Auditory cortical activity in amnestic mild cognitive impairment: relationship to subtype and conversion to dementia

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Mild cognitive impairment (MCI) patients have a high risk of converting to Alzheimer’s disease. The most common diagnostic subtypes of MCI have an episodic memory disorder (amnestic MCI) occurring either alone [single domain (SD)] or with other cognitive impairments [multiple domain (MD)]. Previous studies report increased amplitudes of auditory cortical potentials in MCI, but their relationships to MCI subtypes and clinical outcomes were not defined. We studied subjects with amnestic MCI (n = 41: 28 SD, 13 MD), Alzheimer’s disease (n = 14), and both younger (n = 22) and age-matched older controls (n = 44). Baseline auditory sensory (P50, N100) and cognitive potentials (P300) were recorded during an auditory discrimination task. MCI patients were followed for up to 5 years, and outcomes were classified as (i) continued diagnosis of MCI (MCI-stable, n = 16), (ii) probable Alzheimer’s disease (MCI-convert, n = 18), or other outcomes (n = 7). Auditory potentials were analysed as a function of MCI diagnosis and outcomes, and compared with young, older controls, and mild Alzheimer’s disease subjects. P50 amplitude increased with normal ageing, and had additional increases in MCI as a function of both initial diagnosis (MD > than SD) and outcome (MCI-convert > MCI-stable). P300 latency increased with normal ageing, and had additional increases in MCI but did not differ among outcomes. We conclude that auditory cortical sensory potentials differ among amnestic MCI subtypes and outcomes occurring up to 5 years later.

Keywords: MCI; single domain; multiple domain; event-related potentials; EEG

Abbreviations: MCI = mild cognitive impairment; SD = single domain

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Introduction

Mild cognitive impairment (MCI) is a disorder in older patients that is initially characterized by cognitive decline, such as episodic memory or language function (Flicker et al., 1991; Petersen et al., 2001). Since its inception the term ‘mild cognitive impairment’ has been recognized as referring to a heterogeneous group of patients, in terms of both cognitive deficits and aetiology (Flicker et al., 1991). Recently the diagnosis of MCI has been refined by introducing subtypes based on the presence or absence of an episodic memory disorder (amnestic, non-amnestic) and the number of affected cognitive domains (single domain, SD; multiple domain, MD) (Winblad et al., 2004). Thus, there are four combinations of these factors (e.g. non-amnestic or amnestic-SD, non-amnestic or amnestic-MD). The ‘MCI-SD’ and ‘MCI-MD’ subtypes are distinguished largely on the basis of neuropsychological test results (Winblad et al., 2004). In the context of amnestic MCI the MCI-SD subtype indicates a relatively selective episodic memory impairment, in contrast to the MCI-MD subtype, which indicates substantial deficits in at least one other cognitive domain. The main difference between MCI-MD and mild dementia is that MCI-MD...
patients have relatively intact activities of daily living (Winblad et al., 2004).

Amnestic MCI has been studied intensively because these patients have \( \sim 6 \times \) the risk of converting to Alzheimer’s disease relative to age-matched controls (Petersen et al., 1999), and can have neuropathology similar to early Alzheimer’s disease (Price and Morris, 1999; Kordower et al., 2001; Morris et al., 2001). Thus, amnestic MCI, either with or without additional cognitive deficits, often indicates an early stage of Alzheimer’s disease. Early detection of Alzheimer’s disease in MCI should be both feasible because neuropathology is present before the clinical expression of cognitive deficits (Ohm et al., 1995; Morrison and Hof, 1997), and clinically important because once dementia is manifest substantial brain damage has already occurred (Gomez-Isla et al., 1996; Haroutunian et al., 1998). The presence of medial temporal lobe pathology in amnestic MCI provides a likely basis for their episodic memory deficits (Price and Morris, 1999; Kordower et al., 2001; Morris et al., 2001). In amnestic MCI, if the disorder were to progress to involve other cognitive domains, neocortical structures such as the superior temporal gyrus, frontal gyrus and superior parietal lobule can exhibit Alzheimer’s disease neuropathology (Braak et al., 1998; Riley et al., 2002; Hof and Morrison, 2004) and volume reductions (Pennanen et al., 2005). Thus, changes in cortical function may be an important difference between the isolated episodic memory deficits in MCI-SD and the appearance of more widespread cognitive impairments characteristic of both MCI-MD and mild Alzheimer’s disease.

Event-related potentials and magnetic fields measured from the scalp have been used to quantify activity of cortical sensory areas (Picton et al., 2000). Previous studies have defined some of the changes in event-related potentials and magnetic fields that accompany normal ageing (e.g. Anderer et al., 1996; Goodin et al., 1978a) and neurological disease (e.g. Goodin et al., 1978b). An auditory stimulus elicits a series of electrical potentials that are identified by their polarity (positive = P, negative = N) and their approximate latency from stimulus onset (in milliseconds). These potentials reflect activity of primary and secondary sensory cortical systems (P50, N100, P200), as well as association cortical neural systems (N200, P300). Previous studies have reported that two of these components can distinguish amnestic MCI from older controls: the early sensory P50 is increased in amplitude and the late cognitive P300 latency is delayed in latency in amnestic MCI compared with controls (Frodl et al., 2002; Golob et al., 2002). No significant differences between amnestic MCI and controls were found for the N100, P200 and N200 components. Similar findings have been reported in early Alzheimer’s disease (Polich et al., 1999; Golob and Starr, 2000). It is unclear whether increased P50 amplitude in MCI reflects pathology of auditory cortical neurons themselves or is instead a functional consequence of pathology in remote structures, such as the nucleus basalis and frontal lobe, which are known to regulate activity in auditory cortex (Alexander et al., 1976; Metherate and Ashe, 1993; Chao and Knight, 1998).

In the present study, we followed amnestic MCI subjects for up to 5 years to test two hypotheses. The first hypothesis was that auditory cortical activity would vary with the clinical subtype of MCI (MCI-SD versus MCI-MD). The second hypothesis was that changes in auditory cortical potentials would be more likely in the subset of MCI subjects that later convert to dementia (MCI-convert), relative to the MCI subjects who remained stable (MCI-stable). To test these hypotheses, auditory event-related potentials were measured in MCI and control subjects on entry into the study. The MCI patients were followed clinically for up to 5 years, and classified according to their original diagnoses (MCI-SD or MCI-MD) and to their clinical outcomes (MCI-stable, MCI-convert). We predicted that baseline measures of the sensory auditory cortical potentials (P50, N100) would be larger, and the cognitive P300 latency would be longer in MCI-convert compared with MCI-stable. We also predicted that the amplitude of auditory cortical potentials would be larger in MCI-MD relative to MCI-SD.

### Material and methods

#### Subjects

A total of 134 subjects were tested between 1999 and 2005. There were five groups of subjects at entry to the study: young (n = 22), older controls (n = 44), MCI-SD (n = 28), MCI-MD (n = 13) and mild Alzheimer’s disease (n = 14) subjects. Demographic information for the study groups is presented in Table 1. Note that the numbers of male and female subjects were unequal in some of the groups, a factor that will be taken into consideration when examining auditory potentials because their amplitudes are sometimes larger in females (Michalewski et al., 1980; Hetrick et al., 1996). Older subjects (controls, MCI-SD, MCI-MD) were matched according to age, to reflect that both brain activity measures (evoked potentials) and neuropsychological test scores change with age (Pfefferbaum et al., 1979; Bennett et al., 2004; Golob et al., 2005).

Subjects in the MCI groups were followed longitudinally. There were originally 54 ‘MCI’ subjects, but 13 were excluded for the following reasons: (i) cognitive function in four improved to

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<th>Table 1 Demographic information</th>
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<td>Age</td>
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<td>M/F</td>
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Note: Older subjects (controls, MCI-SD, MCI-MD, Alzheimer’s disease) were matched for age, and all subjects were matched for education. Values are mean ± standard deviation. Abbreviations: MCI-SD = amnestic mild cognitive impairment, single domain. MCI-MD = amnestic mild cognitive impairment, multiple domain.
be in the normal range; (ii) six had incomplete data to define the MCI subtypes of SD versus MD; (iii) two had MCI without an amnestic component and (iv) one died 18 months after the onset of the memory disorder with both clinical features and neuropathological findings at autopsy consistent with Lewy body dementia. Of the remaining 41 MCI subjects, 28 were classified as MCI-SD and 13 as MCI-MD.

MCI subjects were recruited through the UC Irvine Alzheimer’s Disease Research Center (ADRC) and a university clinical practice. Other subject groups were recruited through the campus community (young), the ADRC (mild Alzheimer’s disease), and the UC Irvine Successful Ageing Program (controls). The diagnosis of amnestic MCI or probable Alzheimer’s disease was made by a neurologist using clinical neurological and neuropsychological examinations, routine blood analysis, family interviews and neuroimaging (e.g. MRI) using guidelines of Petersen et al. (1999) and McKhann et al. (1984). MCI subjects had moderate to severe deficits in episodic memory, with performance levels typically 1.5 standard deviations below the age-appropriate mean on tests of episodic memory. If episodic memory was the only area of impairment they were considered to be amnestic MCI-SD. If memory plus other cognitive domains were affected (1.5 standard deviations below age norms) they were considered to be amnestic MCI-MD. MCI subjects did not have evidence of impairments of activities of daily living, as defined by clinical interviews and a questionnaire. Alzheimer’s disease subjects had impairments in episodic memory and at least one other cognitive domain, and were impaired in activities of daily living. Control subjects scored within the normal range on all neuropsychological tests, and were between the ages of 65–86 years, to correspond to the age range of MCI and mild Alzheimer’s disease subjects. Neuropsychological tests were not given to young subjects, who were university students. Young subjects reported themselves to be healthy and without history of major neurological or psychiatric disorders. All subjects signed informed consent forms, and the experiments were performed in accordance with a protocol approved by the UC Irvine Institutional Review Board consistent with the Declaration of Helsinki.

**Study design**

The study tested if brain activity in MCI at time of entry into the study differed as a function of the MCI subtype (MCI-SD, MCI-MD) and their subsequent clinical outcomes (MCI-stable versus MCI-convert). Upon entry to the study baseline neuropsychological performance and auditory event-related potentials were measured. MCI patients were then followed annually with neurological and neuropsychological tests. The clinical status of all MCI subjects was reviewed in February 2006 to define clinical outcomes (MCI versus dementia). Statistical analyses examined baseline measures and tested for significant differences between groups as a function of diagnosis and clinical outcomes.

There were three MCI-MD subjects whose event-related potential data were collected within 3 months before they were reclassified as having converted to dementia. For these three subjects brain activity measures were not included in this article, because their status at the time of event-related potential testing was ambiguous, given that they were classified as demented within a few months. However, the neuropsychological test data and clinical outcomes of these MCI-MD subjects were included in the results.

**Neuropsychological testing**

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, number of words that can be spoken beginning with the letters F, A, and S on separate one minute trials.) (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 of dementia.

**Behavioural paradigm used while measuring auditory cortical activity**

Subjects performed a target detection, or ‘oddball’, task by listening to a sequence of tones having a constant interstimulus interval of 2.5 s. Tones were presented from two speakers placed ~0.75 m in front of the subject (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, 60 targets). Subjects were instructed to listen to the tones and quickly, but accurately, press a button with the thumb of their dominant hand in response to targets. The sequence of tones was randomly determined except for the restrictions that two targets were never presented in a row, and a maximum of nine non-targets could be presented in a row. All subjects could accurately distinguish non-targets from targets (typically >95% accuracy).

**Event-related potential recordings**

Subjects were seated inside a sound attenuating, electrically shielded chamber. Depending on the subject, between eight and ten Ag/AgCl recording electrodes were placed on the scalp according to the 10/20 system (Jasper, 1958). All subjects had electrodes at Fz, Cz, Pz, C3 and C4 sites. Electrode impedances were <5 kΩ. 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. Reference electrodes were placed on the left and right mastoid in a linked mastoid configuration. The EEG and EOG were digitally amplified (DC 100 Hz, sample rate = 500 Hz). Electrophysiological (EEG, EOG) and behavioural data were collected continuously, with additional off-line processing and analysis. An eyeblink correction algorithm was used to correct for artefacts (Gratton et al., 1983). Individual sweeps were then sorted and averaged according to stimulus type (non-target or target). Sweeps to targets were visually inspected for artefacts before being accepted into the average. Sweeps to non-targets were automatically rejected if the voltage on any electrode site exceeded 75 μV.

**Data analysis**

Reaction time was calculated relative to stimulus onset. Accuracy was the percent of correct responses to target tones (out of 60), and false alarms indicated the number of button
presses to non-targets. Median reaction times were calculated for each subject to limit the influence of any outlier reaction times.

Event-related potentials were digitally filtered using FFT and inverse FFT procedures (0.1–16 Hz, 12 dB/octave). Peak latencies of components were calculated relative to stimulus onset. Amplitudes of stimulus-evoked potentials were defined relative to a 100 ms baseline period immediately before stimulus presentation. The P50, N100, P200 components were measured in response to non-targets. Although the P50, N100 and P200 are present for both targets and non-targets, non-targets were analysed alone because they were presented more often than targets, which improves measurement reliability. The P300 was measured to targets, where it has a large amplitude, unlike non-targets which typically do not elicit a substantial P300 component. The P50 component was defined as the maximum positivity between 40 and 80 ms post-stimulus, N100 was the maximum negativity between 80 and 160 ms, and the P200 was the maximum positivity between 150 and 250 ms. The P300 was defined as the maximum positivity between 300 and 700 ms.

Statistical analysis
Event-related potentials and behavioural data from target detection and neuropsychological testing were analysed with analysis of variance using univariate (ANOVA) and multivariate (MANOVA) models. P-values <0.05 were considered significant. The main analyses used ANOVA to test for baseline differences in MCI associated with: (i) diagnostic subtype (MCI-SD versus MCI-MD), and (ii) whether or not the subjects later converted to dementia (MCI-stable versus MCI-convert). Age-matched controls and mild Alzheimer’s disease patients were included for comparison with the MCI subgroups. Univariate ANOVAs were used to analyse group differences followed up by post hoc testing using Tukey tests. Gender was also included as a factor in ANOVA tests to verify that group differences were not attributable to different proportions of males/females among groups. Gender effects were also analysed using a blocked covariate ANCOVA rather than as a factor in the main ANOVA analysis. Results were identical to those including gender as a factor in ANOVA, therefore only the latter will be reported. Cholinesterase inhibitor treatment was also included as a factor to test whether the use of medication influenced the results. The P50, N100 and P200 components were measured from the Cz site, and P300 measures were taken from the Pz site.

Neuropsychological data were analysed using separate MANOVA tests (Wilks lambda criterion) for episodic memory, language, executive function, and visual–spatial domains. For episodic memory MANOVAs WMS-III Logical Memory tests were not included because some subjects were not given these tests. For each comparison a few subjects within the MCI-SD group (3–4) did not complete all of the tests within a domain, and were not included in the MANOVA analysis. Stepwise discriminant function analyses quantified the ability of P50 and P300 measures to successfully classify individuals as either MCI-stable or MCI-convert. Prediction of a given subject’s classification was based upon a model that did not include that subject, known as a ‘jackknife’ resampling procedure.

Results
Diagnosis: baseline neuropsychological testing
Baseline neuropsychological results are shown on the left side of Table 2. MANOVA was used to assess differences among controls, MCI-SD, MCI-MD, and Alzheimer’s disease groups, with separate comparisons among MCI-SD versus MCI-MD. Separate MANOVA tests examined the domains of episodic memory, language, executive function and visual–spatial function.

As expected, there was a significant group effect for episodic memory scores [F(15,207) = 16.5; P < 0.001], with the best performance in controls, intermediate in amnestic MCI groups, and lowest scores in Alzheimer’s disease. A MANOVA comparing MCI-SD and MCI-MD showed no significant effect in the episodic memory domain (P > 0.50). Analysis of the language domain revealed a significant group effect [F(9,195) = 7.1; P < 0.001]. Post hoc Tukey tests showed no significant group differences for letter fluency (FAS). For the Boston naming and CERAD animal naming performance in controls and MCI-SD were both significantly greater than MCI-MD and Alzheimer’s disease (all P-values <0.01). Thus, there were two pairs of groups having similar language scores: controls and MCI-SD and MCI-MD and Alzheimer’s disease, with better performance in controls and MCI-SD. Comparison of MCI-SD and MCI-MD on language tests showed a significant group effect [F(3,32) = 12.0; P < 0.001], with better performance in MCI-SD on all tests, especially Boston Naming and CERAD Animal Naming. Analysis of executive function showed a significant group effect [F(6,154) = 4.3; P < 0.001]. Post hoc testing showed little difference among groups for Trailmaking Test A, with the exception of longer times in Alzheimer’s disease versus controls (P < 0.05). In Trailmaking Test B controls were significantly faster than MCI-MD and Alzheimer’s disease, and MCI-SD was significantly faster than Alzheimer’s disease (P-values <0.01). In the visual–spatial domain there was a significant group effect [F(6,160) = 7.1; P < 0.001]. Post hoc testing for WAIS-III block design indicated that controls and both MCI groups were significantly better than Alzheimer’s disease (P-values <0.04), with no other group differences. In CERAD Constructional Praxis controls also performed significantly better than Alzheimer’s disease subjects (P < 0.05).

In summary, results showed the expected episodic memory deficits in amnestic MCI relative to controls, and MCI groups in turn had better scores than Alzheimer’s disease. Comparison of neuropsychological test scores in MCI-SD and MCI-MD showed a significant difference in the language domain (MCI-SD > MCI-MD), but no significant differences in the episodic memory, executive function, or visual–spatial domains. Language, executive function, and visual–spatial deficits were evident in
Alzheimer’s disease relative to controls and sometimes amnestic MCI groups, depending on the specific test.

### Diagnosis: auditory cortical potentials

Potentials to non-targets are shown in Fig. 1, which compares auditory cortical potentials in different groups of subjects. All older subject groups (controls, MCI-SD, MCI-MD, Alzheimer’s disease) are shown in Fig. 1A. A comparison of the two MCI diagnostic subtypes (MCI-SD, MCI-MD) is shown in Fig. 1B. Age differences are shown in Fig. 1C by comparing young and older controls. Note that the amplitude of the P50 differs as a function of MCI diagnosis (Fig. 1B), and that P50 amplitude also increases in normal ageing (Fig. 1C). Amplitudes of the P50 and N100 components were larger in MCI-MD relative to MCI-SD and controls, which had comparable amplitudes.

Individual P50 amplitudes for subjects of each MCI subtype are presented in Fig. 1D, and amplitudes of the P50 and N100 as a function of group are plotted in Fig. 1E and F. Univariate ANOVAs were used to examine potentials in the older subjects with factors of group (controls, MCI-SD, MCI-MD, Alzheimer’s disease) and gender. Measurements included the amplitudes and latencies of auditory cortical potentials (P50, N100, P200) to non-targets and the P300 component to targets. There was a significant group effect for amplitudes of the P50 component \(F(3,88) = 6.7; P < 0.001\). Post hoc paired comparisons showed that P50 amplitudes in MCI-MD were significantly larger than controls \((P < 0.001)\) and MCI-SD \((P < 0.01)\). There were no significant group effects in latency measures for any of the components to non-targets (P50, N100, P200). For N100 amplitude the group effect did not attain significance \((P = 0.06)\), but there was a small effect of gender \([F(1,88) = 4.1; P < 0.05]\), with larger N100 amplitudes in females versus males. None of the other main effects of gender or group \(\times\) gender interactions were significant.

Potentials to targets as a function of diagnostic group are shown in the left column of Fig. 2. There was a significant group effect for P300 latency \([F(3,88) = 6.4; P < 0.001]\). Post hoc tests showed that P300 latencies were significantly longer in MCI-MD \((P < 0.01)\) and Alzheimer’s disease \((P < 0.001)\), as compared to controls (Fig. 2B). P300 latency in MCI-MD was comparable with MCI-SD and Alzheimer’s disease, but individual variability likely precluded a significant difference relative to controls, in contrast to the P50 results. None of the main effects of gender or group \(\times\) gender interactions attained significance.

The percentage of MCI subjects taking cholinesterase inhibitors was comparable among MCI-SD (59%) and MCI-MD (50%), which suggests that medication effects

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### Table 2 Neuropsychological testing

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<tr>
<th>Test</th>
<th>Initial diagnosis</th>
<th>Outcome</th>
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<tr>
<td></td>
<td>Controls ((n = 38))</td>
<td>MCI-SD ((n = 27))</td>
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<tr>
<td>Cognitive status</td>
<td></td>
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<tr>
<td>Mini-Mental State Examination</td>
<td>290 ± 1.1</td>
<td>274 ± 1.6</td>
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<tr>
<td>Episodic memory</td>
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<tr>
<td>CERAD Word List</td>
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<tr>
<td>Immediate Recall (3 trials)</td>
<td>23.0 ± 3.8</td>
<td>16.6 ± 2.9</td>
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<tr>
<td>5 min Delayed Recall</td>
<td>79 ± 1.8</td>
<td>2.0 ± 1.5</td>
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<tr>
<td>30 min Delayed Recall</td>
<td>71 ± 2.1</td>
<td>1.5 ± 1.7</td>
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<tr>
<td>5 min Delayed Recognition</td>
<td>197 ± 0.8</td>
<td>172 ± 2.0</td>
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<tr>
<td>30 min Delayed Recognition</td>
<td>196 ± 0.9</td>
<td>16.2 ± 2.6</td>
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<tr>
<td>WMS-III</td>
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<tr>
<td>Logical Memory 1</td>
<td>13.1 ± 3.0</td>
<td>7.1 ± 3.3</td>
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<tr>
<td>Logical Memory 2</td>
<td>13.5 ± 3.3</td>
<td>6.0 ± 3.3</td>
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<tr>
<td>Language</td>
<td></td>
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<tr>
<td>Letter Fluency (FAS)</td>
<td>46.0 ± 13.0</td>
<td>44.4 ± 9.9</td>
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<tr>
<td>Boston Naming Test (30 item)</td>
<td>278 ± 2.8</td>
<td>276 ± 2.0</td>
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<tr>
<td>CERAD Animal Naming</td>
<td>21.1 ± 5.9</td>
<td>18.8 ± 5.2</td>
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<tr>
<td>Executive function</td>
<td></td>
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<tr>
<td>Trail Making Test A (s)</td>
<td>377 ± 11.7</td>
<td>42.2 ± 16.1</td>
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<tr>
<td>Trail Making Test B (s)</td>
<td>93.8 ± 36.6</td>
<td>117.5 ± 54.2</td>
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<tr>
<td>Visual–spatial</td>
<td></td>
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<tr>
<td>WAIS-III Block Design</td>
<td>34.4 ± 7.2</td>
<td>35.0 ± 11.4</td>
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<tr>
<td>CERAD Constructional Praxis</td>
<td>10.3 ± 1.1</td>
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Neuropsychological testing results for all subjects that received the same neuropsychological test battery. Control and Alzheimer’s disease subjects were matched to MCI subjects for age and education level. Logical memory test data use scaled scores. Five Alzheimer’s disease subjects did not complete Trailmaking Test B and Logical Memory tests. All scores are expressed as mean ± standard deviation. Group comparisons among groups are presented in the text.
Normal ageing and auditory cortical potentials

Age differences in auditory cortical potentials were defined by comparing young and older control subjects using ANOVA. There was a significant group effect for P50 amplitude \( F(1,62) = 11.7; P < 0.001 \) (Fig. 1E), with larger amplitudes in controls. There was also a small group effect in N100 latency \( F(1,62) = 5.2; P < 0.03 \), with shorter latencies in the young (105 ± 2 ms) versus controls (109 ± 1 ms). P300 amplitude was significantly smaller in control versus young subjects \( F(1,62) = 21.0; P < 0.001 \), and P300 latency was significantly longer in older versus young subjects \( F(1,62) = 10.9; P < 0.001 \) (Fig. 2A and B). There was a significant gender effect on N100 \( F(1,62) = 4.3; P < 0.05 \) and P200 amplitude \( F(1,62) = 5.6; P < 0.03 \), with larger amplitudes in females versus males. There were no significant group \( \times \) gender interactions.

Analysis of reaction time as a function of group (controls, MCI-SD, MCI-MD, Alzheimer’s disease) and gender revealed a significant group effect \( F(3,92) = 4.1; P < 0.01 \). Post hoc tests showed that reaction time was significantly slower for Alzheimer’s disease (489 ± 30 ms) relative to controls (357 ± 17 ms). MCI reaction times were longer than controls (MCI-SD = 408 ± 21 ms; MCI-MD = 439 ± 36), but did not attain significance. Mean accuracy was > 98% in all groups, and did not differ significantly among groups. A subset of subjects was given hearing threshold tests, but the numbers were not large enough across groups to conduct a formal analysis. However, stimuli were presented at suprathreshold and are unlikely to account for the above group differences. This impression was confirmed using ANOVA tests comparing the MCI subgroups using the factor of medication at time of testing (yes, no). There were no significant effects of medication or group \( \times \) medication interactions on any measure (P50, N100, P200, P300 amplitude and latency).
levels in all subjects, and behavioural data showed that performance was at ceiling levels. 

Taken together, the aforementioned findings indicate that P50 amplitude increased during normal ageing, with additional increases for MCI-MD. P300 latency also increased with age, with further prolongation in groups with cognitive deficits (MCI-SD and Alzheimer’s disease), as compared with controls. Although P300 latency in MCI-MD was similar to MCI-SD (410 versus 408 ms, respectively), post hoc comparisons with controls did not attain significance.

MCI outcomes: stable versus conversion to dementia

Among the 41 MCI subjects, 31 could be classified as being either MCI-stable (n = 16) or having converted to dementia (MCI-convert, n = 15) at the time of this study’s outcome measure in February, 2006 (Table 3). The main result was that the conversion percentage in MCI-MD was more than double the conversion percentage in MCI-SD (69 versus 32%, respectively). The greater likelihood of conversion in MCI-MD was supported by a significant $\chi^2$ test of MCI diagnostic subtype at entry (MCI-SD, MCI-MD) and outcomes (MCI-stable, MCI-convert)($\chi^2 = 19.4, P < 0.001$). The annual conversion rate was ~10%, and the time between the initial clinical visit and conversion to dementia ranged from 6 to 60 months (mean = 16 months). Most stable MCI subjects retained their original classification. The one exception was an MCI subject that changed from being classified as MCI-SD at entry to MCI-MD at outcome. Two MCI subjects developed additional cognitive deficits related to cerebrovascular strokes, preventing a clear assignment of outcome. Outcomes in five MCI subjects could not be determined due to insufficient information.

MCI outcomes: baseline neuropsychological testing

Neuropsychological results for MCI-stable and MCI-convert subjects are shown on the right side of Table 2. The Boston Naming Test was the only neuropsychological measure that significantly differed between MCI-stable and MCI-convert ($P < 0.01$), with lower scores in MCI-convert.

MCI outcomes: baseline auditory cortical potentials

Potentials recorded at the time of entry into the study for controls, MCI-stable, MCI-convert, and Alzheimer’s disease are shown in Fig. 3. Comparison of MCI-stable and MCI-convert indicates that the P50 and N100 components were larger in MCI-convert relative to MCI-stable (Fig. 3B). Plots in Fig. 3 show both individual subject data (C) and group data for P50 (D) and N100 (E) components.
MCI-convert also had P300 latencies that were intermediate between MCI-stable and mild Alzheimer’s disease (Fig. 2C and D).

As in the aforementioned analysis of diagnostic group at entry, univariate ANOVAs were used to examine group differences in outcome (controls, MCI-stable, MCI-convert, Alzheimer’s disease) and gender for the amplitudes and latencies of auditory potentials to non-targets (P50, N100, P200) and targets (P300). For P50 amplitude there was a significant main effect of group \[ F(3,81) = 5.4; P < 0.001 \]. Post hoc tests indicated that MCI-convert had significantly larger P50 amplitudes relative to controls \( (P < 0.001 \) and MCI-stable \( (P < 0.02 \). When only MCI-SD subjects were analysed there was also a significant difference among outcomes \[ F(1,21) = 11.9; P < 0.01 \]. There was also a significant main effect for N100 amplitude \[ F(3,81) = 4.5; P < 0.01 \]. Post hoc tests showed that MCI-convert had larger N100 amplitudes compared with controls \( (P < 0.02 \) and Alzheimer’s disease \( (P < 0.01 \). Post hoc comparisons of N100 amplitudes among MCI-SD and MCI-MD did not attain significance. There were no significant latency effects for the P50, N100 or P200 among groups.

As in the aforementioned analysis of diagnostic group there was a significant gender effect for N100 amplitude \[ F(1,81) = 4.9; P < 0.05 \], and also a significant effect for P200 amplitude \[ F(1,81) = 8.7; P < 0.01 \], with larger amplitudes in females for both components. There were no significant effects of gender on P50 amplitude or latency. Also, none of the group \( \times \) gender interactions were significant, indicating that the main effects of group on P50 and N100 amplitudes were not secondary to differences in the proportion of males/females among some groups.

Analyses of the P300 component showed a significant group effect for P300 latency \[ F(3,81) = 6.9; P < 0.001 \]. Post hoc testing showed significantly longer P300 latencies in MCI-convert \( (P < 0.01 \) and Alzheimer’s disease \( (P < 0.001 \) relative to controls. There was a small main effect of gender on P300 amplitude, with females having larger amplitudes than males \[ F(3,81) = 4.5; P < 0.04 \].

Discriminant analysis of MCI outcomes (MCI-stable versus MCI-convert) using P50 amplitude at entry showed a sensitivity of 81% and specificity of 73% (Wilks \( \lambda = 0.58; \chi^2 = 15.8; P < 0.001 \). Inclusion of amplitude and latency measures of other components (N100, P200, P300) did not improve prediction of MCI outcomes. To determine if auditory cortical potential measures provide additional information regarding MCI outcomes beyond the clinical classification (SD versus MD) we conducted a discriminant analysis of outcomes (stable versus convert) within just the MCI-SD group. This group is of special interest because it is distinguished from both Alzheimer’s disease and MCI-MD by having only a single cognitive deficit (memory). A similar analysis was not conducted in MCI-MD because there were too few subjects in this subtype. Within the MCI-SD subtype P50 amplitude at entry showed a sensitivity of 86% and specificity of 67% (Wilks \( \lambda = 0.64; \chi^2 = 9.2; P < 0.01 \). Inclusion of amplitude and latency measures of other components (N100, P200, P300) did not improve prediction of MCI outcomes. Although studies having more subjects are needed, analysis within MCI-SD suggests that baseline differences in auditory cortical potentials have predictive value regarding outcomes (stable versus convert) beyond that associated with diagnostic subtype.

There were no significant group differences in median reaction time for MCI-stable \( (401 \pm 29 \text{ ms}) \) compared with MCI-convert \( (408 \pm 28 \text{ ms}) \).

The percentages of subjects taking cholinesterase inhibitor medications for their memory impairment in the MCI-stable and MCI-convert groups were nearly identical (MCI-stable: 56%, 9/16 subjects; MCI-convert: 60%, 9/15 subjects). ANOVA tests were conducted to compare MCI outcomes using the factor of medication at time of testing (yes, no). There were no significant effects of medication or group \( \times \) medication interactions on any measure (P50, N100, P200, P300 amplitude and latency), indicating that differences in baseline measures were not attributable to differential use of medications.

In summary, the aforementioned findings show that the amplitudes of early auditory cortical potentials (P50 and N100) were larger at the time of entry for those MCI subjects that later converted to dementia, relative to those that remained classified as MCI. There were also group differences in P300 latency, with progressively longer latencies in MCI-stable, MCI-convert, and mild Alzheimer’s disease but the sensitivity and specificity of this measure were low.

**Discussion**

Results in MCI subjects showed that baseline measures of an auditory cortical sensory potential (P50) differed as a function of MCI diagnostic subgroup (SD versus MD), and outcome (maintain MCI diagnosis, MCI-stable, versus convert to dementia, MCI-convert). For diagnostic subgroup P50 amplitudes relative to age-matched controls were significantly larger in MCI-MD but not MCI-SD. Comparison with young, older control, and Alzheimer’s disease subjects indicated that P50 amplitudes increased in normal ageing and had additional increases in MCI-MD. For MCI outcomes P50 was significantly larger for those who converted to dementia than for those who remained stable. Thus, results covaried among diagnostic subgroup and outcome because MCI-MD subjects were much more likely to convert to dementia (69% conversion) compared with MCI-SD (32% conversion). There was also a trend for smaller P50 amplitudes in Alzheimer’s disease relative to MCI-MD and MCI-convert. Neuropsychological test results at baseline were not significantly different between MCI outcomes except for picture naming (Boston Naming Test), which was significantly lower in MCI-convert versus MCI-stable. The auditory cortical N100 potential was larger in
MCI-MD compared with Alzheimer’s disease, and in MCI-convert relative to both controls and Alzheimer’s disease. Latency of the P300 component increased in normal ageing, and had additional increases in MCI-SD, MCI-convert, and Alzheimer’s disease relative to controls. Group differences in event-related potential measures and their implications for the time course of neurophysiological changes during the development of Alzheimer’s disease will be discussed subsequently. Note that the absence of group × gender interactions shows that the group differences cannot be attributed to somewhat different proportions of males/females in the various different groups.

**MCI diagnostic subtypes: single and multiple domain**

The present results show that the auditory cortical P50 component distinguishes MCI-MD from MCI-SD, with significantly larger P50 amplitudes in MCI-MD. There were also substantial differences between MCI-SD and MCI-MD on tests of language (Boston Naming test, CERAD animal naming) but not on episodic memory tests. Previous studies on the development of non-amnestic cognitive deficits in Alzheimer’s disease typically show early abnormalities in executive function (Perry and Hodges, 1999; Albert et al., 2001), and language (Jacobs et al., 1995; Perry et al., 2000; Lambon Ralph et al., 2003). For the MCI-MD patients in our study impaired language function was typical (12/13), whereas deficits in executive function occurred alone in one subject and in conjunction with language in four. The P50 component is thought to reflect neural activity in posterior superior temporal gyrus (see subsequent text), a region that is important for speech and language (Binder and Price, 2001). Thus comparison between MCI-SD and MCI-MD shows an association between abnormally increased P50 amplitudes and abnormal language function. A previous event-related potential study examining language function showed that long-latency brain potentials associated with semantic processing were abnormal in MCI (Olichney et al., 2002).

During normal ageing P50 amplitudes increase until at least the tenth decade of life (Pfefferbaum et al., 1979; Smith et al., 1980; Golob et al., 2005). Thus, it is important to distinguish increases in P50 amplitude as a function of age from increases associated with MCI. Because normal brain ageing is distinct from MCI and Alzheimer’s disease (Morrison and Hof, 1997), it is possible that the mechanisms for P50 amplitude increases in normal ageing are also distinct from those in MCI-MD.

The N100 auditory cortical potential was not significantly different among MCI-SD and MCI-MD or between MCI and controls. The only significant difference among diagnostic groups was between MCI-MD and Alzheimer’s disease, with larger amplitudes in MCI-MD. The pattern of N100 amplitudes suggests somewhat larger amplitudes in MCI-MD and somewhat smaller amplitudes in Alzheimer’s disease, relative to controls and MCI-SD (Fig. 1).

Previous studies show that amnestic MCI patients are at greater risk of converting to Alzheimer’s disease relative to age-matched controls without episodic memory impairments (Petersen et al., 1999). The present findings show that within the category of amnestic MCI those patients having additional cognitive deficits sufficient for a diagnosis of MCI-MD were more likely to convert to dementia as compared with MCI-SD (69 versus 31%, respectively). Another study with a larger sample of MCI patients (n = 81) and a comparable follow-up time period (mean = 3.5 years) also reported a substantially higher conversion percentage for amnestic MCI-MD (54%) versus MCI-MD (25%) (Alexopoulos et al., 2006; Pernecky et al., 2006). Thus, observations from this study and others suggest an approximately 2-fold increased risk of dementia in MCI-MD relative to MCI-SD.

**MCI outcomes: stable MCI versus conversion to dementia**

A previous report speculated that P50 amplitude is increased in amnestic MCI relative to age-matched controls, and then returns to age-appropriate levels in mild-moderate Alzheimer’s disease (Golob et al., 2002). The longitudinal data reported here directly support this profile by showing that amnestic MCI subjects who subsequently converted to probable Alzheimer’s disease, had larger P50 amplitudes at baseline than MCIs who did not yet convert to Alzheimer’s disease. In contrast, baseline P50 amplitudes in MCI-stable were not significantly different from controls. Differences among MCI outcomes suggest that much of the difference in P50 amplitude between controls and amnestic MCI reported in previous studies (Golob et al., 2001; Golob et al., 2002; Irimajiri et al., 2005) is attributable to the subset of MCI subjects that are likely to convert to Alzheimer’s disease within a few years. Consequently, among subjects in the MCI-stable group those having the largest P50 amplitudes may have a greater risk of converting to Alzheimer’s disease, relative to MCI-stable subjects with smaller P50 amplitudes.

Taken together, the present results suggest that in addition to normal age-related increases in P50 amplitude, there are additional increases in those amnestic MCI patients that are likely to convert to dementia. Previous studies in mild–moderate Alzheimer’s disease have shown normal (Pekkonen et al., 1994) or slightly larger P50 amplitudes in Alzheimer’s disease relative to age-matched controls (Golob and Starr, 2000). Thus, P50 amplitude appears to increase during the transition period from MCI to Alzheimer’s disease and then may return close to normal levels during the early stages of dementia. One of our previous studies found a small, but significant increase in P50 amplitude in ‘mild’ Alzheimer’s disease versus controls, which was not found in the present study. This difference
between studies was due to somewhat higher P50 amplitudes in the control group and lower amplitudes in Alzheimer’s disease subjects in the present study, compared with Golob and Starr (2000).

Another auditory cortical potential, the N100, distinguished MCI-convert from controls and Alzheimer’s disease, with larger N100 amplitudes in MCI-convert. N100 amplitudes exhibited some parallels with P50 differences among groups, except the N100 did not distinguish MCI-stable from MCI-MD. Results are consistent with studies indicating little change in N100 amplitude during normal ageing (e.g. Anderer et al., 1996). Previous studies have reported either a non-significant trend for larger N100 amplitudes in MCI versus controls (Golob et al., 2002), a small increase in MCI at slow stimulus rates (Irimajiri et al., 2005), or no significant differences at very short or very long inter-stimulus intervals (Golob et al., 2001). Taken together, there appear to be small increases in N100 amplitude in MCI-MD, and small decreases in mild Alzheimer’s disease, that are sensitive to stimulus rate.

Latency of the P300 component distinguished MCI-convert and Alzheimer’s disease from controls, with shorter latencies in controls. P300 latency was also significantly longer in older controls relative to young subjects, as reported previously (Goodin et al., 1978a; Picton et al., 1984; Iragui et al., 1993), and has additional latency increases in dementing disorders such as Alzheimer’s disease (Goodin et al., 1978b; Polich, 1991). The P300 is generated by a network of neocortical areas that includes parietal, temporal and prefrontal association cortex (Halgren et al., 1998; Kiehl et al., 2001). The present results suggest that increases in P300 latency in MCI-convert may reflect neocortical dysfunction that precedes additional cognitive declines. Unlike P50 amplitude, P300 latency was similarly prolonged in MCI-convert and mild Alzheimer’s disease subjects. Thus, while increases in P50 amplitude seem to reflect changes in neural activity during the transition period between MCI and Alzheimer’s disease, P300 latency increases are associated with neocortical dysfunction that shortly precedes, and then accompanies, the presence of dementia.

**Sensory potentials in MCI and Alzheimer’s disease**

The pathological hallmarks of Alzheimer’s disease, neurofibrillary tangle and β-amyloid plaques, are found in association cortex and subcortical nuclei supplying neuro-modulatory afferents to the cortex (Ohm et al., 1995; Morrison and Hof, 1997). The P50 and N100 potentials reflect neuronal activity in adjacent regions of auditory cortex. The P50 component is principally generated by neurons in primary and/or secondary auditory cortex, while the N100 likely indicates activity in secondary auditory cortex (Reite et al., 1988; Liegeois-Chauvel et al., 1994; Godey et al., 2001). Differences in auditory cortical potentials in MCI are unlikely due to Alzheimer’s disease pathology in auditory cortex because neuropathological studies show that sensory cortices are typically spared until advanced stages of the disease (cf. Lewis et al., 1987; Arnold et al., 1991; Haroutunian et al., 1998; Haroutunian et al., 1999). Another possibility is that P50 changes in MCI might reflect modulation of auditory cortical responses by other cortical and subcortical areas more directly affected by pathology accompanying MCI. The prefrontal cortex and nucleus basalis of Meynert (Kasa et al., 1997; Dekosky et al., 2002) are candidate regions because these areas are known to modulate auditory cortical responses to sounds (Alexander et al., 1976; Metherate and Ashe, 1993; Chao and Knight, 1998). Observations in MCI such as the up regulation of cholinergic enzyme activity in prefrontal regions or pathology in basal cholinergic systems such as the nucleus basalis of Meynert may be relevant to P50 differences in MCI. However, the present results did not show an effect of cholinesterase inhibitors on P50 amplitude in MCI as a function of diagnostic subtype or subsequent clinical outcomes. Interpretation is limited due to possible clinical differences among patients who did versus did not receive medications, but the present findings do not support the idea that the cholinergic system is involved in the P50 changes in MCI.

**Clinical relevance**

The fractionation of MCI into diagnostic subgroups of SD and MD and amnestic versus non-amnestic types is an attempt to refine the categorization of cognitive disorders preceding dementia (Winblad et al., 2004). Differences of auditory potentials as a function of diagnosis (amnestic MCI-SD versus MCI-MD) in the present study provide evidence of differences in cortical function in these clinical subtypes. The abnormally enhanced P50 in MCI-MD may reflect alterations in auditory regions of the temporal lobe involved in the language impairments that characterized our MCI-MD patients. Results using discriminant analysis within MCI-SD to predict outcomes suggest that differences in auditory cortical potentials may occur before more than one cognitive domain is affected. In particular, changes in auditory cortical potentials may anticipate declines in language function. Further study is necessary to determine if the application of event-related potentials and possibly volumetric MRI (Pennanen et al., 2005) can be used to quantify temporal lobe involvement in MCI subtypes for clinical use in following patients with early cognitive decline.

In contrast to the language domain, there were no group differences between MCI-SD and MCI-MD in terms of episodic memory function. Thus, differences in auditory cortical potentials between MCI-SD and MCI-MD may relate to severity of cognitive deficits when severity is defined as the breadth of deficits across cognitive domains in amnestic MCI, in particular deficits within...
the language domain. We suggest that auditory cortical potentials may also become abnormally enhanced in patients with isolated language deficits as in primary progressive aphasia.

The P50 component seems to be particularly sensitive to changes occurring during the transition between normal ageing, MCI and early Alzheimer’s disease. Defining relations between P50 amplitude and clinical status is complicated by the difficulty of determining when conversion from MCI to Alzheimer’s disease takes place. Judgement of conversion to Alzheimer’s disease will vary with the clinician’s experience, the availability of neuropsychological tests and activities of daily living information, and the frequency of reassessments. Another limitation of using the P50 for clinical purposes is that the present results suggest an inverted U-shaped function of P50 amplitude among MCI-SD, MCI-MD and mild Alzheimer’s disease. Thus for a given subject P50 amplitude can be consistent with the average P50 amplitudes of both MCI-SD and mild Alzheimer’s disease. Although P300 latency was not as sensitive or specific as P50 amplitude in separating diagnostic subtypes or outcomes, one benefit of the P300 is that increased disease severity is accompanied by increases in P300 latency.

Examination of individual MCI subjects (Figs 1 and 3) indicates substantial variability in P50 measures. Discriminant analysis using P50 amplitudes to predict conversion to dementia had moderate sensitivity (81%) and specificity (73%) but well below the level necessary for clinical use as a predictor of future dementia. The specificity of P50 amplitude increases in early Alzheimer’s disease relative to other types of dementia and other neurological disorders is unknown. Thus, increased P50 amplitude should not be assumed to be a marker of early Alzheimer’s disease. However, because event-related potentials directly measure cortical activity and differ among MCI diagnostic subtypes and outcomes these measures may complement behavioural and structural MRI measures that are now becoming routine in the clinic. An expanded role for neurobiological measures may be especially useful in developing multivariate methods to predict risk of dementia in individual patients. Formal computational models could include variables such as diagnostic subtypes, neuropsychological test scores, risk factors (genetics, lifestyle), and biological measures (e.g. MRI, event-related potentials). Auditory cortical potentials may be especially useful for assessing cortical activity during the transition from normal ageing to MCI and dementia, especially in relation to domains such as language. From this perspective, the involvement of sensory cortical regions in amnestic MCI may be an indicator of progression from an isolated episodic memory disorder to a disorder affecting multiple cognitive, perceptual, and motor functions which are features of both multiple domain MCI and characteristic of dementia.

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