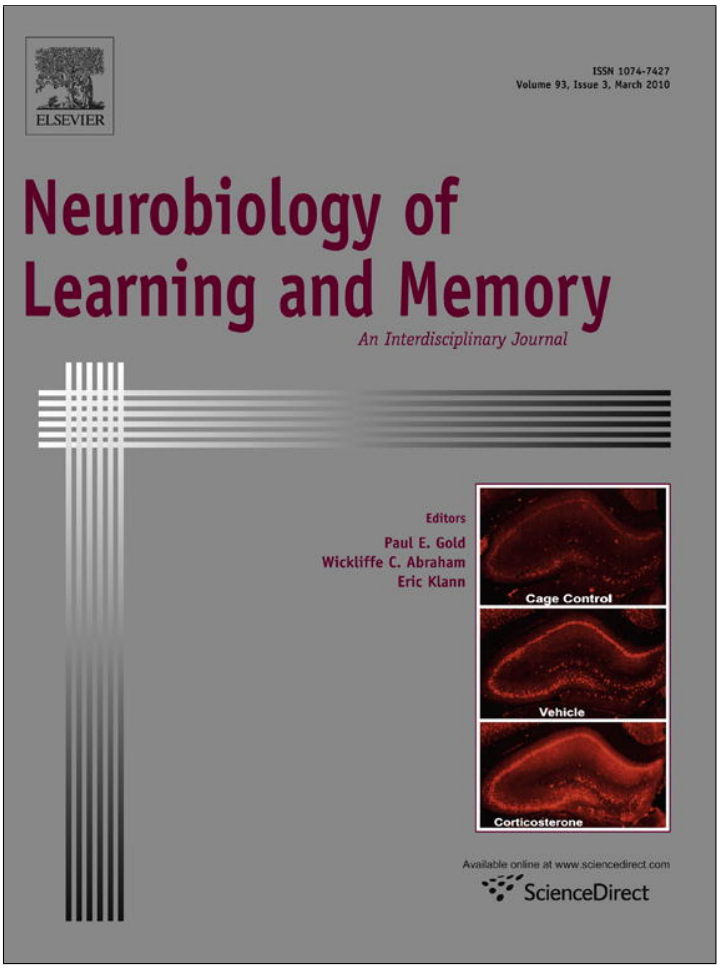

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Active suppression in the mediotemporal lobe during directed forgetting

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ABSTRACT

The aim of the present study was to investigate whether forgetting is merely a passive process or whether it can also be caused by active suppression of memory contents.

We investigated effects of directed forgetting by intracranial event-related potentials (ERPs) in 12 patients with mesial temporal lobe epilepsy. In a single-item directed forgetting paradigm, the patients were presented with words either followed by the instruction that this word has to-be-remembered (TBR) or to-be-forgotten (TBF). All patients were implanted with multicontact depth electrodes along the rhinal cortex and hippocampus as part of their presurgical evaluation.

Patients recognized significantly less TBF than TBR words in a subsequent recognition test. In the hippocampus, TBF cues that caused subsequent forgetting were associated with decreased negative ERPs. In the rhinal cortex, TBF cues elicited a generally prolonged positivity, as compared to TBR cues.

We interpret the decreased hippocampal ERPs following the TBF cues as an indication for an active suppression of hippocampal functions. The increased rhinal activity in response to the TBF cue might indicate an active involvement of this structure in the suppression of hippocampal memory formation.

1. Introduction

Forgetting usually occurs unintentionally and is perceived as a negative consequence of the limited capacity of the memory system. However, forgetting irrelevant information is important for effective information processing, as it avoids interference from irrelevant information (Bjork, 2008). The executive control of forgetting has been examined in experiments on "directed forgetting", where an individual item ("single-item-cueing") or a list of items ("list-cueing") is followed by an instruction to forget or to remember these items. It has been shown that recognition performance for to-be-forgotten (TBF) items is decreased as compared with to-be-remembered (TBR) items (Johnson, 1994). This phenomenon is called the directed-forgetting effect. For list-cueing, directed forgetting is usually attributed to retrieval inhibition that hinders overall access to the list of items associated with the TBF cue (Geiselman & Bagheri, 1985).

For single-item-cueing, more intense rehearsal of TBR than TBF cued words is the predominant explanation for the directed-forgetting effect. Accordingly, the "selective rehearsal model" (Bjork, LaBerge, & LeGrande, 1968) assumes that the presentation of a TBR cue triggers elaborated rehearsal processes, whereas active rehearsal of an item is aborted after the presentation of a TBF cue. This leads to only shallow encoding of the TBF cued words and consequently to a worse recognition performance. The intention to encode the TBR cued word has been assumed to be mediated by the inferior prefrontal cortex, while the mediotemporal lobe (MTL) has been regarded as crucial for successful long-term memory encoding (Davachi, Mitchell, & Wagner, 2003; Reber et al., 2002).

If the directed-forgetting effect is solely based on a less elaborated rehearsal following the TBF cue, forgetting would be a passive process, caused by fading of memory traces. In addition, forgetting might be attained by active inhibition processes. In the directed forgetting condition, rehearsal might be actively aborted or even memory formation actively suppressed. Consistent with the "active-suppression model" (Zacks, Radvansky, & Hasher, 1996), a recent fMRI study indicated that inhibition during directed forgetting is mediated by medial and superior frontal areas (Wylie, Foxe, & Taylor, 2008). The view of frontal inhibition has also been supported by an event-related potential (ERP) study, where TBF cues elicited enhanced positive activity at frontal and prefrontal areas (Paz-Caballero, Menor, & Jimenez, 2004).

If the frontal cortex directly inhibits memory encoding in the MTL, activation in the MTL should be decreased. This assumption is supported by an fMRI study using the think/no think paradigm,

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where the control of unwanted memories was associated with increased dorsolateral prefrontal activation and reduced hippocampal activation (Anderson et al., 2004).

In addition to the frontal cortex, substructures of the MTL themselves might be part of the active suppression system. For instance, it has been proposed that the rhinal cortex actively inhibits information transmission between the neocortex and the hippocampus (de Curtis & Pare, 2004).

Summing up, directed-forgetting effects in single-item-cueing are usually explained by two models: selective rehearsal of TBR cued words or encoding suppression of TBF cued words. While selective rehearsal is without much controversy, it is still an open issue whether an active suppression of MTL structures takes place. The aim of the present study was to clarify the role of the MTL (hippocampus and rhinal cortex) in directed forgetting and to search for evidence for or against the active-suppression model. Therefore, we recorded ERPs from intracranial electrodes implanted in the MTL of epilepsy patients in the course of their presurgical evaluation, since in addition to an excellent temporal resolution, intracranial recordings offer the rare opportunity to measure neural activity directly within MTL structures.

We presented single words that were either followed by a TBR or a TBF cue. The recognition performance in a subsequent recognition test was taken into account as an indicator for the success of the instruction during this procedure. Thus, we differentiated TBR and TBF cues of words which were subsequently remembered or subsequently forgotten.

For the two models of directed forgetting, we predicted different ERP patterns in response to TBF and TBR cues (see Table 1): The selective rehearsal model explains the better encoding of TBR cued words with a more elaborated rehearsal of these words, as compared to TBF words. As consequence of a more elaborated rehearsal, we expected larger mediotemporal ERP amplitudes in response to TBR than to TBF cues. Since a more elaborated rehearsal of words usually leads to a more successful encoding, we further predicted on basis of this model that TBR cues of subsequently recognized words would result in larger ERP amplitudes than TBR cues of subsequently forgotten words (Table 1, 1st line).

In contrast to this model, the active-suppression model assumes that TBR cued words are better remembered because the encoding of TBF words is actively inhibited. This active suppression would be triggered by TBF cues but not by TBR cues. In case that the memory encoding in the MTL structures is suppressed by second brain structures, we predicted to observe decreased mediotemporal ERP amplitudes to TBF cues. Furthermore, ERP amplitudes were expected to be smallest in response to TBF cues of subsequently forgotten words, i.e. for successful suppression (Table 1, 2nd line).

In case that MTL structures themselves actively suppress memory formation, a converse pattern was predicted: The mediotemporal ERP amplitudes to TBF cues were expected to be larger than in response to TBR cues and largest to TBF cues of subsequently forgotten words (Table 1, 3rd line).

However, the two models do not exclude each other. Active rehearsal and memory suppression might take place simultaneously. In that case, the effects shown in Table 1 would both be present. But still, differences in the subsequent memory effects (cues belonging to words later recognized vs. not recognized) would give evidence for the underlying process.

The effects of learning are usually studied by comparison of ERPs elicited by items presented before (old items) and ERPs elicited by newly presented items. The difference between both is called old–new effect. Recently, it has been shown that in the hippocampus the old–new effect is sensitive to depth of encoding (Grunwald et al., 2003). Since both a more intense rehearsal of TBR cued words and an active suppression of the encoding of TBF cued words should lead to a deeper encoding of TBR than of TBF cued words, we expected to see larger hippocampal ERP components in response to TBR words as compared to new words and also as compared to TBF words.

2. Materials and methods

2.1. Subjects

We investigated 24 patients with pharmacoresistant temporal lobe epilepsy. Twelve patients (nine females; nine with left, three with right TLE) were included in the study. The other 12 patients were excluded because of the following reasons: seven due to their generally poor memory performance (no words freely recalled or less than 30 of a total of 200 words recognized). Three patients declared after the testing that they had paid no attention to the cue and one patient erroneously assumed that the cue would forego the memory item. Finally, data of one patient had to be excluded due to a technical failure during the recordings.

The age of included patients ranged from 28 to 56 years (mean age = 43 years) and the duration of their epilepsy from 2 to 28 years (mean epilepsy duration = 13 years). At the time of the recordings, all patients received anticonvulsive medication with plasma levels within the therapeutic range. Participants had normal or corrected-to-normal vision and were right-handed. MRI scans or post-operative histological examinations demonstrated hippocampal sclerosis in eight patients (three with additional temporopolar blurring of the gray–white matter junction; one with bilateral hippocampal sclerosis), temporopolar blurring of the gray–white matter junction without hippocampal sclerosis in one

Table 1
Overview of ERP effects in the mediotemporal lobe (MTL) predicted by the selective rehearsal and active-suppression model.

Models	TBR-R	TBR-F	TBF-R	TBF-F
Selective rehearsal model	↑↑	↑	∅	∅
Active-suppression model				
Encoding related MTL parts are suppressed by other structures	∅	∅	↓	↓↓
Other MTL parts are themselves active suppressors	∅	∅	↑	↑↑

TBR-R, to-be-remembered cue, word subsequently remembered.
TBR-F, to-be-remembered cue, word subsequently forgotten.
TBF-R, to-be-forgotten cue, word subsequently remembered.
TBF-F, to-be-forgotten cue, word subsequently forgotten.
∅, ERP amplitudes in the rhinal cortex/hippocampus should not be affected.
↑, ERP amplitudes in the rhinal cortex/hippocampus should be increased.
↑↑, ERP amplitudes in the rhinal cortex/hippocampus should be increased strongly.
↓, ERP amplitudes in the rhinal cortex/hippocampus should be decreased.
↓↓, ERP amplitudes in the rhinal cortex/hippocampus should be decreased strongly.

patient and no clear lesion in three patients. All but one patient underwent epilepsy surgery later on. The study was approved by the ethics committee of the University of Bonn and all patients gave written informed consent.

2.2. Directed forgetting paradigm

The study was conducted in a special unit for simultaneous video and EEG monitoring with the patient sitting in an adjustable chair and facing a computer screen approximately 80–100 cm away. Patients participated in 4–5 study blocks, each consisting of a study-phase, free recall, and recognition. In each study block, 50 individual words were presented. Each word was either followed by a green or by a red cross, which cued a word as to-be-remembered (TBR) or to-be-forgotten (TBF), respectively (see Fig. 1). After the randomized presentation of 25 TBR and 25 TBF words, the patients underwent a free recall of TBR words. The free recall was followed by a recognition test, including all words from the study-phase plus 50 new words. During the test patients had to indicate by a button press whether a word has been presented during the study-phase or not (irrespective of the cue).

Word blocks were matched according to the word frequency mean (65 per 1 million words according to the CELEX lexical database, version 2.5, Baayen, Piepenbrock, & Gulikers, 1995), as well as the word length (range: 4–7 letters). The assignment to TBR, TBF, and new words was randomized across patients.

2.3. Recordings

ERPs were recorded from multicontact depth electrodes implanted stereotactically along the longitudinal axis of the hippocampus for presurgical evaluation. Each catheter-like, 1 mm thick depth electrode contained 10 cylindrical platinum electrodes of 2.5 mm every 4 mm. In all patients, data from additional six scalp electrodes (Cz, C3, C4, Oz, T5, T6), placed according to the international 10–20 system, were collected.

Electrophysiological data were recorded with the digital EPAS system (Schwarzer, Munich, Germany) and its implemented Harmonie EEG software (Stellate, Quebec, Canada). Depth electroencephalograms were referenced to offline linked mastoids with a sampling rate of 1000 Hz. Impedance of the scalp electrodes was kept below 5 kΩ.

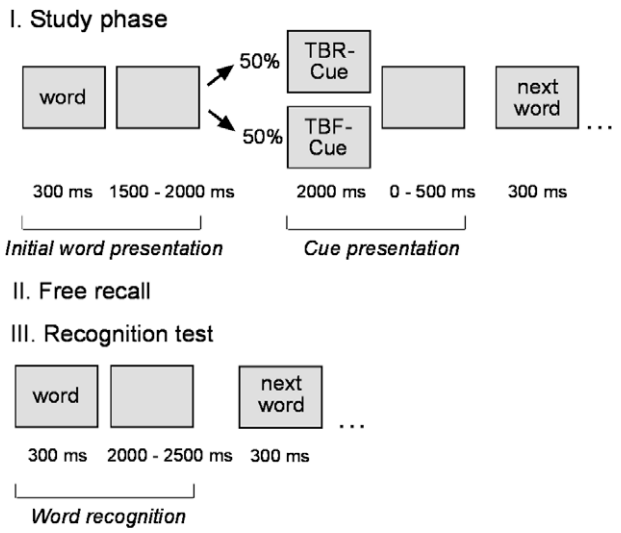

Fig. 1. Study paradigm. Fifty words were presented, each either followed by the cued instruction that this word is to-be-remembered (TBR) or to-be-forgotten (TBF). During free recall, only TBR cued words had to be listed. In the recognition part, subjects were supposed to recognize previously presented words under 50 new words irrespective of the instruction. A total of 4–5 blocks of study-phase, free recall and word recognition were conducted.

EEG segments with a duration of 2200 ms, including a 200 ms pre-stimulus period, were extracted. Data were highpass filtered at 0.1 Hz with a slope of 12 dB/octave, lowpass filtered at 12 Hz with a slope of 48 dB/octave, as well as baseline corrected with respect to the 200 ms pre-stimulus period.

An automated artifact rejection was implemented by using MATLAB 7.5 (Mathworks). Segments were rejected if any data point or step between two successive data points deviated more than four standard deviations from the mean. Thus, segments with abnormally high amplitudes as well as abrupt rises or falls were eliminated. For scalp recordings, an additional ±75 μV step threshold was applied as rejection criterion. On average, 17% of the trials were removed based on these criteria.

In order to analyze subsequent memory effects during word encoding, averages were calculated for epochs associated with words, which were later successfully recognized (“W-R”) and words which were not recognized in the recognition test (“W-F”).

To determine the influence of cueing on the processing of the stimulus material, separate averages were calculated for TBR and TBF cues further taking into account if the associated words were subsequently successfully recognized (“TBR-R”; “TBF-R”) or forgotten (“TBR-F”; “TBF-F”). For the analysis of old–new effects during the recognition test, segments were averaged for correctly identified new words (“new words”), correctly identified TBR and TBF words (“TBR hits”, “TBF hits”) as well as TBR and TBF words erroneously identified as “new words” (“TBR misses”, “TBF misses”).

2.4. Electrode selection

For each patient, one electrode in the rhinal cortex, one anterior hippocampal, and one posterior hippocampal electrode was selected. Usually, the first three of the ten electrodes in the array were located in the rhinal cortex, the next one or two on the border to the amygdala, and up to six along the longitudinal axis of the hippocampus. For each patient, the precise placement of electrode contacts within the hippocampus was verified by axial and coronal 2 mm-sliced T2-weighted and 3 mm-sliced fluid-attenuated inversion recovery (FLAIR) MRIs, routinely acquired after electrode implantation. When possible, data from the non-focal hemisphere were analyzed. For two patients with unilateral implants (one with an extrahippocampal lesion, one with hippocampal sclerosis) as well as for one patient with bilateral hippocampal sclerosis, we included data of the focal side, after verifying that brain potentials were comparable in size and shape to those obtained from the non-focal sides of bilaterally implanted patients.

Word processing has been shown to be associated with a rhinal negativity (AMTL-N400) and a later hippocampal positivity (MTL-P600; Grunwald et al., 2003). The rhinal cortex (“RC”) electrode was defined as the rhinal electrode with the largest AMTL-N400 response to new words between 300 and 600 ms (Grunwald et al., 2003). In the hippocampus, the most anterior (“ant HC”) as well as most posterior (“post HC”) electrodes were selected (see Ludowig et al., 2008, Fig. 1, for the anatomical location of electrodes along the MTL). This separation was motivated by the results of two previous studies showing larger posterior hippocampal effects in a word recognition paradigm (Ludowig et al., 2008) and an oddball paradigm (Ludowig, Bien, Elger, & Rosburg, 2009). Usually, the anterior electrode was located in the hippocampal head and the posterior electrode in the medial or posterior part of the hippocampal body. In four patients, both the selected ant HC and post HC electrodes were located in the anterior hippocampal body due to the poor signal quality in the hippocampal head electrodes. In one patient, the electrode array was dislocated and therefore only

an anterior but no posterior hippocampal electrode was selectable. For scalp recordings, two patients were excluded due to the poor signal quality. Only data recorded at Cz is presented, due to the very small signals at Oz, T5 and T6 and similar effects at C3, C4 as compared to Cz.

2.5. Data analysis

Behavioral measures (reaction times and accuracy for TBR hits, TBF hits, false alarms and correctly rejected new words) were analyzed by paired *t*-tests. For all analyzed electrodes (RC, ant HC, post HC, Cz), ERP mean amplitudes were calculated for four successive time windows of 300 ms length each (300–600, 600–900, 900–1200, 1200–1500 ms) relative to the 200 ms pre-stimulus baseline. These time windows were chosen based on previous reports on different ERP effects in these time windows during word recognition (Grunwald et al., 2003; Ludowig et al., 2008). For word encoding and word recognition, mean amplitudes were submitted to paired *t*-tests for each time window and electrode position separately.

For the evaluation of subsequent memory effects during initial word encoding, ERPs of subsequently remembered vs. forgotten words were compared (W-R vs. W-F). For the analysis of effects during word recognition, paired *t*-tests were applied for old–new effects (TBR hits vs. new words, TBF hits vs. new words, TBR misses vs. new words, TBF misses vs. new words), as well as for the differences between TBR hits vs. TBF hits and TBR misses vs. TBF misses.

Since there were no presumptions concerning critical time windows during cue-presentation, we selected the same time windows for the analysis of cue effects, but applied a repeated-measures ANOVA with CUE (TBR vs. TBF), subsequent memory (SUBSM: R vs. F) and TIME (300–600, 600–900, 900–1200, 1200–1500 ms) as within-subjects factors. A Greenhouse–Geisser correction was applied when necessary, and is indicated by citation of ε-values. When significant effects were found, post hoc ANOVAs and *t*-tests for paired samples were applied.

3. Results

3.1. Behavioral data

Patients showed a clear directed-forgetting effect. They recognized significantly less TBF than TBR words (47.0 ± 22.0% and 63.9 ± 17.6%, respectively; $t_{11} = 4.77$, $p = 0.001$). The recognition of TBF words also took significantly more time than the recognition of TBR words (963 ± 174 ms vs. 904 ± 136 ms; $t_{11} = 3.36$, $p < 0.005$). False alarms (old-responses to new words) occurred significantly less frequently than hits (21.4 ± 14.8%; TBR: $t_{11} = 9.95$, $p < 0.001$; TBF: $t_{11} = 6.07$, $p < 0.001$). False alarms were associated with significantly longer reaction times than correct TBR responses (1015 ± 273 ms; $t_{11} = 2.22$, $p < 0.05$), but not than correct TBF responses ($t_{11} = 1.26$; ns).

Only 8.2 ± 4.6% of the TBR words and 0.9 ± 0.8% of the TBF words were freely recalled. Of these, almost all were subsequently recognized (89.2 ± 13.9% of the TBR and 100 ± 0% of the TBF recalled words). Note, that patients were only supposed to list TBR and not TBF cued words during free recall.

3.2. ERPs in the study-phase

3.2.1. Initial word presentation

In the rhinal cortex, a relatively small AMTL-N400 component was elicited by words (Fig. 2; peak amplitude −16.4 μV, latency 330 ms). In the anterior and posterior hippocampus, very small MTL-P600 components were observed (anterior: 8.0 μV, 500 ms; posterior: −2.7 μV, 515 ms). The paired *t*-tests indicated no subsequent memory effect at any electrode in any time window. At Cz, a P600 in response to words was recorded (peak amplitude 5.9 μV, latency 670 ms), which also showed no subsequent memory effect. The type of cue (TBR or TBF) immediately preceding or succeeding the word had no influence on the ERP elicited by this word.

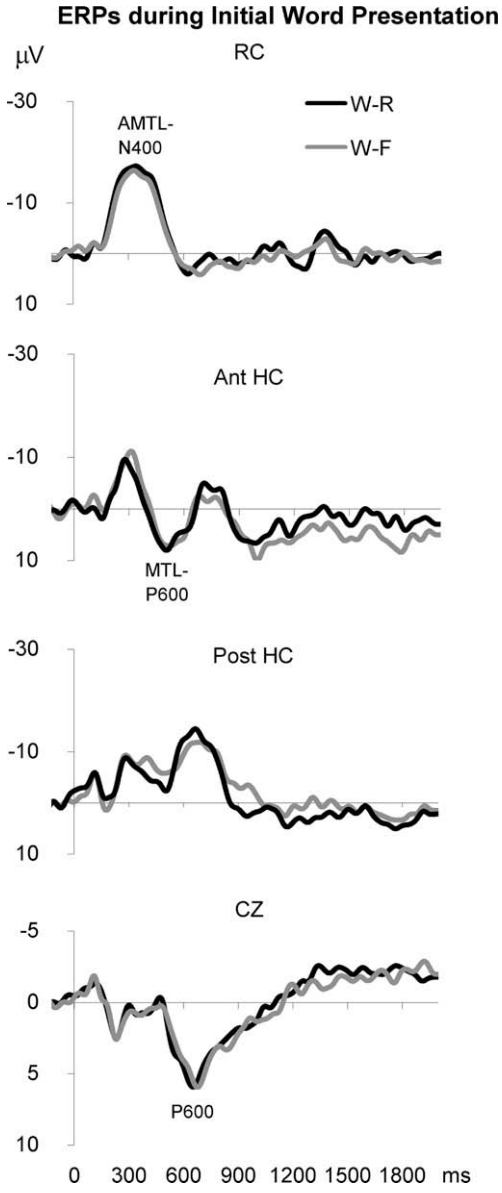

Fig. 2. ERPs during initial word encoding separated for subsequently remembered words (W-R) and subsequently forgotten words (W-F). Shown are the ERPs of the rhinal cortex electrode (RC), the anterior hippocampal electrode (Ant HC), the posterior hippocampal electrode (Post HC) as well as Cz. Negative values are plotted upwards. Statistics indicated no significant differences between subsequently remembered and forgotten words.

3.2.2. Cue-presentation

For this analysis, one female patient was excluded due to an extremely good performance, resulting in too few "forgotten" trials (only 10 trials for TBR-F) for a reliable calculation of ERPs.

In the rhinal cortex, presentation of TBR and TBF cues led to a strong negativity (latency ~250 ms), followed by a positive deflection. For the TBR instruction, this positive deflection returned to the baseline level within 200 ms, while the TBF instruction led to a longer lasting positivity (Fig. 3). This was reflected by a significant main effects of CUE over all time windows ($F_{1,10} = 13.92$, $p < 0.005$). Since we also found a significant interaction between

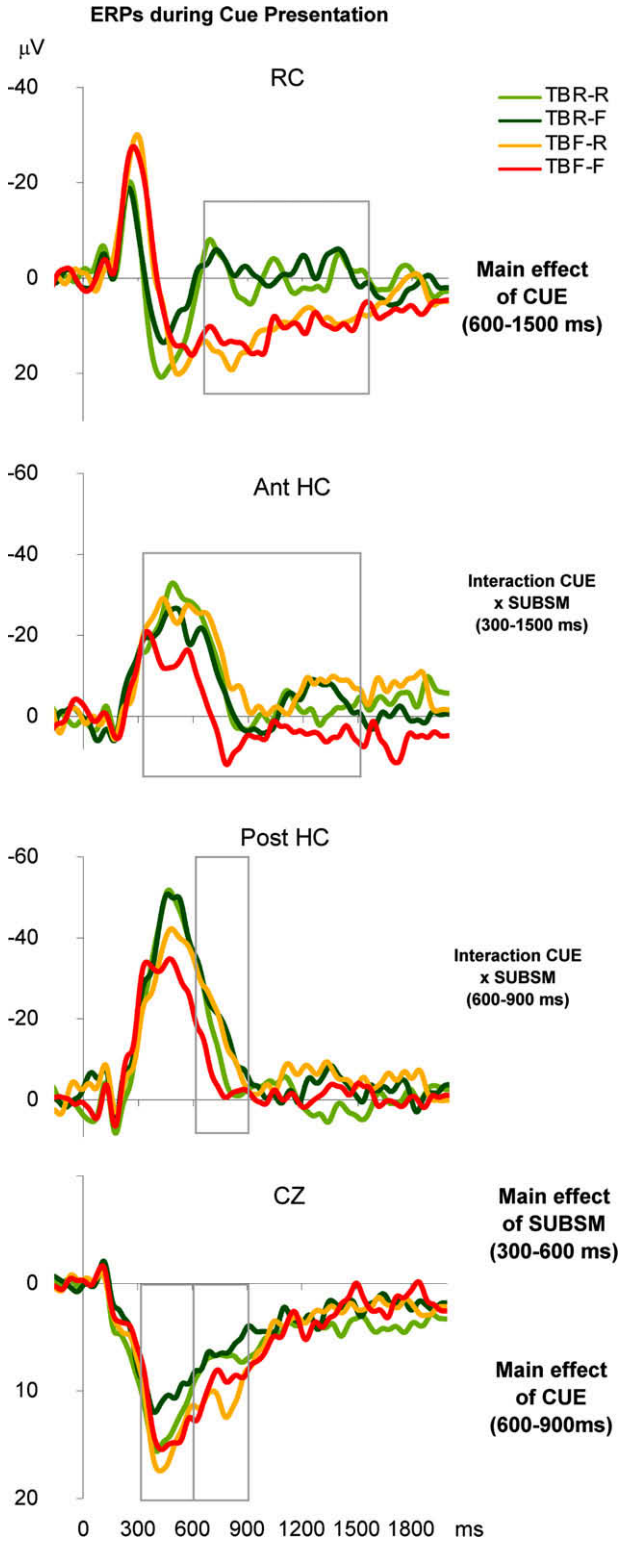

Fig. 3. ERPs in response to TBR cues and TBF cues, separated for cues belonging to subsequently remembered (-R) vs. subsequently forgotten words (-F). Negative values are plotted upwards. Shown are the ERPs of the electrodes RC, ant HC, post HC as well as Cz. Significant results of the ANOVAs concerning SUBSM or CUE effects are indicated by frames that cover the particular time window and are additionally described in the right column.

CUE and TIME ($F_{3,30} = 9.255$, $p < 0.005$; $\varepsilon = 0.541$), we analyzed the four time windows separately. This ANOVA showed that the CUE effect was focused on the three time windows between 600 and 1500 ms (600–900 ms: $F_{1,10} = 12.09$, $p < 0.01$; 900–1200 ms: $F_{1,10} = 12.09$, $p < 0.01$; 1200–1500 ms: $F_{1,10} = 17.44$, $p < 0.005$). Neither a main effect of SUBSM nor a SUBSM × CUE interaction effect was observed for the RC recordings.

In the anterior hippocampus, both kinds of cues elicited a large negativity between 200 and 900 ms. The response was smaller for TBF-F trials than for the other conditions across all time windows, as reflected by a significant interaction between CUE and SUBSM ($F_{1,10} = 7.489$, $p < 0.05$) and post hoc paired t-tests (TBF-F vs. TBF-R: $t_{10} = 2.31$, $p < 0.05$; TBF-F vs. TBR-F: $t_{10} = 2.04$, $p = 0.06$; TBF-F vs. TBR-R: $t_{10} = 2.11$, $p = 0.07$).

In the posterior hippocampus, we found a significant main effect of TIME ($F_{3,27} = 7.25$, $p < 0.05$; $\varepsilon = 0.435$) and a trend towards an interaction between CUE × SUBSM × TIME ($F_{3,27} = 3.18$, $p = 0.055$; $\varepsilon = 0.786$). Therefore, we also analyzed the time windows separately. Here, a significant interaction between CUE and SUBSM between 600 and 900 ms was shown ($F_{1,9} > 6.00$, $p < 0.05$), but post hoc paired t-tests did not reveal significant results. Note, that for one patient no data of the posterior hippocampus were available.

At the scalp (Cz electrode), a broad positive component (lasting from 200 to 1500 ms) was observed. Here, a significant effect of TIME was shown ($F_{3,24} = 11.47$, $p < 0.005$), but no interaction of CUE or SUBSM with TIME. Exploratory analyses of the separate time windows nevertheless revealed that mean amplitudes of the positive component were larger for cues of subsequently remembered than for cues of subsequently forgotten words in the early time window between 300 and 600 ms (SUBSM main effect: $F_{1,8} = 32.94$, $p < 0.001$). In the time window 600–900 ms, a significant CUE main effect was found ($F_{1,8} = 8.11$, $p < 0.05$), with larger mean amplitudes in response to TBF than TBR cues.

3.3. ERPs during word recognition

Within the rhinal cortex, word presentation in the recognition phase elicited an AMTL-N400 component (Fig. 4). Amplitudes between 300 and 600 ms were significantly more negative for correctly rejected new words than for TBR and TBF hits (TBR: $t_{11} = 3.09$, $p = 0.01$; TBF: $t_{11} = 3.29$, $p < 0.01$). The AMTL-N400 component in response to new words returned faster to baseline than in response to TBR and TBF hits. This is reflected in significantly more positive mean amplitudes for recognized TBR as compared to new words (900–1200 ms: $t_{11} = 2.69$, $p < 0.05$), as well as for TBF as compared to new words (600–900 ms: $t_{11} = 3.27$, $p < 0.01$; 900–1200 ms: $t_{11} = 3.12$, $p = 0.01$; 1200–1500 ms: $t_{11} = 2.29$, $p < 0.05$). As shown in Fig. 5, the AMTL-N400 to new words was also more pronounced than for TBF misses, while ERPs for TBR misses and new words did not differ significantly (300–600 ms; TBF: $t_{10} = 4.38$, $p = 0.001$; TBR: $t_{10} = 1.19$, ns). Note that the patient with too less forgotten words had to be excluded in all analyses concerning TBR or TBF misses. The rhinal ERPs of TBR vs. TBF hits or TBR vs. TBF misses did not differ in any time window during recognition.

In the anterior and posterior hippocampus, a small MTL-P600 component was observed without differences between conditions. In the posterior hippocampus, the ERP was followed by a late negative component (LNC). The LNC was larger for TBR hits than for TBF hits (600–900 ms: $t_{10} = 3.15$, $p = 0.01$; 1200–1500 ms: $t_{10} = 2.37$, $p < 0.05$), and also larger for TBR hits than for new words (1200–1500 ms: $t_{10} = 3.31$, $p < 0.01$). The LNC of TBR misses did not differ from the LNC of new words. Concerning hippocampal TBF old–new effects, no differences between TBF hits vs. correctly classified new words ($t_{10} < 1.10$, ns), or TBF misses vs. new words ($t_9 < 1.58$, ns) were detected.

At Cz, a P600 component was observed, which was significantly larger for correctly recognized TBR than for the new words in the early time window between 300 and 600 ms ($t_9 = 5.40$, $p < 0.001$). TBR misses did not differ from new words.

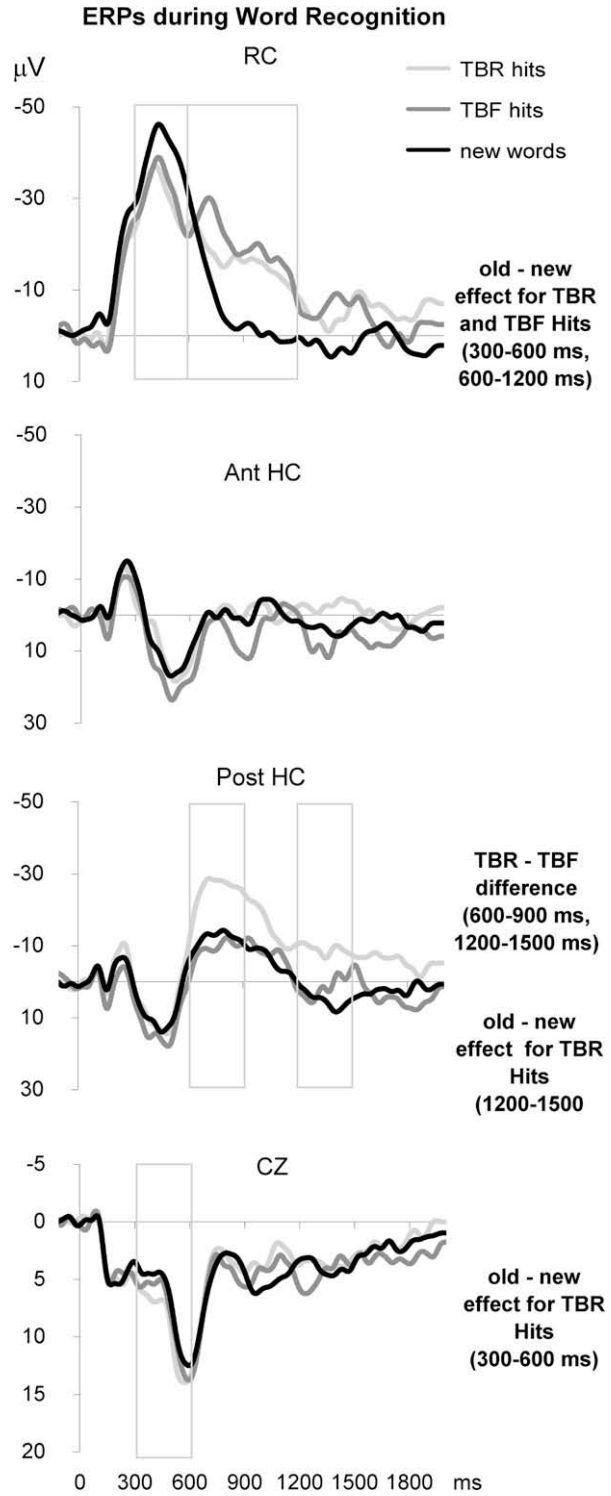

Fig. 4. ERPs during word recognition separated for TBR hits, TBF hits and new words. Shown are the ERPs of the electrodes RC, ant HC, post HC as well as Cz. Negative values are plotted upwards. Significant results of the paired *t*-tests are indicated by frames that cover the particular time window and are additionally described in the right column.

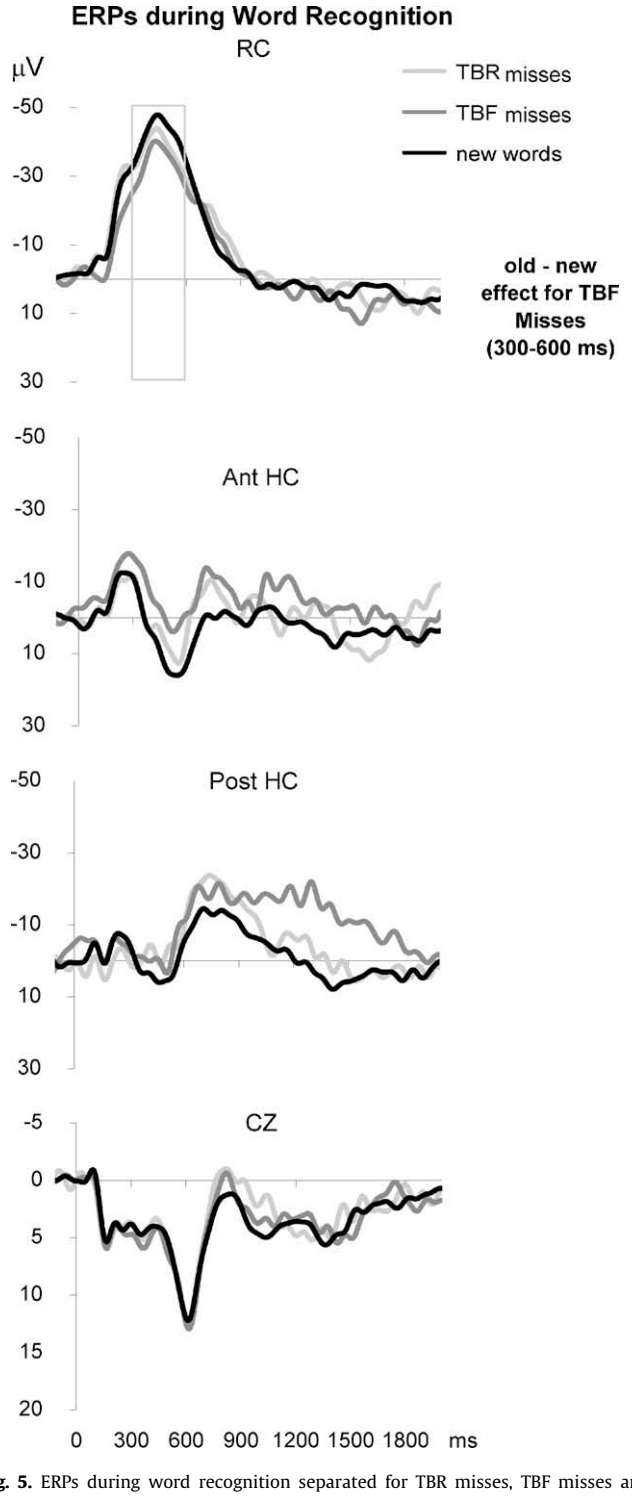

Fig. 5. ERPs during word recognition separated for TBR misses, TBF misses and correctly rejected new words. Shown are the ERPs of the electrodes RC, ant HC, post HC as well as Cz. Negative values are plotted upwards. Significant results of the paired *t*-tests are indicated by frames that cover the particular time window and are additionally described in the right column.

4. Discussion

The current study was conducted to clarify the role of selective rehearsal and active suppression as sources of the directed-forgetting effect by intracranial recordings in mediotemporal lobe structures. Significant differences in the recognition of TBF and TBR words speak in favor of an adequate task-performance of the patients and the success of the experimental manipulation.

In the following, we will discuss our findings in the chronology of the experiment (initial word presentation, cue encoding, and word recognition).

4.1. Initial word presentation

Each trial started with the presentation of a word item. Based on previous studies (Smith, Stapleton, & Halgren, 1986), we expected an AMTL-N400 as well as an MTL-P600 in response to these words. Since both components were shown to increase with successful memory formation (Fernandez et al., 1999), the possibility of subsequent memory effects, already prior to cue-presentation, had to be considered.

We did not find any subsequent memory effects in the MTL or at Cz. Thus, there was no evidence for differences in encoding depth at the time of initial word presentation and subsequent recognition was probably not determined prior to the cue-presentation.

In general, amplitudes of the AMTL-N400 as well as the MTL-P600 were rather small. The MTL might be involved only to a small extent in initial word encoding, because prior to cue instruction, deep word encoding is not yet demanded. At scalp electrodes, words elicited a P600 of comparable size to those that were observed in two previous directed forgetting ERP studies (Paz-Caballero et al., 2004; Ullsperger, 2000).

4.2. Cue encoding

In the rhinal cortex, TBF cues elicited a prolonged positivity, as compared to TBR cues. In the hippocampus, TBF cues that caused subsequent forgetting were associated with a decreased negativity. These results are discussed with respect to the selective rehearsal and active-suppression model.

4.2.1. Selective rehearsal model

The selective rehearsal model explains the directed-forgetting effect with elaborated rehearsal selectively for the TBR cued words, while TBF cues are assumed to cause abortion of rehearsal. Electrophysiologically, selective rehearsal should result in larger ERPs in response to TBR cues as compared to TBF cues (see Table 1). Since more elaborated rehearsal of words usually leads to a better encoding, one would further predict larger subsequent memory ERP effects for the TBR than the TBF cue.

Analyses of the ERPs in our study provided no evidence for a more elaborated rehearsal following TBR as compared to TBF cues in the MTL. In the hippocampus, ERPs did not differ between TBR and TBF cues and no subsequent memory effect for the TBR cues was observed. In the rhinal cortex we even found a larger positivity for TBF than TBR cues and again no significant subsequent memory effect.

Since two previous directed forgetting studies that used fMRI did not find a larger activity for TBR than TBF cues in the MTL as well (Reber et al., 2002; Wylie et al., 2008), one could assume that the MTL is not involved in selective rehearsal following TBR cues. Theoretically, also the TBF cue might be followed by rehearsal processes, however not by rehearsal of the TBF word itself, but of previously presented TBR words. Therefore, it might be possible that the MTL is engaged in word rehearsal, but that the MTL processes following TBR and TBF cues are too similar to be separated by ERPs (or fMRI).

We also did not find a subsequent memory effect for the TBR cues, although the MTL has reliably been shown to be sensitive to encoding success (Davachi et al., 2003; Reber et al., 2002; Wylie et al., 2008). One of the fMRI directed forgetting studies showed subsequent memory effects only in the left parahippocampal cortex as well as left posterior hippocampus (Reber et al., 2002). Therefore, it can be speculated that we missed the effect, since our sample in this analysis comprised the data of nine right and only two left hemispheric electrodes.

At Cz, a broad positive component (presumably a scalp-P300 component) was observed with a tendency towards larger mean amplitudes between 300 and 600 ms for cues of subsequently remembered than forgotten words independent of cue type. This is in line with the Ullsperger (2000) study, who also found a larger P300 for subsequently remembered words.

4.2.2. Active-suppression model

Alternatively to the selective rehearsal model which attributes forgetting to passive fading of memory traces, forgetting might also be obtained by an active suppression process. It has been assumed that frontal inhibition prevents words from being committed to memory (Wylie et al., 2008). This implies that memory-related MTL areas express decreased activity in response to TBF cues as a consequence of frontal suppression. Such a decrease should be larger for successful than for unsuccessful suppression.

In addition to frontal structures, there might be structures within the MTL that act as active suppressors. For these, the active-suppression model predicts larger ERPs for TBF than TBR cues and larger ERPs associated with successful than with unsuccessful inhibition (see Table 1). Our study revealed indication for both mechanisms of active suppression.

In the hippocampus, presentation of the cue elicited a negative component with a peak around 500 ms. Since polarity and latency were consistent with the MTL-P300 reliably found in the hippocampus in oddball-paradigms (Halgren et al., 1995), we consider the positivity in response to cues as an MTL-P300 component. ERP analyses indicated an interaction between CUE and SUBSM for anterior and posterior hippocampal electrodes in the MTL-P300 time window. The basis of this interaction is probably a smaller MTL-P300 for TBF-F as compared to the other conditions. Note that we only found a significant post hoc difference between TBF-F and TBF-R in the anterior hippocampus. This might be explained by the smaller amount of posterior than anterior hippocampal electrodes.

The hippocampus is regarded as one generator (together with a larger assembly of temporal/parietal brain areas) of the scalp P3b (Bledowski, 2004; Halgren et al., 1995). While the scalp P3b has been generally associated with context updating (Donchin & Coles, 1988), the hippocampal P300 was also suggested to be more closely related to memory processes (Halgren, Marinkovic, & Chauvel, 1998; for review Polich, 2007). Thus, the diminished MTL-P300 confined to the TBF-F condition might reflect decreased memory engagement. A reduced hippocampal activity following the intentional attempt not to engage in word recollection has also been shown in the think/no think study of Anderson et al. (2004). Since TBR and TBF did not differ, there was no indication for a general hippocampal suppression caused by the instruction to forget. Reduction of hippocampal activity by TBF cues was limited to those items that were later actually forgotten. Our results suggest that the successfully realized intention to forget word items leads to suppressed hippocampal memory encoding.

In addition to the hippocampal data, the analyses of rhinal ERPs support the active-suppression model. For rhinal ERPs, we observed a significantly larger activity for TBF than TBR cues, while no subsequent memory effect was shown for either cue condition. The rhinal cortex is an important interface between the neocortex and the hippocampus. Ablating the rhinal cortex in monkeys has for example equivalent effects to that of removing the entire hippocampus (Murray & Mishkin, 1998). It is well documented that neocortical stimulation often activates the perirhinal cortex but that this activation is not propagated to the entorhinal cortex or hippocampus (Biella, Uva, & de curtis, 2002). The entorhinal cortex integrates but also rejects input and thus operates as a sensory filter (Lavenex & Amaral, 2000).

It can be speculated that parts of the frontal cortex, which are engaged in active forgetting, project to the perirhinal cortex, which then fires in such a pattern that activity in the entorhinal

cortex and hippocampus is inhibited. The long lasting component, which we observed in response to the TBF cue, might then reflect this perirhinal activity. Since no interaction with subsequent memory was shown, the (peri-)rhinal cortex might mediate the intention to forget, while the success of this intention depends on other structures such as the hippocampus. In a previous study, also a larger general activity for TBF than TBR cues was observed in the parahippocampal gyrus (Wylie et al., 2008), which might be based on similar mechanisms as the rhinal cortex activity found in our study.

At Cz, findings were similar to those in the rhinal cortex. We observed a tendency towards larger P300 in response to TBF than TBR cues, which might also reflect inhibition processes caused by the instruction to forget. These findings are in line with ERP Go-NoGo studies, where a larger and more anterior P300 has been observed for NoGo than for Go trials and interpreted in terms of inhibition (Eimer, 1993; Falkenstein, Hoormann, & Hohnsbein, 1999). However, this finding of an increased P300 to TBF cues is in contrast to previous directed forgetting ERP studies showing a larger P300 to TBR cues (Paller, 1990; Paz-Caballero et al., 2004; Ullsperger, Mecklinger, & Muller, 2000). In these previous studies, the study and recognition phase were only two-staged and thus more TBR words had to be rehearsed in the study block. It can be speculated that this higher memory load led to a strategy of paying special attention towards TBR words, which in turn might have resulted in large P300 effects for TBR cues.

In order to make the task more intuitive, we did not randomize the color of the cue (green[1] for TBR and red for TBF turned out to be best remembered in piloting trials). Although we consider it as likely that the increased rhinal cortex activity to TBF cues has a function in MTL memory processes, we cannot exclude the possibility that it might also reflect perceptual effects. If the rhinal cortex is directly integrated in frontal inhibition networks, then future studies should find strong connectivity between the frontal cortex and rhinal cortex during directed forgetting. In addition, coherence analyses between rhinal cortex and hippocampus might help to disentangle the inhibition networks.

4.3. Word recognition

In the subsequent recognition test, all words from the study-phase plus new words were presented. As already mentioned, an AMTL-N400 component as well as an MTL-P600 component is usually observed following word presentation. Another ERP component that is associated with word processing and especially word recognition is the hippocampal late negative component (MTL-LNC). While the AMTL-N400 is larger for new than repeated old words, the MTL-P600 and MTL-LNC components are larger for correctly recognized old than new words (Grunwald et al., 2003; Smith et al., 1986). Since these old–new effects can be used to explore differences in encoding depth, we compared old–new effects for correctly recognized TBR and TBF trials.

Both of the previously discussed models, selective rehearsal and active suppression predict deeper encoding of TBR than TBF cued words. In a previous intracranial study by Grunwald et al. (2003), ERPs in the hippocampus were only increased in response to explicitly memorized words, while rhinal ERPs were also sensitive to word repetition even following implicit encoding by a categorization task. Therefore, a larger old–new effect for TBR than TBF hits can be expected in the hippocampus, while ERPs in the rhinal cortex might express equally pronounced old–new effects for TBR and TBF hits. Both hypotheses were confirmed by our data.

In the hippocampus, significant effects were only found in the posterior region. This is in line with our previous study, where the posterior hippocampus was more involved in memory recognition than the anterior hippocampus (Ludowig et al., 2008). In the posterior hippocampus, an MTL-LNC component was observed for all conditions, but a significant MTL-LNC old–new effect was exclusively found for the TBR and not for the TBF hits. In addition to the ERP findings, the recognition of TBR words was also significantly faster than the recognition of TBF words. Both findings can be interpreted as evidence for a deeper encoding of TBR than TBF cued words.

In the rhinal cortex, word presentation elicited an AMTL-N400 component, which was significantly larger for new words than for TBR as well as the TBF hits, while there was no difference between the TBR and TBF hits. A larger rhinal activity for new than for the old stimuli, reflecting rhinal repetition suppression effects, is a consistently demonstrated finding not only in intracranial studies (Smith et al., 1986), but also in fMRI (Gonsalves, Kahn, Curran, Norman, & Wagner, 2005) as well as single-unit studies (Brown & Aggleton, 2001). The rhinal cortex is also assumed to be less sensitive to recollection related processes (such as the depth or "consciousness" of encoding) and more closely related to recognition based on familiarity (Grunwald et al., 2003; Ranganath et al., 2004). Since only the rhinal cortex dissociated new words and TBF hits it can be assumed that the recognition of TBF cued words is mediated by familiarity processes. In line with these previous findings, awareness was not a prerequisite for a rhinal old–new effect in our study. New words differed from old words even when these old words were considered as new. Statistically, only the TBF misses differed significantly from correctly rejected new words, but this might be explained by the larger amount of TBF than TBR misses.

At Cz, a larger P600 old–new effect for TBR than TBF hits was found. This is in line with the study by Ullsperger et al. (2000), where the authors did not only observe a larger TBR than TBF old–new effect, but also showed that deeply encoded words resulted in a larger P600 old–new effect than shallowly encoded words. Thus, the scalp P600 depends on encoding depth and a larger scalp P600 old–new effect for TBR than TBF hits gives further evidence for a deeper encoding of TBR cued words.

In addition to the selective rehearsal and active-suppression models, which explain directed forgetting by differential encoding of TBR and TBF cued words, the model of "retrieval inhibition" has been proposed. This model implies that inhibition is not only active during encoding but also during retrieval (Geiselman & Bagheri, 1985; Ullsperger et al., 2000). Such a process, impeding the recognition of TBF cued words, has been shown to result in larger frontal old–new effects for TBF than TBR hits, reflecting the effort of overcoming the inhibition (Ullsperger et al., 2000). In the mediotemporal lobe or at Cz we did not find differences between TBF hits and new words. On the other hand, it might be more likely that in the MTL, retrieval inhibition is reflected in larger old–new effects for TBF than TBR misses, reflecting active inhibition itself. Interestingly, posterior hippocampal electrodes showed some tendency for a larger old–new effect for TBF misses than TBR misses, but an extensive discussion of this finding is not justified, since the effect did not reach significance.

4.4. Limitations of the study

The interpretation of results of intracranial studies in epilepsy patients is always constrained by the possibility that cortical processes are affected by the disease. Memory impairments are a typical characteristic of patients with temporal lobe epilepsy (Gleissner, Helmstaedter, Schramm, & Elger, 2002). Furthermore, polytherapy of anticonvulsive medication was shown to be associ-

[1] For interpretation of color in Fig. 3, the reader is referred to the web version of this article.

ated with (additional) memory impairments (Ortinski & Meador, 2004). As a matter of fact, poor memory performance was the main reason for excluding patients from this study. However, those patients who were included showed a similar performance level in word recognition as healthy subjects in previous directed forgetting studies (Reber et al., 2002). Furthermore, the scalp ERPs of these patients were comparable in size to previous studies on healthy subjects (Paz-Caballero et al., 2004).

Still, the onset of observed ERP effects and their strength might have been affected by disease and medication, as well as by other factors like the age of epilepsy onset or the number of years with continuing seizures. Given the small sample size and the number of potentially confounding factors, it is impossible to assess the impact of these patient characteristics. However, the current study compared the ERPs for TBF and TBR cues within-subjects. Findings in such a within-subject design are much less confounded by sample characteristics than findings in between-subjects designs.

More problematic is that most of our subjects had left-sided TLE. In patients with hippocampal sclerosis, the ERP amplitudes from the ipsilateral side are often strongly attenuated (Grunwald, Lehnertz, Heinze, Helmstaedter, & Elger, 1998; Grunwald et al., 1999). As consequence, the analyzed ERPs were mainly derived from the right MTL. Due to the small number of subjects, we could not statistically compare the two hemispheres and, therefore, cannot rule out, that the observed effects differ between hemispheres. Due to the special role of the left MTL in verbal memory, it might be speculated that directed-forgetting effects could be larger in this hemisphere.

Finally, the decision to implant electrodes and their placement are made solely on clinical grounds. As consequence, some cortical areas which would be of great interest in the context of directed forgetting could not be investigated in the current study. This further means that we currently cannot make any conclusions about the interplay of different brain regions during directed forgetting.

These criticisms notwithstanding, intracranial recordings offer the unique possibility to assess cognitive functions with high anatomical and temporal precision (Münte et al., 2008). The method is superior to functional imaging methods, since intracranial recordings directly reflect neural activity, and their temporal resolution in the order of milliseconds is high enough to distinguish different neural activity patterns. Further only intracranial electrodes allow the recording of electric activity from deep brain structures like the MTL which cannot be assessed with surface EEG. Especially the opportunity to examine both MTL and scalp activity provides an advance over previous directed forgetting studies.

4.5. Conclusion

The present investigation used ERPs from MTL structures to bear upon the controversy, whether directed forgetting might be better explained by selective rehearsal of TBR cued words (Bjork et al., 1968) or by active suppression of TBF cued words during encoding (Zacks et al., 1996).

Although selective rehearsal is the dominant explanation for the directed-forgetting effect, we did not find indication for more intense rehearsal following TBR than TBF cues in the MTL. Concerning the active-suppression model, our findings support the view that memory encoding in the hippocampus can actively be inhibited in directed forgetting. Following the TBF cue, MTL-P300 components were reduced exclusively to those cues that actually resulted in later forgetting. For the accomplishment of active suppression, frontal processes have been assumed to be crucial (Wylie et al., 2008). Our study revealed additional indication of an active involvement of the rhinal cortex in suppression, as reflected by a prolonged positivity following the TBF cue. The rhinal cortex is regarded as an essential link between neocortex and hippocampus that serves as a filter mechanism (de Curtis & Pare, 2004). Thus, it can be speculated that the frontal cortex suppresses hippocampal encoding via the rhinal cortex.

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