Phase/Amplitude Reset and Theta–Gamma Interaction in the Human Medial Temporal Lobe During a Continuous Word Recognition Memory Task

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ABSTRACT: We analyzed intracranial electroencephalographic (EEG) recordings from the medial temporal lobes of 12 epilepsy patients during a continuous word recognition paradigm, contrasting trials of correctly recognized repeated words (hits) and correctly identified new words (correct rejections). Using a wavelet-based analysis, we investigated how power changes and phase clustering in different frequency bands contribute to the averaged event-related potentials (ERPs). In addition, we analyzed the actual mean phases of the different oscillations. Our analyses yielded the following results: (1) power changes contributed significantly only to the late components of the ERPs (>400 ms) (2) earlier ERP components were produced by a stimulus-related broadband phase and amplitude reset of ongoing oscillatory activity about 190 ms after stimulus onset that involved not only the theta band, but also covered alpha and lower beta band frequencies (3) phase and amplitude reset occurred during an epoch of increased phase entrainment over time that lasted for about two oscillation periods for all involved frequencies and was more pronounced for correct rejections than for hits. The broad-band phase and amplitude reset was observed for both hits and correct rejections, and therefore, did not appear to support a specific cognitive function, but rather to act as a general facilitating factor for the processes involved in this memory task. Further analyses of synchronization between oscillations and power changes in different frequency bands revealed a task-dependent modulation of gamma activity by the entrained theta cycle, a mechanism potentially related to memory encoding and retrieval in the rhinal cortex and hippocampus, respectively. © 2005 Wiley-Liss, Inc.

KEY WORDS: event-related potentials; intracranial EEG; epilepsy; theta reset; phase entrainment

INTRODUCTION

The medial temporal lobe (MTL) in humans is known to play an important role in the encoding and retrieval of declarative memories, i.e., consciously accessible events and facts (e.g., Eichenbaum, 2000; Squire et al., 2004). It is difficult to obtain reliable information about the electrophysiological correlates of memory processes within human MTL structures based on surface recordings, in particular, since hippocampal activity is known to be electrically shielded by the radial cylindrical arrangement of hippocampal pyramidal layers (Klee and Rall, 1977). Therefore, investigations using depth-recorded event-related brain potentials (ERPs) in patients with MTL epilepsy have contributed significantly to our understanding of mechanisms underlying mnemonic processes (e.g., Smith et al., 1986; Halgren and Smith, 1987; McCarthy et al., 1995; Grunwald et al., 1998a,b; Fernández et al., 1999).

Contrary to ERP components recorded from surface electrodes, which are filtered and modulated by multiple layers of tissue, ERPs recorded invasively in epilepsy patients, offer a particularly high spatial resolution at a high signal-to-noise (S/N) ratio. The intracranially recorded so-called anterior medio-temporal N400 (AMTL-N400) is found after visual word presentation similar to the broadly distributed surface N400 (Halgren and Smith, 1987), and seems to be associated with processes indirectly supporting declarative memory (Nobre and McCarthy, 1995; Fernández et al., 2002). The source of the AMTL-N400 could be localized within the rhinal, probably perirhinal cortex (McCarthy et al., 1995). Like the surface N400, the AMTL-N400 is reduced in amplitude for the repeated presentation of a certain word (e.g., Smith et al., 1986; Nobre and McCarthy, 1995; Grunwald et al., 1998a). Accompanying the AMTL-N400 in the rhinal cortex, a late negative component (LNC) has been observed in the ERPs recorded within the hippocampus that exhibits an increase in amplitude for repeated items (Grunwald et al., 1995).

In theory, ERP components can result from either a stimulus-evoked increase in EEG power or from increased phase clustering of ongoing oscillatory EEG activity, i.e., a stimulus-related concentration of phases (e.g., Basar et al., 1984; Demiralp et al., 1998; Yordanova and Kolev, 1998; Sannita et al., 2001; Penny et al., 2002; Shah et al., 2004; Duzel et al., in press; Gruber et al., 2005). Stimulus-evoked power changes are thought to correspond to the event-related activation of a neural assembly distinct from ongoing background dynamics that are present in each trial and, after averaging, produce the ERP. On the other hand,
phase entrainment of ongoing oscillatory activity can produce an ERP component without additional recruitment of activated neurons. The frequency-specific analysis of both amplitude (power) changes and phase clustering, based, e.g., on the wavelet transform (Lachaux et al., 1999), has been shown to be capable to differentiate between these two contributing factors for different ERP components (Makeig et al., 2002; Shah et al., 2004; Fell et al., 2005).

With respect to the oscillatory activity that constitutes averaged ERPs obtained during cognitive processes, experimental studies have reported an increased theta activity in the MTL during complex cognitive tasks in rodents (see e.g., Kahana et al., 2001 or Buzsáki, 2002 for an overview) and humans (Raghavachari et al., 2001). In particular, the phenomenon of a stimulus-locked theta phase reset was found to play an important role in rodent working memory (Givens, 1996; Williams and Givens, 2003). The phase of background theta activity at which stimuli arrive in the hippocampus has been shown to determine the direction of long-term plasticity (potentiation or depression) (Huerta and Lisman, 1995). Stimulus-related phase reset was found to facilitate long-term potentiation (LTP) after stimulus presentation (McCartney et al., 2004). Only recently, studies using magnetoencephalographic data in combination with source analysis (Tesche and Karhu, 2000) or intracranial recordings (Rizzuto et al., 2003) have provided evidence for a similar phenomenon associated with working memory tasks in humans. Furthermore, interactions between different EEG rhythms in the MTL have been investigated both in rodents (Buzsáki and Draguhn, 2004 and references therein) and human recordings (Bragin et al., 1999). The relationship of single-cell activity with respect to the underlying theta phase has been shown to represent the spatial position of a moving animal (O’Keefe and Recce, 1993); similarly, it has been suggested that the phase relationship of gamma and theta oscillations enables sequence encoding in humans (Jensen and Lisman, 2005). Encoding and retrieval of memories have been hypothesized to be associated with an interaction of theta and gamma oscillations (Buzsáki, 1989; Fell et al., 2003), and it was shown in animal models that task-related gamma oscillations are modulated by the theta cycle within the hippocampus and entorhinal cortex (Bragin et al., 1995; Chrobak and Buzsáki, 1998; Chrobak et al., 2000). To date, however, it has not been investigated whether such a task-related gamma/theta modulation is also present in humans.

In this study, we analyzed ERPs recorded intracranially from both the rhinal cortex and the hippocampus in epilepsy patients performing a continuous word recognition paradigm. Using a wavelet-based power and phase analysis, we investigated to what extent the AMTL-N400 and the LNC are produced by recruitment of additional neuronal activity or by phase entrainment of ongoing oscillatory activity, respectively. In addition, we used a novel synchronization analysis to evaluate interactions between different oscillating rhythms, constituting the observed ERP components with particular respect to the question whether power changes in certain frequency bands are modulated by phase oscillations in other bands.

**Subjects**

Twelve patients with pharmacoresistant, unilateral temporal lobe epilepsy (5 women, 7 men, mean age: 40.3 ± 10.1 yr) participated in the study. Seven patients had a hippocampal sclerosis; in five patients we found other benign MTL lesions like cortical dysplasias. In six patients seizures originated always in the right MTL, in the other six patients always in the left MTL. Recordings were performed between 2001 and 2003 at the Department of Epileptology, University of Bonn, Germany. Bilateral implantation of depth electrodes and unilateral seizure onset served as inclusion criteria.

**Depth Electrodes**

Bilateral, multicontact depth electrodes were inserted using a computed tomography-based stereotactic insertion technique (Van Roost et al., 1998). Depth electrode recordings were necessary before resective surgery because the seizure onset zone could not be determined unequivocally from surface recordings. The location of electrode contacts was ascertained by magnetic resonance images (MRI) in each patient. Contacts were mapped by transferring their positions from MRI to standardized anatomical drawings (Jackson and Duncan, 1996). MRI scans were acquired in sagittal and adjusted coronal planes, perpendicular to the longitudinal axis of the hippocampus (repetition time = 3,719 ms, echo time = 120 ms, flip angle = 90°, field of view = 22 cm; thickness = 2.0 mm; gap = 0.3 mm; 1.5 T) (ACS-II, Philips, Eindhoven, Netherlands).

Only EEG recordings from the MTL contralateral to the zone of seizure origin were analyzed in the present study to reduce poorly controllable effects introduced by the epileptic process (Grunwald et al., 1995). If seizures are proved to originate unilaterally, electrodes in the healthy MTL enable recordings of quasi-normal brain activity unrelated to epilepsy (Paller et al., 1992). Unilateral seizure onset was indicated in each patient by the fact that all recorded seizures originated exclusively in depth recordings of one MTL.

At the time of the experiment, all patients were under stable anticonvulsive medication without benzodiazepines, barbiturates, or phenytoin, i.e., anticonvulsive drugs known to affect oscillatory EEG activity. No seizure occurred within 24 h before the experiment. The ERP study was approved by the local medical ethics committee and each patient gave written informed consent.

**Experimental Paradigm**

In a continuous visual word recognition paradigm (Rugg and Nagy, 1989), 300 common German nouns were presented sequentially in uppercase letters (white against black background), in central vision (horizontal visual angle 3.0°), and for a duration of 200 ms (randomized interstimulus interval: mean: 1,800 ms, range: 1,400–2,200 ms). Half of these words were repeated after 3 ± 1 (early) or 14 ± 4 (late) intervening stimuli.
Patients were asked to indicate whether an item was new or old by pressing one of two buttons of a computer mouse in their dominant hand. Because earlier studies have revealed no reliable differences between MTL-ERPs to early and late repetitions (Grunwald et al., 1998a; Guillemin et al., 1999), averages were collapsed across both lags for the present analysis.

**EEG Recording**

Depth electroencephalograms were referenced to linked mastoids, band-pass filtered (0.01 Hz (6dB/octave) to 70 Hz (12dB/octave)), and recorded at a sampling rate of 200 Hz. For the present analyses, recordings from the nonpathological hemispheres were selected as described earlier. EEG trials were visually inspected for artifacts (e.g., epileptiform spikes), and about 5% of all trials were excluded from analysis. From the contralateral (nondominant) electrode in each patient, one hippocampal contact was chosen that was located in the hippocampus and related to the LNC with the largest peak-amplitude and one anterior parahippocampal position was chosen with the maximum AMTL-N400 peak-amplitude in the continuous visual word recognition paradigm. Since our methods cannot clearly separate perirhinal and entorhinal generators, we use the term rhinal cortex without indicating an integrated rhinal processing stage.

**Analysis of Phase Clustering and Power Changes**

We used the following definitions of EEG spectral bands: Delta (0.5–4 Hz), Theta (4–8 Hz), Alpha (8–13 Hz), Beta (13–30 Hz), and Gamma (above 30 Hz). EEG trials were filtered in the frequency range from 0.5 Hz to 50 Hz (0.5 Hz steps) by continuous wavelet transforms implementing Morlet wavelets of five cycles length (e.g., Daubechies, 1990; Torrence and Compo, 1998). The filtered signals $w_{j,k}$ ($j$, time point within a trial; $k$, trial number) hereby result from the time convolution of original signals and the complex wavelet function. To avoid edge effects, the trials entering the wavelet transform were segmented from −2.0 s to 3.0 s with respect to stimulus presentation. An interval of 1.8 s at the beginning and the end of the trials was afterwards discarded.

Note that since the wavelet decomposition partitions the frequency domain logarithmically, the frequency resolution of 0.5 Hz used in this study can be regarded as sufficient for frequencies above 2 Hz, since the spectral bands for different center frequencies overlap in terms of their full width at half maximum (compare Daubechies, 1990).

From the wavelet-transformed signals $w_{j,k}$, the phases $\phi_{j,k}$ ($\phi_{j,k} = \arctan(\text{Im}(w_{j,k})/\text{Re}(w_{j,k}))$) and the power values $P_{j,k}$ ($P_{j,k} = \text{Re}(w_{j,k})^2 + \text{Im}(w_{j,k})^2$) were extracted for each time point $j$ of each trial $k$. Power values were averaged separately for each condition. The calculation of intertrial phase locking values was done by a procedure suitable for the evaluation of small trial numbers. In contrast to phase locking estimates based on calculations of circular variance (e.g., Mormann et al., 2000, Fell et al., 2001), this method is not biased by the number of trials. For this purpose, phase distributions for hits and correct rejections were divided into eight boxes of 45° covering the range from −180° to +180°. Distribution probabilities $X_{ij}$ (i.e., probabilities that a phase at time $j$ falls into box $i$) were calculated for each box, $i$, and at each time point, $j$. Phase locking values $PL_j$ were then evaluated based on a normalized entropy measure (Tass et al., 1998).

$$PL_j = 1 + \sum_{i=1}^{8} X_{i,j} \times \log X_{i,j}/\log(8)$$

To allow a finer phase resolution, calculations were iterated for 45 shifts of the boxes about 1°, and finally the phase locking values resulted from the averages of these iterations.

For statistical analyses, power and phase locking values were averaged for nonoverlapping successive time windows of 100 ms duration from −200 to 1,000 ms (12 windows in total). Afterwards, power and phase locking values were normalized with respect to the prestimulus time window from −200 to −100 ms separately for each subject and each filter frequency. For the graphical depiction, power and phase locking values were normalized to the prestimulus time window and then transformed into dB scale (10 $\times$ log_{10}). Because of the intrinsic logarithmic frequency scaling of the wavelet decomposition, higher frequencies are not statistically independent if sampled too closely on an equidistant frequency scale. On the other hand, a wider sampling interval may be too coarse to adequately sample the lower frequency range. As a compromise for statistical analysis, we therefore included frequencies with steps of 2 Hz, i.e., 2, 4, ..., 50 Hz.

The calculation of mean phases over trials for each time point $j$ was performed using circular statistics (Mardia, 1972).

$$\bar{\phi}_j = \arg\left[\frac{1}{N} \sum_{k=1}^{N} e^{i \phi_{j,k}}\right]$$

**Analysis of Phase and Power Modulation**

To investigate whether power changes in certain frequency bands are modulated by phase changes in other bands, we analyzed the degree of phase synchronization between them. The mean phases calculated during the wavelet analysis were compared with phase angles extracted from the wavelet power time series $\phi_{j,\text{pow}}$, via the Hilbert transform (e.g., Mormann et al., 2000). These phase angles were calculated for the first 1,200 ms after stimulus presentation. The Hilbert transform was used instead of the wavelet transform to extract the phases belonging to the dominant frequency of the power changes rather than investigating band-pass filtered phases rendered by a wavelet transform. Since for this analysis, statistics were not calculated over trials but over time, an index based on the circular variance could be used for the quantification of modulation (Mardia, 1972), without any bias caused by different numbers of trials:

$$R = \frac{1}{N} \sum_{j=1}^{N} |\bar{\phi}_j - \phi_{j,\text{pow}}|^2$$
Phase synchronization values $R$ between power changes and mean oscillatory phases were determined separately for each condition and location and for all possible combinations of analyzed frequencies (4, 4.5, 5, ..., 50 Hz). The delta band, i.e., the frequency range below 4 Hz, was excluded from the analysis since for the given time length of 1,200 ms too few oscillation periods would be covered to be sufficient for accurate statistics.

The resulting modulation matrices for each patient were transformed via Daniels’ arcsine transform (Daniels and Kendall, 1947) to ensure a normal distribution for the statistical analyses, then averaged over patients and transformed back for graphical depiction.

**Statistical Analyses**

For statistical evaluation of power, phase clustering, and phase/power modulation values, we conducted three-way ANOVAs with time (window) and stimulus (hits vs. correct rejections) as repeated measures and frequency as independent variable. For statistical evaluation of the synchronization between power changes and mean phases, we performed three-way ANOVAs with stimulus (hits vs. correct rejections) as repeated measure and frequency1 (for the power changes) and frequency2 (for the mean phases) as independent variables. $P$-values were Huynh–Feldt corrected for inhomogeneities of covariance when necessary (Huynh and Feldt, 1976).

**RESULTS**

**Behavioral Results**

In the continuous word recognition experiment patients correctly identified (70.5 ± 12.7)% of the old words (hits) and correctly rejected (75.9 ± 19.6)% of the new words (correct rejections).

**AMTL-N400: Average ERP Waveforms**

The average AMTL-N400 waveforms recorded from the rhinal cortex elicited by hits (correctly identified repeated words) and correct rejections (correctly identified new words) are shown in Figure 1 (left). Within the rhinal cortex, correct rejections were associated with a pronounced negative potential peaking about 420 ms after stimulus onset. Across all patients, mean peak amplitudes (± standard deviation (SD)) of the AMTL-N400 component were $-61 ± 28 \mu V$, mean peak latencies were $423 ± 73$ ms. Hits elicited comparatively smaller and earlier negative waveforms with amplitudes reaching $-52 ± 26 \mu V$ and peaking at $405 ± 56$ ms (paired two-tailed $t$-tests: $t_{11} = 2.64, P < 0.05; t_{11} = 1.83, P < 0.1$).

**Hippocampal LNC: Average ERP Waveforms**

Within the hippocampus, correct rejections were associated with a negative potential peaking about 870 ms after stimulus onset. Across all patients, mean peak amplitudes (± standard deviation (SD)) of the LNC component were $-37 ± 32 \mu V$, mean peak latencies were $868 ± 84$ ms (Fig. 1, right). Hits elicited comparatively larger and earlier negative waveforms with amplitudes reaching $-62 ± 52 \mu V$ and peaking at $806 ± 82$ ms (paired two-tailed $t$-tests: $t_{11} = 2.68, P < 0.05; t_{11} = 2.01, P < 0.1$).

**Rhinal Cortex: Power Changes**

For both hits and correct rejections, power increases in the delta and theta band mainly occurred within time ranges succeeding the peaks of the AMTL-N400 components in the averaged ERPs (main effects for the factors time ($P < 0.0001$; $F_{12,3168} = 21.38; \varepsilon = 0.320$) and frequency ($P < 0.0001$; $F_{23,264} = 2.67$)). For hits (repeated words) the power changes appeared earlier (significant stimulus × time interaction ($P < 0.0001$; $F_{12,3168} = 10.19; \varepsilon = 0.233$)) and the power increase appeared to be more pronounced for hits than for correct rejections (Fig. 2, upper row). However, this effect did not reach
statistical significance. Furthermore, power enhancements in the gamma band about 35 Hz occurred about 250 ms and 450 ms after onset of word presentation for both hits and correct rejections.

**Rhinal Cortex: Phase Clustering**

Both correct rejections and hits exhibited phase clustering increases mainly in the theta and alpha band (Fig. 2, middle row; main effect for frequency ($P < 0.0001; F_{23,264} = 10.63$)). In addition, there was an increased phase clustering in the delta band located about 2 Hz that lasted longer than the increase in the theta and alpha band (up to 900 ms after stimulus onset). Phase clustering changes roughly corresponded to the time range of the AMTL-N400 (main effect for time ($P < 0.0001; F_{12,3168} = 60.77; \eta = 0.180$)), but were more extended for correct rejections (significant stimulus $\times$ time interaction ($P < 0.0001; F_{12,3168} = 10.14; \eta = 0.200$)). In parallel to the ERP amplitudes, phase clustering changes were more pronounced for correct rejections than for hits (main effect for stimulus ($P < 0.0001; F_{1,264} = 15.00$)).
Rhinal Cortex: Mean Phases

Analysis of mean phases showed an alignment of phases over a broad range of frequencies occurring about 190 ms after stimulus onset both for hits and correct rejections (Fig. 2, lower row). At this instant, oscillations in the frequency bands from 4 to 20 Hz simultaneously attained identical phase values of about 90° (π/2). These phase values correspond to a positive-to-negative zero-crossing of the respective oscillations, followed by a trough for all oscillations in the respective frequency range. The synchronized zero-crossing over a considerable frequency range acts as an amplitude reset independent of the power of the oscillation at this instant.

Note that the phase locking values in the phase clustering analysis (Fig. 2, middle row) can be regarded as a reliability measure for the mean phases (Fig. 2, lower row), since they are correlated to the circular variance (cf. Mardia, 1972). Phase clustering analysis thus indicates a reduced variability of the mean phases for at least two periods after resetting for each individual frequency band that is present for both hits and correct rejections, but is more pronounced for the latter.

Hippocampus: Power Changes

For both hits and correct rejections, power increases in the delta and theta band mainly occurred within the time range of the LNC (Fig. 3, upper row; main effects for the factors time ($P < 0.0001$; $F_{12,3168} = 10.56$; $\epsilon = 0.311$) and frequency ($P < 0.0001$; $F_{23,264} = 3.38$)). For hits the power changes appeared earlier and were less extended in the frequency domain.
(stimulus × time × frequency interaction ($P < 0.0001; F_{276.3168} = 3.76; \epsilon = 0.407$)). In parallel to the LNC amplitudes, the power increase was more pronounced for hits than for correct rejections (main effect for stimulus ($P < 0.0001; F_{1.264} = 39.29$)). For hits, there was a pronounced increase in theta power about 400 ms, followed by an even more pronounced decrease in theta/alpha power.

**Hippocampus: Phase Clustering**

Correct rejections as well as hits showed phase clustering increases mainly in the theta and alpha band (Fig. 3, middle row; main effect for frequency ($P < 0.0001; F_{23.264} = 7.64$)). In addition, there was an increased phase clustering in the delta band located about 2 Hz that lasted longer than the increase in the theta and alpha band (up to 1,100 ms after stimulus onset). Phase clustering changes in the theta and alpha band roughly corresponded to the time range of the positive deflection temporally related to the AMTL-N400 and preceding the LNC (main effect for time ($P < 0.0001; F_{12.3168} = 55.22; \epsilon = 0.159$)). Although ERP amplitudes of the positive component exhibited no differences between hits and correct rejections, these phase clustering changes were more pronounced for correct rejections than for hits (main effect for stimulus ($P < 0.0001; F_{1.264} = 13.92$)) and were more extended in the time and frequency domain (significant stimulus × time × frequency interaction ($P < 0.0001; F_{276.3168} = 1.95; \epsilon = 0.180$)). Phase clustering changes in the delta band, on the other hand, corresponded to the time range of the LNC and tended to be more pronounced for hits than for correct rejections.

**Hippocampus: Mean Phases**

Analysis of mean phases showed an alignment of phases over a broad range of frequencies occurring about 190 ms after stimulus onset for both hits and correct rejections (Fig. 3, lower row). As in the rhinal cortex, the phase alignment in the hippocampus was confined to the frequency range from 4 to 20 Hz, with phase values about 90° ($\pi/2$). These phase values correspond to an amplitude resetting, followed by a consecutive trough in the frequency range from 4 to 20 Hz. Again phase clustering analysis (Fig. 3, middle row) indicates a reduced variability of the mean phases (Fig. 3, lower row) for about two periods after resetting in each individual frequency band that is more pronounced for correct rejections than for hits.

**Rhinal Cortex: Phase/Power Modulation (Synchronization Between Power Changes and Mean Phases)**

For both hits and correct rejections, we detected an increased synchronization between the mean phases in the theta band about 4 Hz (main effect for frequency2 ($P < 0.0001; F_{23.6336} = 2.66$)) and the power changes in the beta and gamma band (Fig. 4, upper row; main effect for frequency1 ($P < 0.0001; F_{23.6336} = 6.37$)). While for hits, one pronounced maximum was observed in the beta range between 18 and 26 Hz, for correct rejections there were two distinct maxima, one in the beta band between 18 and 22 Hz, and one the gamma band between 44 and 50 Hz (stimulus × frequency1 interaction ($P < 0.0001; F_{23.6336} = 4.50$)). Overall, synchronization for hits was stronger than for correct rejections (main effect for stimulus ($P < 0.0001; F_{1.6336} = 15.08$)).

**Hippocampus: Phase/Power Modulation (Synchronization Between Power Changes and Mean Phases)**

For both hits and correct rejections, we observed an increased synchronization between the mean phases in the theta band from 4 to 8 Hz (main effect for frequency2 ($P < 0.0001; F_{23.6336} = 2.65$)), and the power changes in the beta and gamma band (Fig. 4, lower row); main effect for frequency1 ($P < 0.0001; F_{23.6336} = 7.20$). While for hits, maxima were found in the alpha range at 12 Hz, in the beta range at 20 Hz, and in the gamma range at 46 Hz, for correct rejections there were two pronounced maxima, one in the alpha/beta band between 12 and 16 Hz, and one in the beta band between 24 and 30 Hz (stimulus × frequency1 interaction ($P < 0.0001; F_{23.6336} = 5.40$)). In contrast to rhinal recordings, synchronization for correct rejections was stronger than for hits at hippocampal sites (main effect for stimulus ($P < 0.02; F_{1.6336} = 6.16$)).

**DISCUSSION**

In this study, we have analyzed ERPs recorded from intracranial depth electrodes in the rhinal cortex and hippocampus of the hemisphere contralateral to the epileptic focus during a continuous word recognition memory task. Evaluation of the averaged ERP waveforms showed a pronounced negativity within the rhinal cortex (AMTL-N400) as well as a LNC within the hippocampus. The amplitudes of the rhinal AMTL-N400 showed a significant decrease for hits (correctly recognized repeated words) in comparison with correct rejections (correctly recognized new words), while the opposite effect was observed for the hippocampal LNC. This standard analysis is in accordance with earlier word recognition studies, using intracranial recordings (Smith et al., 1986; Grunwald et al., 1995, 1998a,b, 1999; Nobre and McCarthy, 1995).

Analysis of power changes revealed no significant differences between hits and correct rejections for the first 400 ms after stimulus onset, in the frequencies relevant for constituting the averaged ERP waveforms. The most prominent effect was an increase in theta activity about 600 ms, followed by a decrease in theta and alpha activity about 900 ms after stimulus onset in the hippocampus for hits compared with rejections.

Analysis of mean phases and phase clustering produced three major findings:

- A stimulus-related decrease in variability of phases across trials corresponding to a maximum phase clustering at about 200 ms that was evident over the entire frequency range from 4 to 20 Hz.
in both the rhinal cortex and the hippocampus. The corresponding mean phases (reflecting the oscillatory periods) showed that the duration of this decreased variability was approximately two oscillation periods for every frequency band involved (phase entrainment over time). In addition, we found an extended increase in phase clustering in the delta band located about 2 Hz. A stimulus-related alignment of phases over a broad range of frequencies (4–20 Hz) occurring about 190 ms after stimulus onset corresponding to a phase reset in this frequency range (broad-band phase reset).

A positive-to-negative zero-crossing caused by this broadband phase reset which results in a momentary amplitude reset of the averaged ERP (irrespective of the oscillatory signal power), followed by a trough of the oscillations in this frequency range (amplitude reset).

While the phase entrainment over time in the theta and alpha band was more pronounced for correct rejections than for hits, the broad-band phase and amplitude reset showed no distinct difference for these conditions. With respect to differences between the rhinal cortex and the hippocampus, we found the phase entrainment over time to be alike in both structures. Interestingly, the phase and amplitude reset apparently was not accompanied by a recruitment of additional neuronal activity, which would have been reflected by a relative increase in power.

Our findings thus show that separate analysis of event-related power and phase effects can reveal additional information compared with conventional ERP evaluation. The averaged AMTL-N400 recorded from within the rhinal cortex showed a new-minus-old repetition effect (Smith et al., 1986; Nobre and McCarthy, 1995; Grunwald et al., 1998a, 1999) which would
commonly be interpreted as indicating that more neural assemblies within rhinal cortex are involved in the processing of new compared with repeated words. However, contrary to the traditional interpretation, the event-related power increase within the rhinal cortex appeared to be even more pronounced for correctly recognized repeated words compared with new words, although this effect did not reach statistical significance. According to our analysis, the enhanced averaged amplitude of the AMTL-N400 for new words compared with repeated words rather seems to be caused by an increased phase clustering. This suggests that verbal novelty in comparison with verbal recognition is associated with a reduced variability of the timing of stimulus processing, but not with an increased recruitment of neural assemblies within the rhinal cortex. As for the actual waveforms of the averaged ERPs, it appears that the old/new effect is produced mainly by the late changes in phase clustering found in the delta band.

The waveform itself can be explained by the finding of a broadband phase and amplitude reset of ongoing background activity including in particular delta and theta frequencies that account for the negative deflection of the AMTL-N400.

With respect to the ERPs recorded in the hippocampus, our analysis suggests that the early components, in particular the negative deflection about 200 ms after stimulus onset, are caused by the phase and amplitude resetting of background activity in the theta and alpha band, while the phase shift observed in the delta band is responsible for the positive deflection at 500 ms and the consecutive negative deflection about 800 ms LNC. The difference in amplitude of the LNC found between old and new words, could be caused both by the difference in phase clustering found in the delta band (which tended to be more pronounced for hits) and/or by the relative increase in delta/theta power (which was more pronounced for hits) about 600 ms after stimulus onset, i.e., at the beginning of the negative deflection resulting in the LNC.

Of the findings discussed so far, the phenomenon of a broadband phase and amplitude reset appears to be a rather unspecific mechanism of cognitive processing that does not allow to distinguish between the mnemonic functions involved in the different conditions of our experimental paradigm (hits vs. correct rejections). This finding is in line with evidence from rodent data for a resetting of the theta rhythm by behaviorally relevant stimuli (Givens, 1996; Williams and Givens, 2003), and recent findings from recordings of human magnetoencephalographic and intracranial EEG data (Tesche and Karhu, 2000; Rizzuto et al., 2003) where theta phase reset was observed in a working memory task and hypothesized to act as a facilitating factor for cognitive processes. Furthermore, a recent study (McCarrtney et al., 2004) provided evidence that resetting of hippocampal theta in rodents after a memory-relevant stimulus produces optimal conditions for LTP, a possible neural mechanism for information encoding. Earlier studies had already shown LTP to be highly sensitive to the phase of ongoing theta activity (Huerta and Lisman, 1993; Hölscher et al., 1997).

To investigate whether interactions between different neuronal rhythms exist that are specifically related to the two conditions of our experimental paradigm, we tested whether oscillatory activity in certain frequency bands was modulated by the cycle of oscillations in other frequency bands. A modulation of this type, namely, the modulation of gamma activity by the theta cycle has been described in rodents (Bragin et al., 1995; Chrobak and Buzsáki, 1998; Chrobak et al., 2000) and has been hypothesized to play a fundamental role in a model of hippocampal memory (Jensen and Lisman, 2005).

Results from our analysis showed that it was predominantly the theta cycle that modulated power changes particularly in the beta band between 10 and 20 Hz. In addition, we found an increase in modulation of gamma activity between 40 and 50 Hz by the theta cycle of about 6 Hz in the rhinal cortex that was more pronounced for correct rejections than for hits. In the hippocampus, we found a similar theta/gamma modulation, but here it was more pronounced for hits than for correct rejections. Although the conditions in our paradigm are not clearly related to a particular mnemonic process such as encoding or retrieval, there are still defined differences, e.g., only correct rejections involve the encoding of a new item, while hits are predominantly based on the retrieval of previously stored information. Our findings might therefore be interpreted as a possible substrate of encoding mechanisms in the rhinal cortex associated with the presentation of new words and retrieval mechanisms in the hippocampus associated with the presentation of repeated words. However, further research involving other experimental paradigms is necessary to validate this hypothesis.

In summary, our findings indicate that the cognitive processes during a word recognition paradigm are associated with a broadband phase and amplitude reset of ongoing activity in the theta band that also covers higher frequencies of the alpha and lower beta band. This phase and amplitude reset along with an increased phase entrainment over time predominantly constitutes the ERP components of the averaged waveforms, particularly during the first 400 ms after stimulus onset. This finding is in favor of the hypothesis that a theta reset acts as an unspecific facilitating factor for memory processes. The specific cognitive functions of encoding of new words and retrieval of old words, on the other hand, might be supported by gamma activity in the rhinal cortex and hippocampus, respectively (Bragin et al., 1995; Jensen and Lisman, 1998; Fell et al., 2001), that is modulated by the entrained theta activity.

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PHASE/AMPLITUDE RESET AND THETA–GAMMA INTERACTION


