February 2021 to February 2022, in which 25 patients with early AD and 22 patients with MCI were from eligible subjects attending the Department of Neurology, the First Affiliated Hospital of Zhejiang University School of Medicine and the Mental Health Center of Zhejiang University School of Medicine. 22 age and sex matched healthy controls were recruited from the community.

Inclusion criteria: (1) age 55–80; (2) can communicate normally using Mandarin; (3) can cooperate to complete the relevant tests; (4) agree to complete the relevant tests and sign the informed consent form.

Exclusion criteria: (1) self-reported or clinically tested hearing impairment; (2) current use of steroids, benzodiazepines, or antipsychotics; (3) history of neuropsychiatric disorders other than MCI or AD.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine and was conducted in accordance with the Declaration of Helsinki. All subjects or their legal guardians signed an informed consent form.

2.2. Clinical evaluation

Demographic characteristics, past medical history, life history, family medical history, and other relevant clinical characteristics of the participants were collected through a questionnaire designed specifically for the study at enrollment. The demographic characteristics included age, sex, years of education, and handedness. Past medical history was obtained from patients' self-reported and clinical data of previous diagnosed diseases, including: cardiovascular disease, cerebrovascular disease, hypertension, diabetes, hyperlipidemia, and other psychiatric diseases. Life history included history of smoking ($\geq$1 cigarette/day for $\geq$1 year), history of alcohol consumption (at least once a week for drinking $>$50 mL for $>$6 months, or other drinking alcohol converted to alcohol based on general alcohol content as specified above). Family medical history referred to parents and siblings with clinically diagnosed Alzheimer's disease.

The cognitive assessment was conducted by a team of cognitive assessment professionals at the First Affiliated Hospital of Zhejiang University School of Medicine, using the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA) (MoCA-basic for those with $\leq$6 years of education) and the Clinical Dementia Rating (CDR) to assess overall cognitive function.

2.3. Diagnosis criteria

Clinical diagnosis was made by experienced neurologists based on the following criteria. In each group, all the criteria must be met simultaneously.

Normal controls (referred to as the NC group below): (1) age 55–85 years; (2) with normal MMSE and MoCA scores. The MMSE was based on the following criteria: 0 years of education $>$19, less than 7 years $>$ 24, and more than or equal to 7 years $>$ 27. The MoCA (or MoCA-Basic) was $>$24.

Amnestic mild cognitive impairment (referred to as the MCI group below): (1) age 55–85 years; (2) meeting Peterson's MCI diagnostic criteria [7]; (3) CDR = 0.5; (4) MMSE: MMSE $\geq$17 for those with 0 years of education, $\geq$20 for those with less than 7 years, and $\geq$24 for those with more than or equal to 7 years; (5) prominent memory loss, which may also be accompanied by impairment in other cognitive domains; (6) insidious onset and slow progression; (7) not reaching dementia level.

Mild Alzheimer's Dementia (referred to as the AD group below): (1) age 55–85 years; (2) meets the core clinical criteria for likely AD dementia in the NIA-AA revised diagnostic criteria for AD [8]; (3) CDR score of 0.5 or 1; (4) MMSE: $<$17 points for those with 0 years of education, $<$20 points for those with less than 7 years, and $<$24 points for those with greater than or equal to 7 years; (5) able to independently complete neuropsychological examination.

2.4. Auditory task paradigms

Task 1: Staggered spondaic word test (SSW) was used to evaluated the binaural function. Spondee is derived from the ancient Greek poetic rhyme concept "libation", which refers to a rhyme step composed of two repeated syllables, and the spondee case word in Chinese refers to a double syllable word [9]. The corpus of this study was the "Modern Chinese Corpus Word Frequency Table" (http://corpus.zhonghuayuwen.org/resources.aspx) provided by the Computational Linguistics Research Laboratory of the Institute of Linguistic Applications of the Ministry of Education. 20 pairs of spondaic words which were similar frequency, neutral mood and nouns were selected as the experimental corpus The words were digitally audible as the audiometric material. The audio was given to the left and right ears interleaved, with the second syllable of the first word overlapping with the first syllable of the second word (Supplemental Fig. 1). Each syllable lasting 600 ms. The vocalization level was 40–50 dB above the speech acceptance threshold, and the subject was asked to repeat. Subjects' repetition accuracy was recorded and EEG was monitored simultaneously.

Task 2: Auditory working memory task, referring to the auditory n-back paradigm of Jablonska et al. [10]. The auditory material was five consonants (B G L M Z) four vowels (A E O Y) randomly composed of nonsense monosyllables, each lasting 300 ms and spaced 1700 ms. In the 1-back task, the current syllable was the target stimulus when it was identical to the previous one, and the current syllable was the target stimulus when it was identical to the two previous syllables in the 2-back task (Supplemental Fig. 2). Each segment consisted of 40 stimuli, with the target stimulus occurring at a frequency of 0.6. Subjects were asked to press the response key when the target stimulus appeared. Subjects' accuracy was recorded and the EEG was monitored simultaneously.

2.5. EEG acquisition and analysis

During EEG data acquisition, subjects were seated calmly in a quiet room and received auditory stimuli through built-in soundproof headphones. EEG data were acquired using a 64-conductor BrainCap (Brain Products GmbH, Germany) with electrodes placed according to the Internationally Standardized 10–20 System. The online reference electrode was FCz, the sampling rate was 1000 Hz, and all electrode impedances were kept below 10 kΩ.

EEGlab toolbox in Matlab software [11]was used to pre-process the EEG data. The reference point for off-line analysis was the average reference. The data was downsampled to 512 Hz, high-pass filtered at 0.1 Hz and low-pass filtered at 30 Hz. The noise channels were identified and removed and interpolated for bad conductance calculation. The eye movement signals, electrocardiosignals and head movement signals were rejected by independent component analysis (ICA)., In the SSW task, the 200 ms before and the 2500 ms after each stimulus occurrence were intercepted as an epoch. The 100 ms before the stimulus was set as the baseline, and the signals of each channel were averaged separately to obtain the average ERPs [4]. The detected P1–N1–P2 waves were the ERP components reflecting auditory processing (Fig. 1), and the time windows of the ERP components (i.e., P1: 680–700 ms, N1: 860–880 ms, P2: 940–980 ms) were determined based on the average waveforms for all conditions and participants. Data for the ERP components were extracted from electrodes corresponding to the central frontal and parietal regions (Fz, F3, F4, Pz, P3, and P4). For each component, the following ERP components were studied: peak amplitude, peak latency.

In the n-back task, the 100 ms before and the 1000 ms after of each stimulus were intercepted as an epoch. The 100 ms before the stimulus was set as the baseline, and the ERP signals of each channel were averaged separately to obtain the average ERPs [12]. The main electrophysiological results were set for P3 peak amplitude and P3 peak latency (Fig. 2), and the time windows of P3 components were established between 200 and 400 ms. Since the prefrontal cortex is involved in working memory, we identified Fz, Cz, Pz, F3, and F4 as the channels of interest. Cz was interpolated using the five surrounding channels. No participants were manually removed from

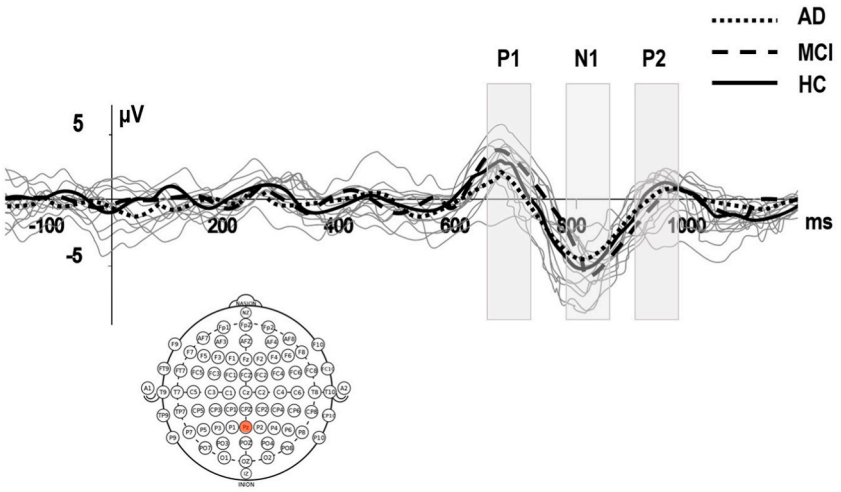

Fig. 1. Representative event-related potential waveform at Pz for the three groups in SSW. SSW: staggered spondaic word test; AD: Alzheimer's Disease group; MCI: mild cognitive impairment group; HC: Healthy control group.

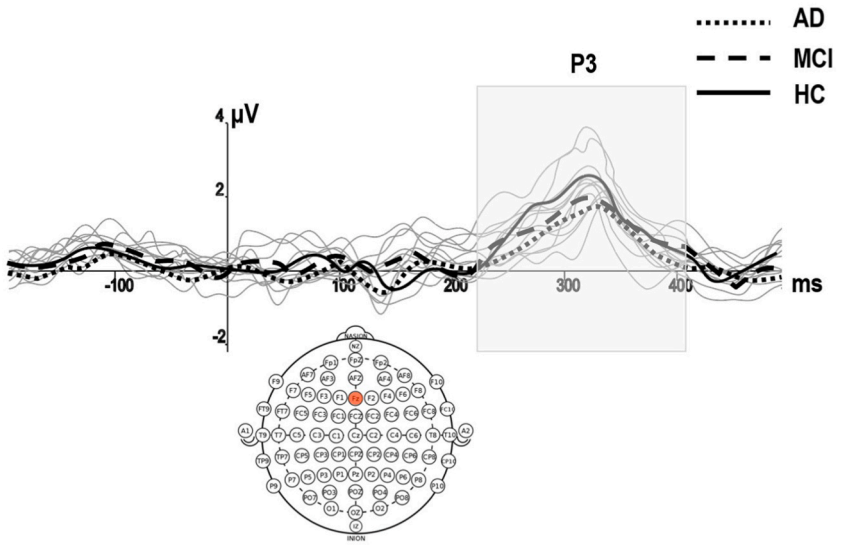

Fig. 2. Representative event-related potential waveform at Fz for the three groups in nback test. AD: Alzheimer's Disease group; MCI: mild cognitive impairment group; HC: Healthy control group.

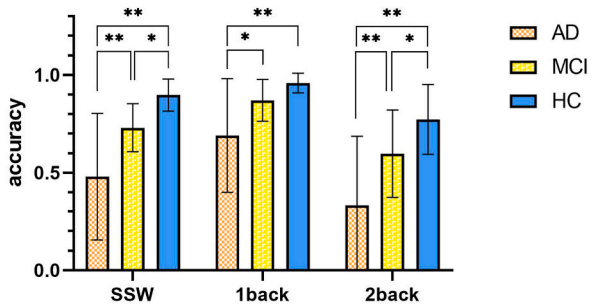

Fig. 3. The accuracy of SSW, 1-back and 2-back paradigms. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. SSW: staggered spondaic word test; AD: Alzheimer's Disease group; MCI: mild cognitive impairment group; HC: Healthy control group; Tukey's multiple comparison test was used for pairwise post-hoc comparisons of multiple groups of continuous variables.

the analysis, but five subjects were not included in the 2-back analysis because of inability to complete the 2-back task (see Fig. 3).

2.6. Function connection analysis

Higher neural functions are often synergistic in multiple brain regions. FC reflects the degree of association between different brain regions, which is an effective indicator of synergistic brain activity and may have clinical implications for identifying different brain states or pathological activities. In this study, the FCLAB toolbox [13] and the brain connectivity toolbox [14] were used to assess and compare the FC of three groups of subjects in different tasks.

In the calculation of global network, the imaginary part of coherency (iCOH) method in this study was used to calculate the following parameters reflecting the network characteristics in the full frequency band: characteristic path length (CPL) and global efficiency (GE). In addition, the phase correlation consistency was measured for different frequency bands (δ: 1–3.99 Hz, θ: 4–7.99 Hz, α: 8–12.99 Hz and β: 13–29.99 Hz). Correlation coherence matrices were reported for the three groups of subjects in each paradigm and each frequency band, and the differences in correlation coherence connections between the different groups were calculated.

2.7. Statistic analysis

Count data were expressed as n (%), while continuous data were expressed as median (interquartile range interquartile range [IQR]) (non-normal distribution) or mean ± standard deviation standard deviation (SD) (normal distribution). When comparing characteristics between groups, categorical variables were analyzed using the $\chi 2$ test for minimum theoretical frequencies ≥ 5, Fisher exact analysis for minimum theoretical frequencies <5, ANOVA for normally distributed continuous variables, and Mann-Whitney *U* test for non-normally distributed measures. Post hoc two-by-two comparisons of multiple continuous variables were performed using

Tukey' s multiple comparisons test. Correlations between continuous variables were analyzed using Pearson correlation analysis, and Spearman correlation analysis for correlations containing categorical variables. Multiple repeated tests were performed using Bonferroni correction.

In the comparison of behavioral and EEG measures, Cohen η2 was reported as an effect size indicator because ANOVA was used in the comparison between groups. The reference criteria are as follows: small effect is less than 0.010, 0.010–0.059 is medium effect, and 0.059–0.138 is large effect.

The behavioral indicators were tested using a multifactorial analysis of covariance (ANCOVA) with the dependent variables SSW correct, 1-back correct, and 2-back correct, the independent variables being the different subject groupings, and the possible confounders being age, gender, and education level.

All statistical analyses were performed using SPSS v20.0 (Statistical Product and Service Solutions, SPSS Inc., IBM Corporation, Chicago, IL, USA). Structural model analyses were performed using the IBM SPSS Amos component. All statistical tests were two-tailed and considered statistically significant at $p < 0.05$.

3. Results

3.1. Participant characteristics

A total of 25 patients with early AD, 22 patients with MCI, and 22 healthy controls underwent complete profile registration and cognitive psychological assessment, of whom all completed the SSW and 1-back tests, with 5 patients in the AD group not completing the 2back test. 25 (36.23%) of the 69 subjects were male. The mean age was 66.46 ± 8.17 and the median years of education was 9.0 (6.0–12.0) years. All were right-handed. There were no significant differences in sex, age, education, clinical history, life history and family medical history ($p > 0.05$). For cognitive assessment, the AD group [MMSE: 17.0 (14.0–23.0); MoCA: 14.0 (8.0–18.0)] was lower than the MCI group [MMSE: 26.0 (25.0–27.0); MoCA: 23.0 (19.0–24.0)] and lower than the HC group [MMSE: 29.0 (28.0–29.0); MoCA: 26.0 (25.0–27.0)], while post hoc tests showed a significant difference between the two ($p < 0.01$). The demographic characteristics, clinical characteristics and cognitive function scores of the three groups were detailed in Table 1.

Table 1
Characteristics of patients.

Variables	Total (n = 69)	AD (n = 25)	MCI (n = 22)	HC (n = 22)	*P*
Demographic characteristics					
Age (years), mean ± SD	66.46 ± 8.17	66.89 ± 8.71	68.30 ± 6.34	66.50 ± 6.83	0.729
Male, n (%)	25(36.23)	10(40.00)	7(31.82)	8(36.36)	0.901
Education (years), median (IQR)	9.0(6.0–12.0)	9.0(6.0–12.0)	12(6.0–15.0)	9.0(5.0–12.5)	0.540
Right handedness, n (%)	68(98.55)	24(96.00)	20(100.00)	22(100.00)	0.999
Past medical history					
Cardiovascular disease, n (%)	5(7.25)	3(12.00)	0(0)	2(9.09)	0.075
Cerebrovascular disease, n (%)	1(1.45)	0(0)	0(0)	1(4.55)	0.398
Hypertension, n (%)	21(30.43)	7(28.02)	8(36.36)	6(27.27)	0.611
Diabetes, n (%)	14(20.29)	3(13.64)	6(27.27)	3(13.64)	0.097
Hyperlipidemia, n (%)	5(7.25)	3(12.04)	0(0)	2(9.09)	0.075
Other mental disorders, n (%)	0(0)	0(0)	0(0)	0(0)	0.999
Life history					
Smoking, n (%)	9(13.04)	3(12.07)	3(13.64)	3(13.64)	0.991
Drinking, n (%)	8(11.59)	2(8.08)	4(18.18)	2(9.09)	0.559
Family history[a], n(%)	14(20.29)	6(24.09)	4(18.18)	4(18.18)	0.588
Neuropsychological					
MMSE, median(IQR)	27.0(21.5–29.0)	17.0(14.0–23.0)	26.0(25.0–27.0)	29.0(28.0–29.0)	<0.01**
MoCA, median(IQR)	22.0(16.5–26.0)	14.0(8.0–18.0)	23.0(19.0–24.0)	26.0(25.0–27.0)	<0.01**
Behavioral index					
Accuracy of SSW (%), mean ± SD	70.16 ± 26.96	47.95 ± 32.39	73.00 ± 12.29	89.77 ± 8.23	<0.01** $\eta^2 = 0.406$[d]
Accuracy of 1-back (%), mean ± SD	83.92 ± 21.36	69.08 ± 29.14	87.09 ± 10.72	95.87 ± 5.00	<0.01** $\eta^2 = 0.262$
Accuracy of 2-back (%), mean ± SD	58.64 ± 30.77[b]	33.24 ± 35.38[c]	59.72 ± 22.39	77.29 ± 17.88	<0.01** $\eta^2 = 0.316$

*p < 0.05 , **p < 0.01.
SD: standard deviation; IQR: Interquartile range; SSW: staggered spondaic word test.
AD: Alzheimer's Disease; aMCI: Amnestic mild cognitive impairment; HC: Healthy control.
a: Parents and siblings with clinically diagnosed Alzheimer's disease; b: n = 59; c: n = 17; d: η^2 means Cohen η^2, and it's a indicator of the effect size. Small effect is less than 0.010, 0.010–0.059 is medium effect, and 0.059–0.138 is large effect.

3.2. Behavioral results

The behavioral results of the three groups were shown in Table 1. In the SSW test, the difference in accuracy between the three groups was significant ($p < 0.001$), and a two-by-two post-hoc comparison showed that the AD group was significantly less accurate than the MCI ($p < 0.01$) and HC groups ($p < 0.001$), and the MCI group was also significantly less accurate than the HC group ($p < 0.05$). In the 1-back test, the difference in accuracy between the three groups was significant ($p < 0.01$), with the AD group significantly lower than the MCI group ($p < 0.05$) and the HC group ($p < 0.01$), In the 2-back test, the difference in accuracy between the three groups was significant ($p < 0.01$), with the AD group significantly lower than the MCI group ($p < 0.01$) and the HC group ($p < 0.001$), and the MCI group was also significantly lower than the HC group ($p < 0.05$). Using the multifactorial ANCOVA model, these three behavioral indicators remained significant across diagnostic subgroups after correction for gender, age, and education (Table 2).

3.3. ERP characteristics

The differences in the ERP components (P1–N1–P2) triggered by SSW in the three groups of subjects are shown in Fig. 4 (A-F), where the wave amplitudes of N1 have been transformed to the corresponding absolute values. The P1 component exhibited significant group differences in wave amplitude at the Pz ($p < 0.05$, $\eta^2 = 0.026$) and P4 electrodes ($p < 0.05$, $\eta^2 = 0.012$) (Fig. 4A), in which the MCI group had significantly higher latencies than the AD group at the F3 electrode ($p < 0.05$, $\eta^2 = 0.010$) (Fig. 4B). The N1 component exhibited significant group differences in wave amplitude at the F3 ($p < 0.05$, $\eta^2 = 0.008$) and Pz electrodes ($p < 0.05$, $\eta^2 = 0.015$), and the MCI group had significantly greater amplitude than the AD group ($p < 0.01$) and the HC group ($p < 0.01$) at the Pz electrode (Fig. 4C). The P2 component showed significant intergroup differences in wave amplitude at the Pz ($p < 0.05$, $\eta^2 = 0.006$) and P4 electrodes ($p < 0.05$, $\eta^2 = 0.005$) (Fig. 4E), and the MCI group had a significantly lower latency at the F3 electrode than the AD group ($p < 0.01$, $\eta^2 = 0.034$) (Fig. 4F). On the P4 electrode the MCI group was significantly higher than the HC group ($p < 0.05$, $\eta^2 = 0.014$). The intergroup differences in amplitude and latency of the P1–N1–P2 components on the remaining leads were not significant ($p > 0.05$, $\eta^2 < 0.010$).

In 1-back, significant intergroup differences in the amplitude of P3 were observed, mainly in the F3 electrode (AD group vs. HC group, $p < 0.01$, $\eta^2 = 0.025$) (Fig. 5A); significant differences in the latency of P3 were observed in all electrodes ($p < 0.05$, $0.021 < \eta^2 < 0.032$) (Fig. 5B). In the 2-back, significant intergroup differences in the amplitude of P3 were observed in the Cz electrode (AD group vs. HC group, $p < 0.05$, $\eta^2 = 0.018$) (Fig. 5C); in the F3 electrode, both the AD group ($p < 0.05$) and the MCI group ($p < 0.05$) were lower than the HC group; the latency of P3 was significantly different in all electrodes except Pz ($p < 0.05$, $0.009 < \eta^2 < 0.027$) (Fig. 5D).

3.4. Function connection

The global FC in the SSW paradigm was shown in Fig. 6. Statistical calculation of the FC matrix showed that the FC distribution in the total frequency band showed significant differences between the AD group and the MCI and HC groups, respectively ($p < 0.05$), and the FC distribution in the δ-band showed significant differences between the AD, MCI, and HC groups ($p < 0.05$). The FC distribution in the θ band showed significant differences between the AD and MCI groups ($p < 0.05$). The MCI and HC groups showed significant differences in the distribution of functional connectivity in the α-band ($p < 0.05$), and the three groups did not show significant differences in the β-band ($p > 0.05$). In the δ-band, the HC group showed a significant increase in the association of frontal leads with the whole brain, and this increase was lateralized, mainly in the left frontal lobe. This laterality was diminished in the MCI group, and no increase in the FC of the left frontal leads with the whole brain was observed in the AD group.

The global FC in the auditory n-back paradigm is shown in Fig. 7. Statistical calculations of the FC matrix showed that the AD and MCI groups exhibited significant differences ($p < 0.05$) from the HC group in the FC distribution in the total frequency band, and this difference was also reflected in the FC distribution in the δ-band ($p < 0.05$), while the theta-band, α-band and β-band did not show significant differences ($p > 0.05$). In the δ-band, the HC group showed a significant increase in the association of frontal leads with central and parietal leads, which was not lateralized, while the MCI group showed a weaker association of frontal leads with central and parietal leads, and the AD group did not show any significant increase in the association of leads.

Table 2
The Effects of independent variables and covariables on accuracy difference between groups.

	SSW		1back		2back	
	F	P	F	P	F	P
diagnosis	7.708	<0.01**	7.832	<0.01**	9.521	<0.01**
sex	0.118	0.755	0.254	0.617	0.295	0.653
age	0.858	0.359	0.135	0.715	0.019	0.891
education year	6.766	0.013*	1.728	0.195	4.118	0.048*

*p < 0.05 , **p < 0.01.
SSW: staggered spondaic word test.
The multifactor ANCOVA model was used, with "diagnosis" as the independent variable and "sex", "age" and "years of education" as the correction variable.

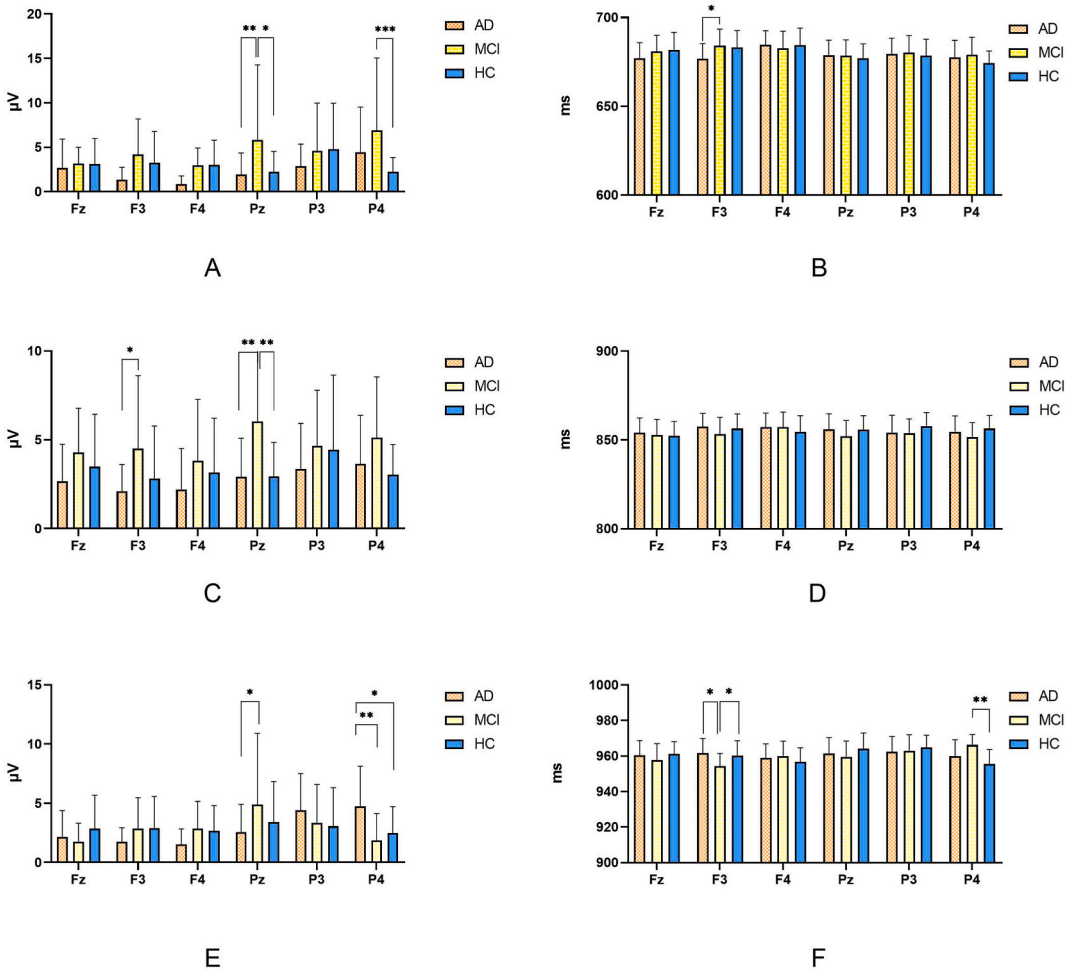

Fig. 4. The amplitude and potential of ERPs in SSW paradigm. *p < 0.05 , **p < 0.01 , ***p < 0.001. SSW: staggered spondaic word test; AD: Alzheimer's Disease; MCI: mild cognitive impairment; HC: healthy control. Fz, F3, F4, Pz, P3 and P4: the channel names of the corresponding frontal center and apex center. A: The amplitude of P1 components in the interested channels, B: The potential of P1 components in the interested channels, C: The amplitude of N1 components in the interested channels, (conversion for absolute value), D: The potential of N1 components in the interested channels, E: The amplitude of P2 components in the interested channels, F: The potential of P2 components in the interested channels.

3.5. Related factors of EEG in CAP function

EEG-related indicators (including ERP component indicators and FC indicators) were correlated with age, education, cognitive assessment scores (MMSE, MoCA), and behavioral indicators (SSW, 1-back, and 2-back accuracy), respectively (Fig. 8). The results showed that ERPs in the SSW paradigm were associated with cognitive assessment, age, and education significantly (Fig. 8A and B). The amplitude of P3 evoked by 1-Back paradigm was positively correlated with cognitive assessment and auditory working memory, but not statistically significant ($p > 0.05$), while the P3 amplitude evoked in the 2-back paradigm was significantly positively correlated with MMSE scores ($p < 0.05$) and MoCA scores ($p < 0.05$) in the F4 channel. Except for the Pz channel, 1-back and 2-back evoked P3 latencies in all channels were negatively correlated with cognitive assessments and behavioral indicators ($p < 0.05$). No significant correlations were seen between the remaining ERP components and demographic variables, cognitive assessments, and behavioral indicators (Fig. 8C).

The FC indicators measured in both paradigms were significantly associated with cognitive function assessment results as follows: CPL in both the n-back and SSW paradigms were significantly negatively correlated with MMSE scores and MoCA scores ($p < 0.01$), GE was significantly positively correlated with MMSE scores and MoCA scores ($p < 0.01$), CPL in the n-back paradigm was significantly negatively correlated with 1-back accuracy ($p < 0.05$), GE was significantly positively correlated with 1-back accuracy ($p < 0.05$), and both were not significantly correlated with 2-back accuracy; CPL in the SSW paradigm was significantly negatively correlated with SSW accuracy ($p < 0.01$), and GE was significantly positively correlated with SSW accuracy ($p < 0.01$).

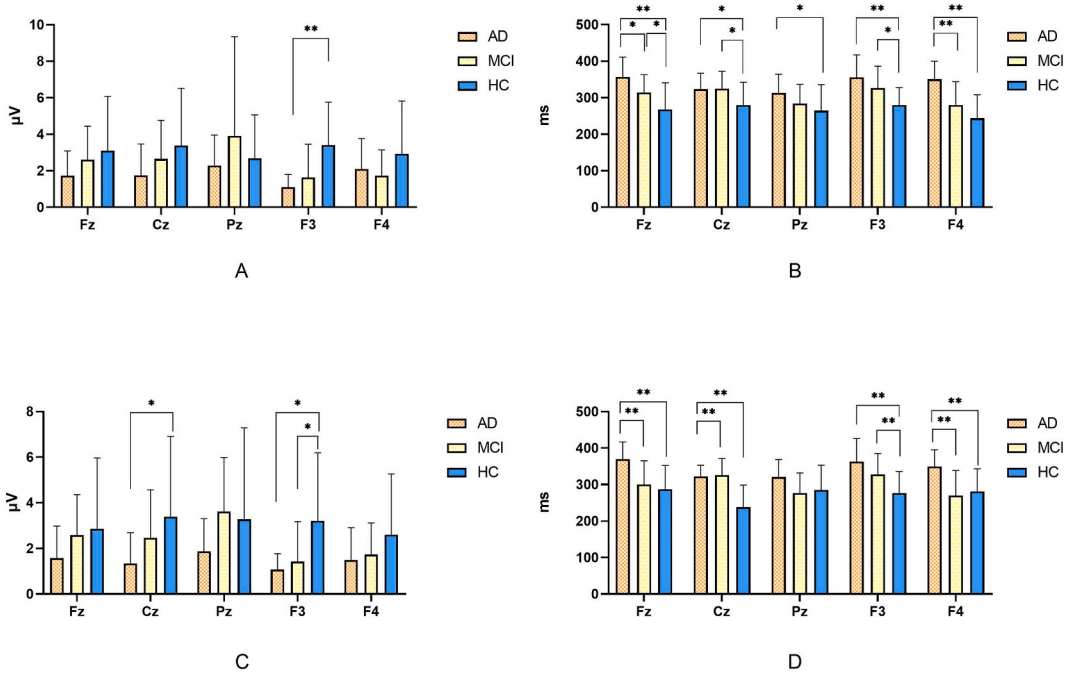

Fig. 5. The amplitude and potential of ERPs in auditory n-back paradigm. *p < 0.05，**p < 0.01，***p < 0.001. AD: Alzheimer's Disease; MCI: mild cognitive impairment; HC: healthy control. Fz, F3, F4, Pz, P3 and P4: the channel names of the corresponding frontal center and apex center. A: The amplitude of P3 components in the interested channels evoked by 1-back paradigm, B: The potential of P3 components in the interested channels evoked by 1-back paradigm, C: The amplitude of P3 components in the interested channels evoked by 2-back paradigm, D: The potential of P3 components in the interested channels evoked by 2-back paradigm.

4. Discussion

In the present study, a total of 69 subjects, 25 AD, 22 MCI and 22 HC were included. Cognitive assessment was performed on the three groups of subjects, and binaural processing function and auditory working memory function were assessed using the SSW test and auditory n-back test respectively, in the meanwhile the subjects' EEG was monitored. We found that there were significant differences in binaural processing and auditory working memory functions among the three groups and that this CAP function was significantly correlated with reduced cognitive function.

The binaural processing function refers to the localization and lateralization of auditory stimuli, reduction of masking thresholds, detection of signals in noisy environments, and binaural integration through the two ears working together as an important component of CAP function [15]. In a prospective cohort study, researchers found that performance on a binaural function test was associated with an increased risk of all-cause dementia and AD in subjects at 7–8 years of follow-up [16] Binaural integration paradigm has also been used to identify binaural processing deficits in patients with AD and aMCI [4]. In the present study, the SSW paradigm yielded the same results. There was a significant decline in binaural processing in patients with MCI and early AD, and this decline was consistent with a decrease in cognitive function. The differences in the ERP components induced by the SSW paradigm in this study were complex across the three groups of subjects. In a recent study using the break in correlation (BIC) paradigm to explore binaural processing function in AD patients, the investigators also reported the complexity of the group differences exhibited by their ERPs and accordingly suggested that in Alzheimer's disease patients, there was a neural compensatory mechanism for CAP function, of which the result is that when CAP and cognitive function decline, neural electrical activity does not decline together [4].

One study assessed auditory working memory impairment in MCI and AD patients using the auditory-verbal Sternberg memory task and found significant differences in the AD and healthy control groups, while no significant differences were found in the MCI group [17,18], which is similar to the results obtained in the present study using the auditory 1-back paradigm. On the other hand, the results of the auditory 2-back paradigm in the present study showed significant differences between the two in the three groups of AD, MCI and healthy controls, which may indicate that the auditory 2-back paradigm is more sensitive to the MCI group when assessing auditory working memory. In the present study, in the ERPs evoked by auditory n-back, there was a gradual decrease in the amplitude and increase in the latency of the P3 potential from the HC group to the AD group, which was present in both the 1-back paradigm and the 2-back paradigm. The ERPs evoked by auditory n-back paradigm were generally consistent with the behavioral performance. The auditory n-back-evoked ERP changes in the present study are also similar to the results obtained by other researchers using the visual n-back paradigm, suggesting the presence of diminished neuroelectrical activity consistent with cognitive impairment throughout the course of AD, in both auditory and visual working memory [12,14]. In addition, in this study, binaural auditory processing, a classical CAP function, and auditory working memory, a function that can serve as a bridge between auditory processing and cognitive function,

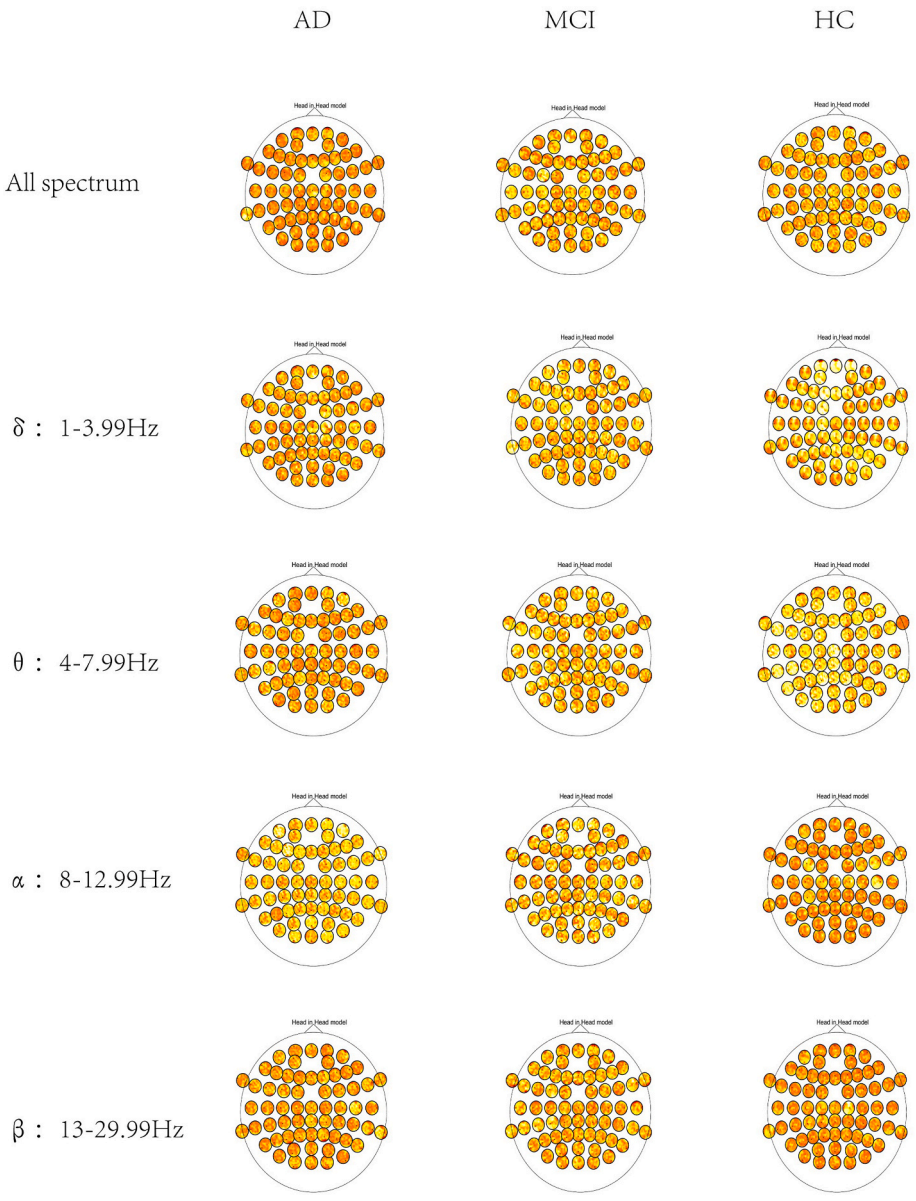

Fig. 6. The head-in-head figure of functional connection in SSW paradigm. SSW: staggered spondaic word test; AD: Alzheimer's Disease; MCI: mild cognitive impairment; HC: healthy control. Head-in-head map: On the large scalp map, each small scalp map represents a channel, and the color of each small scalp map shows the functional connection degree of the corresponding channel with other channels. The three figures in the first row show the functional links of all frequency bands in the three groups, and the second to fifth shows the functional links of different frequency bands.

were measured in the same group of subjects. When the results of the two paradigms were analyzed together, it was found that the behavioral of both paradigms showed a decline consistent with cognitive function, but only the ERPs invoked by n-back showed a change consistent with cognitive function, further confirming the possible compensatory mechanism of brain activity in central auditory processing.

The brain regions that process sound information are highly distributed, including precognitive auditory processing in brainstem pathways, auditory cognition in auditory cortices, and general cognitive processes in connected cerebral regions. The spread of pathogenic proteins in neurodegenerative dementias targets these networks rather than the peripheral organs of hearing [19]. In the analysis of FC, we found that healthy participants in the SSW paradigm showed a significant left frontal to whole brain connectivity enhancement in the δ-band. The δ-band is considered to be the working band, and there is also a significant relationship with speech processing and a left-sided dominance of speech processing. The neural structural basis of CAP overlaps with AD pathological processes, including the prefrontal, inferior parietal lobule, middle temporal gyrus and parieto-temporal junction cortex [19]. Some hypotheses have been proposed for the relationship between CAP function and AD, for example: (1) Common pathology due to AD

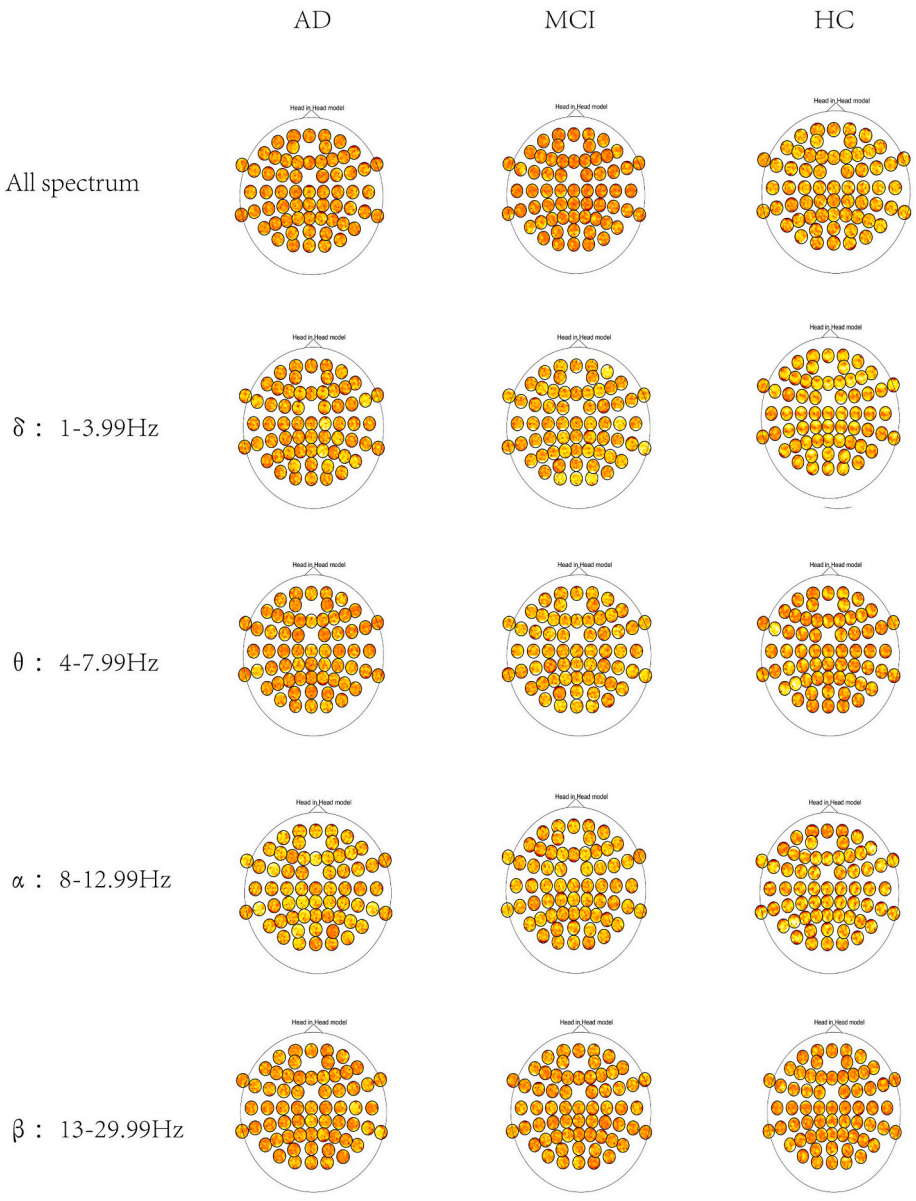

Fig. 7. The head-in-head figure of functional connection in n-back paradigm. AD: Alzheimer's Disease; MCI: mild cognitive impairment; HC: healthy control. Head-in-head map: On the large scalp map, each small scalp map represents a channel, and the color of each small scalp map shows the functional connection degree of the corresponding channel with other channels. The three figures in the first row show the functional links of all frequency bands in the three groups, and the second to fifth shows the functional links of different frequency bands.

affects the cochlea and/or the ascending pathway (causing hearing loss) and medial temporal lobe (MTL) (causing dementia); (2) Increased brain activity in the MTL during CAP competes for the resources within that network that are also needed for other aspects of higher cognition; (3) Interaction between altered activity related to pattern analysis in the MTL during difficult listening and the pathology of AD, which is based on synaptic changes associated with AD [20]. The present study analyzed the binaural processing function in comparison to the CAP function, which had a more obvious relationship with the frontal lobes. Moreover, the decline in CAP-related specific connections in AD and MCI is consistent with the dysfunction and atrophy of the temporo-parietal 'default mode' network that is essential to Alzheimer's disease pathogenesis, suggesting that the decrease in brain functional connections in AD patients also occurs during auditory processing, which supports hypothesis one and hypothesis three.

In the present study, when the FC network associated with the auditory n-back paradigm was analyzed, differences in the association of frontal leads with central and parietal leads were also found in the δ-band, and the association was diminished in AD compared to MCI patients and healthy controls, suggesting that the functional network associated with the auditory n-back paradigm is more sensitive to early changes in AD. A study that used the same auditory n-back paradigm as the present study but applied it to a

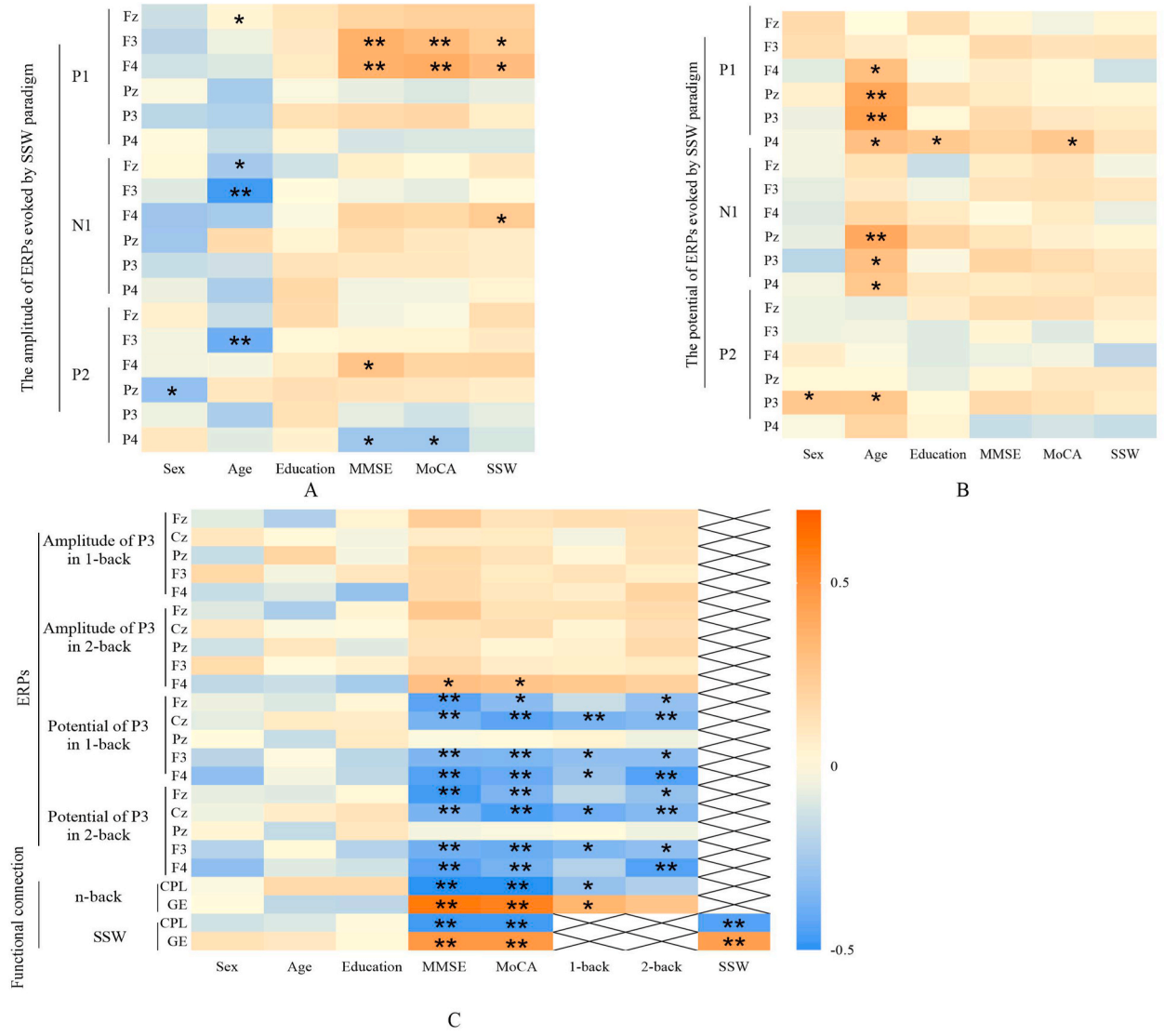

Fig. 8. The Factors associated with EEG of central auditory processing function. *p < 0.05 , **p < 0.01. SSW: staggered spondaic word test; ERP: event-related potential; CPL: characteristic path length; GE: global efficiency; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment. P1, N1 and P2 on the ordinate in Figure A and B are ERP components evoked by SSW paradigm. Fz, F3, F4, Pz, P3, P4 are the channel names analyzed in SSW normal form. In Figure C, Fz, Cz, Pz, F3 and F4 are the channel names analyzed in auditory n-back paradigm. SSW on the abscissa is the behavioral accuracy of SSW paradigm. 1-back and 2-back are the behavioral accuracy in n-back paradigm. Figure A: Correlation between amplitude of ERPs evoked by SSW and demographic variables, cognitive assessment, and behavioral performance; Figure B: Correlation between latency of ERPs evoked by SSW and demographic variables, cognitive assessment, and behavioral performance; Figure C: Correlation among amplitude and latency of ERPs evoked by n-back, FC measured in both paradigms, demographic variables, cognitive assessments, and behavioral performance.

normal elderly population showed by functional magnetic resonance imaging (fMRI) that the brain networks and activities associated with auditory working memory were mainly composed of the prefrontal cortex (middle frontal gyrus, inferior frontal gyrus, superior frontal gyrus), the inferior and superior parietal lobules [10], which also correlates with the increased association of frontal leads, central leads and parietal leads in the present study.

The study also has some limitations. Firstly, we pioneered the use of ERP monitoring for the experimental procedure of SSW, and the meaning of ERPs evoked by this paradigm represents a need for more studies to decode. Secondly, CAP function is a collective term for a series of complex central neural activities involving auditory processing, and in view of objective factors such as experimental length and operability, only two tests were selected in this study paradigm to explore the CAP function, which can only represent one aspect of it. Finally, this study explored the phenomena associated with the CAP function with EEG alterations, and the follow-up can be based on this to build a better model for MCI and early AD recognition and discover better non-pharmacological intervention targets for early AD to be applied in clinical practice.

5. Conclusions

Patients with MCI and early AD have reduced CAP function, including binaural function and auditory working memory function. The reduction is significantly associated with reduced cognitive function. This impairment is reflected in different patterns of changes in ERPs and FC in the brain.

Author contribution statement

Jiarui Li: Performed the experiments; Wrote the paper.
Xiaoying Zhang and Meiduo Gesang: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
Benyan Luo: Conceived and designed the experiments.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

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Abbreviations

CAP	central auditory processing
AD	Alzheimer's Disease
MCI	mild cognitive impairment
EEG	electroencephalograph
ERP	event-related potential
FC	functional connection
HC	healthy control
MMSE	Mini-Mental State Examination
MoCA	the Montreal Cognitive Assessment
CDR	Clinical Dementia Rating
SSW	Staggered spondaic word test
CPL	characteristic path length
GE	global efficiency
IQR	interquartile range interquartile range
SD	standard deviation standard deviation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15641.

References

[1] G. Livingston, J. Huntley, A. Sommerlad, D. Ames, C. Ballard, S. Banerjee, C. Brayne, A. Burns, J. Cohen-Mansfield, C. Cooper, S.G. Costafreda, A. Dias, N. Fox, L. N. Gitlin, R. Howard, H.C. Kales, M. Kivimaki, E.B. Larson, A. Ogunniyi, V. Orgeta, K. Ritchie, K. Rockwood, E.L. Sampson, Q. Samus, L.S. Schneider, G. Selbaek, L. Teri, N. Mukadam, Dementia prevention, intervention, and care: 2020 report of the Lancet Commission, Lancet (N. Am. Ed.) 396 (2020) 413–446.
[2] N. Back, A. Crippa, T. Riechi, L.D. Pereira, Central auditory processing and cognitive functions in children, Int. Arch. Otorhinolaryngol. 26 (2022) e20–e31.
[3] K. Jablonska, M. Piotrowska, H. Bednarek, A. Szymaszek, A. Marchewka, M. Wypych, E. Szelag, Maintenance vs. Manipulation in auditory verbal working memory in the elderly: new insights based on temporal dynamics of information processing in the millisecond time range, Front. Aging Neurosci. 12 (2020) 194.

[4] C. Wang, Z. Wang, B. Xie, X. Shi, P. Yang, L. Liu, T. Qu, Q. Qin, Y. Xing, W. Zhu, S.J. Teipel, J. Jia, G. Zhao, L. Li, Y. Tang, Binaural processing deficit and cognitive impairment in Alzheimer's disease, Alzheimers Dement 18 (2022) 1085–1099.
[5] Y.N. Chen, S. Mitra, Distinctions between spatial and verbal working memory: a study using event-related potentials, Chang Gung Med. J. 32 (2009) 380–389.
[6] K. Nowak, J. Costa-Faidella, A. Dacewicz, C. Escera, E. Szelag, Altered event-related potentials and theta oscillations index auditory working memory deficits in healthy aging, Neurobiol. Aging 108 (2021) 1–15.
[7] R.C. Petersen, G.E. Smith, S.C. Waring, R.J. Ivnik, E.G. Tangalos, E. Kokmen, Mild cognitive impairment: clinical characterization and outcome, Arch. Neurol. 56 (1999) 303–308.
[8] G.M. McKhann, D.S. Knopman, H. Chertkow, B.T. Hyman, C.J. Jack, C.H. Kawas, W.E. Klunk, W.J. Koroshetz, J.J. Manly, R. Mayeux, R.C. Mohs, J.C. Morris, M. N. Rossor, P. Scheltens, M.C. Carrillo, B. Thies, S. Weintraub, C.H. Phelps, The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement 7 (2011) 263–269.
[9] G.E. Bruder, J.W. Stewart, P.J. McGrath, D. Deliyannides, F.M. Quitkin, Dichotic listening tests of functional brain asymmetry predict response to fluoxetine in depressed women and men, Neuropsychopharmacology 29 (2004) 1752–1761.
[10] K. Jablonska, M. Piotrowska, H. Bednarek, A. Szymaszek, A. Marchewka, M. Wypych, E. Szelag, Maintenance vs. Manipulation in auditory verbal working memory in the elderly: new insights based on temporal dynamics of information processing in the millisecond time range, Front. Aging Neurosci. 12 (2020) 194.
[11] A. Delorme, S. Makeig, EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis, J. Neurosci. Methods 134 (2004) 9–21.
[12] H. Devos, J.M. Burns, K. Liao, P. Ahmadnezhad, J.D. Mahnken, W.M. Brooks, K. Gustafson, Reliability of P3 event-related potential during working memory across the spectrum of cognitive aging, Front. Aging Neurosci. 12 (2020).
[13] V.C. Pezoulas, A. Athanasiou, G. Nolte, M. Zervakis, A. Fratini, D.I. Fotiadis, M.A. Klados, FCLAB: an EEGLAB module for performing functional connectivity analysis on single-subject EEG data, in: IEEE EMBS International Conference on Biomedical & Health Informatics (BHI)2018, 2018, pp. 96–99.
[14] M. Rubinov, O. Sporns, Complex network measures of brain connectivity: uses and interpretations, Neuroimage 52 (2010) 1059–1069.
[15] N. Back, A. Crippa, T. Riechi, L.D. Pereira, Central auditory processing and cognitive functions in children, Int. Arch. Otorhinolaryngol. 26 (2022) e20–e31.
[16] A. Mohammed, L.E. Gibbons, G. Gates, M.L. Anderson, S.M. McCurry, W. McCormick, J.D. Bowen, T.J. Grabowski, P.K. Crane, E.B. Larson, Association of performance on dichotic auditory tests with risk for incident dementia and alzheimer dementia, JAMA Otolaryngol. Head Neck Surg. 148 (2022) 20–27.
[17] M. Karrasch, M. Laine, J. Orinne, P. Rapinoja, E. Sinervä, C.M. Krause, Brain oscillatory responses to an auditory-verbal working memory task in mild cognitive impairment and Alzheimer's disease, Int. J. Psychophysiol. 59 (2) (2006) 168–178.
[18] F. Borgo, L. Giovannini, R. Moro, C. Semenza, M. Arcicasa, M. Zaramella, Updating and inhibition processes in working memory: a comparison between Alzheimer's type dementia and frontal lobe focal damage, Brain Cognit. 53 (2003) 197–201.
[19] J. Johnson, C.R. Marshall, R.S. Weil, D.E. Bamiou, C. Hardy, J.D. Warren, Hearing and dementia: from ears to brain, Brain 144 (2021) 391–401.
[20] T.D. Griffith, M. Lad, S. Kumar, E. Holmes, B. McMurray, E.A. Maguire, A.J. Billig, W. Sedley, How can hearing loss cause dementia? Neuron. Nov 11 (3) (2020) 401–412, 108.