Patients with MCI and N400 or P600 abnormalities are at very high risk for conversion to dementia

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ABSTRACT

Objective: We sought cognitive event-related potential (ERP) biomarkers of disease progression and subsequent conversion to dementia in mild cognitive impairment (MCI).

Background: Two ERP components, the P600 and N400, are sensitive to abnormal episodic/declarative memory and semantic processing. When congruous category-exemplars are repeated, smaller P600s (relative to initial presentation) are normally elicited. Repetitions of semantically incongruous words yield smaller N400 amplitude. In mild Alzheimer disease (AD), abnormalities of both the N400 and P600 repetition effects are present, suggesting a widespread failure of synaptic plasticity.

Methods: Patients with amnestic MCI (n = 32) were longitudinally studied annually with an ERP paradigm in which semantically congruous (50%) and incongruous target words are repeated 10 to 140 seconds after initial presentation. ERP data were analyzed to contrast MCI-to-AD converters (within 3 years) vs nonconverters, using split-plot analyses of variance.

Results: A statistically significant P600 congruous word repetition effect was found only in the nonconverter group ($F = 9.9$, $p = 0.005$ vs MCI converters). This effect correlated with verbal memory measures. Repetition of incongruous words produced a significant N400 amplitude attenuation (across right-hemisphere sites) in nonconverters, but not in converters. Patients with MCI with abnormal/reduced N400 or P600 word repetition effects had an 87 to 88% likelihood of dementia within 3 years while those with normal/spared N400 and P600 repetition effects had only an 11 to 27% likelihood.

Conclusions: Abnormalities of the P600 or N400 in mild cognitive impairment are associated with an increased risk of subsequent conversion to Alzheimer disease (AD). These event-related potential components may offer useful biomarkers for the detection and staging of very early AD. *Neurology*® 2008;70:1763–1770

GLOSSARY

AD = Alzheimer disease; **ADRC** = Alzheimer's Disease Research Center; **ANOVA** = analyses of variance; **CDR** = Clinical Dementia Rating scale; **CVLT** = California Verbal Learning Test; **ERP** = event-related potential; **LPC** = late positive component; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **PPV** = positive predictive value; **UCSD** = University of California, San Diego.

Mild cognitive impairment (MCI), as originally proposed,[1] is considered a transitional stage between normal aging and Alzheimer disease (AD). This is supported by the high rate of conversion[1,2] and high prevalence of AD neuropathology.[3-5] The criteria[1] require history and objective evidence of memory difficulties, relative sparing of general cognition, and intact activities of daily living.

Cognitive ERPs, comprised of summated EPSPs and IPSPs,[6] provide an excellent tool for measuring the timing of synaptic processing. A late positive component (LPC), a.k.a. the P600, has been implicated in both memory encoding and retrieval processes.[7,8] In word list

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recognition experiments, a consistent finding has been larger late positivities (with left parietal maxima) for recognized words.[9] In contrast, when semantically predictable words are repeated, P600 amplitudes are generally smaller (relative to initial).[10,11] P600 generators have been identified in several regions important for episodic/declarative memory (i.e., hippocampus, entorhinal, cingulate, and ventral prefrontal cortex).[12-14] We have previously reported severely reduced P600 word repetition effects in circumscribed amnesia[10] and mild AD.[15]

The N400 component may also be related to verbal learning/memory.[16] N400 amplitude is proportional to semantic processing load and inversely proportional to semantic expectancy.[17,18] Invasive electrophysiology (and magnetoencephalography) reveal N400 generators in the anterior fusiform,[19] lateral parahippocampal gyri,[19] and the superior temporal sulcus.[14,20,21] Our studies of circumscribed amnesia[10] showed relatively normal N400 effects (e.g., larger N400s to new than old incongruous words). In contrast, patients with mild AD generally have absent N400 word repetition effects.[15]

To seek biomarkers/predictors of subsequent conversion to AD, we conducted annual longitudinal ERP assessments in MCI. We hypothesized that 1) patients with MCI with poorer memory or subsequent conversion would show reduced P600 word repetition effects, and 2) MCI converters will exhibit pronounced N400 abnormalities (decreased repetition and congruity effects) as they develop incipient dementia and subtle impairments in semantic/linguistic processing.

METHODS

Design. Individuals with amnestic MCI were studied longitudinally (annually) with a cognitive ERP word-repetition paradigm that reliably elicits and modulates the N400 and P600 components. We studied each patient with MCI with annual ERP and clinical assessments until either conversion to dementia (with one ERP recording performed at or soon after conversion) or dropout.

Participants. Thirty-two patients with MCI (mean age = 74.8) were studied after providing informed consent according to the guidelines of the University of California, San Diego (UCSD) Human Research Protection Program. Participants were recruited primarily from the Shiley-Marcos Alzheimer's Disease Research Center (ADRC) at UCSD. All were assessed at least annually with the Clinical Dementia Rating scale (CDR),[22] neurologic examination, and neuropsychological testing. All participants had laboratory tests screening for treatable causes of cognitive impairment (e.g., B12, TSH), and a neuroimaging study (generally MRI) prior to enrollment, which revealed no cause for their memory deficit. All patients with MCI met Petersen criteria for MCI,[1] now termed amnestic MCI,[23] and did not meet criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders–IV)[24] or AD.[25] All had baseline CDR global scores of 0.5. See table 1 for demographic and selected neuropsychological data. Six patients with MCI (two at baseline/year 1) were on cholinergic or other pharmacologic treatments for AD during the interval of this report. Exclusion criteria included stroke, epilepsy, CNS-active medications (e.g., benzodiazepines), or neuropsychiatric conditions associated with cognitive deficits.

National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria[25] for probable/possible AD were used to define conversion, independent of, and blinded to, the ERP data. Thus, decline in two or more cognitive domains, and functional decline (per CDR,[22] ADCS-MCI ADL, or FAQ[26]) were both required for conversion. Sixteen patients with MCI subsequently converted to AD within 3 years of their baseline ERP (mean interval to AD diagnosis = 1.6 ± 0.8 years).

The MCI stable group have all remained in the MCI stage for ≥3 years (mean follow-up = 4.9 ± 1.5 years). Six participants with MCI are not classified as either converters or stable due to either having ≤3 years of follow-up or technically inadequate ERP data.

ERP data from 14 elderly (mean age = 74.0) normal controls (NC), primarily from the ADRC at UCSD, are also in this report. Their baseline ERP data were published in a cross-sectional study,[27] which included 11 patients with MCI in this report.

ERP paradigm/procedure. Between 19 and 32 channel EEG was recorded at 250 Hz (bandpass = 0.16 to 100 Hz, re-referenced off-line to linked mastoids[10]) while subjects performed a semantic judgment task. Auditory category statements were followed (~1 second later) by a visual target word (duration = 300 msec, visual angle 0.4°). After a 3-second pause, participants read the target word followed by yes/no, indicating if it fit the preceding category. Three blocks of 144 trials were recorded, each lasting 20 minutes.

The details of the experimental stimuli have been published previously.[10] Half of the target words were semantically congruous (medium-typicality exemplars) and half were incongruous; half were new and half were repeats. Repeated targets followed the same category as on first presentation, with intervening time intervals ranging from ~10 to 140 s (1 to 14 trials later).

EEG was recorded from midline (Fz, Cz, Pz), and lateral (F7/F8, T5/T6, O1/O2) sites in the International 10-20 System[28] and from sites which approximate Broca area (BL/BR), Wernicke area (WL/WR), and their right-hemisphere homologues, and Brodmann area 41 (41L/41R). ERPs were derived after off-line rejection of trials with eye movement (monitored by electro-oculography), or other artifacts (using a semiautomated computer algorithm).[29] For the 26 patients with MCI (converters or stable) 34% of the trials were rejected across years 1 and 2.

Table 1 Demographics and behavioral data in mild cognitive impairment groups

	MCI (all)	MCI stable	MCI converters
N	32	10	16
Age, y	74.8 (7.4)	71.1 (7.5)	75.2 (7.1)
Sex	18 M, 14 F	6 M, 4 F	10 M, 6 F
Education, y	15.9 (3.0)	14.4 (3.8)	16.7 (2.7)
Handedness	30R, 2L	9R, 1L	15R, 1L
MMSE, year 1	27.6 (1.7)	28.0 (1.9)	27.3 (1.8)
MMSE, year 2	26.0 (3.0)	27.8 (1.6)	24.9 (3.2)*
CDR—Global year 1	0.5	0.5	0.5
CDR—Sum of boxes year 1	2.2 (1.0)	1.6 (0.6)	2.5 (1.0)*
CDR—Sum of boxes year 2	2.4 (2.2)	1.3 (0.9)	3.1 (2.5)*
CVLT Short Delay Free Recall, year 1	4.4 (2.9)	5.3 (2.7)	3.3 (2.7)
CVLT Short Delay Cued Recall, year 1	6.2 (3.0)	7.3 (2.2)	5.1 (3.2)
CVLT Long Delay Free Recall, year 1	4.8 (3.1)	5.7 (2.0)	3.4(2.7)*
CVLT Long Delay Cued Recall, year 1	5.8 (3.2)	7.3 (2.4)	4.1 (2.8)*
CVLT Discriminability (%), year 1	79.8 (13.9)	86.5 (5.0)	73.3 (15.2)*
Category Decision Task, % correct year 1	98.8 (0.9)	98.8 (0.9)	98.7 (0.9)
Category Decision Task, % correct year 2	98.2 (1.5)	98.5 (1.1)	97.9 (1.7)

Values are mean (SD).
*$p < 0.05$, MCI stable vs MCI converters.
MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating Scale; CVLT = California Verbal Learning Test.

ERP data were analyzed to contrast the MCI converters vs stable groups using mixed-design analyses of variance (ANOVA) with the factors of group, timepoint (year 1/year 2), condition (repetition or congruity), and electrode. Follow-up ANOVAs (e.g., done within group or timepoint) were performed where appropriate. The 300 to 550 msec and 500 to 800 msec latency windows, which consistently captured the N400 and P600 potentials across the participants, were chosen to quantify the N400 and P600 amplitude. Two-tailed p values of ≤ 0.05 (with Greenhouse-Geisser correction where appropriate) were considered significant.

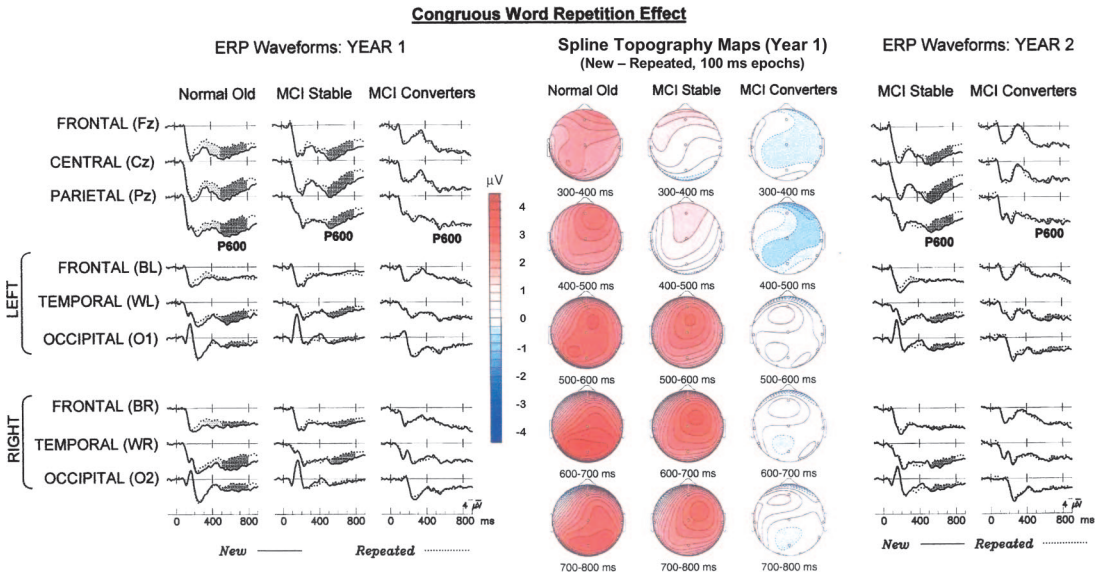
RESULTS **Behavioral data.** Both MCI subgroups performed near ceiling on the category decision task (table 1). ANOVA of the accuracy data (group × congruity × timepoint) showed a significant effect of timepoint ($F = 7.26$, $p = 0.01$), indicating a small decline in performance from year 1 to 2. There was no main effect of group or group × timepoint interaction.

ERP analyses. ***Congruous words: P600 repetition effects.*** In normal elderly subjects, repeated target words elicited smaller P600s than did their initial presentation (figure 1). A similar decrement of the P600 can be appreciated in the MCI stable group's grand average ERPs for both year 1 and year 2. However, note that their congruous word repetition effect (shaded area) had a somewhat later onset latency than NC. The MCI converters, in contrast, show no P600 congruous word repetition effect: new and repeated target words elicited identical P600s at both year 1 and year 2 (when n = 6 had developed probable AD and n = 10 were still MCI).

The longitudinal analysis of the P600 amplitude in MCI showed a main effect of repetition [$F(1,24) = 16.1$, $p = 0.0005$] with larger P600s to new than old target words across MCI participants. A group × repetition interaction was present [$F(1,24) = 9.96$, $p = 0.005$ across all channels; $F = 18.4$, $p = 0.0002$ across midline sites] indicating the MCI stable group had larger P600 repetition effects than MCI converters. Within group ANOVAs showed the MCI stable group had a significant P600 repetition effect [$F(1,9) = 18.4$, $p = 0.002$], while the MCI converters did not [$F(1,15) = 0.27$, $p = 0.61$].

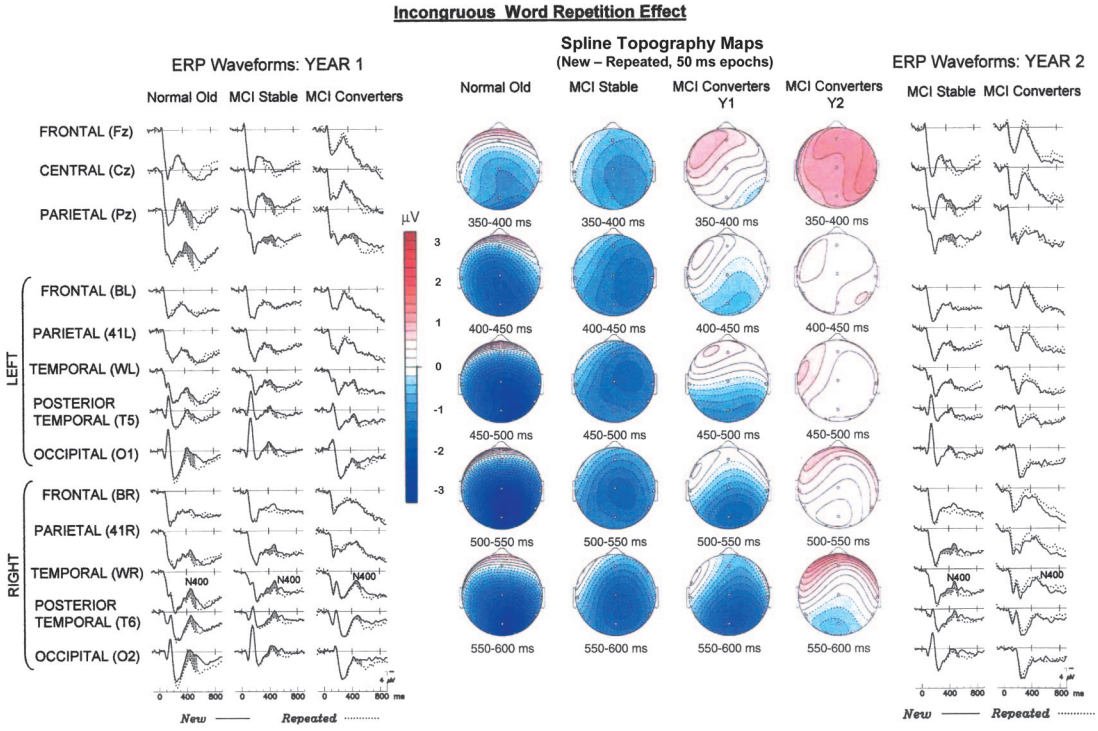
Incongruous words: N400 repetition effects. In normal elderly, larger N400s (starting at 300 msec, peaks at 500 msec) were elicited by new than repeated incongruous words (figure 2). The MCI stable and MCI converters had similar N400 repetition effects at year 1, somewhat smaller than in NC, especially for the MCI converters (compare columns 1 and 3 in left side of figure 2). By year 2, the MCI converters group showed a complete loss of the N400 repetition effect, while the MCI stable group ERP resembled those of year 1.

Figure 1 Grand average event related potentials (ERPs) for normal old, mild cognitive impairment (MCI) stable, and MCI converter groups elicited by new (solid lines) and repeated (dotted lines) semantically congruous words at year 1 (left side) and year 2 (right side)



The P600 congruous word repetition effect, which normally shows greater positivity to new words, is indicated at Pz (dark shading between 500 and 800 msec). Spherical spline topographic maps illustrating the congruous word repetition effect (ERPs to new minus old words at year 1) in consecutive 100 msec epochs for normal old (left), MCI stable (middle), and MCI Converter (right) groups are shown in the center.

Figure 2 Grand average event related potentials (ERPs) for normal old, mild cognitive impairment (MCI) stable, and MCI converter groups elicited by new (solid lines) and repeated (dotted lines) semantically incongruous words at year 1 (left side) and year 2 (right side)



The N400 incongruous word repetition effect, which normally shows smaller N400s to repeated words, is indicated at WR (shaded between 300 and 550 msec). Spherical spline topographic maps (in color, center) illustrate the incongruous word repetition effect (ERPs to new minus old words) in consecutive 50 msec epochs for normal old (left) and MCI stable (left middle) groups at year 1, and MCI converters at year 1 (right middle) and year 2 (right).

The longitudinal analysis of the N400 amplitude showed a significant group × electrode interaction [$F(14,336) = 4.2$, $p = 0.009$] indicating the MCI stable group had more posteriorly distributed N400s than the MCI converters, who had an atypically anterior distribution (especially at year 2, see top right of figure 2). There was a marginal group × repetition interaction [$F(1,24) = 3.14$, $p = 0.089$] due to a relatively larger N400 repetition effect in the MCI stable group. Within-group ANOVAs showed a significant N400 repetition effect of the MCI stable group across the right hemisphere [$F(1,9) = 9.47$, $p = 0.01$], which was of marginal significance across all channels [$F(1,9) = 4.33$, $p = 0.067$]. By contrast, the MCI converters had a nonsignificant N400 repetition effect [$F(1,15) = 0.30$, $p = 0.59$ across the right hemisphere; $F(1,15)$ $F = 0.29$, $p = 0.60$ across all channels]. Within-group ANOVA of the NC group (year 1 data) showed a highly significant effect of repetition [$F(1,13) = 7.55$, $p = 0.016$ across all channels]. The N400 repetition effect in MCI converters was slightly delayed and spatially restricted to far posterior channels (see year 1 topographies in figure 2).

New words: N400 congruity effects. The difference between the ERPs elicited by initial presentations of congruous vs incongruous words defines the N400 congruity effect. Semantically incongruous words elicited larger N400s than congruous words in all groups. The N400 congruity effect is normally maximal in right posterior channels (see the NC grand average ERP in figure e-1 on the *Neurology*® Web site at www.neurology.org). The MCI stable group's N400 effect had a similar distribution, but was prolonged in duration (persists after 550 msec, unshaded in figure e-1). In year 1, the MCI converter group ERP resembled the MCI stable group. However, in year 2, the MCI converters showed a decreased N400 congruity effect (mainly due to increased N400 amplitude to congruous words).

ANOVA of the N400 amplitude to new words showed a group × congruity interaction [$F(1,24) = 4.69$, $p = 0.04$] with a larger congruity effect in MCI stable than in MCI converters. Within-group ANOVAs showed the MCI stable group had an N400 congruity effect [$F(1,9) = 18.59$, $p = 0.002$ across all channels], which was significant at year 1 ($p = 0.004$) and year 2 ($p = 0.002$). The MCI converters had a N400 congruity effect at year 1 [$F(1,15) = 5.32$, $p = 0.036$] but not across years 1 and 2 [$F(1,15) = 2.88$, $p = 0.11$].

Correlations between ERP word repetition effects and memory. Correlational analyses of the P600 repetition effect (new – old words, mean voltage difference at Pz, 500 to 800 msec) within MCI showed significant correlations with all the main CVLT measures of verbal learning and memory (r in 0.42 to 0.68 range, table 2). Very similar results were found for correlations with the P600 repetition effect at the vertex (Cz). The P600 repetition effect correlated with the CDR sum of boxes but not with the Mini-Mental State Examination score. In contrast, the N400 repetition effect (amplitude at T6) did not significantly correlate with verbal learning/memory or global measures. Educational level was inversely correlated with both P600 and N400 repetition effect amplitudes at year 1, suggesting that patients with MCI and higher education level might have more advanced AD pathology while still in the MCI stage.[30]

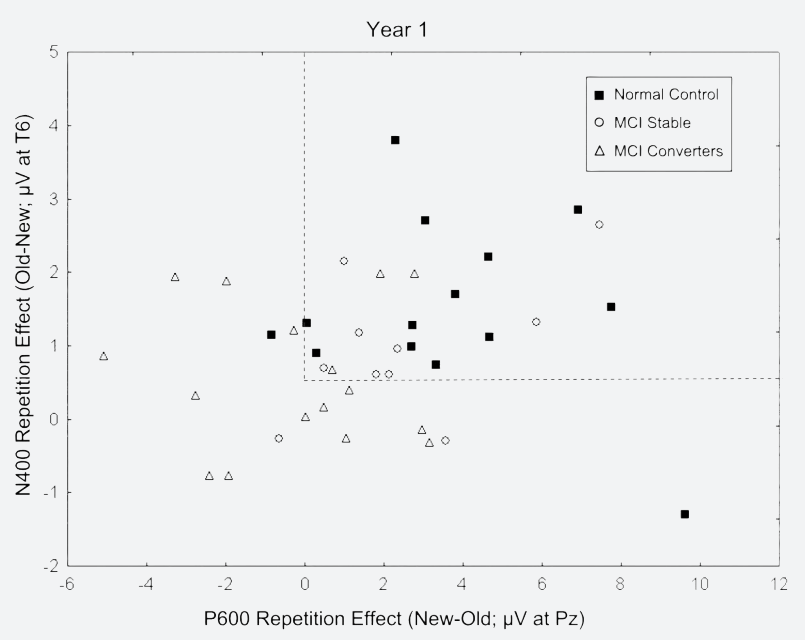
Table 2 Correlations of word repetition effects with verbal memory and global measures in mild cognitive impairment (year 1)

	P600 rep effect, r*	N400 rep effect, r†
CVLT List A, trials 1–5	0.68‡	0.13
CVLT Short Delay Free Recall	0.42§	0.09
CVLT Short Delay Cued Recall	0.46§	0.16
CVLT Long Delay Free Recall	0.48¶	0.24
CVLT Long Delay Cued Recall	0.57¶	0.13
CVLT Discriminability	0.43§	0.36
MMSE	0.10	−0.16
CDR Sum of Boxes	−0.47§	−0.05
Age	−0.22	−0.16
Education	−0.40§	−0.39§

*P600 repetition effect (new–old words) at Pz, mean amplitude 500 to 800 ms.
†N400 repetition effect (old–new words) at T6, mean amplitude 300 to 550 ms.
‡$p \leq 0.001$, §$p < 0.05$, ¶$p \leq 0.01$.
CVLT = California Verbal Learning Test; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating Scale.

Prediction value/classification. Figure 3 plots the N400 and P600 repetition effect amplitudes at year 1 (dashed lines = 10th percentile cutoffs in normal elderly). Patients with MCI with either an abnormal N400 or P600 word repetition effect had a higher likelihood of progressing to AD within 3 years (positive predictive value [PPV] = 87% to 88%; table 3). Conversely, patients with MCI with normal N400 and P600 word repetition effects had a low likelihood of converting (PPV = 11 to 27% depending on which criteria were applied). The sensitivity of the ERP measures was high in MCI converters (81 to 94%), with relatively high specificity (79 to 86% in normal el-

Figure 3 N400 and P600 word repetition effects (mean amplitude difference to new vs old words, in microvolts, at year 1)



Individual subject data are plotted for all normal control, mild cognitive impairment (MCI) converters, and MCI stable subjects. Tenth percentile cutoffs for normal elderly shown as dashed vertical and horizontal lines (values within normal limits are in the upper right quadrant with larger N400 and P600 repetition effects).

derly). However, the sensitivity was only fair (58 to 65%) when applied to all patients with MCI. Between 81 and 89% of the MCI subjects could be correctly classified as converters vs stable by these ERP criteria. For comparison, the main CVLT measures classified between 65 and 77% (e.g., 20/26 with long delay cued recall) of patients with MCI correctly.

Table 3 Sensitivity, specificity, positive predictive value, and discrimination for event-related potential criteria (abnormal vs normal)

	Criteria 1*	Criteria 2†
PPV (of conversion)		
Either abnormal P600 or N400 repetition effect	87% (13/15)	88% (15/17)
Abnormal P600 repetition effect	89% (8/9)	91% (10/11)
Abnormal N400 repetition effect	82% (9/11)	82% (9/11)
Both effects normal	27% (3/11)	11% (1/9)
Sensitivity		
All MCI	58% (15/26)	65% (17/26)
MCI converters	81% (13/16)	94% (15/16)
Specificity (normal old)	80-86% (12/14)	79% (11/14)
Correct classification of MCI		
Stable vs converters	81% (21/26)	89% (23/26)

*Below 10th percentile cutoffs for normal elderly: P600 repetition effect <0.05 μV (Pz, year 1) or N400 repetition effect <0.5 μV (T6, year 1).
†Optimal discrimination for MCI converters vs stable subgroups: P600 repetition effect <0.6 μV (Cz, year 1) or N400 repetition effect <0.6 μV (T6, year 1).
MCI = mild cognitive impairment; PPV = positive predictive value.

DISCUSSION These data demonstrate that in patients with amnestic MCI, abnormal ERP word repetition effects (P600 or N400) confer a high risk of conversion to AD. A total of 81% of the MCI converters had abnormal (<10th percentile) ERP word repetition effects at year 1. Over 80% of participants with MCI with abnormal ERP word repetition effects at baseline declined and satisfied criteria for dementia within 3 years.

The longitudinal group analyses showed that P600 abnormalities were already pronounced at baseline in MCI converters, with P600 repetition effects already near floor. In contrast, the MCI stable group demonstrated a P600 repetition effect, but with delayed latency relative to NC. Across MCI participants, smaller P600 word repetition effect amplitudes correlated with poorer verbal memory and advanced disease stage (CDR sum of boxes). This is consistent with many previous studies which have linked the P600 to declarative memory.[31,32]

In contrast to what we observed in patients with chronic amnesia (e.g., Korsakoff syndrome), MCI converters also showed abnormal N400 effects (loss of both the N400 repetition effect and N400 congruity effect). These abnormalities were present in some MCI converters at year 1, and became pronounced by year 2. Thus, the N400 (an index of semantic memory accessibility) appears sensitive to the transition from MCI to AD, when deficits in non-memory cognitive domains (e.g., language, problem solving) emerge. We believe these N400 abnormalities in MCI likely reflect subtle dysfunction of semantic memory processes. It is also noteworthy that the MCI converters show an atypically anterior N400 distribution, similar to mild AD.[15]

We are only aware of one published longitudinal ERP study of MCI, in which three annual auditory P300 assessments were obtained in elderly subjects with memory complaints.[33] Thirty of these subjects received a final clinical diagnosis (2 years later) of MCI and 28 had a final diagnosis of AD. While P300 latency was delayed at baseline and 24 months in AD, no significant P300 abnormalities were found in MCI. In contrast, a cross-sectional study[34] found a 30 msec delay of the auditory P300 latency in MCI. Here we focus on ERP repetition effects, not just the latency or amplitude of specific components.

We believe that cognitive ERPs deserve further consideration as a biomarker for very early AD. Specifically, the loss of ERP word repetition effects is very common in early AD[15] and usually precedes dementia in MCI. ERPs have limited

spatial resolution, but offer unsurpassed temporal resolution and several practical advantages (e.g., inexpensive, noninvasive). The well-recognized sensitivity of ERPs to subtle changes in speed of cognitive processing also supports their candidacy as a cost-effective biomarker for AD.

Current basic research suggests that amyloid oligomers are a strong candidate for being the initiating and causative factor for the amnesia characteristic of AD.[35,36] Some animal AD models display impaired synaptic plasticity prior to the appearance of A-β containing plaques and appreciable brain atrophy.[36,37] Thus, ERP word repetition effects could prove to be more sensitive to very early AD than volumetric MRI. Interestingly, the sensitivity of our ERP measures to MCI appears comparable to recent amyloid imaging studies (with PIB-PET) of MCI.[38,39] Further research that concurrently measures these biomarkers in MCI cohorts is needed to test their relative sensitivity and to determine which measures provide complementary vs redundant information.

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Patients with MCI and N400 or P600 abnormalities are at very high risk for conversion to dementia

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