PAPER

Abnormal verbal event related potentials in mild cognitive impairment and incipient Alzheimer's disease

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Background: It has been reported that patients with amnesia have a reduced effect of word repetition upon the late positive component of the event related potential (ERP), which peaks at around 600 ms after word onset.
Objective: To study a word repetition ERP paradigm in subjects with mild cognitive impairment.
Subjects: 14 patients with mild cognitive impairment (mean mini-mental state examination score = 27); 14 normal elderly controls.
Methods: Auditory category statements were each followed by a single visual target word (50% "congruous" category exemplars, 50% "incongruous") while ERPs were recorded. N400 (an ERP component elicited by semantically "incongruous" words) and LPC amplitude data were submitted to analysis of variance.
Results: The latency of the N400 was slower in mild cognitive impairment. In normal controls, the ERPs to "congruous" targets showed a late positive component to new words, which was greatly diminished with repetition. This repetition effect in normal subjects started before 300 ms at right frontal sites, and peaked at ~600 ms post-stimulus over posterior sites. In contrast, the group with mild cognitive impairment had a reduced repetition effect ($p < 0.02$), which started around 500 ms, with a more central distribution. Further comparisons within the cognitive impairment group showed no appreciable congruous word repetition effect among seven individuals who subsequently converted to probable Alzheimer's disease. The congruous word repetition effect in the group with mild cognitive impairment was almost entirely accounted for by the non-converters. The amplitude of the congruous late positive component word repetition effect was significantly correlated ($0.38 \leqslant r \leqslant 0.73$) with several verbal memory measures.
Conclusions: The congruous word repetition ERP effect appears sensitive to the memory impairment in mild cognitive impairment and could have value in predicting incipient Alzheimer's disease.

Alzheimer's disease is characterised by the early emergence of deficits in both episodic and semantic memory. Episodic memory impairment, with rapid forgetting of newly learned material (verbal and non-verbal), is the most common presenting symptom in Alzheimer's disease.[1] Many patients with early Alzheimer's disease also show deficits in semantic memory (that is, knowledge normally retained in long term stores), with loss of overlearned facts and concepts.[2] These deficits are well accounted for by the Braak[3] staging of neurofibrillary pathology in Alzheimer's disease, wherein the earliest lesions are found in the entorhinal cortex and neighbouring medial temporal structures critical for episodic memory, followed by lesions in temporal neocortical areas important for semantic memory.

Physiological measures of episodic or semantic memory may prove useful in the early detection of Alzheimer's disease. Cognitive event related potential (ERPs), comprised primarily of summed excitatory and inhibitory postsynaptic potentials,[4] have excellent temporal resolution and are sensitive to a variety of task manipulations. ERP studies in normal subjects have shown that the late positive component (LPC), or "P600",[5] can be a useful index of verbal episodic memory processes. Words that are more deeply encoded,[6 7] subsequently remembered,[8] or recognised as old/familiar[9] are associated with increased LPC amplitude. While repeating words in a list format normally results in an increased LPC amplitude, preceding semantic contexts which increase the probability of a word's reoccurrence have resulted in *decreased* LPC amplitudes for repeated words.[10–12] Van Petten and colleagues unified these observations by proposing that the LPC represents the updating of working memory with the contents of long term memory.[10] Because semantically predictable words are more likely to be in working memory at the time of repeated exposure, this obviates the need for new retrieval from long term memory. Intracranial recordings have revealed that the hippocampus, entorhinal, rhinal, posterior cingulate, and other "paralimbic" cortices can generate LPCs.[13]

Another ERP component, the N400, is sensitive to semantic manipulations. Previous studies have shown that N400 amplitude is small for words that are semantically "congruous" with their context, but large when words occur within a semantically "incongruous" context.[14] N400 amplitude is reduced by the repetition of words in lists of unrelated items[15] or in natural discourse.[10]

We have designed an ERP word repetition paradigm that reliably elicits the N400 and LPC. Using this paradigm, we have found severely attenuated LPC word repetition effects in patients with well circumscribed amnesia.[12] The degree of attenuation was correlated with episodic memory abilities within both amnesic and normal groups. Consistent with having preserved semantic memory, the N400 was relatively normal in people with amnesia. In contrast, previous studies in mild Alzheimer's disease have found abnormalities of the N400 and semantic memory.[16–18]

Abbreviations: CDR, clinical dementia rating; CERAD, consortium to establish a registry for Alzheimer's disease; CVLT, California verbal learning test; DRS, dementia rating scale; ERP, event related potential; LPC, late positive component; MCI, mild cognitive impairment; MMSE, mini-mental state examination

Table 1 Neuropsychological test results for the mild cognitive impairment group

	Reference No	N	Mean (SD)	Normative* mean (SD)	Maximum
Global					
MMSE	29	14	27.0 (1.7)	29.3 (1.0)	30
DRS total	30	13	131.8 (7.4)	140.8 (2.9)	144
DRS subscales	30				
Attention		13	35.9 (0.6)	36.4 (0.9)	37
Construction		13	5.6 (0.6)	5.7 (0.7)	6
Conceptualisation		13	37.5 (1.3)	38.1 (1.1)	39
Initiation/perseveration		13	32.2 (4.2)	36.3 (1.6)	37
Memory		13	20.7 (4.2)	24.4 (1.0)	25
Verbal memory					
CVLT list A, trials 1–5 (raw)	31	14	32.4 (9.9)	53.3 (8.3)	80
CVLT long delay free recall	31	14	3.6 (2.8)	11.6 (2.7)	16
CVLT long delay cued recall	31	14	4.8 (2.8)	12.2 (2.5)	16
CVLT short delay free recall	31	14	3.4 (2.5)	11.0 (2.8)	16
CVLT short delay cued recall	31	14	5.6 (2.9)	11.5 (3.1)	16
CVLT discrimination (%)	31	14	74.8 (13.6)	94.4 (5.3)	100
CERAD immediate memory (trial 3)	32	10	6.7 (1.3)	7.9 (1.6)	10
CERAD delayed recall		10	3.9 (2.7)	6.8 (1.9)	10
Non-verbal memory					
WMS-R visual reproduction I	33	13	10.3 (3.8)	12.0 (4.1)	21
WMS-R visual reproduction II		13	5.5 (4.4)	8.9 (4.1)	21
Language					
Vocabulary (WAIS-R), scaled	34	13	11.4 (3.1)	12.2 (2.8)	19
Boston naming test	35	13	26.0 (3.0)	27.5 (2.3)	30
Category fluency† (animals, fruits, vegetables)	36	12	34.8 (9.0)	46.8 (8.8)	NA
Letter fluency† (f, a, s words)	37	13	34.1 (11.8)	40.8 (12.1)	NA
Visuospatial					
Cube copy	38	12	11.2 (2.2)	12.0 (1.2)	13
WISC-R block design	39	13	36.0 (11.9)	41.8 (10.4)	62
Executive function					
WCST, categories achieved	40	13	4.8 (1.6)	5.3 (1.3)	6
WCST, preservation errors	40	13	1.2 (2.5)	2.0 (5.1)	NA
Trails B (seconds)	41	13	147.4 (56.0)	103.1 (47.5)	300
Attention					
Digit span (WAIS-R, scaled score)	34	13	9.2 (2.0)	10.0 (2.7)	19
Trails A (seconds)	41	13	58.6 (22.8)	48.5 (20.8)	150

DRS, Mattis dementia rating scale; CERAD, consortium to establish a registry for Alzheimer's disease; CVLT, California verbal learning test; MMSE, mini-mental state examination; NA, not applicable; WAIS-R, Wechsler adult intelligence scale, revised; WCST, Wisconsin card sorting test, modified; WISC-R, Wechsler intelligence scale for children, revised; WMS-R, Wechsler memory scale, revised.
"Maximum" indicates the highest possible score on a test.
*Normative means and SDs listed are from large published cohorts (n=51–101) of comparably aged ADRC normal participants,[42,43] except for the CERAD word list where normative elderly data are cited from Welsh *et al*.[44]
†Category fluency score is the total number of correct words provided in 60 seconds for each category. Letter fluency is the total number of f, a, s words provided over 60 seconds for each letter.

We therefore applied our ERP paradigm to a group of patients with mild cognitive impairment (MCI), a condition usually accompanied by Alzheimer's disease pathology[19] which often precedes dementia. The cognitive deficits in mild cognitive impairment are primarily of memory, but owing to the absence of functional decline, criteria for dementia[20] or probable Alzheimer's disease[21] are not satisfied. Patients with mild cognitive impairment convert to Alzheimer's disease at the rate of 12–15% a year.[22 23] Severity of episodic memory impairment is one of the best known predictors of subsequent conversion.[24 25]

We hypothesised that, compared with normal elderly people, patients with mild cognitive impairment would have attenuated ERP effects of word repetition for "congruous" (category exemplar) words, which normally elicit the LPC but not the N400. We predicted that greater reductions in the LPC word repetition effect would be associated with poorer episodic memory and subsequent conversion to Alzheimer's disease.

METHODS

Participants

Fourteen patients with mild cognitive impairment (MCI group; mean age 74.6 years) and 14 normal elderly controls (mean age 74.0 years) served as volunteers after providing informed consent according to the guidelines of the University of California, San Diego (UCSD) human research protection program. All participants were right handed and 15 were male (eight in the MCI group, seven controls). Mean educational level was 15.1 years in the MCI group and 16.0 years in the control group ($t_{26} = 0.77$, $p = 0.45$).

Subjects were recruited primarily from the UCSD Alzheimer's Disease Research Center (ADRC), where they received annual evaluations which included the clinical dementia rating scale[26] (CDR), medical history, neurological examination, laboratory tests, and extensive neuropsychological testing,[27 28] including global assessments,[29 30] and tests of verbal and non-verbal memory,[31–33] language,[34–37] visuospatial function,[38 39] executive function,[40 41] and attentional abilities[34 41] (listed in table 1).

The inclusion criteria for mild cognitive impairment were:

- subjective memory complaints or a history of memory problems according to a reliable informant;
- mild cognitive impairment on neuropsychological testing, with deficits predominantly in memory;

- absence of any definite functional decline;
- not meeting criteria for dementia[20] or Alzheimer's disease (probable or possible).[21]

The patients with mild cognitive impairment had baseline CDR global scores of 0.5 ("questionable dementia") and a mean mini-mental state examination (MMSE) score of 27.0. The neuropsychological data for the MCI group are summarised in table 1, with normative reference data.[42–44] These data show moderately severe deficits in both verbal and non-verbal memory, with relatively intact performance in other cognitive domains. Most of the patients were diagnosed as being "at risk for Alzheimer's disease" at the time of ERP testing, before the widespread use of "mild cognitive impairment" as a diagnostic label. None was on cholinergic or other pharmacological treatments for Alzheimer's disease.

Exclusions were a history of stroke, epilepsy, schizophrenia, any CNS-active drug, or other neuropsychiatric conditions which could cause the observed cognitive deficits.

In annual follow up assessments, NINCDS-ADRDA criteria[21] for probable/possible Alzheimer's disease were used to define conversion to Alzheimer's disease. Thus a decline in two or more cognitive domains, and functional decline (on the CDR[26] or Pfeffer functional activities questionaire[45]) were both required for conversion. Seven patients with mild cognitive impairment subsequently converted to a diagnosis of Alzheimer's disease.

The mean (SD) follow up period was 2.0 (1.5) years, not counting the interval after Alzheimer's disease was diagnosed in the converters. To reduce the likelihood of age related Alzheimer's disease pathology in the control group, we excluded "normal" elderly people with mild memory impairment (mean age corrected z score ≤ -1 on delayed verbal memory tests).

Procedures

Subjects were fitted with an electrode cap and seated 125 cm from a video monitor. Category statements were read aloud, each followed (about one second later) by a visually presented target word (duration 300 ms). Subjects were instructed to sit quietly for three seconds following a target, then to say the perceived word followed by "yes" or "no," indicating whether or not it was an exemplar of the defined category. The ERP recordings were done in three blocks of 144 trials, each lasting slightly over 20 minutes. The entire ERP procedure, including setup and brief interblock rests, takes around 90 minutes.

Stimuli

The stimuli were 216 phrases describing a category (for example, "a breakfast food"), each followed by a target word. Categories and targets were selected with the aid of published norms and locally administered normative questionnaires.[12] Half the target words ("congruous" words) were medium typicality category exemplars (for example, "pancake" for "a breakfast food"). The other half of the targets were concrete nouns that were "incongruous" in their associated category, but were matched to the congruous target words for length and frequency of usage.[12 46]

Each subject was assigned to one of three stimulus lists (in a counterbalanced manner), which included 36 congruent targets presented once, 36 presented twice, 36 presented three times, and equal numbers of incongruent targets in the same repetition conditions, for a total of 432 trials. Half the stimuli were congruous and half incongruous; half were new and half were repeats. Repeated targets always appeared with the same category as on the first presentation. For singly repeated category–target pairings, the lag between first and second presentations was 0–3 intervening trials (spanning 10–40 s). For doubly repeated items, the lag for both second and third presentations was 10–13 intervening trials (~120 s).

Electrophysiological recording

The EEG was recorded from tin electrodes embedded in an elastic cap from midline central (Cz), and lateral frontal (F7,F8), temporal (T5,T6), and occipital sites (O1,O2) defined by the international 10-20 system.[47] Additional lateral sites included electrode pairs which approximate Broca's area (Bl,Br), Wernicke's area (Wl,Wr), and their right hemisphere homologues, and a third pair one third of the interaural distance lateral to Cz over the superior temporal lobe (41L and 41R).[12] All scalp electrodes and the right mastoid electrode were referenced on-line to the left mastoid, then re-referenced off-line to an average of the left and right mastoids. Vertical and horizontal eye movements were monitored with electrodes below the right eye, and at the outer canthi of each eye. Most subjects (24) also had three additional electrodes (a total of 19 channels), which were left lower eye (Lle), midline frontal (Fz), and parietal (Pz).

The EEG was recorded with a 0.016–100 Hz bandpass and digitised using a 250 Hz sampling rate. ERPs to the visual target words were averaged after off-line rejection of trials contaminated by eye movements or other artefacts.[48] In controls, 27.6% of the trials were rejected as compared with 36.9% in the cognitive impairment group ($t_{26} = 1.51$, $p = 0.14$).

ERP analyses

The ERP data were submitted to split-plot analyses of variance (ANOVA) with the between subject factor *group*, and three within subject factors: *condition* (either congruity or repetition), *latency* (300–550 ms and 550–800 ms epochs were used to quantify the N400 and LPC time windows, respectively), and *electrode*. The latency windows chosen captured the N400 and LPC consistently across subjects. Two tailed p values of ≤ 0.05 were considered significant. The Greenhouse-Geiser correction[49] was applied where appropriate to correct for violations of sphericity. ANOVAs were also performed with the additional factor of time lag (short *v* long lag) between new and repeated stimuli, which showed no differential effects of time delay and have been omitted for brevity.

RESULTS

Behavioural results

Although performance on the category decision task was near ceiling in the MCI group (98.5 (1.2)% correct), it was significantly worse than in the control group (99.7 (0.3)% correct) (Mann-Whitney U test =17.0, $p = 0.0002$). Accuracy was higher for incongruous items (99.0% in cognitive impairment, 99.9% in controls) than for congruous items (98.1% in cognitive impairment, 99.5% in controls).

ERP results

Semantic congruity

Figure 1 shows the ERPs elicited by new congruous target words (thick solid lines) and incongruous target words (dotted lines) in the control and MCI groups. The large N400 elicited by new incongruous words was most prominent in the right temporal and posterior channels. The congruity effect—that is, the difference between the ERPs to incongruous and congruous words—began around 300 ms after stimulus onset and peaked at about 450 ms (slightly later in the MCI group). The congruity effect terminated by 600 ms at most sites in the control group, but persisted until around 700 ms at many sites in the MCI group. Mean amplitudes within latency windows of 300–550 ms and 550–800 ms post-stimulus (relative to a 100 ms pre-stimulus baseline) defined the N400 and LPC amplitudes, respectively. These were subjected to ANOVA as described above. The fractional area latency of this congruity effect (or "N400 effect"[16]) was submitted to ANOVAs across all right hemisphere channels and at Cz, but was not reliably

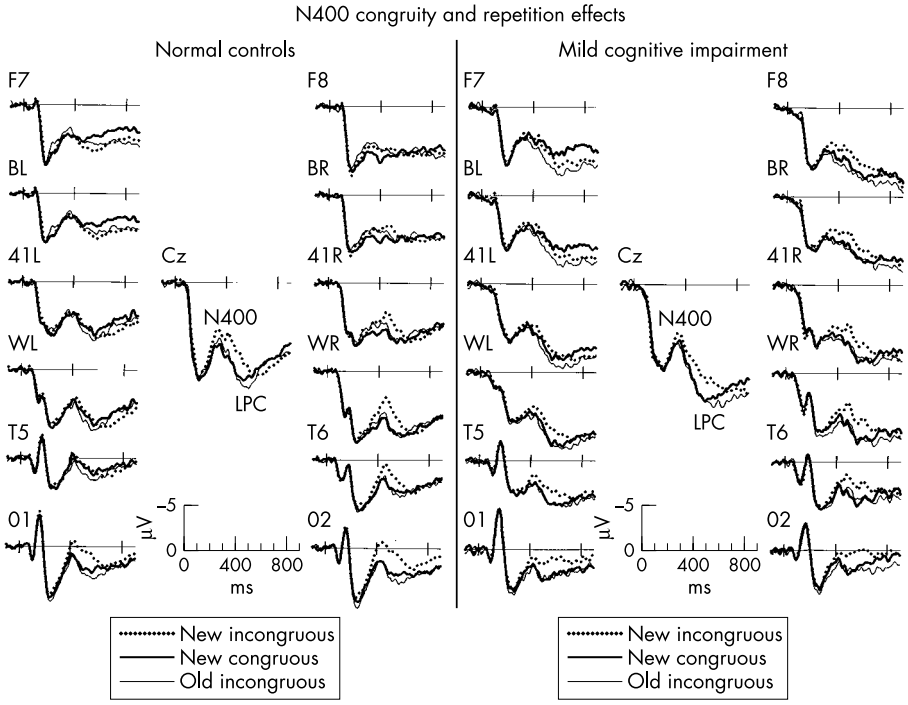

Figure 1 Grand average event related potentials (ERPs) of the normal control (NC) and mild cognitive impairment (MCI) groups to new semantically congruous words (thick continuous lines), new incongruous words (dotted lines), and repeated incongruous words (thin continuous lines). Negative voltage is plotted up with left hemisphere electrodes on the left and right hemisphere electrodes on the right. The N400 and late positive component (LPC) are indicated at the vertex.

present across subjects in left hemisphere channels. The fractional area latency is the time point by which 50% of the congruity effect occurred (area beneath the incongruous–congruous difference wave).

A larger negativity (N400) was present in the earlier (300–550 ms) than the later (550–800 ms) latency window (effect of latency: $F(1,26) = 5.58$, $p = 0.026$). The congruity effect occurred nearly entirely within the 300–550 ms epoch (latency × congruity interaction: $F(1,26) = 11.57$, $p = 0.0022$; main effect of congruity: $F(1,26) = 3.90$, $p = 0.059$). Analyses restricted to the "N400" epoch (300–550) showed the effect of congruity was highly significant ($F(1,26) = 14.74$, $p = 0.0007$). There were neither significant group effects nor group interaction effects on the ERP amplitude.

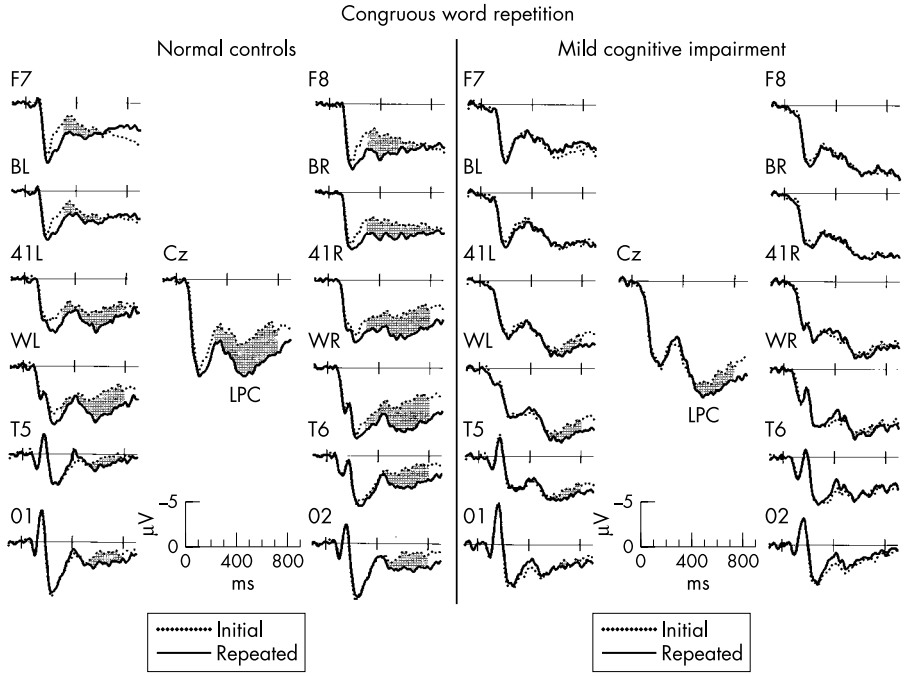

Figure 2 Grand average event related potentials (ERPs) for normal control (NC) and mild cognitive impairment (MCI) groups elicited by new and repeated semantically congruous words. The "congruous word repetition effect" (between 300 and 800 ms), which normally shows greater positivity to new words, has been shaded.

Table 2 Correlations between the event related potential (ERP) repetition effects and memory performance

	LPC repetition effect (550–800 ms, Cz)		Global LPC repetition effect (550–800 ms, all sites)	
	MCI (n=14)	All (n=28)	MCI (n=14)	All (n=28)
CVLT[31]				
List A, total 1–5	0.73**	0.53*	0.68**	0.53**
Short delay – free recall	0.60*	0.51*	0.54*	0.51**
Short delay – cued recall	0.51	0.41*	0.37	0.41*
Long delay – free recall	0.41	0.38*	0.33	0.44*
Long delay – cued recall	0.46	0.35	0.29	0.38*
Discriminatability	0.56*	0.44*	0.50	0.44*
CERAD word list[32]				
Immediate recall	0.67*	0.37	0.71*	0.43*
Delayed recall	0.59	0.37	0.65*	0.47*
Other				
DRS[30] – memory	0.40	0.40*	0.29	0.36
DRS – total	0.05	0.20	0.07	0.29
Age	–0.27	–0.30	–0.35	–0.25
Education	–0.48	–0.16	–0.49	–0.10

Pearson correlations between ERP repetition effects (mean amplitude of difference between new and repeated items in a 550 to 800 ms latency window for congruous items) and neuropsychological tests of verbal memory.
*p < 0.05; **p < 0.01.
CERAD, consortium to establish a registry for Alzheimer's disease; CVLT, California verbal learning test[31]; DRS, dementia rating scale[30]; LPC, late positive component; MCI, mild cognitive impairment.

The fractional area latency of the N400 congruity effect was significantly delayed in the MCI group at Cz (MCI (mean (SD)): 532 (66) ms; controls: 471 (68) ms; $F(1,26) = 5.97$, $p = 0.02$), and across all right hemisphere sites (MCI: 543 (74) ms; controls: 503 (64) ms; $F(1,26) = 4.60$, $p = 0.04$).

Repetition of incongruous words

Figure 1 includes the ERPs for initial presentations (dotted lines) and repeated presentations (thin solid lines) of incongruous targets, collapsed across repetition lags. Both groups had larger N400s to new than to repeated words. Visual inspection shows that the MCI group had a prolonged incongruous word repetition effect compared with the controls. Note that, while the incongruous repetition effect remained in the positive direction until ⩾ 800 ms in all channels in the MCI group, the control group showed a small reversal in the direction/polarity of this effect after around 600 ms at several locations (for example, channels Cz, WL, and WR).

The ERPs to incongruous items were analysed by split plot ANOVA with factors of *group*, *repetition* (first *v* repeated presentations), *latency window* (300–550 and 550–800 ms), and *electrode*. This showed that a larger negativity (N400) was present in the "early" (300–550 ms) than in the "late" latency window (effect of latency: $F(1,26) = 6.80$, $p = 0.015$). Repeated incongruous words elicited significantly more positive voltages than initial presentations (effect of repetition: $F(1,26) = 7.00$, $p = 0.014$), which appears primarily to reflect a reduction of the N400 (fig 1). In support of this interpretation, the latency × repetition interaction was marginally significant ($F(1,26) = 3.96$, $p = 0.057$), with a larger effect during the earlier (300–550 ms) window. There was a slightly delayed incongruous repetition effect in MCI compared with controls (three way interaction of group × latency × repetition: $F(1,26) = 4.03$, $p = 0.055$).

Repetition of congruous words

Figure 2 (left side) shows the ERPs elicited from the control subjects by the first and repeated presentations of congruous items. The new congruous words elicited a large late positivity (peaking at around 550–600 ms), which was reduced with repetition. This "congruous word repetition effect," opposite in polarity to the incongruous word repetition effect, was largest in posterior channels and peaked at around 600 ms. The congruous word repetition effect was greatly attenuated in the MCI group (fig 2, right side), in which a very small late modulation of the LPC was evident only at the vertex and left temporal sites. New words elicited larger positivities than repeated words (effect of repetition: $F(1,26) = 7.35$, $p = 0.01$). This repetition effect tended to be larger in the 550–800 ms epoch than in the 300–550 ms epoch (repetition × latency interaction: $p = 0.07$). The mean amplitude of the congruous repetition effect (300–800 ms) was smaller in the MCI group than in the control group (group × repetition interaction: $F(1,26) = 6.36$, $p=0.018$). The mean amplitude of the congruous repetition effect in the MCI group was < 0.1 μV and not significantly different from zero. The congruous repetition effect was largest at the vertex and bilateral temporal sites. A three way group × repetition × electrode interaction was present ($F(12,312) = 2.59$; $\epsilon = 0.33$, $p = 0.04$), indicating that the congruous repetition effect had a different scalp distribution in the two groups (fig 2).

Correlations of ERPs with memory and language

Correlational analyses were conducted for the "LPC repetition effect" (mean voltage difference in the 550–800 ms epoch at Cz for new–old congruous words), and the "global LPC repetition effect" (mean voltage difference averaged across all scalp channels during this epoch). Both these measures were significantly correlated with several measures of verbal memory (on the CVLT (California verbal learning test)[31] and the CERAD (consortium to establish a registry for Alzheimer's disease) word list[32]) in the MCI group and in the sample as a whole (table 2). The LPC repetition effect also correlated with the DRS (dementia rating scale[30]) memory subscale, but did not correlate significantly with global cognitive impairment (DRS total), or with any other DRS subscales (all r values < 0.17); neither did the LPC repetition effect correlate with the measures of non-verbal memory or language listed in table 1.

The "N400 repetition effect" (mean amplitude of the difference between old–new incongruous items between 300 and 550 ms at T6, where the effect was most consistently present) showed no significant correlation with verbal memory, non-verbal memory, or language measures. However, the fractional area latency of the N400 congruity effect at T6 was inversely correlated with verbal fluency ($r = –0.47$ with category fluency, $r = –0.50$ with letter fluency) and with performance on some verbal memory measures ($–0.55 \leqslant r\text{'s} \leqslant –0.45$ with CVLT long delayed cued recall, and

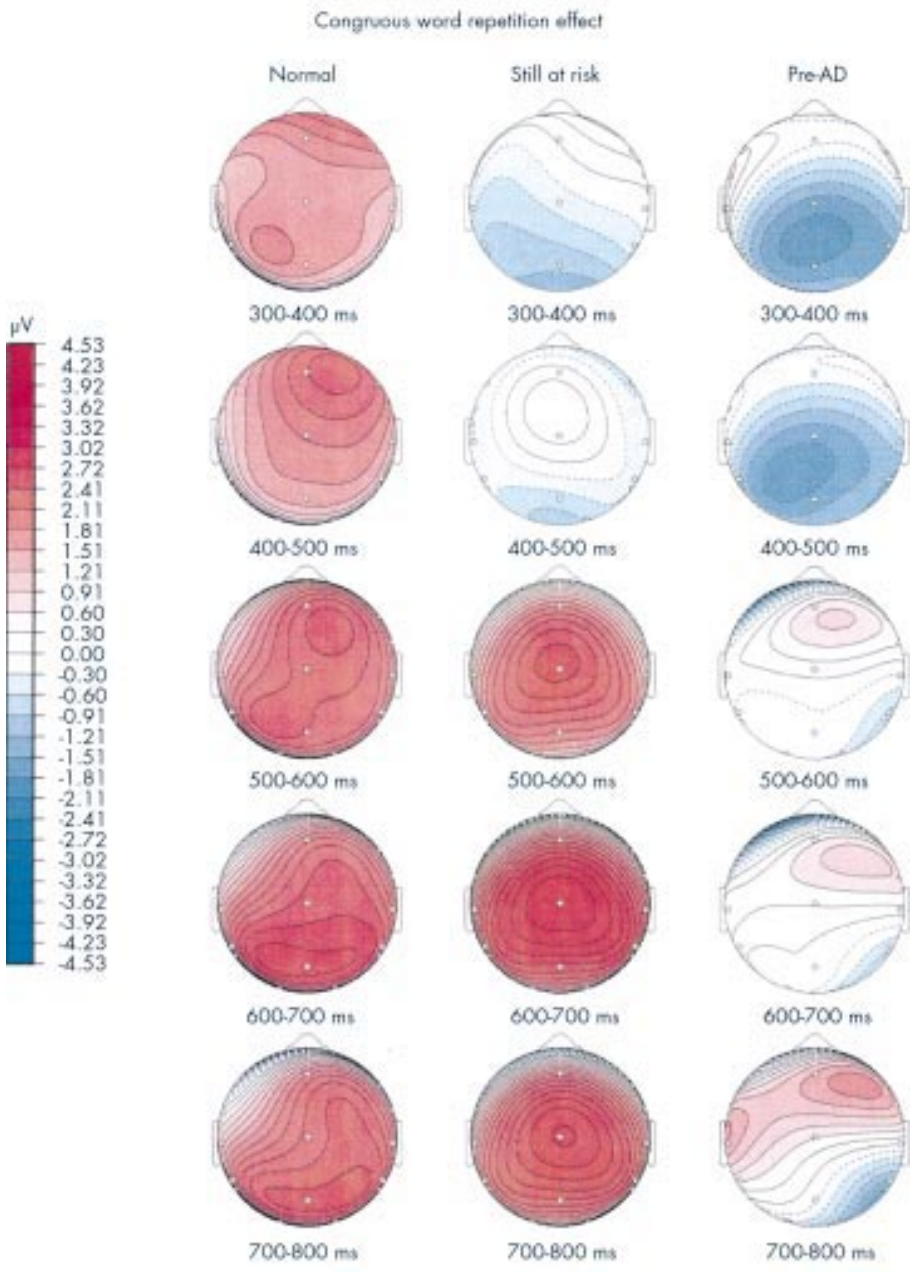

Figure 3 Spherical spline topographical maps illustrating the congruous word repetition effect (event related potentials to new minus old words) in 100 ms epochs for the following subject groups: normal elderly people, "still at risk" (mild cognitive impairment, non-converters), and "pre-AD" (mild cognitive impairment, later converting to Alzheimer's disease).

CERAD word list immediate and delayed recall). Unlike the LPC repetition effect, none of the correlations with verbal memory was significant within the MCI group ($-0.36 \leqslant r\text{'s} \leqslant 0.09$), suggesting that these correlations were driven by inter-group differences.

ERP abnormalities and conversion to Alzheimer's disease

Figure 3 shows the topographical scalp distribution of the congruous repetition effect in the controls and two MCI subgroups: those who subsequently converted to Alzheimer's disease ("pre-AD", n = 7), and those who did not convert ("still at risk", n = 6). This shows that the congruous word repetition effect starts earliest in the normal controls, with a right frontal maximum initially which progresses to a fairly symmetrical posterior maximum after around 600 ms. The "still at risk" subgroup had a later onset of the congruous repetition effect (after about 500 ms), with a somewhat more anterior/central distribution than in the normal individuals during the later time windows. The "pre-AD" patients showed a nearly complete absence of any congruous word repetition effect in the "normal" direction (positive depicted as red, for new minus old words). Despite the small samples, the LPC repetition effect was significantly reduced in the "pre-AD" group compared with those "still at risk" ($t_{11} = 2.2$, $p = 0.05$). In contrast, the MMSE did not discriminate between these patient subgroups (mean MMSE scores 26.6 and 27.5; $t_{11} = 0.93$, $p = 0.37$).

When we applied a "normal" cut off of any value between 1.79 and 2.89 μV for the LPC repetition effect—similar to the cut off (~2.5 μV) which we previously found discriminated amnesic subjects from controls[12]—we correctly classified 85% of the MCI subjects (11/13) as converters or non-converters. By comparison, optimal cut off points on the CVLT list A trials

1–5 total score (≥ 30) or CVLT discriminability (≥ 0.80) each yielded 77% correct classification. One case was lost to follow up and was therefore excluded from these analyses. The two "misclassified" patients were interesting in that the "false positive" MCI case had a stroke with hemiparesis around three months later. The "false negative" MCI case developed an abnormal LPC repetition effect when retested one year later (when he also met criteria for probable Alzheimer's disease). By comparison, around 82% of normal elderly people tested on this ERP paradigm had LPC repetition effects of > 2.2 μV (11/14 in this study).

DISCUSSION

We found a diminished LPC repetition effect in people with mild cognitive impairment. This was to be expected as such individuals have quite pronounced memory deficits. Our study replicates the correlation between the LPC repetition effect amplitude and verbal memory abilities which we reported previously in patients with amnesia.[12] It is noteworthy that the ERP abnormalities were present before the development of Alzheimer's disease dementia. The early detection of Alzheimer's disease is especially important now that primary prevention strategies are being developed to delay the progress of the disease. This ERP paradigm may provide an objective measure of memory dysfunction which could prove useful in the early prediction or diagnosis of Alzheimer's disease in challenging cases (for example, in mild cognitive impairment, in people with memory complaints that are worse than deficits, or in those with depressive symptoms). Previous work has shown that progression to Alzheimer's disease can be well predicted by certain verbal[24 25] and non-verbal memory tasks.[50 51] It remains to be seen whether ERP measures such as these will provide a more accurate prediction than traditional neuropsychological and memory tests.

Even more striking is our preliminary finding that the LPC repetition effect was absent or severely reduced in the bulk of the individuals who subsequently converted to Alzheimer's disease. ERP studies of cohorts who carry apolipoprotein E4 or other genetic risks for Alzheimer's disease and were tested when cognitively normal in their sixth decade have found abnormalities of P50, N200, and P300.[52 53] Golob *et al* recently showed P300 latency abnormalities in people with mild cognitive impairment.[54] We are not aware of previous ERP studies of the LPC or N400 in mild cognitive impairment.

Some previous ERP studies which used word lists and measured the repetition effects only on non-target items reported intact word repetition effects in Alzheimer's disease.[55 56] Because these stimuli were not supported by a semantically congruous preceding context, their results may be more akin to the intact incongruous word repetition effects that we find in patients with mild cognitive impairment or amnesia. Word list experiments normally produce an ERP repetition effect in the same direction as repeating incongruous words (increased positivities with old items), but opposite in polarity to the congruous word repetition effect. Our results are more consistent with the findings of Tendolkar and colleagues,[57] who reported large reductions in the ERP difference—normally present between 400 and 1000 ms in left temporal channels—to new–old words in Alzheimer's disease. They used an explicit memory (recognition) task, closer to our paradigm in that episodic memory is normally robust for our congruous category exemplar words.[12]

The medial temporal lobe is thought to be particularly important for encoding relations between an item and its context—that is, "binding" together the various features of an episode as a unified memory trace.[58 59] Bilateral lesions of the medial temporal lobe often cause isolated deficits in declarative memory[60] which resemble the deficits in mild cognitive impairment. It is likely that the reduced LPC repetition effect in mild cognitive impairment (most severe over the temporal and posterior scalp) reflects pathology or dysfunction of the medial temporal lobe. The medial temporal lobe is both where the main LPC generators are likely to reside and the primary predilection site for the neurofibrillary pathology of early Alzheimer's disease.[3] Very large LPCs have been recorded within the human hippocampus,[13] but it is not known to what extent these contribute to the scalp LPC. While the LPC amplitude is not generally reduced (across conditions) in mild cognitive impairment, the repetition sensitive quality of the LPC generators is clearly diminished, and it was absent in most patients in our MCI group who converted to Alzheimer's disease. This suggests a loss of the neural plasticity of the LPC generators, which may be directly attributable to local Alzheimer's disease pathology or may result from a disconnection of these generators.[61]

We also found some evidence of N400 abnormalities in mild cognitive impairment, though these were not as robust as the LPC repetition effect abnormalities. While the overall N400 amplitude appears similar to that in normal elderly people, the fractional area latency of the N400 was delayed in our patients with mild cognitive impairment; furthermore, the mildly delayed incongruous word repetition effect in this condition also suggests slower N400s. These findings are consistent with previous reports of abnormal N400s in patients with mild Alzheimer's disease.[16–18]

Conclusions

In summary, we found a reduced effect of word repetition (for semantically congruous words) on the LPC in people with mild cognitive impairment. Our data suggest that a markedly reduced LPC repetition effect may be an index of incipient Alzheimer's disease dementia. Caution is warranted, however, until larger cohorts of patients with mild cognitive impairment can be studied for longer periods and our findings replicated. Additional diagnostic value, beyond that provided by the tests routinely used in the assessment of dementia, would need to be demonstrated in order to justify the time and costs involved.

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