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Word repetition in amnesia
Electrophysiological measures of impaired and spared memory

John M. Olichney,[1,3] Cyma Van Petten,[4] Ken A. Paller,[5] David P. Salmon,[1] Vicente J. Iragui[1,3] and Marta Kutas[1,2]

Departments of [1]Neurosciences and [2]Cognitive Science, University of California, San Diego, [3]Neurology Service, San Diego Veterans Affairs Medical Center, [4]Department of Psychology, University of Arizona and [5]Department of Psychology, Northwestern University, USA

Correspondence: John M. Olichney, MD, Neurology Service (9127), San Diego Veteran Affairs Medical Center, 3350 La Jolla Village Drive, San Diego, CA 92161, USA
E-mail: olichney@cogsci.ucsd.edu

Summary

Amnesic patients often show improved performance when stimuli are repeated, even in the absence of conscious memory for those stimuli. Although these performance changes are typically attributed to perceptual or motor systems, in some cases they may be related to basic language processing. We examined two neurophysiological measures that vary with word repetition in 12 amnesic patients and 12 control subjects: (i) a late positive component of the event-related potential (ERP) linked to conscious memory and (ii) the N400 component that varies with language comprehension. In each trial, the subject heard a category name, then viewed a word, and then decided whether the word was semantically congruous or incongruous (e.g. 'yes' for 'baby animal: cub'; 'no' for 'water sport: kitchen'). Recall and recognition testing at the end of the experiment showed that control subjects had better memory for congruous than for incongruous words, as did the amnesic patients, who performed less well overall. In contrast, amnesic patients were unimpaired on the category decisions required in each trial and, like the control subjects, showed a large N400 for incongruous relative to congruous words. Similarly, when incongruous trials were repeated after 0–13 intervening trials, N400s were reduced in both groups. When congruous trials were repeated, a late positive repetition effect was observed, but only in the control group. Furthermore, the amplitude of the late positive repetition effect was highly correlated with later word recall in both patients and controls. In the patients, the correlation was also observed with memory scores from standardized neuropsychological tests. These data are consistent with a proposed link between the late positive repetition effect and conscious memory. On the other hand, the N400 repetition effect was not correlated with episodic memory abilities, but instead indexed an aspect of memory that was intact in the amnesic patients. The preserved N400 repetition effect is an example of preserved memory in amnesia that does not easily fit into the categories of low-level perceptual processing or of motor learning. Instead, the sensitivity of the N400 to both semantic context and repetition may reflect a short-term memory process that serves language comprehension in realtime.

Keywords: amnesia; repetition; memory; event-related potential; N400

Abbreviations: ANOVA = analysis of variance; ERP = event-related potential; LPC = late positive component

Introduction

Repetition of nearly any type of experimental stimulus has profound consequences on cognitive and perceptual processing. Seeing or hearing something a second time improves recall, and speeds reaction time or increases accuracy in tasks such as the identification of words or pictures, lexical decision and pronunciation, object decision and word-fragment completion. However, data from a variety of techniques have suggested that more than one brain system contributes to the benefits of repetition. Patients with organic amnesia may show improved performance in tasks that do not require conscious recollection of an item's prior occurrence, in the absence of accurate recall or recognition of that item (for review, see Squire *et al.*, 1993). Some memory researchers have thus proposed that multiple functional systems are responsible for the benefits of repetition (e.g. Tulving and Schacter, 1990; Schacter *et al.*, 1991; Johnson, 1992;

Moscovitch, 1992). Declarative memory is multimodal, supports conscious recollection, and is more sensitive to the interpretation of items than to their perceptual details. Pathology of the medial temporal lobe and/or diencephalon commonly causes severe deficits in declarative memory, while sparing perceptual and motor learning (Squire, 1987).

Language comprehension is an important human ability which spans sensory modalities, and which clearly requires memory. In text or conversation, no single word or sentence can convey its full meaning without some recollection of what came before. The consequences of repetition have thus been the topic of psycholinguistic studies, but the distinctions drawn by these researchers have often diverged from those typically drawn in memory research. Reaction time benefits for repeated words can be observed across changes of sensory modality, so that these cannot be purely perceptual (Scarborough *et al.*, 1979). Performance in numerous tasks also benefits from prior presentation of a word (or environmental sound or picture) that is physically discrepant, but semantically related to the target word (Carr *et al.*, 1982; Vanderwart, 1984; Van Petten and Rheinfelder, 1995). These findings suggest that the typical word repetition effect may include a large semantic (and amodal) component.

The present study examines the semantic aspect of word repetition effects, and its relationship to declarative memory in patients with organic memory impairment. Our primary dependent measures are two components of the event-related potential (ERP): the N400, which has been previously linked to semantic processing, and a late positive component (LPC) which has been linked to recollection of previously studied items. Both are sensitive to stimulus repetition in neurologically intact individuals.

The N400 component has been utilized in psycholinguistic research as an index of semantic integration: N400 amplitude is small for printed or spoken words presented after a semantically related context (single word or sentence fragment), but large when words occur in the absence of a related context (see Kutas and Van Petten, 1988, 1994 for reviews). N400 amplitude is also reduced by the repetition of words in lists of unrelated items, by the repetition of entire sentences, and by the repeated use of words in natural discourse (Neville *et al.*, 1986; Smith and Halgren, 1987; Rugg *et al.*, 1988, 1992; Bentin and Peled, 1990; Karayanidis *et al.*, 1991; Van Petten *et al.*, 1991; Besson *et al.*, 1992; Besson and Kutas, 1993; Mitchell *et al.*, 1993). The N400 repetition effect begins ~250 ms poststimulus onset, and is somewhat larger over right than left scalp. The repetition effect can readily be observed across tasks which do not explicitly call for the detection of repeated items (e.g. silent reading for comprehension, semantic categorization, lexical decision). In contrast to robust N400 repetition effects for words (and perhaps other semantically interpretable stimuli), meaningless items such as novel geometric shapes elicit no N400 on first presentation, and consequently no change in N400 amplitude with repetition, whether or not they can be recognized as studied items (Van Petten and Senkfor, 1996).

The longest retention interval, or repetition lag, that yields a reliable N400 repetition effect has not been clearly defined. Within lists of unrelated words, Rugg (1990) observed no N400 difference between new and repeated items at a 15 min lag. Other investigators have reported N400 repetition effects across quite long intervals when the repeated words occurred in the context of coherent sentences which served as retrieval cues for their individual words (Besson *et al.*, 1992; Besson and Kutas, 1993). Overall, it is plausible to view the reduced amplitude of the N400 for repeated items as a sign of facilitated semantic processing engendered by the item's previous presentation, but the relationship between this phenomenon and declarative memory has been largely unexplored.

The second reliable ERP concomitant of word repetition is a change in the amplitude of a late positive component (LPC), which typically begins ~400 ms poststimulus onset, and is often larger over left than right scalp. Several lines of evidence suggest that the LPC repetition effect reflects conscious recollection of previously encountered items, but is not sensitive to all of the processes which may differentiate new from repeated items. Paller and colleagues have varied the initial presentation conditions for words later to be repeated during lexical decision, perceptual identification or semantic monitoring tasks (Paller and Kutas, 1992; Paller *et al.*, 1995, 1998; Paller and Gross, 1998). Initial study conditions that fostered high levels of recall or recognition in subsequent testing also led to larger LPC repetition effects than did study-phase tasks yielding less accurate episodic memory. In contrast, changes in the physical format of words between presentations influenced measures of perceptual priming (such as lexical decision speed), but did not influence the amplitude of the LPC repetition effect. Van Petten and Senkfor (1996) similarly reported that incidental repetitions of novel visual patterns result in faster perceptual judgements without a concomitant increase in LPC amplitude.

The hypothesis that the LPC repetition effect indexes conscious recollection is bolstered by observations of a similar effect during explicit recognition tests. When participants are explicitly asked to indicate whether or not an item was previously studied, correctly recognized old items elicit larger LPCs than unrecognized old items (misses) or new items regardless of whether these are judged 'old' or 'new' (Van Petten and Senkfor, 1996; Rugg *et al.*, 1998; Senkfor and Van Petten, 1998; Rubin *et al.*, 1999). Additionally, the LPC elicited by hits in recognition tests is larger when participants express high confidence in their 'old' judgements than when they are less confident, and larger when participants indicate that they 'remember' a word rather than merely 'knowing' that it was studied previously (Smith, 1993; Rubin *et al.*, 1999). In explicit recognition tasks, a larger LPC for recognized items than unstudied items is also observed for non-verbal stimuli such as line drawings and environmental sounds as well as meaningless geometric shapes (Friedman 1990*b*; Chao *et al.*, 1995; Van Petten and Senkfor, 1996; Van Petten *et al.*, 2000).

The majority of word repetition studies have used random lists with no links between individual items, and observed larger LPCs on second relative to initial presentations (Rugg, 1985, 1990; Rugg *et al.*, 1988, 1992, 1993; Smith and Halgren, 1989; Bentin and Peled, 1990; Karayanidis *et al.*, 1991; Van Petten and Senkfor, 1996). Besson and colleagues, however, observed that semantically predictable final words of sentences elicited smaller late positivities when the sentences were repeated (Besson *et al.*, 1992; see also Mitchell *et al.*, 1993). The natural re-occurrences of words in passages of text also elicit smaller LPCs than on initial presentation (Van Petten *et al.*, 1991). We have suggested that the presence or absence of semantic context results leads to the differential engagement of memory retrieval processes. Although it may be difficult to predict when any particular word in a long list of words will be repeated, it is likely that it will be recognized as a repetition when presented. In contrast, repeated words are more likely to be anticipated in advance during sentences and text, especially when the preceding context is also familiar. As a consequence, semantically predictable words are more likely to be in working memory at the time of repeated exposure, obviating the need for new retrieval from long term memory upon repeated exposure.

In summary, previous results from healthy subjects have clearly distinguished two repetition-sensitive components of the ERP differing in latency, scalp distribution (indicative of different anatomical substrates), and perhaps in sensitivity to retention interval. The LPC repetition effect has been linked with successful retrieval of an item's prior presentation, whereas the mnemonic characterization of the N400 repetition effect remains elusive. Although this summary would meet with widespread agreement among cognitive ERP researchers, it is important to note that the observed dissociations between the two repetition-sensitive components have often been fortuitous, and that the two components have not been clearly separable in many experiments. Separability of the two components is hindered by several factors. First, the N400 and LPC occupy overlapping latency windows. Studies of semantic processing without a deliberate memory manipulation show that N400 effects are typically largest from 300 to 500 ms poststimulus onset, but often extend to 700 or 800 ms poststimulus. Studies of explicit old/new recognition typically show that differences between correctly recognized studied items and unstudied items occur between 400 and 700 ms — somewhat later than the N400's peak latency range, but overlapping. Differential topography across multiple scalp recording sites is a sure sign that two ERP effects reflect the activity of different neuronal populations, but the N400 and LPC also have overlapping scalp distributions; both components are largest over central, parietal and posterior temporal scalp, and smallest frontally. Although both components tend to be asymmetric (N400 bigger on the right, LPC bigger on the left), symmetric topographies are not uncommon, particularly when the subject population cannot be restricted to right-handers without left-handed family members (Kutas *et al.*, 1988; Senkfor and Van Petten, 1998). The clearest dissociations between the two repetition-sensitive components in normal participants have relied on experimental manipulations such as stimulus meaningfulness or retention interval to disentangle the N400 and LPC, rather than latency or scalp distribution alone.

Previous studies have shown that temporal lobe epilepsy, anterior temporal lobectomy and cerebral hypoxia produce both verbal memory deficits and reductions of the ERP repetition effect (Smith and Halgren, 1989; Rugg *et al.*, 1991; Helmstaedter *et al.*, 1997; Mecklinger *et al.*, 1998). However, these studies employed simple repetition manipulations which did not facilitate separation of the N400 and LPC components of the repetition effect, leading Rugg and colleagues to conclude that 'future work examining this question would do well to employ an experimental manipulation that is known to dissociate old/new effects attributable to N400 and "P600" ' (which we refer to more generally as LPC) (Rugg *et al.*, 1991). Moreover, previous experiments using scalp-recorded ERP measures (Smith and Halgren, 1989; Rugg *et al.*, 1991; Mecklinger *et al.*, 1998) have not shown clear relationships between the severity of the memory deficit and the reduced ERP effect across individual patients. On the assumption that the N400 and LPC portions of the ERP repetition effect reflect different aspects of memory, relationships between brain electrical activity and memory performance will be better understood by evaluating the two ERP components separately.

The present experiment was designed to exploit the N400's sensitivity to semantic context so as to provide a clear separation between the two repetition-sensitive components. Semantically congruous pairings of category names and exemplars which elicit little N400 activity on initial presentation were selected so that their repetition would lead to only negligible reduction of N400 amplitude. In this way, it will be possible to assess changes in LPC amplitude elicited by repetition of these semantically congruous items, largely uncontaminated by changes in N400 amplitude. Similarly, semantically incongruous pairings of category names and exemplars were selected to elicit large N400s on initial presentation, so that their repetition can be used to assess a relatively pure N400 repetition effect. A strong prediction is that the LPC repetition effect is absent in patients to the extent that they are unable to form an episodic memory for an item's initial presentation. However, given that such patients do show behavioural benefits from repetition in other paradigms, it will be of some theoretical interest to determine whether these amnesic patients do show N400 repetition effects. A dissociation between the two components may suggest that some aspects of lexical processing access a memory system distinct from that supporting conscious recollection and the LPC component.

Methods

Patients

Twelve amnesic patients aged 28–78 years (mean 61.0 years) served as volunteers after providing informed consent

Table 1 *Neuropsychological test results for the amnesic patient group*

	Mean (maximum)	SD	Range	*n*
Global				
DRS total*	126.8 (144)	6.1	117–135	11
DRS subscales				
Attention	36.2 (37)	0.8	35–37	11
Constructions	5.8 (6)	0.4	5–6	11
Conceptualization	36.6 (39)	1.9	32–39	11
Initiation/preservation	33.4 (37)	3.4	28–37	11
Memory***	14.9 (25)	3.5	10–20	11
Verbal memory				
CVLT list A, trials 1–5***	23.8 (80)	7.7	11–36	12
CVLT long delay FR***	1.0 (16)	1.5	0–4	12
CVLT long delay CR***	2.5 (16)	2.4	0–7	12
CVLT discrimination (%)***	68.4 (100)	11.3	48–84	12
WMS-R logical memory I*	14.8 (50)	8.1	3–31	12
WMS-R logical memory II**	1.9 (50)	3.6	0–12	12
Non-verbal memory				
Visual reprod. I (WMS-R or WMS)	51% (100%)	23%	19–83%	12
Visual reprod. II (WMS-R or WMS)*	16% (100%)	18%	0–51%	12
Language				
Vocabulary (WAIS-R)	51.6 (70)	9.0	33–66	12
ANART	112	9.6	96–123	11
Boston Naming Test	56.6 (60)	3.6	50–60	11
Category fluency*	30.6 (n.a.)	7.1	22–48	11
Letter fluency	31.9 (n.a.)	7.9	18–44	12
Visuospatial				
Cube Copy	11.7 (13)	1.2	9–13	9
Parietal Lobe Battery, copy	8.3 (9)	1.2	7–9	3
Abstraction/problem solving				
Similarities (WAIS-R)	18.5 (24)	5.1	9–24	12
Similarities; age-scaled	11.1	2.5	6–14	12
Arithmetic (WAIS-R)	11.5 (19)	2.3	9–16	12
Arithmetic; age-scaled	10.3	2.0	7–14	12
Attention				
Digit span (WAIS-R)	14.7 (28)	3.0	12–22	12
Digit span; age-scaled	10.6	2.0	8–14	12

DRS = Mattis Dementia Rating Scale; CVLT = California Verbal Learning Test; WMS-R = Wechsler Memory Scale, Revised; WAIS-R = Wechsler Adult Intelligence Scale, Revised; ANART = American National Adult Reading Test. 'Maximum' indicates the highest possible score on a test. Asterisks denote means which are at least 1 SD below the population norm (adjusted for age) on a given measure: *1 SD below the norm, **2 SD, ***3 SD. WMS = Wechsler Memory Scale, visual reproduction test with modification by Russell (Russell, 1975), scores expressed as percentage of maximum.

according to the guidelines of the human subjects committee at the University of California, San Diego, which approved the study. Eleven were male; 11 were right handed and one was ambidextrous. Mean educational level was 14.6 years. The primary inclusion criterion was the presence of clinically evident memory impairment in the absence of significant deficits in other cognitive domains. A neuropsychological battery showed severe deficits in mnemonic abilities in all cases, while attentional, linguistic, visuospatial and problem solving abilities were within normal limits (mean score for each patient in each domain <1 SD below age-adjusted norms). Table 1 summarizes the results of the neuropsychological battery, which is described in Salmon and Butters (1992).

The patients underwent an extensive medical workup including neurological examination and CT or MRI scans. The patient group included five with diagnosed Korsakoff's syndrome, two with post-traumatic amnesia (one from boxing, one from a motor vehicle accident), one with carbon monoxide poisoning (with MRI evidence of bilateral hippocampal and globus pallidus damage), and one recovered from herpes simplex encephalitis (with MRI evidence of bilateral medial temporal damage). An additional three patients were diagnosed with idiopathic amnesic syndrome at the time of the experiment, but experienced more widespread cognitive decline subsequently, thereby meeting criteria for probable Alzheimer's disease (McKhann *et al.*, 1984) 2–3 years after the experiment. The patients were in fairly good general health without active significant medical problems (e.g. no hepatic or renal failure, no significant cardiac or respiratory disease). Three took daily medication affecting the CNS, i.e. diphenytoin, Hydergine or sertraline.

Controls

The normal controls were paid volunteers from the San Diego community who were matched to the patients for age (mean difference 3.1 years), educational level (mean difference 1.6 years), gender and handedness. They had no history of neurological disease or serious medical illness. Two control subjects took calcium-channel blockers for hypertension (diltiazem or verapamil).

Stimuli

The stimuli were 216 phrases describing a category (e.g. 'a type of wood', 'a breakfast food') together with single target words which either fit (congruent) or did not fit (incongruent) the category. Categories and targets were selected from published norms (Battig and Montague, 1969; Shapiro and Palmero, 1970) or constructed by the experimenters with the aid of normative questionnaires. Half of the target words were medium typicality exemplars of the selected categories, usually the fourth or fifth most common exemplar (e.g. 'cedar' and 'pancake' for the categories above). Half of the targets were concrete nouns which were incongruent with their associated category, but matched for frequency of usage (mean of 32, SD = 48; Francis and Kucera, 1982) and word length (5.8 characters, SD = 1.6).

Each subject was assigned to one of three stimulus lists, 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. Overall, half of the stimuli were congruent and half incongruent; half were new and half were repeats. The repeated targets were counterbalanced across the three stimulus lists, so that across subjects, each item appeared in each repetition condition. 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 (spanning ~120 s).

General procedure

Subjects were seated 125 cm from a microcomputer video monitor. The first author read the category statement aloud, followed 1 s later by visual presentation of a target word (stimulus duration = 300 ms). Subjects were instructed to sit quietly for 3 s following a target, then to say the perceived word aloud followed by a 'yes' or 'no' indicating whether or not it was an exemplar of the defined category. Performance in this simple semantic task was near-perfect for all subjects: a mean of 99.7% for controls and 98.3% for patients.

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), placed according to the International 10–20 System. Additional lateral sites included a pair placed halfway between F7 and T3 and F8–T4 (approximating Broca's area and its right hemisphere homologue, Bl and Br), a second pair 30% of the interaural distance lateral and 12.5% of the nasion–inion distance posterior to Cz (approximating Wernicke's area and its right hemisphere homologue, Wl and Wr), and a third pair 33% of the interaural distance lateral to Cz over the superior temporal lobe (LT and RT). All of the scalp electrodes plus the right mastoid electrode were referenced to the left mastoid during recording, then re-referenced off-line to an average of the left and right mastoids. Vertical eye movements and blinks were recorded via an electrode below the right eye (Le) referenced to the mastoids; horizontal eye movements (Heog) were monitored by two electrodes at the outer canthi of the two eyes (left minus right).

The EEG was amplified by Grass model 78D amplifiers with a bandpass of 0.02–100 Hz and digitized on-line with a 250 Hz sampling rate. ERPs to the visual target words were averaged after rejection of trials contaminated by horizontal eye movements, amplifier saturation or excessive muscle activity—8% of the trials were rejected for the control subjects and 18% for the patients. A low-pass filter at 15 Hz was used, and then trials with blink artefacts were corrected via a spatial adaptive filtering algorithm developed by A. Dale (Massachussetts General Hospital, USA).

Behavioural tests of memory

Immediately after the ERP recordings were completed, paper and pencil tests of free recall, cued-recall, and recognition were administered in that order. In the free recall task, subjects were asked to recall all the target words they could, independent of whether they were congruent or incongruent. In the cued-recall task, subjects were given a printed list of the category statements and asked to fill in the word that was presented earlier, or to provide the 'first word that comes to mind' if they could not recall. The forced-choice recognition task consisted of category statements accompanied by six possible completions: four category exemplars and two incongruous words. The five foils were words never used during the experiment.

Results

Memory performance

Accuracies in the three paper-and-pencil memory tests are shown in Table 2. Analyses of variance (ANOVA) with repeated measures used factors of Group, Congruity and Repetition (one versus two versus three presentations). The patients performed worse than controls on all three tests

Table 2 *Accuracy of memory for the experimental words (paper and pencil tests)*

	Free recall		Cued recall		Recognition	
	Control	Patient	Control	Patient	Control	Patient
Congruous						
1 presentation	15.3 (3.6)	1.0 (0.7)	68.1 (5.2)	16.2 (3.5)	81.6 (4.4)	32.8 (5.5)
2 presentations	29.6 (5.0)	1.0 (0.7)	80.4 (4.9)	19.4 (5.3)	91.0 (2.9)	34.0 (7.8)
3 presentations	43.1 (4.6)	3.0 (1.6)	87.2 (4.1)	29.4 (7.2)	93.4 (2.0)	39.9 (7.6)
Incongruous						
1 presentation	3.0 (1.1)	0.3 (0.3)	2.7 (0.9)	0.0 (0.0)	75.7 (3.7)	5.4 (3.0)
2 presentations	4.0 (1.0)	0.7 (0.5)	3.3 (1.2)	0.7 (0.7)	83.8 (3.7)	12.0 (6.9)
3 presentations	16.2 (3.6)	2.7 (1.1)	8.4 (2.1)	1.7 (1.3)	89.9 (3.1)	10.3 (5.3)

Percentages correct, standard error in parentheses.

[$F(1,22) = 66.6$, 65.8 and 106.6 for free recall, cued recall and recognition, respectively, all P-values < 0.0001]. Memory was generally better for the congruous than incongruous items [$F(1,22) > 52$, $P < 0.0001$]. Multiple presentations of the words enhanced performance in all three measures [$F(2,44) > 14.3$, $P < 0.0001$].

Significant two- and three-way interactions between Group, Congruity and Repetition were observed in the omnibus analyses for all three tasks. Paired comparisons between items presented once versus three times were conducted to determine the conditions which yielded improved memory performance with repetition. Multiple presentations of congruous items improved free recall, cued recall and recognition in the control group [$F(1,11) > 13.8$, $P < 0.005$]. The controls similarly demonstrated better memory for incongruous items given additional study opportunities [$F(1,11) > 14.9$, $P < 0.005$]. Additional presentations of congruous items resulted in less robust improvement for the patient group, significant for cued recall [$F(1,11) = 8.7$, $P < 0.05$] but not for free recall [$F(1,11) = 1.94$, $P = 0.19$] or recognition [$F(1,11) = 3.06$, $P = 0.11$]. Three presentations of incongruous words yielded no better performance than one presentation in the patient group [$F(1,11) = 3.48$, 1.54 and 2.28 for free recall, cued recall and recognition, respectively].

In summary, the results of the behavioral memory tests showed: (i) impaired memory in the patient group relative to the controls; (ii) superior memory for congruous compared with incongruous category exemplars; (iii) a learning curve across multiple presentations in the control subjects for both congruous and incongruous items; and (iv) weak learning across multiple presentations of congruous items in the patients, and no benefit from repeating incongruous items.

Event-related potentials

The ERP results below describe: (i) the influence of semantic congruity on first presentation; (ii) repetition effects for congruous words; (iii) repetition effects for incongruous words; (iv) influence of repetition lag; (v) relationships among the ERP repetition effects, memory for the experimental items, and neuropsychological measures of cognitive abilities.

Semantic congruity

Figure 1 (left side) shows the ERPs elicited by congruous and incongruous category words on first presentation in the control subjects. The large N400 elicited by incongruous words is most prominent over the right posterior scalp. The congruity effect begins at ~250 ms poststimulus onset, peaks at ~450 ms, and is over by 700 ms at most sites. Measurements consisted of mean amplitudes within latency windows of 300–500 and 500–800 ms poststimulus onset (both relative to a 100 ms prestimulus baseline), to cover the peak latency range of the N400 and a later window. These were subjected to ANOVA with factors of Congruity, Latency Window, Laterality (left versus right), and another spatial factor reflecting the anterior-to-posterior location of the lateral electrode sites (Anterior/Posterior, six levels).

The main effect of Congruity was not significant [$F(1,11) = 3.21$]. Rather, the restricted latency range of the congruity effect yielded an interaction of Congruity × Latency Window [$F(1,11) = 8.14$, $P < 0.02$]. The right-greater-than-left asymmetry of the effect similarly led to an interaction between Congruity and Laterality [$F(1,11) = 18.7$, $P < 0.002$]. Separate analyses of the two latency windows confirmed these results. The 300–500 ms window yielded a main effect of Congruity [$F(1,11) = 5.69$, $P < 0.05$] and an interaction of Congruity × Laterality [$F(1,11) = 11.8$, $P < 0.01$]. Between 500 and 800 ms, the main effect of Congruity was no longer significant ($F < 1$), although a significant Congruity × Laterality effect suggests that the N400 difference persists into this time window [$F(1,11) = 10.9$, $P < 0.01$].

The right side of Fig. 1 shows that the effect of semantic congruity in the patient group was similar to that of the controls. The right-sided asymmetry of the congruity effect resulted in an interaction of Congruity × Laterality [$F(1,11) = 31.2$, $P < 0.0002$], whereas the main effect of Congruity

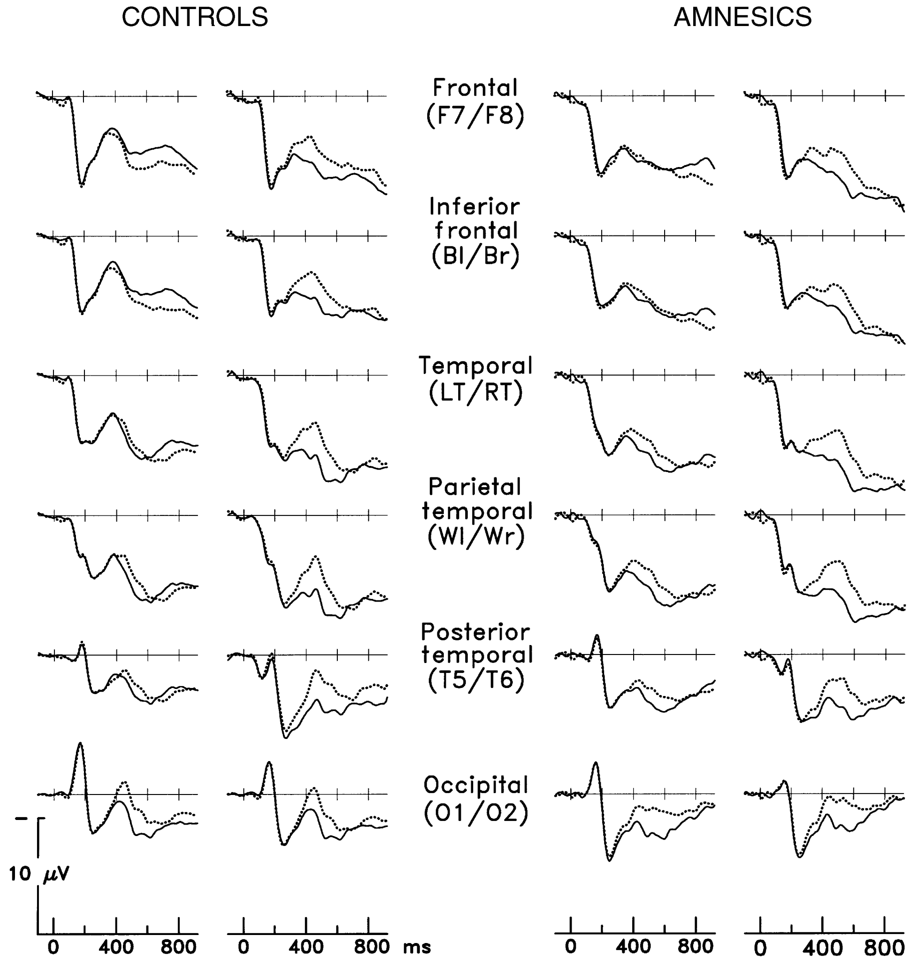

Fig. 1 Grand average ERPs from the control and amnesic groups elicited by the first presentation of semantically congruous (continuous lines) and incongruous (dotted lines) words. Negative voltage is plotted in the upward direction. Top to bottom in the figure reflects the anterior to posterior (frontal to occipital) location of the electrodes. For both the controls and the patients, electrode sites on the left side of the head are in the left column, electrode sites on the right in the right column.

was marginal [$F(1,11) = 4.55$, $P = 0.06$]. Separate analyses of the two latency windows yielded a significant main effect of Congruity in the early, but not late window [300–500 ms: $F(1,11) = 10.6$, $P < 0.01$; 500–800 ms: $F = 2.16$]. The Congruity × Laterality interaction was significant in both windows [300–500 ms: $F(1,11) = 31.1$, $P < 0.0002$; 500–800 ms: $F(1,11) = 21.3$, $P < 0.001$]. The impact of congruity was thus similar to that of the controls in being greatest between 300 and 500 ms poststimulus onset, but with a small amplitude difference continuing beyond 500 ms.

Repetition of congruous words

Figure 2 (left side) shows the ERPs elicited from the control subjects by the first and repeated presentation of congruous items, collapsed across repetition lag. The most prominent effect of repetition was the reduction of a late positivity at temporal and occipital posterior scalp sites, beginning at ~400 ms, peaking near 600 ms, and extending to at least 900 ms poststimulus. The repetition effect was analysed in the same manner as the semantic congruity effect, using factors of Repetition (all first versus all repeated presentations), Latency Window (300–500 and 500–800 ms), Laterality, and Anterior/Posterior scalp location. This yielded a main effect of Repetition [$F(1,11) = 7.43$, $P < 0.02$], together with an interaction of Repetition × Latency Window reflecting the larger repetition difference in the later time range [$F(1,11) = 15.8$, $P < 0.002$]. In contrast to the semantic congruity effect, separate analyses of the two latency windows indicated that the repetition effect was significant only in the late time epoch [main effect of repetition, 300–500 ms: $F < 1$; 500–800 ms: $F(1,11) = 18.0$, $P < 0.002$]. Within the late epoch, the repetition effect was larger over the right at anterior scalp sites (F8 and Br compared with F7 and Bl), but larger over the left at posterior sites [Repetition × AP × Laterality, $F(5,55) = 18.4$, $P < 0.0001$, epsilon = 0.41].

The right side of Fig. 2 shows that there was no apparent effect of repeating congruous items in the patient group.

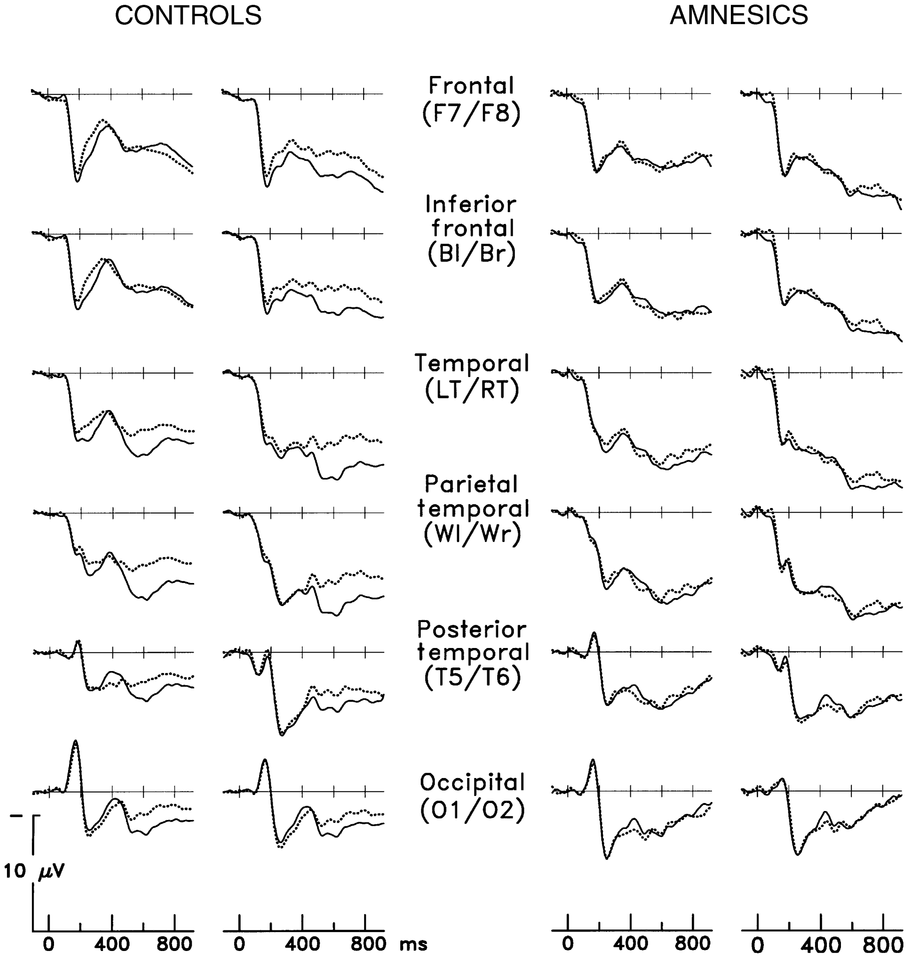

Fig. 2 Grand average ERPs from the control and amnesic groups elicited by new (continuous lines) and repeated (dotted lines) words which were semantically congruous. Negative voltage is plotted in the upward direction.

Analyses parallel to those above yielded no significant main effect or interactions involving the repetition factor for any latency window (all *F*-values < 1.2).

Repetition of incongruous words

In contrast to the congruous items, repeated incongruous items elicited more positive ERPs in the control subjects, as seen in Fig. 3 [$F(1,11) = 10.1$, $P < 0.01$]. The repetition effect for these items occurred primarily in the N400 latency range of 300–500 ms [$F(1,11) = 6.10$, $P < 0.05$] and was no longer significant in the 500–800 ms epoch ($F = 3.48$, $P = 0.09$). Within the early epoch, the repetition effect was larger over the right than left for all of the lateral electrode pairs [Repetition × Laterality, $F(1,11) = 6.57$, $P < 0.02$]. Overall, the data are most consistent with viewing the repetition effect for semantically incongruous items as largely a reduction in the amplitude of the N400 elicited on first presentation.

In contrast to their null repetition effect for congruous category exemplars, Fig. 3 shows that the amnesic patients displayed a robust repetition effect for incongruous words. The analysis with both latency windows yielded a main effect of Repetition [$F(1,11) = 4.59$, $P = 0.05$] and an interaction of Repetition × Laterality reflecting the larger amplitude of the effect at right scalp sites [$F(1,11) = 15.4$, $P < 0.002$]. The 300–500 ms latency window yielded a main effect of Repetition, and a Repetition × Laterality interaction [$F(1,11) = 4.49$, $P = 0.05$; $F(1,11) = 9.31$, $P < 0.01$, respectively]. The later time window yielded a trend toward a main effect of Repetition [$F(1,11) = 4.34$, $P = 0.06$], which was also larger over the right than left at all electrode sites, suggesting that it was likely to reflect the final phase of the N400 effect [Repetition × Laterality, $F(1,11) = 8.60$, $P < 0.02$].

As in the control group, the incongruous repetition effect in the amnesic patients can largely be attributed to a reduction in the amplitude of the N400 elicited by repetitions of the semantically incongruous words. The similarity of this preserved repetition effect to the initial semantic congruity effect for new words is evident in difference waves comparing the two experimental effects, displayed in Fig. 4. At most

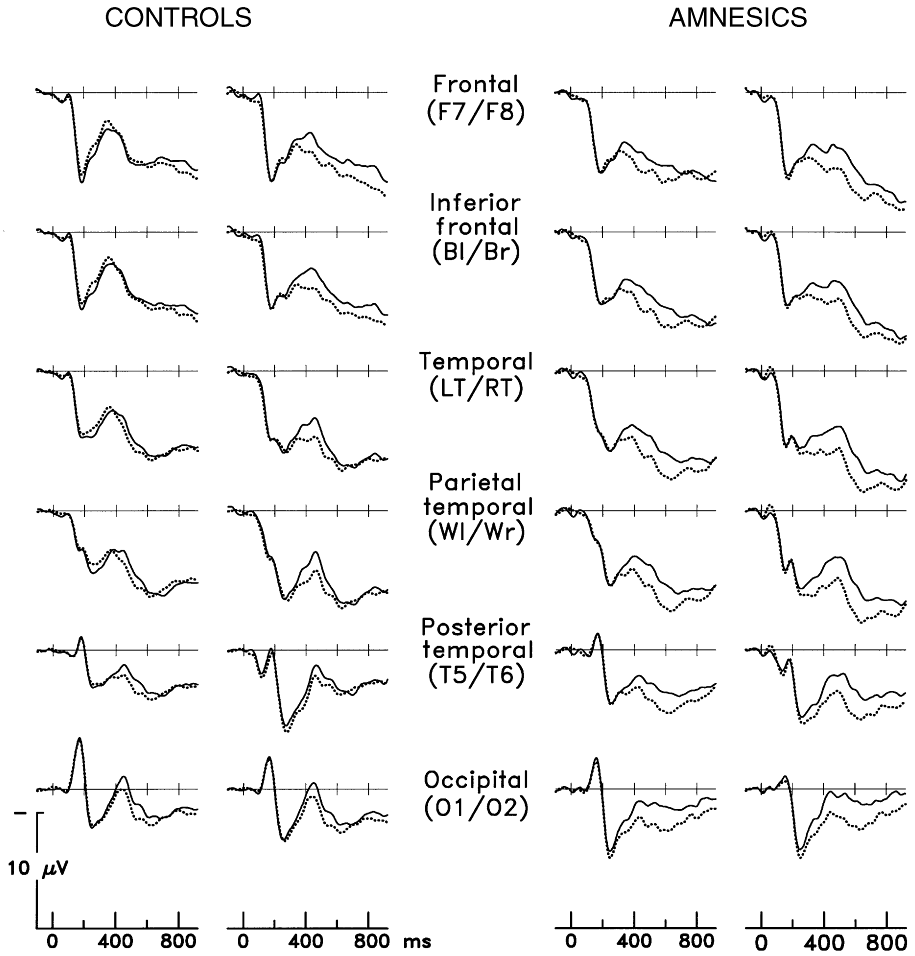

Fig. 3 Grand average ERPs from the control and amnesic groups elicited by new (continuous lines) and repeated (dotted lines) words which were semantically incongruous. Negative voltage is plotted in the upward direction.

electrode sites, the initial congruity effect and the repetition effect for incongruous items have the same timecourse, waveshape and amplitude. The scalp distributions of the two effects were compared via ANOVAs taking ‘effect type’ (Congruity versus Repetition), Anterior/Posterior, and Laterality as factors after using an amplitude normalization procedure (see McCarthy and Wood, 1985). Within the N400 latency range of 300–500 ms, no significant interactions between ‘effect type’ and scalp location were observed in either the control or patient groups, indicating similar scalp distributions for the N400 congruity and repetition effects.

Repetition lag and number of repetitions

The foregoing analyses considered all repeated items as a single condition to maximize the signal-to-noise ratio of the ERPs. Repetition lag is also of some interest, given that short-lag repetitions occurred only 10–40 s after initial presentation and may fall within the working memory span of the patients. These more fine-grained divisions of the stimuli produce less robust comparisons given the smaller number of trials contributing to the ERP averages. The ERPs elicited by once- and twice-repeated items did not differ in either the control or patient groups.

The N400 repetition effect for incongruous words tended to be larger for short- than long-lag repetitions in both controls and patients, as seen in Fig. 5. However, even long-lag repetitions elicited smaller N400s than new items in both the controls [Repetition × Laterality: $F(1,11) = 6.13$, $P < 0.05$] and the patients [Repetition: $F(1,11) = 5.67$, $P < 0.05$; Repetition × Laterality: $F(1,11) = 5.11, P < 0.05$].

For the control subjects, long-lag repetitions of congruous items were as effective as short-lag repetitions in reducing the amplitude of the late positivity, as seen in the left half of Fig. 6 [500–800 ms epoch: long-lag versus new, $F(1,11) = 21.3$, $P < 0.001$; long-lag versus short-lag, $F < 1$]. In contrast, the right half of Fig. 6 shows no influence of long-lag repetitions in the patient group ($F < 1$). This figure also suggests some trend toward a short-lag LPC repetition effect in the patients, but this was not statistically significant given individual variability within the patient group [$F(1,11) = 1.10$, $P = 0.32$].

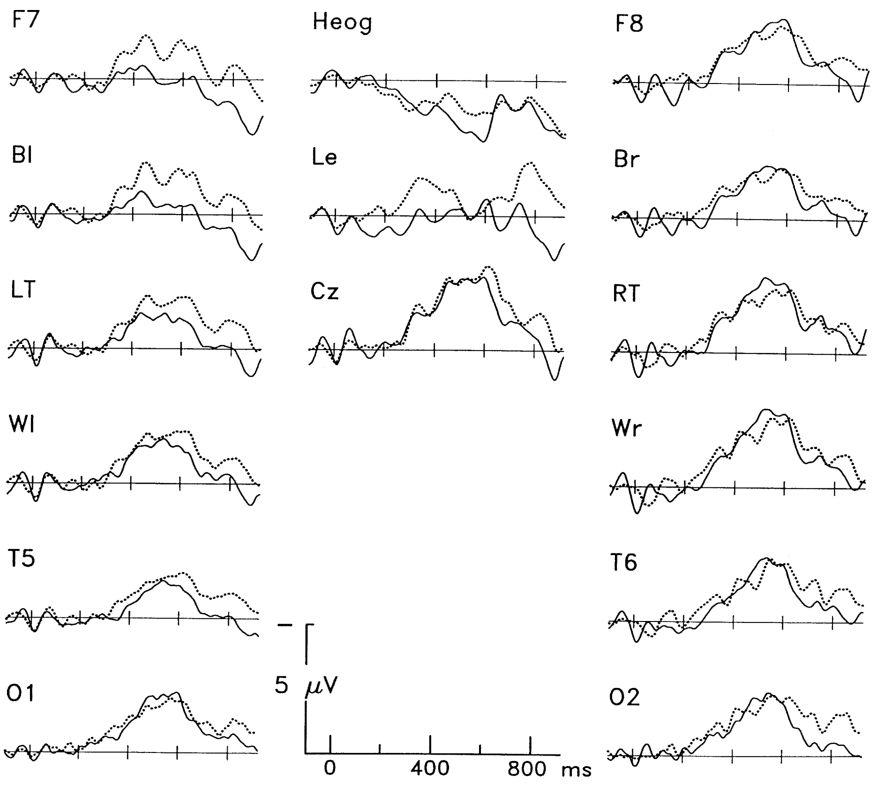

Fig. 4 Comparison of the initial semantic congruity effect and the effect of repeating incongruous items, for the patient group. Both the continuous and dotted lines were formed by point-by-point subtraction of two conditions. The continuous line reflects the difference between semantically congruous and incongruous items presented for the first time (the two waveforms shown in Fig. 1).
The dotted line reflects the difference between incongruous items presented for the first time versus when they were repeated (the two waveforms shown in Fig. 3). Negative voltage is plotted in the upward direction.

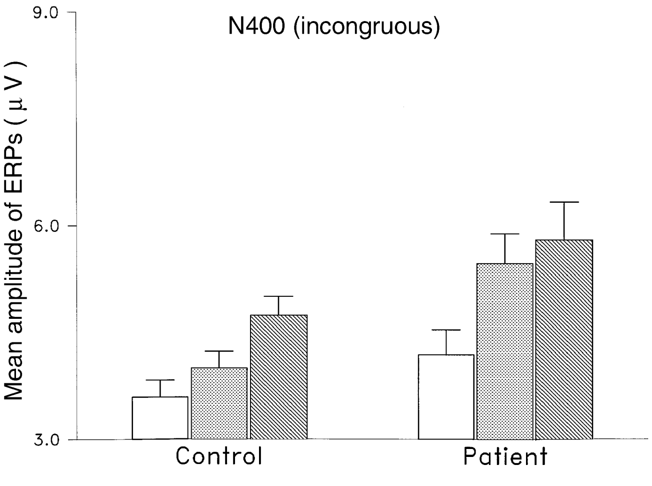

Fig. 5 Mean amplitude of the ERPs in the time interval of 300–500 ms poststimulus onset, relative to the prestimulus interval, elicited by the initial presentation of incongruous words (open columns), long lag repetitions of these items (dotted columns), and short lag repetitions (cross-hatched columns). Error bars reflect the standard error of the mean of the control and patient groups.

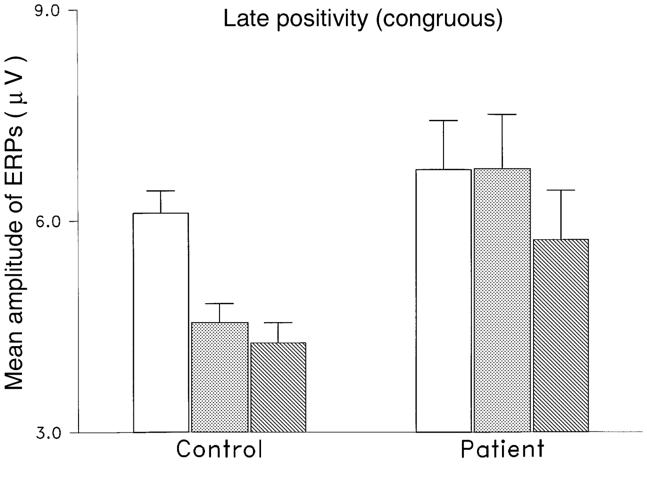

Fig. 6 Mean amplitude of the ERPs in the time interval of 500–800 ms poststimulus onset, relative to the prestimulus interval, elicited by the initial presentation of congruous words (open columns), long lag repetitions of these items (dotted columns), and short lag repetitions (cross-hatched columns). Error bars reflect the standard error of the mean of the control and patient groups.

Table 3 *Correlations between the ERP repetition effects and memory performance for the experimental stimuli*

	Congruous repetition effect (LPC)			Incongruous repetition effect (N400)		
	Control	Patient	All	Control	Patient	All
Free recall						
Congruous	0.63*	–	–	0.45	–	–
Incongruous	0.58*	–	–	−0.03	–	–
All words	0.71**	0.57*	0.48*	0.34	0.11	−0.11
Cued recall						
Congruous	0.25	0.65*	0.51**	0.21	0.01	−0.16
Incongruous	0.62*	–	–	0.21	–	–
All words	0.36	0.69*	0.54**	0.23	0.04	−0.15
Recognition						
Congruous	0.28	0.47	0.49*	0.06	−0.03	−0.19
Incongruous	0.47	0.51	0.45*	0.03	0.03	−0.20
All words	0.40	0.51	0.48*	0.05	−0.01	−0.20

Pearson correlations between ERP repetition effects (mean amplitude of difference between new and repeated items in a 500–800 ms latency window for congruous items, 300–500 ms for incongruous, both relative to a 100 ms prestimulus baseline) and accuracy in subsequent memory tests for the experimental stimuli. $n = 12$ for controls, $n = 12$ for patients, $n = 24$ for all subjects. Asterisks denote significant correlations: $*P < 0.05$, $**P < 0.01$. Dashes (–) indicate that no correlation was conducted because most of the patients scored zero correct.

Correlations between individual ERPs and memory for the experimental items

Although the average amplitude of the LPC repetition effect within the patient group was near zero (Fig. 2), there was substantial individual variability. Eight of the 12 patients had LPC repetition effects >1 SD below the mean of the control subjects; three were below, but closer to the control mean, and one patient showed a large LPC repetition effect. The aetiology of the amnestic syndrome didn't readily account for this variability. The four patients who were within 1 SD of the control mean included two of the Korsakoff's patients (of five tested), one of the patients with incipient Alzheimer's disease (of three tested), and one of the posttraumatic amnesia patients (of two tested). Instead of aetiology, it was the severity of the memory deficit that was strongly correlated with the size of the LPC repetition effect, as detailed below.

The N400 repetition effect observed for incongruous items was defined as the mean amplitude of the difference between repeated and initial presentations from 300–500 ms, collapsed across repetition lag and scalp site. The late positive repetition effect for congruous items was measured as the 500–800 ms difference. The within-subject correlation between the two ERP measures of repetition were non-significant in both groups ($r = 0.40$, controls; $r = –0.09$, patients).

For the controls, correlations with the ERP repetition effects were examined for free recall, cued recall, and recognition of both congruous and incongruous items. Table 4 shows that the LPC repetition effect was strongly correlated with performance in the memory tests which proved most difficult for the control subjects—free recall of both congruous and incongruous items, as well as cued recall of incongruous items. Many of the controls scored at ceiling in the cued recall of congruous items and in the recognition tests; these measures yielded positive but nonsignificant correlations with the LPC repetition effect. In contrast, the N400 repetition effect was not significantly correlated with any of the behavioural measures of memory in the control group.

In the patient group, only a subset of the performance measures could be examined given floor effects. For those measures that were off the floor in the patient group, the patients showed a pattern of results similar to the controls: significant relationships between cued-recall performance and the LPC measure, but not the N400 measure (Table 4). Finally, combining patients and controls into a single larger group yielded sufficient statistical power to show significant correlations between the LPC effect and the recognition measure although these correlations were weaker than those for the recall measures. Figure 7 illustrates the relationship between the recall measures and the LPC repetition effect at the midline electrode site (Cz).

Correlations among the two ERP repetition effects and the standard neuropsychological tests were also examined in the patient group (for all tests with $n \geqslant 11$, see Table 1). None of the tests in the neuropsychological battery showed a significant correlation with the N400 repetition effect elicited by incongruous items, an outcome that echoes the lack of relationship between this ERP measure and subsequent memory for the experimental stimuli. The LPC (congruous) repetition effect was significantly correlated with Logical Memory II in the Wechsler Memory Scale—Revised (delayed

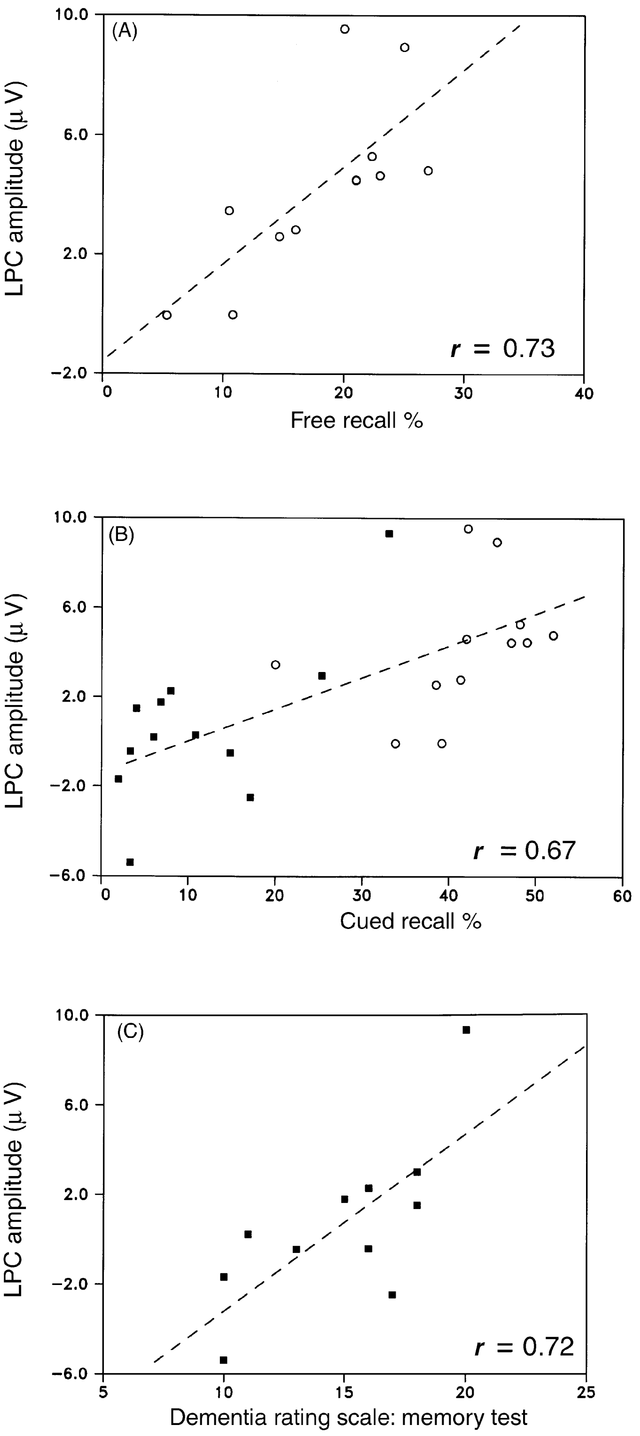

Fig. 7 Relationships between memory performance and the amplitude of the LPC repetition effect at scalp site Cz (new minus repeated items, mean amplitude 500–800 ms poststimulus onset), r = Pearson correlation. Overall, a *post hoc* cut-off of 2.5 μV for the LPC repetition effect correctly classified 20 of the 24 subjects as belonging to the patient versus control groups (10/12 in each group). (**A**) Free recall of all the experimental words in the control subjects; (**B**) cued recall of all the experimental words in both patients and controls; (**C**) scores on the memory scale of the Matthis Dementia Rating Scale in the patients.

recall of paragraph-length stories, $r = 0.76$, $P = 0.005$) and with the memory subscale of the Dementia Rating Scale ($r = 0.67$, $P < 0.02$). None of the other Dementia Rating Scale subscales, or other tests shown in Table 1, were significantly correlated with the LPC repetition effect ($r < 0.31$; $P > 0.35$). Neither age nor education of the patients correlated with either ERP repetition effect ($r < 0.26$).

Discussion

When category exemplars were presented for the first time, the amnesic patients were much like controls in showing a smaller N400 to words that fit the preceding category label, compared with words that did not fall within the category. When incongruous items were repeated, both patients and controls generated smaller N400s than on initial presentation. The impact of both semantic congruity and repetition on the N400 were largest over right posterior scalp in the controls and patients alike. The similarity of the N400 repetition effect between patients and controls indicates preservation of some aspect of memory in the amnesic participants, despite their poor performance in all of our declarative memory tests.

Repetition of congruous words influenced the ERPs of the control subjects in a different manner than repetition of incongruous items, yielding a less positive ERP on repeated than initial presentation. The repetition effect for congruous items was later in onset than the N400 repetition effect, and left-lateralized over posterior regions. Overall, the impact of repetition in neurologically intact individuals was qualitatively different for congruous than incongruous items, with the congruous repetition effect consisting primarily of the modulation of a late positive component rather than the N400. The timing and general morphology of the congruous repetition effect suggest that it is the same LPC memory effect previously described in the normal population. The direction of the LPC repetition effect observed here (less positive with repetition) is the opposite to that in experiments using isolated words as stimuli, but like two studies in which repeated words occurred after semantically predictive contexts, much like the congruous category exemplars used here (see Van Petten *et al.*, 1991; Besson *et al.*, 1992). The combined manipulation of semantic congruity and repetition was thus successful in achieving our initial goal of producing a clear separation between the two repetition-sensitive components of the ERP.

Considered as a group, the amnesic patients lacked an LPC repetition effect despite their preserved N400 repetition effect. This dissociation both confirms and extends prior studies of scalp-recorded ERPs in patients with temporal lobe pathology (Smith and Halgren, 1989; Rugg *et al.*, 1991; Mecklinger *et al.*, 1998). Those studies showed substantial reductions of the difference between new and repeated items, but no obvious relationship between the ERP reduction and level of recognition accuracy across individual patients. The present results indicate that when the electrophysiological repetition effect is fractionated into its subcomponents, the

N400 portion of the effect indeed shows no relationship to long-term memory for the experimental stimuli, or to standardized tests of memory ability. In addition to the null correlations between the amplitude of the N400 repetition effect and the memory performance measures, it is relevant to note that even the control subjects showed very poor subsequent recall of the semantically incongruous words that triggered the N400 repetition effect. In contrast to the N400, the LPC portion of the repetition effect was strongly related to behavioural measures of long-term memory ability. The results thus suggest that measuring the ERP repetition effect as a unitary phenomenon dilutes the relationship to long term memory that is evident when the two subcomponents of the effect are distinguished.

The LPC/memory relationship was evident both in patient/control group differences, and in correlations between LPC amplitude and individual memory abilities for all participants (patients and controls). The correlational data showed that an individual's LPC amplitude was strongly predictive of his or her overall long-term verbal memory abilities. To our knowledge, this is the first report of a relationship between scalp-recorded ERPs and memory abilities in normal or memory-impaired subjects. The strongest relationships in the current data were between recall measures and LPC amplitude, whereas the large majority of prior ERP memory studies have used recognition measures that yielded weaker correlations in the present data as well.

It is important to note that the LPC/performance correlations included recall of both the congruous and incongruous words, in addition to standardized memory tests. Thus, the pattern of results should not be taken to suggest that congruous and incongruous items are served by distinct memory systems. Rather, we attribute the larger LPC elicited by congruous items to their greater memorability. It is well known that semantically coherent material is easier to learn than random word lists, and as expected, the control subjects of the present study demonstrated greatly superior recall of the congruous items compared with the incongruous items when tested at the end of the experiment. It is plausible to assume that repetitions of congruous items during the ERP recording were also more likely to contact declarative memories of their initial presentation than were repetitions of incongruous items, and thus it was largely the congruous items that elicited LPC repetition effects.

The observed link between the repetition-sensitive LPC and long-term declarative memory accords well with prior research in healthy participants. The more surprising finding was the observation of perfectly intact N400 repetition effects in patients with severe deficits in declarative memory. The presence of a normal N400 repetition effect in these patients indicates that one functional brain system was sensitive to prior experience, and yet had no relationship to any of our behavioural measures of memory performance. This system is unlikely to be related to the perceptual priming effects reported in amnesic patients because such effects are dependent on exact repetitions which preserve physical format (see Gabrieli, 1998 for review). In contrast, the semantic manipulation used here crossed modalities (spoken context, visual target), and the semantic context effect was indistinguishable from the N400 repetition effect.

A more plausible interpretation is that the sensitivity of the N400 to both semantic context and repetition reflects the continued accessibility of representations of recent stimuli for integration with current stimuli. A semantically-interpreted record of recent input is necessary for successful language comprehension, the aspect of cognitive processing which has been most closely linked to the N400 in previous research (Kutas and Van Petten, 1994; St George *et al.*, 1994; Van Petten, 1995; Van Petten *et al.*, 1997). A memory system in the service of immediate comprehension need not leave a long-term record, consistent with the lack of relationship between the N400 repetition effect and memory for the experimental stimuli assessed after a substantial delay. However, the optimum span of such a memory system would certainly need to encompass more than a few individual words, given that single propositions can require fairly long and complex sentences, or even entire paragraphs to express. In the present study, N400 repetition effects were detectable even when 10–13 unrelated trials occurred between initial and repeated presentations. One previous study likewise reports N400 repetition effects across at least 20 intervening words of coherent prose (Van Petten *et al.*, 1991). The sensitivity of the N400 to semantic context can span a full paragraph (St George *et al.*, 1994; Van Petten, 1995; Van Berkum *et al.*, 1999). The span of the memory system indexed by the N400 may thus be a bit longer than the 'seven plus or minus two' capacity traditionally ascribed to short term memory (if the count refers to individual words).

The conclusion that the N400 repetition effect reflects facilitated semantic processing of repeated items suggests that it may be the neural correlate of 'conceptual priming' effects previously described as intact in amnesic patients. Despite impaired recall and recognition of category exemplars, patients are likely to generate previously studied words as examples of their respective categories (Graf *et al.*, 1985; Keane *et al.*, 1997). In contrast to perceptual priming effects, conceptual priming effects cross sensory modalities are dependent on the strength of the semantic relationship between a contextual cue and the primed word, and appear across retention intervals which are roughly consistent with those described above for the N400 (Woltz, 1996; Vaidya *et al.*, 1997).

The neural generators of the scalp-recorded N400 and LPC are imperfectly understood, although intracranial recordings in epilepsy patients have shown locally generated potentials in the temporal lobe for both semantic and repetition manipulations (Smith *et al.*, 1986; Nobre *et al.*, 1994). Nobre and colleagues recorded N400-like potentials (P400s), which showed polarity reversals in regions deep to the anterior fusiform gyri and parahippocampal gyri (i.e. on both sides of the collateral sulcus) bilaterally (Nobre *et al.*, 1994; McCarthy *et al.*, 1995). Our proposal that the N400 repetition effect reflects a relatively short-term memory system in the service of comprehension, whereas the LPC repetition effect is more closely linked to long term memory processes is consistent with the conclusions drawn by Elger and colleagues on the basis of intracranially recorded ERPs in patients with temporal lobe epilepsy (Elger *et al.*, 1997; Helmstaedter *et al.*, 1997). This group has evaluated locally-generated ERPs in medial temporal lobe structures and lateral temporal neocortex during initial and repeated presentations of single words. The amplitudes of repetition effects in the lateral temporal lobe (particularly the left hemisphere) were correlated with measures of immediate recall, whereas repetition effects in anterior mesial structures [usually maximal near the inferior border of the amygdala, the most anterior depth electrode in their montage, but also recorded near the collateral sulcus and within the hippocampal head (Grunwald *et al.*, 1998)] were correlated with delayed recall (Helmstaedter *et al.*, 1997). The functional correlates of the medial temporal repetition effect were thus much like the LPC recorded here. This group refers to both the lateral and medial repetition effects as N400 changes rather than adopting the two-component model used here. However, some of their data (e.g. Helmstaedter *et al.*, 1997; Fig. 1) suggest that the medial temporal repetition effect is of longer latency than the lateral effect, much as the scalp-recorded LPC repetition effect is delayed relative to the scalp-recorded N400 effect. This same group of investigators have also recorded large word repetition effects on a late negative component (termed the LNC or LN_W) present at more posterior sites within the body of the hippocampus, which have a latency similar to the scalp LPC (Grunwald *et al.*, 1995, 1999). A definitive mapping between the scalp-recorded components isolated by the present study and the different anatomical foci of intracranial repetition effects will require further research. It will be useful to evaluate scalp-recorded ERPs in patients with more focal lesions than the amnesic participants of the present study, as well as to record intracranial ERPs in paradigms which can evaluate the relationships between semantic processing and verbal memory. Even without focal anatomical correlates, our non-invasive ERP paradigm was successful in isolating different memory subsystems, and may be clinically useful in distinguishing organic impairments of long term memory from other deficits, particularly those involving language comprehension.

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