

Auditory event-related potentials during target detection are abnormal in mild cognitive impairment

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Abstract

Objective: To define brain activity and behavioral changes in mild cognitive impairment (MCI), an isolated memory deficit in the elderly that is a major risk factor for Alzheimer's disease.

Methods: Brain potentials and reaction time were examined in elderly controls ($n = 12$) and MCI ($n = 15$) using a target detection paradigm. Subjects listened to a sequence of tones and responded to high-pitched target tones ($P = 0.20$) that were randomly mixed with low-pitched tones ($P = 0.80$). Measures were a pre-stimulus readiness potential (RP), post-stimulus potentials (P50, N100, P200, N200, P300), and reaction time.

Results: Accuracy was equivalent between groups, but there was a trend for longer reaction times in MCI ($P = 0.08$). Two potentials differed between groups: (1) P50 amplitude and latency were significantly increased in MCI, and (2) P300 latency was significantly longer in MCI. Results from two MCI subjects that converted to Alzheimer's disease are also discussed.

Conclusions: Brain potentials in MCI subjects during target detection have certain features similar to healthy aging (RP, N100, P200, N200), and other features similar to Alzheimer's disease (delayed P300 latency, slower reaction time). P50 differences in MCI may reflect pathophysiological changes in the modulation of auditory cortex by association cortical regions having neuropathological changes in early Alzheimer's disease. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Alzheimer's disease; Age associated memory impairment; P50; P1; P300

1. Introduction

Mild cognitive impairment (MCI) is a clinical condition that characterizes elderly individuals with an episodic memory impairment that is more severe than in normal aging, while other cognitive functions are relatively normal (Petersen et al., 1999; Ritchie and Touchon, 2000; reviewed in Collie and Maruff, 2000). MCI has been shown to be an important risk factor for Alzheimer's disease (Smith et al., 1996; Petersen et al., 1999; Celsis, 2000). The conversion rate (i.e. percentage of MCI patients who subsequently decline to meet the criteria for Alzheimer's disease) is estimated at about 12% per year, which is approximately a 6-fold increased risk of Alzheimer's disease as compared to elderly subjects without memory impairments (Petersen et al., 1999). Neuropsychological testing also suggests that group differences with controls are greatest in tests of episodic memory, with lesser declines or no significant group

differences in other tests (Berent et al., 1999; Petersen et al., 1999).

Alzheimer's disease has a long preclinical period, lasting years to decades, when β -amyloid plaques and neurofibrillary tangles accumulate in the brain without appreciable clinical abnormalities (Morrison and Hof, 1997; Celsis, 2000; Elias et al., 2000; Small et al., 2000). The long preclinical period of Alzheimer's disease coupled with the observation that many MCI patients convert to Alzheimer's disease within a few years implies that many MCI patients have neuropathology similar to Alzheimer's disease. Consistent with this notion, Price and Morris, 1999 described extensive β -amyloid plaques in both nondemented and mildly demented subjects. A recent study also reported that MCI subjects had neuropathological findings characteristic of Alzheimer's disease (Morris et al., 2001).

The neurobiological changes associated with MCI, and their significance for psychological functioning, are poorly understood. To address this issue a target detection task was employed that has previously been shown to reveal abnormalities in brain activity, measured via event-related potentials, and reaction time in subjects with Alzheimer's disease

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(e.g. Polich, 1998; Polich and Herbst, 2000). It was hypothesized that similar changes may be present in MCI but to a lesser degree.

In the auditory target detection paradigm subjects press a button to infrequent (high-pitch) target tones that are embedded within a sequence of standard (low-pitch) tones (Sutton et al., 1965). Event-related potentials are recorded in response to each stimulus. Relative to age-matched controls, subjects with Alzheimer's disease have slower reaction times, and both smaller amplitudes and longer latencies for a brain potential associated with stimulus classification (P300) (e.g. Goodin et al., 1978; Polich et al., 1990; Williams et al., 1991; Golob and Starr, 2000). In addition, mild Alzheimer's disease patients are reported to have an attenuated prestimulus readiness potential (RP) and a small increase in the amplitude of an early stimulus-evoked potential (P50) (Golob and Starr, 2000).

The purpose of this study was to determine if there are behavioral and event-related potential differences between MCI subjects and controls during target detection. Reaction time, RP, P50 and P300 components were of particular interest because these measures are abnormal in Alzheimer's disease.

2. Methods

2.1. Subjects

Twelve healthy elderly controls and 15 MCI subjects were recruited through the UC Irvine Alzheimer's Disease Research Center (ADRC). Demographic information is presented in Table 1. There were no significant differences between controls and MCI subjects in age or educational level. Control subjects were selected from the UC Irvine Successful Aging program, which includes annual neuropsychological testing. All control subjects scored within the normal range on all tests from the standard neuropsychological battery (see Table 2). Eleven out of 15 MCI subjects were recruited from the UC Irvine ADRC clinic. Four out of 15 MCI subjects were participating in the national Alzheimer's Disease Cooperative Study (ADCS) Mild Cognitive Impairment trial. In the ADRC clinic, a diagnosis of MCI was made using neurological and neuropsychological exam-

Table 1
Demographic information^a

	Controls	MCI
<i>n</i>	12	15
Age	72.8 ± 7.8	76.5 ± 2.7
Education	16.7 ± 2.5	16.1 ± 2.4
M/F	3/9	11/4
MMSE	29.2 ± 0.8	27.7 ± 1.9*

^a Values are mean ± SD. **P* < 0.05 (*t* test). MMSE, Mini-Mental State Examination.

Table 2
Neuropsychological test results^a

	Controls	MCI	<i>P</i> value (<i>t</i> tests)
<i>n</i>	12	11	–
CERAD Word List			
Sum of trials 1–3	23.7 ± 3.4	17.3 ± 4.3	< 0.001
5 min delay	8.3 ± 1.2	2.8 ± 1.9	< 0.0001
30 min delay	8.3 ± 1.1	1.7 ± 1.8	< 0.0001
5 min recognition	19.8 ± 0.5	17.4 ± 1.7	< 0.001
30 min recognition	19.9 ± 0.3	16.2 ± 2.3	< 0.0001
WMS-III logical memory ^b			
Immediate recall	47.4 ± 11.1	30.1 ± 14.9	< 0.01
Delayed recall	28.8 ± 8.3	11.3 ± 10.8	< 0.001
Boston Naming Test ^c	28.7 ± 1.3	24.9 ± 3.6	< 0.01
Animal Fluency	24.3 ± 5.6	17.5 ± 3.6	< 0.01
FAS Verbal Fluency ^d	53.6 ± 11.1	45.5 ± 13.5	0.15
CERAD Constructional Praxis	11.0 ± 0.0	10.4 ± 1.0	< 0.05
WAIS-III Block Design ^e	12.2 ± 1.9	12.9 ± 2.5	0.47
Trailmaking test A (s)	34.8 ± 10.0	32.3 ± 9.3	0.52
Trailmaking test B (s)	83.3 ± 21.7	88.4 ± 27.3	0.62

^a Neuropsychological results from MCI subjects (*n* = 11) presented above were a subgroup of all MCI subjects (*n* = 15) that were given the standard test battery. Values are mean ± SD.

^b Raw scores reported; 3 controls did not receive, and one MCI subject refused to complete, the WMS-III Logical Memory subtest.

^c 30-item version of the Boston Naming Test.

^d Two controls did not complete FAS Verbal Fluency.

^e Age-adjusted scaled scores; two controls did not complete the WAIS-III Block Design.

inations, routine blood analysis, family interviews, and neuroimaging (e.g. magnetic resonance imaging). The remaining 4 subjects were diagnosed with MCI as part of the ADCS Mild Cognitive Impairment trial. Diagnosis of MCI was based on the criteria of Smith et al. (1996). MCI subjects exhibited moderate to severe deficits in episodic memory without similar impairments on other neuropsychological tests. MCI subjects were not impaired in activities of daily living. Four of the MCI subjects were taking donepezil for their memory complaints at the time of testing, and 4 other MCI subjects were part of the double blind study using donepezil.

The electrophysiological study was performed a mean of 130 days from the time of neuropsychological testing (range 0–10 months). All subjects signed informed consent forms, and the experiments were performed in accordance with a protocol approved by the UC Irvine Institutional Review Board.

2.2. Neuropsychological data

A subset of archival data from a neuropsychological battery was selected to profile multiple cognitive abilities in controls and 11/15 MCI subjects. Episodic memory was assessed using the WMS-III Logical Memory subtest (Wechsler, 1997) and the CERAD Word List Learning Task (Morris et al., 1989). Language tests included the 30-item version of the Boston Naming Test (Kaplan et al.,

1983), CERAD Animal Naming (Morris et al., 1989), and Controlled Oral Word Association (FAS Fluency) (Spreen and Benton, 1977). Executive function was tested with the Trailmaking test A and B (Reitan, 1958). Visual-spatial skills were evaluated with the WAIS-III Block Design test (Wechsler, 1981) and the CERAD Constructional Praxis test (Morris et al., 1989). The Mini-Mental State Examination (Folstein et al., 1975) was used as a screening test for dementia.

The remaining 4 MCI subjects, recruited from an ongoing ADCS clinical trial, were also given a battery of neuropsychological test assessing episodic memory, language, and executive function as part of the clinical trial. The neuropsychological test battery administered to the 4 MCI subjects from the ADCS study was different from the battery given to all of the controls and 11 of the MCI subjects. The neuropsychological results from these 4 MCI subjects were not included in the analysis below.

2.3. Behavioral paradigm

The target detection task was a two-tone discrimination, or ‘oddball’, paradigm containing a sequence of 300 tones with a constant inter-stimulus interval of 2.5 s. Tones were presented from two speakers placed ~ 0.75 m in front of the subject at ~ 70 dB peak SPL, as measured from a sound level meter placed where the subject sat. The stimuli were 100 ms in duration (5 ms rise and fall times). Frequent stimuli were 1000 Hz pure tones delivered with a probability of .80 (240 tones/sequence). Target tones were 2000 Hz pure tones presented with a probability of .20 (60 tones/sequence). Subjects were instructed to listen to the tones and quickly, but accurately, press a response button with the thumb of their dominant hand in response to targets. The sequence of tones was randomly determined with the exception that two targets were never presented in a row. Subjects reported they could clearly detect the auditory stimuli, and all performed the task accurately (see Section 3).

2.4. Electrophysiological recordings

Subjects were seated inside a sound attenuating, electrically shielded chamber. For most subjects 8 Ag/AgCl recording electrodes (Fz, Cz, Pz, Oz, C3, C4, T3, T4) were placed on the scalp according to the 10–20 system (Jasper, 1958). In 5 subjects (4 MCI, one control) electrodes were placed at 10 sites (Fz, Cz, Pz, Oz, F3, C3, P3, F4, C4, P4). Electrode impedances were < 5 k Ω . Two electrodes were placed above and below the left eye to monitor eye movements, and one electrode was placed on the forehead to serve as the ground. Electrodes placed on the left and right mastoid served as references in a linked mastoid configuration. The EEG and EOG were digitally amplified with a bandpass of DC–100 Hz and a digitization rate of 500 Hz. Electrophysiological (EEG, EOG) and behavioral data were collected continuously, with additional processing and analysis performed off-line. First, an eyeblink correction

algorithm was used to correct for artifacts (Gratton et al., 1983). Individual sweeps were then sorted and averaged according to stimulus type (frequent or target). Sweeps to target stimuli were visually inspected for artifacts before being accepted into the average. Sweeps to frequent tones and the combined frequent and target tone average used to measure the prestimulus RP were automatically rejected if the voltage on any electrode site exceeded 75 μ V.

2.5. Data analysis

Reaction time was calculated relative to stimulus onset. Accuracy was measured as the percent of correct responses to target tones (out of 60), and the number of button presses in response to frequent tones during the sequence (false alarms). Median reaction times were calculated for each subject, in order to minimize the influence of any outlier reaction times.

Reaction time was also analyzed as a function of the number of frequent tones occurring before each target because a previous study reported differences between subjects with mild Alzheimer’s disease and healthy controls (Golob and Starr, 2000). Three sub-averages of reaction times were compiled for targets preceded by: 1 or 2 frequent, 3 or 4 frequent, and 5 through 9 frequent in a row.

The EEG was digitally filtered using FFT and inverse FFT procedures, and filter settings were adjusted depending on the component of interest. The EEG was lowpass filtered (DC–3 Hz, 12 dB/octave) when measuring the RP. For P50, N100, P200, N200, and P300 components the EEG was bandpass filtered (0.1–16 Hz, 12 dB/octave).

Amplitude of the RP was quantified using a window measurement of the mean potential between -600 and 0 ms relative to stimulus presentation. The baseline period for RP amplitude measures was -1000 to -900 ms. Because the RP occurs before stimulus presentation, frequent and target sweeps were combined into one average.

Peak latencies of components were calculated relative to stimulus onset. Amplitudes of components following stimulus presentation (P50, N100, P200, N200, P300) were defined relative to a 100 ms baseline period immediately before stimulus presentation. For frequent and target tones the P50, N100, P200 components were measured. In addition, the 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 was the maximum positivity between 150 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 250 and 600 ms.

2.6. Statistical analysis

Evoked potentials and behavioral data were analyzed using *t* tests or analysis of variance (ANOVA). When appropriate, the Greenhouse-Geisser correction was applied to control type I error for within subject effects. When the Greenhouse-Geisser correction was utilized the adjusted *P* values were reported. Two-tailed differences of $P < 0.05$ were considered significant.

Analysis included the factors of Group (elderly controls, MCI), Stimulus Type (frequent, target) and Electrode Site (Fz, Cz, Pz, C3, C4). For the overall comparisons P50, N100, P200, and N200 measures were taken from the Cz site, and P300 measures were taken from the Pz site. Topographic analyses were conducted using the Fz, Cz, Pz, C3, and C4 sites.

Reaction times to targets were subdivided into 3 categories as a function of the number of frequent tones presented after the last target, but before the current target (Stimulus Sequence factor: 1 or 2 frequent, 3 or 4 frequent, 5–9 frequent before target).

3. Results

3.1. Neuropsychological testing

On the Mini-Mental State Exam MCI subjects scored significantly lower than controls ($t(24) = -1.4$, $P < 0.05$) (see Table 1). All MCI subjects scored ≥ 24 , out of 30 possible points, on the Mini-Mental State Exam. Results

from the most recent neuropsychological testing, relative to the experimental session, are shown in Table 2. The MCI group had significantly lower scores on all memory tests relative to controls (CERAD Word List, WMS-III Logical Memory). There were also significant differences between MCI and controls on two tests of language (Boston Naming Test and animal fluency). One test of visual-spatial function (CERAD constructional praxis task) also differed significantly between groups, although there was a ceiling effect in controls (11/11 controls had perfect scores). The groups did not differ on the tests of executive function and FAS verbal fluency. Overall, individual MCI subjects performed within 2 standard deviations from standard published means on all non-memory tasks, with the exception of one subject who performed in the severe impairment range on the Boston Naming Test. All controls performed within the normal range on all tests.

3.2. Target detection task: behavior

There were no significant group differences for accuracy ($98.8 \pm 0.5\%$ controls, $98.7 \pm 0.5\%$ MCI) or false alarms (0.3/sequence controls, 0.9/sequence MCI).

Mean group reaction times as a function of the number of frequent tones preceding target tones (stimulus sequence) are shown in Fig. 1A. The group difference in reaction time did not attain statistical significance ($P = 0.08$, see Table 3). Median reaction times of individual subjects are shown in Fig. 1B to illustrate the overlap between groups. Although there was a mean difference of ~ 55 ms between groups, the wide range of MCI values and a single outlier in

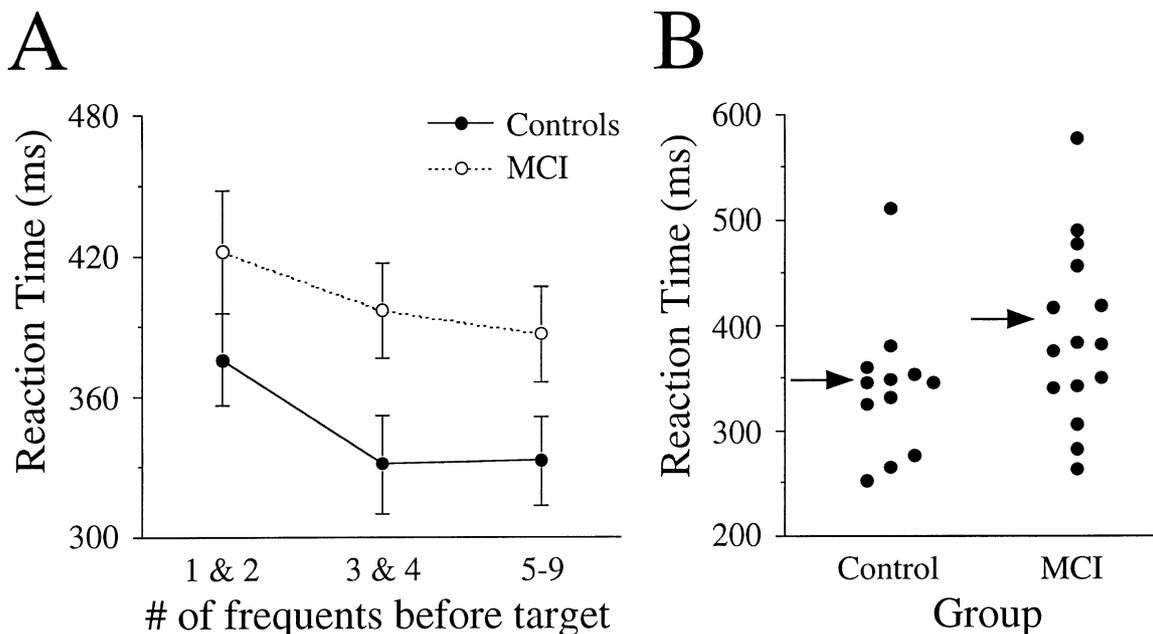


Fig. 1. Reaction time in MCI and control groups. (A) Reaction time to targets as a function of the number of frequent tones in a row before the target. Both groups had faster reaction times when ≥ 3 frequent tones preceded targets, relative to 1 or 2 frequent tones before a target. (B) Mean reaction times of individual subjects in MCI and controls. Group differences in mean reaction time did not attain significance ($P = 0.08$) due to a single control subject with a prolonged reaction time (513 ms).

Table 3
Event-related potential amplitudes and latencies: Frequent and Target tones^a

Component		Amplitude (μV)		Latency (ms)	
		Frequents	Targets	Frequents	Targets
P50 ^{b,c,d}	Control	3.0 \pm 0.5	2.1 \pm 0.6	46.8 \pm 1.6	48.6 \pm 2.3
	MCI	5.4 \pm 0.5	4.1 \pm 0.5	54.2 \pm 1.4	57.6 \pm 2.1
N100 ^c	Control	- 8.9 \pm 0.7	7.8 \pm 0.8	106.3 \pm 2.0	108.4 \pm 2.9
	MCI	- 10.7 \pm 0.7	- 9.0 \pm 0.7	111.2 \pm 1.8	113.8 \pm 2.6
P200 ^e	Control	4.9 \pm 0.6	4.4 \pm 1.2	207.0 \pm 9.3	181.1 \pm 6.7
	MCI	6.2 \pm 0.6	5.3 \pm 1.1	212.5 \pm 8.4	191.9 \pm 6.0
N200	Control	N/A	- 2.8 \pm 1.0	N/A	244.3 \pm 10.7
	MCI	N/A	- 2.7 \pm 0.9	N/A	261.2 \pm 9.6
P300 ^f	Control	N/A	8.2 \pm 1.2	N/A	372.2 \pm 14.8
	MCI	N/A	7.2 \pm 1.1	N/A	416.0 \pm 13.2
RP amplitude ^g	Control	- 1.5 \pm 0.5	-	N/A	-
	MCI	- 1.3 \pm 0.3	-	N/A	-
Reaction time	Control	346.3 \pm 22.2			
	MCI	401.6 \pm 19.8			

^a N/A, not applicable. All component measures from Cz site except P300 (Pz).

^b Amplitude-Group: $P < 0.01$.

^c Amplitude-Stimulus type: $P < 0.01$.

^d Latency-Group: $P < 0.01$.

^e Latency-Stimulus type: $P < 0.01$.

^f Latency-Group: $P < 0.05$.

^g Frequents and targets combined.

the control group (2.5 SD above mean) precluded a significant group difference in reaction time. Analysis excluding the single control outlier showed a significant group effect ($F(1, 24) = 6.5$; $P < 0.02$). There was a significant main effect for stimulus sequence ($F(2, 50) = 20.1$; $P < 0.0001$), however, the group \times stimulus sequence interaction was not significant.

These results indicate that reaction time is somewhat slowed in MCI, but stimulus sequence effects are normal. In contrast, subjects with mild Alzheimer's disease perform-

ing the same task had significantly slower mean reaction times and an abnormal pattern of reaction time as a function of stimulus sequence (Golob and Starr, 2000).

3.3. Target detection: grand averages of evoked potentials to frequent and target stimuli

Grand average event-related potentials for both groups are shown in Fig. 2 for frequent (A) and target (B) stimuli at the Cz electrode site. A negative slow potential, the RP,

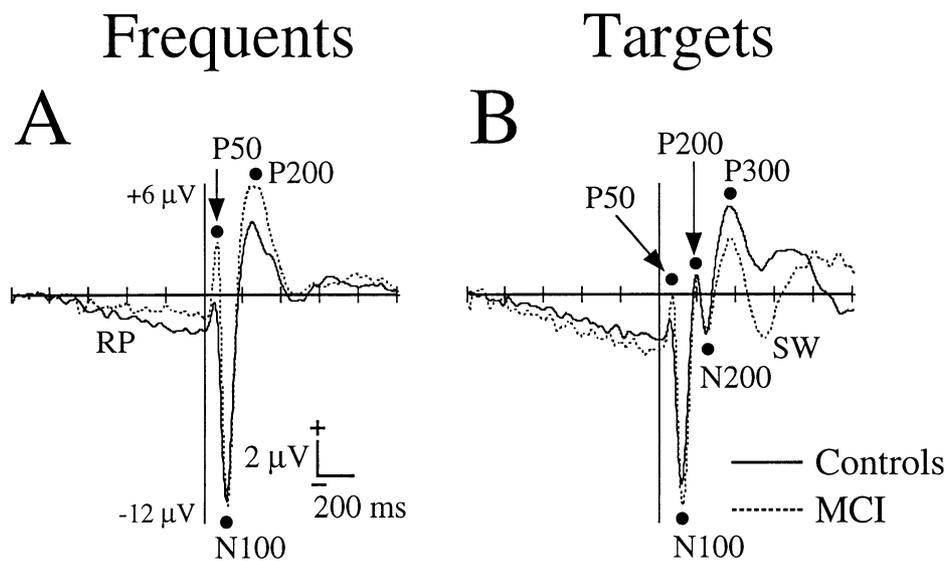


Fig. 2. Grand average potentials for MCI and control groups to frequent (A) and target (B) tones at the Cz electrode site. Significant group differences were observed for P50 amplitude and latency, and P300 latency. Two second epochs are shown (1 s before to 1 s after stimulus onset), and potentials were lowpass filtered (DC–16 Hz).

was present before stimulus presentation in both groups. Frequent tones elicited P50, N100 and P200 components, while target tones elicited an additional N200/P300 complex followed by a negative-going slow wave. Mean amplitude and latency data for all components are presented in Table 3.

3.3.1. Group differences (controls/MCI)

P50 amplitudes were significantly different between groups ($F(1, 25) = 10.6$; $P < 0.01$). Grand average potentials at midline sites are shown in Fig. 3. P50 amplitudes to frequent tones for individual subjects are depicted in Fig. 4A. Note that P50 amplitudes in 13/15 MCI subjects were greater than the mean amplitude of control subjects.

P50 latencies were also significantly different between

groups ($F(1, 25) = 13.0$; $P < 0.001$). Individual P50 latencies are shown in Fig. 4B. Although there was greater overlap between groups than was observed for P50 amplitude, separation between the groups is apparent. There was also a significant positive correlation between P50 amplitude and latency ($r = 0.62$, $P < 0.001$; $n = 27$, frequent tones). In both groups small P50 amplitudes tended to have short latencies, and large P50 amplitudes tended to have long latencies.

Controls appeared to have a bimodal distribution of P50 amplitude and latency values. Five out of 12 control subjects had values of P50 amplitude, latency, or both that were > 2 SD lower than the MCI group. The remaining 7 control subjects had P50 amplitude and/or latency values comparable to the lower portion of the MCI group.

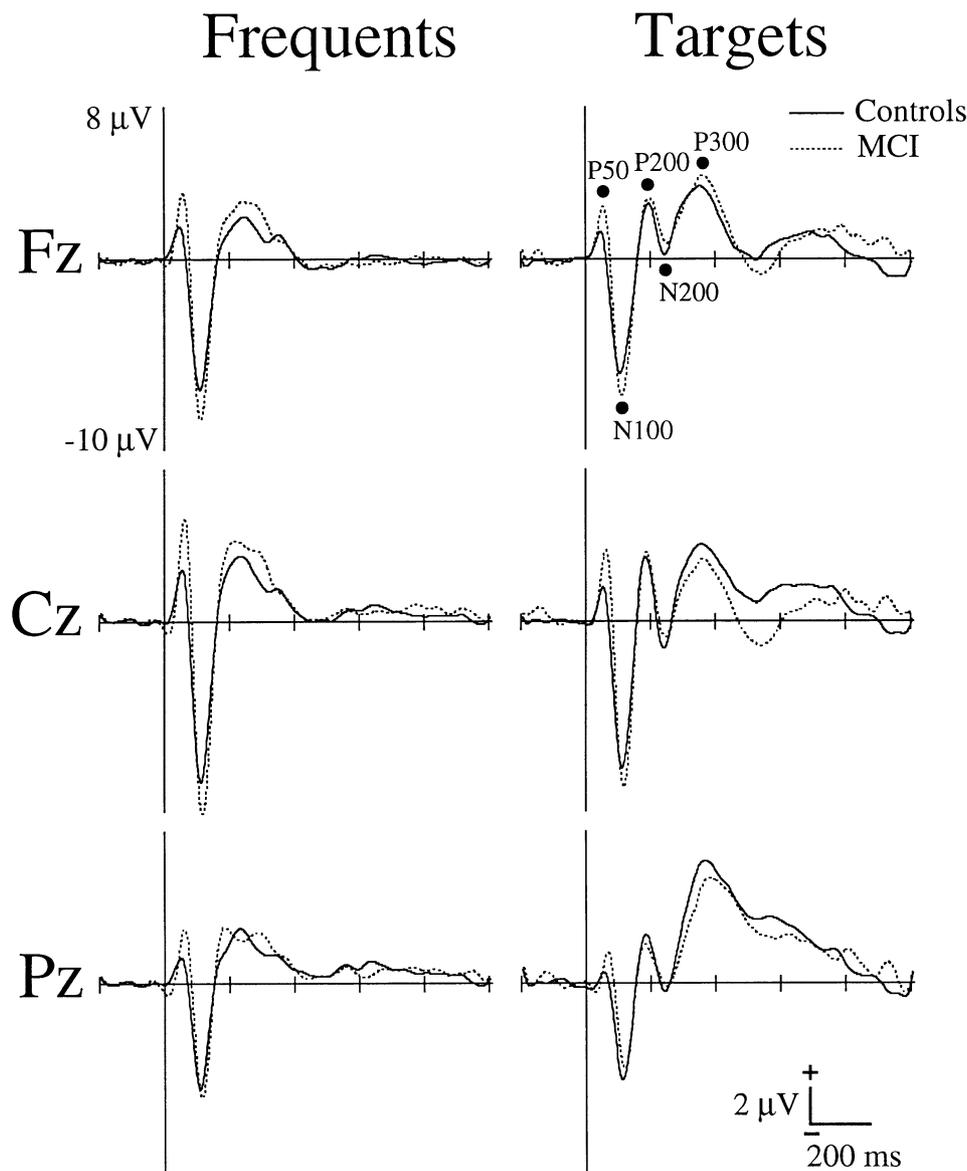


Fig. 3. Grand average potentials in MCI and controls across midline electrode sites (Fz, Cz, Pz). Larger P50 amplitudes and longer P50 latencies are evident in MCI, relative to controls, at all sites for frequent and target tones. P300 amplitude and latency to targets in MCI is comparable to controls at the Fz site, but latency increases in MCI are seen at the Pz site. Averages were bandpass filtered (0.1–16 Hz).

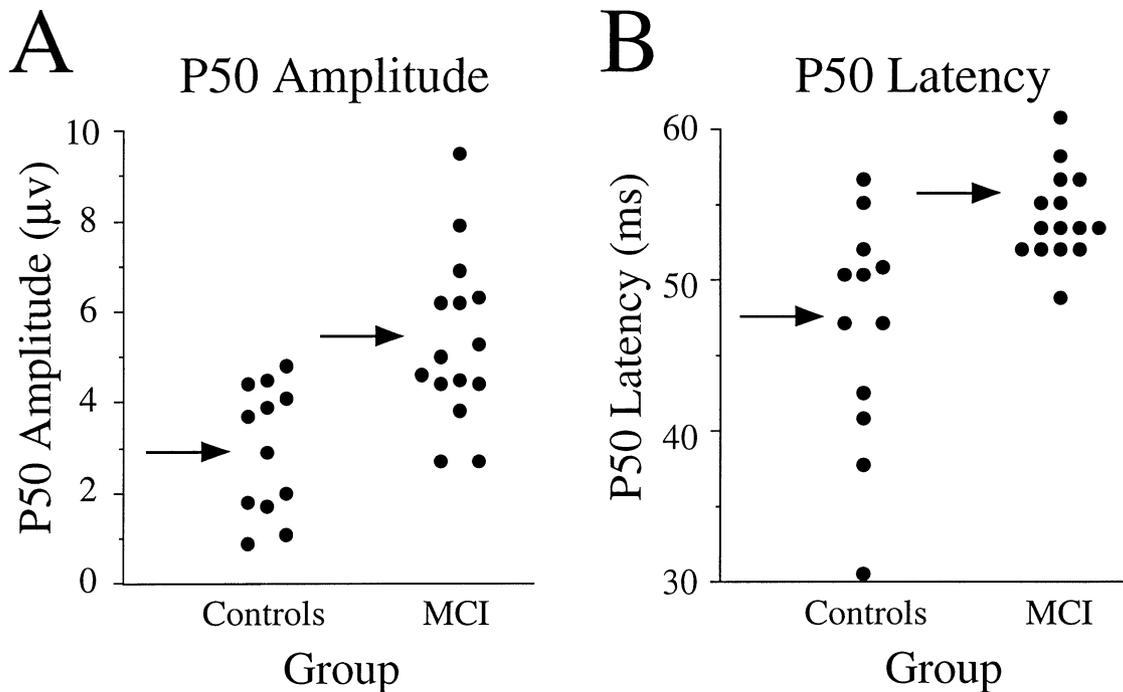


Fig. 4. Plots of P50 amplitude (A) and latency (B) for individual subjects in MCI and control groups. For most MCI subjects both P50 amplitude and latency were above control group mean. P50 amplitudes and latencies in controls did not appear to be normally distributed. Instead, a subgroup of controls had P50 amplitude and/or latency values in the lower range of the MCI group.

P300 amplitudes were not significantly different between groups at the Pz site, and there were no significant topographic differences across midline sites (Fz, Cz, Pz) (see Fig. 3).

P300 latencies were significantly different between groups at the Pz site ($F(1, 25) = 4.9$; $P < 0.04$), with MCI subjects having a delay of ~ 30 ms compared with controls. When midline sites were analyzed (Fz, Cz, Pz) there was a significant latency difference across sites ($F(2, 50) = 31.0$; $P < 0.001$), with the Fz site having shorter P300 latencies than Cz and Pz. The group \times site interaction was not significant.

There were no significant group differences in the amplitude of the RP, N100, P200, or N200 components. Although mean N100 amplitudes were larger in MCI, there was substantial overlap between groups. For the RP there were no significant topographic differences across midline (Fz, Cz, Pz) or lateral sites (C3, C4) between groups. There were no significant group effects for N100, P200, or N200 latencies.

3.3.2. Stimulus type (frequent/target)

Stimulus type was analyzed for the P50, N100, and P200 components. There were significant overall amplitude differences for the P50 ($F(1, 25) = 13.9$; $P < 0.001$) and N100 ($F(1, 25) = 12.6$; $P < 0.01$) components (see Table 3). For both the P50 and N100 components amplitudes to frequent tones were greater than to target tones.

P200 latency was significantly different between frequent

and target tones ($F(1, 25) = 22.9$; $P < 0.001$). Latencies for targets were less than frequent tones, possibly due to overlap with the developing N200 component, an effect that could shift the apparent peak of the P200 to an earlier timepoint. There were no significant effects of stimulus type on P50 and N100 latencies.

3.3.3. Interactions (group \times stimulus type)

There were no significant group \times stimulus type interactions for P50, N100, or P200 amplitudes and latencies.

3.4. MCI subjects subsequently diagnosed with probable Alzheimer's disease

Out of 10 MCI subjects that received a follow-up clinical exam after the experimental session, two subjects converted from MCI to probable Alzheimer's disease. Follow-up information was not available for 5 MCI subjects (one dropped out of the ADCS study, 4 have not had their yearly clinical examination since the experimental session). The diagnosis of Alzheimer's disease was based on declines in activities of daily living and the presence of additional cognitive deficits in addition to episodic memory. Both subjects met NINCDS-ADRDA criteria for probable Alzheimer's disease (McKhann et al., 1984). Declines in cognitive domains other than episodic memory were verified quantitatively by neuropsychological testing.

Results of the initial assessment of the two MCI subjects who subsequently converted to Alzheimer's disease are

Table 4
Individual subject conversion from MCI to probable Alzheimer's disease^a

Measure	Subject 1			Subject 2		
	Value	Z score	Rank	Value	Z score	Rank
Reaction time	492.6	1.2	14/15	343.3	-0.5	41/5
RP amplitude	-0.1	1.1	12/15	-0.9	0.5	8/15
P50 amplitude	6.2	0.5	11/15#	6.9	0.8	13/15
P50 latency	60.6	2.9	15/15	56.6	1.3	13/15#
P300 amplitude	5.4	-0.4	9/15	10.1	0.9	3/15
P300 latency	596.3	6.2	15/15	367.1	-1.2	4/15

^a Follow-up interval between experimental testing, when diagnosed as MCI, and subsequent diagnosis of probable Alzheimer's disease was 228 (Subject 1) and 253 (Subject 2) days. Interval between diagnosis of MCI and later experimental testing was 184 (Subject 1) and 112 (Subject 2) days. Rankings for reaction time and latencies are from fastest (#1) to slowest (#15) values. Rankings of P50 amplitudes are from smallest (#1) to largest (#15) amplitude values. RP and P300 amplitudes were ranked from largest (#1) to smallest (#15) values. Z scores for each measure are relative to the distribution of the results from the remaining 13 MCI subjects. P50 values were measured from frequent tones, and P300 values were measured from target tones. # indicates shared ranking with one other subject. Reaction time and latencies values are in ms, amplitude values are in μ V.

shown in Table 4. Subjects within the MCI group were rank ordered from high to low according to reaction time (high = short reaction time, low = long reaction time), RP amplitude (high = large amplitude, low = small amplitude), P50 amplitude (small to large amplitude), P300 amplitude (large to small amplitude), and P50 and P300 latency (short to long latency). Subject 1 was ranked low for most of the included measures, relative to their MCI peers. Subject 2 was ranked average to above-average relative to the MCI group in reaction time, RP amplitude, and P300 amplitude and latency measures, while P50 amplitude and latency measures were ranked low relative to the MCI group.

4. Discussion

As a group MCI subjects are characterized by isolated episodic memory impairments on a battery of neuropsychological tests, and are at greater risk of converting to Alzheimer's disease (Smith et al., 1996; Petersen et al., 1999). In the target detection task MCI subjects were distinguished from healthy elderly controls by (1) significantly larger P50 amplitudes and longer P50 latencies, (2) significantly longer P300 latencies, and (3) somewhat longer reaction times.

4.1. P50 and P300 abnormalities in mild cognitive impairment

There were significant differences in the amplitude and latency of the P50 (sometimes called P1) component in MCI subjects during target detection. An abnormal P50 response may be characteristic of MCI because larger P50 amplitudes in MCI subjects were reported in a different experiment (Golob et al., 2001). There is also some evidence that at risk relatives of Alzheimer's disease patients may have larger P50 amplitudes (Boutros et al., 1995). Additionally, in the present experiment both subjects that were initially diagnosed as MCI but later converted to Alzheimer's disease showed larger P50 amplitudes and longer P50 latencies, as compared with other MCI subjects that did not

convert to Alzheimer's disease. Taken together, these findings suggest that increases in P50 amplitude and latency may be associated with an increased risk of Alzheimer's disease.

The P50 component has been shown to be generated by neurons located in primary/secondary auditory cortex (Reite et al., 1988; Woldorff et al., 1993; Liegeois-Chauvel et al., 1994; Yoshiura et al., 1995). Although pathological changes may be present within auditory cortex in MCI, neuropathological studies of Alzheimer's disease have shown that primary and secondary auditory cortices are typically spared until late in the disease process (Arnold et al., 1991). Assuming that some MCI subjects may be in the earliest stages of Alzheimer's disease, the auditory cortex in these subjects is unlikely to have substantial pathology. This suggests that the P50 differences in MCI may not be attributable to pathology within the auditory cortical areas that generate the P50 component.

Another possibility is that P50 changes in MCI reflect impaired modulation of auditory cortical responses by other cortical areas that are more directly affected by pathology associated with MCI. The prefrontal cortex is a candidate region because (1) β -amyloid plaques are seen in many association areas in early Alzheimer's disease, including prefrontal cortex (Haroutunian et al., 1998) and (2) a mechanism has been identified in animal studies for attenuating the response of auditory cortex to auditory stimuli. The prefrontal cortex can attenuate the response of auditory cortical neurons to sound stimuli; possibly via direct connections between the prefrontal cortex and auditory cortex (Alexander et al., 1976), and/or indirectly through corticofugal connections with the thalamus (Yingling and Skinner, 1975, 1976). Knight and colleagues (Knight et al., 1989; Chao and Knight, 1997) have shown that prefrontal lesions and healthy aging are both associated with larger amplitude evoked potentials generated in auditory cortex, including the P50/P1 component (Alho et al., 1994). Similar enhancements of early auditory and visual evoked potentials have been observed after cooling orbitofrontal afferents to

the thalamus in the cat preparation (Skinner and Lindsley, 1971). Thus, P50 amplitude increases in MCI may be related to reductions in prefrontal inhibition over auditory cortical responsiveness.

The P50 component is sensitive to cholinergic manipulations, with amplitude reductions following administration of a cholinergic antagonist (scopolamine) in normal young subjects (Buchwald et al., 1991). Although the cholinergic system is compromised in Alzheimer's disease, a recent study suggests that levels of cholinergic enzyme markers in neocortex are largely normal until patients are in the moderate stages of Alzheimer's disease (Davis et al., 1999). Therefore, the P50 differences in MCI may not be attributable to cholinergic dysfunction because (1) reductions in cholinergic activity decrease, rather than increase, P50 amplitude, and (2) MCI patients may not have substantial deficits in cholinergic activity.

The evolution of P50 changes during the development of Alzheimer's disease is unclear. Abnormal P50 responses have been reported in Alzheimer's disease, with the suggestion that the P50 is essentially absent in a subgroup of Alzheimer's disease patients (Buchwald et al., 1989; Green et al., 1992; Green et al., 1997; cf. O'Mahony et al., 1994). However, other studies have shown normal P50 amplitudes at longer inter-stimulus intervals (≥ 1 s) in Alzheimer's disease (Fein et al., 1994; Phillips et al., 1997; Pekkonen et al., 1999). Methodological differences between studies may be a factor, but in general it appears that the P50 component is typically present in mild to moderate Alzheimer's disease patients provided the inter-stimulus interval is $> \sim 1$ s. In the P50/P1 experiments cited above Alzheimer's disease patients were usually in the mild to moderate stages of the disease, with Mini-Mental Status Exam scores of about 20/30 possible. In a target detection study of mild Alzheimer's disease there was a small increase in P50 amplitude, and no differences in P50 latency (Golob and Starr, 2000). The subjects in Golob and Starr (2000) were at an earlier stage of Alzheimer's disease (mean mini-mental status exam score = 23/30) compared to subjects in the studies showing no P50 changes.

Collectively, the findings from MCI, mild Alzheimer's disease, and mild-moderate Alzheimer's disease suggest that increases in P50 amplitude and latency seen in MCI, and to a lesser degree in mild Alzheimer's disease, may reflect pathophysiological changes that precede obvious dementia. The P50 increase may be mediated by reduced modulation of association cortical areas, such as prefrontal cortex, over auditory cortical activity. Once dementia is clearly evident P50 amplitudes may return to normal levels. Normal P50 amplitudes during mild-moderate dementia, as well as a putative subgroup that does not exhibit a P50 component at short inter-stimulus intervals, may be due to pathology affecting the cholinergic system.

It is well established that increases in P300 latency, and sometimes reductions in P300 amplitude, can accompany dementing disorders (e.g. Goodin et al., 1978; Polich,

1991). Increased P300 latency in MCI, relative to healthy controls, suggests that P300 latency increases may be associated with increased risk of Alzheimer's disease. Consistent with this notion, a recent report showed P300 latency increases in middle-aged asymptomatic subjects at risk for Alzheimer's disease due to family history and ApoE status (Green and Levey, 1999).

The P300 component is elicited by task-relevant stimuli, such as target tones, and is thought to be associated with stimulus evaluation and memory updating (Donchin and Coles, 1988). A widespread network of cortical structures, including association areas in the parietal, temporal, and prefrontal cortex, as well as the hippocampus, are associated with the P300 component (Halgren et al., 1998; Tarkka and Stokic, 1998; Kirino et al., 2000; Kiehl et al., 2001). The involvement of many brain regions in P300 generation is compatible with the notion that the P300 can be a general indicator of cognitive functioning that is vulnerable to disruption in a variety of disorders. Although there were significant differences in P300 latency in the MCI group, there was substantial variability across subjects. Follow-up studies are required to determine if this heterogeneity is related to differences between subjects in their likelihood of converting to dementia in the future.

The use of donepezil in at least 4 MCI subjects (4 confirmed, 4 potential users who were in a double blind study) may have reduced P300 latencies slightly in the MCI group. A recent report showed that donepezil reduced P300 latencies by ~ 9 ms (Reeves et al., 1999). Because only 4 MCI subjects in the present study were known to be taking donepezil at the time of testing, it could not be determined if donepezil influenced the results.

4.2. Mild cognitive impairment compared with Alzheimer's disease

There are two notable differences in target detection between MCI and mild Alzheimer's disease. First, previous work from our laboratory indicates longer mean reaction times in mild Alzheimer's disease subjects (~ 520 ms, $n = 16$) (Golob and Starr, 2000) vs. MCI (~ 400 ms), a result that is significantly different ($t(29) = -2.4$; $P < 0.03$) (data not shown). Longer reaction times in mild Alzheimer's disease, relative to healthy controls, have been observed in other tasks, (Ferris et al., 1976; Pirozzolo and Hansch, 1981; Goldman et al., 1999). As with P300 latency, there was considerable variability in reaction time across MCI subjects, and this variability could be related to the likelihood of conversion to Alzheimer's disease.

The RP component also differed between MCI and mild Alzheimer's disease. In mild Alzheimer's disease RP amplitude is attenuated (Golob and Starr, 2000), while MCI subjects in the present study had normal RP amplitudes. The RP in target detection appears to be related to motor preparation because RP amplitude is strongly attenuated when subjects are instructed to keep a mental count of the

target tones (Starr et al., 1995). Abnormal response preparation per se is probably not a defining feature of Alzheimer's disease. Instead, motor preparation, or the utilization of advance information in general which could include attentional factors as well as motor preparation, may be one cognitive process that is typically compromised in mild Alzheimer's disease but not in MCI.

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