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Research Report

Correlation of auditory event-related potentials and magnetic resonance spectroscopy measures in mild cognitive impairment

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ARTICLE INFO

Article history:
Accepted 28 April 2010
Available online 12 May 2010

Keywords:
Mild cognitive impairment
Event-related potential
Magnetic resonance spectroscopy
Cognitive tests
Correlation

ABSTRACT

This study was aimed to examine the changes in auditory event-related potentials (AERPs) and their relationship with brain metabolic changes in mild cognitive impairment (MCI). 34 MCI patients and 34 healthy elderly controls were subjected to auditory stimulus oddball task, and then post-stimulus potentials (P50, N100, P200, N200, and P300) were obtained, levels of N-acetylaspartate (NAA), creatine (Cr) and the ratio of NAA/Cr were measured by proton magnetic resonance spectroscopy (1H-MRS) in left frontal, left temporal and right parietal cortex. Compared with the control group, the MCI group had significantly increased P50 amplitudes and P300 latency, and the NAA/Cr was abnormal. Linear progression analysis revealed a strong negative correlation between P50 amplitudes and NAA/Cr in left frontal cortex, and negative correlation between P300 latency and NAA/Cr in left frontal and left temporal, as well as correlation of AERP components and MRS metabolites with clinical scores of cognitive tests. These findings suggest that metabolic abnormalities of different brain regions may reflect the changes of underlying brain activities that are instrumental in the MCI. Therefore AERPs and MRS measurements may offer a mean to track changes of brain activities associated with functional changes, and to assess early cognitive impairment in MCI.

1. Introduction

Characterized as disturbances in cognitive functions such as memory and language, mild cognitive impairment (MCI) is a disorder in elderly people and a major risk factor for Alzheimer's disease (AD). The risk of progression to Alzheimer's disease (AD) in MCI patients is approximately six times higher than that in the some population without memory impairments (Petersen et al., 1999a, b; Celsis, 2000). Some investigators believe that MCI is in fact a syndrome prodromal AD because neuropathological characteristics of MCI resemble those of AD (Morris and Price, 2001). Previous studies suggested that Alzheimer-type neurofibrillary degeneration constitutes the majority of the pathologic abnormality in MCI (Mufson et al., 1999; Price and Morris, 1999; Bennett et al., 2005). Because neuropathology is present before the clinical expression of cognitive deficits (Ohm et al., 1995; Morrison and Hof, 1997), early detection of MCI is necessary.

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doi:10.1016/j.brainres.2010.04.078

AERP is a reliable neuroelectric measure of brain activity in responses to auditory stimuli that help to confirm the assessment of mental status and cognitive disorders (Polich et al., 1990). Event-related potentials in response to auditory stimulus oddball task have been used to quantify activities of cortical sensory and cognitive functions. Subjects are required to identify infrequent target stimuli embed within a sequence of standard tones (Sutton et al., 1965). Frequent non-target tones elicit three event-related potential waves, the P50, N100, and P200; infrequent targets elicit N200 and P300 waves (Donchin and C. M, G, 1988). In MCI, P50 amplitudes and P300 latency are enhanced (Golob and Starr, 2000, 2007). Changes of electrophysiological sensory and cognitive responses can occur prior to behavioral dysfunctions, which is consistent with the clinical experience that the disease symptoms may be delayed relative to the abnormal laboratory and imaging findings.

Proton magnetic resonance spectroscope (1H-MRS) provides a noninvasive in vivo measure of biochemical components in the brain. Using this methodology, prior studies have found decreased NAA in the temporal, parietal and frontal regions in patients with AD (Valenzuela and Sachdev, 2001). Interestingly, decreases in NAA and NAA/Cr have also been identified in MCI patients from the same brain regions (Kantarci et al., 2000; Catani et al., 2001; Pilatus et al., 2009). Since a lower NAA level has been associated with poor performance in memory tests in AD patients (Ross and Sachdev, 2004), decreased NAA and NAA/Cr in MCI patients predict a higher risk for AD (Modrego et al., 2005; Metastasio et al., 2006).

A number of previous studies have reported changes in auditory cortical potentials, brain metabolitic levels and cognitive performance in MCI (Golob et al., 2002; Modrego et al., 2005; Golob et al., 2007; Pilatus et al., 2009), but the relationships among these physiological parameters have not been well-studied. By examining AERP and brain biochemical components, this study was aimed to identify the changes of these parameters in MCI subjects, correlate abnormalities of AERP components with the biochemical components in different brain regions, and correlate abnormalities in AERP and MRS with the clinical cognitive test scores.

2. Results

2.1. *Neuropsychological testing*

As shown in Table 1, among the set of cognitive tests, performance of all the healthy control subjects was within the normal range, but the MCI group received significantly lower scores on all the items in the two memory tests (Recall of Auditory Verbal Learning Test and Wechsler Memory Scale) and the language test Boston Naming Test 30 items. However, patients and controls showed no significant differences in the results of the other language test Verbal Fluency Test, the two visual–spatial function tests (WAIS-RC Block Design and Clock-Drawing test), and the two executive function tests (Trail Making Tests A and B).

2.2. *Auditory event-related potentials*

2.2.1. *In response to non-targets*

Auditory event-related potentials in response to non-target frequent tones at the Cz site are presented as a time-curve for all elderly subjects in Fig. 1A. P50 amplitudes in MCI patients were significantly increased over those of the controls ($t=3.4$, $P<0.001$). P50 amplitudes and latencies for individual subjects are depicted as a dot-plot in Figs. 2A and B. P50 amplitudes were larger in 28/34 MCI subjects than the mean P50 amplitude

Table 1 – Neuropsychological testing results.

Name of the test	Controls ($n=34$)	MCI ($n=34$)	P value (t tests)
Cognitive status			
Mini-Mental State Examination—Chinese version	28.1±1.5	24.4±3.8	<0.0001
Recall of Auditory Verbal Learning Test			
First time recall	5.3±2.2	3.3±1.3	<0.001
Second recall	7.2±1.4	5.4±2.0	<0.001
Third recall	8.0±1.4	6.4±1.8	<0.001
Short delayed recall	6.6±1.2	4.8±2.4	<0.001
Long delayed recall	6.9±1.6	5.2±2.2	<0.001
Wechsler Memory Scale (Chinese Revised Version)			
Logical memory immediate recall	12.1±2.7	9.0±3.8	<0.001
Logical memory delayed recall	12.3±2.4	9.5±3.6	<0.001
Language			
Verbal fluency test	13.4±3.2	12.8±3.8	0.86
Boston Naming Test (30 item)—Chinese version	25.0±2.5	22.9±3.6	<0.01
Executive function			
Trail Making Test A—Chinese version (s)	68.6±25.2	63.6±27.5	0.66
Trail Making Test B—Chinese version (s)	177.0±52.6	208.4±101.2	0.11
Visual–spatial			
WAIS-RC Block Design	7.0±2.2	6.4±2.5	0.58
Clock-drawing test	2.8±0. 6	2. 5±1.2	0.36

Control subjects were matched to MCI subjects for age and education level. All subjects received the same neuropsychological text battery, and complete the tests presented as instructed. Test scores are expressed as means±standard deviations.

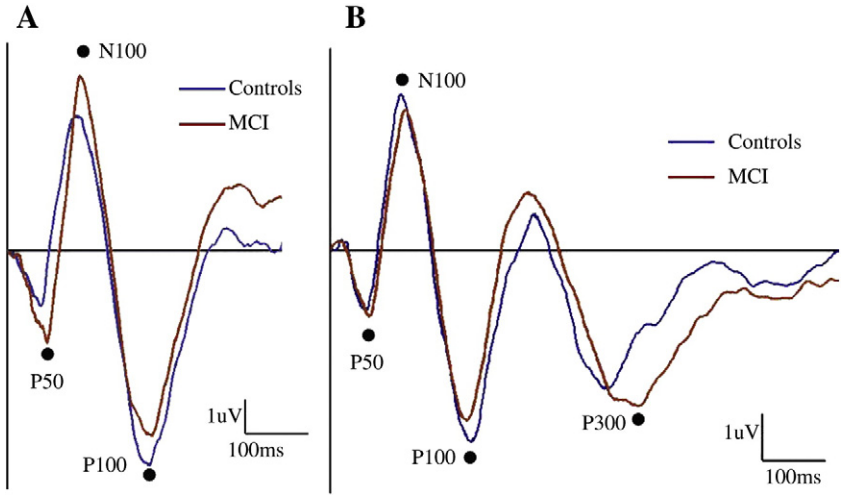

Fig. 1 – Auditory event-related potentials in response to non-target tones at the Cz site (A), or to targets at the Pz site (B). The vertical lines for (A) and (B) indicate stimulus onset.

of the control subjects, but there were no significant group differences in the latency of P50, the amplitudes or latencies of N100 and P200 components.

2.2.2. *In response to target infrequent tones*

Auditory event-related potentials in response to targets at the Pz site for all elderly subjects are shown in Fig. 1B. MCI patients showed a prolonged P300 latency ($t=2.5$, $P<0.05$) and lower amplitude ($t=2.4$, $P<0.05$) than the controls. P300 was delayed by 35 ms in MCI group compared with the controls. P300 amplitudes and latencies in response to targets tones for individual subjects are depicted in Figs. 2C and D. 62% of the MCI patients had P300 latencies above the mean of controls.

2.3. *Metabolite levels and ratios by MRS*

The levels of two metabolites NAA and creatine and their ratios in the three brain areas of controls and MCI patients are shown in Table 2. Compared with the healthy subjects, MCI patients had significantly lower mean values of NAA and NAA/Cr in the left prefrontal ($P<0.01$) and left temporal cortex ($P<0.05$), but not in the right parietal cortex. On the other hand, mean values of Cr were not significantly different between the two groups in all the three brain areas. In Fig. 3, examples of proton spectra of NAA and Cr in one control subject and one MCI patient also confirmed the same observation. Scatter plots for the NAA/Cr ratios in the prefrontal cortex also showed a decreased mean value in MCI patients (Fig. 4).

2.4. *Relationship of P50 and P300 with cerebral metabolites*

Relationship between AERP parameters and cerebral NAA/Cr ratios were examined by linear regression analysis. For the correlations between P50 and NAA/Cr, we examined P50 to the standard tones at the Cz site. For the correlations between P300 and NAA/Cr, we examined P300 at the Pz site in response to the target tones. P50 amplitudes were negatively correlated with NAA/Cr in the left prefrontal cortex ($r=-0.71$, $P<0.001$, Fig. 5A), but not with NAA/Cr in left temporal ($r=-0.20$, $P>0.1$, not shown) and right parietal cortex($r=-0.22$, $P>0.1$, not

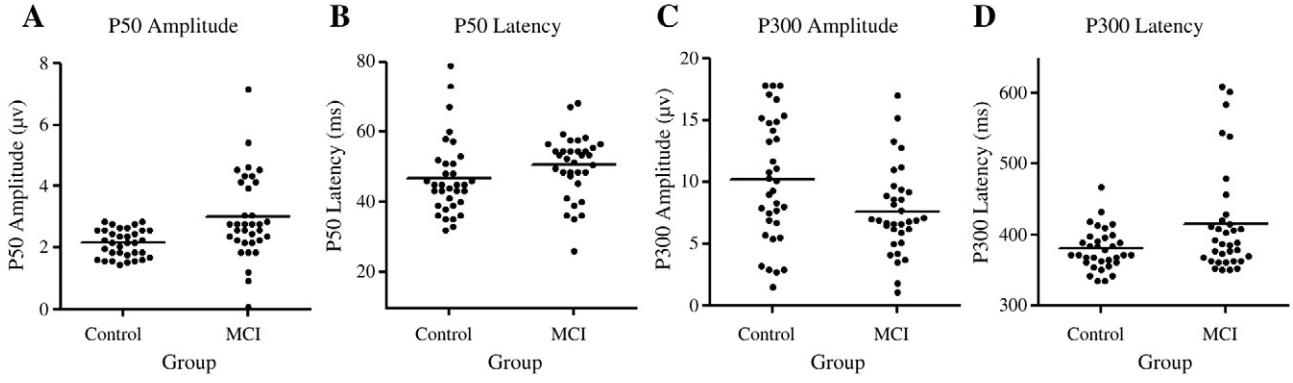

Fig. 2 – Dot-plots of P50 amplitudes (A) and P50 latency (B) in response to non-targets; P300 amplitudes (C) and P300 latency (D) to targets. Averaged potentials were measured at the Cz site for P50, N100 and P200 components in response to frequent tones and at the Pz site for N200 and P300 components. Black horizontal bars indicate mean values in A , B, C and D for the controls or MCI patients.

Table 2 – NAA, Cr concentrations and NAA/Cr ratios measured by H1-MRS.

Brain metabolite	Location	Control (N=34)	MCI (N=34)	t, P value
NAA	Left prefrontal	58.59±12.46	50.23±12.95	2.71, <0.01
	Left temporal	57.18±12.00	51.72±10.41	2.00, <0.05
	Right parietal	60.57±15.77	64.07±11.67	−1.04, 0.30
Cr	Left prefrontal	39.44±7.52	39.19±10.50	0.11, 0.91
	Left temporal	37.62±7.07	38.62±7.38	−0.57, 0.57
	Right parietal	43.90±9.28	46.67±10.01	1.18, 0.24
NAA/Cr	Left prefrontal	1.50±0.22	1.32±0.29	2.76, <0.01
	Left temporal	1.56±0.21	1.40±0.34	2.41, <0.05
	Right parietal	1.40±0.28	1.43±0.44	−0.39, >0.05

NAA: N-acetylaspartate; Cr: creatine. P values were obtained from t test.

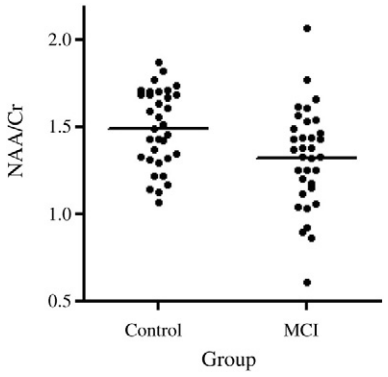

Fig. 4 – Scattered plots of NAA/Cr ratios obtained from the prefrontal cortex in two subject groups. Black horizontal bars indicate respective mean values (t=2.3, P=0.02).

shown). P300 latency at the Pz site was negatively correlated with NAA/Cr in left prefrontal ($r=-0.53$, $P<0.01$, Fig. 5B) and left temporal cortex ($r=-0.60$, $P<0.01$, Fig. 5C). Individuals with longer P300 latency exhibited significantly lower levels of NAA/Cr in both areas.

2.5. *Relationship between the cognitive test scores and auditory and MRS measures*

MCI patients and control subjects showed significant differences in all the memory scores but not other cognition test scores. Through a simple linear regression analysis, all the memory scores were positively correlated with NAA/Cr in the left prefrontal and left temporal cortex but negatively correlated with P50 amplitudes and P300 latencies (Table 3).

3. Discussion

In this study, we presented data to show that MCI subjects responded with significantly larger P50 amplitudes and prolonged P300 latencies to auditory stimulus oddball task, and had significantly lower levels of NAA and NAA/Cr ratios in selected brain regions. The changes of P50 amplitudes and P300 latencies are associated with the changes of NAA/Cr ratios in different brain regions, and both AERP components and brain metabolites measured by MRS are correlated with clinical scores in the cognitive tests.

3.1. *Auditory event-related potentials in MCI*

3.1.1. *N100 and P200*

In this study, N100 and P200 auditory cortical potentials were not significantly different between MCI and controls. Previous studies also reported that change in N100 amplitudes (Golob et al., 2002) is not significant or just a small increase at slow stimulus rates (Golob et al., 2001) in MCI patients. Therefore, our results are consistent with these previous studies.

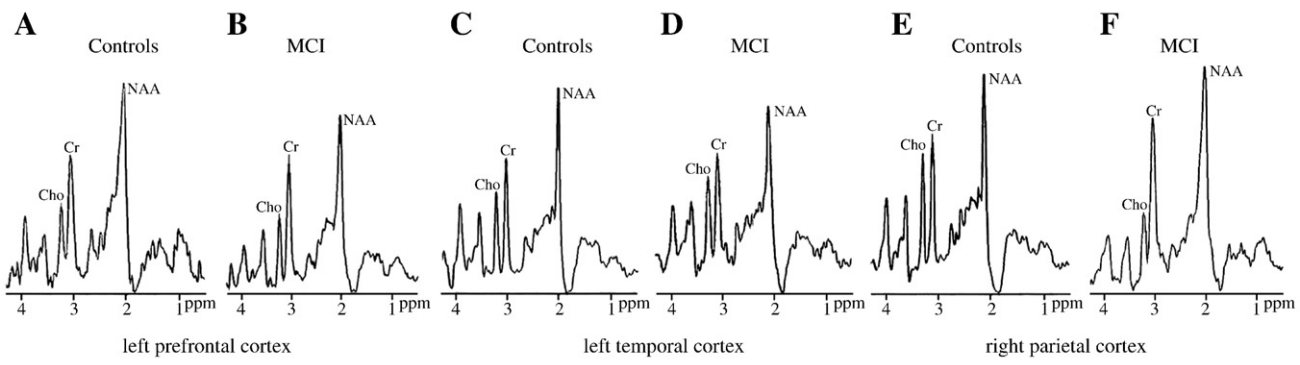

Fig. 3 – Proton spectra showing peaks of N-acetylaspartate and creatine ratio from the left prefrontal (A,B), left temporal (C,D) and right parietal (E,F) cortex in a randomly picked control subject (A,C,E) and one MCI patient (B,D,F).

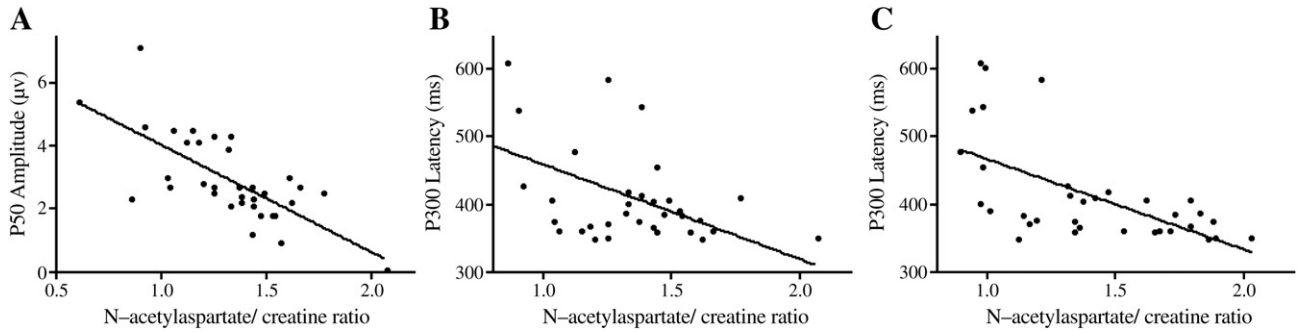

Fig. 5 – Scattered plots of linear analysis regression showing correlation between NAA/Cr in left prefrontal cortex and P50 amplitude (A); between NAA/Cr in left prefrontal cortex and P300 latency (B); and between NAA/Cr in left temporal cortex and P300 latency.

3.1.2. *P50 abnormalities*

Previous studies reported that P50 amplitudes increased (Reite et al., 1988; Boutros et al., 1995) or both P50 amplitudes and latency increased in auditory target detection in MCI patients (Golob et al., 2002). MCI has been considered a prodromal stage of AD and increased P50 amplitudes may present a greater risk for AD. MCI patients who later developed AD showed larger P50 amplitudes at the time of diagnosis as compared with those MCI subjects who did not develop AD (Golob et al., 2007) later in life. Since pathological change in auditory cortices occur only late during the AD progression (Romanski and Goldman-Rakic, 2002; Apostolova et al., 2007), abnormality of P50 in MCI patients is unlikely attributed to the pathology within the auditory cortical areas that generate the P50 component.

Cortical responses to auditory stimuli may be modulated by impairment in auditory cortex or areas such as the prefrontal cortex. The prefrontal cortex plays an important role in auditory communication. By receiving auditory afferents, it can influence other brain regions involved in temporal auditory association cortex. The connectivity of the frontal lobes makes it a likely candidate for integrating auditory signals (Jacobson and Trojanowski, 1977; 3rd GGW et al., 2005; Evans et al., 2005; Romanski et al., 2005). Previous studies showed the link of prefrontal cortices with superior temporal areas (Petrides and Pandya, 1988; Chao and Knight, 1997; Hackett et al., 1999; Kondo et al., 2003).

3.1.3. *P300 abnormalities*

The P300 wave is a reliable neuroelectric marker for brain cognitive functions often used to assess cognitive disorders (Polich et al., 1990). The P300 amplitudes are reduced and P300 latencies prolonged in AD patients (Kugler et al., 1996). One recent report showed the similar prolongation of P300 latencies among MCI patients and its positive correlation with the severity of dementia. P300 latency prolongation thus may indicate an increased risk for developing dementia in MCI patients (Egerhazi et al., 2008). Similar P300 abnormalities in

Table 3 – Correlations between AERP and MRS measure and cognitive test scores.

Test	NAA/Cr (left prefrontal)	NAA/Cr (left temporal)	P50 amplitudes	P300 latencies
	r *P* value	*r* *P* value	*r* *P* value	*r* *P* value
Recall of Auditory Verbal Learning Test				
First time recall	0.68	0.54	−0.64	−0.53
	<0.01	<0.05	<0.01	<0.05
Second recall	0.65	0.48	−0.68	−0.55
	<0.01	<0.05	<0.01	<0.05
Third Recall	0.66	0.53	−0.67	−0.48
	<0.01	<0.05	<0.01	<0.05
Short delayed recall	0.67	0.55	−0.63	−0.51
	<0.01	<0.05	<0.01	<0.05
Long delayed recall	0.65	0.49	−0.64	−0.52
	<0.01	<0.05	<0.01	<0.05
Wechsler Memory Scale (Chinese Revised Version)				
Logical memory immediate recall	0.67	0.51	−0.66	−0.52
	<0.01	<0.05	<0.01	<0.05
Logical memory delayed recall	0.64	0.52	−0.63	−0.49
	<0.01	<0.05	<0.01	<0.05

The memory scores of MCI subjects had a positive correlation with NAA/Cr in the left prefrontal and left temporal cortex, as well as a negative correlation with P50 amplitudes and P300 latencies.

MCI subjects were also identified in this study and by others (Golob et al., 2007); thus, P300 latencies can provide useful information about MCI patients. P300 may have multiple intracerebral generators, with the hippocampus and various association areas of the neocortex all contributing to the scalp-recorded potentials (Polich, 2004). P300 latency increases may be associated with neocortical dysfunction that shortly precedes, and then accompanies the presence of dementia.

3.2. *Brain metabolism abnormalities in MCI*

Primarily located in neuron bodies, axons and dendrites, NAA is a marker for neuronal integrity, neuronal density or viability (Braak and Braak, 1991). Cr is another marker for the health of systemic energy use and its storage is relatively stable (Valenzuela and Sachdev, 2001). NAA has been suggested as a surrogate marker for progressing pathology and decline in neuronal integrity during the transition from MCI to manifestation of dementia (Pilatus et al., 2009). A decrease in NAA/Cr develops later in the course of the disease (Kantarci et al., 2000), and the decrease of NAA or NAA/Cr occurs in various brain regions in MCI patients (Braak and Braak, 1991; Schuff et al., 1997; Falini et al., 2005; Sarazin et al., 2007). The similar regional changes of NAA or NAA/Cr in MCI and AD suggest that NAA/Cr may be sensitive to the biochemical changes during the pathologic progression of AD. Therefore NAA/Cr may be useful for predicting prodromal AD.

We also identified brain metabolic abnormalities in MCI patients affecting the prefrontal and temporal cortex, consistent with previous reports from the literature (Kantarci, 2007). The decreased NAA levels and NAA/Cr ratios might be resulted from neural cell death in the neocortex and/or anterograde axonal degeneration of neurons and axons following neuronal damage and decreased functionality or metabolic integrity. MCI displays the same metabolic pattern with AD, suggesting a similar pathological process in these brain regions. Our data demonstrated that 1H-MRS is a useful research modality to characterize brain metabolic alterations in MCI.

3.3. *Relationship between AERPs and brain metabolism*

The present AERP and MRS results replicate previous findings of increased P50 amplitudes, prolongation of P300 latency (Golob et al., 2002, 2007), and reduction of NAA/Cr ratio in the frontal cortex and temporal (Schuff et al., 1997; Pilatus et al., 2009) in MCI. Moreover, our study extended the above findings by identifying the relationship of auditory cortical potentials with MRS measures in MCI.

P50 amplitudes were found to be negative correlated with NAA/Cr ratio in the left prefrontal cortex, but not in the temporal and parietal cortex. This relationship indicates a potential contribution of P50 to the metabolic changes in prefrontal cortex, which is in agreement with the regional distribution of pathology in AD (Arnold et al., 1991). Therefore, examination of metabolite concentrations in prefrontal cortex and P50 amplitudes may be important in MCI assessment. Change of NAA/Cr in prefrontal and temporal cortex was also correlated with a longer P300 latency. Previous observations also showed that AERPs and regional brain metabolism changes are consistent with pathological alterations (Tiraraboschi et al., 2004; Forman et al., 2007).

3.4. *Relationship of AERP and MRS measurements with cognitive tests*

Our results also showed that the brain metabolism and brain functional abnormalities in MCI patients are related to clinical scores. Memory scores in clinical cognitive tests are positively correlated with NAA/Cr ratio measured by 1H-MRS in the left prefrontal and left temporal cortex. They are also negatively correlated with P50 amplitudes in response to frequent tones at the Cz site and P300 latencies in response to targets at the Pz site. These results demonstrated the clinical values of the AERP and the MRS measurements in the assessment of MCI.

Together, data presented in this study suggest that abnormalities in metabolites and AERP may be the primary dysfunction in MCI that can be identified during the MCI evaluation. 1H-MRS and AERP yield quantitative measurements to track cortex metabolic and functional changes, in support of the clinic observation of cognition impairments. Future studies investigating the course of metabolic and AERP changes in association with cognitive changes would help better characterize the functional progression of MCI to AD throughout the brain cortex.

4. Experimental procedures

4.1. *Subjects*

In this study, 34 MCI patients and 34 age-matched healthy elderly control subjects were recruited from the neurological department and the health examination center, respectively, in the People's Hospital of Guizhou Province. Demographic information for the study groups is presented in Table 4. The diagnosis of MCI was made based on clinical neurological and neuropsychological assessments, routine blood tests, family interviews and magnetic resonance imaging (MRI) according to the guidelines of Petersen et al. (Petersen et al., 1999a, b). MCI subjects showed moderate to severe deficits in memory; their performance levels were typically 1.5 times the standard deviations below the age-appropriate mean but without impairments on other neuropsychological functions, or daily life activities. Control subjects scored within the normal range on all neuropsychological tests. All subjects signed informed consent forms, and the study protocol was approved by the Institutional Review Board of the hospital in accordance with the Declaration of Helsinki.

Table 4 – Demographic information.

	Controls	MCI
Number of patients	34	34
Age	71.6±5.7	72.5±5.4
Education	7.8±1.2	7.6±1.2
F/M	11/23	13/21

All subjects (controls and MCI patients) were matched for age and educational level. Values are mean±standard deviation.

4.2. Study design

MCI and the control subjects were compared for the ERPs in responses to auditory stimuli and MRS recordings of the neurometabolic activities in three brain areas at the study entry and during the study. Brain metabolic data were collected three days after AERPs were examined in all subjects. Statistical analyses were applied to all the measurements in order to assess the significance of the differences between groups, the relationship between AERP components and brain neurometabolism in three brain areas, and the association of AERP and brain neurometabolism with the cognitive tests.

4.3. Neuropsychological testing

Memory was assessed using the WMS-CR Logical Memory Subtest (Yao-xian, 1983) and the Recall of Auditory Verbal Learning Test (GUO et al., 2001). Language tests included the 30-item version of the Boston Naming Test—Chinese version and Verbal Fluency Test (GUO et al., 2006). Executive function was tested with the Trail Making Tests A and B—Chinese version (LU et al., 2006). Visual–spatial skills were evaluated with the Wechsller Adult Intelligent Scale-Reversed Chinese (WAIS-RC) Block Design test (Yao-xian, 1983) and Clock-Drawing Test (ZHOU and JIA, 2008). The Mini-Mental State Examination—Chinese version was used as a screening test of dementia (SUN et al., 2008).

4.4. Event-related potential recordings

Subjects were seated inside an electrically shielded and sound attenuated room. Depending on the subject, between 8 and 10 Ag/AgCl recording electrodes were placed on the scalp according to the 10/20 system (Homan et al., 1987). All subjects had electrodes at Fz, Cz, Pz, C3 and C4 sites. Electrode impedances were kept below 5 kΩ. Two electrodes were placed above and below the left eye to monitor eye movement, and one ground electrode was placed on the forehead. A reference electrode was placed on the right mastoid. Subjects performed a target detection task by listening to a sequence of tones having a constant inter-stimulus interval of 2 s. Tones were presented through headphones (70 dB SPL, 100 ms duration, 5 ms rise/fall times). Pure tones were either 1000 Hz "non-targets" or 2000 Hz "targets". Probability of presentation was 0.80 and 0.20 for non-target and target tones, respectively. A total of 300 tones were presented (240 non-targets and 60 targets). Subjects were instructed to listen to the tones and quickly, but accurately, press a button with the thumb of their dominant hand after hearing them. The sequence of tones was randomly determined except that two targets were never presented in a row, and no more than nine non-targets were allowed to be presented in a row.

4.5. Event-related potentials

Electrophysiological (EEG or EOG) and behavioral data were collected continuously, and digitally amplified (DC — 100 Hz, sample rate = 500 Hz). Data were further processed and analyzed. An eyeblink algorithm was used to correct artifacts. Individual sweeps were then sorted and averaged according to stimulus type (non-target or target). Sweeps to targets were visually inspected for artifacts before being accepted into the average. Sweeps to non-targets were automatically rejected if the voltage on any electrode site exceeded 75 μV. Analysis focused on midline electrodes (Cz, Pz). For the overall comparisons, P50, N100, P200, and N200 measurements were taken from the Cz site, and P300 measurements were taken from the Pz site.

The EEG was digitally filtered using FFT and inverse FFT procedures, and filter settings were adjusted depending on the component of interest. A low-pass filter was used (DC—3 Hz, 12 dB/octave) for RP and a band-pass filter was used for P50, N100, P200, N200, and P300 components (0.1–16 Hz, 12 dB/octave). Peak latencies of components were calculated relative to the stimulus onset. Amplitudes of components following stimulus presentation (P50, N100, P200, N200, and P300) were defined relative to a 100 ms baseline period immediately before stimulus presentation. P50, N100, and P200 components were measured for both the frequent and target tones, and additional N200 and P300 potentials were measured for target tones. Amplitude and latency of the P50 were defined as the point of maximum positivity between 40 and 80 ms post-stimulus. N100 amplitude and latency were defined as the maximum negativity between 80 and 160 ms, while P200 amplitude and latency were the maximum positivity between150 and 250 ms. The N200 was defined as the maximum negativity between 175 and 250 ms that immediately preceded the large P300 wave. P300 amplitudes and latencies were defined as the maximum positivity between 300 and 600 ms.

4.6. 1H-MRS measures

Upon completion of the medical history, neuropsychological examination and AERPs, all participants underwent 1H-MRS of the brain in three different areas constituting most of the brain tissue (Fig. 6): left frontal, left temporal and right parietal cortex. McLean et al. have not identified any differences between the right and left sides of the brain regarding the concentrations of brain metabolites (Sijens et al., 1997). Single-voxel 1H-MRS was performed on a 1.5-T clinical scanner (SIEMENS Symphony 1.5 T MR system, Germany) using a standard head coil (Vision; Siemens AG, Erlangen). An automated hybrid two-dimensional chemical shift imaging (CSI) sequence (repetition time [TR]/echo time [TE] 1500/30 ms) was used (Irimajiri et al., 2005). The volume of region-of-interest selection was 10 × 10 × 15 (cm). 1H-MRS acquisition time was 6:31 min. The automated post-processing procedure included multiplication of the time domain data with a Gaussian function, three-dimensional Fourier transformation, phase and baseline adjustment, and quantification using the standard Numaris-3 software package provided with the MR system (Irimajiri et al., 2005). Each spectrum was automatically fitted to two peaks corresponding to levels of N-acetylaspartate (NAA) (2.02 ppm) and total creatine (Cr) (3.03 ppm). The metabolite intensity ratios were obtained using physiologically stable metabolite Cr as the reference metabolite. Conventional biochemical ratios averaged over the whole spectral maps were calculated.

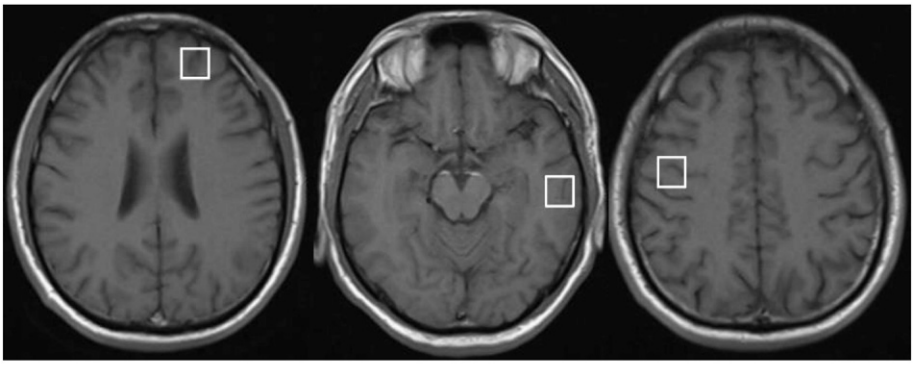

Fig. 6 – Images of proton magnetic resonance spectroscopy on region-of-interests (ROI) selected from the controls and MCI patients in three indicated brain areas.

4.7. *Statistical analysis*

The SPSS16.0 software package was used. Results are presented as mean±SE. AERP and 1H-MRS data were analyzed with analysis of variance using t test. *P* values <0.05 were considered significant. Correlation of variables was assessed via the Pearson correlation coefficient. Linear regression analysis was computed to correlate the MRS data, P50 amplitudes, AERP and brain neurometabolism with the cognitive tests.

Acknowledgments

The authors thank doctor Xiangxiang Gui for his assistance in the initial study setup and subject recruitment and doctor Xingfa Li for his assistance in statistical analysis. This study was supported by Guizhou Science and Technology Fund, Guizhou Qian Ke He Zi [2009, No. 2169] from Science and Technology Department of Guizhou Province in China.

REFERENCES

3rd GGWMacLean, K.A., Hauser, M.D., Cohen, Y.E., 2005. The neurophysiology of functionally meaningful categories: macaque ventrolateral prefrontal cortex plays a critical role in spontaneous categorization of species-specific vocalizations. J. Cogn. Neurosci. 17, 1471–1482.

Apostolova, L.G., Steiner, C.A., Akopyan, G.G., Dutton, R.A., Hayashi, K.M., Toga, A.W., Cummings, J.L., Thompson, P.M., 2007. Three-dimensional gray matter atrophy mapping in mild cognitive impairment and mild Alzheimer disease. Arch. Neurol. 64, 1489–1495.

Arnold, S.E., Hyman, B.T., Flory, J., Damasio, A.R., Van Hoesen, G. W., 1991. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cereb. Cortex 1, 103–116.

Bennett, D.A., Schneider, J.A., Bienias, J.L., Evans, D.A., Wilson, R.S., 2005. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. Neurology 64, 834–841.

Boutros, N., Torello, M.W., Burns, E.M., Wu, S.S., Nasrallah, H.A., 1995. Evoked potentials in subjects at risk for Alzheimer's disease. Psychiatry Res. 57, 57–63.

Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82, 239–259.

Catani, M., Cherubini, A., Howard, R., Tarducci, R., Pelliccioli, G.P., Piccirilli, M., Gobbi, G., Senin, U., Mecocci, P., 2001. (1)H-MR spectroscopy differentiates mild cognitive impairment from normal brain aging. NeuroReport 12, 2315–2317.

Celsis, P., 2000. Age-related cognitive decline, mild cognitive impairment or preclinical Alzheimer's disease. Ann. Med. 32, 6–14.

Chao, L.L., Knight, R.T., 1997. Prefrontal deficits in attention and inhibitory control with aging. Cereb. Cortex 7, 63–69.

Donchin, E., C. M, G, 1988. Is the P300 component a manifestation of context updating. Behav. Brain Sci. 11, 357–427.

Egerhazi, A., Glaub, T., Balla, P., Berecz, R., Degrell, I., 2008. P300 in mild cognitive impairment and in dementia. Psychiatr. Hung. 23, 349–357.

Evans, T.A., Howell, S., Westergaard, G.C., 2005. Auditory–visual cross-modal perception of communicative stimuli in tufted capuchin monkeys (Cebus apella). J. Exp. Psychol. Anim. Behav. Process. 31, 399–406.

Falini, A., Bozzali, M., Magnani, G., Pero, G., Gambini, A., Benedetti, B., Mossini, R., Franceschi, M., Comi, G., Scotti, G., Filippi, M., 2005. A whole brain MR spectroscopy study from patients with Alzheimer's disease and mild cognitive impairment. Neuroimage 26, 1159–1163.

Forman, M.S., Mufson, E.J., Leurgans, S., Pratico, D., Joyce, S., Leight, S., Lee, V.M., Trojanowski, J.Q., 2007. Cortical biochemistry in MCI and Alzheimer disease: lack of correlation with clinical diagnosis. Neurology 68, 757–763.

Golob, E.J., Starr, A., 2000. Effects of stimulus sequence on event-related potentials and reaction time during target detection in Alzheimer's disease. Clin. Neurophysiol. 111, 1438–1449.

Golob, E.J., Miranda, G.G., Johnson, J.K., Starr, A., 2001. Sensory cortical interactions in aging, mild cognitive impairment, and Alzheimer's disease. Neurobiol. Aging 22, 755–763.

Golob, E.J., Johnson, J.K., Starr, A., 2002. Auditory event-related potentials during target detection are abnormal in mild cognitive impairment. Clin. Neurophysiol. 113, 151–161.

Golob, E.J., Irimajiri, R., Starr, A., 2007. Auditory cortical activity in amnestic mild cognitive impairment: relationship to subtype and conversion to dementia. Brain 130, 740–752.

GUO, Q.H., LU, C.S., HONG, Z., 2001. Auditory verbal memory test in Chinese elderly. Chin. Ment. Heal. J. 15, 13–15.
GUO, Q.H., HONG, Z., SHI, W.X., 2006. Boston naming test in Chinese elderly, patient with mild cognitive impairment and Alzheimers dementia. Chin. Ment. Heal. J. 20, 81–84.
Hackett, T.A., Stepniewska, I., Kaas, J.H., 1999. Prefrontal connections of the parabelt auditory cortex in macaque monkeys. Brain Res. 817, 45–58.
Homan, R.W., Herman, J., Purdy, P., 1987. Cerebral location of international 10–20 system electrode placement. Electroencephalogr. Clin. Neurophysiol. 66, 376–382.
Irimajiri, R., Golob, E.J., Starr, A., 2005. Auditory brain-stem, middle- and long-latency evoked potentials in mild cognitive impairment. Clin. Neurophysiol. 116, 1918–1929.
Jacobson, S., Trojanowski, J.Q., 1977. Prefrontal granular cortex of the rhesus monkey. I. Intrahemispheric cortical afferents. Brain Res. 132, 209–233.
Kantarci, K., 2007. 1H magnetic resonance spectroscopy in dementia. Br. J. Radiol. 80 (Spec No 2), S146–152.
Kantarci, K., Jack Jr, C.R., Xu, Y.C., Campeau, N.G., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Boeve, B.F., Kokmen, E., Tangalos, E.G., Petersen, R.C., 2000. Regional metabolic patterns in mild cognitive impairment and Alzheimer's disease: a 1H MRS study. Neurology 55, 210–217.
Kondo, H., Saleem, K.S., Price, J.L., 2003. Differential connections of the temporal pole with the orbital and medial prefrontal networks in macaque monkeys. J. Comp. Neurol. 465, 499–523.
Kugler, C.F., Petter, J., Platt, D., 1996. Age-related dynamics of cognitive brain functions in humans: an electrophysiological approach. J. Gerontol. A Biol. Sci. Med. Sci. 51, B3–16.
LU, J.C., GUO, Q.H., HONG, Z., 2006. Trail making test used by Chinese elderly patients with mild cognitive impairment and mild Alzheimer's dementia. Chin. J. Clin. Psychol. 14, 118–120.
Metastasio, A., Rinaldi, P., Tarducci, R., Mariani, E., Feliziani, F.T., Cherubini, A., Pelliccioli, G.P., Gobbi, G., Senin, U., Mecocci, P., 2006. Conversion of MCI to dementia: role of proton magnetic resonance spectroscopy. Neurobiol. Aging 27, 926–932.
Modrego, P.J., Fayed, N., Pina, M.A., 2005. Conversion from mild cognitive impairment to probable Alzheimer's disease predicted by brain magnetic resonance spectroscopy Am. J. Psychiatry 162, 667–675.
Morris, J.C., Price, A.L., 2001. Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. J. Mol. Neurosci. 17, 101–118.
Morrison, J.H., Hof, P.R., 1997. Life and death of neurons in the aging brain. Science 278, 412–419.
Mufson, E.J., Chen, E.Y., Cochran, E.J., Beckett, L.A., Bennett, D.A., Kordower, J.H., 1999. Entorhinal cortex beta-amyloid load in individuals with mild cognitive impairment. Exp. Neurol. 158, 469–490.
Ohm, T.G., Muller, H., Braak, H., Bohl, J., 1995. Close-meshed prevalence rates of different stages as a tool to uncover the rate of Alzheimer's disease-related neurofibrillary changes. Neuroscience 64, 209–217.
Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999a. Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 56, 303–308.
Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999b. Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 56, 303–308.
Petrides, M., Pandya, D.N., 1988. Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. J. Comp. Neurol. 273, 52–66.
Pilatus, U., Lais, C., Rochmont, A.M., Kratzsch, T., Frolich, L., Maurer, K., Zanella, F.E., Lanfermann, H., Pantel, J., 2009. Conversion to dementia in mild cognitive impairment is associated with decline of N-actylaspartate and creatine as revealed by magnetic resonance spectroscopy. Psychiatry Res. 173, 1–7.
Polich, J., 2004. Clinical application of the P300 event-related brain potential. Phys. Med. Rehabil. Clin. N. Am. 15, 133–161.
Polich, J., Ladish, C., Bloom, F.E., 1990. P300 assessment of early Alzheimer's disease. Electroencephalogr. Clin. Neurophysiol. 77, 179–189.
Price, J.L., Morris, J.C., 1999. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann. Neurol. 45, 358–368.
Reite, M., Teale, P., Zimmerman, J., Davis, K., Whalen, J., Edrich, J., 1988. Source origin of a 50-msec latency auditory evoked field component in young schizophrenic men. Biol. Psychiatry 24, 495–506.
Romanski, L.M., Goldman-Rakic, P.S., 2002. An auditory domain in primate prefrontal cortex. Nat. Neurosci. 5, 15–16.
Romanski, L.M., Averbeck, B.B., Diltz, M., 2005. Neural representation of vocalizations in the primate ventrolateral prefrontal cortex. J. Neurophysiol. 93, 734–747.
Ross, A.J., Sachdev, P.S., 2004. Magnetic resonance spectroscopy in cognitive research. Brain Res. Brain Res. Rev. 44, 83–102.
Sarazin, M., Berr, C., De Rotrou, J., Fabrigoule, C., Pasquier, F., Legrain, S., Michel, B., Puel, M., Volteau, M., Touchon, J., Verny, M., Dubois, B., 2007. Amnestic syndrome of the medial temporal type identifies prodromal AD: a longitudinal study. Neurology 69, 1859–1867.
Schuff, N., Amend, D., Ezekiel, F., Steinman, S.K., Tanabe, J., Norman, D., Jagust, W., Kramer, J.H., Mastrianni, J.A., Fein, G., Weiner, M.W., 1997. Changes of hippocampal N-acetyl aspartate and volume in Alzheimer's disease. A proton MR spectroscopic imaging and MRI study. Neurology 49, 1513–1521.
Sijens, P.E., den Bent, M.J. v, Nowak, P.J., van, D.P., Oudkerk, M., 1997. 1H chemical shift imaging reveals loss of brain tumor choline signal after administration of Gd-contrast. Magn. Reson. Med. 37, 222–225.
SUN, L., ZHANG, X.Q., TANG, Z., 2008. Study of the change of cognition function and predictor factors in the patients with Alzheimer's disease before and after onset. J. Clin. Neurol. 21, 91–93.
Sutton, S., Braren, M., Zubin, J., John, E.R., 1965. Evoked-potential correlates of stimulus uncertainty. Science 150, 1187–1188.
Tiraboschi, P., Hansen, L.A., Thal, L.J., Corey-Bloom, J., 2004. The importance of neuritic plaques and tangles to the development and evolution of AD. Neurology 62, 1984–1989.
Valenzuela, M.J., Sachdev, P., 2001. Magnetic resonance spectroscopy in AD. Neurology 56, 592–598.
Yao-xian, G., 1983. Wechsler Adult Intelligence Scale amendment in China. Acta. Psychol. Sin. 3, 362–369.
Zhou, A.H., Jia, J.P., 2008. The value of the clock drawing test for identifying mild vascular cognitive impairment and mild vascular dementia. Chin. J. Nerve. Ment. Dis. 34, 72–75.