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Auditory brain-stem, middle- and long-latency evoked potentials in mild cognitive impairment

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Abstract

Objective: Mild cognitive impairment (MCI) is a selective episodic memory deficit in the elderly with a high risk of Alzheimer's disease. The amplitudes of a long-latency auditory evoked potential (P50) are larger in MCI compared to age-matched controls. We tested whether increased P50 amplitudes in MCI were accompanied by changes of middle-latency potentials occurring around 50 ms and/or auditory brain-stem potentials.

Methods: Auditory evoked potentials were recorded from age-matched controls ($n = 16$) and MCI ($n = 17$) in a passive listening paradigm at two stimulus presentation rates (2/s, 1/1.5 s). A subset of subjects also received stimuli at a rate of 1/3 s.

Results: Relative to controls, MCI subjects had larger long-latency P50 amplitudes at all stimulus rates. Significant group differences in N100 amplitude were dependent on stimulus rate. Amplitudes of the middle-latency components (Pa, Nb, P1 peaking at approximately 30, 40, and 50 ms, respectively) did not differ between groups, but a slow wave between 30 and 49 ms on which the middle-latency components arose was significantly increased in MCI. ABR Wave V latency and amplitude did not differ significantly between groups.

Conclusions: The increase of long-latency P50 amplitudes in MCI reflects changes of a middle-latency slow wave, but not of transient middle-latency components. There was no evidence of group difference at the brain-stem level.

Significance: Increased slow wave occurring as early as 50 ms may reflect neurophysiological consequences of neuropathology in MCI.

1. Introduction

Mild cognitive impairment (MCI) describes elderly individuals having a decline in episodic memory function relative to other cognitive abilities (Collie and Maruff, 2000; Morris, 2003; Petersen et al., 1999; Smith et al., 1996). MCI patients are approximately 6-fold more likely to progress to Alzheimer's disease relative to healthy older individuals (Morris et al., 2001; Petersen et al., 1999). Alzheimer's disease has a long preclinical period where neuropathological deposits (i.e. β-amyloid plaques, neurofibrillary

tangles) gradually accumulate in the brain without sufficient neuronal damage to cause clinically detectable dementia (Giannakopoulos et al., 2003; Morris and Price, 2001; Ohm et al., 1995). Neuropathological studies report that both the extent of neuronal loss (Kordower et al., 2001) and the regional accumulation of β-amyloid plaques and neurofibrillary tangles (Dekosky et al., 2002; Morris and Price, 2001; Mufson et al., 1999) in MCI are similar to early Alzheimer's disease. Taken together, the greater risk of Alzheimer's disease in MCI and the similarity in neuropathological features to early Alzheimer's disease suggests that MCI can be a transition state between normal aging and Alzheimer's disease.

A previous study in MCI using auditory long-latency cortical potentials in a target detection, or 'oddball' task, demonstrated an increased amplitude and delayed latency

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for a component having a peak latency of ~ 50 ms (P50) (Golob et al., 2002). P50 amplitude increases in MCI are not specific to the use of an auditory discrimination task as P50 amplitudes are also increased relative to controls when passively listening to tones (Golob et al., 2001). P50 is thought to reflect neural activity in primary/secondary auditory cortex (Liegeois-Chauvel et al., 1994; Reite et al., 1988; Yoshiura et al., 1995) and the definition of large P50 amplitudes in MCI compared to controls may reflect group differences at auditory sensory cortex.

It is well known that the amplitude of sensory cortical potentials is affected by rate of stimulation (Picton et al., 1974). We examined 3 variables that could influence the amplitudes of auditory long-latency P50 component. First, stimulus rate affects P50 amplitudes. Amplitudes decrease as stimulus rate increases, a process known as a 'refractory effect' (Butler, 1973; Davis et al., 1966; Naatanen and Picton, 1987; Nelson and Lassman, 1973; Roth et al., 1976). The amplitude differences between MCI and controls might be due to differences in refractory effects in the two groups. We therefore measured the effects of stimulus rate on P50 amplitudes differences in MCI and controls to define if (a) MCI subjects exhibit an overall increase in auditory P50 amplitudes that is independent of stimulus presentation rate or (b) P50 amplitudes may vary as a function of stimulus rate differently in MCI than controls.

The second variable that could affect long-latency P50 amplitudes involves changes in middle-latency responses with latencies between ~ 20 and 60 ms, a time domain that overlaps that of the long-latency P50 component. The middle-latency responses are typically high-pass filtered (>10 Hz) attenuating slow potentials and enhancing 3 transient components, Pa, Nb, and P1, also known as P30, N40, and P50, respectively (Picton et al., 1974).

The third variable that could affect long-latency P50 amplitudes involves an increase of activity in the ascending auditory pathway in MCI. We measured auditory brain-stem responses (ABRs) to identify if there were changes that accounted for the long-latency P50 amplitude increases in MCI.

2. Methods

2.1. Subjects

Healthy older controls ($n = 16$) and MCI patients ($n = 17$) were recruited through the Successful Aging Program and Alzheimer's Disease Research Center at the University California, Irvine (UCI). Demographic information is shown in Table 1. There were no significant differences between controls and MCI subjects in age or educational level. All patients and controls were classified as having MCI using neurological and neuropsychological examinations, family interviews and brain imaging (Smith et al., 1996). MCI subjects exhibited moderate to severe deficits in

Table 1
Demographic information

	Controls	MCI	*P* value (*t*-tests)
n	16	17	
Gender (male/female)	6/10	10/7	
Age (years)	75.8±4.0	74.8±8.3	n.s.
Education (years)	15.3±2.2	15.7±2.0	n.s.

Values are means±SD; n.s., not significant.

episodic memory, typically >1.5 SD below the mean of age-matched normative scores on episodic memory tests without notable impairments on other neuropsychological tests. MCI subjects were not impaired in activities of daily living as determined by the assessments of Bristol Activities of Daily Living Scale (Bucks et al., 1996), Functional Activities Questionnaire (Pfeffer et al., 1982), Blessed-Roth Dementia Scale (Blessed et al., 1968), and Dementia Rating Severity Scale (Clark and Ewbank, 1996). Eight MCI subjects were taking cholinesterase inhibitor, such as donepezil hydrochloride, at the time of evoked potential testing. All subjects signed informed consent forms, and the study was performed in accordance with a protocol approved by the UCI institutional review board.

2.2. Neuropsychological tests

Neuropsychological test battery was used to establish a cognitive profile in 15 control subjects and 17 MCI. The one control subject who was not tested works full-time without limitations in the University and has no memory complaints. The Mini-Mental State Examination was used to screen for dementia (Folstein et al., 1975). Episodic memory function was assessed using the WMS-III Logical Memory subtest (Wechsler, 1997) and the CERAD Word List Learning Task (Morris et al., 1989). Language was evaluated with the 30-item Boston Naming (Kaplan et al., 1983), CERAD Animal Naming (Morris et al., 1989), and Controlled Oral Word Association (FAS Fluency) tests (Spreen and Benton, 1977). Visual-spatial skills were evaluated with the WAIS-III Block Design test (Wechsler, 1981) and CERAD Constructional Praxis test (Morris et al., 1989). Executive function was tested with the Trailmaking test A and B (Reitan, 1958). The Geriatric Depression Scale (Yesavage et al., 1983) was administered to exclude depression.

2.3. Audiological measures

Pure tone thresholds to monaurally presented tones (0.5, 1, 2, 4, 6, 8 kHz) were measured in 14 controls and 12 MCI subjects in a sound attenuating chamber.

2.4. Design

Auditory middle- and long-latency potentials for all subjects ($n = 33$) were measured in two separate blocks

having fixed presentation stimulus rates of 2/s and 1/1.5 s. The 18 subjects last recruited (controls = 10, MCI = 8) received an additional stimulus at 1/3 s to determine if the amplitudes of long-latency components were similarly affected at an even slower stimulus rate.

Pure tones (100 dB SPL, 25 ms duration, 3 ms rise/fall times) were presented to the right ear via insert earphones. In 3 subjects (2 MCI) stimuli were presented to the left ear because the right ear had a higher pure tone threshold (> 10 dB). Between 800 and 1000 stimuli were presented at a rate of 2/s, 200 stimuli were delivered at a rate of 1/1.5 s, and 100 stimuli were presented at a rate of 1/3 s. ABRs in response to condensation clicks (100 dB SPL, 11/s, 2000–3000 stimuli presented) were recorded. In all subjects middle- and long-latency potentials were recorded first, followed by ABR testing. Subjects were instructed to keep their eyes open and remain awake during the study, and short rest breaks were provided between blocks.

2.5. Electrophysiological recordings

Subjects were seated inside a sound attenuating, electrically shielded chamber. Three Ag/AgCl recording electrodes (Cz, C3, C4) were placed on the scalp according to the 10/20 system (Jasper, 1958). For middle- and long-latency responses, electrodes placed on the left and right mastoid served as references in a linked mastoid configuration. Electrodes were also placed above and below the left eye to monitor eye movements, and one electrode was placed on the forehead to serve as the ground. Electrode impedances were < 5 kΩ. For middle- and long-latency potentials electrophysiological data (EEG, EOG) were collected continuously, with additional processing and analysis performed off-line. The sample rate for both middle- and long-latency potentials was 2000 Hz, and the EEG was bandpass filtered (1–500 Hz). Middle-latency potentials can be contaminated by post-auricular muscle activity beginning at a latency of ∼ 10–20 ms. Factors such as high stimulus levels and head position influence neck muscle activity (Bickford et al., 1964; O'Beirne and Patuzzi, 1999). To avoid the contamination of evoked potentials by post-auricular muscle activity, the present study used relatively moderate stimulus intensities (100 dB SPL), and subjects reclined on a comfortable chair with their head supported by a pillow. Drowsiness and certain stages of sleep are known to be associated with attenuated amplitudes of middle-latency responses (Deiber et al., 1989; Erwin and Buchwald, 1986; Mendel and Goldstein, 1971). During data collection the EEG and EOG were monitored to ensure that subjects kept their eyes open and there were no indications of drowsiness. An offline eye blink correction algorithm was used to correct for ocular artifacts (Gratton et al., 1983). If the voltage on any electrode site exceeded 75 μV, sweeps were not included in the average. The mean number of sweeps for middle- and long-latency potentials at stimulus presentation rates of 2/s, 1/1.5 s, and 1/3 s were 700, 178 and 92, respectively.

Two channel recordings of ABRs were made using Cz individually referenced to the ipsilateral or contralateral mastoid. Sampling rate of ABRs was 100,000 Hz, and filter settings were 30–3000 Hz. The ABR epoch lasted from −2 to 10 ms, relative to click onset. Sweeps voltages having > 50 μV on either channel were automatically rejected. For 5 subjects (1 MCI), sweeps having amplitudes > 40 μV were rejected.

2.6. Data analysis

The EEG was digitally filtered using FFT and inverse FFT procedures, and filter settings were adjusted depending on the component of interest. Auditory long-latency potentials were filtered from 1 to 30 Hz (12 dB/octave) to attenuate high frequency transients and reveal components with low frequency spectral energy, P50, N100, and P200. For middle-latency potentials two filter settings were used. The first filter settings, 10–200 Hz (12 dB/octave), attenuated slow potentials without affecting transient middle-latency components, Pa, Nb, and P1, and are those recommended for use in evaluating the transient components (Starr and Don, 1988). The second filter settings (1–30 Hz) were identical to those used for the long-latency potentials and attenuated the transient middle-latency components to reveal a slow potential occurring in the same time period as the long-latency P50 component.

Component amplitudes were calculated relative to a baseline period prior to stimulus presentation. For long-latency components the baseline was 100 ms, middle-latency components had a baseline of 20 ms, and ABRs had a baseline of 2 ms. Peak latencies were defined relative to stimulus onset. For long-latency components the P50 was defined as the point of maximum positivity between 25 and 80 ms, the N100 was the maximum negativity between 60 and 130 ms, and the P200 was the maximum positivity from 120 to 245 ms. For middle-latency components the Pa was defined as the maximum positivity between 20 and 45 ms, the Nb was the maximum negativity from 27 to 57 ms, and the P1 was the maximum positivity between 40 and 65 ms. Slow wave amplitudes during middle-latency potentials were analyzed in 4 time windows: 30–34, 35–39, 40–44, and 45–49 ms. The amplitude for each 5 ms window was the mean value of measures at every 0.5 ms. The purpose of using 5 ms time windows was to quantify middle latency slow wave amplitudes occurring during the ascending portion of the long-latency P50 component.

The amplitude and latency of Wave V component in the ABRs were defined at the point of maximum positivity between 5.0 and 6.6 ms.

2.7. Statistical analysis

Group comparisons of audiological measures and neuropsychological tests were made using t-tests. Evoked potential data from the Cz electrode were analyzed using

t-tests or analysis of variance (ANOVA) with Greenhouse–Geisser correction for repeated measures. Two-tailed *P* values <0.05 were considered significant. ANOVA tests for middle- and long-latency components included the factors of group (controls, MCI), stimulus rate (2/s, 1/1.5 s, and 1/3 s, the latter only for long-latency potentials), and 5 ms time window (30–34, 35–39, 40–44, 45–49 ms). A correlation analysis was made for the amplitudes of long-latency P50 component and neuropsychological and demographic data within the MCI group. Analysis of the amplitude and latency of Wave V of the ABRs used *t*-tests to evaluate group differences.

3. Results

3.1. Audiological measures

Pure tone thresholds in controls and MCI showed a mild hearing loss (20–40 dB) at low frequencies and a moderate loss (40–60 dB) at 6 and 8 kHz. The extent of the loss at 6 kHz was significantly greater in MCI (e.g. 8 kHz for MCI = 67.5 dB) than in controls (8 kHz for controls = 47.1 dB). However, hearing thresholds at 1 kHz, the frequency of the tones used for evoked potentials measures, did not differ between the groups (controls = 20.8 dB; MCI = 19.6 dB).

3.2. Neuropsychological tests

Neuropsychological test results are shown in Table 2. There were significant group differences for all episodic memory tests, and the Mini-mental state exam (MMSE) and executive function (Trailmaking Test B), and smaller differences for tests of language (Boston Naming Test) with relative to controls MCI having lower scores.

3.3. Long-latency evoked potentials: P50, N100, P200

The results for 33 subjects tested with two rates of stimulation (2/s, 1/1.5 s) are presented beginning with long-latency potentials followed by middle-latency potentials and then auditory brain-stem responses.

Grand average long-latency potentials from controls and MCI patients at the Cz site are shown in Fig. 1 for the stimulus rates of 2/s (A) and 1/1.5 s (B). Mean amplitude values for P50 (A), N100 (B) and P200 (C) are shown in Fig. 2. Peak amplitudes and latencies of the components were assessed using separate 2 (group) × 2 (stimulus rate) ANOVAs.

Group. There was a significant group effect for P50 amplitude [$F_{(1,31)} = 5.262$; $P < 0.03$], with larger amplitudes in MCI subjects ($n = 16$) than in controls ($n = 17$). Individual P50 amplitudes are shown in Fig. 3. Although there was a single outlier in the MCI group (>3 SD above mean at 2/s and 1/1.5 s), the group effect remained significant after

Table 2
Neuropsychological test results[a]

	Controls	MCI	*P* value (*t*-tests)
n	15	16	
MMSE score[b]	29.3 ± 0.8	27.5 ± 1.7	<0.001
WMS-III logical memory			
Immediate recall	44.4 ± 8.1	24.5 ± 10.4	<0.001
Delayed recall	28.7 ± 6.7	7.7 ± 7.0	<0.001
CERAD word list[c]			
Sum of trials 1–3	24.9 ± 3.4	16.2 ± 4.9	<0.001
5 min delayed recall	8.9 ± 1.2	3.1 ± 2.3	<0.001
30 min delayed recall	7.7 ± 2.7	1.9 ± 2.2	<0.001
5 min delayed recognition	19.9 ± 0.3	17.9 ± 1.9	<0.001
30 min delayed recognition	19.6 ± 0.7	15.6 ± 5.0	<0.005
Boston naming test[d]	28.3 ± 3.0	25.9 ± 3.5	<0.07
CERAD animal naming	20.1 ± 5.9	16.8 ± 6.0	n.s.
FAS verbal fluency	46.3 ± 12.0	45.7 ± 14.6	n.s.
WAIS-III block design[d]	12.1 ± 2.8	12.2 ± 2.9	n.s.
CERAD constructional praxis[d]	10.7 ± 0.5	10.2 ± 1.1	n.s.
Trailmaking test A (s)	35.8 ± 11.2	44.0 ± 22.7	n.s.
Trailmaking test B (s)	86.1 ± 25.2	110.3 ± 33.8	<0.03
Geriatric depression rating scale[d]	1.0 ± 1.1	1.0 ± 1.4	n.s.

n.s., not significant.
[a] Neuropsychological results reported as raw scores except for WAIS-III Block Design that used age-adjusted scaled scores. Neuropsychological test results from one MCI subject were not included because raw scores were not available. Values are means ± SD.
[b] MMSE, mini-mental state examination.
[c] One MCI subject had results only for the sum of the trials 1–3.
[d] One control subject was not tested on tests.

excluding the outlier subject ($P < 0.02$). There were no significant group effects for P50 latency, or N100 and P200 amplitudes or latencies.

Stimulus rate. There were significant main effects of stimulus rate on P50 [$F_{(1,31)} = 7.0$; $P < 0.01$], N100 [$F_{(1,31)} = 166.3$; $P < 0.001$], and P200 [$F_{(1,31)} = 157.5$; $P < 0.001$] amplitudes. For each component, amplitudes
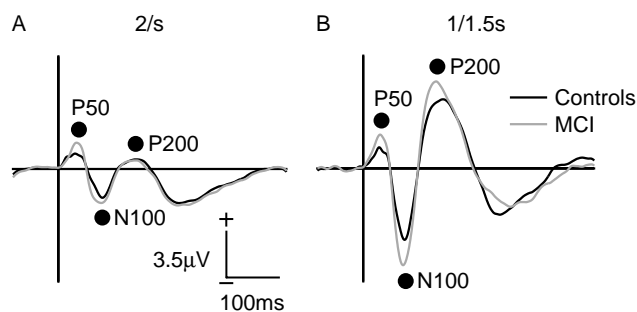

Fig. 1. Grand average long-latency evoked potentials for healthy older controls and MCI (mild cognitive impairment) at the stimulus presentation rates of 2/s (A) and 1/1.5 s (B) at Cz electrode site. Long-latency P50 amplitudes were significantly larger in MCI relative to controls at both stimulus rates. N100 amplitudes were significantly larger in MCI compared to controls at 1/1.5 s but not at 2/s. The changes of P200 amplitudes in the figure were not significantly different between groups. The vertical line indicates stimulus onset, and averaged potentials were bandpass filtered from 1 to 30 Hz. The epoch lasts from −100 to 500 ms relative to tone onset.
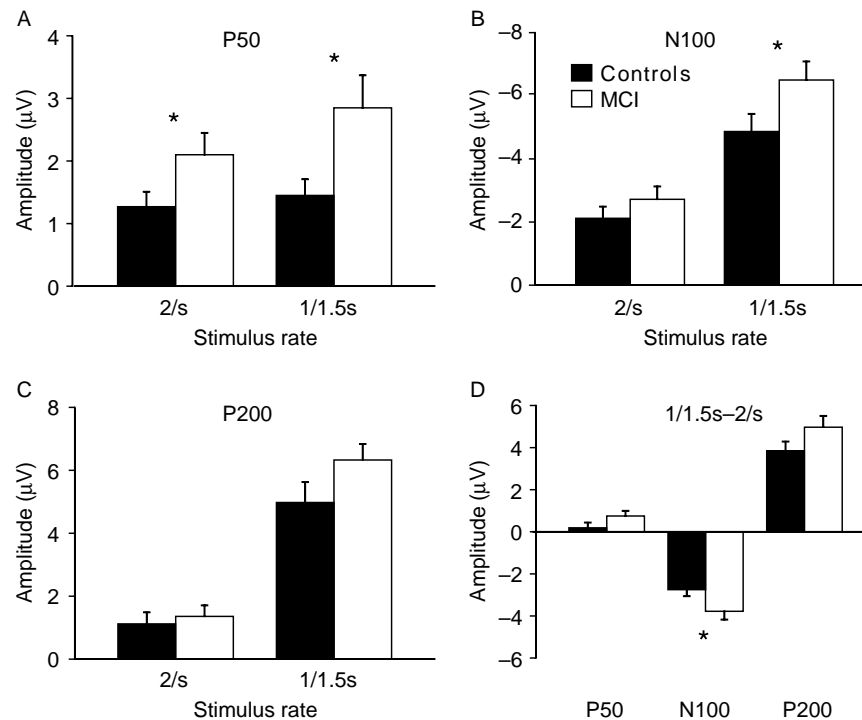
Fig. 2. Mean amplitudes at Cz electrode site (bars), standard errors (vertical lines), and significant effects at $P < 0.05$ (*) of P50 (A), N100 (B), and P200 (C) as a function of stimulus rate for controls and MCI. The effect of stimulus rate for each component (D) was defined by the amplitude difference between 1/1.5 s and 2/s. There were significant effects only for N100 amplitudes.

were larger for the slower stimulus rate (1/1.5 s > 2/s). There were significant main effects of stimulus rate for P50 [$F_{(1,31)} = 5.2$; $P < 0.03$] and N100 [$F_{(1,31)} = 11.8$; $P < 0.002$] latencies, with longer latencies for 2/s relative to 1/1.5 s. There was no significant rate effect for the P200 latency.

Group×stimulus rate. The group×stimulus rate interaction for P50 amplitude was not significant ($P > 0.10$). In contrast, there was significant group×stimulus rate effect for N100 amplitude [$F_{(1,31)} = 4.1$; $P < 0.05$]. Post hoc testing indicated that compared to controls, MCI had larger N100 amplitudes at a rate of 1/1.5 s ($P = 0.05$), but were comparable at a rate of 2/s. The stimulus rate effects for each component are illustrated in Fig. 2(D) by calculating the amplitude difference between stimulus rates of 1/1.5 and 2/s (1/1.5 s–2/s). There were no significant group×stimulus rate effects for P200 amplitude and latency or P50 and N100 latencies.

3.3.1. Long-latency evoked potentials as a function of 3 stimulus presentation rates

A subgroup of the subjects (controls = 10, MCI = 8) received tones at 3 stimulus rates (2/s, 1/1.5 s, 1/3 s). Peak amplitudes and latencies of the components (P50, N100, P200) were assessed using 2 (group)×3 (stimulus rate) ANOVAs.

Group. For P50, the group effect in the subset of subjects given 3 stimulus rates approached significance ($P < 0.07$), with a trend for larger P50 amplitudes in MCI. There were

no significant group effects for P50 latency, or for N100 and P200 amplitudes or latencies.

Stimulus rate. There was no significant main effect of stimulus rate on P50 amplitude. In contrast, there were
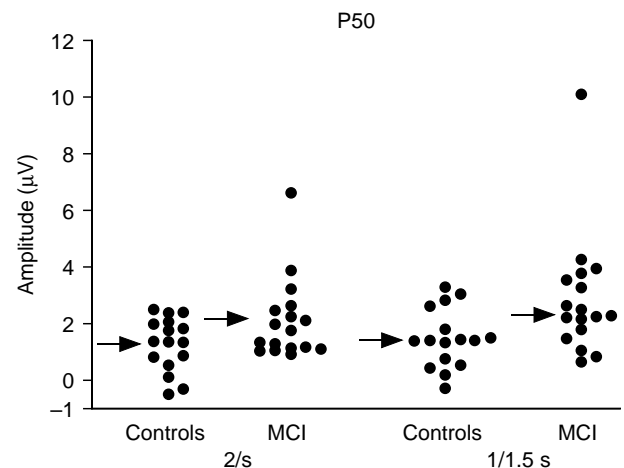

Fig. 3. Long-latency P50 amplitude (filled circles) for individual subjects and their mean (arrows) for control and MCI groups as a function of stimulus rate (2/s, 1/1.5 s). Values derived from the Cz electrode. There was an overall means increase (arrows) in P50 amplitudes for MCI relative to controls. More than half of the MCI subjects (8/15 MCI at 2/s, 11/15 MCI at 1/1.5 s) had P50 amplitudes greater than the mean amplitude of controls at each stimulus rate. There was a single outlier in the MCI group (>3 SD above mean at 2/s and 1/1.5 s). The group effect remained significant even after excluding this outlier.

significant main effects of stimulus rate on N100 [$F_{(2,32)} = 63.9$; $P < 0.001$] and P200 [$F_{(2,32)} = 65.6$; $P < 0.001$] amplitudes, with amplitudes increasing from 2/s to 1/1.5 s, and comparable amplitudes for 1/1.5 s and 1/3 s. For the measurement of latency, there was no significant main effect of rate for P50 component. In contrast, there were significant main effects of rate on N100 [$F_{(2,32)} = 7.4$; $P < 0.008$] and P200 [$F_{(2,32)} = 3.3$; $P < 0.07$] latencies, with significantly longer latencies at the fastest rate (2/s) relative to the slower rates (1/1.5 s, 1/3 s).

Group × stimulus rate. There were no significant group × stimulus rate effects for P50, N100 and P200 amplitudes or latencies.

3.3.2. P50 amplitude in MCI: medication effects

Eight out of 17 MCI subjects took a cholinesterase inhibitor, such as donepezil, at the time of evoked potential testing. To define the effect of donepezil on long-latency P50 amplitude at two stimulus rates, MCI subjects were divided into two groups: MCI without donepezil treatment (MCI-no drug; $n = 9$), and MCI with donepezil treatment (MCI-drug; $n = 8$). Mean amplitude values of P50 component for controls, MCI-no drug and MCI-drug are shown in Fig. 4 for the stimulus rates of 2/s and 1/1.5 s. Peak amplitudes of P50 component were assessed using separate 3 (group) × 2 (stimulus rate) ANOVAs.

Result showed a significant group effect [$F_{(2,30)} = 5.0$; $P < 0.01$]. Post hoc testing indicated significantly larger P50 amplitudes in MCI-no drug compared to controls ($P < 0.01$). There were no significant differences between MCI-drug and controls, or MCI-drug vs. MCI-no drug. Thus, paired

Fig. 4. Mean amplitudes of long-latency P50 component (bars), standard errors (vertical lines), and significant effect at $P < 0.05$ (*) for controls, MCI without donepezil treatment (MCI-no drug) and MCI with donepezil treatment (MCI-drug) at the stimulus presentation rates of 2/s and 1/1.5 s recorded from Cz electrode site. There was a significant group effect among controls, MCI-no drug, and MCI-drug. Post hoc testing showed that MCI-no drug had significantly larger P50 amplitudes compared to controls. There were no significant differences between MCI-drug and controls, or MCI-drug and MCI-no drug.

comparisons between controls and each MCI subgroup suggests that P50 amplitudes may be attenuated following donepezil treatment, but direct comparison between the MCI subgroups did not reveal a significant effect of drug treatment. We note that these results must be viewed as preliminary because of the small number of subjects in each MCI subgroup.

3.3.3. P50 amplitude in MCI with neuropsychological and demographic data

The possibility of significant linear relationship between long-latency P50 amplitudes (the mean P50 amplitudes at 2/1 s and 1/1.5 s rates) and each of neuropsychological and demographic (age, sex and educational level) data within MCI group was examined. Results showed that none of the neuropsychological scores and demographic factors were significantly correlated with the amplitudes of P50 component.

In summary, when P50 amplitude of the entire subject population ($n = 33$) was analyzed, there was a significant increase ($P < 0.03$) in MCI compared to controls at stimulus rates of 2/1 s and 1/1.5 s. Analysis of a subgroup of 18 subjects tested at 3 stimulus rates (2/1 s, 1/1.5 s, 1/3 s) showed P50 amplitudes to be larger in MCI than controls, but the significance was only borderline ($P < 0.07$). We attribute the borderline significance in this latter analysis to the small number of MCI subjects studied ($n = 8$). In support of this possibility a previous study of a larger number of MCI ($n = 15$) with a stimulus rate at 1/2.5 s showed significantly increased amplitudes of long-latency P50 component for MCI compared to controls (Golob et al., 2002). Group differences in N100 amplitudes depended on stimulus rate, with larger amplitudes in MCI at slower presentation rate (1/1.5 s), but comparable amplitudes at the fastest rate (2/s).

3.4. Middle-latency evoked potentials: components (Pa, Nb, P1) and slow wave

Superimposed individual subjects averaged middle-latency potentials (1–200 Hz) are shown in Fig. 5A for controls and MCI, with the grand averaged potentials for each group shown immediately below. The middle-latency domain comprises both transient components indicated by filled circles (Pa at 30 ms; Nb at 40 ms; P1 at 50 ms) superimposed on a slow wave that arises from the baseline at about 20 ms and plateaus between 30 and 50 ms. To measure both the transient middle-latency components and the slow wave we used two filter settings. The individual averages were bandpass filtered at 10–200 Hz to attenuate the slow wave and enhance the middle-latency components (Fig. 5B). Filter settings of 1–30 Hz were used to attenuate the transient components and enhance the slow wave (Fig. 5C).

The variability of peak latency between subjects likely contributes to the dispersed appearance of the components
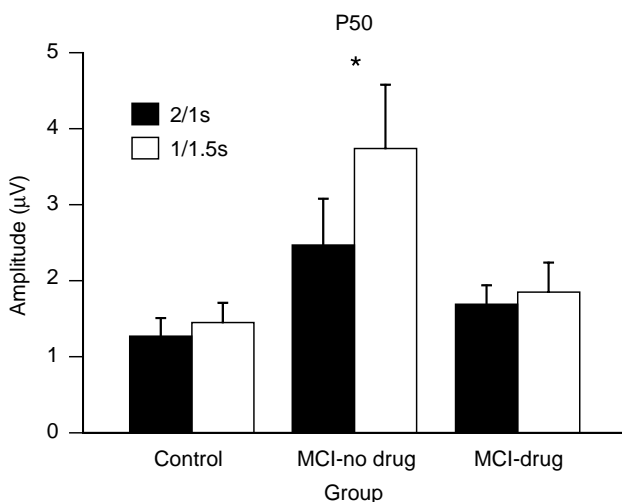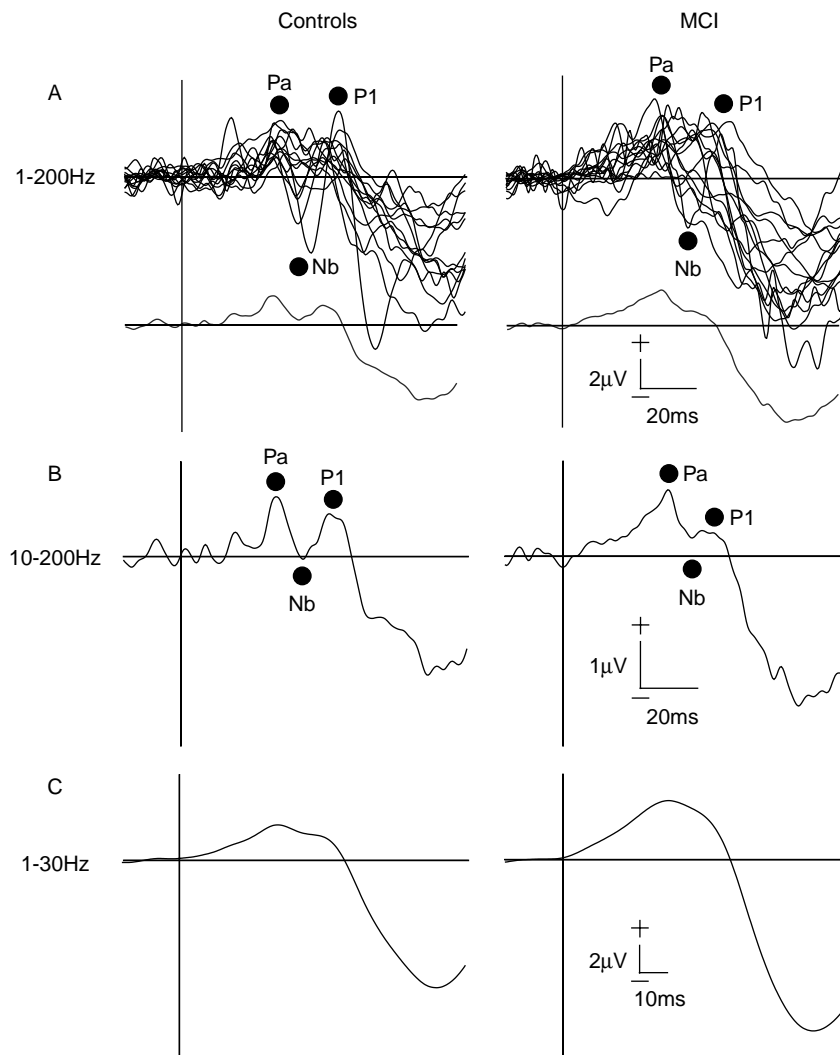
Fig. 5. Middle-latency transient components and middle-latency slow wave for controls (left side) and MCI (right side) recorded at the stimulus rate of 1/1.5 s (Cz electrode site). (A) Superimposed individual averages filtered at 1–200 Hz showed both a slow wave shift between 20 and 60 ms and middle-latency components (Pa, Nb, P1) superimposed on the slow shift. The grand averaged potentials for each group are immediately below. (B) Grand averaged middle-latency potentials when filtered at 10–200 Hz attenuated the slow wave and enhanced the components. The gain is twice that in (A). There were no significant amplitude differences between MCI and controls. (C) Grand averaged middle-latency responses filtered at 1–30 Hz to attenuate the components and enhance the slow wave. The slow wave was significantly larger in MCI than controls.

in the superimposed individual averages shown in Fig. 5A. The slow wave is evident in both the superimposed individual traces as well as in the grand average. Peak amplitudes and latencies of both the slow wave and of the transient middle-latency components were analyzed using 2 (group)×2 (stimulus rate) ANOVAs. There were 5 subjects (2 control and 3 MCI) without all transient components who were not included in the statistical analyses of the components.

3.4.1. Component analysis

Group. There were no significant group effects for Pa, Nb, and P1 amplitudes. The latencies of the transient components did not differ significantly between controls (Pa: 33.6 ± 2.0; Nb: 43.0 ± 4.0; P1: 52.2 ± 4.4) and MCI (Pa: 34.4 ± 5.5; Nb $43.3: \pm 7.3$; P1: 53.0 ± 6.7).

Stimulus rate. There were significant main effects of stimulus rate on the amplitudes of Pa $[F_{(1,26)} = 32.6; P < 0.001]$, Nb $[F_{(1,26)} = 6.4; P < 0.02]$ and P1 $[F_{(1,26)} = 7.1; P < 0.01]$. For each component, amplitudes were larger at rates of 2/s relative to 1/1.5 s. There were no significant rate effects for Pa, Nb, and P1 latencies.

Group×stimulus rate. There were no significant group×stimulus rate effects for Pa, Nb, and P1 amplitudes or latencies (Fig. 6 for mean amplitudes of Pa (A), Nb (B) and P1 (C) at the stimulus rates of 2/s and 1/1.5 s).

3.4.2. Slow wave analysis

The slow wave was analyzed for amplitude changes using a 2 (group)×2 (stimulus rate)×4 (window) ANOVA (Fig. 7 for the stimulus rates of 2/s (A) and 1/1.5 s (B)).
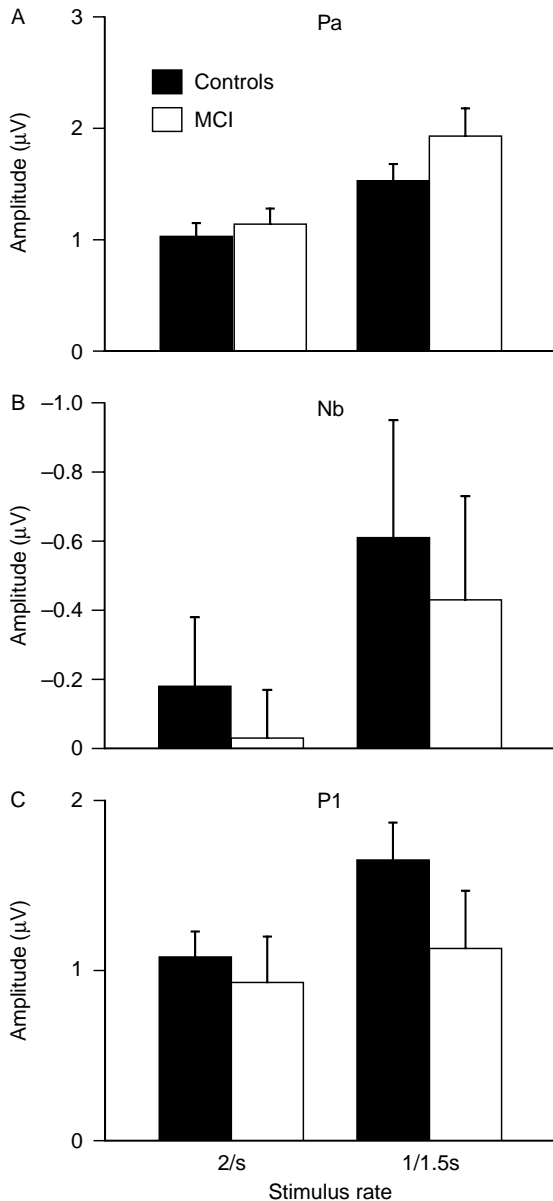
Fig. 6. Mean amplitudes (bars), standard errors (vertical lines) of transient middle-latency components of Pa (A), Nb (B) and P1 (C) as a function of stimulus rate for a subgroup of controls and MCI. There were no significant group effects or group×stimulus rate effects for the component amplitudes.

Follow-up analysis used 2 (group)×2 (stimulus rate) ANOVAs for each time window.

Group. There was a significant group effect [$F_{(1,31)}=4.0$; $P<0.05$], with larger overall amplitudes in MCI compared with controls. Individual ANOVA's at each time window showed significant group effects at 30–34 [$F_{(1,31)}=7.1$; $P<0.01$] and 35–39 [$F_{(1,31)}=6.5$; $P<0.02$] ms. The group effect did not attain significance at 40–44 ms [$F_{(1,31)}=3.3$; $P<0.08$], but there was a trend for larger slow wave amplitudes in MCI than in controls. There was no group effect at the 45–49 ms window.

Stimulus rate. There was a marginally significant effect of stimulus rate [$F_{(1,31)}=3.7$; $P<0.06$], with larger amplitudes

at stimulus rates of 1/1.5 s compared to 2/s. Significant stimulus rate effects were present at 30–34 [$F_{(1,31)}=13.3$; $P<0.001$] and 35–39 [$F_{(1,31)}=6.4$; $P<0.02$] ms.

Interactions. There were no significant group interactions. There was a significant window×rate interaction [$F_{(3,93)}=4.8$; $P<0.03$], indicating a significant effect of stimulus rate between 30 and 39 ms but not between 40 and 49 ms.

3.5. Auditory brain-stem responses (ABRs)

Grand average ABRs are shown in Fig. 8. There was one MCI subject without a clear Wave V who was not included in the analysis. There were no significant group differences in Wave V latency (controls=5.9 ms, MCI=6.0 ms) or amplitude (controls=0.15 μV, MCI=0.19 μV). We cannot exclude that the lack of a significant group difference of Wave V amplitude may be associated with a Type II error.

4. Discussion

The present study showed that relative to elderly controls, MCI subjects had larger long-latency P50 amplitudes during passive listening at all stimulus rates (2/s, 1/1.5 s, 1/3 s), suggesting that the amplitude difference in MCI is not the results of altered auditory cortical recovery functions for the P50 component, but rather a feature of P50 in the group of MCI subjects. Increased long-latency P50 amplitudes in MCI were not due to the effect of donepezil as suggested by the results of post hoc testing. There were no significant correlations between P50 amplitudes and each of neuropsychological and demographic data within MCI. Group differences in N100 amplitude varied as a function of stimulus rate. Post hoc testing indicated significantly larger amplitudes in MCI at slower rate (1/1.5 s), but not at the fastest rate tested (2/s). The time domain of the long-latency P50 overlaps the time of middle-latency potentials (∼30–50 ms). We found that the amplitude of a slow wave portion of the middle-latency response was significantly increased in MCI relative to normal controls, whereas the transient components (Pa, Nb, P1) present at the same time as the slow wave were not different between the groups. Correlations of the amplitudes of long-latency P50 component and middle-latency slow wave were significant ($P=0.0001$) with r values approaching 1.0 (controls=0.95, MCI=0.98). The data support the idea that these two potentials (long-latency P50 and middle-latency slow wave) are in fact a single event displayed on different time bases. There was no evidence that group differences in the middle-latency responses and the long-latency P50 component are due to alterations of ascending auditory inputs as the latency and amplitude of ABR Wave V were comparable between groups. ABR findings in Alzheimer's disease patients have been mixed. Compared with healthy older subjects, some studies report comparable Wave V latencies in Alzheimer's disease patients (Grimes et al., 1987; Kuskowski et al.,
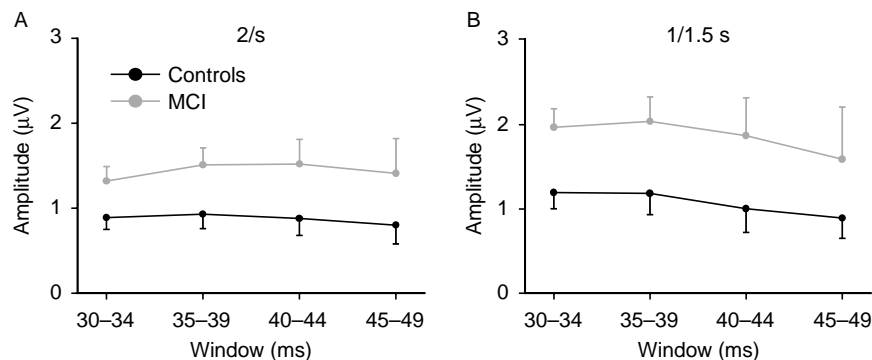
Fig. 7. Mean amplitudes of slow wave (lines), standard errors (vertical lines) in 5 ms windows (30–34, 35–39, 40–44, 45–49) for controls and MCI at the stimulus presentation rates of 2/s (A) and 1/1.5 s (B) recorded from Cz electrode site. There was a significant group effect, with larger overall amplitudes in MCI compared with controls ($P < 0.05$).

1991; Tachibana et al., 1996), but another study indicated prolonged latencies of Wave V in Alzheimer's disease (Harkins, 1981).

4.1. Rate effects of long-latency evoked potentials

Long-latency P50 amplitudes were significantly larger in MCI compared with controls during passive listening at all stimulus rates tested. Large long-latency P50 amplitudes in MCI were also observed in previous studies using both an auditory target detection task (stimulus rate 1/2.5 s) (Golob et al., 2002) and when passively listening to stimulus pairs (600 ms inter-stimulus interval, 9.4 s inter-pair interval) (Golob et al., 2001). Asymptomatic family members of Alzheimer's disease patients, who also have an increased risk of Alzheimer's disease, have significantly larger P50 amplitudes in auditory target detection task (Boutros et al., 1995). The above findings show that, relative to healthy controls, MCI have an overall increase in P50 amplitudes across a range of stimulus rates and task conditions (active or passive listening).

Relative to controls, MCI patients had significantly larger N100 amplitudes at slower stimulus presentation rate (1/1.5 s), but were similar to controls at the fastest rate (2/s). In contrast P50 amplitudes were larger in MCI than controls at both stimulus rates. The differences between the recovery functions of P50 and N100 in MCI may be due to different generator sites in auditory cortex (Liegeois-Chauvel et al., 1994; Onitsuka et al., 2000; Reite et al., 1988; Yoshiura et al., 1995) and/or to changes in connectivity specific to the N100 generator (Chao and Knight, 1998). There were no significant group effects for the P200 component, a result consistent with previous studies (Golob et al., 2001, 2002).

Amplitude increases in MCI are pronounced for the P50, less evident for the N100, and absent for the P200 component. A similar pattern among auditory cortical responses (P50, N100, P200) is present for the time course of refractory effects. P50 long-latency component reaches near maximum amplitude at stimulus rates of 1/8 s (Zouridakis and Boutros, 1992). N100 amplitude

progressively increased as stimulus rate slowed reaching an asymptote at stimulus rates of about 1/10 s (Davis et al., 1966; Naatanen and Picton, 1987; Nelson and Lassman, 1968). The P50 reaches asymptote at faster stimulus rates than longer latency components, such as the N100, which in turn attains asymptotic levels at faster stimulus rates than the P200 (Megela and Teyler, 1979; Roth et al., 1976).

The neural mechanisms underlying the refractory effects remain unclear (Naatanen and Picton, 1987). Single unit recording studies from primary auditory cortex indicate decreased firing rates elicited by stimuli presented at fast relative to slow stimulus rates (Hocherman and Gilat, 1981). A functional MRI study has also defined reduced activation in primary and secondary auditory cortex to the second of a pair of auditory stimuli (Inan et al., 2004).

4.2. Cholinergic transmission and the long-latency P50 component in mild cognitive impairment and Alzheimer's disease

The effect of donepezil on long-latency P50 amplitude revealed a significant group effect among controls,
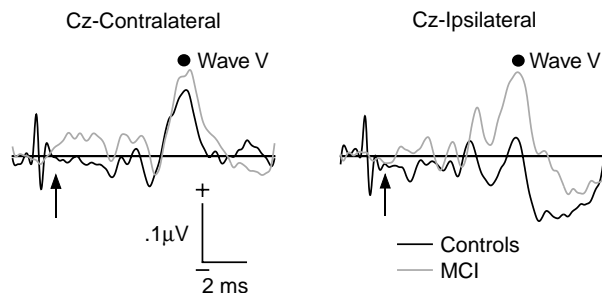

Fig. 8. Grand average ABRs for controls and MCI at Cz referenced to the ipsilateral and contralateral mastoid (30–3000 Hz bandpass filter) to condensation 0.1 ms duration 'clicks' at 100 dB peak SPL. Wave V latency and amplitude were not significantly different between groups. Arrows indicate the time of arrival of the acoustic stimulus at the tympanic membrane. The artifact of the stimulus voltage applied to the earphone was evident 0.85 ms before the arrow. The epoch lasts from −2 to 10 ms relative to sound onset.

MCI-drug, and MCI-no drug. Post hoc testing showed that MCI-no drug had significantly larger P50 amplitudes relative to controls. There were no significant P50 amplitude differences between MCI-drug and controls. However, there were also no significant differences between the MCI subgroups (MCI-no drug vs. MCI-drug), as would be expected if donepezil treatment reduced P50 amplitudes in MCI. We conclude that there are some indications that P50 amplitudes may be attenuated following donepezil treatment, but the effects of donepezil on P50 amplitudes in MCI need to be further investigated given the mixed results, which are likely due to the small number of subjects in the MCI subgroups.

Previous studies have shown that acetylcholine can modulate the activity of auditory cortex (Buchwald et al., 1991; Metherate, 2004). There is also an increase in cholinergic enzyme activity in certain cortical regions in MCI (Dekosky et al., 2002). Thus, changes in the cholinergic system may be associated with the modulation of auditory cortical activities in MCI and Alzheimer's disease. Relative to controls, MCI has larger P50 amplitudes (Golob et al., 2002). In mild Alzheimer's disease P50 is reduced in amplitude compared to MCI, but still remains larger than in controls (Golob and Starr, 2000). In moderate Alzheimer's disease, the P50 component diminishes further in amplitude and is not significantly different from controls (Fein et al., 1994; Pekkonen et al., 1999). Cholinergic and other transmitter systems are likely to be involved in affecting this sequence of activity change in the auditory cortex during the progression from MCI to dementia.

4.3. Neuropsychological data and the amplitude of long-latency P50 component in mild cognitive impairment

The absence of significant correlations between long-latency P50 amplitude and neuropsychological data within MCI may be due to a relatively small number of MCI subjects ($n = 17$) and restricted range of the data for the analysis of correlations. Alternatively there may be no direct relationship between P50 amplitude and neuropsychological measures but rather, the changes in P50 amplitude in MCI reflect alterations in other cortical regions, e.g. frontal lobes, that are intimately, but not equally involved in both cognitive and sensory functions.

4.4. Middle-latency evoked potentials in normal aging and mild cognitive impairment

Prior studies have noted increased amplitude of middle-latency potentials during normal aging (Amenedo and Diaz, 1998; Chambers, 1992; Chambers and Griffiths, 1991; Woods and Clayworth, 1986). Chambers (1992) considered that this increase reflected both an absolute amplitude increase of Pa, Nb and P1 components and an overall 'positive baseline shift'. The increase of potentials occurring around 50 ms (referred to also as P1) in normal aging was commented upon by Pfefferbaum et al. (1979) and has been found to be further enhanced in MCI (Golob et al., 2002). In the present study, the increase of this early long-latency P50 component is attributable to changes of a slow wave appearing between 20 and 50 ms of the middle-latency potentials and not to the short duration components (Pa, Nb, P1) that arise from the slow wave.

The dissociation in MCI between the amplitude changes of middle-latency slow wave and the middle-latency transient components suggest their origins derive from different generators. A similar pattern of slow and fast components is also evident in ABRs in which the transient components reflect discharges of nerve fibers at different levels of the brain-stem auditory pathway that are superimposed on a slow potential shift peaking at the time of Wave V (Achor and Starr, 1980; Suzuki et al., 1986). The generators of the slow potential comprising the ABR have been suggested as reflecting volume conduction of field potentials arising in neurons of the brain-stem and inferior colliculus rather than from nerve fibers (Moller and Jannetta, 1983). We suggest that the differential change in MCI subjects of middle-latency slow wave peaking at the time of P1 without changes in the transient components (Pa, Nb) are consistent with their origins from two different generator processes. The early transient components (Pa, Nb) of the middle-latency potentials could reflect activity of ascending thalamic projections to auditory cortex (Woods et al., 1987) that would appear to be unaffected in MCI. In contrast, the large slow wave amplitudes of the middle-latency potentials in MCI could reflect enhanced field potentials of auditory cortical neurons in response to afferent input and may characterize changes in brain function in MCI. Further studies of auditory middle-latency slow wave may provide insights into cortical mechanisms affected in MCI.

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