

Comparative Electrophysiological and Hemodynamic Measures of Neural Activation During Memory-Retrieval

Emrah Düzel,^{1*} Terence W. Picton,² Roberto Cabeza,³
Andrew P. Yonelinas,⁴ Henning Scheich,⁵ Hans-Jochen Heinze,¹ and
Endel Tulving³

¹Department of Neurology II, O.v.G. University of Magdeburg, Magdeburg, Germany

²Rotman Research Institute, University of Toronto, Baycrest Centre for Geriatric Care, North York, Ontario, Canada

³Center for Cognitive Neuroscience, Duke University, Durham, North Carolina

⁴Department of Psychology, University of California, Davis, Davis, California

⁵Institute for Neurobiology, O.v.G. University of Magdeburg, Magdeburg, Germany

Abstract: The spatial and temporal characteristics of the brain processes underlying memory retrieval were studied with both event-related potentials (ERP) and positron emission tomography (PET) techniques. Subjects studied lists of 20 words and then performed episodic (old/new judgment) or semantic (living/nonliving decision) retrieval tasks on multiple four-item test lists, each lasting 10 sec. The PET and ERP measurements at test were assessed in relation to both the task (episodic vs. semantic) and the item (old vs. new or living vs. nonliving). Episodic retrieval was associated with increased blood flow in the right frontal lobe (Brodmann Area 10) and a sustained, slowly developing positive ERP shift recorded from the right frontopolar scalp. Semantic retrieval was associated with increased blood flow in the left frontal (Area 45) and temporal (Area 21) lobes but no clear ERP concomitant. The two retrieval tasks also differed from each other in the ERPs to single items in an early (300–500 ms) time window. Item-related comparisons yielded convergent results mainly if the retrieved information was relevant to the given task (e.g., old/new items during episodic retrieval and living/nonliving items during semantic retrieval). Episodically retrieved old items were associated with increased blood flow in the left medial temporal lobe and a transient increase in the amplitude of the late positive component (500–700 ms) of the ERP. Semantically retrieved living items were associated with increased blood flow in the left frontal cortex and anterior cingulate and a transient late frontal slow wave (700–1,500 ms) in the ERPs. These results indicate that the brain regions engaged in memory retrieval are active in either a sustained or transient manner. They map task-related processes to sustained and item-related processes to transient neural activity. But they also suggest that task-related factors can transiently affect early stages of item processing. *Hum. Brain Mapping* 13:104–123, 2001. © 2001 Wiley-Liss, Inc.

Grant sponsor: Bundesministerium für Bildung und Forschung; Grant number: BMWF/BEO 11 TW 10574. Grant sponsor: Natural Sciences and Engineering Council of Canada. Grant sponsor: Deutsche Forschungsgemeinschaft; Grant number: Du 280/1-1 (E.D.).

*Correspondence to: Dr. Emrah Düzel, Department of Neurology II, O.v.G. University of Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany. E-mail: emrah.duezel@medizin.uni-magdeburg.de
Received for publication 12 April 1999; accepted 31 January 2001

INTRODUCTION

In the past years, comparative interpretations of electrophysiological and hemodynamic studies [Rugg, 1998] have made important contributions to our understanding of the functional organization of memory retrieval. Together, the two modalities access the tim-

ing and the anatomy of brain activity to an extent that is not yet possible by either technique alone [Heinze et al., 1994]. This allows a more complete characterization of processes engaged during episodic and semantic retrieval. One of the recent contributions of such comparative studies has been the characterization of sustained and short-lasting brain activity patterns as indices of task-related and item-related retrieval processes [Duzel et al., 1999; Rugg and Wilding, 2000].

This paper describes in more detail the findings of a comparative event-related potential (ERP) and positron-emission tomography (PET) study that investigated task-related and item-related processes and their interaction during episodic and semantic retrieval [Duzel et al., 1999]. Task-related retrieval processes are established by task instructions and maintained throughout the duration of the task [Duzel et al., 1999]. During episodic retrieval, task-related processes index episodic retrieval mode, which, as formulated by Tulving in 1983 for the first time [Tulving, 1983], is a neurocognitive set that allows subjects to think back to their personal past and treat items as retrieval cues to past events [Wheeler et al., 1997; Lepage et al., 2000]. In a typical experiment, episodic retrieval instructions ask subjects to think back to “microevents” of experiencing items in a study list and to decide whether a retrieval cue was part of such a microevent, for instance by making a recognition judgment. Item-related processes are elicited as a result of the interaction of old (studied) and new (presented for the first time) items that serve as retrieval cues with task-related processes and with preexisting semantic and/or episodic memories. Against the background of episodic retrieval mode, appropriate retrieval cues (old items) will lead to the recovery of stored episodic information, a situation referred to as *ecphory* [Schacter et al., 1978]. Because task-related processes are time-locked to the onset and the duration of the retrieval task they should have a sustained time course, whereas item-related processes should have a more transient time course coupled to the presentation of individual items.

PET measures neuronal activation by estimating local cerebral blood flow on the basis of detecting the concentration of radioactive-labeled $^{15}\text{H}_2\text{O}$ [Fox et al., 1984]. Blood flow changes follow the patterns of neural activity by several seconds [Kim et al., 1997; Roland, 1993]. Present PET techniques record over periods of time of approximately 1 min and integrate the hemodynamic brain responses to many items. While this gives a spatially accurate image of neural activity, it does not distinguish among transient, sustained, or intermittent temporal patterns of activity. Event-re-

lated potentials record the electric fields generated by active regions of the brain [Nunez, 1981; Vaughan and Arezzo, 1987]. Source analysis [Scherg and Picton, 1991; Picton et al., 1995; Scherg and Berg, 1996] allows us to model the neural generators for the recorded ERP fields and, by applying constraints as to what is physiologically and anatomically feasible [Achim, 1995], to derive generators that are accurate within reasonable confidence limits [Miltner et al., 1994]. The comparative use of ERPs and PET might therefore lead to measuring both the when and the where of cerebral activation [Heinze et al., 1994].

A number of PET and functional magnetic resonance imaging (fMRI) studies have measured brain activity during episodic and semantic retrieval using the subtraction method [for a review, see Cabeza and Nyberg, 2000]. A recent meta-analysis of four PET studies that used recognition as the episodic retrieval task [Lepage et al., 2000] revealed that increased blood flow in six brain areas could be contributed to episodic retrieval mode, five of which were in the prefrontal cortex including Brodmann Areas (BA) 10, 45/47, and 8/9. While these prefrontal areas were found bilaterally (with the exception of BA 8/9, which was found only on the right), they were clearly lateralized to the right hemisphere. This suggested that the so-called hemispheric retrieval and encoding asymmetry (HERA) pattern of cerebral blood flow according to which episodic retrieval elicits higher right hemispheric blood flow than encoding [Tulving et al., 1994] could be mostly contributed to task-related retrieval processes [Lepage et al., 2000]. Other brain regions have been reported to be activated during episodic retrieval, among which the dorsolateral prefrontal cortex [Henson et al., 1999], the medial temporal lobes [Nyberg et al., 1996; Schacter et al., 1996; Lepage et al., 1998; Tulving et al., 1999], the medial parietal and posterior cingulate regions [Krause et al., 1999; Maguire et al., 1999; Shallice et al., 1994], and the parietal cortex [Nyberg et al., 2000] are the most frequent. Semantic retrieval has also been investigated using PET and fMRI [for a review, see Cabeza and Nyberg, 2000]. One group of studies has reported activation patterns resulting from subtractions of a semantic retrieval task and a control task. These more task-related measurements of semantic retrieval included semantic categorization (e.g., does an item denote something living or nonliving) and generation tasks (e.g., word stem completion tasks, verbal fluency tasks). A consistent finding during semantic retrieval has been increased blood flow in ventrolateral (BAs 45/47) [Kapoor et al., 1994; Demb et al., 1995], ventromedial (BA 11) [Jennings et al., 1997], and middorsal (BAs 9 and

46) [Kapur et al., 1994; Demb et al., 1995] areas of the left prefrontal cortex. PET studies that contrasted items from different semantic categories described higher blood flow for animals than for manmade tools in the temporal (BA 21) [Damasio et al., 1996] and medial occipital (BAs 18/19) [Perani et al., 1995; Martin et al., 1996] lobes and higher blood flow for manmade tools in the left prefrontal cortex and the left middle temporal gyrus [Martin et al., 1996]. These more item-related PET findings of category specific brain areas have been recently extended with fMRI [Ishai et al., 1999].

ERPs have been used extensively to investigate neural correlates of memory retrieval [Rugg, 1995]. If the data are acquired with direct-coupled (DC) techniques [Rockstroh et al., 1989], they can measure sustained neural activity lasting several seconds as well as transient neural activity in the millisecond time range. However, because DC recordings are technically difficult to perform, most ERP studies of memory retrieval have concentrated on measuring transient neural activity in the time range of several hundred ms. As with PET, ERPs elicited by repeated items have been compared to ERPs elicited by items presented for the first time [Rugg, 1995]. The difference, usually referred to as the ERP old/new effect, is typically a more positive ERP following the repeated words [Rugg, 1995]. It can be observed both when the retrieval task is implicit [Bentin and Moscovitch, 1990; Paller et al., 1995; Swick and Knight, 1997] and when the task is explicit [Rugg and Nagy, 1989; Rugg et al., 1995; Wilding and Rugg, 1996; Düzel et al., 1997]. The effect can begin as early as 200 ms [Besson and Kutas, 1993] and last as late as 1,900 ms [Düzel et al., 1997]. During this time, several separate ERP components can be distinguished on the basis of their scalp distribution. Recognition tasks that require a simple, two-choice old/new discrimination are mainly associated with two transient components of the ERP repetition effect, one in the time window of the so-called N400 wave (300–500 ms) and one in the time window of the late positive component (LPC) (500–800 ms) [Smith and Halgren, 1989]. They appear to be functionally dissociable in that the LPC effect is increased under conditions that are associated with a high probability of recollection, whereas the N400 effect is not [Paller et al., 1995; Van Petten and Senkfor, 1996; Rugg et al., 1998]. The N400 effect has therefore been associated with retrieval based on familiarity [Rugg et al., 1998; Curran, 1999] and knowing [Düzel et al., 1997] rather than recollection and remembering whereas the LPC effect has been correlated with successful recollection [Wilding and Rugg, 1996] and with remembering [Dü-

zel et al., 1997]. A third, long-lasting (400–1,900 ms) ERP difference between old and new words is elicited over right frontal scalp areas in explicit tasks that require retrieving episodic information beyond that necessary to perform recognition [Allan et al., 1998]. These tasks involve the retrieval of source information [Wilding and Rugg, 1996; Senkfor and Van Petten, 1998], associative recognition and recall [Donaldson and Rugg, 1999], and “remember” or “know” judgments on the recognized words [Düzel et al., 1997]. The timing of the right frontal ERP effect and the cognitive retrieval demands that increase it have led to the assumption that it is an index of postretrieval processes [Allan et al., 1998].

Here we employed a design that allowed us to register the electrophysiological signature of sustained as well as transient neural activity during memory retrieval. To obtain more precise anatomical information, we used a similar design to record hemodynamic measurements with PET in the same subjects. The paradigm involved four-item test lists lasting 10 sec that required either episodic (old or new) or semantic (living or nonliving) two-choice discriminations. ERPs were averaged over periods of 10 sec to monitor the sustained activities occurring during the different tasks and over periods of 2 sec to monitor the transient neural activity of retrieving items from episodic or semantic memory. Source analysis was applied to compare the locations of the ERP source dipoles to the locations of PET activation.

EXPERIMENTAL PROCEDURES

Participants

Eleven healthy native English speakers (6 female), mean age 25 years (range: 19–39), participated in the experiment after giving informed consent. All were right-handed and had no left-handed relatives in their immediate family. All had normal or corrected-to-normal vision. Seven of the subjects underwent the PET studies prior to the ERP recordings, and four underwent the ERP recordings first.

Stimuli

The stimuli were two sets of 480 nouns (one for PET and the other for ERPs), between 4 and 9 (average 5.7) letters in length, selected using the Oxford psycholinguistic database [Quinlan, 1992]. Half of the words represented living things (e.g., rabbit) and half non-living things (e.g., sword). The stimuli were divided into 12 sets of 40 items. From each set, a study list of

20 words (10 living and 10 nonliving) was selected. Ten different test lists comprising four stimuli were then constructed using four types of stimuli: the 10 studied living items, the 10 studied nonliving items, 10 new living items, 10 new nonliving items. Five of the test lists were used for episodic retrieval and the other five were used for semantic retrieval. Five more lists each containing four nonwords were used for a sensorimotor control task.

Experimental paradigm

Subjects were initially presented with a study list of 20 words. The words were presented in lowercase, in white, at the center of a black computer screen. They were 8 mm high and between 30 and 60 mm wide, and subjects were seated at a distance of 30 cm (vertical visual angle of 1.5 and average horizontal visual angle of 8.7 degrees). Each word was displayed for 1,700 ms and the stimulus onset asynchrony was 2,000 ms. During study the participants made a pleasant/unpleasant judgment about each word. These judgments were not recorded.

For the ERP studies, the test lists began 30 sec after the end of each of the 12 study lists. Each test list began with the task instructions, which were presented just above the center of the screen. These instructions preceded the first stimulus of the test list by 2 sec and remained until 2 sec after the last (fourth) stimulus. For episodic retrieval, subjects were instructed to decide whether the word was old (presented in the study list) or new (had not occurred before in the experiment). For semantic retrieval, subjects were instructed to decide whether the object represented by the word was living or nonliving. The four stimuli of each list appeared at a rate of one every 2 sec. They were displayed for 300 ms and replaced by a central fixation cross for 1,700 ms. Subjects responded to each stimulus by pressing one of two buttons with the index or middle finger of the right hand. Responses were accepted within 300 to 1,900 ms after the onset of the stimulus. Between each test list of four items, there was a period of 4,400 ms with only a central fixation cross on the screen until the next task instruction appeared. Participants were told that they could blink during this time. During the ERP recordings, the test lists were completely randomized as to the order of their appearance and the relative numbers of old/new and living/nonliving items within a list.

The paradigm for the PET studies of memory retrieval differed from that used for the ERPs. One study-test block was performed for each scan (eight in total). The number of study and test items in each

block was the same as in the ERP study. The study list was presented prior to each scan followed by the test lists 30 sec later. As for the ERPs, the subjects performed multiple retrieval tasks using the four-item lists, but the random ordering of the tasks and the items was adjusted during the time of the scan. The onset of the first four-item test list was approximately 10 sec after the injection of the radioactive tracer and 20 sec prior to the start of image acquisition, which lasted for 60 sec. From 10 sec prior until 5 sec after acquisition, task and item distribution in the test lists was controlled such that only one task (episodic or semantic retrieval) was performed and 85% of the stimuli were of one item type. In that time window, subjects were presented with a total of 20 test items: 17 test items (85%) of the same property together with three items (15%) from a condition in which items had the opposite value on the two manipulated dimensions. Thus, old/living test items were mixed new/nonliving items, old/nonliving with new/living, new/living with old/nonliving, and new/nonliving with old/living. Four scans were recorded for these four types of item types in which each four-item test list in the scanning window was coupled with an episodic retrieval task. Four other scans were conducted in which the same item-types were coupled with the semantic retrieval task. The test items and task instructions outside the scanning window constituted a random sequence of the 40 remaining words and letter strings and the two remaining tasks. The order of the first four scans was randomized across subjects, and for each subject, scans four through eight occurred in reverse order from the first four.

An additional sensorimotor control task was also included in both the ERP and PET recordings to provide a baseline measure against which activations equally elicited for the episodic and semantic retrieval task could be detected. In this task the subject pressed one of the two buttons randomly in response to unpronounceable letter strings. Unfortunately, the subjects found this task much more demanding than it was supposed to be, and some subjects expended much effort to ensure that their responses were truly random and properly timed. Because the behavioral, ERP, and PET results were very variable from subject to subject, we decided not to include this condition in our analyses.

Behavioral methods

The reaction times for correct responses and the accuracy of performance were assessed using repeated measures ANOVAs. For task-related effects, a two-

way ANOVA looked at the effects of task and the location of the stimulus in the test list. For item-related effects, the analysis considered old versus new responses in the episodic task and living versus nonliving responses in the semantic task.

PET methods

PET scans were obtained with a GEMS-Scanditronix PC2048-15B head scanner using a bolus injection of 35 Mci of $^{15}\text{O-H}_2\text{O}$. The PET data were analyzed with the Statistical Parametric Mapping technique (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Inc.). The analysis involved the following steps: the different images from each subject were realigned to the first image using a rigid body transformation. These realigned images from each subject were then transformed into a standard space [Talairach and Tournoux, 1988] by matching to a reference image that already conforms to the standard space. These images were then smoothed using an isotropic Gaussian kernel with full-width/half-maximum of 15 mm. The effects of the conditions (cognitive tasks) on the regional cerebral blood flow at each voxel were then estimated using a general linear model, wherein the changes in global counts are considered as a covariate [Friston et al., 1991, 1995]. The effects of each comparison are estimated using linear contrasts. These contrasts yield a *t*-statistic for a given comparison at each voxel, which is usually expressed as a standardized *Z* score. An activation was considered significant if its peak had a $Z > 3.1$ ($P < .001$, uncorrected), and its spatial extent (i.e., the number of voxels above the significance level) had a probability smaller of .05 (no correction necessary). The subtractions were performed in a reciprocal manner (i.e., old minus new and new minus old) in order to demonstrate the increased blood flow associated with either of the two conditions.

ERP methods

EEG signals were recorded with Neuroscan Synamp DC amplifiers from 35 scalp Ag/AgCl electrodes mounted in a cap (Electro-Cap International) and 11 additional electrodes located near the eyes and on the mastoids and neck. The interelectrode impedance was kept below 2 kOhm to prevent skin potential artifacts by using abrasion with a blunt needle for scalp sites and puncturing with a fine needle for facial sites [Picton and Hillyard, 1972]. Recordings were made with a low-pass filter of 35 Hz and a digitization rate of 200. All signals were referenced to Cz during acquisition

and transformed to an average reference for analysis. Trials containing large artifacts caused by blinks, excessive muscle activity, and blocking of the DC amplifiers were rejected from further analysis using a criterion of $\pm 600 \mu\text{V}$. ERPs were combined across the 12 study-test blocks. List ERPs were separately averaged for the episodic and semantic retrieval tasks, using only trials with at least three (of four) correct responses. The number of trials per subject contributing to the list ERP for each task varied between 40 and 60. The averaging sweep began 500 ms before the instructions and lasted 10,000 ms. Stimulus ERPs were separately averaged for the old and new words presented in the episodic and semantic retrieval task, using only correct trials. The averaging sweep began 200 ms before each stimulus and lasted 1,700 ms. The number of trials per subject contributing to the stimulus ERP for each item varied between 160 and 220. The averaged data were then converted to the data format of Brain Electric Source Analysis [Berg and Scherg, 1994]. Artifacts caused by eye movements and blinks were removed from the averaged ERP waveforms using ocular source components [Berg and Scherg, 1991; Lins et al., 1993] derived from data obtained in a separate recording of vertical and horizontal eye movements and blinks that preceded the experimental recording.

ERPs were analyzed by measuring peak and mean amplitudes and peak latencies. For list ERPs, mean amplitudes were measured in a time window from 4,000 to 9,500 ms. Peak amplitudes relative to the preceding and following negative peaks and latencies of the late positive component (LPC) were measured separately for the first, second, third, and fourth word in the lists, collapsing over item type. The results of this analysis are reported in Düzel et al. [1999]. For stimulus ERPs, mean amplitudes were measured in the N400 (300–500 ms), the LPC (500–700 ms), and late slow wave (LSW, 700–1500 ms) time windows. Peak amplitudes and latencies were measured for the P300, N400, LPC, and LSW in the stimulus ERPs. Topographic distributions of the voltage and the current source density (estimated from the second spatial derivative of the voltage distribution) were obtained using the Brain Electric Source Analysis software [Berg and Scherg, 1994].

ANOVAs for the effects of task and item on the stimulus and list ERPs were analyzed at the electrodes where the measurements were largest. For the stimulus ERPs, these were four anterior frontal electrodes (AF3/AF4, Fp1/Fp2) and four central (C3/4, FC1/2) and four parietal electrodes (P3/P4, PO3/PO4). For list ERPs, four dorsolateral frontal electrodes (F3/4,

FC5/6) were included instead of the central electrodes. Separate ANOVAs were conducted to analyze experimental effects and topographical distributions. For the experimental effects on stimulus ERPs, three-way ANOVAs with the factors task (episodic, semantic retrieval), item (old, new), and electrode were conducted separately for anterior, central, and posterior electrode groups, with each analysis considering four electrodes. For topographical analyses of stimulus ERPs, the measurements were normalized (over all electrodes) to remove confounding effects of the experimental manipulation [McCarthy and Woods, 1985] and four-way ANOVAs were conducted with the factors task (episodic, semantic retrieval), item (old, new), laterality (left, right), and location (anterior, posterior). For list ERPs, the same analyses were conducted except that there was no item factor and dorsolateral frontal electrodes were included. Statistical analyses of peak latencies were performed at the electrode Pz, with a two-way ANOVA with the factors task and item. All ANOVAs were carried out using the Greenhouse-Geisser correction for inhomogeneity of variance.

To make the statistics of the ERP data more comparable to that of the PET data (PET analysis applies a fixed effects statistical model to the data in which subject \times condition interactions are not employed in the error term, whereas the conventional ANOVA used for the ERP data treats the subjects as a random effect), and to take all electrodes into account, multiple *t* tests were computed for every electrode site and the resulting alpha values were Bonferroni corrected for multiple comparisons according to a procedure reported by Hopf and Mangun [2000]. Because close electrodes probably pick up correlated cortical activity, the underlying *true* degree of statistical independence among electrodes is estimated by considering the number of principal components, explaining 95% of the variance over all subjects and experimental conditions in the time window of interest. By applying this correction, alpha values were lowered from .05 to .012. To illustrate the statistical results significant *P* values resulting from the *t* test at each electrode were mapped using a nearest neighbor interpolation.

Source analysis of the ERPs

The source analysis for the ERPs was conducted in relation to the anatomical locations provided by the PET scans. The PET images showed differences in blood flow between conditions (episodic vs. semantic tasks, old vs. new items, and living vs. nonliving items). We therefore analyzed difference waveforms obtained by subtracting the list ERP recorded in the

semantic task from that recorded in the episodic task. This task difference waveform displayed long-lasting potentials. Item difference waveforms were obtained by subtracting the stimulus ERP for the new item from the stimulus ERP for the old item and by subtracting the stimulus ERP for the nonliving item from the stimulus ERP for the living item. These waveforms displayed transient waves lasting between 100 and 500 ms. Source analysis was performed using Brain Electric Source Analysis (BESA) [Scherg and Berg, 1994]. The difference waveforms were modeled using regional dipole sources [Berg and Scherg, 1996], the locations of which were fit to give a minimum residual variance between the modeled and the actual scalp waveforms. The orthogonal constraints of the components of this source were then removed and the orientations fitted to determine whether the three-dipole regional source could be replaced with fewer dipoles. We generally used two regional sources and adjusted the fitting criteria to minimize the total current in the generators (energy criterion, 20%) as well as the residual variance. Sources that localized to areas that were nearly symmetrical in location between the hemispheres were arbitrarily made symmetrical. If the dipole moments in the symmetrically located sources were asymmetrical, we evaluated the possibility of using only one of the sources to explain the scalp-recorded activity. Because the analysis was modeling difference waveforms, which do not have as good signal-to-noise characteristics as unmanipulated ERPs, and because the goal was to look for a small number of sources for relation to the foci of activity measured in PET, we derived solutions with only one or two sources rather than more complex solutions. BESA fits a sphere to the shape of the skull and uses a coordinate system based on the center of the sphere rather than on the anterior commissure as in Talairach and Tournoux [1988]. The BESA locations were therefore converted to approximately the same locations as the PET data by adding 19 mm to the *y* dimension (the approximate distance between the anterior commissure and the center of the sphere) [Towle et al., 1993]. We also performed the source analyses by “seeding” sources at the locations of the areas of activation shown on the PET scans [Heinze et al., 1994; Mackinnon et al., 1996]. The source waveforms were very similar to those obtained by fitting only on the basis of the electrical data, but these sources at these locations did not fit the data as well as those derived from the electrical analyses. To allow the electrical data to be as independent as possible of the blood flow data (and therefore to make any relationships more powerful), we elected to use

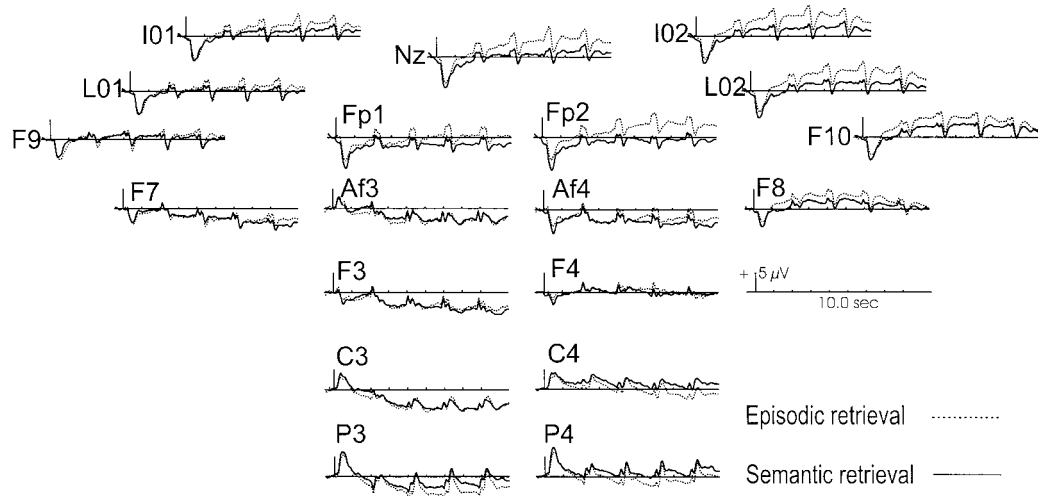


Figure 1.

Event-related potential waveforms elicited by lists presented during the episodic and semantic retrieval tasks. ERPs to episodic retrieval lists are presented with dotted lines and ERPs to semantic retrieval lists with solid lines. The displayed epoch of 10 sec encompasses the entire list, starting at 500 ms prior to onset of task instruction and ending 1,500 ms after the presentation of the

fourth (last) item. Electrode labels: odd numbers indicate left hemisphere electrodes. I01/2: vertical ocular; L01/2: horizontal ocular; Nz: nasion; F9/10: face; Fp1/2: frontopolar; F7/8: fronto-temporal; Af3/4: anterior frontal; F3/4: frontal; C3/4: central; P3/4: parietal.

the sources obtained solely on the basis of the electrical recordings.

RESULTS

ERP results

List ERPs

Figure 1 shows the list ERPs for the episodic and semantic retrieval tasks. The displayed epochs start 500 ms prior to and end 9.5 sec after the onset of the presentation of each task instruction. Transient ERPs elicited by each word are superimposed on slow DC shifts lasting through the test list. In both tasks there is a sustained negative DC shift during the list that is maximally recorded over the left frontocentral regions. Compared to semantic retrieval, episodic retrieval was associated with more positive DC shifts over right fronto-polar electrodes and more negative DC shifts bilaterally over parietal electrodes. This positivity started with the onset of the task cue, increased until the presentation of the second word in the test list, and stayed constant between the second and the fourth word. A significant main effect of task was found in the time window 4.0–9.5 sec for anterior electrodes ($F(1,10) = 5.2, P < .05$) and approached significance for posterior electrodes ($F(1,10) = 4.3, P = .06$).

Figure 2 shows the topography of the DC shifts in each of the experimental conditions and in the difference waveform. Statistical analysis of topography in the 4.0–9.5-sec time window showed a significant task X location interaction ($F(1,10) = 5.7, P < .05$) when location included anterior and posterior electrodes. When location included anterior and dorsolateral frontal electrodes, the same ANOVA showed a significant task X location ($F(1,10) = 4.9, P < .05$) and task X location X laterality interaction ($F(1,10) = 5.6, P < .05$) indicating that the DC-shifts were larger over the right anterior frontal regions during episodic retrieval.

Figure 1 also illustrates that the DC-shift difference between the episodic and semantic task extends to the eye (L01 and I02) and face (F10) electrodes. Because these electrodes cannot be used for creating maps, statistical t-test maps underestimate the extent of the DC-shift difference between the two tasks and were not considered.

Stimulus ERPs

Figure 3 shows stimulus ERPs elicited by all items in the two tasks. The displayed epochs start 200 ms prior to and end 1,500 ms after the onset of each word. In the ERP waveforms, five major components can be seen: P100, N200, P280, N400, LPC, and a late slow wave (LSW). Of these, the P280, N400, LPC, and LSW were significantly affected by experimental manipulations. The topography of the difference waveforms

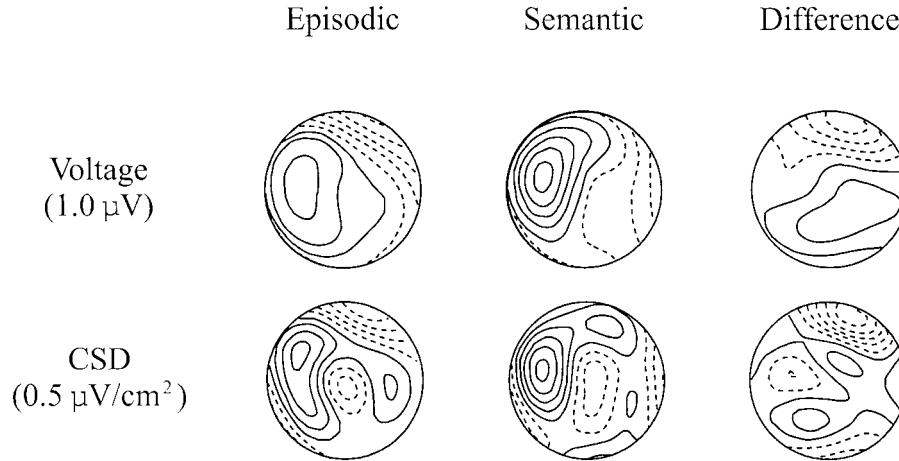


Figure 2.

Scalp distributions of the slow potential shifts during the different retrieval tasks. This figure shows the spline-interpolated scalp distributions of the voltage and current source density (CSD) measured between 4,000 and 9,500 ms after the cue instructions for the task. The continuous lines represent contours at negative voltages and the dashed lines represent contours at positive voltages. The scalp is viewed from above with the nose at the top of

the figure. The outer edge of the circle shows the scalp down to 20 degrees below the “equator” of the idealized sphere, i.e. down to about the level of the mastoids. The unsubtracted measurements show a clear left frontocentral negativity in both the episodic and the semantic task. The episodic task shows an additional right frontal positivity. This shows up more clearly when the difference waveforms are mapped (right column).

that results from the subtraction of ERPs elicited by old minus ERPs is illustrated in Figure 5.

The peak latencies (Table I) of the N400 and the LPC were significantly later for new items in both tasks

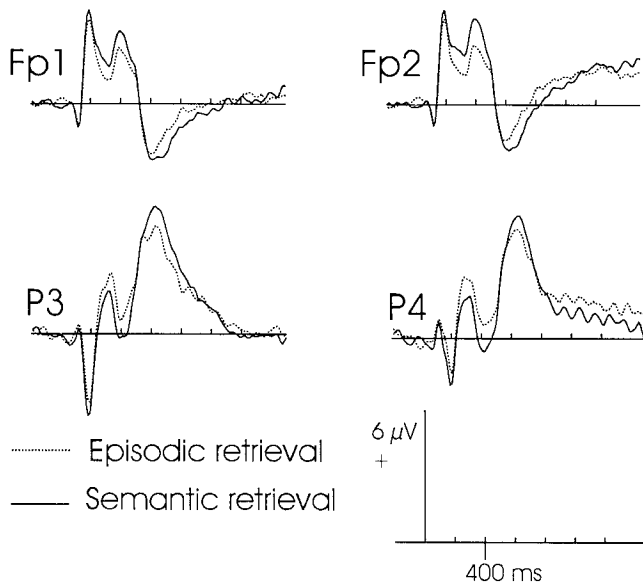


Figure 3.

Event-related potentials elicited by all items presented during episodic (dotted lines) and semantic (solid lines) retrieval. The displayed epoch starts 200 ms before and lasts until 1,500 ms after the onset of the stimulus.

($F(1,10) = 5.5, P < .05$ and $F(1,10) = 11.8, P < .01$, respectively), but the latencies showed no task effects or task by item interactions.

The amplitude in the 300–500 ms time window at posterior electrodes was significantly more positive (with a phase reversal at frontopolar electrodes) during the episodic than the semantic task ($F(1,10) = 8.5, P < .05$) irrespective of item type (Fig. 3). Topographic analysis indicated that this effect was larger over the right hemisphere ($F(1,10) = 6.2, P < .05$). Significant old/new item effects were observed for the N400 and the LPC, but a significant interaction between task and item was apparent for the LPC only (Fig. 4). The N400 was more positive for old than for new items in both tasks ($F(1,10) = 7.95, P < .05$ in the semantic task; $F(1,10) = 4.9, P < .05$ in the episodic task). The LPC was larger for the old items than for the new items, and this effect was much more prominent during the episodic task ($F(1,10) = 5.2, P < .05$) and at posterior electrodes, where the wave was maximally recorded ($F(1,10) = 17.7, P < .01$). Topographic analysis indicated that this wave was larger over the left hemisphere at posterior electrodes ($F(1,10) = 6.7, P < .05$).

Statistical t-test maps (Fig. 6) illustrate the distribution of the old/new item effect in the N400 and the LPC time windows in the episodic and semantic task. It can be seen that the N400 old/new difference in shifted more anteriorly in the semantic task. The LPC

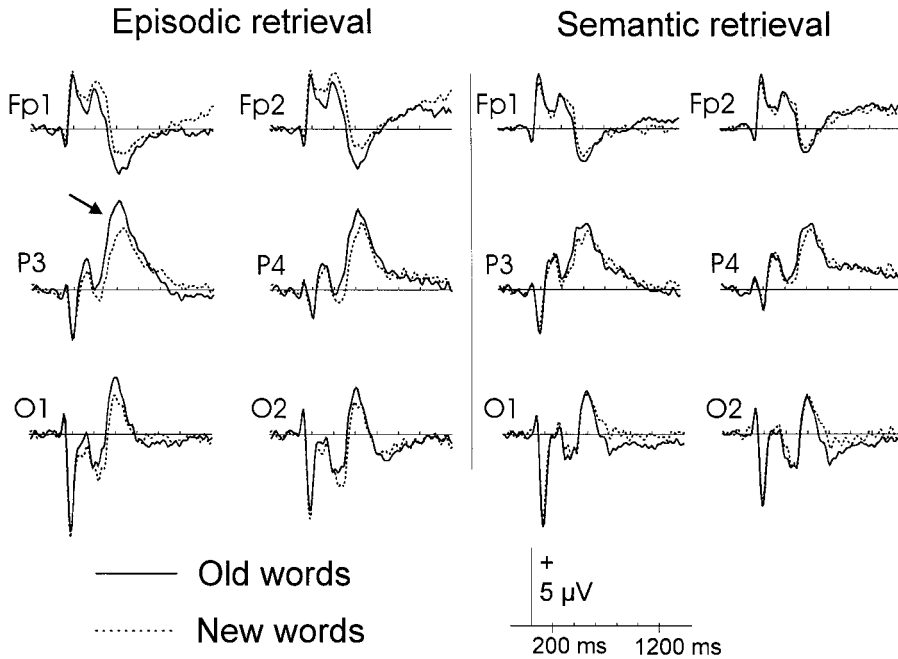


Figure 4. Event-related potentials elicited by old (solid lines) and new (dashed lines) items during episodic (left side) and semantic (right side) retrieval. The displayed epoch starts 200 ms before and lasts until 1,500 ms after the onset of the stimulus.

old/new difference is found only in the episodic task and shows a left parietal distribution.

Figure 7 shows the ERPs to words denoting living and nonliving things. Significant living/nonliving item differences were found in the N400 time range ($F(1,10) = 6.13, P < .05$) and in a sustained late time window (700–1,500 ms) ($F(1,10) = 5.48, P < .05$). These differences were elicited only in the semantic but not the episodic retrieval task (task by item inter-

action: N400 time range: $F(1,10) = 8.2, P < .05$; late time window: $F(1,10) = 7.35, P < .05$).

Statistical t-test maps (Fig. 6) illustrate the distribution of the living/nonliving item difference in the very late time window (700–1,500 ms) in the semantic retrieval task (no differences were found in the episodic retrieval task). It can be seen that the two-item categories elicited different ERPs at fronto-central and occipital-posterior scalp sites.

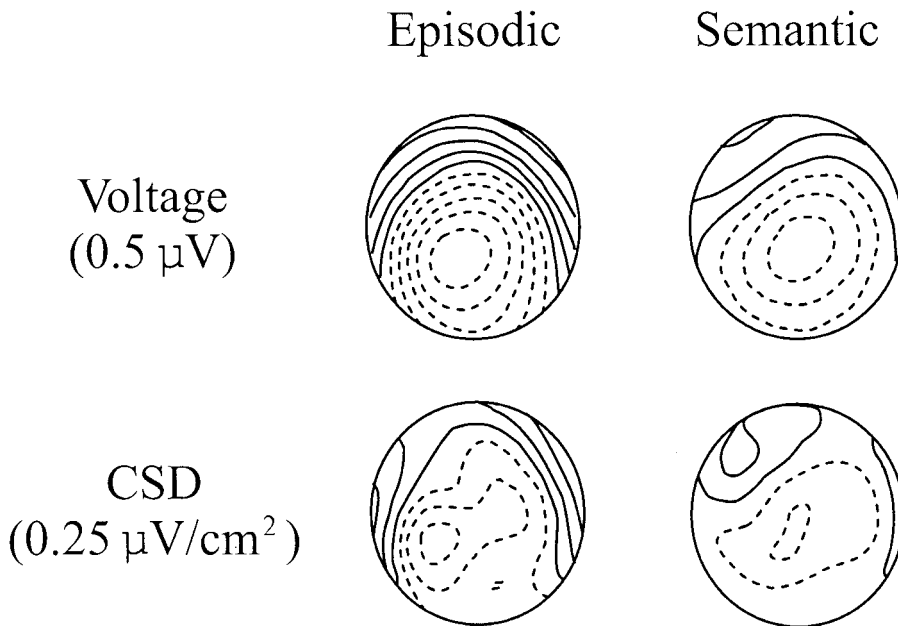


Figure 5. Scalp distribution of the late positive component (LPC). These scalp distributions are plotted in the same way as described for Figure 2. Measurements for the LPC were taken at latencies 540 ms and 515 ms in the episodic and semantic tasks.

TABLE I. Latencies of ERP peaks in stimulus ERPs*

Task	Peak	Old	New
Episodic retrieval	P280	277 (50)	285 (32)
	N400	379 (36)	400 (27)
	LPC	613 (62)	664 (38)
Semantic retrieval	P280	299 (44)	287 (33)
	N400	397 (41)	405 (39)
	LPC	608 (74)	677 (94)

* Mean latencies (in ms) relative to stimulus onset. Standard deviations in brackets.

PET activations and their relation to ERP source analysis

Regions showing significant task-related and item-related PET activations are shown in Figure 8. Table II summarizes the corresponding coordinates together with the results from the ERP source analysis of the related ERP difference waveforms.

Episodic retrieval was associated with higher blood flow in right posterior cingulate (a) and right frontopolar (b) regions, whereas semantic retrieval was related to blood flow increases in left frontal (c) and left temporal (d) areas (Fig. 8). Figure 9 shows the related results of the source analysis of the difference waveform obtained by subtracting the semantic list ERP from the episodic list ERP. A source in the right frontal lobe accurately modeled the right frontal positive shift. This source could be obtained by fitting a single regional source to the difference waveform (either directly or after low-pass filtering at 1 Hz) and then rotating one component of this source to fit the recorded data by simply fitting one dipole, or by fitting symmetrical dipoles (the left frontal dipole showing little activity). The location of the left frontal source was deeper than the location of the right frontal activation (b) in the PET analysis. The small deflections on the DC shifts (caused by differences in the LPC between the two tasks) could be modeled by symmetrical dipoles in the medial temporal regions. These sources were fit over the 500–700 ms latency period following each of the last three items.

Item-related PET activations (Fig. 8, Table II) differed depending on the task during which they occurred and the type of item. During the episodic retrieval task, old items were associated with increased neural activity in the left medial temporal lobe (e, f), while new items were not associated with significant blood flow increases. The ERP difference waveforms (old minus new) in the episodic task were reasonably well explained on the basis of a source in the left

medial temporal regions (Fig. 10), with a location (Table II) similar to the PET activation in the medial temporal region (e). Bilateral symmetrical sources explained the data better (decreasing the residual variance by approximately 1%), but for the sake of simplicity, the figure shows the results of fitting with one source. The waveforms for the bilateral sources were very similar with the amplitude of the left-sided source waveform being about half as large as that on the right.

During the semantic retrieval task (Fig. 8), old items were related to increased neural activity in the right prefrontal cortex (g, h), and new items were associated with activations in bilateral ventromedial temporal regions (i, j), left temporal (k), and right anterior cin-

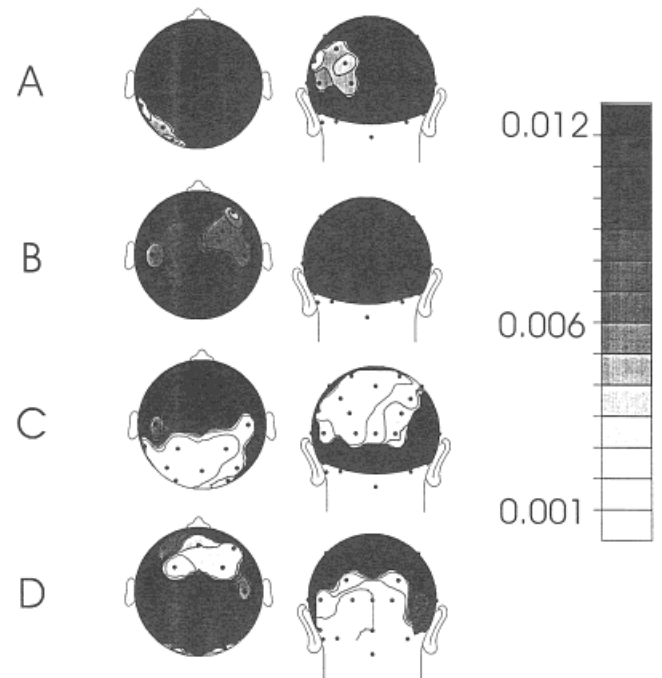


Figure 6.

Statistical maps of t tests for ERP mean amplitudes. (A): Maps of t tests between ERPs to old and new words elicited between 300–500 ms in the episodic task. (B): The same comparison for the semantic task. (C): Maps of t tests between ERPs to old and new words elicited between 500–800 ms in the episodic task (the corresponding comparison for the semantic task did not yield any significant effects). (D): Maps of t tests between the ERPs to living and nonliving words presented in the semantic retrieval task (the corresponding comparison for the episodic task did not yield any significant effects). The maps are derived from the alpha-values obtained from t tests at each of the 46 electrodes using a nearest neighbor interpolation of four neighboring electrodes. Left-sided maps provide a view from above, right-sided maps a view from the back. ERP differences are significant at an alpha value of 0,012 (see Methods for the Bonferroni correction procedure).

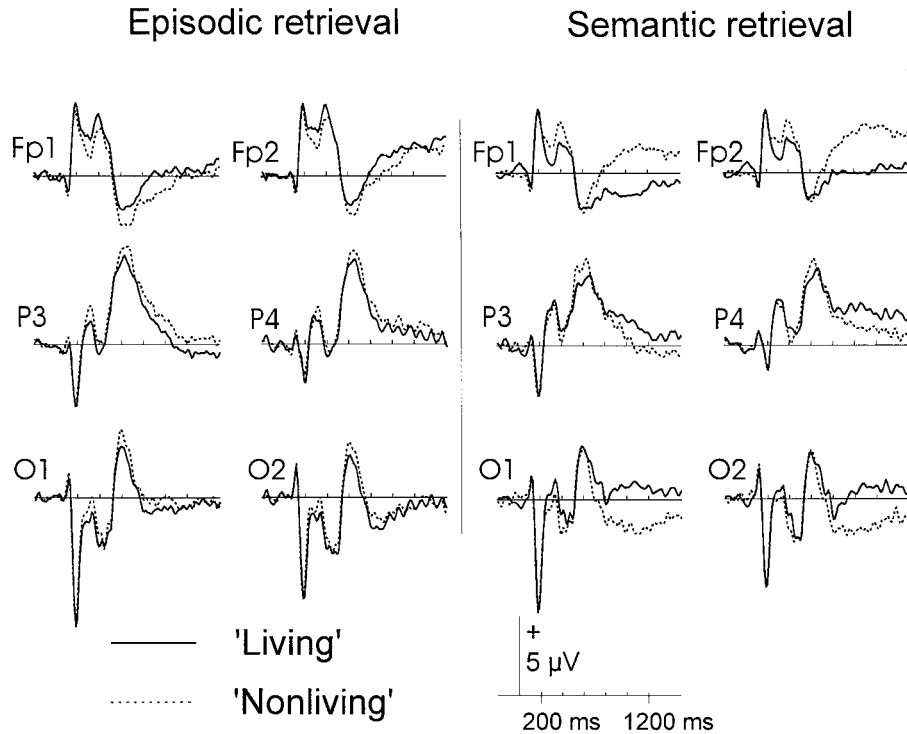


Figure 7.

Event-related potentials elicited by living (solid lines) and nonliving (dashed lines) items elicited during episodic (left side) and semantic (right side) retrieval. The displayed epoch starts 200 ms prior and lasts until after 1,500 ms after the onset of presentation.

gulate (l) regions. Source analysis of the ERP difference waveforms for old and new items in the semantic task was quite difficult as the waveforms were of low amplitude (Fig. 11). The early part of the difference waveform could be explained by the same medial temporal source as in the analysis of the episodic task difference waveforms (e). However, the later parts of the waveform derived from different generators: the analysis settled on bilateral sources in the temporo-occipital regions with a single right-sided source explaining the data reasonably well. The location of this source (Table II) was similar to that of the right medial temporal activation on the PET scans (i).

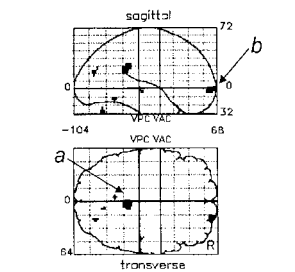
The item-related effects on the living/nonliving dimension during the semantic task (Fig. 8) indicated PET activations in the left anterior cingulate (m) and left frontal (n) regions for the words denoting living things compared to those denoting nonliving things. The source analysis of the living/nonliving difference waveform suggested a deep-seated source in the frontal midline (Fig. 12). This source may have represented the combined activity of multiple areas in the frontal regions, but it was impossible to distinguish these since the electrical activity did not vary its topography

over time. The source location (Table II) was closest to that of the anterior cingulate activation on the PET scans (m).

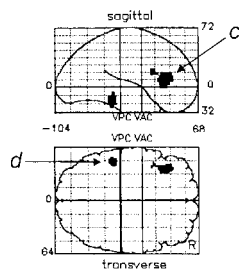
DISCUSSION

This experiment used two different techniques to measure neural activity during memory retrieval. In some instances, the two techniques provide complementary information. In other instances there are discrepancies: areas of activation on the PET scan do not appear to have concomitant ERP activities and vice versa. These discrepancies may arise from the different physiological bases of the two measurements, from the algorithms used in the measurements, and from the fact that the recordings were made at two different times and used slightly different stimulus paradigms. Despite the difficulties in relating findings between the techniques, our results show some clear homologies between PET and ERP and allow us to outline some new ideas about the spatial and temporal organization of neural activity associated with memory retrieval.

Task comparisons



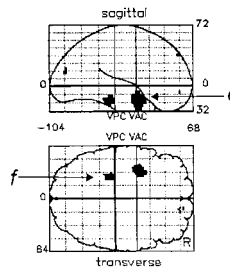
Episodic minus Semantic



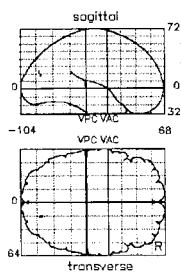
Semantic minus Episodic

Item comparisons

Episodic retrieval

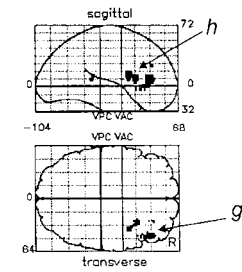


Old minus New

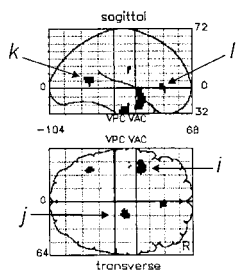


New minus Old

Semantic retrieval

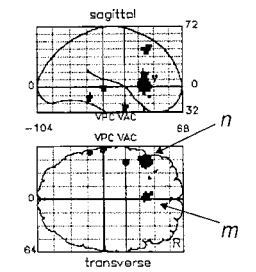


Old minus New

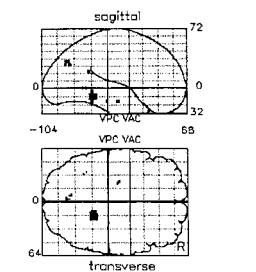


New minus Old

Semantic retrieval



Living minus Nonliving



Nonliving minus Living

Figure 8.

PET blood flow differences obtained from the task-related and item-related comparisons are displayed in the form of SPM contrasts. The letters mark activations in reference to Table II.

Task-related neural activity

We found sustained shifts in the DC potential associated with the episodic retrieval task (Fig. 1). Figure 1 displays the extent of the shift over a larger set of electrodes than shown in a previous report [Düzel et al., 1999]. Transient neural activities, apparent in the ERPs elicited by single items, are superimposed on these sustained shifts. Sustained DC shifts lasting throughout the task have not been previously reported in association with episodic retrieval. We believe that we were able to detect them because we used DC recordings and because our ERP paradigm allowed the subject to set up specifically for episodic retrieval during the 10-sec period of the task.

To achieve convergence between the PET and ERP data, differences between the DC shifts elicited during episodic and semantic retrieval tasks were of particular interest. The most prominent difference was found over the right frontopolar scalp. Episodic retrieval was associated with a sustained positive shift over right frontopolar electrodes, but semantic retrieval was not. The right frontopolar scalp-topography (Fig. 2) of this shift was compatible with a neural generator in the

right frontal Area 10 as depicted by the PET subtraction of episodic minus semantic retrieval (Fig. 8). Our source analysis indicated a dipole source that was located deeply in the right frontopolar region (Fig. 9). This probably represents the equivalent dipole for the curved and more superficially located cortex [Picton et al., 1995]. Based on this convergence between PET and DC measures, we can consider the activity of the Area 10 to begin at the onset of the episodic retrieval task and to last through the duration of the task.

Two other possibilities might be considered. The cerebral blood flow is related to the accumulation of potassium ions and/or other molecules in the extracellular spaces and in the glia when neurons are active [Roland, 1993]. Because the accumulation of potassium ions in glia can cause slow electric fields [Somjen, 1973], it is possible that the slowly developing DC shift during the task represents in part the same process (and time course) as the increased cerebral blood flow. It might then follow after and/or integrate intermittent bursts of neural activity rather than portray a sustained activity. We think that this possibility is unlikely because of the improvement in episodic recall as the DC shift develops [Düzel et al., 1999]. It prob-

ably takes several seconds for the subject to adjust to the necessary mind-set for episodic retrieval and this fits well with the time course of the developing DC shift. Furthermore, other regions of the brain where there is repeated activity during this paradigm, such as the visual cortices, do not show such a sustained DC shift.

Another possibility is that the overall DC shift during episodic retrieval is caused by the superposition of prolonged slow waves evoked transiently by each item in the test list. Such slow waves might be associated with neural activity underlying the conscious evaluation of each item [Mangels et al., 1996]. This type of slow wave is seen in the frontal regions in association with processing the living items in the semantic task (Fig. 7). However, the stimulus ERPs (recorded over a 2-sec period), when collapsed over all

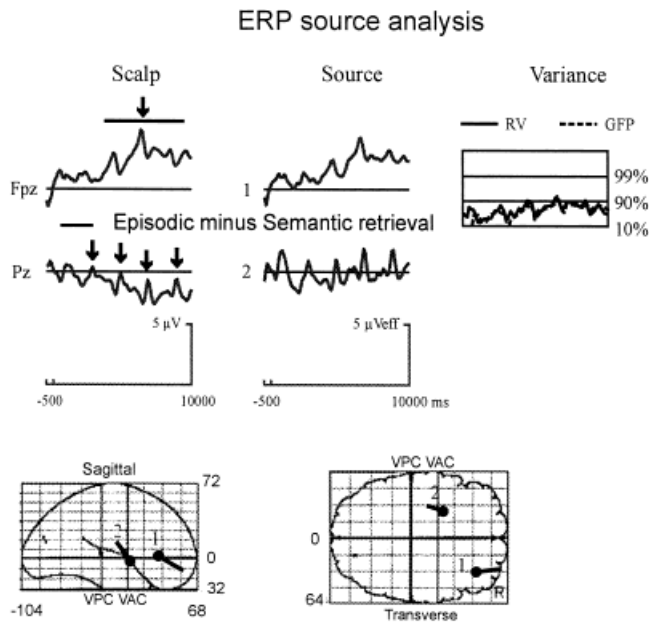


Figure 9.

The results of source analysis of the task-related ERP effects. Sample waveforms recorded from the scalp are shown in the left column. The arrows point to the sustained positive shift over the right frontal region and the late positive waves recorded at the parietal electrode with each stimulus. The time courses of activity in the two derived sources are shown in the middle column. The first source increases its activity over the recording whereas the second source is active intermittently following the instruction cue and each of the words in the test list. The residual variance (RV) between the modeled activity and the recorded activity is shown in the right column together with the global field power (GFP) of the recorded activity. To allow comparability to Figure 8, the locations (Talairach coordinates are listed in Table II) and orientations of the derived sources are shown in an anatomical reference frame adopted from SPM.

ERP source analysis

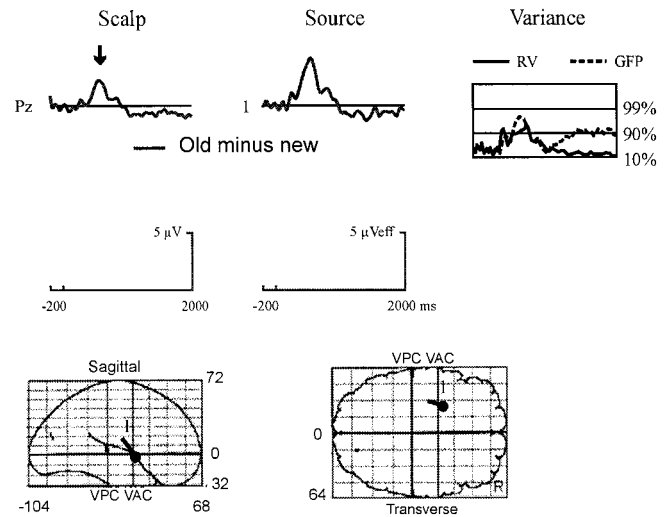


Figure 10.

Source analysis of the item-related difference waveforms of ERPs elicited by old minus new words in the episodic retrieval task. The figure is set up in the same way as in Figure 9. The arrow in the left column indicates the difference in the late positive wave recorded maximally at the midparietal electrode.

item types, did not reveal task-related ERP effects of this type in the frontal regions. Figure 3 illustrates that transient differences between the episodic and the semantic retrieval task in the stimulus ERPs were limited to the N400 time window. Topographically, this transient task-related ERP effect was larger over the right hemisphere but did not show the frontopolar maximum of the sustained task-related DC shift.

The close relationships of the right frontopolar DC shift to the onset and duration of the task and to the efficacy of performance [Düzel et al., 1999] indicate that the right prefrontal region mediates a neurocognitive set for the task of episodic retrieval. The activity of the associated PET activation in Area 10 can thus be related to episodic retrieval mode as a task-related process.

In a recent meta-analysis, Lepage and colleagues [2000] reported six brain regions whose activation pattern fulfilled their definition of episodic retrieval mode: “i) becomes differentially activated during attempted retrieval of past events and ii) does so independently of the level of ephory.” In the present study we have extended this definition by including time course as an additional dimension. We proposed that a sustained time course is a requirement for task-related processes such a retrieval mode. However, the transient task-related effects on stimulus ERPs (Fig. 3) illustrates that task-related brain activity patterns can

TABLE II. Relation of PET activations and ERP source analysis

PET activations								ERP source analysis			
		BA	X	Y	Z	Z score	Figure	X	Y	Z	Distance
Task-related activations											
Episodic/semantic	R post cingulate	23	4	-40	24	3.7	a				
	R prefrontal	10	22	56	-4	3.6	b	32	25	5	34
Semantic/episodic	L prefrontal	45	-38	30	8	4.0	c				
	L temporal	21	-46	-38	-12	3.8	d				
Item-related activations											
Episodic retrieval											
Old/new	L med temporal	28	-36	0	-20	3.9	e	-21	5	-3	23
	L med temporal	36	-26	-32	-16	3.8	f				
Living/nonliving	R putamen		26	16	-4	3.4					
	R temporal	22	54	6	0	3.3					
Semantic retrieval											
Old/new	R prefrontal	45	46	32	8	3.6	g				
	R prefrontal	44	38	6	16	3.4	h				
New/old	R med temporal	28	16	-14	-28	3.9	i	35	-15	-13	24
	L ant temporal	38	-38	4	-16	3.9	j				
	L temporal	37	-36	-54	8	3.6	k				
	R ant cingulate	24	4	32	0	3.6	l				
Living/nonliving	L ant cingulate	32	-4	24	44	3.7	m	5	3	8	24
	L frontal	47	-48	24	0	4.0	n				
Nonliving/living	R cerebellar		16	-44	-8	3.8					

Only subtractions that yielded significant PET activations are listed. BA = Brodmann area. The coordinates are from the atlas of Talairach and Tournoux (1988), where x, y, and z correspond to the right-left, anterior-posterior, and superior-inferior dimensions, respectively. The letters in the figure columns refer to the location of the PET activations depicted in Figure 8. The coordinates for the ERP sources are displayed in the same row as the closest PET activations. Distances of the ERP sources from the PET activations are calculated as the square root of the sum of the squares of the distances in each of the three dimensions.

also be measured on a short time scale in early stages of stimulus processing. We therefore propose that task-related processes can be dissociated into sustained, so called state-related [Lepage et al., 2000] as well as transient patterns of brain activity, which still need to be determined and characterized. The possibility should therefore be considered that some of the regions reported by Lepage and colleagues [2000] as retrieval mode regions have a transient time course of activity. One possible functional interpretation of the transient task-related ERP effects could be that they reflect early gating of item processing into the episodic and semantic memory systems.

The lack of a left hemispheric difference in the DC shifts for the semantic and episodic retrieval task stands in contrast to the left frontal and temporal blood flow differences between semantic and episodic retrieval on the PET data (Fig. 8). The location of the PET blood flow increase involved the part of Area 45 that is folded inwardly, involving two opposing cortical layers. Electrical fields generated in opposing layers of Area 45 would tend to cancel each other

because of the opposing polarities generated by each side of the sulcus. This might explain why DC shifts did not differ for episodic and semantic retrieval. However, both tasks were associated with a prominent negative DC shift over the left frontal scalp electrodes (Fig. 1, electrode F3), which might represent some general supervisory or linguistic process common to the two retrieval tasks [Rösler et al., 1995] and/or the motor activity involved in pressing the button with the right hand and maintaining the hand in readiness to respond.

Item-related neural activity

Transient neural activity was measured in relation to the presentation of single items. While the best convergence between ERP and PET findings was obtained for item comparisons that were separately performed for episodic and semantic retrieval, it was better for old and new items presented during episodic retrieval and living and nonliving items presented for semantic retrieval, but not vice versa. The

information of being old or new is relevant during episodic but not semantic retrieval, and the information of being living or nonliving is relevant during semantic but not episodic retrieval. Therefore, the convergence between transient ERP responses and PET data is best if the comparisons are related to the type of information that is relevant within a given task. To account for this finding, we will discuss the convergence of ERP and PET separately for task relevant and irrelevant item-information.

Episodic retrieval and relevant item-information (old/new)

As in previous studies, old words elicited transiently more positive ERP from 300 to 700 ms during episodic retrieval (Fig. 4) [Rugg et al., 1998], and they also induced increased blood flow in the Areas 28 and 36 of the left medial temporal lobe (Fig. 8). The old/new effect on the LPC and the blood flow difference in the left medial temporal lobe, showed a task X item interaction, indicating that they were significantly less prominent during semantic retrieval. The source analysis (Fig. 10) of the LPC portion of the old/new difference waveform suggested a neural generator in the left medial temporal lobe or generators in both medial

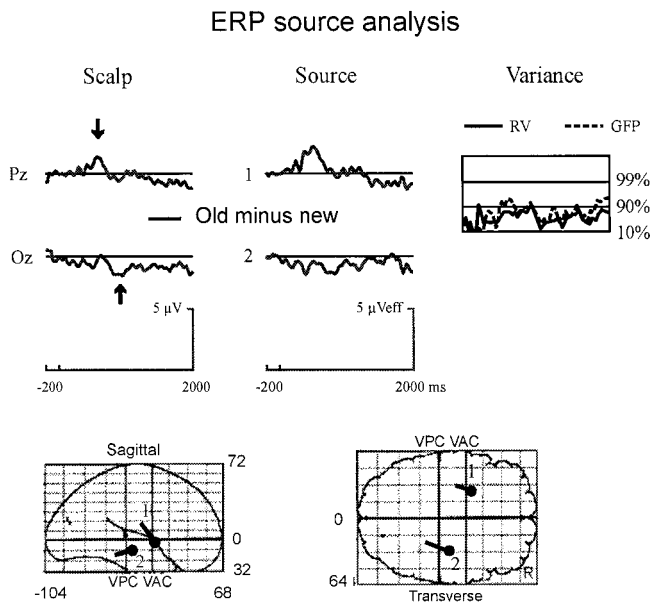


Figure 11.

Source analysis of the item-related difference waveforms of ERPs elicited by old minus new words in the semantic retrieval task. The figure is set up in the same way as in Figure 9. The arrows in the left column indicate the difference in the late positive wave recorded maximally at the midparietal electrode and the late slow wave recorded as a negative deflection at the occipital electrode.

ERP source analysis

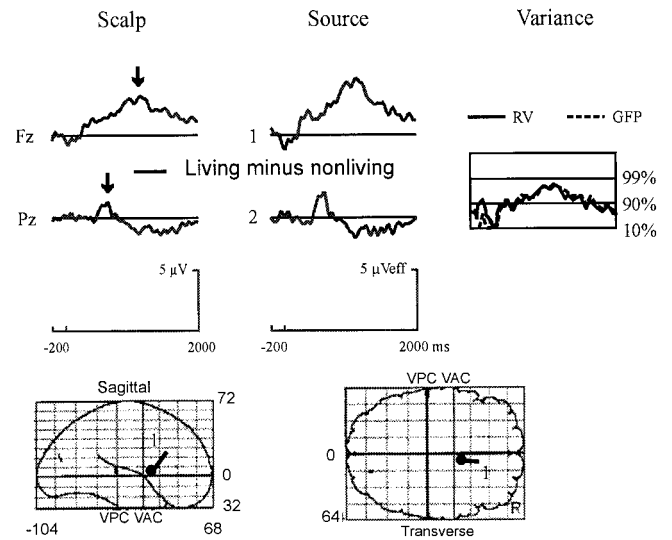


Figure 12.

Source analysis of the item-related difference waveforms of ERPs elicited by living minus nonliving words in the semantic retrieval task. The figure is set up in the same way as in Figure 9. The arrows in the left column indicate the late positive slow wave recorded maximally in the frontal regions when the word represented a living thing and the difference in the late positive wave recorded maximally at the midparietal electrode.

temporal lobes, with greater activity on the left. Our comparative hemodynamic and electrophysiological data provide support for previous assumptions that the left medial temporal lobe contributes to the generation of the LPC effect of recognition [Smith and Halgren, 1989].

In a series of recent studies, late (1,400–1,900 ms) right frontal ERP differences between old and new words have been reported [Allan et al., 1998]. These studies had in common that in addition to recognition they required the retrieval of more specific episodic information. Typically, recognition was followed by a second decision such as a remember/know judgment [Düzel et al., 1997], a judgment on the specific episodic context in which a word was presented [Wilding and Rugg 1996, 1997; Allan et al., 1998; Senkfor and Van Petten, 1998] and/or associative cued recall [Donaldson and Rugg, 1999]. Given the cognitive demands of these paradigms it has been proposed that one aspect of such right frontal activity may be related to postretrieval processes that follow recognition and act on the products of initial retrieval [Allan et al., 1998]. The relative rapidity and simplicity of our recognition task may not have entailed significant postretrieval processing of the recognized words. It is therefore not

surprising that a late right frontal ERP difference between old and new words in the episodic task did not occur in the present investigation.

Episodic retrieval and task-irrelevant item information (living/nonliving)

The distinction of living and nonliving item is not relevant for episodic retrieval. PET showed significant activations, which distinguishes this type of item information (Table II) even if the subject performed an episodic retrieval (old/new discrimination). Concurrent ERP effects were subtle and confined to the N400 time window only (Fig. 6).

Semantic retrieval and task-relevant item-information (living/nonliving)

The task-relevant item-related information retrieved in the semantic retrieval task concerned the differences between words denoting living and nonliving things. This type of information is essentially different from that retrieved in the episodic task in that equivalent information (the living or nonliving attribute of the thing) was retrieved from memory for both types of items. In the episodic task, pertinent item-related information (about recent prior experience) was only retrieved for old items. Prominent ERP effects distinguished the living and nonliving words during semantic retrieval in N400 as well as in a late (700–1,500 ms) time window (late slow wave, LSW) (Fig. 7). Both ERP effects showed an interaction with task type. In PET (Fig. 8), prominent anterior cingulate and left frontal activity differences were found between living and nonliving items presented for semantic retrieval. The two data sets partially converged in the source analysis (Fig. 12): the LSW could be modeled by a generator in the vicinity of the anterior cingulate gyrus.

Recent imaging studies have reported category-specific brain regions for animate and inanimate stimuli [Damasio et al., 1996; Perani et al., 1995; Martin et al., 1996; Caramazza and Selton, 1998]. Insofar, the ERP differences between living and nonliving things found here suggest that it might be possible to detect these differences in category representation also with ERPs. But it is unclear why in our experiment a prominent interaction between the living/nonliving discrimination and task emerged, both in the N400 and in the LSW time window. If either of the ERP differences is an index of category-specific representation it should be similar across tasks. One reason for the interaction could be that the two categories were not easy to

distinguish in our experiment because they were not “pure” in entailing unambiguously to categorize living (for instance animals) and nonliving (for instance tools) things. Creating such pure categories was not possible because of the large number items that had to be selected for the ERP and the PET study. A possible explanation of the differences between living and nonliving items both with PET and ERPs could therefore be uncertainty about the decision when the word denotes something living.

Semantic retrieval and task-irrelevant item information (old/new)

Although the old/new distinction was not relevant to the semantic retrieval task, there were prominent hemodynamic differences between old and new items. New items elicited increased blood flow in the right medial temporal lobe (Area 28), the left temporal lobe (Areas 38/37), and right anterior cingulate (Area 24) (Fig. 8). Old items elicited higher blood flow in the Areas 45/46 of the right dorsolateral frontal lobe (Fig. 8). In contrast to the prominent PET effects, ERP indices of item-related old/new differences were subtle. Old items elicited more positive ERPs in the N400 time window (300–500 ms) and more negative ERPs later on (700–900 ms) (Fig. 4). The prominent modulation of the LPC by old words that was found in the episodic retrieval task was absent in the semantic task. The sources obtained for the old/new difference in the semantic task should be interpreted with caution as the amplitudes are very small (Fig. 11). The finding that item type (old vs. new) interacted with task instructions (episodic vs. semantic) in the case of the LPC (but not the N400) effect is consistent with the view that the former reflects recollection whereas the latter reflects familiarity [Rugg et al., 1998; see also Donaldson and Rugg, 1999]. This view is supported by evidence that the N400 effect partly reflects implicit memory whereas the LPC effect reflects explicit memory [Van Petten and Senkfor, 1996; Rugg et al., 1998]. The statistical t-test maps (Fig. 6) of the N400 old/new difference show that the difference shifts anteriorly in the semantic when compared to the episodic retrieval task. This indicates that the topography of the N400 old/new effect differs under explicit (episodic retrieval) and implicit (semantic retrieval) conditions.

Caveats and new directions for convergence

Transient ERP effects were most prominent for those types of items that were relevant for the particular task, e.g., old and new items presented for epi-

sodic retrieval and living and nonliving items presented for semantic retrieval. In contrast, PET measurements depicted prominent blood flow differences between types of items even if they are not relevant to the task. Why are changes in neural activity induced by irrelevant item types visible in one but not the other technique? We propose two accounts. First, in the PET measures, irrelevant and relevant types of items had to be transiently separated (blocked for the duration of the scan), while they were randomly intermixed in the ERPs. This might have led to changes in the experimental context, leading to discrepancies between the PET and ERP measures [Schacter et al., 1997]. A second explanation is that when subjects perform the episodic and semantic retrieval tasks, neural activity associated with the task-relevant information may be temporally more time-locked, less “jittered” with respect to the onset of the item, than it is if information is not relevant to the task. Measuring such jittered neural activity electrically would diminish the ERP amplitude associated with old and new words during semantic retrieval and living and nonliving words during episodic retrieval. Because time locking has little effect on the hemodynamic measurements, PET may show similar activations when the items are task relevant or not.

Our results suggest that memory retrieval is associated with a task-related sustained activation of the right frontal cortex and an intermittent activation of the medial temporal regions, particularly on the left, as item-related information is retrieved. But, they also suggest that task-related processes can operate transiently at early stages of stimulus processing. Conversely, there is now evidence that item-related patterns of brain activity can be associated with sustained changes caused by the particular sequence in which items are presented [E. Düzel and H.J. Heinze, unpublished research].

The convergence of the electrical and the hemodynamic measurements reported here was not perfect enough to resolve these issues entirely by delineating for different brain regions their precise time course. New developments in electrical source analysis [Dale and Sereno, 1993; Picton et al., 1999] should allow both sets of data to be recorded and analyzed in single subjects using the same MRI-based model of the head. New developments in the measurement of cerebral blood flow with fMRI will allow paradigms more akin to those used in ERP studies [Buckner et al., 1996; Zarahn et al., 1997; Josephs et al., 1997]. The spatial resolution of ERP studies is becoming more precise [Picton et al., 1999] and the temporal resolution of fMRI is becoming more exact [Menon et al., 1998]. It is

doubtful that either will attain the characteristics of the other, but the convergence will become easier. In the future, we should be able to make blood flow and electrical recordings simultaneously and analyze both in the same image space.

CONCLUSION

Taking into account the existence of spatially distinct sustained and transient processes in memory retrieval allowed us to compare spatial information from PET with temporal information from ERPs. The convergence between the two techniques was better when the retrieved information was relevant to the current task set. The convergence indicates that brain regions can be active in either a sustained or a transient way during memory retrieval. Here we linked sustained activity in the right BA 10 to episodic retrieval mode. It remains to be determined in future studies to what extent sustained and transient activity patterns map onto components parts of task- and item-related processes.

ACKNOWLEDGMENTS

We thank Drs. Shitij Kapur, Sylvain Houle, and Randy McIntosh, and two anonymous reviewers, for helpful comments. Parts of the results presented here were published in Düzel et al. [1999].

REFERENCES

- Achim A (1995): Cerebral source localization paradigms: spatiotemporal source modeling. *Brain Cogn* 27:256–287.
- Allan K, Wilding EL, Rugg MD (1998): Electrophysiological evidence for dissociable processes contributing to recollection. *Acta Psychol (Amst)* 98:231–252.
- Bentin S, Moscovitch M (1990): Psychophysiological indices of implicit memory performance. *Bull Psychonomic Soc* 28:346–352.
- Berg P, Scherg M (1991): A multiple source approach to the correction of eye artifacts. *Electroencephalogr Clin Neurophysiol* 90:229–241.
- Berg P, Scherg M (1994): *Brain electric source analysis handbook*. Munich: Megis EEG Imaging Software.
- Besson M, Kutas M (1993): The many facets of repetition: a cued-recall and event-related potential analysis of repeating words in same versus different sentence contexts. *J Exp Psychol Learn Mem Cogn* 19:1115–1133.
- Birbaumer N, et al. (1981): EEG and slow cortical potentials in anticipation of mental tasks with different hemispheric involvement. *Biological Psychol* 13:251–260.
- Boynton GM, Engel SA, Glover GH, Heeger DJ (1996): Linear systems analysis of functional magnetic resonance imaging in human V1. *J Neurosci* 16:4207–4221.
- Brunia CH (1993): Waiting in readiness: gating in attention and motor preparation. *Psychophysiology* 30:327–339.

- Buckner RL, Bandettini PA, O'Craven KM, Savoy RL, Petersen SE, Raichle ME, Rosen BR (1996): Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. *Proc Natl Acad Sci U S A* 93:14878–14883.
- Cabeza R, Nyberg L (1997): Imaging cognition: an empirical review of PET studies with normal subjects. *J Cogn Neurosci* 9:1–26.
- Cabeza R, Nyberg L (2000): Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* 12:1–47.
- Caramazza A, Shelton JR (1998): Domain-specific knowledge systems in the brain: the animate-inanimate distinction. *J Cogn Neurosci* 10:1–34.
- Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV (1998): An area specialized for spatial working memory in human frontal cortex. *Science* 179:1347–1351.
- Courtney SM, Ungerleider LG, Keil K, Haxby JV (1997): Transient and sustained activity in a distributed neural system for human working memory. *Nature* 386:608–612.
- Curran T. (1999): The electrophysiology of incidental and intentional retrieval: ERP old/new effects in lexical decision and recognition memory. *Neuropsychologia* 37:771–785.
- Dale AM, Buckner RL (1997): Selective averaging of rapidly presented individual trials using fMRI. *Hum Brain Mapp* 5:329–340.
- Dale AM, Sereno MI (1993): Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: a linear approach. *J Cogn Neurosci* 5:162–176.
- Damasio H, Grabowski TJ, Tranel D, Hichwa RD, Damasio AR (1996): A neural basis for lexical retrieval [see comments] [published erratum appears in *Nature* 381:810]. *Nature* 380:499–505.
- Demb JB, Desmond JE, Wagner AD, Vaidya CJ, Glover GH, Gabrieli JD (1995): Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. *J Neurosci* 15:5870–5878.
- Donaldson DI, Rugg MD (1999): Event-related potential studies of associative recognition and recall: electrophysiological evidence for context dependent retrieval processes. *Brain Res Cogn Brain Res* 8:1–16.
- Duzel E, Cabeza R, Picton TW, Yonelinas AP, Scheich H, Heinze HJ, et al. (1999): Task-related and item-related brain processes of memory retrieval. *Proc Natl Acad Sci U S A* 96:1794–1799.
- Duzel E, Yonelinas AP, Mangun GR, Heinze HJ, Tulving E (1997): Event-related brain potential correlates of two states of conscious awareness in memory. *Proc Natl Acad Sci U S A* 94:5973–5978.
- Fabiani M, Donchin E (1995): Encoding processes and memory organization: a model of the von Restorff effect. *J Exp Psychol* 21:224–240.
- Fox PT, Mintun MA, Raichle ME, Herscovitch P (1984): A noninvasive approach to quantitative functional brain mapping with H₂(15)O and positron emission tomography. *J Cereb Blood Flow Metab* 4:329–333.
- Gardiner JM, Java RI, Richardson-Klavehn A (1996): How level of processing really influences awareness in recognition memory. *Can J Exp Psychol* 50:114–122.
- Heinze HJ, Mangun GR, Burchert W, Hinrichs H, et al (1994): Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature* 372:543–546.
- Henson RN, Rugg MD, Shallice T, Josephs O, Dolan RJ (1999): Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *J Neurosci* 19:3962–3972.
- Hopf J, Mangun GR (2000): Shifting visual attention in space: an electrophysiological analysis using high spatial resolution mapping. *Clin Neurophysiol* 111:1241–1257.
- Ishai A, Ungerleider LG, Martin A, Schouten JL, Haxby JV (1999): Distributed representation of objects in the human ventral visual pathway. *Proc Natl Acad Sci U S A* 96:9379–9384.
- Jennings JM, McIntosh AR, Kapur S, Tulving E, Houle S (1997): Cognitive subtractions may not add up: the interaction between semantic processing and response mode. *Neuroimage* 5:229–239.
- Josephs O, Turner R, Friston K (1997): Event-related fMRI. *Hum Brain Mapp* 5:243–248.
- Kapur S, Craik FI, Tulving E, Wilson AA, Houle S, Brown GM (1994): Neuroanatomical correlates of encoding in episodic memory: levels of processing effect [see comments]. *Proc Natl Acad Sci U S A* 91:2008–2011.
- Kapur S, Craik FIM, Jones C, Brown GM et al. (1995): Functional role of the prefrontal cortex in retrieval of memories: a PET study. *Neuroreport* 6:1880–1884.
- Kim SG, Richter W, Ugurbil K (1997): Limitations of temporal resolution in functional MRI. *Magn Reson Med* 37:631–636.
- Krause BJ, Schmidt D, Mottaghy FM, Taylor J, Halsband U, Herzog H et al. (1999): Episodic retrieval activates the precuneus irrespective of the imagery content of word pair associates. A PET study. *Brain* 122:255–263.
- Kwong KK (1995): Functional magnetic resonance imaging with echo planar imaging. *Magn Reson Q* 11:1–20.
- Lepage M, Ghaffar O, Nyberg L, Tulving E (2000): Prefrontal cortex and episodic memory retrieval mode. *Proc Natl Acad Sci U S A* 97:506–511.
- Lepage M, Habib R, Tulving E (1998): Hippocampal PET activations of memory encoding and retrieval: the HIPER model. *Hippocampus* 8:313–322.
- Lins OG, Picton TW, Berg P, Scherg M (1993): Ocular artifacts in recording EEGs and event-related potentials. II: Source dipoles and source components. *Brain Topogr* 6:65–78.
- Maguire EA, Frith CD, Morris RG (1999): The functional neuroanatomy of comprehension and memory: the importance of prior knowledge. *Brain* 122:1839–1850.
- Mangels JA, Picton TW, Craik FIM (1996): Neurophysiological (ERP) correlates of encoding and retrieval from verbal episodic memory. *Soc Neurosci Abs* 22:1450.
- Martin A, Wiggs CL, Ungerleider LG, Haxby JV (1996): Neural correlates of category-specific knowledge. *Nature* 379:649–652.
- Menon RS, Luknowsky DC, Gati JS (1998): Mental chronometry using latency-resolved functional magnetic resonance imaging. *Proc Natl Acad Sci U S A* 95:10902–10907.
- Miltner W, Braun C, Johnson R Jr, Simpson GV, Ruchkin DS (1994): A test of brain electrical source analysis (BESA): a simulation study. *Electroencephalogr Clin Neurophysiol* 91:295–310.
- Nunez P (1981): *Electric fields of the brain*. New York: Oxford University Press.
- Nyberg L, Persson J, Habib R, Tulving E, McIntosh AR, Cabeza R et al (2000): Large scale neurocognitive networks underlying episodic memory. *J Cogn Neurosci* 12:163–173.
- Nyberg L, McIntosh AR, Houle S, Nilsson LG, Tulving E (1996): Activation of medial temporal structures during episodic memory retrieval. *Nature* 380:715–717.
- Nyberg L, Tulving E, Habib R, Nilsson LG et al (1995): Functional brain maps of retrieval mode and recovery of episodic information. *Neuroreport* 7:249–252.

- Paller KA, Kutas M, Mayes AR (1987): Neural correlates of encoding in an incidental learning paradigm. *Electroencephalogr Clin Neurophysiol* 67:360–371.
- Paller KA, Kutas M (1992): Brain potentials during memory retrieval provide neurophysiological support for the distinction between conscious recollection and priming. *J Cogn Neurosci* 4:375–391.
- Paller KA, Kutas M, McIsaac HK (1995): Monitoring conscious recollection via the electrical activity of the brain. *Psychol Sci* 6:107–111.
- Perani D, Cappa SF, Bettinardi V, Bressi S, Gorno-Tempini M, Matarrese M et al (1995): Different neural systems for the recognition of animals and man-made tools. *Neuroreport* 6:1637–1641.
- Picton TW (1992): The P300 wave of the human event-related potential. *J Clin Neurophysiol* 9:456–479.
- Picton TW, Alain C, Woods DL, John MS, Scherg M, Valdes-Sosa P, Bosch-Bayard J, Trujillo NJ (1999): Intracerebral sources of human auditory evoked potentials. *Audiol Neuro-Otol* 4:64–79.
- Picton TW, Hillyard SA (1972): Cephalic skin potentials. *Electroencephalogr Clin Neurophysiol* 33:419–424.
- Picton TW, Lins O, Scherg M (1995): The recording and analysis of event-related potentials. In: Johnson Jr R, editor. *Event-related brain potentials and cognition*. Amsterdam: Elsevier, p 3–73.
- Puce A, Allison T, McCarthy G (1999): Electrophysiological studies of human face perception. III: Effects of top-down processing on face-specific potentials. *Cereb Cortex* 9:445–458.
- Quinlan PT (1992): *Oxford psycholinguistic database*. Oxford: Oxford University Press.
- Rösler F, Heil M, Glowalla U (1993): Monitoring retrieval from long-term memory by slow event-related brain potentials. *Psychophysiology* 30:170–182.
- Rösler F, Heil M, Hennigshausen E (1995b): Exploring memory functions by means of brain electrical topography: a review. *Brain Topogr* 7:301–313.
- Rösler F, Heil M, Hennigshausen E (1995a): Distinct cortical activation patterns during long-term memory retrieval of verbal, spatial, and color information. *J Cogn Neurosci* 7:51–65.
- Rajapakse JC, Kuggel F, Maisog JM, von Cramon DY (1998): Modeling hemodynamic response for analysis of functional time-series. *Hum Brain Mapp* 6:283–300.
- Rockstroh B, Elbert T, Canavan A, Lutzenberger W, Birbaumer N (1989): *Slow cortical potentials and behavior*. Baltimore: Urban and Schwarzenberg.
- Rockstroh B, Muller M, Wagner M, Cohen R et al (1993): “Probing” the nature of the CNV. *Electroencephalogr Clin Neurophysiol* 87:235–241.
- Roland PE (1993): *Brain activation*. New York: Wiley.
- Rugg MD, Mark RE, Walla P, Schloerscheidt AM, Birch CS, Allan K (1998): Dissociation of the neural correlates of implicit and explicit memory. *Nature* 392:595–598.
- Rugg MD, Wilding EL (2000): Retrieval processing and episodic memory. *Trends Cogn Sci* 4:108–115.
- Rugg MD (1998): Convergent approaches to electrophysiological and hemodynamic investigations of memory. *Hum Brain Mapp* 6:394–398.
- Rugg MD (1995): ERP studies of memory. In: Rugg MD, editor. *Electrophysiology of mind: event-related brain potentials and cognition*. Oxford Psychology Series, No. 25, M.G.H.C. Oxford: Oxford University Press, p 133–170.
- Rugg MD, Cox CJ, Doyle MC, Wells T (1995): Event-related potentials and the recollection of low and high frequency words. *Neuropsychologia* 33:471–484.
- Rugg MD, Fletcher PC, Frith CD, Frackowiak RS, Dolan RJ (1996): Differential activation of the prefrontal cortex in successful and unsuccessful memory retrieval. *Brain* 119:2073–2083.
- Rugg MD, Nagy ME (1989): Event-related potentials and recognition memory for words. *Electroencephalogr Clin Neurophysiol* 72:395–406.
- Schacter DL, Eich JE, Tulving E (1978): Richard Semon’s theory of memory. *J Verbal Learning Verb Behav* 17:721–743.
- Schacter DL, Alpert NM, Savage CR, Rauch SL, Albert MS (1996): Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. *Proc Natl Acad Sci U S A* 93:321–325.
- Schacter DL, Buckner RL, Koutstaal W, Dale AM, Rosen BR (1997): Late onset of anterior prefrontal activity during true and false recognition: an event-related fMRI study. *Neuroimage* 6:259–269.
- Scherg M (1990): Fundamentals of dipole source potential analysis. In: Grandori F, Hoke M, Romani GL, editors. *Auditory evoked magnetic fields and electric potentials*. *Advances in Audiology*, Vol 5. Basel: Karger, p 40–69.
- Scherg M, Berg P (1996): New concepts of brain source imaging and localization. In: Barber C, Celesia G, Comi GC, Mauguire F, editors. *Functional neuroscience (EEG Suppl 46)* Amsterdam: Elsevier, p 127–137.
- Scherg M, Picton TW (1991): Separation and identification of event-related potential components by brain electric source analysis. In: Brunia C, Mulder G, Verbaten M, editors. *Event-related brain research*. *Electroencephalogr Clin Neurophysiol (Suppl 42)*. Amsterdam: Elsevier, p 24–37.
- Senkfor AJ, Van Petten C (1998): Who said what? An event-related potential investigation of source and item memory. *J Exp Psychol Learn Mem Cogn* 24:1005–1025.
- Shallice T, Fletcher P, Frith CD, Grasby P, Frackowiak RS, Dolan RJ (1994): Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature* 368:633–635.
- Shiffrin RM, Schneider W (1984): Automatic and controlled processing revisited. *Psychol Rev* 91:269–276.
- Smith ME, Halgren E (1989): Dissociation of recognition memory components following temporal lobe lesions. *J Exp Psychol Learn Mem Cogn* 15:50–60.
- Somjen GG (1973): Electrogenesis of sustained potentials. *Prog Neurobiol* 1:199–237.
- Squire LR, Ojeman JM, Miezin FM, Petersen SE, Videen TO, Raichle ME (1992): Activation of the hippocampus in normal humans: a functional anatomical study of memory. *Proc Natl Acad Sci U S A* 89:1837–1841.
- Swick D, Knight RT (1997): Event-related potentials differentiate the effects of aging on word and nonword repetition in explicit and implicit memory tasks. *J Exp Psychol Learn Mem Cogn* 23:123–142.
- Talairach J, Tournoux P (1988): *Coplanar stereotaxic atlas of the human brain*. New York: Thieme.
- Towle VL, Bolanos J, Suarez D, Tan K, Grzeszczuk R, Levin DN, Cakmur R, Frank SA, Spire JP (1993): The spatial location of EEG electrodes: locating the best-fitting sphere relative to cortical anatomy. *Electroencephalogr Clin Neurophysiol* 86:1–6.
- Tulving E, Habib R, Nyberg L, Lepage M, McIntosh AR (1999): Positron emission tomography correlations in and beyond medial temporal lobes. *Hippocampus* 9:71–82.
- Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S (1994): Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc Natl Acad Sci U S A* 91:2016–2020.

- Tulving E, Markowitsch HJ, Craik FE, Habib R, Houle S (1996): Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cereb Cortex* 6:71–79.
- Tulving E (1983): *Elements of episodic memory*. Oxford: Clarendon.
- Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S (1994): Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc Natl Acad Sci U S A* 91:2016–2020.
- Van Petten C, Senkfor AJ (1996): Memory for words and novel visual patterns: repetition, recognition, and encoding effects in the event-related brain potential. *Psychophysiology* 33:491–506.
- Vaughan HG Jr, Arezzo JC (1988): The neural basis of event-related potentials. In: Picton TW, editor. *Handbook of electroencephalography and clinical neurophysiology*. Rev. Series. Vol. 3. Human event-related potentials. New York: Elsevier, p 45–96.
- Wheeler MA, Stuss DT, Tulving E (1997): Toward a theory of episodic memory: the frontal lobes and autonoetic consciousness. *Psychol Bull* 121:331–354.
- Wilding EL, Rugg MD (1997): An event-related potential study of memory for words spoken aloud or heard. *Neuropsychologia* 35:1185–1195.
- Wilding EL, Rugg MD (1996): An event-related potential study of recognition memory with and without retrieval of source. *Brain* 119:889–905.
- Wood CC (1982): Application of dipole localization methods to source identification of human evoked potentials. *Ann NY Acad Sci* 38:139–155.
- Wood CC (1994): Human brain mapping in both time and space (Editorial). *Hum Brain Mapp* 1: iii–vi.
- Zarahn E, Aguirre G, D’Esposito M (1997): A trial-based experimental design for fMRI. *Neuroimage* 6:122–138.