

## Absent event-related potential (ERP) word repetition effects in mild Alzheimer's disease

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### Abstract

**Objective:** We hypothesized that an ERP word repetition paradigm, which reliably elicits and modulates the P600 and N400 components, would be particularly sensitive to the memory deficits and altered synaptic plasticity in mild Alzheimer's disease (AD). The P600 (a late positive component, or 'LPC'), and the N400, are sensitive indices of memory encoding and semantic processing, respectively.

**Methods:** We studied 11 patients with mild AD (mean MMSE=22.9) and 11 elderly (mean age=77.1) normal controls (NC) on a paradigm in which semantically 'congruous' category statement/exemplar pairs (50%) and 'incongruous' category statement/non-exemplar pairs (50%) repeat at 10–140 s intervals. A minimum of 19 channels ERP data were recorded and submitted to split-plot ANOVAs.

**Results:** Normal ERP data showed: (1) a significant word repetition effect for congruous words, with a wide-spread late positivity between ~300 and 800 ms post-stimulus (P600) that is larger for New than Old words; (2) a significant N400 repetition effect for incongruous words, with a right posterior negativity that is reduced for Old relative to New words. By contrast, neither of these word repetition effects was reliably present in the mild AD group. Good group discrimination was achieved by requiring that both these repetition effects were  $\geq$  the 10th percentile, with 100% sensitivity and 82% specificity.

**Conclusions:** We found significant abnormalities of the N400 and P600 in mild AD, with both potentials showing markedly reduced sensitivity to word repetition.

**Significance:** The absence of normal N400 and LPC/P600 word repetition effects suggests impaired functioning of their neural generators, several of which are located in medial temporal lobe predilection sites (e.g. anterior fusiform, parahippocampal gyrus, hippocampus) for AD/tau pathology.

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### 1. Introduction

The early emergence of memory dysfunction is a cardinal feature of Alzheimer's disease (AD). The traditional neuroanatomical explanation for this is provided by

the Braak staging of neurofibrillary AD pathology, in which the entorhinal cortex and surrounding medial temporal structures are the earliest predilection sites (Braak and Braak, 1991). As these lesions extend further, from the entorhinal and transentorhinal cortical regions into the inferior and lateral temporal neocortex, one would expect deficits in episodic memory to be followed by semantic memory deficits.

Some investigators have viewed the amnesia of early AD as evidence for a primary disorder of synaptic plasticity

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(Mesulam, 1999; Selkoe, 2002). Clinico-neuropathologic studies have also implicated the synapse as a primary mediator of dementia severity. Terry and colleagues found that nearly 90% of the variance in dementia severity could be accounted for by the density of pre-synaptic terminals stained by synaptophysin in mid-frontal cortex (Terry et al., 1991).

Cognitive ERPs, composed mainly of summated excitatory and inhibitory post-synaptic potentials (EPSPs and IPSPs), provide an excellent tool for measuring synaptic plasticity and the precise timing of neural/cognitive processes evoked by novel and familiar stimuli. ERPs have an unsurpassed temporal resolution (millisecond level) and good signal-to-noise ratios. ERPs have also proven sensitive to a whole host of task manipulations. Two ERP components particularly relevant to AD are the N400 and a late positive component (LPC) termed the ‘P600’. ERP studies of language have shown that N400 amplitude is strongly correlated with semantic processing demands (Chwilla Brown, and Hagoort, 1995; Kutas and Hillyard, 1980, 1984; Kutas and Iragui, 1998). Depth recording studies have consistently found N400 generators in the inferior anterior temporal lobes (bilateral anterior fusiform and parahippocampal gyri) (McCarthy et al., 1995; Nobre et al., 1994), with additional candidate generators also reported near the superior temporal sulcus, posterior parietal and ventral prefrontal cortical regions (Halgren et al., 1994, 2002). The P600<sup>1</sup> has been implicated as an important index of memory encoding (Fernández et al., 1999; Paller et al., 1987). Neural generators for the P600 include the medial temporal lobe (i.e. hippocampus, entorhinal cortex), and several paralimbic cortical regions (i.e. cingulate, orbito-frontal cortex and temporal pole) (Guillem et al., 1999; Halgren et al., 1994). Depth recordings in some association neocortical (ventrolateral, prefrontal, lateral temporal and anterior fusiform) regions have shown biphasic ERP components which resemble N400–P600 complexes (Guillem et al., 1999; Halgren et al., 1994).

Using an ERP word repetition paradigm with category–target word pairs which reliably elicits and modulates the N400 and P600, we have previously demonstrated reduced P600 word repetition effects (to New–Old words in a semantically supported context) in patients with mild cognitive impairment (MCI) (Olichney et al., 2002a) or well-circumscribed amnesia due to other etiologies such as Korsakoff’s Syndrome (Olichney et al., 2000). This finding was particularly robust in MCI patients who subsequently

converted to AD (Olichney et al., 2002a). While new congruous words (i.e. category exemplars) elicit large P600s in both normals and amnesics, only normal subjects show large decrements in the P600 amplitude with repetition. In contrast, patients with amnesia show relatively normal N400 potentials, sensitive to both semantic congruity and word repetition (of semantically incongruous items), perhaps due to preserved long-term semantic memory stores. Contrary to these findings in amnesia, several studies of mild AD have shown abnormalities of the N400 amplitude and/or N400 latency (Ford et al., 1996; Iragui et al., 1996; Olichney and Hillert, 2004; Olichney et al., 2002b; Ostrosky-Solís et al., 1998; Schwartz et al., 1996).

Considering the background above, we decided to apply our ERP word repetition paradigm to a cohort with mild AD. We thought that this ERP paradigm would provide sensitive measures for detecting mild AD and could prove useful in staging the extent of AD pathology. We hypothesized that patients with AD would have abnormalities of both the P600 and N400, reflecting their impairments in episodic memory and semantic memory, respectively. Considering their demonstrated abnormalities of synaptic morphology and function, we hypothesized that both the P600 and N400 word repetition effects would be diminished in AD.

## 2. Methods

### 2.1. Participants

Participants were 11 mild AD patients and 11 matched normal elderly controls (NC), who served as volunteers after providing informed consent according to the guidelines of the University of California, San Diego (UCSD) Human Research Protection Program. The majority of subjects were male (8 AD, 7 NC). All were right-handed, except for one left-handed AD patient and one ambidextrous NC. The mean age and education ( $\pm$ SD) was  $79.4 \pm 7.2$  and  $15.9 \pm 3.3$  in the AD group, which was not significantly different from the age ( $77.1 \pm 2.9$ ) and education ( $15.9 \pm 2.9$ ) of the NC group ( $t_{20} = 0.98$ ,  $P = 0.34$  for age;  $t_{20} = 0.03$ ,  $P = 0.97$  for education). Subjects were recruited primarily from the UCSD Alzheimer’s Disease Research Center (ADRC), where they received annual evaluations, medical history, neurological examination, laboratory tests, and extensive neuropsychological testing. The neuropsychological test battery included tests of global abilities (MMSE, DRS), verbal and non-verbal memory (e.g. CVLT, WMS-R Logical memory and the Heaton modified WMS-R visual reproduction test), language (Boston naming test, WAIS-R Vocabulary, category and letter fluency), visuospatial (cube copy and modified parietal lobe battery), executive/abstraction/problem solving function (e.g. trails A and B, WAIS-R similarities and arithmetic), and attentional (WAIS-R digit span) abilities (Olichney et al., 2000; Salmon and Butters,

<sup>1</sup> The term ‘P600’ has also been used to refer to a ‘syntactic positive shift’ (SPS) observed at a similar latency in response to syntactic violations such as noun–verb number disagreement (Hagoort et al., 1993; Osterhout and Holcomb, 1992), and other linguistic violations (Münte et al., 1998). We do not wish to imply that these are the same brain potential, although both types of P600 may share some features, such as sensitivity to stimulus probability and saliency, with the well-studied P300 or P3b component (Coulson et al., 1998).

1992). At the time of ERP testing, all AD patients met criteria for probable or possible AD. The mean MMSE score was  $22.9 \pm 3.9$ . Most ( $n=8$ ) were not on any pharmacological treatment for AD, except for 3 AD patients on cholinesterase therapy (donepezil; mean dosage = 6.7 mg/day). Exclusions for both groups were history of stroke, epilepsy, schizophrenia, or other neuropsychiatric conditions that could cause the observed cognitive deficits. To reduce the likelihood of age-related AD pathology in the NC group, we excluded 'normal' elderly with mild memory impairment (mean age-corrected  $z$ -score  $\leq -1$  on delayed verbal memory tests). The mean MMSE in the NC group was 29.6 (SD = 0.50).

## 2.2. Procedure

Subjects were fit with an electrode cap and seated 125 cm from a video monitor. Category statements were read aloud, each followed ( $\sim 1$  s later) by a visually presented target word (duration = 300 ms). Subjects were instructed to sit quietly for 3 s 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 3 blocks of 144 trials, each lasting slightly over 20 min.

## 2.3. Stimuli

The stimuli were 216 phrases, each describing a category (e.g. 'a breakfast food', 'a continent', or 'a citrus fruit'), and followed by a specific target word. Categories (216) and target words (216) were selected with the aid of published norms and locally administered normative questionnaires (Olichney et al., 2000). Half of the target words (108 'congruous' words) were medium-typicality category exemplars (e.g. 'pancake' for 'a breakfast food'). The other half of the targets were 108 concrete nouns, each 'incongruous' with their associated category (e.g. 'port' for 'a citrus fruit'), but matched to the congruous target words for length and frequency of usage (Francis and Kucera, 1982).

Each subject was randomly assigned to one of 3 counterbalanced stimulus lists, which included 36 congruent targets presented once, 36 presented twice, 36 presented 3 times, and equal numbers of incongruent targets in the same repetition conditions, for a total of 432 trials. Half of the stimuli were congruous and half were incongruous; half were new and half were repeats. Repeated targets always appeared with the same category as on 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 ( $\sim 120$  s).

## 2.4. Electrophysiological recording

The electroencephalogram (EEG) was recorded from tin electrodes embedded in an elastic cap from midline (Fz, Cz, Pz), lateral frontal (F7, F8), temporal (T5, T6) and occipital sites (O1, O2) defined by the International 10–20 System (Jasper, 1958). 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 33% of the interaural distance lateral to Cz over the superior temporal lobe (41L, 41R). Six subjects had additional electrodes at 4 frontal (FP1, FP2, F3, F4) and two parietal sites (P3, P4), and one of these subjects also had electrodes at FC1, FC2, CP1, CP2, PO7, and PO8. 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 by electro-oculogram (EOG) recording from 4 electrodes, one below and one at the outer canthus of each eye. The EEG was recorded with a 0.016–100 Hz bandpass and digitized 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 artifacts. Occasionally, trials contained speech artifacts, which were rejected by customized peak-to-peak amplitude tests employed on frontal channels (generally F7 and F8). In NC, 27.7% of the trials were rejected versus 43.1% in AD ( $t_{20} = 1.96$ ,  $P = 0.063$ ), with a maximum of 61.6% trials rejected among the NC subjects and a maximum of 68.7% in the AD subjects. There was an average of 312 trials accepted in NC and 245 trials in AD.

## 2.5. ERP analyses

The ERP data were submitted to split-plot ANOVAs with the between-subject factor of group, and 3 within-subject factors: condition (either congruity or repetition), latency window (e.g. 300–550 ms vs. 550–800 ms), and electrode location. These time windows were chosen because they best captured the N400 and P600 potentials across all participants. However, because the N400 repetition effects (new-repeated incongruous words) rarely occurred before 400 ms in these older participants, the 400–550 ms window was chosen to quantify this effect. Two-tailed  $P$ -values of  $\leq 0.05$  were considered significant. The Greenhouse–Geisser correction was applied where appropriate to correct for violations of sphericity (Geisser and Greenhouse, 1959). We elected not to apply the McCarthy and Wood normalization procedure (1985) to apparently significant group  $\times$  condition  $\times$  electrode interactions, because even where these interactions remain significant after correction it can not be safely assured that the underlying neural generators are distinct. Rather, significantly different scalp distributions may be produced by (1) the same generators, which differ only in relative strength (Picton et al., 2000), or (2)

generators which differ in polarity, or (3) generators which truly differ in location (Urbach and Kutas, 2002).

### 3. Results

#### 3.1. Behavioral results

Although performance on the semantic category decision task was near ceiling in both groups ( $96.8 \pm 2.0\%$  correct in AD,  $99.7 \pm 0.4\%$  correct in NC), the performance of the NCs was significantly better (Mann–Whitney  $U = 11.0$ ,  $P = 0.0012$ ). Across both groups, performance was slightly better on the incongruous items (percent correct:  $98.5\%$  correct in the AD group and  $99.9\%$  in the NC group) than on congruous items ( $98.3\%$  correct in AD,  $99.7\%$  correct in NC), but this difference was not significant (main effect of congruity:  $F = 0.35$ ,  $P = 0.56$ ). There was no group  $\times$  congruity interaction effect ( $P = 0.97$ ).

#### 3.2. N100 analyses

The N100 potential was defined as the largest negative peak occurring between 100 and 250 ms post-stimulus onset. N100 peak amplitude and latency were subjected to ANOVAs with the between-subject factor of group, and within-subject factors of congruity, repetition, and electrode. Only the posterior electrode sites (T5, T6, O1, O2), where the N100 was most prominent and reliably present across subjects were used for the analysis. There were no significant differences or interactions in N100 latency between mild AD patients and NCs (all  $P$ 's  $> 0.10$ ). Analysis of the N100 amplitude, however, revealed a main effect of group ( $F(1,20) = 5.23$ ,  $P = 0.03$ ), with the AD subjects exhibiting smaller N100 potentials than NC. A significant group  $\times$  electrode interaction was also present ( $F(3,60) = 3.47$ ,  $P = 0.04$ ), indicating different scalp distributions of the N100 between the two groups. The N100 was more posteriorly distributed in NC (e.g. note O1 and O2 negativities  $> T5$  and T6 negativities in Fig. 1A) than in AD.

#### 3.3. N400: semantic congruity effects for new words

Fig. 1A shows the ERPs elicited by congruous and incongruous category words on first presentation in NC (left) and AD (right) subjects. The N400 elicited by incongruous words, and its congruity effect (incongruous vs. congruous words), are both most prominent in right and midline channels for the NC group. In contrast, the N400 is attenuated with a less well-defined peak at posterior electrode sites in the mild AD group. The congruity effect, i.e. the difference between the ERPs to incongruous and congruous words, was defined between 300 and 550 ms. These data were submitted to a repeated measures ANOVA with factors of group, congruity, and electrode location.

There was a main effect for congruity ( $F(1,20) = 14.06$ ,  $P = 0.0013$ ), with initial incongruous words producing larger negativities (N400s) than congruous words. The potentials elicited by congruous vs. incongruous words had different scalp distributions (congruity  $\times$  electrode interaction:  $F(14,280) = 3.97$ ,  $P = 0.012$ ). Further, there was a marginally significant group  $\times$  electrode interaction ( $F(14,280) = 2.28$ ,  $\epsilon = 0.22$ ,  $P = 0.085$  after Greenhouse–Geisser correction), which indicates the AD group had relatively smaller N400s at posterior and midline locations (see channels T5, O1, O2 and Pz in Fig. 1A) but relatively larger negativities in anterior locations (with more prominent group differences on the right, see channels F8, BR and 41R). This pattern of results prompted additional analyses, with separate repeated-measures ANOVAs for each subject group (NC and AD) with the within-subject factors of congruity and electrode location. Despite the congruity  $\times$  group interaction not reaching significance in the main analysis ( $F = 2.18$ ,  $P = 0.15$ ), a significant main effect of congruity was present in the NC group data (analyzed across all channels:  $F(1,10) = 9.24$ ,  $P = 0.012$ ) which barely achieved statistical significance in the AD group ( $F(1,10) = 4.96$ ,  $P = 0.050$ ). A congruity  $\times$  electrode interaction was found to be significant in the NC group ( $F(14,140) = 4.68$ ,  $P = 0.009$ ), but not in AD ( $F(14,140) = 1.14$ ,  $P = 0.34$ ). Fig. 1B plots the mean amplitude of the N400 congruity effect across channels. This shows the NC group's effect (blue) is largest in posterior midline and right hemisphere channels, but the effect in AD (red) is smaller, more uniform, and only exceeds  $1 \mu\text{V}$  in channel WR. Note that the relatively larger frontal negativities in AD (to both incongruous and congruous words; Fig. 1A) showed little or no congruity effect, as would be expected if this activity emanated from a normal N400 generator.

Analysis of the N400 fractional area latency (the latency by which 50% of the congruity effect occurs, measured as area under the difference wave to incongruous vs. congruous words between 300 and 800 ms) was conducted for those channels where the N400 congruity effect was consistently present across subjects (i.e. posterior right and midline locations). This showed that while the AD group's N400 congruity effect tended to occur later than the normal control group, the group differences failed to reach statistical significance (e.g. at electrode T6 mean and  $SD = 558 \pm 54$  ms in AD vs.  $520 \pm 50$  ms in the normal control group;  $t = 1.68$ ,  $P = 0.107$ ).

#### 3.4. Repetition of congruous words (P600)

Fig. 2 shows the ERPs elicited from the NC and AD subjects by the first and repeated presentations of congruous items, collapsed across repetition lag. The new congruous words elicited a large late positivity (peaking at approximately 550–600 ms post-stimulus), which was reduced with repetition. This 'congruous word repetition effect' (i.e. the reduction of a late positivity) in the NC group (left side) was

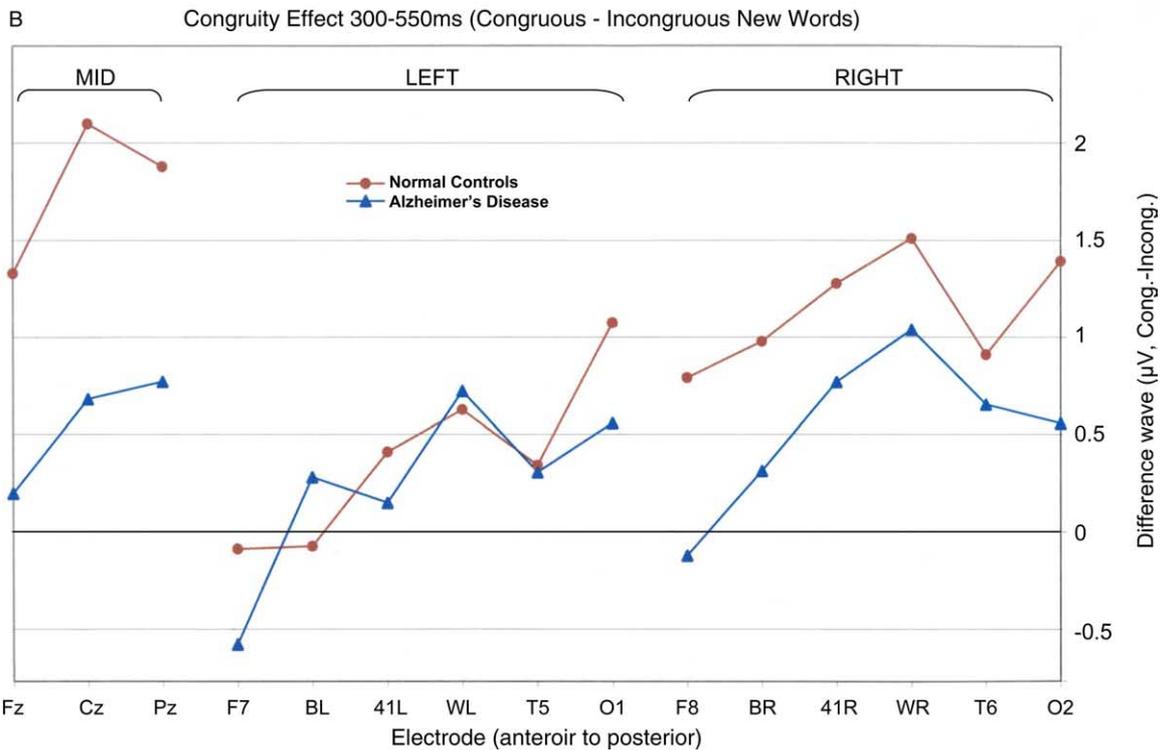
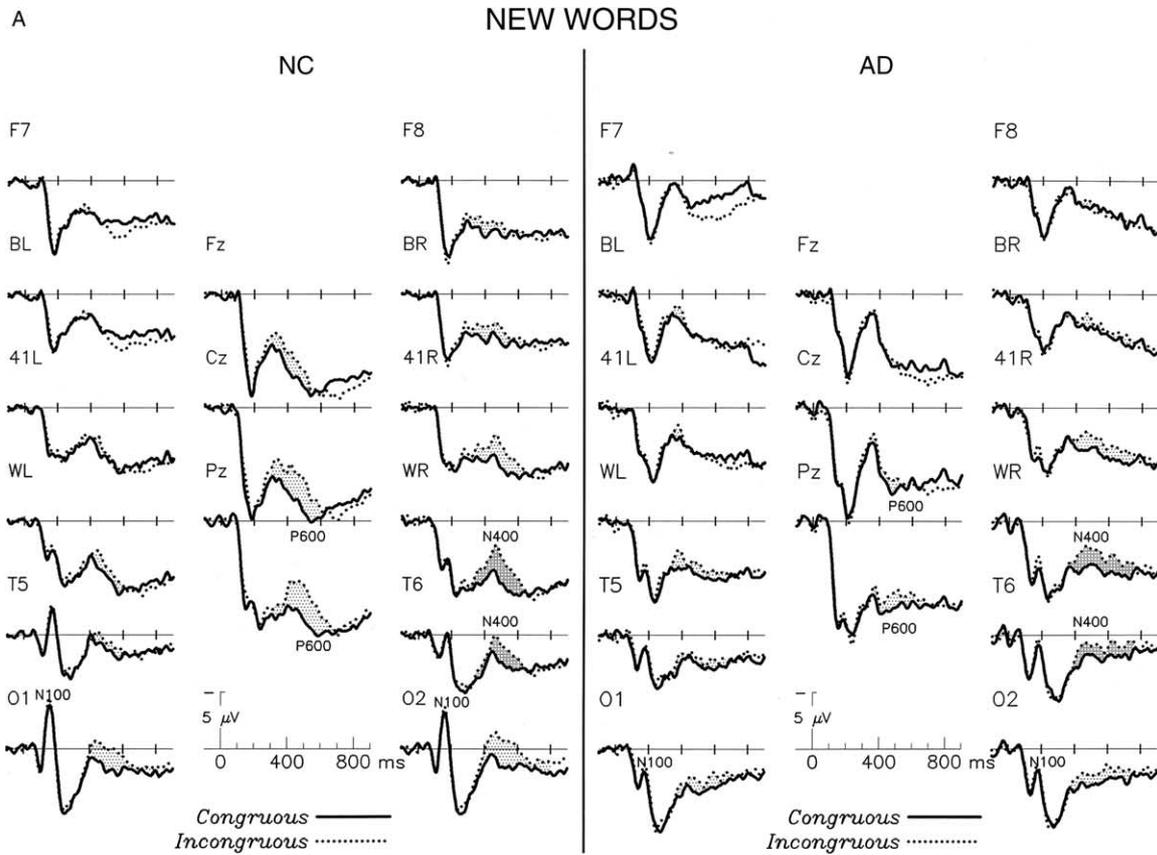


Fig. 1. (A). Grand average event related potentials (ERPs) of the normal control (NC) and mild Alzheimer's disease (AD) groups to new semantically congruous words (solid lines), and new incongruous words (dotted lines). Negative voltage is plotted up with left hemisphere electrodes on the left, midline electrodes in the middle, and right hemisphere electrodes on the right. The N100, N400, and P600 potentials are indicated at O1 and O2; WR, T6 and Pz; and Cz and Pz, respectively. (B). Mean amplitudes of the N400 congruity effect (congruous–incongruous target words), measured between 300 and 550 ms, for normal control (NC, red) and Alzheimer's disease (AD, blue) groups. Midline, left-hemisphere and right-hemisphere channels are each plotted left to right from most anterior to most posterior location.

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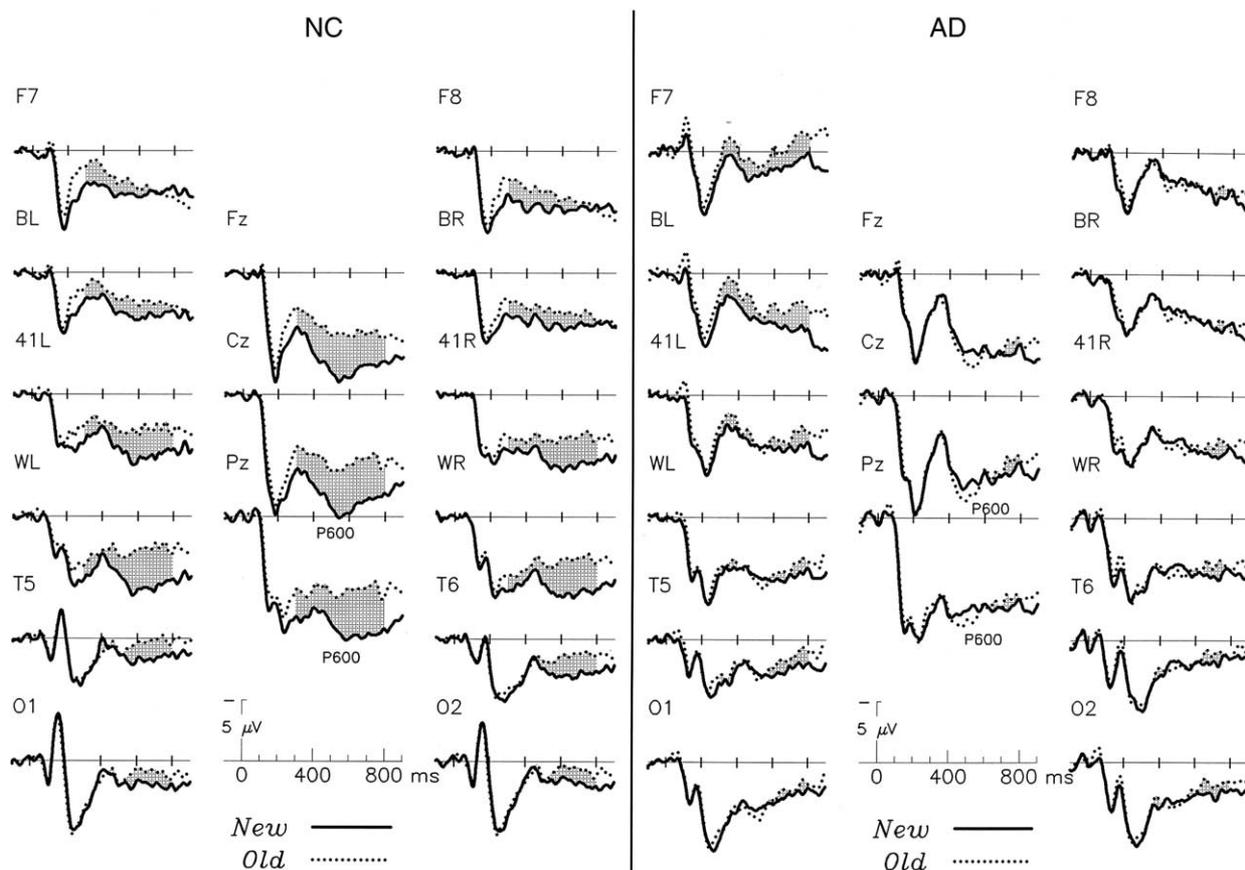


Fig. 2. Grand average ERPs for normal control (NC) and mild Alzheimer's disease (AD) groups elicited by new (solid lines) and repeated (dotted lines) semantically congruous words. The 'congruous word repetition effect', which normally shows greater positivity to new words, has been shaded between 300 and 800 ms.

largest at midline electrode sites and was present during most of the epoch (200–900 ms). In contrast, the AD group's (right side) congruous repetition effect was almost entirely absent, with a small effect evident mostly at left lateral electrode sites between 600 and 900 ms.

The congruous repetition effect was defined as the amplitude difference between new and old congruous words over the 300–800 ms epoch. These data were analyzed by a repeated measures ANOVA with factors of group, repetition (all first vs. all repeated presentations), latency window (300–550 and 550–800 ms), and electrode location. A main effect of repetition was present, such that new words elicited larger positivities than repeated words ( $F(1,20)=10.65$ ,  $P=0.004$ ). The congruous repetition effect was largest at the vertex, as indicated by a repetition  $\times$  electrode interaction ( $F(14,280)=6.23$ ,  $P=0.0009$ ). The NC group had a larger congruous repetition effect than the AD group (group  $\times$  repetition interaction:  $F(1,20)=4.53$ ,  $P=0.046$ ). A significant 3-way group  $\times$  repetition  $\times$  electrode interaction was present ( $F(14,280)=3.95$ ,  $P=0.006$ ), which signifies that the repetition effects in NC and AD had different scalp distributions (Fig. 3). From this alone,

however, we cannot determine whether or not the responsible neural generators in the two groups truly differ in their locations (Urbach and Kutas, 2002).

The repetition effect was more prominent in the later (550–800 ms) than the early (300–550 ms) time window (repetition  $\times$  latency window interaction:  $F(1,20)=7.20$ ,  $P=0.014$ ). A repetition  $\times$  latency  $\times$  electrode interaction was also significant ( $F(14,280)=3.97$ ,  $P=0.0055$ ), which shows that the scalp distribution of this effect was different between the two latency windows. Therefore, the data were analyzed separately for the early (300–550) and late (550–800) time windows by ANOVAs with the factors of Group, Repetition, and Electrode location. A main effect of repetition was only significant in the later P600/LPC time window ( $F(1,20)=18.71$ ,  $P=0.0003$ ), such that new congruous words elicited larger late positivities than repeated congruous words. A significant group  $\times$  repetition interaction was present ( $F(1,20)=4.83$ ,  $P=0.040$ ), indicating that the NC group had a larger P600 repetition effect than the AD group. This repetition effect was most prominent in midline channels for the NC group, which contrasted with the AD group's atypically distributed late

### Congruous Word Repetition Effect

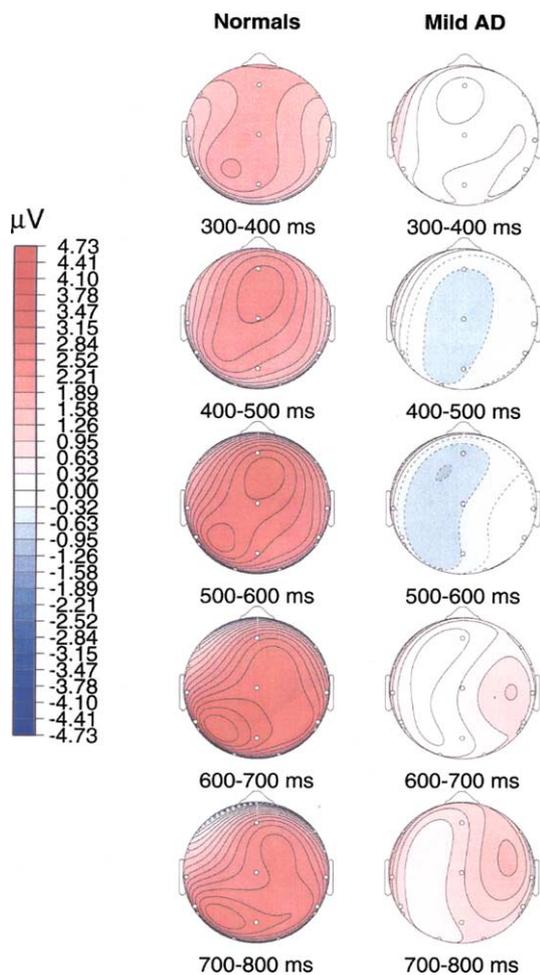


Fig. 3. Spherical spline topographical maps illustrating the congruous word repetition effect (ERPs to new minus old words) in consecutive 100 ms epochs for the normal control (left) and mild AD (right) groups.

repetition effect (largest in left frontal channels), which resulted in a significant 3-way group  $\times$  repetition  $\times$  electrode interaction ( $F(14,280)=4.02$ ,  $P=0.005$ ).

### 3.5. Repetition of incongruous words (N400)

Fig. 4 illustrates the ERPs for initial and repeated presentations of incongruous targets. The AD group did not have an appreciable repetition effect (mean amplitude for the new vs. repeated target amplitude was  $<0.05 \mu\text{V}$  apart in the 400–550 ms epoch), while the NC group's repetition effect was present reliably between  $\sim 400$ –600 ms at the vertex and right posterior channels. The incongruous repetition effect was defined between 400 and 550 ms, and the data were submitted to a repeated-measures ANOVA analogous to the ANOVA used for congruous words.

The incongruous repetition effect was largely restricted to midline and posterior electrode sites (repetition  $\times$  electrode interaction:  $F(14,280)=5.14$ ,  $\epsilon=0.29$ ,  $P=$

0.001), as is typical for N400 effects. Both the spatial distribution and polarity of this effect differed between the AD and NC groups (3way interaction of group  $\times$  repetition  $\times$  electrode:  $F(14,280)=3.00$ ,  $\epsilon=0.29$ ,  $P=0.023$ ). A group  $\times$  repetition interaction of marginal significance ( $F(1,20)=3.66$ ,  $P=0.07$ ) was also found, prompting separate ANOVAs for the AD and NC groups. These analyses showed that a significant main effect for repetition was only found in the NC group ( $F(1,10)=6.79$ ,  $P=0.026$ ). In the AD group, there was no significant repetition effect ( $F(1,10)=0.01$ ,  $P=0.93$ ).

### 3.6. Correlations between ERP repetition effects and neuropsychological tests

Correlational analyses were conducted for the 'P600 repetition effect' (mean voltage difference between 550 and 800 ms at Pz for new–old congruous words), hypothesized to reflect verbal memory abilities (Olichney et al., 2000). The P600 repetition effect amplitude was significantly correlated with all our main measures of verbal (e.g.  $r=0.58$  with delayed recall on the CERAD word list), but not with non-verbal memory (Table 1). The P600 repetition effect also correlated with global abilities as measured by the DRS total ( $r=0.47$ ,  $P=0.029$ ). While the DRS subscales for memory and initiation/perseveration were significantly correlated with the P600 repetition effect ( $r$ 's = 0.45,  $P$ 's = 0.037), the other 3 DRS subscales (attention, conceptualization, and construction) were not ( $0.14 \leq r$ 's  $\leq 0.40$ ).

### 3.7. Group discrimination

When we used a 'normal' cutoff of  $\geq 2.5 \mu\text{V}$  for the P600 repetition effect, similar to the cutoff which distinguished patients with amnesia from normal subjects in a prior study (Olichney et al., 2000), we achieved 91% sensitivity to AD, with 73% specificity (i.e. 8 of 11 normal elderly were above this cutoff; see Fig. 5). If we define a normal N400 repetition effect as  $\geq 0.5 \mu\text{V}$  (any cutoff between 0.12 and 0.73  $\mu\text{V}$  gives the same results), specificity is excellent at 91%, but sensitivity is only 55%. By using both these measures and requiring that subjects be at or above the 10th percentile on both measures, we achieved 100% sensitivity and 82% specificity. As Fig. 5 illustrates, none of our mild AD patients had normal repetition effects for both congruous and incongruous words. Clearly, this excellent degree of group discrimination is a preliminary finding that needs to be replicated in other independent samples. Nonetheless, these results are very promising, especially considering the high prevalence of 'incidental' mild AD pathology among the non-demented elderly (Braak et al, 1996). It is of interest that the two normal controls misclassified (outside shaded area in Fig. 5) are both heterozygous apolipoprotein  $\epsilon 4$  carriers. Also interesting is the apparent inverse correlation between the

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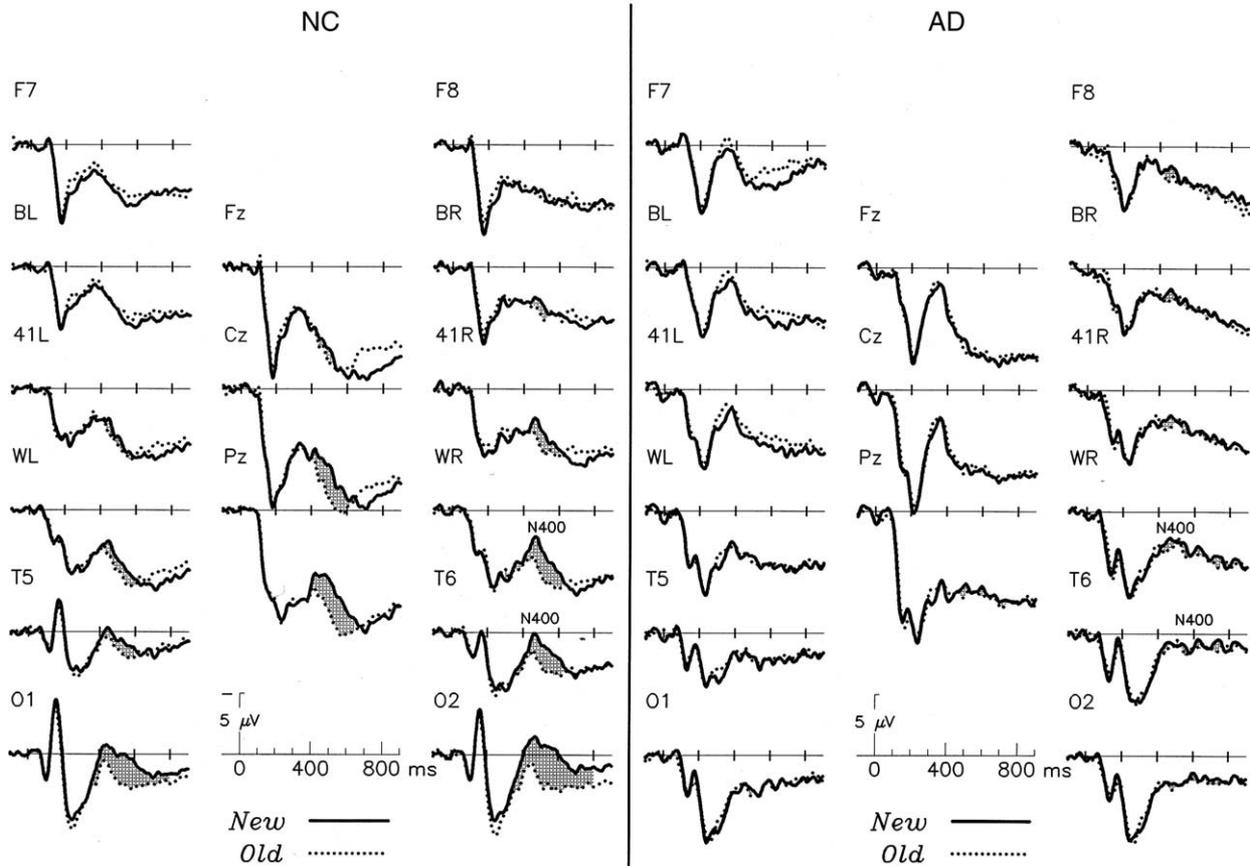


Fig. 4. Grand average event related potentials (ERPs) for normal control (NC) and mild Alzheimer's disease (AD) groups elicited by new (solid lines) and repeated (dotted lines) semantically incongruous words. The 'incongruous word repetition effect', which shows smaller N400s to repeated words, has been shaded between 300 and 800 ms where present.

N400 and LPC repetition effect in AD ( $r = -0.66, P = 0.03$ ). This indicates that AD patients with repetition effects in the 'normal' direction on one of these measures usually had a reversed polarity for the other (e.g. a 'normal' decrement of the LPC to congruous words would be

associated with a reversed (abnormal) increased N400 to incongruous words). In other words, the preserved word repetition effects in some AD patients were of the same polarity and insensitive to semantic congruity. In contrast,

Table 1

Correlations between memory (verbal and non-verbal) tests and the congruous (P600) word repetition effect

	P600 Rep effect (Pz, 550–800 ms) <i>r</i>
CVLT list A, trials 1–5	0.59*
CVLT short delay free recall	0.55*
CVLT short delay cued recall	0.53**
CVLT long delay free recall	0.57*
CVLT long delay cued recall	0.49**
CVLT discrimination	0.50**
Wechsler logical memory I	0.51**
Wechsler logical memory II	0.52**
CERAD word list—total	0.56**
CERAD delayed recall	0.58*
Visual reproduction I	0.19
Visual reproduction II	0.30

\* $P < 0.05$ ; \*\* $P \leq 0.01$ .

Incongruous vs. Congruous Repetition Effect

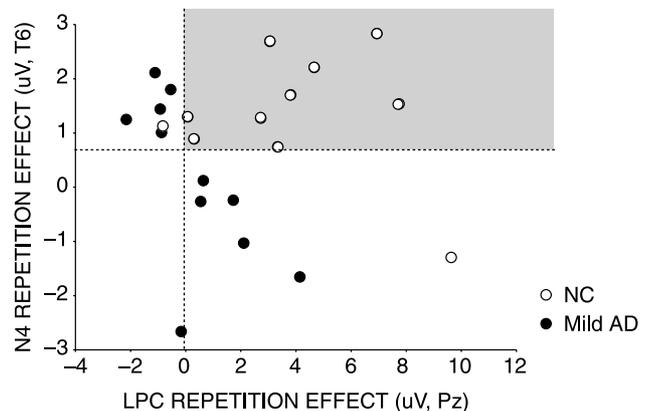


Fig. 5. Scatterplot of individual subject data for the 'P600 repetition effect' (mean voltage difference between 550 and 800 ms at Pz for new minus old congruous words) and 'N400 repetition effect' (mean voltage between 400 and 550 ms at T6 for old minus new incongruous words).

normal subjects tested on this paradigm quite consistently display a congruity  $\times$  repetition interaction in which ERPs to congruous words are more positive on initial presentation, but ERPs to incongruous words are initially more negative. The amplitude of the N400 and LPC repetition effects in NCs were not significantly correlated with each other ( $r = -0.19$ ,  $P = 0.57$ ).

#### 4. Discussion

Using the ERP technique during a semantic categorization task, we found that patients with mild AD have reduced word repetition effects in response to both semantically congruous and incongruous words. The congruous word repetition effect normally elicited by our paradigm consists primarily of a large decrement in a late positive component (LPC, also termed the 'P600') to repeated items (i.e. 'congruous' category exemplars). All but one (10/11) of our mild AD patients were characterized by reduced P600 word repetition effects. Previously, we reported that patients with severe well-circumscribed amnesia show a similar, severe attenuation of this ERP effect (Olichney et al., 2000). The most common etiological diagnosis in that case series was Korsakoff's syndrome, but 3 elderly patients with idiopathic amnesic syndromes were noted to subsequently progress to AD dementia. We have also confirmed the sensitivity of the congruous word repetition effect to incipient AD in a cohort of 14 patients with mild cognitive impairment (MCI) (Olichney et al., 2002a). Therefore, we were not surprised by the present results, in which the congruous word repetition ERP effect is 'absent' (not statistically significant) in our mild AD group. Likewise, the significant correlations present between the P600 repetition effect amplitude and multiple measures of declarative verbal memory are similar to the findings that we previously reported in amnesia, MCI, and normal subjects (Olichney et al., 2000, 2002a). The consistency of these findings buttress our view that the ERP word repetition effect to congruous words on this paradigm is an electrophysiological index of successful memory encoding, which may prove clinically useful in confirming the presence of an 'organic' memory disorder.

While several prior studies have demonstrated ERP word repetition effects to be present in AD, these used paradigms that were substantially different from the present study. For example, Friedman et al. (1992) reported preserved LPC repetition effects to non-target words in most mild AD patients, using an incidental repetition paradigm with both a semantic task and an orthographic task. Rugg et al., (1994) used a similar task (visually presented words, discriminate non-animals vs. animals with button press response) and also found 'intact' word repetition effects upon the LPC (analyzed between 400 and 700 ms) in AD, although a trend for smaller repetition effects with more intervening items (6 vs. 1) was noted. Unlike the present study, both of these

experiments used word list paradigms, which produce an increase in the LPC, opposite in polarity to the effect normally seen on our paradigm (Olichney et al., 2000), or when words repeat in natural text (Van Petten et al., 1991). Also, the prior studies used short time-lags (<1 min) between initial and repeat presentations, and measured repetition effects to the less task-relevant (non-target) words. Neither paradigm made use of contextual cues or specific semantic associates (e.g. category–target pairs), the formation and storage of which are particularly impaired in AD (Vaidya et al., 1999). Our results are more consistent with the study of Tendolkar et al. (1999), in which AD patients showed large reductions in their ERP difference to new–old words (normally present between 400 and 1000 ms in left temporal channels) in an explicit memory (recognition) task with relatively longer time lags ( $\sim 5$  min). It should be noted that additional analyses (omitted for brevity) in our AD patient group showed no significant LPC repetition effect at either short-lag ( $\sim 10$ – $40$  s) or long-lag ( $\sim 2$  min), demonstrating that time delay is not the only factor which, across studies, determines if AD patients have significant new–old word ERP differences. In summary, we believe our word repetition paradigm is more sensitive to AD than most previously published word repetition experiments, perhaps because episodic memory (cued recall and recognition) is normally robust for our congruous category exemplar words (Olichney et al., 2000). This paradigm has also shown sensitivity to incipient AD cases while still in the MCI stage prior to dementia (Olichney et al., 2002a).

We also found a reduced incongruous word repetition effect in AD. This incongruous word repetition effect, as displayed by the normal elderly control group, is produced by a diminution in the N400 amplitude elicited by repeated vs. new incongruous target words. The loss of this effect in mild AD is in contrast to what we have found in prior studies of patients with amnesia or MCI (Olichney et al., 2000, 2002a). We interpreted the relative sparing of this ERP word repetition effect in amnesia as being secondary to implicit memory processes, likely related to their ability to show semantic 'priming' effects (Graf et al., 1985; Keane et al., 1991; Shimamura, 1986; Shimamura et al., 1987). Therefore, one plausible explanation of this abnormality in AD is that the loss of the N400 repetition effect to incongruous words reflects impairment in semantic priming, as has often been demonstrated in several, but not all, behavioral studies of AD (Albert and Milberg, 1989; Keane et al., 1991; Salmon et al., 1988; Vaidya et al., 1999). It is, however, also possible that the reduced N400 repetition effect in AD is due to impairments in explicit/declarative memory (although there were no significant correlations present with most measures of verbal recall;  $r$ 's in 0.29–0.44 range with main measures on the CVLT, data not shown). Also making this possibility unlikely is the observation that many patients with severe amnesia have shown relative sparing of this ERP effect (Olichney et al., 2000). Furthermore, the N400

repetition effect amplitude did not correlate with verbal memory measures in our prior analyses of MCI, amnesia or normal subject groups (Olichney et al., 2000, 2002a). But since other reports (Elger et al., 1997) have implicated N400 amplitude as being important for memory abilities in epilepsy patients, one should keep an open mind to this possibility. The main N400 generators are currently thought to reside in the anterior fusiform gyrus, but also include adjacent structures in the medial temporal lobe such as the parahippocampal gyrus (McCarthy et al., 1995; Nobre et al., 1994). Outputs from the perirhinal cortex have been shown, in animal studies, to be very important for the consolidation of visual long-term memory (Suzuki, 1996). Depth recordings in several paralimbic and association neocortical regions have shown N400–P600 potentials (Guillem et al., 1999; Halgren et al., 1994), which suggest a very intimate relationship and possible interdependency between these two late components. Guillem et al. (1999), however, found that N400 repetition effects, unlike P600 repetition effects, were generally only present in the neocortex when shorter inter-item lags ( $\sim 25$  s) were used in a visual recognition memory task.

Most prior studies of the N400 in AD have found either latency or amplitude abnormalities. For example, there are several reports of decreased ‘N400 effect’ amplitudes, based on subtraction waveforms to semantically primed vs. unprimed words (Auchterlonie et al., 2002; Ford et al., 2001; Iragui et al., 1996; Ostrosky-Solís et al., 1998; Revonsuo et al., 1998; Schwartz et al., 1996). While we did not replicate this finding in our mild AD cohort, we did find a trend towards longer N400 latencies and an atypically anterior N400 distribution, in addition to the greatly reduced or absent N400 repetition effects discussed above. We are not aware of any similar previously published studies of N400 repetition effects in AD. We advise caution before concluding that the N400 repetition effect is more sensitive to early AD pathology than N400 effects based on manipulations of semantic congruity, although this appeared to be the case with this specific cohort and experimental paradigm, which compares medium-typicality category exemplars to incongruous non-exemplars. This word repetition paradigm was not designed to elicit the full range of N400 amplitudes. Larger ‘difference waves’ between incongruous and congruous items could have been produced by using higher typicality category exemplars for the congruous words, or by selecting incongruous words which more strongly violate semantic expectancy.

The loss of the N400 word repetition effect in mild AD stands in contrast to patients with MCI, who displayed significant N400 repetition effects on this paradigm. It should be noted that MCI patients also tend to have slower N400s than normal elderly, per measures of fractional area latency (Olichney et al., 2002a). Furthermore, because the NC group in our previous ERP study of MCI was younger and had earlier N400 latencies than NCs in the present study, the MCI group’s prolongation in N400 fractional

area latency reached significance at several electrode sites. However, the mean fractional area latency reported in MCI was similar to (and slightly faster than) the mild AD group in the present study (e.g.  $543 + 74$  ms in MCI vs.  $569 + 58$  ms in AD across all right-hemisphere channels).

We also found a significant reduction in the N100 amplitude of our AD patients. This was an unexpected finding in that most prior studies have found normal N100s in AD (Dabic-Jeftic and Mikula, 1993; Goodin and Aminoff, 1987; Yokoyama et al., 1995), a disorder that generally spares the earlier ERP components, which are more sensitive to sensory and perceptual factors. Speculatively, this decreased visual N100 amplitude might indicate a decreased ability of AD patients to switch attention between modalities (i.e. interference from unfinished processing of the preceding auditory category phrase) (Eimer and Schröger, 1998; Woods et al., 1992). One prior study (Tarkka et al., 2002) found a modest, but significant, decrease in the auditory N100 amplitude among patient groups with sporadic and familial AD. In addition, decreased auditory adaptation of the N100 was found in their cohort ( $n=22$ ) with familial AD. Another study has reported that the amplitude of the auditory N100 global field power is reduced in AD (Hirata et al., 2000).

The prominent abnormalities in the ERP repetition effects to both semantically congruous and incongruous words supports a more generalized failure of synaptic plasticity in AD compared with well-circumscribed amnesia. A prior electron micrography study of cortical biopsies in early- to mid-stage AD found approximately a 30% decrease in synaptic density and a 25% decrease in synapses per neuron (Davies et al., 1987). As mentioned above, pre-synaptic terminal density is one of the strongest neuropathological predictors of dementia severity (Terry et al., 1991). Recent studies of transgenic AD models have shown that inhibition of long-term potentiation (LTP) and reduced synaptic transmission are often prominent before the appearance of extensive classic AD pathology (i.e. amyloid plaques and neurofibrillary changes) or neuron loss (Moechars et al., 1999; Rowan et al., 2003). Therefore, much current basic research is investigating the mechanisms of synaptic dysfunction in AD. For example, Walsh and colleagues found that microinjection of A- $\beta$  oligomers strongly inhibits long-term potentiation in the rat hippocampus (Walsh et al., 2002). In autopsied AD cases, Bertoni-Freddari et al. (2002) found a large increase in the proportion of deafferented synapses on hippocampal neurons. Thus, AD may be conceived as a diffuse deafferentation syndrome, in which both the neocortex and hippocampus have lost a critical proportion of their normal inputs. Hyman and colleagues have previously noted that AD resembles a hippocampal disconnection syndrome, especially in its early stages (Hyman et al., 1984). It is plausible that the loss of the P600 word repetition effect in AD is a reflection of a functional disconnection between

mesial temporal and cortical (e.g. orbitofrontal, temporal pole, middle temporal gyrus) P600 generators, several of which have convergent reciprocal connections with the parahippocampal gyrus (Buzsáki, 1996; Guillem et al., 1999; Traub and Miles, 1991). As patients progress into the advanced stages of AD (Braak stages V and VI), a more global disturbance of neocortical function develops, which can be quantified by electrophysiological measures such as the N400, P600 or P300 components. It is also possible that the atypically anterior scalp distribution of both the N400 component and the P600 word repetition effect in AD may represent compensatory mechanisms in which additional brain regions are recruited in order to perform a relatively simple semantic classification task.

In conclusion, ERP word repetition effects appear very sensitive to mild AD. All 11 mild AD patients tested had either an abnormal P600 or an abnormal N400 repetition effect or both. Not only does this ERP paradigm provide measures relevant to memory and language, it also measures synaptic processes in a relatively direct manner. Possible clinical applications include aiding the early detection of AD, staging AD pathology, measuring disease progression, or providing sensitive measures to longitudinally assess pharmacological treatments for the cognitive deficits in AD. Studies of larger AD cohorts are needed to further test the clinical utility of these ERP measures.

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