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Untersuchungen zum Gedächtnis – Intrakranielle Ableitungen im menschlichen Temporallappen

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Zusammenfassung

Das deklarative Gedächtnis ermöglicht die Erinnerung an vergangene Erlebnisse und an gelernte Fakten. Im Gehirn ist diese Funktion eng an den medialen Temporallappen gebunden.

In der vorgestellten Arbeit wurden Gedächtnisprozesse mit Hilfe intrakranieller Ableitungen bei Patienten mit unilateralen Temporallappenepilepsien untersucht. Diesen Patienten wurden im Rahmen der prächirurgischen Diagnostik Elektroden implantiert, die entlang des rhinalen Kortex und der Längsachse des Hippokampus lokalisiert waren. Im Rahmen der Arbeit sollten Zielreizentdeckung, erfolgreiche Gedächtnisenkodierung und Abruf sowie erfolgreiches Vergessen von Informationen untersucht werden.

In einem visuellen Oddball-Paradigma wurden seltene Zielreize unter häufigen Standardreizen präsentiert. Sobald ein Zielreiz erschien, sollte der Proband eine Taste betätigen. Die Zielreizentdeckung wurde von einer großen Negativierung begleitet, die vom anterioren zum posterioren Hippokampuskörper linear an Größe zunahm. Im rhinalen Kortex lösten Zielreize und Standardreize ein negatives ereigniskorreliertes Potential (EKP) aus, welches eine kürzere Latenz als das hippokampale EKP zeigte.

Im Rahmen eines kontinuierlichen Wortwiederholungsparadigmas sollten die Probanden entscheiden, ob ein Wort zum ersten Mal präsentiert wurde, oder ob es sich um eine Wiederholung handelte. EKP Effekte, die in früheren Studien mit der erfolgreichen Gedächtniseinspeicherung und Wiedererkennung assoziiert wurden, waren größer im posterioren als im anterioren Hippokampuskörper. Nur im Hippokampuskopf zeigte sich eine größere Aktivierung auf neue als auf alte Wörter. Dies spricht für eine Rolle des anterioren Hippokampus bei der Erkennung von neuen Reizen.

Prädiktoren für die erfolgreiche Wortenkodierung im kontinuierlichen Wortwiederholungsparadigma wurden zusätzlich mit Hilfe von Frequenzanalysen untersucht. Hier zeigte sich, dass eine Kombination aus rhinaler und hippokampaler Inter-Trial-Phasenkopplung in verschiedenen Frequenzbändern, sowie eine rhinal-hippokampale Phasensynchronisation im Gamma-Frequenzbereich am zuverlässigsten den Erfolg der Enkodierung vorhersagten. Die präzise zeitliche Abfolge mediotemporaler Prozesse scheint daher kritisch für die erfolgreiche Gedächtniseinspeicherung zu sein.

Im Rahmen eines Paradigmas zum Instruierten Vergessen sollte untersucht werden, ob Vergessen lediglich das Resultat von zu schwachen Gedächtnisspuren ist, oder ob späteres Vergessen auch durch eine aktive Hemmung der Gedächtnisenkodierung verursacht werden könnte. Die Instruktion, ein Wort zu vergessen, löste im rhinalen Kortex eine lang anhaltende Negativierung aus. Falls das dazugehörige Wort später tatsächlich nicht wiedererkannt wurde, war die Instruktion zudem mit einer reduzierten hippokampalen Aktivierung assoziiert. Dies kann als Hinweis für eine Unterdrückung der hippokampalen Gedächtniseinspeicherung interpretiert werden. Der rhinale Kortex scheint an dieser Unterdrückung aktiv beteiligt zu sein.

Elektrophysiologische Unterschiede zwischen rhinalem Kortex und Hippokampus haben sich demnach in allen Studien gezeigt. Im Vergleich zum Hippokampus reagiert der rhinale Kortex mit kürzerer Latenz und geringerer Selektivität auf die Reize. Dies steht in Einklang mit der Annahme eines hierarchisch organisierten mediotemporalen Gedächtnissystems.

Abstract

Declarative memory enables the recollection of past events and facts. Anatomically, this memory function is strongly linked to the medial temporal lobe. In the present study, memory processes were examined via intracranial recordings in patients with unilateral temporal lobe epilepsy. Multicontact depth electrodes were implanted along the rhinal cortex and longitudinal axis of the hippocampus as part of the presurgical evaluation. The aim of the study was to evaluate differences between the rhinal cortex and hippocampus in target detection, successful encoding and retrieval, as well as successful forgetting.

In a visual oddball paradigm, rare target stimuli and frequent standard stimuli were presented. Subjects had to respond to the target stimuli by pressing a button. Target detection resulted in a large hippocampal negativity, which increased linearly from anterior to posterior hippocampal body. In the rhinal cortex, target and standard stimuli elicited an early negativity.

In a continuous word recognition paradigm, subjects had to indicate whether words were new or already previously presented. ERP effects, previously associated with successful encoding and retrieval, were larger in the posterior than anterior hippocampal body. These findings suggest a predominant posterior hippocampal involvement in both verbal encoding and retrieval. Additionally, only the hippocampal head showed a larger response to new than old stimuli, indicating a role of this region in novelty detection.

Successful word encoding in the continuous word recognition paradigm was additionally evaluated by frequency analyses. A combination of early rhinal and hippocampal inter-trial phase-locking in different frequency ranges and rhinal-hippocampal gamma-synchronisation turned out to be the best predictors of subsequent memory. This result implies that the precise chronology of early mediotemporal processes is crucial for memory encoding.

In a directed forgetting paradigm, we investigated whether forgetting is merely the result of weak memory traces or whether it can also be caused by active suppression of memory encoding. The instruction to forget a previously presented word elicited a prolonged rhinal positivity, and in case of subsequent forgetting, it was further associated with a decreased hippocampal activity. These findings support the view that memory encoding in the hippocampus is inhibited by the instruction to forget and that the rhinal cortex is actively involved in this suppression.

All studies showed differences in electrophysiological responses between the rhinal cortex and the hippocampus. As compared to the hippocampus, the rhinal cortex responded with shorter latency and smaller selectivity to the stimuli. This is in line with hierarchical memory processing within the mediotemporal lobe.

1 Einleitung

1.1 Allgemeine Einführung

Was man vergisst, hat man im Grunde nicht erlebt.
Ernst R. Hauschka

Die Erinnerung an persönlich erlebte Episoden und der Abruf erlernter Fakten sind wichtige Gedächtnisfunktionen, die unter dem Begriff „deklaratives Gedächtnis“ zusammengefasst werden. Spätestens seit der bekannten Fallstudie über den Patienten H.M. weiß man, dass die hippokampale Region im medialen Temporallappen (MTL) entscheidend an der deklarativen Gedächtnisverarbeitung beteiligt ist. Bei H.M. wurde zur Behandlung einer Epilepsie beidseitig der Hippokampus sowie angrenzende Gebiete entfernt, was dazu führte, dass er keine neuen Informationen mehr einspeichern und abrufen konnte (Scoville & Milner, 1957). Andere sensorische, motorische und kognitive Fähigkeiten blieben erhalten. Auch die übrigen Gedächtnisfunktionen wie das prozedurale, implizite und emotionale Gedächtnis, sowie das Arbeitsgedächtnis blieben weitgehend unbeeinträchtigt.

In den letzten 30 Jahren gehörten die Pyramidalzellen des Hippokampus zu den am häufigsten untersuchten Zellen des Gehirns (Andersen *et al.*, 2007). Die Besonderheit der hippokampalen Zellen liegt in ihrer hohen synaptischen Plastizität. Diese Plastizität ist der Mechanismus, auf den Gedächtnisfunktionen basieren (Hebb, 1949). Der Hippokampus ist jedoch nur die oberste und komplexeste Stufe eines hierarchischen mediotemporalen Gedächtnissystems (Mormann *et al.*, 2008).

Nach dem Modell von Eichenbaum (2000) wird die Gedächtnisverarbeitung durch drei aufeinander folgende Phasen ermöglicht. Zunächst erzeugen neokortikale Areale spezifische, perzeptuelle Repräsentationen, die über einen kurzen Zeitraum aufrecht erhalten werden können. Diese Gedächtnisspuren ermöglichen unter anderem den perzeptuellen Vergleich zwischen aktuellen und gespeicherten Repräsentationen und unterstützen die Kurzzeitwiedererkennung. Im zweiten

Schritt erreichen die Repräsentationen die parahippokampale Region, in der funktionell unterschiedliche Informationen, z.B. aus mehreren Modalitäten, zusammenfließen. Diese kombinierten Repräsentationen bleiben im parahippokampalen Bereich über beachtliche Zeiträume und Interferenzen hinweg erhalten. Aufeinanderfolgende Informationen können miteinander verglichen werden. Dies ermöglicht eine gute Leistung in Aufgaben wie dem „delayed non-match to sample", in dem zunächst ein Reiz präsentiert wird und nach einer variablen Zeitspanne gerade dieser Reiz nicht ausgewählt werden soll. Der Hippokampus schließlich enkodiert nicht nur einzelne sensorische Reize. Er ist auf die Speicherung einer Information in einem Kontext oder auch auf die Speicherung von Sequenzen von Ereignissen spezialisiert. Der Hippokampus greift dazu auf den sensorischen Speicher der parahippokampalen Region zu und verarbeitet diese Informationen weiter. Es besteht eine ständige Wechselwirkung zwischen den beiden Regionen.

In der vorliegenden Arbeit sollen funktionelle Spezialisierungen einzelner medio-temporaler Areale bei verschiedenen Gedächtnisfunktionen mit der Methode intrakranieller EEG-Ableitungen bei Epilepsiepatienten untersucht werden. Der Fokus liegt auf Unterschieden zwischen rhinalem Kortex und Hippokampus, aber auch auf Unterschieden in Substrukturen des Hippokampus.

1.2 Anatomie

Der mediale Temporallappen setzt sich aus der hippokampalen Formation und dem parahippokampalen Gebiet zusammen. Die hippokampale Formation besteht aus dem Hippokampus, dem Gyrus dentatus und dem Subiculum. Das parahippokampale Gebiet umfasst den rhinalen Kortex (bestehend aus entorhinalem und perirhinalem Kortex), das Präsubiculum, das Parasubiculum sowie den parahippokampalen Gyrus (Witter, 2002). Der Hippokampus ist bogenförmig und wird nach posterior schmaler. Er kann in seiner Längsachse in drei verschiedene Subareale unterteilt werden: in den Hippokampuskopf, den Hippokampuskörper und den Hippokampusschwanz (siehe Abbildung 1). Die Gesamtlänge des Hippokampus beträgt zwischen 4 und 4,5 cm. Im Bereich des Hippokampuskopfes ist er etwa 1,5 bis 2 cm breit, während die Breite im Hippokampuskörper nur etwa 1cm misst (Duvernoy, 1988).

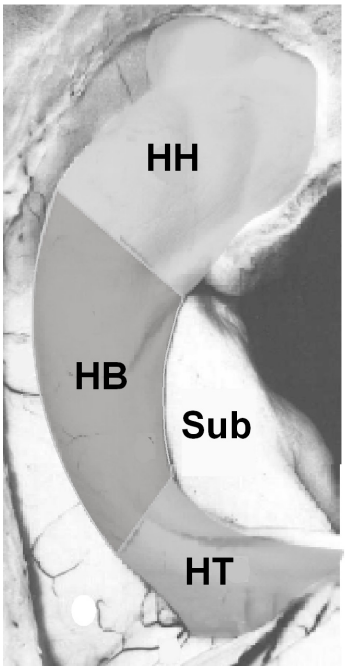

Abbildung 1: Darstellung der hippokampalen Formation. Der Hippokampus mit seiner Einteilung von anterior nach posterior in den Hippokampuskopf (HH), -körper (HB) und -schwanz (HT). Sub= Subiculum (veränderte nach Fig.2, Duvernoy, 1988).

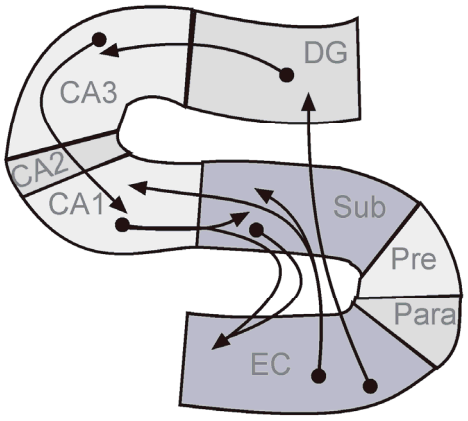

Abbildung 2: Projektionen der hippokampalen Formation und angrenzender Strukturen im parahippokampalen Gebiet. DG: Gyrus dentatus; Sub= Subiculum; Pre= Präsubiculum; Para= Parasubiculum; EC= Entorhinaler Kortex (verändert nach Fig.3.1, Amaral, 2007).

Die mediotemporalen Projektionsbahnen wurden hauptsächlich bei Ratten nachgewiesen, da die meisten neuroanatomischen Tracing-Techniken die Injektion von Tracern in das lebende Hirn voraussetzen (Amaral & Lavenex, 2007).

Der Großteil der neokortikalen Efferenzen erreicht den Hippokampus über den entorhinalen Kortex (siehe Abbildung 2). Neuronen der Schicht II im entorhinalen Kortex projizieren zum Gyrus dentatus und CA3 Feld des Hippokampus über den perforanten Pfad. Neurone der Schicht III des entorhinalen Kortex ziehen zum CA1 Feld des Hippokampus und zum Subiculum über den perforanten und alvearen Pfad. Die granulären Zellen des Gyrus dentatus wiederum projizieren über Moosfasern zum CA3 Feld des Hippokampus. Pyramidalzellen in CA3 erreichen CA1 über Schaffer-Kollaterale. Pyramidalzellen in CA1 ziehen zum Subiculum. CA1 und das Subiculum schließlich projizieren zurück zu den tiefen Schichten des entorhinalen Kortex (Amaral & Lavenex, 2007).

Die hippokampale Formation ist eine der wenigen Hirnregionen, die stark vorverarbeitete, multimodale sensorische Informationen von einer Vielzahl neokortikaler

Quellen empfängt. Informationen aus verschiedensten sensorischen Modalitäten zu integrieren, ist die besondere Fähigkeit dieser Region (Amaral & Lavenex, 2007).

1.3 Gedächtnisfunktionen im MTL

In einem funktionierenden Gedächtnissystem sollten insbesondere relevante Informationen gespeichert werden. Relevant sind häufig solche Informationen, die neu für den Organismus sind. Neben der allgemeinen Anforderung an ein Gedächtnissystem, Informationen erfolgreich zu enkodieren, ist zudem das „Nicht-Enkodieren" bzw. Vergessen irrelevanter Informationen eine wichtige Fähigkeit. Zuletzt muss die eingespeicherte Information wieder abgerufen werden können. Vorbefunde zeigen, dass der rhinale Kortex und der Hippokampus in unterschiedlicher Weise an diesen Gedächtnisfunktionen beteiligt sind. Auf einige dieser Vorbefunde soll im Folgenden eingegangen werden.

1.3.1 Die Entdeckung von seltenen, handlungsrelevanten Reizen

Eine Voraussetzung für eine effektive Gedächtnisverarbeitung ist die Entdeckung handlungsrelevanter Informationen. Ein in diesem Zusammenhang häufig angewendetes Paradigma zur basalen Zielreizentdeckung ist das Oddball-Paradigma. Hier werden seltene Zielreize (wie einzelne Buchstaben oder Symbole) unter häufigen Standardreizen präsentiert. Die Aufgabe des Probanden ist eine Reaktion (zum Beispiel ein Tastendruck) auf die seltenen Zielreize.

Eine selektive Aktivierung in Reaktion auf die Zielreize wurde in einer Vielzahl von kortikalen und subkortikalen Arealen im Parietal-, Frontal-, und Temporallappen beobachtet (Bledowski *et al.*, 2004). Halgren *et al.* unterschieden auf Basis der Befunde mehrerer Studien mit intrakraniellen ereigniskorrelierten Potentialen (EKPs) zwischen zwei funktionellen Systemen (Baudena *et al.*, 1995; Halgren *et al.*, 1995a; Halgren *et al.*, 1995b). Inferior parietale, dorsolateral präfrontale Areale und der Gyrus cinguli wurden einem System zur Ausrichtung der Aufmerksamkeit zuge-

rechnet, während Hippokampus, superior temporaler Sulcus, lateral orbitofrontaler Kortex sowie intraparietaler Sulcus einem System zur Enkodierung relevanter Ereignisse zugeordnet wurden.

Im Hippokampus war die Entdeckung der Zielreize von einer starken Negativierung begleitet, die bereits in vielen intrakraniellen Studien mit ereigniskorrelierten Potentialen (EKPs) beschrieben wurde (Brazdil *et al.*, 2001; Halgren *et al.*, 1995a; McCarthy *et al.*, 1989; Smith *et al.*, 1986). Die Negativierung konnte durch visuell, auditorisch und somatosensorisch dargebotene Zielreize ausgelöst werden (Brazdil *et al.*, 2003; McCarthy *et al.*, 1989), und auch die Auslassung erwarteter Zielreize erzeugte die Hippokampusaktivierung (McCarthy *et al.*, 1989). Sie reflektiert demnach nicht nur basale sensorische Prozesse. Die endogene Erwartung des Probanden ist entscheidend. Je mehr Zeit beispielsweise seit der letzten Präsentation des Zielreizes vergangen ist (umso wahrscheinlicher also auch ein baldiges Wiederauftreten ist), desto größer ist die Negativierung (Squires *et al.*, 1976). In einer Studie von Roman *et al.* (2005) konnte zudem gezeigt werden, dass die hippokampale Negativierung zeitlich weder direkt an den Stimulus noch an die Reaktion auf den Stimulus gebunden ist und daher möglicherweise die Integration von Stimulus- und Reaktionsverarbeitung reflektiert. Da diese Eigenschaften sehr den Eigenschaften der Oberflächen-P300 ähneln, wurde die hippokampale Negativierung „MTL-P300“ genannt (Grunwald *et al.*, 1999b).

Die funktionelle Rolle des Hippokampus bei der einfachen Zielreizerkennung ist bisher nicht eindeutig geklärt. Generell ist es bemerkenswert, dass die relativ einfach zu bewältigende Aufgabe der Entdeckung einzelner Zielreize ein sehr weit verbreitetes Netz neo- und subkortikaler Areale aktiviert. Möglicherweise werden alle auch nur potentiell nützlichen Gebiete mitaktiviert, selbst wenn die Einbindung für die eigentliche Aufgabenbewältigung nicht zwangsläufig notwendig ist (Halgren *et al.*, 1995a). Der Hippokampus könnte die Aufgabe haben, ein Muster der präsentierten Reize aufrechtzuerhalten, um einen Vergleich mit neuen Reizen zu

ermöglichen (Knight & Nakada, 1998). Es ist daher denkbar, dass weniger die Handlungsrelevanz an sich, als vielmehr die Abweichung der seltenen Zielreize von den Standardreizen entscheidend ist (Kumaran & Maguire, 2006).

In manchen Studien wurden zudem größere hippokampale Effekte anterior als posterior (Halgren *et al.*, 1995a), oder in anderen Fällen auch größere Effekte posterior als anterior beschrieben (Crottaz-Herbette *et al.*, 2005; McCarthy *et al.*, 1989). Im rhinalen Kortex wurde ebenfalls eine Aktivierung im MTL-P300 Zeitbereich gezeigt, die meistens eine positive, teilweise aber auch eine negative Polarität aufwies (Halgren *et al.*, 1995a; McCarthy *et al.*, 1989). Konsistenter wurde eine etwas frühere Negativierung gefunden, die aufgrund ihrer Ähnlichkeit zur Oberflächen-N200 „AMTL-N200" genannt wurde (Fabiani *et al.*, 2000). Während der Hippokampus nur eine ausgeprägte MTL-P300 auf die Zielreize zeigte, wurde die AMTL-N200 auch für Standardreize beschrieben (Kukleta *et al.*, 2003).

Schon bei der basalen Funktion der Reizentdeckung gibt es demnach Hinweise für Unterschiede zwischen rhinalem Kortex und Hippokampus sowie für Unterschiede entlang der Hippokampuslängsachse.

1.3.2 Die Erkennung von neuen Reizen

Die Identifizierung von neuen Informationen bzw. die Unterscheidung von neuen und alten Informationen ist eine wichtige Fähigkeit, die die Grundlage für die erfolgreiche Wiedererkennung bildet. Im perirhinalen Kortex von Ratten und Affen finden sich beispielsweise Neuronen, die stärker feuern, wenn ein Reiz zum ersten Mal präsentiert wird oder zumindest die letzte Präsentation schon länger als 24 Stunden zurück liegt („Novelty- Neuronen"). Die Reaktion verläuft automatisch und ist unabhängig davon, ob ein Reiz handlungsrelevant ist oder nicht (Brown *et al.*, 1987). Der zugrunde liegende Mechanismus ist wahrscheinlich eine Unterdrückung neuronaler Aktivität bei der Wiederholung von Reizen („Repetition Suppression"). Spätere Studien (Brown & Xiang, 1998) haben neben den Novelty- Neuronen auch noch zwei andere Neuronentypen im perirhinalen Kortex gefunden. Der erste Typ

(„Recency – Neuron“) zeigte nur eine unterdrückte Aktivierung, wenn der Stimulus sofort wiederholt wurde. Lagen ein paar Items zwischen der letzten und der aktuellen Präsentation, so unterschieden Recency-Neuronen nicht länger zwischen alt und neu. Ein Neuron schließlich, welches die Familiarität kodiert („Familiarity-Neuron“), zeigt eine kumulative Reduktion auf Wiederholungen, unabhängig davon, wie viele andere Reize dazwischen präsentiert werden. Dieses Neuronensystem ist ideal geeignet für die Unterscheidung alter und neuer Informationen und somit indirekt für die erfolgreiche Wiedererkennung (siehe auch Brown & Aggleton, 2001). Bei intrakraniellen Ableitungen bei Menschen mit Temporallappenepilepsie wurde analog dazu eine rhinale Komponente (AMTL-N400) mit kleineren Amplituden auf wiederholte als auf neue Reize beobachtet. Diese Reize konnten Wörter (Grunwald *et al.*, 1995) oder Gesichter sein (Dietl *et al.*, 2005).

Im Hippokampus wurden die oben beschriebenen Novelty-, Recency-, oder Familiarity-Neuronen nur sehr selten gefunden (Brown *et al.*, 1987). Generell scheint der Hippokampus für die Erkennung neuer Einzelitems weniger entscheidend zu sein. In einer Tierstudie, in der der dopaminerge perforante Pfad zwischen entorhinalem Kortex und Hippokampus manipuliert wurde, zeigten sich beispielsweise Störungen, räumliche Neuheit zu erkennen, aber nicht darin, die Neuheit von Einzelitems zu identifizieren (Vago & Kesner, 2008). Dies passt zu der Theorie von Kumaran und Maguire (2007), nach der der Hippokampus insbesondere dann eingebunden ist, wenn „assoziative Neuheit“ auftritt, also die Beziehung mehrerer Einzelitems zueinander neu ist oder auch ein Einzelitem in einem bestimmten Kontext erstmalig auftritt.

Andererseits scheint der Hippokampus zumindest teilweise an der Entstehung der „Neuheits-sensitiven“ rhinalen AMTL-N400 beteiligt zu sein, die in Reaktion auf einzelne Wörter gemessen wurde. Die Amplituden der AMTL-N400 auf neue Wörter korreliert signifikant mit der Neuronendichte der Pyramidalzellen im hippokampalen CA1 Areal (Grunwald *et al.*, 1999a). Zudem zeigte sich, dass bei Patienten

mit einer Hippokampussklerose die AMTL-N400 auf neue, nicht aber auf alte Wörter in ihrer Amplitude signifikant reduziert war (Grunwald *et al.*, 1998). In einer Studie von Daselaar *et al.* (2006) konnte eine Dissoziation innerhalb des Hippokampus gezeigt werden. Nur im anterioren Hippokampus und im rhinalen Kortex zeigte sich eine stärkere Aktivierung auf neue als auf alte Wörter, während der posteriore Hippokampus eine stärkere Aktivierung auf alte als auf neue Wörter zeigte.

Bei der Identifizierung von neuen Reizen scheinen demnach rhinaler und hippokampaler Kortex in unterschiedlichem Maße involviert zu sein. Die uneinheitlichen Befunde bezüglich des Hippokampus könnten darauf basieren, dass nur manche Teile (wie zum Beispiel der anteriore Teil) des Hippokampus an der Neuheitserkennung beteiligt sind.

1.3.3 Erfolgreiche Enkodierung

Informationen, die uns im Alltag begegnen, können später nur erinnert werden, wenn sie erfolgreich eingespeichert („enkodiert“) wurden. Ein an der erfolgreichen Enkodierung beteiligtes Hirnareal sollte eine stärkere Aktivierung auf Reize zeigen, die später erinnert werden als auf solche, die später nicht erinnert werden. Dieser Effekt nennt sich „Subsequent-Memory Effekt“.

In Studien mit funktioneller Magnetresonanztomographie (fMRT) wurden sowohl im rhinalen Kortex als auch im Hippokampus Subsequent-Memory Effekte nachgewiesen (Reber *et al.*, 2002b; Tendolkar *et al.*, 2007). Wahrscheinlich gibt es zudem anterior-posterior Unterschiede entlang des Hippokampus, allerdings sind die Ergebnisse hier widersprüchlich. Manche Studien fanden eine hauptsächlich anterior hippokampale Aktivierung bei der Enkodierung (Lepage *et al.*, 1998), andere eine hauptsächlich posteriore Aktivierung (Greicius *et al.*, 2003; Schacter & Wagner, 1999). Studien, die mit intrakraniellen EKPs den Subsequent-Memory Effekt untersuchten, haben ebenfalls sowohl im Hippokampus als auch im rhinalen Kortex Effekte gefunden (Fernandez *et al.*, 1999). Die Amplituden der rhinalen AMTL-N400 und die

einer hippokampalen Positivierung (MTL-P600) waren größer, wenn ein Wort später erfolgreich erinnert wurde.

Ein Subsequent-Memory Effekt wurde nicht nur mit EKP-Analysen sondern auch mit Frequenzanalysen nachgewiesen. Diese geben Auskunft darüber, welcher Frequenzanteil zu einem bestimmten Zeitpunkt wie stark im Signal vertreten ist. Erfolgreiches Enkodieren war beispielsweise ab 100 ms nach dem präsentierten Wort bis ungefähr zum Beginn der AMTL-N400 mit einer signifikanten Zunahme der Phasensynchronisation rhinaler und hippokampaler EEG-Aktivität im Gamma-Band assoziiert. Die Phasensynchronisation ist ein Maß für die Kopplung zwischen zwei Arealen. Eine solche Synchronisation fand sich dagegen nicht bei der Präsentation von Wörtern, die nicht gelernt, bzw. später wieder vergessen wurden (Fell *et al.*, 2003). Auch bei der Power, die ein Maß für die Amplitudenstärke in den verschiedenen Frequenzen darstellt, zeigten sich Subsequent-Memory Effekte im Gamma- und Alpha-Beta-Bereich (Sederberg, 2007).

Verschiedene Maße scheinen geeignete Prädiktoren für die erfolgreiche Gedächtniseinspeicherung zu sein und sowohl der rhinale Kortex als auch der Hippokampus spielen eine wichtige Rolle bei der Enkodierung. In Bezug auf Subregionen des Hippokampus gibt es Hinweise auf Unterschiede entlang der Hippokampuslängsachse.

1.3.4 Instruiertes Vergessen

Nicht jede Information, die wir im Alltag aufnehmen, ist für die Zukunft relevant. Daher ist es interessant zu untersuchen, was eigentlich passiert, wenn Inhalte explizit nicht langfristig eingespeichert werden sollen. Dieser Frage widmen sich Studien zum Instruierten Vergessen („directed forgetting“). Üblicherweise wird zunächst ein Reiz präsentiert (z.B. ein Wort) und zeitverzögert ein Hinweis gegeben, ob dieser Reiz relevant ist („to be remembered“; TBR) oder nicht. Irrelevante Reize sollen wieder vergessen bzw. nicht noch tiefer eingespeichert werden („to be forgotten“; TBF). In einem späteren Abruf werden die TBF-Items üblicherweise weniger gut

wiedererkannt als die TBR-Items („Directed-Forgetting Effekt“). Dies kann zum einen durch Unterschiede in der Zeitdauer der Einspeicherung erklärt werden. Gemeint ist, dass die Wörter nach dem TBR-Hinweis wahrscheinlich noch einmal intensiv wiederholt werden, während die aktive Einspeicherung (das „Rehearsal“) nach dem TBF-Hinweis abgebrochen wird. Die reduzierte Enkodierung könnte andererseits aber auch durch eine aktive Hemmung der Gedächtniseinspeicherung unterstützt werden. Auf Basis der Ergebnisse einer fMRT-Studie zum Instruierten Vergessen wurde vorgeschlagen, dass frontale Hemmprozesse zu einer reduzierten Gedächtnisverarbeitung im MTL führen (Wylie *et al.*, 2008). Inwieweit hier eine Separierung zwischen verschiedenen Arealen des MTL vorliegt, bleibt offen.

1.3.5 Erfolgreicher Gedächtnisabruf

Eine vergangene Episode wird häufig dadurch erinnert, dass zunächst ein Element der Episode erneut erlebt und wiedererkannt und anschließend der dazugehörige Kontext rekonstruiert wird. Im Alltag begegnet man beispielsweise einer Person, die man schon einmal getroffen hat. Wahrscheinlich wird sie einem bekannt vorkommen, aber nicht immer erinnert man sich, woher man diese Person kennt oder wie ihr Name lautet. In der Gedächtnisforschung werden diese beiden Prozesse, das Gefühl der Bekanntheit (die „Familiarität“) und der Abruf von dazugehörigen Informationen (die „Rekollektion“) von einander unterschieden. Es gibt viele Hinweise darauf, dass innerhalb des medialen Temporallappens der rhinale Kortex die Familiarität und der Hippokampus die Rekollektion unterstützt (Daselaar *et al.*, 2006; Ranganath *et al.*, 2004).

Die neuronale Grundlage für die Familiaritätsunterscheidung im rhinalen Kortex bieten die schon in Abschnitt 1.3.2 erläuterten unterschiedlichen Neuronentypen (Familiarity-, Recency- und Novelty- Neuronen). Hippokampale Neuronen hingegen kodieren Assoziationen zwischen Einzelitems oder auch zwischen einem Item und dem Kontext (Rolls *et al.*, 1989). Dennoch wurde in vielen Studien bei der Wiedererkennung von Einzelitems eine Aktivierung im Hippokampus beobachtet. So zeigt

sich zum Beispiel in intrakraniellen EKP-Studien eine hippokampale MTL-P600 und MTL-LNC auf einzelne Wörter (Grunwald *et al.*, 1995; Grunwald *et al.*, 2003). Weiterhin deuten viele Studien darauf hin, dass insbesondere der posteriore Hippokampus bei der Rekollektion der alten Informationen mitwirkt (Daselaar *et al.*, 2006).

Während der rhinale Kortex unabhängig von der Enkodierungstiefe die Bekanntheit eines Reizes kodiert, so ist die Reaktion im Hippokampus abhängig von der Enkodierungstiefe. Bei der Wiedererkennung von Wörtern, die vorher nicht explizit eingespeichert werden sollten, wurde beispielsweise eine rhinale AMTL-N400, aber keine oder nur eine sehr kleine hippokampale MTL-P600 bzw. MTL-LNC beobachtet (Grunwald *et al.*, 2003).

Zusammengenommen zeigt dies, dass beim Abruf bzw. der Wiedererkennung von gelernten Informationen deutliche Unterschiede zwischen rhinalem Kortex und Hippokampus bestehen. Der Hippokampus erlaubt die Rekollektion von Einzelitems und Items in einem Kontext nach genügend tiefer Enkodierung, während die Aktivierung im rhinalen Kortex die Familiarität unabhängig von der Enkodierungstiefe reflektiert. Zudem sprechen die vorhandenen Studien für Spezialisierungen entlang der Hippokampuslängsachse.

1.4 Problemstellung

Wie also trägt der mediale Temporallappen zu deklarativen Gedächtnisprozessen bei und inwieweit unterstützen verschiedene Subregionen unterschiedliche Teilprozesse?

Eine gute Möglichkeit zur Untersuchung von Unterschieden zwischen rhinalem Kortex und Hippokampus aber auch zur Untersuchung von Unterschieden entlang der Hippokampuslängsachse bieten intrakranielle Ableitungen bei Patienten mit Temporallappenepilepsien.

Frühere intrakranielle EKP-Studien haben im Hippokampus auf seltene, handlungsrelevante Reize eine ausgeprägte MTL-P300 EKP Komponente gefunden (siehe

Abschnitt 1.3.1). Unklar ist bislang, ob es Unterschiede entlang der Hippokampuslängsachse gibt. Im rhinalen Kortex wurde eine frühere AMTL-N200 Komponente auf relevante und irrelevante Reize gezeigt, während sich nur teilweise eine positive P300-ähnliche Komponente anschloss. Das Ziel von Studie I ist daher die Untersuchung von topographischen Unterschieden der MTL-P300 entlang des Hippokampus sowie von Unterschieden zwischen rhinalem Kortex und Hippokampus. Dazu wird ein visuelles Oddball-Paradigma verwendet.

Der Hippokampus zeigt eine erhöhte Aktivierung, wenn ein Einzelitem erfolgreich eingespeichert wird. Unklarheit besteht jedoch darüber, ob im Hippokampus der anteriore oder posteriore Teil wichtiger für die erfolgreiche Einspeicherung ist (siehe Abschnitt 1.3.3). An der erfolgreichen Wiedererkennung von Informationen ist wahrscheinlich eher der posteriore Hippokampus beteiligt (siehe Abschnitt 1.3.5). Offen ist auch, ob der Hippokampus an der Erkennung von Neuheit beteiligt ist (siehe Abschnitt 1.3.2). Das Ziel von Studie II ist daher die Untersuchung regionaler Unterschiede entlang der Hippokampuslängsachse bei der Enkodierung und dem Abruf von Wörtern in einem kontinuierlichen Wortwiederholungsparadigma.

Erfolgreiche Enkodierung lässt sich nicht nur mit Hilfe der Analyse von EKPs sondern auch durch die Analyse von Frequenzbändern nachweisen (siehe Abschnitt 1.3.3). In Studie III wird neben den EKPs auch die rhinale und hippokampale Inter-Trial-Phasenkopplung, die Power sowie die rhinal-hippokampale Phasensynchronisation untersucht, da systematische Untersuchungen an einer großen Stichprobe bisher fehlen. Es wurden ebenfalls Daten aus dem kontinuierlichen Wortwiederholungsparadigma ausgewertet.

In Studien zum Instruierten Vergessen ist die Instruktion, ein Item zu vergessen, mit einer schlechteren Wiedererkennungsleistung für dieses Item assoziiert (siehe Abschnitt 1.3.4). In Studie IV soll mit einem Wortparadigma untersucht werden, ob dieser Directed-Forgetting Effekt besser durch ein selektives Rehearsal der TBR-Wörter oder durch eine aktive Hemmung der Enkodierung der TBF-Wörter erklärt

werden kann. Unabhängig von diesen beiden Erklärungsansätzen sollte die Instruktion, ein Wort zu vergessen, zu einer geringeren Enkodierungstiefe führen als die Instruktion, ein Wort zu erinnern. Bisherige Studien zeigen, dass der rhinale Kortex auf Reize unabhängig von der Enkodierungstiefe reagiert, während der Hippokampus nur tiefer enkodierte Reize von neuen Reizen unterscheidet. Daher soll mit Studie IV zusätzlich untersucht werden, ob sich bei der Wiedererkennung der TBR- und TBF-Wörter Unterschiede zwischen rhinalem Kortex und Hippokampus zeigen.

2 Überblick über die Studien

Studie I Two separate depth-P300 generators in the hippocampal formation probed by a visual oddball paradigm E. Ludowig, C.G. Bien, C.E. Elger, T. Rosburg *Hippocampus, 2009 May 12 [Epub ahead of print].*	*Fragestellung:* Welche Strukturen sind Generatoren der MTL-P300? Gibt es topographische Unterschiede entlang des Hippokampus bzw. zwischen rhinalem Kortex und Hippokampus?	*Angewendetes Paradigma:* Visuelles Oddball-Paradigma *Untersuchte Strukturen:* Rhinaler Kortex, (Amygdala), Subiculum, Hippokampus *EEG-Maße:* Mittlere Ampl. AMTL-N200 & MTL-P300 n = 53
Studie II Intracranially recorded memory-related potentials reveal higher posterior than anterior hippocampal involvement in verbal encoding and retrieval E. Ludowig, P. Trautner, M. Kurthen, C. Schaller, C.G. Bien, C.E. Elger, T. Rosburg *Journal of Cognitive Neuroscience, 2008,20:5, pp. 841-851.*	*Fragestellung:* Gibt es entlang des Hippokampus anterior-posterior Unterschiede in Bezug auf die Neuheitser-kennung, Wortenkodierung oder Wortabruf?	*Paradigma:* Wortwiederholungs-Paradigma *Untersuchte Strukturen:* Hippokampus *EEG-Maße:* Mittlere Ampl. der MTL-P600 und MTL-LNC n = 27
Studie III Phase-locking within human mediotemporal lobe predicts memory formation J. Fell, E. Ludowig, T. Rosburg, N. Axmacher, C.E. Elger *Neuroimage, 2008, 43:2, pp. 410-419.*	*Fragestellung:* Welche EEG-Maße (EKPs, rhinale und hippokampale Phasenkopplung, Power, rhinal-hippokampale Phasensynchronisation) sind Prädiktoren für die erfolgreiche Enkodierung?	*Angewendetes Paradigma:* Wortwiederholungs-Paradigma *Untersuchte Strukturen:* Rhinaler Kortex, Hippokampus *EEG-Maße:* Mittlere Ampl. AMTL-N400 & MTL-P600; Phasenkopplung; Synchronisation; Power n = 31
Studie IV Active suppression in the mediotemporal lobe contributes to the directed forgetting effect E. Ludowig, J. Möller, C.G. Bien, T.F. Münte, C.E. Elger, T. Rosburg *Neurobiology of Learning and Memory, under review.*	*Fragestellung:* Welche Auswirkung hat die Instruktion, ein Wort zu vergessen, auf den rhinalen Kortex/ Hippokampus? Gibt es Unterschiede zwischen den Strukturen bei der späteren Wiedererkennung?	*Angewendetes Paradigma:* Directed-Forgetting Paradima *Untersuchte Strukturen:* Rhinaler Kortex, Hippokampus *EEG-Maße:* Mittlere Ampl. der AMTL-N400, MTL-P600, MTL-LNC, MTL-P300 n = 12

Bevor die einzelnen Studien vorgestellt werden, soll ein grober Überblick gegeben und die allgemeine Methodik eingeführt werden. Die genauen Patientencharakteristika, die Details über die EEG-Aufnahmen sowie die angewendeten Statistiken können in den Einzelartikeln gefunden werden.

2.1 Allgemeine Methodik

2.1.1 Stichprobe

Alle vier Studien wurden mit Patienten mit pharmakoresistenter Temporallappen-Epilepsie durchgeführt. Den Patienten wurden im Rahmen der prächirurgischen Diagnostik Stabelektroden in den medialen Temporallappen implantiert. Bei fokalen Epilepsien, die pharmakoresistent sind, kommt eine operative Therapie zur Reduktion der Anfälle in Betracht, bei der beispielsweise Teile des MTL entfernt werden. Bei unklarem Fokus können zu diagnostischen Zwecken Tiefenelektroden in den MTL implantiert werden. Eine solche Tiefenelektrode hat üblicherweise eine stabartige Form und verfügt über mehrere Elektrodenkontakte, die entlang des rhinalen Kortex, der Amygdala und der Längsachse des Hippokampus verteilt sind (siehe Abbildung 3). Es wurden nur Patienten mit bilateralen Implantationen eingeschlossen, bei denen sich später herausstellte, dass die Anfälle von einer Hemisphäre generiert wurden. Dementsprechend wurden nur Aufnahmen der gesunden anderen Seite ausgewertet. Eine Ausnahme bildet die vierte Studie zum Instruierten Vergessen, in der auf Grund der kleinen Stichprobe bei zwei Patienten auch Daten der unilateral implantierten Elektrode auf der fokalen Seite eingeschlossen wurden.

2.1.2 Elektrodenauswahl

Jede Stabelektrode verfügt über zehn Kontakte. Üblicherweise liegen die anterioren 1-2 Kontakte im rhinalen Kortex, 3-4 in oder inferior zur Amygdala und die posterioren 5-10 Kontakte entlang des Hippokampus. Manchmal liegt die Elektrode auch insgesamt weiter inferior, so dass sie entlang des Subiculums positioniert ist.

Nach der Implantation der Elektroden wird routinemäßig eine strukturelle MRT-Messung durchgeführt. Auf Basis der axialen und koronaren 2 mm- FLAIR (fluid-attenuated inversion recovery) MRT-Aufnahmen wurden die Elektrodenpositionen den anatomischen Strukturen zugeordnet (Duvernoy, 1988). In Abbildung 4 ist ein MRT-Bild zu sehen, in dem eine rhinale Elektrode (RC) sowie eine anterior hippokampale Elektrode markiert wurden.

Eine genaue Einteilung in entorhinalen und perirhinalen Kortex ist zur Zeit nur histologisch und nicht über MRT-Aufnahmen möglich (Amaral & Lavenex, 2007). Im rhinalen Kortex wurde für jeden Patienten jeweils ein Elektrodenkontakt ausgewählt. Dies war entweder der rhinale Kontakt, an dem das stärkste Signal gemessen wurde (Studie 3 und 4) oder ein Kontakt, der bei allen Probanden an einer homogen anatomischen Stelle lokalisiert war (Studie 1). Im Hippokampus wurde in Studie 3 ebenfalls der Kontakt mit den größten Signalen ausgewählt. In den drei anderen Studien, in denen Unterschiede entlang der Hippokampuslängsachse untersucht werden sollten, wurde weiterhin in anteriore und posteriore Elektroden (Studie 4) bzw. in Hippokampuskopf und Hippokampuskörperelektroden unterschieden (Studie 1 und 2). In Studie 1 wurden zusätzlich Daten aus der Amygdala und dem Subiculum ausgewertet.

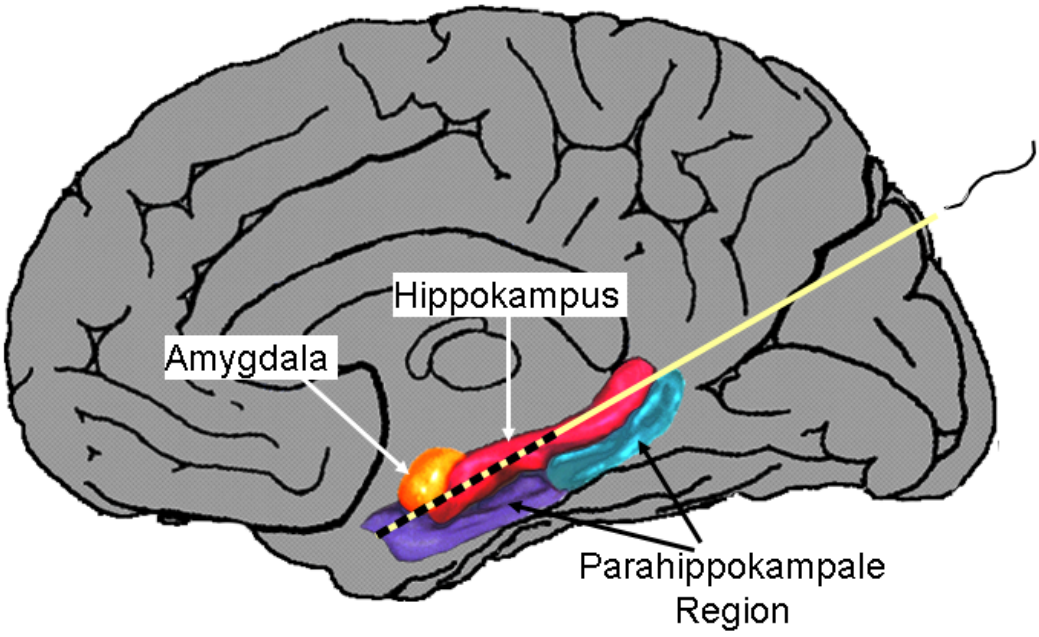

Abbildung 3: Darstellung der Lage von hippokampaler Formation, Amygdala und parahippokampalem Gebiet im Gesamtgehirn (Grafikabteilung, Klinik für Epilepsie, Universitätsklinik Bonn).

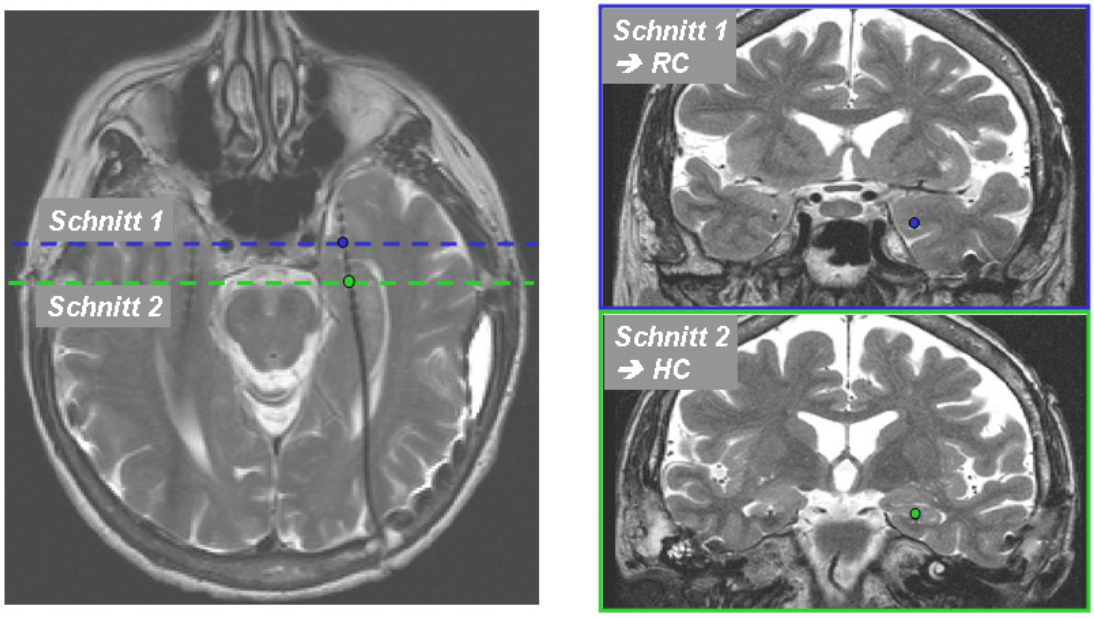

Abbildung 4: Lage der bilateralen Tiefenelektroden in einer 1,5-Tesla MRT-Aufnahme. Links: Sagittalschnitt mit rhinaler Elektrode in blau (Schnitt 1) und anterior hippokampaler Elektrode in grün (Schnitt 2). Rechts: Koronarschnitt von rhinalem Kortex (oben, RC) und Hippokampus (unten, HC).

2.1.3 Vor- und Nachteile der Methode

Die Elektroden werden stets nur aus klinischen Gründen implantiert. Ort und Anzahl der Elektroden sind daher vorbestimmt und können nicht an die jeweilige Fragestellung der Studie angepasst werden. Die Anzahl implantierter Patienten sowie die zur Verfügung stehende Zeit sind somit limitiert. Ein weiterer Nachteil der Methode ist, dass die Daten nicht in einem gesunden Gehirn gemessen werden und Daten aus der Anfallsregion daher ausgeschlossen werden müssen (Axmacher *et al.*, 2008).

Auf der anderen Seite bieten intrakranielle Ableitungen wertvolle Informationen über Funktionsweisen des Gehirns. Der Vorteil im Vergleich zu bildgebenden Verfahren oder Oberflächen-Ableitungen liegt in der Kombination von großer räumlicher und zeitlicher Auflösung. Zudem ist das intrakranielle EEG ein direktes Maß neuronaler Aktivität. Eine Alternative bieten Tierstudien, in denen Elektroden in größerer Menge eingesetzt und präziser platziert werden können. Neben anatomischen Unterschieden zwischen den Gehirnen von Tieren und Menschen (Amaral & Lavenex, 2007) sind aber insbesondere bei der Erforschung höherer kognitiver Funktionen in Tierstudien Grenzen gesetzt.

2.1.4 Untersuchte EEG-Maße

EKPs

In der vorliegenden Arbeit wurden ereigniskorrelierte Potentiale (EKPs) untersucht (siehe Fabiani *et al.*, 2000, für eine Einführung in die Methode). Ähnlich wie bei Oberflächenableitungen werden die Komponenten auch bei intrakraniellen Ableitungen nach ihrer Latenz und der Polarität benannt. Für viele intrakranielle Potentiale fanden sich Übereinstimmungen zu Oberflächenpotentialen. In diesen Fällen wird üblicherweise die Oberflächennomenklatur übernommen, auch wenn sich Abweichungen in der Latenz oder Polarität ergeben. Ein Beispiel ist die P300, die durch seltene Zielreize in Oddball-Paradigmen ausgelöst wird. An der Oberfläche hat die P300 eine positive Polarität und einen Peak bei etwa 300 ms (Sutton *et*

al., 1965). Im Hippokampus lösen die seltenen Zielreize eine spätere Negativität bei etwa 400 ms aus (Halgren *et al.*, 1995a; McCarthy *et al.*, 1989). Diese späte mediotemporale Negativität wird in Anlehnung an die Oberflächenpotentiale „P300" genannt, und mit dem Kürzel „MTL" versehen („MTL-P300"). In anterioren mediotemporalen Arealen, wie dem rhinalen Kortex, findet sich eine Negativierung mit einer Latenz von ~ 200 ms auf die Zielreize. Diese wird entsprechend AMTL-N200 genannt.

In Reaktion auf Wörter zeigt sich im Oberflächen-EEG üblicherweise eine N400, die größere Amplituden für neue als für wiederholt präsentierte Wörter zeigt, während die P600 größer für wiederholte als für neue Wörter ist (Curran, 1999). In intrakraniellen Ableitungen resultiert die Wortpräsentation in einer rhinalen Negativierung um die ~ 460 ms sowie in einer hippokampalen Positivierung bei ~ 620 ms (Smith *et al.*, 1986). Diese Komponenten werden analog „AMTL-N400" und „MTL-P600" genannt. Im Hippokampus zeigt sich weiterhin eine späte Negativierung (MTL-LNC), die ebenfalls stärker für alte als für neue Wörter ausgeprägt ist (Grunwald *et al.*, 1995).

Trotz dieser Übereinstimmungen reflektiert das Oberflächenpotential immer ein Summenpotential, welches die Aktivität vieler Gebiete auffängt. Auch wenn spekuliert werden kann, dass im MTL Generatoren der Oberflächen-N200, N400, P300 und P600 zu finden sind, gibt es wahrscheinlich mehrere Generatoren. Dies belegt unter anderem eine Studie, in der eine Resektion des MTL die Oberflächen P300 nicht reduzierte (Johnson, 1988). Die Schwierigkeit in der Verknüpfung von Oberflächen- und Tiefenableitungen ist der Grund, warum in der vorliegenden Arbeit nicht auf Ergebnisse aus Oberflächenmessungen eingegangen wird. Diese bieten zwar hervorragende Möglichkeiten, psychologische Prozesse zu differenzieren, allerdings ist es nicht möglich, Strukturen innerhalb des MTL zu unterscheiden.

Frequenzanalysen

Neben der Auswertung von EKPs erfolgte in Studie III die Auswertung von Frequenzspektren. Ein EEG setzt sich immer aus verschiedenen Frequenzen zusammen. In einer EKP- Komponente wie der N400, P300, P600 etc. zeigen sich eher die langwelligen Frequenzen im Delta- (0-4 Hz) und Theta- (4-8 Hz) Bereich (Herrmann *et al.*, 2005). Kurzwelligere Frequenzen wie z.B. Gamma-Oszillationen sieht man auf Grund der geringeren Amplituden kaum im gemittelten EKP. Zudem sind nur solche Oszillationen sichtbar, die gleichzeitig mit dem Stimulus beginnen („evozierte Potentiale"). Oszillationen können aber auch an den Stimulus gekoppelt sein und dennoch leicht in der Phase variieren oder erst verzögert einsetzen. Solche „induzierten Potentiale" sind nicht im gemittelten EKP sichtbar, und es müssen spezielle Verfahren, wie z.B. Wavelet-Analysen zur Auswertung genutzt werden. Mit einer Wavelet-Analyse kann für jede Frequenz und jeden Zeitpunkt jedes Trials die Amplitude und die Phase ermittelt werden. Dies ermöglicht Aussagen über die Phasenkorrelation zwischen den einzelnen Trials in einer bestimmten Elektrode („inter-trial-phase-locking", im Folgenden nur als „Phasenkopplung" bezeichnet) aber auch über die Phasenkorrelation zwischen verschiedenen Elektrodenpositionen („Phasensynchronisation"). Die Amplitudenstärke, die neben der Phase aus dem EEG für die einzelnen Frequenzen extrahiert werden kann, wird als „Power" bezeichnet. Für eine ausführlichere Einführung in die Methode sei auf Herrmann *et al.* (2005) verwiesen.

2.2 Studie I: Einfache Zielreizerkennung in einem Oddball-Paradigma

In dieser Studie wurden Unterschiede zwischen rhinalem Kortex und Hippokampus sowie zwischen anterioren und posterioren Subarealen des Hippokampus bei der Entdeckung von handlungsrelevanten Zielreizen untersucht.

Es wurde ein visuelles Oddball-Paradigma genutzt, in dem ein Standardreiz (der Buchstabe „X“) mit einer Wahrscheinlichkeit von 80% und ein Zielreiz (der Buchstabe „O“) mit einer Wahrscheinlichkeit von 20% präsentiert wurden. Insgesamt wurden 280 Reize gezeigt. Sobald ein Zielreiz am Bildschirm erschien, sollte der Proband eine Taste betätigen. Im Hippokampus zeigte sich, ähnlich wie in früheren Studien (Halgren *et al.*, 1995a; McCarthy *et al.*, 1989), auch in der vorliegenden Arbeit eine ausgeprägte MTL-P300 auf Zielreize. Die MTL-P300 war im gesamten Hippokampus beobachtbar, aber die Größe der Komponente nahm linear vom anterioren zum posterioren Hippokampuskörper an Größe zu (siehe Abbildung 5).

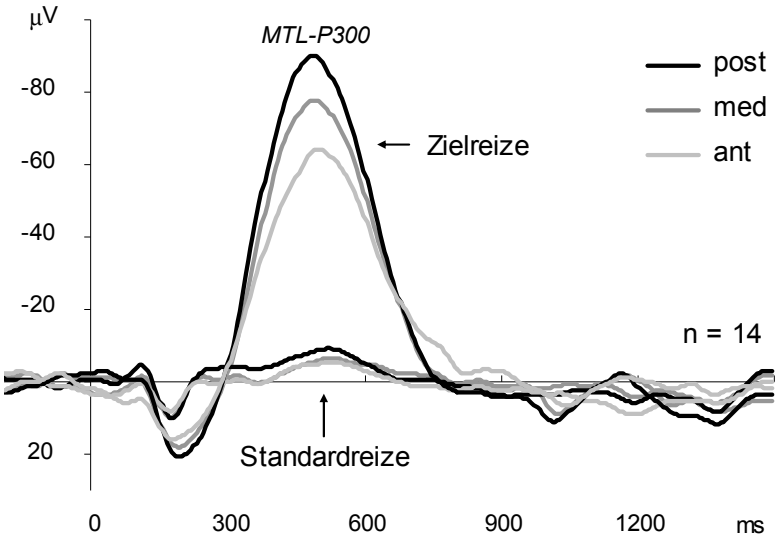

Abbildung 5: EKPs für Zielreize (oben) und Standardreize (unten) im Hippokampuskörper. Nur die Zielreize lösen eine MTL-P300 aus. Gezeigt sind Daten der anterioren (ant), medialen (med) und posterioren (post) Elektroden.

Dies deutet auf einen posterioren Generator der hippokampalen MTL-P300 hin. Eine größere posterior hippokampale Aktivierung auf visuelle Reize wurde vorher auch in einer Studie mit intrakraniellen Ableitungen (McCarthy *et al.*, 1989) und in einer fMRT Studie beobachtet (Crottaz-Herbette *et al.*, 2005).

Die funktionelle Rolle des Hippokampus bei der Zielreizentdeckung ist bislang nicht geklärt (siehe Abschnitt 1.3.1). Es wurde von verschiedenen Autoren vorgeschlagen, den Hippokampus als einen Komparator zu verstehen, der Informationen vergleicht, umstrukturiert und so Gedächtnisbildung ermöglicht (Kumaran & Maguire, 2006; Vinogradova, 2001). Eine ähnliche Rolle wird auch dem Subiculum zugeschrieben (Naber *et al.*, 2000). Dies ist deshalb interessant, weil in der vorliegenden Studie auch ein zweiter, latenzgleicher MTL-P300 Generator im anterioren Subiculum gefunden wurde.

Im rhinalen Kortex zeigte sich in der vorliegenden Studie eine negative AMTL-N200 Komponente auf relevante und irrelevante Reize, wobei diese signifikant größer in Reaktion auf die relevanten Zielreize war. Dies steht in Einklang mit einer früheren Studie, in der die AMTL-N200 in der Amygdala und im parahippokampalen Gyrus ebenfalls häufig auf Standardreize beobachtet wurde (Kukleta *et al.*, 2003). Die AMTL-N200 war in den meisten Fällen von einer Positivierung im MTL-P300 Zeitbereich gefolgt, die stark in der Größe variierte. Wahrscheinlich stellt diese Positivierung eher eine Spiegelung der hippokampalen MTL-P300 dar als eine eigenständige Komponente (siehe dazu McCarthy *et al.*, 1989). Dies könnte die inkonsistenten Vorbefunde erklären (Halgren *et al.*, 1995a; McCarthy *et al.*, 1989).

2.3 Studie II: Anterior-posterior Unterschiede im Hippokampus bei verschiedenen Gedächtnisfunktionen

Im Rahmen dieser Studie wurden Unterschiede zwischen anterioren und posterioren Subarealen des Hippokampus bei a) der Erkennung von Neuheit, b) der Enkodierung und c) dem Abruf von Wörtern untersucht.

In einem kontinuierlichen Wortwiederholungsparadigma wurden 450 deutsche Wörter nacheinander präsentiert. 150 dieser Wörter wurden nur einmal gezeigt, während weitere 150 Wörter zweimal präsentiert wurden. Nach jedem Wort sollten die Probanden entscheiden, ob es sich um ein neues oder eine wiederholtes Wort handelt.

Im Hippokampuskopf zeigte sich eine späte Negativierung, die größer für neue als für alte Wörter ausgeprägt war. Ein anterior hippokampaler Mechanismus zur Erkennung von Neuheit steht in Einklang mit verschiedenen fMRT Studien, in denen ebenfalls eine anteriore Aktivierung auf neue Reize im Hippokampus gefunden wurde (Daselaar *et al.*, 2006; Dolan & Fletcher, 1997; Strange *et al.*, 1999).

In Studien mit intrakraniellen Ableitungen findet sich üblicherweise eine stärkere Positivierung (MTL-P600) auf erfolgreich enkodierte im Vergleich zu später vergessenen Wörtern (Fernandez *et al.*, 1999). In der vorliegenden Studie zeigte sich ein linearer Anstieg dieses Subsequent-Memory Effektes entlang der Hippokampuslängsachse. Nur im posterioren Hippokampuskörper erreichte der Effekt statistische Signifikanz. Somit stehen die Ergebnisse in Einklang mit der Annahme einer vorwiegend posterioren hippokampalen Beteiligung an der Enkodierung von Wörtern (Fernandez *et al.*, 1998; Greicius *et al.*, 2003).

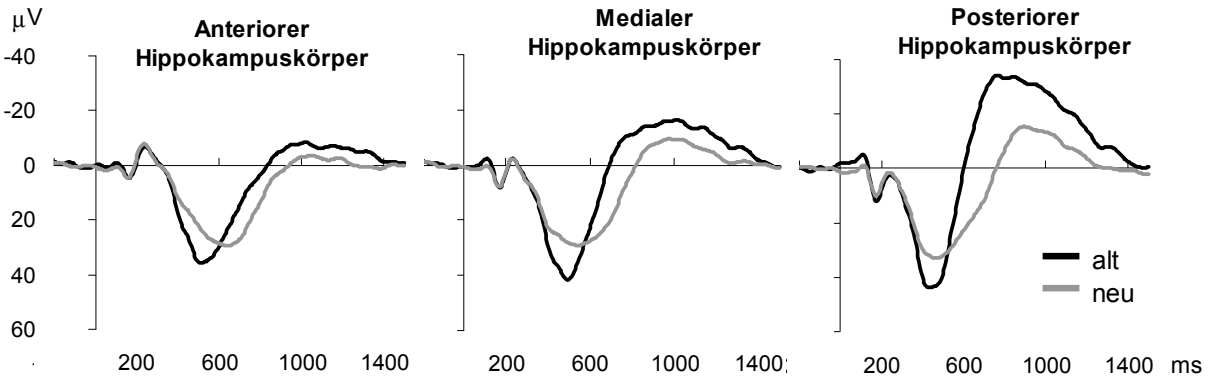

Abbildung 6: EKPs für korrekt wiedererkannte, alte Wörter und neue, erstmalig präsentierte Wörter. Der alt-neu Effekt zwischen 600 bis 900 ms ist posterior am stärksten ausgeprägt.

In der vorliegenden Arbeit fand sich ein linearer Anstieg des MTL-LNC alt-neu Effektes entlang des Hippokampus mit signifikanten Effekten nur im medialen und posterioren Hippokampuskörper (siehe Abbildung 6). Dies steht in Einklang mit der Annahme einer vorwiegend posterior hippokampalen Einbindung in den Gedächtnisabruf (Daselaar *et al.*, 2006; Henson *et al.*, 1999; Lepage *et al.*, 1998; Stark & Squire, 2000).

Insgesamt zeigte sich also, dass hippokampale EKP-Maße, die in früheren Studien mit der erfolgreichen Gedächtniseinspeicherung und dem erfolgreichen Gedächtnisabruf assoziiert wurden, stärker ausgeprägt waren je weiter posterior im Hippokampus gemessen wurde. Daraus kann geschlossen werden, dass ähnliche posterior hippokampale neuronale Netzwerke bei der Enkodierung und dem Abruf einzelner Wörter beteiligt sind. EKP-Effekte, die die Neuheit von Wörtern reflektieren, waren nur im Hippokampuskopf zu beobachten. Obwohl die Enkodierung von Informationen und die Erkennung von Neuheit verwandte Prozesse sind, scheint es innerhalb des Hippokampus eine räumliche Dissoziation zu geben.

Studie III: Prädiktoren für die erfolgreiche Gedächtnis-einspeicherung

In der vorliegenden Studie wurde die erfolgreiche Enkodierung von Wörtern sowohl mit klassischen EKP-Auswertungen als auch mit Frequenzanalysen untersucht. Es wurden Daten ausgewertet, die während der Durchführung des Wortwiederholungsparadigmas erhoben wurden (siehe Studie II).

In der EKP-Auswertung zeigte sich ein signifikanter Subsequent-Memory Effekt sowohl für die AMTL-N400 im rhinalen Kortex als auch für die MTL-P600 im Hippokampus. Dieses Ergebnis steht in Einklang mit früheren Studien (Fernandez *et al.*, 1999; Fernandez *et al.*, 2002).

Für die Frequenzanalysen wurden für den rhinalen Kortex und den Hippokampus getrennt die Phasenkopplung sowie die Power für jeden Zeitpunkt und jede Frequenz ermittelt. Ebenfalls für jeden Zeitpunkt und jede Frequenz wurde die Phasensynchronisation zwischen rhinalem und hippokampalem Kortex bestimmt.

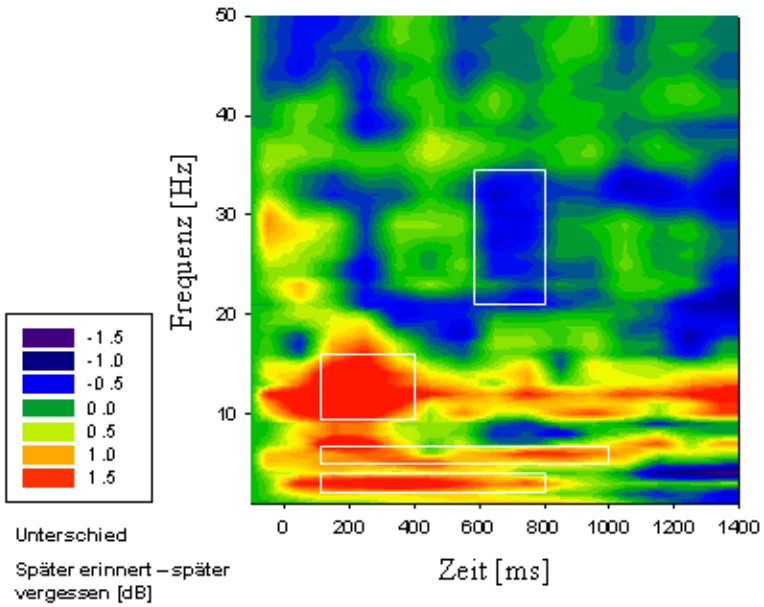

Abbildung 7: Rhinale Inter-Trial Phasenkopplung. Gezeigt ist der Unterschied der Phasenkopplung für die später erinnerten vs. später vergessenen Wörter. Die Phasenkopplungswerte wurden Baseline-korrigiert und in dB umgerechnet (siehe Originalarbeit für die Details). Die ausgewerteten Frequenzbänder sind eingerahmt.

Anschließend wurden auf Basis früherer Studien sowie post-hoc Zeit- und Frequenzfenster ausgewählt, über die anschließend gemittelt wurde. So ergab sich beispielsweise das Maß „hippokampale Phasenkopplung im Gamma-Bereich zwischen 38 und 49 Hz in einem Zeitfenster von 300 bis 800 ms".

Der beste Prädiktor für eine erfolgreiche Gedächtniseinspeicherung war in der vorliegenden Studie die Phasenkopplung. Diese stellt einen Index für die Stabilität der Phasen über die Einzeltrials hinweg dar. Eine größere Stabilität der Phasen zwischen den Trials für die Wörter, die später erinnert wurden, als für die Wörter, die später vergessen wurden, zeigte sich beispielsweise im rhinalen Kortex im Alpha-Beta Bereich zwischen 100 und 400 ms (siehe Abbildung 7). Im Hippokampus zeigte sich eine ähnlich signifikante Erhöhung der Phasenkopplung im Alpha-Beta Bereich. Daher kann spekuliert werden, dass das gleichzeitige Auftreten der frühen rhinalen und hippokampalen Alpha-Beta-Phasenkopplung die spätere Informationsaufnahme erleichtert. Rhinal war neben dem Alpha-Beta Frequenzband auch die Phasenkopplung im Delta- und Thetabereich ab 100 ms signifikant stärker ausgeprägt, wenn ein Wort erfolgreich enkodiert wurde.

Offen ist, wie die erhöhte MTL-Phasenkopplung funktionell interpretiert werden kann. Es wurde vorgeschlagen, dass der zeitliche Phasenverlauf der langwelligen EEG-Wellen die Erregbarkeit von kortikalen Netzwerken kontrolliert (Elbert und Rockstroh, 1987; Schupp *et al.*, 1994). Auf diese Weise könnten Gedächtnisrepräsentationen kodiert werden (Jensen und Lisman, 2005). Die frühe mediotemporale Phasengleichheit ermöglicht vielleicht die frühe Synchronisation zwischen rhinalem Kortex und Hippokampus, die sowohl in der vorliegenden Studie, als auch in früheren Studien im Gamma-Frequenzbereich beobachtet wurde (Fell *et al.*, 2001).

Der Erhöhung der Gamma-Synchronisation für erfolgreich eingespeicherte Wörter folgte eine Verminderung der Gamma-Synchronisation in einem breiten Zeitbereich zwischen 400 und 1100 ms nach Wortpräsentation, während sich im Hippokampus zwischen 300 und 800 ms wiederum eine Erhöhung der Phasenkorrelation im

Gammabereich zeigte. Möglicherweise reflektiert die Verminderung der Gamma-Synchronisation die Beendigung der rhinal-hippokampalen Interaktion, die Raum schafft für die spezifisch hippokampale Gedächtniseinspeicherung. Die erfolgreiche Enkodierung scheint generell entscheidend von der zeitlichen Abfolge früher Prozesse im MTL abzuhängen.

Studie IV: Instruiertes Vergessen von Wörtern

In dieser Studie wurde untersucht, ob das Vergessen von Informationen lediglich die Folge von zu schwachen Gedächtnisspuren ist, oder ob die mediotemporale Gedächtnisenkodierung auch aktiv gehemmt werden kann. Außerdem wurde geprüft, ob es Abweichungen zwischen dem Abruf tief und leicht enkodierter Wörter gibt. Es wurden jeweils Unterschiede zwischen rhinalem Kortex und Hippokampus, sowie Unterschiede zwischen anteriorem und posteriorem Hippokampus betrachtet.
In einem Paradigma zum Instruierten Vergessen von Wörtern wurde zunächst ein Wort gezeigt und einige Sekunden später folgte die Anweisung, ob dieses Wort zu erinnern (TBR) oder zu vergessen (TBF) sei. Nach der Präsentation vieler dieser Wort-Instruktions-Paare folgte ein Wiedererkennungsteil, in dem alle alten sowie neue Wörter präsentiert wurden.
Üblicherweise zeigt sich in der späteren Wiedererkennung eine deutlich schlechtere Leistung für solche Wörter, die vergessen werden sollten. Ein solcher Directed-Forgetting Effekt wurde auch in der vorliegenden Studie gefunden. Während 64% der TBR-Wörter korrekt wiedererkannt wurden, waren es nur 47% der TBF-Wörter.
Die bessere Wiedererkennung der TBR-Wörter könnte einerseits durch eine längere und intensivere Einspeicherung dieser Wörter erklärt werden. Das präsentierte Wort wird vor der Instruktion wahrscheinlich zunächst nur aufrechterhalten oder leicht eingespeichert. Sobald dann die Instruktion folgt, dass das Wort erinnert werden soll, wird es reaktiviert und beispielsweise durch Wiederholung tiefer eingespeichert

(„selektives Rehearsal“). Wenn jedoch die Instruktion folgt, dass das Wort nicht eingespeichert werden soll, wird die Enkodierung abgebrochen (Bjork *et al.*, 1968).
Elektrophysiologisch sollte sich der Unterschied der Intensität der Enkodierung in einer stärkeren Aktivierung auf die TBR- als TBF-Instruktion widerspiegeln. Wenn die TBR-Instruktion tatsächlich zu einer Reaktivierung und tiefen Einspeicherung des zuvor gezeigten Wortes führt, sollte sich zusätzlich ein Subsequent-Memory Effekt nachweisen lassen. Gemeint ist, dass die Aktivierung zum Zeitpunkt der TBR-Instruktion größer sein sollte für später erfolgreich wiedererkannte als für nicht wiedererkannte Wörter. Für die TBF-Instruktion wäre ein Subsequent-Memory Effekt weniger wahrscheinlich oder sollte zumindest kleiner ausfallen.
Die Ergebnisse der Studie stützen diese Hypothese des selektiven Rehearsals nicht. Im Hippokampus unterschieden sich die EKPs für die TBR und TBF Instruktionen nicht signifikant und für die TBR-Instruktion wurde kein Subsequent-Memory Effekt gefunden. Im rhinalen Kortex zeigte sich sogar eine größere Negativierung für die TBF als für die TBR Instruktion. Diese Resultate stehen in Einklang mit zwei fMRT-Studien, die ebenfalls keine stärkere Aktivierung auf TBR- als TBF-Instruktionen im MTL gefunden haben (Reber *et al.*, 2002b; Wylie *et al.*, 2008).
Alternativ zu diesem Erklärungsansatz für den Directed-Forgetting Effekt wurde vorgeschlagen, dass neben Unterschieden in der Länge der Enkodierung auch aktive, frontale Hemmprozesse die Enkodierung im MTL reduzieren könnten (Paz-Caballero *et al.*, 2004; Wylie *et al.*, 2008). In Strukturen, die aktiv gehemmt werden, sollte sich eine reduzierte Aktivierung bei Präsentation der TBF-Instruktion im Vergleich zur TBR-Instruktion finden lassen. Da die aktive Hemmung nur bei der TBF-Instruktion eintreten sollte und besonders erfolgreich war, wenn das Wort später erfolgreich nicht-erinnert wird, lässt sich ein Subsequent-Memory Effekt nur für die TBF- nicht aber für die TBR-Instruktion erwarten.
Ein solcher Effekt zeigte sich im anterioren und posterioren Hippokampus. TBF Instruktionen, die zu erfolgreichem Vergessen führten, waren mit einer signifikant

kleineren MTL-P300 assoziiert als solche, die nicht zu erfolgreichem Vergessen führten (siehe Abbildung 8, rechte Seite). Da die hippokampale MTL-P300 in früheren Arbeiten mit Gedächtnisfunktionen in Verbindung gebracht wurde (Halgren *et al.*, 1995a; Polich, 2007), kann die reduzierte MTL-P300 auf später erfolgreich vergessene Wörter als Hinweis für eine Unterdrückung hippokampaler Gedächtniseinspeicherung angesehen werden. Eine reduzierte hippokampale Aktivierung, ausgelöst durch den bewussten Versuch, ein Wort nicht zu erinnern, wurde auch in einer früheren fMRT Studie gezeigt (Anderson *et al.*, 2004).

In Anlehnung an Vorbefunde handelt es sich bei der auslösenden Struktur dieser Hemmung wahrscheinlich um frontale Areale (Paz-Caballero *et al.*, 2004; Wylie *et al.*, 2008). Dennoch ist es denkbar, dass einzelne Substrukturen im MTL aktive Suppressoren sind. Gehemmt werden sollte nur in Folge der TBF-Instruktion. Elektrophysiologisch wäre daher eine Mehraktivierung bei TBF-Instruktionen im Vergleich zu TBR Instruktionen zu erwarten.

In der vorliegenden Studie zeigte sich ein solcher Effekt im rhinalen Kortex. Dort zeigte sich ein signifikanter Unterschied zwischen den EKPs in Reaktion auf die TBR- und TBF-Instruktionen. Es war eine lang anhaltende Negativierung auf TBF, aber nicht auf TBR Instruktionen beobachtbar (siehe Abbildung 8, linke Seite). Der rhinale

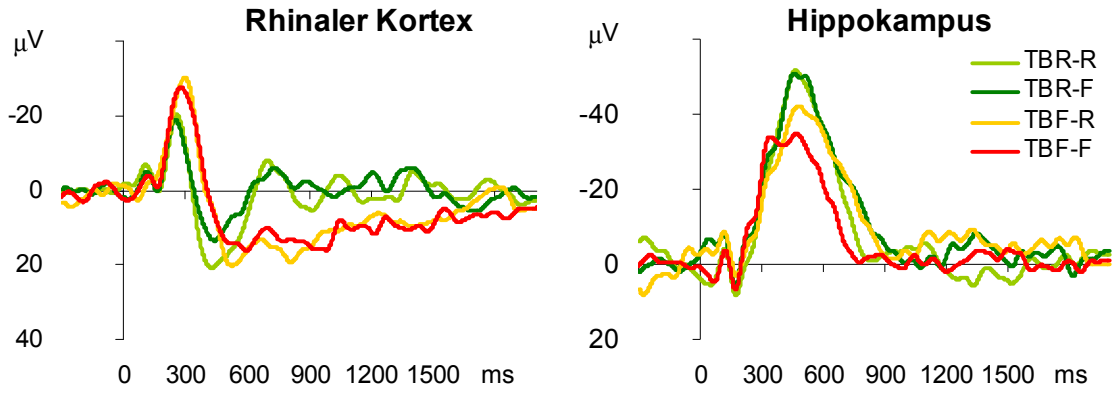

Abbildung 8: EKPs in Reaktion auf die TBR- und TBF-Instruktion, getrennt für Istruktionen, die zu Wörtern gehören, die später erinnert (-R) bzw. vergessen (-F) wurden.

Kortex (insbesondere der entorhinale Anteil) kann als ein sensorischer Filter angesehen werden, der zwar neokortikale Inhalte integriert und an den Hippokampus weitergibt, aber manche Inhalte auch zurückhält (Lavenex & Amaral, 2000). Die lang anhaltende, rhinale Negativierung, assoziiert mit der TBF Instruktion, könnte daher eine Inhibition der hippokampalen Verarbeitung reflektieren.

Allgemein führt die Instruktion, eine Information zu vergessen, wahrscheinlich zu einer geringeren Enkodierungstiefe, unabhängig davon, ob dies an einer reduzierten Enkodierungsintensität liegt (selektives Rehearsal) oder an einer aktiven Hemmung der Enkodierung. Frühere Studien haben gezeigt, dass der rhinale Kortex auf Reize unabhängig von der Enkodierungstiefe reagiert, während der Hippokampus nur tiefer enkodierte von neuen Reizen differenziert (Grunwald *et al.*, 2003). Daher sollte mit dieser Studie zusätzlich untersucht werden, ob sich bei der Wiedererkennung der Wörter Unterschiede zwischen rhinalem Kortex und Hippokampus zeigen und ob es Unterschiede entlang der Hippokampuslängsachse gibt.

In der vorliegenden Studie zeigte sich zunächst, dass der erfolgreiche Abruf von den ehemals TBR-instruierten Wörtern signifikant schneller ging als von den TBF-instruierten Wörtern. Dies unterstützt die Annahme, dass die TBR-instruierten Wörter tiefer enkodiert wurden als die TBF-instruierten Wörter.

Im rhinalen Kortex zeigte sich eine signifikant größere AMTL-N400 auf neue als auf korrekt wiedererkannte alte Wörter (siehe Abbildung 9). Ob es sich bei den alten Wörtern um die tiefer enkodierten TBR-Wörter oder die weniger tief enkodierten TBF-Wörter handelte, wirkte sich nicht auf die rhinalen EKPs aus. Im Hippokampus zeigte sich im posterioren Hippokampus eine deutliche MTL-LNC Komponente. Diese war am stärksten ausgeprägt für die Wiedererkennung der tief enkodierten TBR-instruierten Wörter, während sich die EKPs auf die erfolgreich wiedererkannten TBF-Wörter nicht von den EKPs auf die neuen Wörter unterschieden. Diese Ergebnisse unterstützen die Annahme, dass der rhinale Kortex allgemein auf

bekannte Reize unabhängig von der Enkodierungstiefe reagiert, während der Hippokampus nur auf tief enkodierte Reize eine Mehraktivierung zeigt.

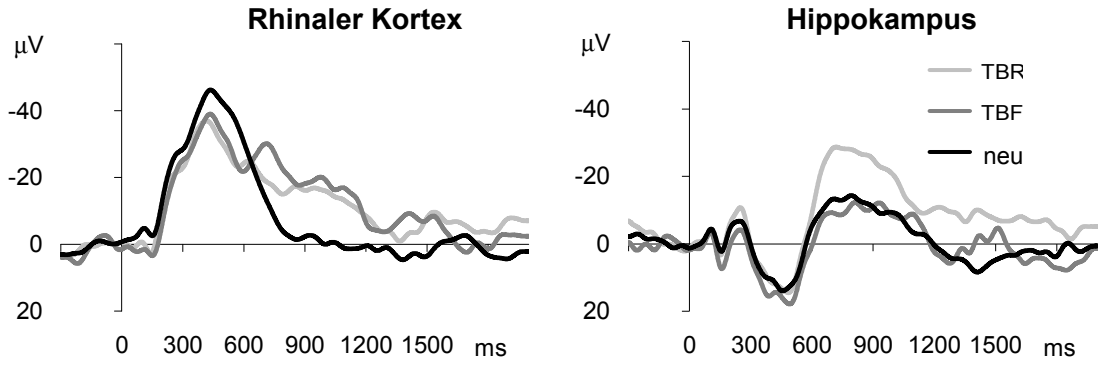

Abbildung 9: EKPs bei der Wortwiedererkennung, unterschieden danach, ob ein TBR-Wort oder ein TBF-Wort erfolgreich wiedererkannt wurde bzw. eine Erstpräsentation korrekt als neu erkannt wurde.

3 Diskussion

Die Studien wurden mit dem Ziel durchgeführt, die Rolle von rhinalem Kortex und Hippokampus bei der einfachen Zielreizentdeckung, der Erkennung von neuen Wörtern, der erfolgreichen Enkodierung bzw. erfolgreichen „Nicht"-Enkodierung von Wörtern (Instruiertes Vergessen) und der erfolgreichen Wortwiedererkennung zu untersuchen. Daher werden die Ergebnisse der einzelnen Studien zunächst diesen Gedächtnisbereichen zugeordnet (siehe dazu auch Abbildung 10) und anschließend auf höherer Ebene diskutiert.

An der einfachen Zielreizentdeckung sind der rhinale Kortex und der Hippokampus beteiligt. Während jedoch sowohl die seltenen Zielreize als auch die häufigen Standardreize eine AMTL-N200 im rhinalen Kortex auslösten, zeigte sich im Hippokampus nur auf die seltenen Zielreize eine deutliche MTL-P300. Die MTL-P300 wird wahrscheinlich im posterioren Hippokampus generiert (Studie I).

Die Präsentation von Wortreizen erzeugte im rhinalen Kortex eine AMTL-N400 (Studie III, IV). Handelte es sich bei dem präsentierten Wort um eine Erstpräsentation, so war die rhinale AMTL-N400 im Vergleich zu wiederholten Wörtern negativer ausgeprägt (Studie IV). Eine ähnliche Sensitivität auf neue Reize zeigte sich auch im anterioren Hippokampus. Dort waren neue Wörter mit größeren MTL-LNC Amplituden assoziiert als alte Wörter (Studie II).

Die Amplituden der rhinalen AMTL-N400 für neue Wörter waren dann besonders groß, wenn die Enkodierung erfolgreich war und das Wort später wiedererkannt wurde (Studie III). Die Größe der MTL-P600 korrelierte ebenfalls mit dem Erfolg der Wortendkodierung (Studie II, III).

Da der MTL-P600 Subsequent-Memory Effekt entlang des Hippokampus linear an Größe zunahm, scheint speziell der posteriore Hippokampus an der erfolgreichen Enkodierung beteiligt zu sein (Studie II). Die erfolgreiche Enkodierung war mit einer frühen Alpha-Beta Phasenkopplung im rhinalen Kortex und im Hippokampus

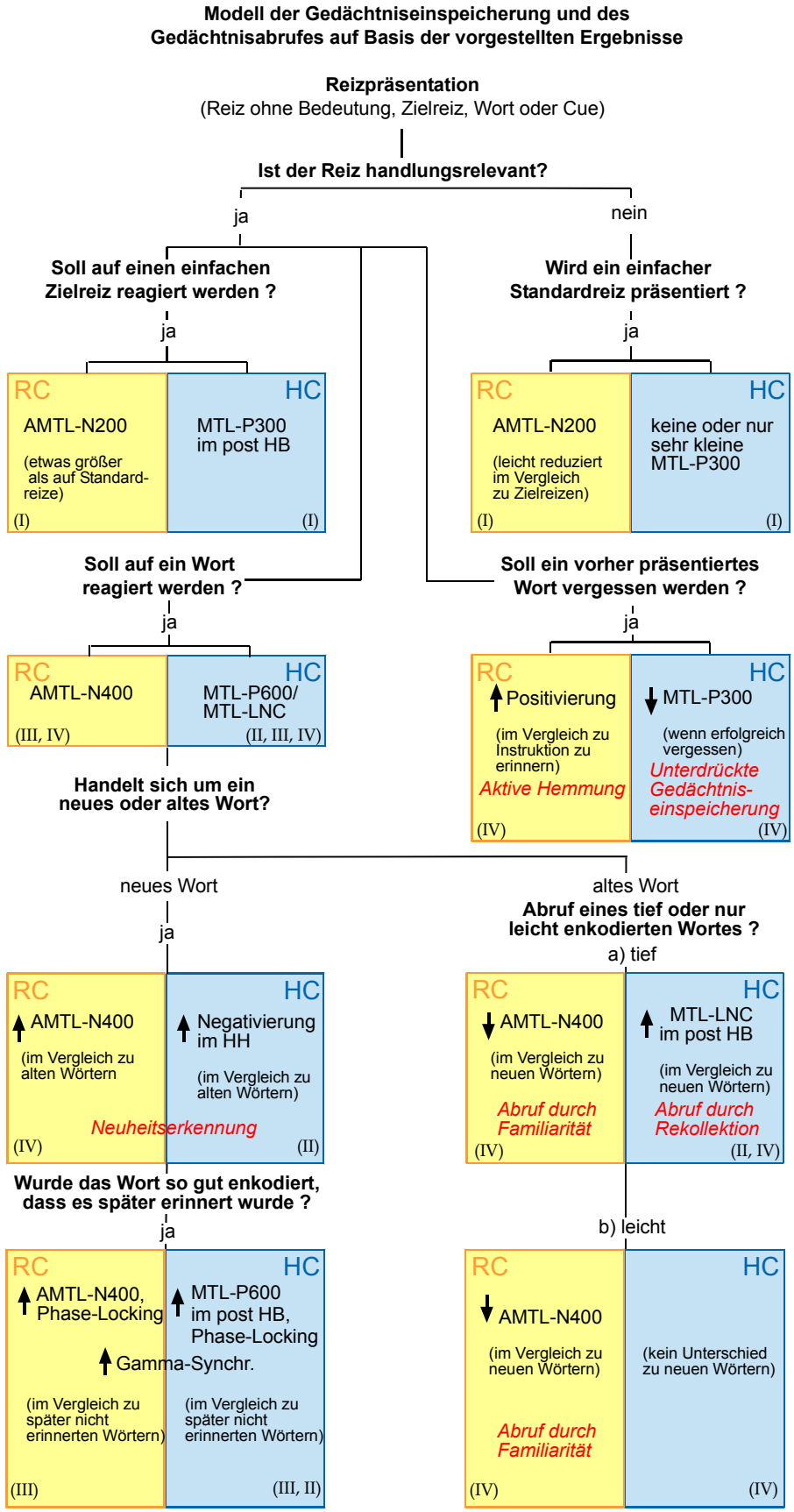

Abbildung 10: Modell der Gedächtnisspeicherung und des Gedächnisabrufen auf Basis der Studienergebnisse. RC= rhinaler Kortex, HC= Hippokampus, I- IV= Verweis auf die Studien I bis IV.

assoziiert, der zunächst eine Erhöhung der Gamma-Synchronisation zwischen den beiden Strukturen und schließlich eine Phasenkopplung im Gamma-Bereich im Hippokampus folgte (Studie III).

Sollte ein Wort gerade nicht tiefer eingespeichert werden, so zeigte sich im rhinalen Kortex auf die Instruktion, ein Wort zu vergessen, eine allgemeine, lang anhaltende Positivierung. Wurde in Folge der TBF-Instruktion das Wort später tatsächlich nicht wiedererkannt, so zeigte sich im Hippokampus eine reduzierte MTL-P300 (Studie IV). Es kann spekuliert werden, dass frontale Areale die hippokampale Gedächtniseinspeicherung über den rhinalen Kortex hemmen (Anderson *et al.*, 2004; Wylie *et al.*, 2008).

Ein Maß für den erfolgreichen Gedächtnisabruf ist die MTL-LNC Komponente, die üblicherweise eine größere Amplitude auf alte als auf neue Wörter zeigt (Grunwald *et al.*, 2003). An der erfolgreichen Wiedererkennung war der posteriore stärker als der anteriore Hippokampus beteiligt (Studie II). Wurde ein vormals nur leicht enkodiertes Wort erfolgreich wiedererkannt, so unterschied die hippokampale Aktivierung nicht zwischen diesen Wörtern und neuen Wörtern (Studie IV). Im rhinalen Kortex zeigte sich, wie schon angesprochen, eine kleinere AMTL-N400 auf wiedererkannte alte als auf neue Wörter. Dabei war es nicht entscheidend, ob das alte Wort tief oder weniger tief eingespeichert wurde. In beiden Fällen unterschieden sich die alten von den neuen Wörtern (Studie IV). Während der rhinale Kortex alte und neue Reize wahrscheinlich auf Basis der Familiarität unterschied, erfolgte im Hippokampus für die weniger tief eingespeicherten Wörter kein kompletter Gedächtnisabruf. Die vollständige Rekollektion scheint nur bei tief enkodierten Reizen möglich zu sein (Grunwald *et al.*, 2003).

In allen untersuchten Bereichen der Gedächtnisverarbeitung finden sich demnach Unterschiede zwischen rhinalem Kortex und Hippokampus. Über die Gedächtnisbereiche hinweg betrachtet, lassen sich die Unterschiede auf die Faktoren Latenz und Selektivität herunterbrechen.

Die Latenzen der EKPs im rhinalen Kortex waren kürzer als die der EKPs im Hippokampus (siehe dazu auch: Fernandez *et al.*, 1999; Grunwald *et al.*, 1995; Smith *et al.*, 1986). Auf einfache Reize zeigten sich eine rhinale AMTL-N200 mit einer Latenz von etwa 250 ms und eine hippokampale MTL-P300 mit einer Latenz von etwa 500 ms. Die Präsentation von Wörtern löste eine rhinale AMTL-N400 bei etwa 430 ms und eine hippokampale MTL-P600 bei etwa 500 ms sowie eine lang anhaltende hippokampale MTL-LNC ab etwa 700 ms aus.

Der Hippokampus zeigte eine höhere Selektivität als der rhinale Kortex. Während seltene Zielreize und häufige Standardreize eine rhinale AMTL-N200 auslösten, reagierte der Hippokampus nur auf die abweichenden handlungsrelevanten Reize mit einer deutlichen MTL-P300. Die Instruktion, ein Wort zu vergessen, löst eine allgemeine Negativierung im rhinalen Kortex aus, während die hippokampale MTL-P300 selektiv für die später tatsächlich nicht wiedererkannten Wörter reduziert ist. Bei der späteren Wiedererkennung zeigt der rhinale Kortex sowohl für die erfolgreich wiedererkannten TBR- als auch für die TBF-Wörter eine reduzierte AMTL-N400. Der Hippokampus reagiert selektiv nur auf die wiedererkannten, tiefer enkodierten TBR-Wörter.

Die Ergebnisse der vorgestellten Studien stützen daher die Annahme eines hierarchischen Gedächtnissystems. Informationen erreichen zunächst den rhinalen Kortex und andere parahippokampale Gebiete, werden dort gefiltert und anschließend an den Hippokampus weitergegeben (Eichenbaum, 2000). Diese Sicht steht in Einklang mit einer kürzlich erschienenen Studie, in der mit Mikroelektroden im menschlichen Temporallappen abgeleitet wurde. Dort zeigten Neuronen im parahippokampalen Gebiet ebenfalls eine kürzere Latenz und geringere Selektivität als die hippokampalen Neuronen (Mormann *et al.*, 2008). Innerhalb des Hippokampus scheint zudem der posteriore eine wichtigere Rolle als der anteriore Teil bei der Enkodierung und dem Abruf von Informationen zu spielen.

4 Ausblick

In der Zukunft wäre es zunächst sinnvoll, die vorhandenen Daten aus dem Oddball-Paradigma (Studie I), dem Wortwiederholungsparadigma (Studie II) und der Paradigma zum Instruierten Vergessen (Studie IV) auch mit Frequenzanalysen auszuwerten. Die Ergebnisse aus den EKP-Auswertungen der Studie IV legten eine Hemmung der hippokampalen Gedächtniseinspeicherung durch den rhinalen Kortex nahe. Eine solche Hemmung könnte sich beispielsweise in Veränderungen der Phasensynchronisation widerspiegeln. Interessant wäre auch, ob im Wortwiederholungs-, oder im Oddball-Paradigma eine Phasensynchronisation zwischen rhinalem Kortex und speziell dem posterioren Hippokampuskörper besteht. Generell ist bisher unklar, ob die größeren Amplituden der MTL-LNC im posterioren Hippokampus im Vergleich zu weiter anterior lokalisierten Elektroden durch eine erhöhte Power oder erhöhte Phasenkopplung zustande kommen. Auch dies ließe sich mit Frequenzanalysen klären.

Bisherige Studien haben einen Zusammenhang zwischen der AMTL-N200 in Oddball-Studien und der AMTL-N400 auf Wörter vermutet (Smith *et al.*, 1986). Auch die MTL-P300 ist möglicherweise mit der MTL-P600 oder sogar der MTL-LNC verwandt. Ein Vergleich der Daten solcher Patienten, die an beiden Studien, dem Oddball-Paradigma und dem Wortwiederholungsparadigma teilgenommen haben, könnte hier Klarheit bringen.

In der vorliegenden Arbeit wurden Elektroden im Subiculum nur in der Oddball-Studie ausgewertet. Würden weitere Daten in den anderen Paradigmen erhoben werden, so könnten diese Elektrodenpositionen auch dort analysiert werden. Interessant wäre beispielsweise, ob das Subiculum auch eine MTL-P600, MTL-LNC oder sogar eine eigene Komponente generiert.

Untersucht wurde einerseits die Entdeckung von Neuheit für komplexe Stimuli (Wörter), sowie die Entdeckung einfacher Stimuli (Buchstaben). Um eine Brücke

zwischen diesen beiden Funktionen zu schlagen, könnte eine bekannte Variante des Oddball-Paradigmas angewendet werden. In dieser Variante werden zusätzlich zu den seltenen Zielreizen und den häufigen Standardreizen auch seltene Distraktoren gezeigt. Diese Distraktoren sind jedes Mal neue, nicht aufgabenrelevante Reize (siehe Polich, 2007). Auf diese Weise könnte zusätzlich die Entdeckung von Neuheit für einfache Reize untersucht werden. Möglicherweise ist das Subiculum bei der Entdeckung von neuen Reizen stärker involviert als der Hippokampus (Halgren *et al.*, 1995a).

In der vorliegenden Arbeit wurde die Verarbeitung von Buchstaben und Wörtern untersucht. Theoretisch sollten die Effekte auch für andere visuelle Reize wie Gesichter oder Objekte nachweisbar und generell modalitätsunabhängig sein (McCarthy *et al.*, 1989). Es wäre aber denkbar, dass es im Hippokampus je nach Modalität unterschiedliche Gradienten entlang der anterior-posterior Achse gibt (Crottaz-Herbette *et al.*, 2005).

Anatomisch ist bisher unklar, wie ein solcher anterior-posterior Gradient entlang des Hippokampus interpretiert werden kann. Die anatomischen Unterschiede im Hippokampus liegen eher in der dorsal-ventralen Orientierung. Mit den vorhandenen 1,5-Tesla-MRT-Bildern und der durch die Elektrodenkontakte verursachten Artefakte im Bild war eine Unterscheidung der Areale CA1 bis 3 (bzw. 4) und auch der ento- und perirhinalen Bereiche in der vorliegenden Studie nicht möglich. Allerdings werden Aufnahmen mit größerer Tesla-Stärke auch aus Sicherheitsgründen in der Universitätsklinik Bonn nicht durchgeführt, da sich die Elektroden theoretisch erhitzen könnten (Patterson *et al.*, 2007). Eine höhere räumliche Auflösung könnte mit Mikroelektroden erreicht werden (Mormann *et al.*, 2008). Auch eine Kombination von MRT- und CT-Bildern könnte unter Umständen eine Verbesserung der Lokalisierbarkeit bieten (Dalal *et al.*, 2008).

5 Zentrale Thesen

- Die Erkennung von einfachen Zielreizen in einem visuellen Oddball-Paradigma erzeugt eine frühe Reaktion im rhinalen Kortex und eine etwas spätere Reaktion im anterioren Subiculum und posterioren Hippokampuskörper. Es handelt sich hier um drei unabhängige Generatoren.
- Während sich im Hippokampus nur auf seltene Zielreize eine Aktivierung zeigt, reagiert der rhinale Kortex sowohl auf die seltenen Zielreize als auch auf die nicht handlungsrelevanten Standardreize.
- Der rhinale Kortex und der Hippokampus sind an der Einspeicherung einzelner Wörter beteiligt. Frequenzanalysen zeigen, dass die erfolgreiche Enkodierung von einer präzisen zeitlichen Abfolge und Interaktion zwischen rhinalem Kortex und Hippokampus abhängt.
- Innerhalb des Hippokampus gibt es funktionelle Unterschiede entlang der Hippokampuslängsachse. Posteriore Subareale sind stärker an der Entdeckung von Zielreizen, der erfolgreichen Enkodierung und dem erfolgreichen Abruf von Wörtern beteiligt als anteriore Subareale. Anterior-hippokampale Areale hingegen sind in die Erkennung von Neuheit involviert.
- Die Instruktion, ein Wort zu vergessen, führt zu einer Reduktion hippokampaler Gedächtniseinspeicherung durch aktive rhinale Hemmung.
- Sowohl der rhinale Kortex als auch der Hippokampus zeigen alt-neu Effekte in Reaktion auf einzelne Wörter. Während jedoch der rhinale Kortex alt-neu Effekte unabhängig von der Enkodierungstiefe zeigt, unterscheidet der Hippokampus nur tief enkodierte Wörter von neuen Wörtern.

- Allgemein sind die Latenzen der EKPs im rhinalen Kortex kürzer als die der EKPs im Hippokampus. Zudem zeigt der Hippokampus eine höhere Selektivität als der rhinale Kortex. Dies stützt die Annahme eines hierarchischen Gedächtnissystems.

6 Studie I

Two P300 generators in the hippocampal formation

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Abstract

The presentation of rare target stimuli results in P300 scalp event-related potentials (ERPs). Generators of this ERP component were found in various brain areas, indicating that multiple cortical and subcortical areas subserve target detection. One of these structures is the mediotemporal lobe (MTL). In the hippocampus, large negative MTL-P300 potentials are usually observed, while reports concerning the rhinal cortex and subiculum are inconsistent. The aim of the present study was to investigate the topography of the mediotemporal P300.

ERPs were recorded in epilepsy patients from multicontact depth electrodes, implanted along the longitudinal axis of MTL. Patients had to respond to rare visual target stimuli by a button press. ERP data from the non-focal hemisphere of 53 patients were included in the analysis.

Target detection resulted in large MTL-P300 potentials in the hippocampus and subiculum. Latency did not differ between these structures. The hippocampal P300 increased linearly from anterior to posterior hippocampal body. In contrast, an inverse gradient with larger mean amplitudes in anterior parts was observed for the subiculum.

Our results indicate two separate generators of the MTL-P300, one in the anterior subiculum and one in the posterior hippocampal body. Since latencies did not differ, a parallel activation via the entorhinal cortex might have initiated the simultaneous MTL-P300. Hippocampus and subiculum are essential parts of the MTL-memory system. Their function within target detection might be to maintain a template of previous stimuli for a comparison with incoming sensory stimuli.

Introduction

One of the most studied event-related potentials (ERPs) is the P300, which is elicited by infrequent, task-relevant stimuli. This positive scalp component, first described by Sutton *et al.* (1965), has its maximum amplitude at posterior (parietal) scalp locations with a peak latency between 300 and 600 ms and a duration often greater than 300 ms. The P300 is regarded as an endogenous potential since it is related to the subject's psychological reaction to the stimulus and not just to the characteristics of the physical stimulus itself.

Usually, the P300 is investigated in the so-called oddball paradigms (for review Polich, 2007). In oddball paradigms, low-probability (target) stimuli are intermixed with high-probability (standard) stimuli. Regardless of whether the task is to push a button in response to the targets or to silently count target stimuli, directed attention is required for the emergence of a target-related P300. Completely ignored stimuli do not evoke a P300 (McCarthy *et al.*, 1989). Interestingly, the amplitude depends on subjective rather than objective probability (Squires *et al.*, 1976) and also strongly on the interstimulus interval (Polich, 1990). The P300 can be elicited by auditory, visual and somatosensory stimuli (McCarthy *et al.*, 1989).

In a variation of the oddball task, infrequent distractor stimuli are presented in addition to targets and standards. It has been shown that distractors also elicit a P300 component, but with a more frontal scalp distribution (Squires *et al.*, 1975). Therefore, the P300 has been subdivided into a frontal P3a and a parietal P3b. In this study, only the P300 (P3b) in response to targets is explored.

Within their influental context-updating model, Donchin and Coles (1988) suggested that the P300 is a manifestation of activity occurring whenever the current model of the environment has to be revised. It is an important ability of the adaptive brain to maintain a proper representation of the environment (the "context"). Whenever this context changes, novel or improbable events must be integrated in the current representation, especially when the context is critical for a successful task

performance. Such an updating process should have implications for the response to future events, including the subsequent memory for the event itself (Fabiani *et al.*, 2000). Within these lines, some authors suggested an association between the P300 and memory functions (Halgren *et al.*, 1998; Fabiani *et al.*, 2000; Polich, 2007). However, there are alternative interpretations of the P300 function: Desmedt (1980) and Verleger (1988) proposed that the P300 is related to the termination or "closure" of cognitive processes, Rösler (1986) suggested that the P300 reflects controlled processing, and Kok *et al.* (2001) regarded the P300 as a measure of processing capacity.

Studies using scalp electroencephalography (Goto *et al.*, 1996), intracranial recordings (Halgren *et al.*, 1995a; Halgren *et al.*, 1995b), magnetoencephalography (Rogers *et al.*, 1991) and functional magnetic resonance imaging (Bledowski *et al.*, 2004; Linden *et al.*, 1999) have attempted to localize the generators of the scalp P300. It has been concluded from these studies that the scalp P300 is generated by multiple cortical and subcortical brain areas in the frontal, parietal, and temporal lobe.

One structure recognized as a generator of the P300 is the mediotemporal lobe (MTL). MTL generators (especially in the hippocampus) have been extensively described in previous studies with intracranial recordings (Halgren *et al.*, 1980; Stapleton and Halgren, 1987; McCarthy *et al.*, 1989; Halgren *et al.*, 1995a; Brazdil *et al.*, 2001). All of these studies have reported a large, mostly negative ERP in response to the target stimulus. Since this negativity depended on the same stimulus and task conditions than did the scalp P300 (McCarthy *et al.*, 1989; Brazdil *et al.*, 2003; Squires *et al.*, 1976), the intracranial potential was labeled the "MTL-P300" (Grunwald, 1995).

Concerning other MTL structures such as the subiculum, rhinal cortex, and amygdala, negative and positive potentials were reported in the MTL-P300 time window. Within the hippocampus, single-case observations indicated sometimes larger negativities in the posterior than anterior hippocampus (McCarthy *et al.*, 1989; Paller *et al.*, 1992) and sometimes larger negativities in the anterior than posterior

hippocampus (Halgren *et al.*, 1995a). Thus, it remained somewhat unclear which MTL structures in addition to the hippocampus exhibit P300 responses and whether there is a systematic topography within the MTL structures.

The aim of the current study was a more precise investigation of the topography of the MTL-P300. For this purpose, we recorded ERPs from intracranial electrodes implanted in the hippocampus, subiculum, rhinal cortex, and amygdala of epilepsy patients. ERPs to visual targets and standards were analyzed. We were interested in differences between the structures, as well as in anterior-posterior gradients along the hippocampus and subiculum.

Materials and Methods

Participants

Patients with pharmacoresistant epilepsy, who were implanted with bilateral depth electrodes along the longitudinal axis of the MTL during presurgical evaluation, participated in the study. 53 patients (24 females) with recordings in the amygdala, rhinal cortex, subiculum or hippocampus were included. Data from 4 other patients were completely excluded due to poor signal quality. Patients ranged in age from 16 to 65 years (mean age = 39 yrs) and in duration of their epilepsy from 4 to 57 years (mean = 26 yrs). All participants had normal or corrected-to-normal vision. MRI scans or post-operative histological examinations demonstrated unilateral hippocampal sclerosis in 33 patients (5 with additional extrahippocampal pathologies), unilateral extrahippocampal temporal lesions without signs of hippocampal sclerosis in 12 patients, unilateral extratemporal lesions in 4 patients, and no clear lesion in 4 patients (see Table 1 for more detail). All but 4 patients underwent subsequent epilepsy surgery after implantation. The study was approved by the ethics committee of the University of Bonn and all patients gave a written informed consent.

TABLE 1. Patients´ characteristics.

Subject	Non-focal side	Sex	Age	Duration of epilepsy	Pathology of focal side
1	R	f	28	24	Amygdala -ganglioglioma
2	L	m	47	39	Temporal arteriovenous Malformation
3	R	m	22	17	Cerebral hemiatrophy
4	L	f	35	22	Cerebral hemiatrophy
5	L	m	43	30	HS
6	L	f	40	38	HS
7	L	m	46	20	HS
8	L	f	56	21	HS
9	R	f	33	18	HS
10	R	m	48	46	HS
11	R	f	57	30	HS
12	R	m	54	45	HS
13	L	m	58	14	HS
14	L	f	24	18	HS
15	R	m	61	57	HS
16	R	m	45	25	HS
17	R	m	53	42	HS
18	R	m	29	23	HS
19	R	m	38	18	HS
20	L	m	38	26	HS
21	R	f	36	34	HS
22	L	m	51	38	HS
23	L	f	41	14	HS
24	L	m	42	34	HS
25	R	f	54	32	HS
26	R	f	55	33	HS
27	R	f	44	43	HS
28	R	f	38	37	HS
29	R	m	40	35	HS
30	R	m	27	18	HS
31	R	m	27	23	HS
32	L	f	40	36	HS
33	L	f	20	18	HS + hamartia gyrus frontalis inferior
34	L	f	45	32	HS + cerebral hemiatrophy
35	R	m	25	23	HS + cerebral hemiatrophy
36	R	f	31	8	HS + lesion gyrus temporalis medius
37	R	m	46	35	HS + Temporopolal blurring of the grey-white matter junction
38	R	m	22	10	No clear lesion
39	R	f	38	10	No clear lesion
40	L	m	16	4	No clear lesion
41	R	m	28	9	No clear lesion
42	R	m	55	9	Occipital cavernoma
43	R	m	21	17	Temporal astrogliosis
44	R	f	25	18	Temporopolal blurring of the grey-white matter junction
45	R	f	22	8	Temporopolal blurring of the grey-white matter junction
46	R	f	48	29	Temporopolal blurring of the grey-white matter junction
47	L	m	35	6	Temporal cavernoma
48	R	f	65	53	Temporal cavernoma
49	R	m	26	7	Temporal ganglioglioma
50	L	m	50	34	Temporal lobe dysplasia
51	L	f	18	16	Temporal lobe dysplasia
52	R	m	57	17	Temporal necrosis
53	R	f	38	37	temporo-occipital tumor

R= right, L= left; m= male, f= female; HS= hippocampal sclerosis

Experimental 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 monitor approximately 80 to 100 cm away. In a visual oddball paradigm, the standard letter `X` was presented with a probability of 80 %, while the target letter `O` was presented with a probability of 20 %. In total, 280 stimuli were presented for a duration of 100 ms with an interstimulus interval of 1000 to 1200 ms. 15 patients participated in a longer version of the task, consisting of 560 stimuli. Patients were instructed to press a button when the target letter appeared. The stimuli were presented in white color on a black background with a height of ~2° and a width of ~2° visual angle. The test paradigm is part of the routine presurgical workup in patients with hippocampal depth electrodes (Grunwald, 1995).

EEG Recordings

ERPs were recorded from multicontact depth electrodes implanted stereotactically along the longitudinal axis of the hippocampus and adjacent regions. Each catheter like, 1 mm thick depth electrode contained 10 cylindrical platinum electrodes with a longitudinal extension of 2.5 mm every 4 mm. The first three of these ten electrodes were located in the rhinal cortex, the next one or two in or near the amygdala, and up to six along the longitudinal axis of the hippocampus or subiculum. 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 against offline linked mastoids with a sampling rate of 200 Hz or 1000 Hz. Data were segmented into epochs of 1,700-ms with a 200-ms prestimulus period as baseline, target, and standard stimuli separately. 1000 Hz recorded data were re-sampled to 200 Hz. Data were highpass filtered at 0.1 Hz with a slope of 12 dB/octave, lowpass filtered at 12 Hz with a slope of 12 dB/octave, as well as baseline corrected.

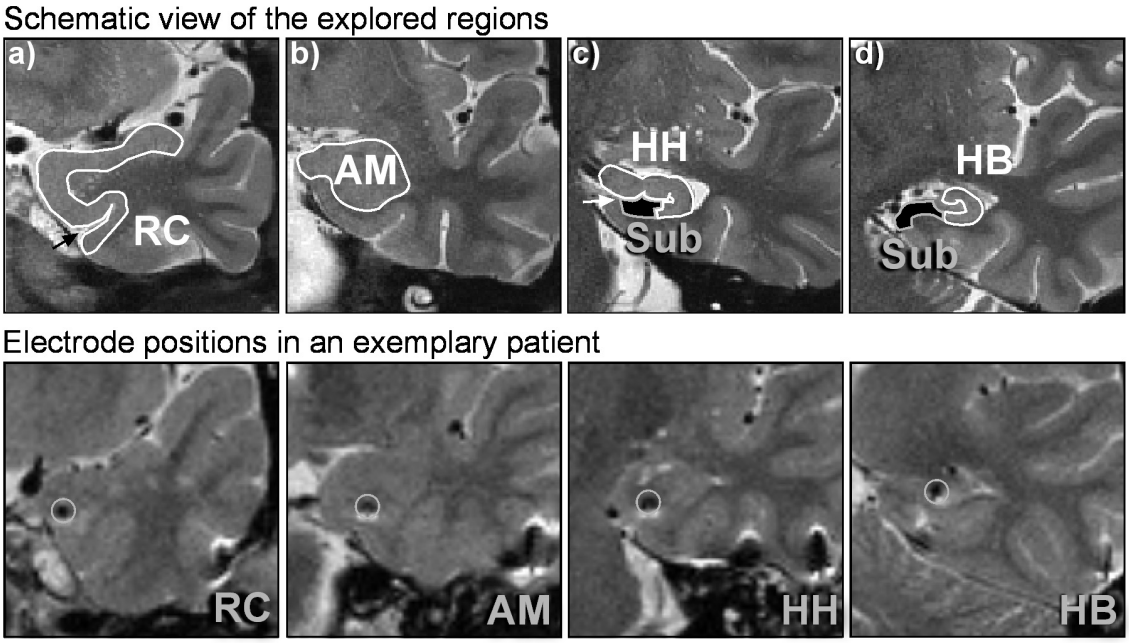

Fig. 1: Electrode classification. Top: Coronar images (pre-implantation 3 Tesla image of patient No.50) that schematically show the boundaries of the explored structures (white outlines). Four levels from anterior (left) to posterior (right) are depicted.

a) The appearance of the collateral sulcus (black arrow) marks the beginning of the rhinal cortex (RC). Entorhinal and perirhinal cortex were not separated.

b) The boundaries of the amygdala (AM). Electrodes in the RC below the amygdala were not included.

c) Level of the hippocampal head (HH) and subiculum (Sub). Since a clear separation of the HH and the Sub is not possible with usual MRIs, electrodes above the sulcus uncinatus (white arrow) were assigned to the HH and electrodes medially below the sulcus uncinatus were assigned to the Sub. In the problematic transition zone between both structures, electrodes were not assigned to either structure, but were labeled "HHSub" instead. Presubiculum, prosubiculum and subiculum were not separated.

d) Level of the hippocampal body (HB) and subiculum. On this level, the subiculum is still visible medial to the HB, but was not analyzed due to imprecision in the separation of Sub and HB electrodes.

Bottom: Electrode positions in a post-implantation 1.5 Tesla image of patient No.14.

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 4 standard deviations from the mean. Thus, segments with abnormally high amplitudes as well as abrupt rises or falls were eliminated. On average, 11 % of the trials were removed based on these criteria. Only trials associated with the correct behavioral response (button-press in response to targets, no response to standards) were included. The corresponding segments were separately averaged for targets and standards.

Explored brain structures and electrode selection

Only data of the non-pathological MTL were analyzed. Electrodes were grouped in rhinal cortex (RC), amygdala (AM), subiculum, and hippocampus electrodes according to the anatomy atlas of Duvernoy (1988). For each patient, the precise placement of electrode contacts within the MTL 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. The hippocampus was further subdivided into hippocampal head (HH) and hippocampal body (HB), with the beginning of the hippocampal body defined as the first coronar section where the fimbria is visible and the uncus disappears. On the level of the hippocampal body, the subiculum is located medial to the HB. Due to imprecision in the anatomical separation of Sub and HB electrodes based on the MRIs, we only analyzed the subiculum on the level of the hippocampal head. Here, electrodes above the sulcus uncinatus were assigned to the HH and electrodes below the sulcus uncinatus were either assigned to the Sub, or in a transition zone between HH and Sub, classified as "HHSub". See Fig. 1 for a detailed description of electrode classification.

Within each structure, we selected the most anterior and the most posterior electrode (labeled with "ant" and "post"). If more than two electrodes were available within

one structure, also a medial electrode ("med") was selected, which was either located exactly in the middle of the anterior and posterior electrodes, or, if this was not possible, the mean average of two medial electrodes. This kind of classification has already been used in a previous study (Ludowig *et al.*, 2008). See Figure 2 for an example of the sub-classification within the hippocampal body.

Data analysis

Due to the variabilities in electrode placement across patients in the anterior-posterior and also inferior-superior direction, numbers of included patients varied for the different analyses. For the analysis of the MTL-P300, we quantified the mean ERP amplitudes between 300 and 650 ms in response to targets and standards relative to the baseline. This time window was selected based on a previous MTL-P300 intracranial study (Grunwald, 1995).

For a comparison of the most anterior and most posterior position within a structure, a repeated measures analysis of variance (ANOVA) with POSITION (ant vs. post) and CONDITION (target vs. standard) was conducted for the P300 amplitude in each structure of the hippocampal formation separately (HH, HHSub, Sub and HB). Data of patients with more than two electrodes in the Sub or HB were included in an additional ANOVA with POSITION (ant, med, post) and CONDITION (target vs. standard) as within-subject factors.

Within the hippocampus, P300 differences between HH and HB were analyzed with an ANOVA where POSITION (post HH vs. ant HB) and CONDITION (target vs. standard) were within-subject factors. Furthermore, P300 amplitudes of the most anterior electrode in the hippocampal formation ("HipForm"; HH, HHSub and Sub combined) were compared to the posterior electrodes in the RC and AM. For the RC and AM separately, ANOVAs with POSITION (RC or AM vs. ant HipForm) and CONDITION (target vs. standard) as within-subject factors were applied.

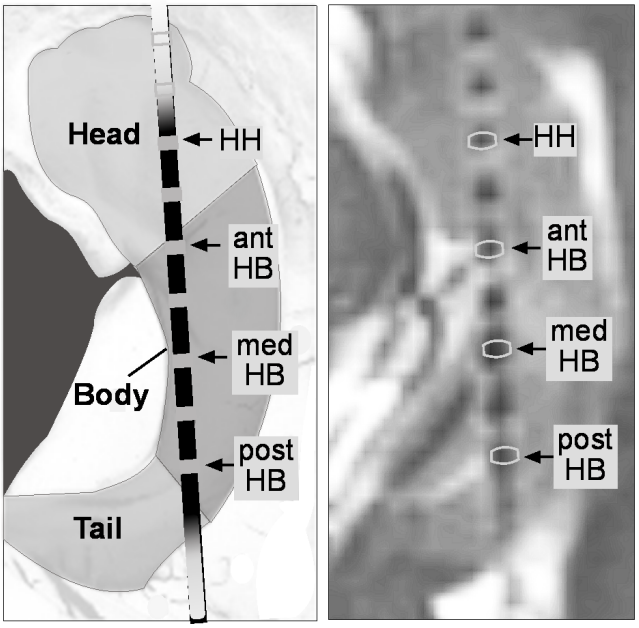

Abb. 2: Schematic overview (left) and exemplary data of one patient (right) of hippocampal electrodes in an axial view. Location of HH and HB electrodes. The HB electrodes were subdivided into anterior HB (ant HB), medial HB (med HB), and posterior HB (post HB) electrodes. (Modification of Fig.1 in Ludowig et. al, 2008).

A similar analysis was conducted for a comparison between RC and AM. Here, an ANOVA with POSITION (RC vs. AM) and CONDITION (target vs. standard) as within-subject factors was applied. For all ANOVAs, a Greenhouse-Geisser correction was used when necessary. Due to the high-variability between subjects, we did not implement between-subject comparisons. All comparisons were also conducted for MTL-P300 latencies instead of mean amplitudes.

Results

On average, 96.9 % (± 2.5 %) of the targets were correctly identified. Mean reaction time for correct target responses was 396 ms (± 74 ms).

MTL-P300 anterior-posterior differences within the structures

For the analysis of anterior-posterior differences concerning the MTL-P300 mean amplitudes, 8 patients for the HH, 14 patients for the Sub, 12 for the HHSub and 18 for the HB with at least two electrodes within the structures were included. For all structures, a significant main effect of CONDITION was indicated, with larger mean amplitudes for targets than standards (HH: $F_{1,7} = 5.882$, $p < 0.05$; Sub: $F_{1,13} = 16.242$, $p = 0.001$; HHSub: $F_{1,11} = 30.440$, $p < 0.001$; HB: $F_{1,17} = 39.488$, $p < 0.001$), reflecting large MTL-P300 potentials in response to targets but not to standards in the subiculum and hippocampus (Figure 3).

Anterior-posterior differences were found in the Sub and HB (main effect of POSITION; Sub: $F_{1,13} = 13.550$, $p < 0.005$; HB: $F_{1,17} = 8.325$, $p = 0.01$). While the mean amplitudes were significantly larger for the anterior as compared to the posterior position in the subiculum, the inverse gradient with larger amplitudes at the posterior position was found for the HB.

For the HB electrodes, a significant interaction between POSITION and CONDITION was found ($F_{1,17} = 5.375$, $p < 0.05$). Post-hoc tests indicated significant anterior-posterior differences only for targets and not for standards ($t_{17} = 2.702$, $p < 0.05$, Figure 3). Of note is that the latencies did not differ significantly between or within the structures (mean latencies: Sub: 446 ± 55 ms; HH: 429 ± 96 ms; HB: 486 ± 69 ms).

The linear gradients in the Sub and HB were also confirmed in the smaller group of patients with an additional medial electrode (linear effect of POSITION; Sub: $F_{1,5} = 8.912$, $p < 0.05$; HB: $F_{1,13} = 7.023$, $p < 0.05$). See Fig. 4 for ERPs.

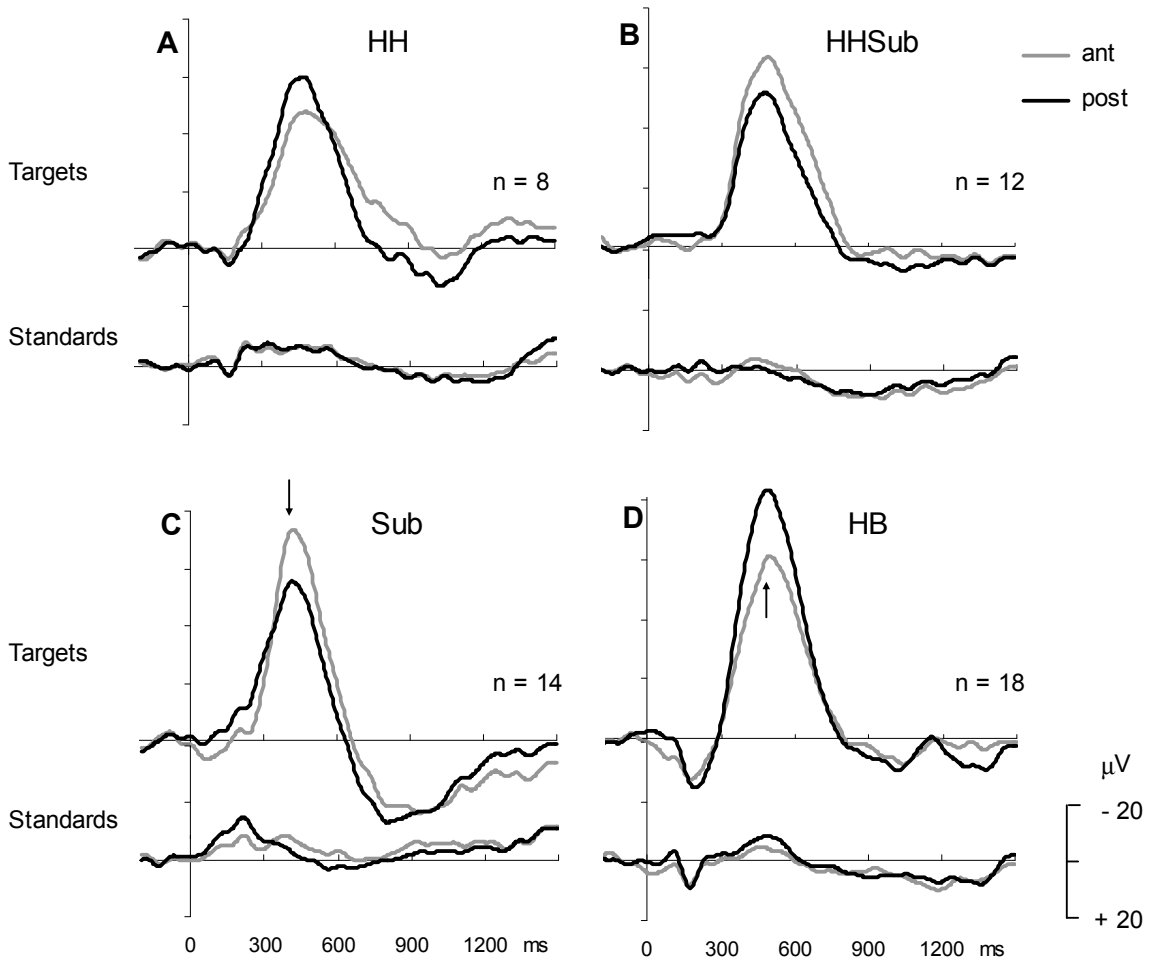

Fig. 3: ERPs to targets and standards in the a) hippocampal head (HH), b) transition zone between hippocampal head and subiculum (HHSub), c) subiculum (Sub) and d) hippocampal body (HB). Shown are the most anterior (ant) and most posterior (post) electrode in each structure. Significant main effects of position (ant vs. post) are marked with an arrow. Inverse effects were found in subiculum and hippocampal body. Negative values are plotted upwards.

MTL-P300 differences between the structures

MTL-P300 differences between structures were analyzed, in addition to the topographical differences within structures. In the ANOVA including 11 patients with a post HH and an ant HB electrode, a significant main effect of CONDITION ($F_{1,10} = 12.417$, $p < 0.01$), but no position differences between HH and HB was shown.

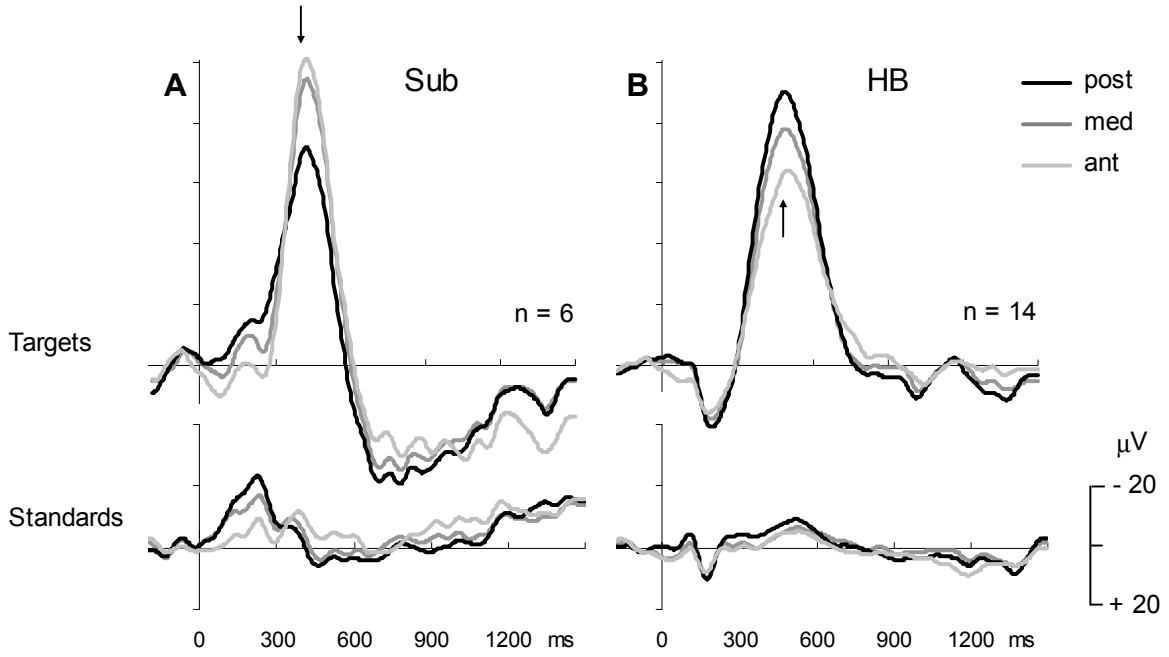

Fig. 4: ERPs to targets and standards in the a) subiculum (sub) and b) hippocampal body (HB). Shown are the most anterior (ant), the medial (med) and most posterior (post) electrode in each structure. Significant main effects of position (ant vs. med vs. post) are marked with an arrow. Inverse effects were found in subiculum and hippocampal body. Negative values are plotted upwards.

We did not compare hippocampus and subiculum since electrodes were either implanted along the subiculum or along the hippocampus.

Twenty five patients were included for the comparison of the RC with the hippocampal formation. For the comparison of the AM with the hippocampal formation, 10 patients with electrodes in both structures were included. For both comparisons, a main effect of POSITION (RC: $F_{1,24} = 32.244$, $p < 0.001$; AM: $F_{1,9} = 13.959$, $p = 0.005$), a main effect of CONDITION (RC: $F_{1,24} = 29.178$, $p < 0.001$; AM: $F_{1,9} = 37.726$, $p < 0.001$), as well as a significant interaction of CONDITION with POSITION emerged (RC: $F_{1,24} = 20.173$, $p < 0.001$; AM: $F_{1,9} = 10.276$, $p < 0.05$). Post-hoc paired t-tests revealed a difference between RC and hippocampal formation as well as AM and hippocampal formation for targets only (RC: $t_{24} = 5.559$, $p < 0.001$; AM: $t_9 = 3.837$, $p < 0.005$). Visual inspection of the individual data revealed that a negative MTL-P300

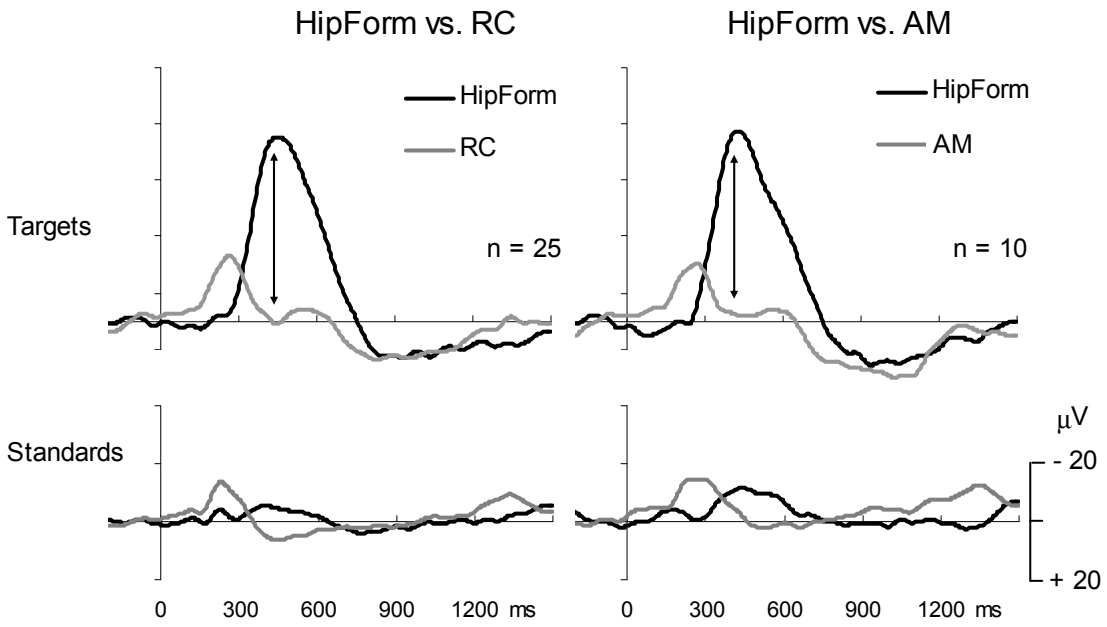

Fig. 5: ERPs to targets and standards for the anterior electrode in the hippocampal formation (HipForm, including subiulum and hippocampal head electrodes) compared to electrodes a) in the rhinal cortex (RC) or b) in the amygdala (AM). Negative values are plotted upwards.

potential was only observed in a small number of patients. More often, a small positivity was found in the MTL-P300 time window.

The direct comparison between P300 amplitudes at RC and AM electrodes revealed no significant differences (n = 14). See figure 5 for ERPs in the RC and AM in comparison to ERPs recorded in the hippocampal formation.

ERPs within the rhinal cortex and amygdala

Within the RC, mean amplitudes of data from 40 patients revealed no difference between targets and standards for the 300 to 650 ms window. The same was true for the data from16 patients with electrodes in the amygdala.

In most patients (30 of 40 patients with electrodes in the RC, 11 of 16 patients with electrodes in the AM) the small positivity in the MTL-P300 time window was preceded by an early negativity with a latency of around 260 ms. The corresponding

time window of 200 to 300 ms was analyzed post-hoc for the evaluation of this N200-like potential in the anterior mediotemporal lobe (AMTL-N200). Here, the mean amplitudes in response to targets were singificantly larger than those in response to standards (RC: $t_{39} = 2.327$, $p < 0.05$; AM: $t_{15} = 2.458$, $p < 0.05$). RC and AM did not differ in respect to the AMTL-N200.

Discussion

A pronounced MTL-P300 was observed in the hippocampal formation. A linear increase of MTL-P300 mean amplitudes was shown along the longitudinal axis of the hippocampal body, with largest amplitudes in the posterior hippocampal body. In the subiculum, the inverse gradient was found, with larger MTL-P300 mean amplitudes at anterior electrodes. Negative MTL-P300 components were not observed in the rhinal cortex and amygdala. Here, in response to targets an AMTL-N200 was followed by a positivity whose latency was similar to the hippocampal P300.

MTL-P300 in hippocampus and subiculum

Previous intracranial studies have consistently shown a negative hippocampal P300 with large amplitudes in response to visual oddballs (Halgren *et al.*, 1995a; Fell *et al.*, 2005; Roman *et al.*, 2005; McCarthy *et al.*, 1989; Brazdil *et al.*, 2001; Grunwald *et al.*; 1999b). Data of the subiculum is only rarely described. In the study of Halgren *et al.* (1995a) the subicular P300 was small and positive, while other authors observed large negative subicular-P300 potentials in humans (McCarthy *et al.*, 1989).

Electrodes anteriorly, posteriorly and superiorly to the hippocampal formation usually show positive deflections (human data: McCarthy *et al.*, 1989; Halgren *et al.*, 1995a; Brazdil *et al.*, 2001; Grunwald *et al.*, 1999b; animal data: Paller *et al.*, 1992).

These polarity inversions in adjacent structures have been regarded as evidence for a local generation of the MTL-P300 within the hippocampus.

Our study indicated large negative MTL-P300 components both in the hippocampus and in the subiculum. Anteriorly to the hippocampus in the rhinal cortex and amygdala, a positivity with similar latency as the MTL-P300 in the subiculum and hippocampus was found. This positivity might be a polarity inversed MTL-P300. Thus, ERPs in the hippocampus and ERPs anteriorly to the hippocampus differed considerably in their morphology. This finding indicates, in line with previous studies, that the hippocampal P300 does not result from volume conduction. The hippocampus and the subiculum are anatomically suited for producing ERPs. Synaptic currents are likely to summate rather than cancel out in the laminated structures (Smith *et al.*, 1986; Amaral and Lavenex, 2007).

In addition, we found local voltage gradients along the longitudinal axis of the hippocampal body and subiculum. These gradients were oriented in opposite directions, with larger amplitudes posterior than anterior in the hippocampal body and larger amplitudes anterior than medial in the subiculum. Therefore, we suggest that at least two separate generators in the MTL elicit the MTL-P300 potentials: one in the anterior subiculum and one in the posterior hippocampus. Of note, we analyzed electrodes in the anterior half of the subiculum only.

Anterior-posterior differences in the MTL were not systematically described in previous intracranial studies. Concerning the hippocampus, some case studies suggested the existence of gradients. McCarthy *et al.* (1989) mentioned that at more anterior locations within the hippocampus the MTL-P300 tended to decrease in amplitude in visual and auditory oddball paradigms. This was also shown for visual and auditory targets in a single case described by Paller *et al.* (1992). On the other hand, larger amplitudes were shown by Halgren (1995a) for anterior than posterior leads in response to auditory targets. Crottaz-Herbette *et al.* (2005) further suggested modality differences in anterior-posterior gradients. In contrast, our data suggest that

both kinds of gradients exist within the visual modality, pointing towards the notion of two MTL-P300 generators.

ERPs in the rhinal cortex and amygdala

In the rhinal cortex and amygdala, previous studies reported an early negative AMTL-N200 peaking at ~250 ms, followed by a positivity at ~400 ms. This positivity has been shown to have the same latency as the negative MTL-P300 in the hippocampus (Halgren *et al.*, 1995a; Smith *et al.*, 1986; Kukleta *et al.*, 2003; McCarthy *et al.*, 1989).

In line with the previous studies, we also found an AMTL-N200 with a latency of ~ 270 ms in the rhinal cortex and amygdala, which was followed by a predominantly positive ERP with a latency of ~ 450 ms. The AMTL-N200 was signficantly larger for targets than standards, while no such difference was found for the positivity. ERPs in the amygdala and rhinal cortex did not differ significantly. The positive rhinal and amygdalar ERP in the MTL-P300 time window might rather be a polarity inverted MTL-P300 than an individual potential. The AMTL-N200 potential, which has been shown to be particularly large in the rhinal cortex, is probably locally generated in it (Halgren *et al.*, 1995a). A local generation of the AMTL-N200 in the amygdala is less likely, since neurons of the amygdala are multipolar with dendrites passing in all directions (McDonald, 1992) and synaptic currents in the amygdala would therefore probably not spatially summate.

Anatomical considerations

To summarize, our data suggest a rhinal AMTL-N200 generator, as well as two separate MTL-P300 generators, one in the anterior subiculum and one in the posterior hippocampus. The subiculum is classically regarded as the primary output structure of the hippocampus (Amaral and Lavenex, 2007). In our study, no latency differences were found between the hippocampal and subicular MTL-P300. This may

imply a parallel activation of these structures. Possible anatomical sources are the parallel projections from the entorhinal cortex to the subiculum and hippocampus.
The rhinal AMTL-N200 might constitute the first stage of information processing in the peri- or entorhinal cortex. While the MTL predominantly responded to targets, standards elicited an AMTL-N200 in this as well as previous studies (Kukleta, 2003). In our previous study (Rosburg *et al.*, 2007), a similar early rhinal negativity was observed in a passive auditory oddball paradigm.

Functional considerations

Our data suggests an involvement of the posterior hippocampus as well as the anterior subiculum in the generation of the oddball MTL-P300. Target detection in a classical oddball paradigm is usually not very demanding for the subjects. Nevertheless, this task causes widespread activation of multiple brain regions in frontal, parietal, and temporal areas. Therefore, all systems that might be relevant in the rapid evaluation and processing of the stimulus seem to be engaged (Kiehl *et al.*, 2001). According to Halgren *et al.* (1998), all areas potentially useful for the task are activated, even if the probability is low that they will contribute to task performance. This would allow the creative interpretation of unexpected events, incidental learning, and self-monitoring.
The function of the hippocampus in an oddball paradigm might be to maintain a template of previous stimuli for a comparison with incoming sensory stimuli (Knight and Nakada, 1998). Another potentially related ability of the hippocampus is the detection of novelty (Strange and Dolan, 2001; Sokolov and Nezlina, 2004). The subiculum also receives and compares signals and acts as a distributor of processed information (Naber *et al.*, 2000). Both, the hippocampus and the subiculum are essential parts of the MTL-memory system and build a highly developed comparator system that allows novelty detection and memory formation (Vinogradova, 2001).

Within the classical oddball paradigm that we applied, a functional separation between the subiculum and hippocampus is not possible. Future studies are needed to ascertain whether the MTL-P300 potentials in the two structures respond differentially to certain task conditions. Halgren *et al.* (1995a) for example have suggested an involvement of the subiculum in the attention network. In this case, ERPs in the subiculum should also show a sharp P3a in response to infrequent distractor stimuli, which were not part of our stimulation procedure.

We did not find hemispheric differences in this study. This is in line with previous studies, showing bilateral hippocampal activity in response to oddballs in intracranial (Grunwald *et al.*, 1999b) and fMRI studies (Crottaz-Herbette *et al.*, 2005).

Conclusions

This is the first study that shows two separate MTL-P300 generators in the human hippocampal formation. One generator is assumed to be located in the anterior subiculum and the other in the posterior hippocampal body. Since latencies did not differ, parallel activation via the entorhinal cortex might have initiated the simultaneous MTL-P300 response in both structures. It remains open, whether the MTL-P300 generators support similar or different functions during target and deviance detection.

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7 Studie II

Intracranially recorded memory-related potentials reveal higher posterior than anterior hippocampal involvement in verbal encoding and retrieval

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Abstract

The human hippocampus is essential for both encoding and recollection, but it remains controversial whether there is a functionally different involvement of anterior versus posterior parts of the hippocampus in these memory processes. In the present study, we examined encoding and retrieval processes via intrahippocampal recordings in 27 patients with unilateral temporal lobe epilepsy. Multicontact depth electrodes were implanted along the longitudinal axis of the hippocampus as part of the presurgical evaluation. In a continuous word recognition test, subjects had to indicate whether words were new or already presented. Recognized old words, as compared to new words, resulted in a larger P600 component, as well as in a larger late negative component (LNC, 600 to 900 ms). In addition, subsequently remembered words elicited a larger positivity (400 to 900 ms) than later forgotten words. We found differences concerning the distribution along the hippocampus for the LNC old-new effect, reflecting successful retrieval, as well as for the subsequent memory effect, reflecting successful encoding. Both effects were larger the further posterior an electrode was located in the hippocampus. Findings are suggestive for a predominant posterior hippocampal involvement in both verbal encoding and retrieval.

Introduction

Since the famous case study of H.M., it is generally accepted that the hippocampus is critical for explicit memory in humans (Scoville and Milner, 1957). Hippocampal activity has been associated with both encoding and recollection processes (Squire, 1992), but within the hippocampus a further specialization might exist. A functional separation with encoding in the anterior half and retrieval in the posterior half of the hippocampus was proposed by a meta-analysis of PET memory studies (Lepage *et al.*, 1998). In contrast to this concept, Greicius *et al.* (2003) suggested that the middle and posterior hippocampus is activated more strongly than the anterior hippocampus by both verbal encoding and retrieval. A predominantly posterior hippocampal involvement in encoding was also concluded from a review of fMRI studies (Schacter and Wagner, 1999).

The functional separation of anterior and posterior parts of the hippocampus in memory processes has remained an open issue as yet (see also Henson, 2005). Beside differences in study material and experimental paradigms, inconsistencies between fMRI findings might be related to the problem of susceptibility artefacts, which diminish the sensitivity of fMRI to detect an activation especially in the anterior MTL (Ojemann *et al.*, 1997; Greicius *et al.*, 2003).

In contrast to fMRI and PET, event related potentials (ERPs) have a very high temporal resolution and give a direct estimation of neuronal activity, but it is not possible to measure hippocampal activity with scalp ERPs because the hippocampus is arranged cylindrically, forming a closed field (Klee and Rall, 1977). This problem is illustrated by the P300 component, which is reliably recorded in the hippocampus (Halgren *et al.*, 1980). However, the scalp P300 is not affected by hippocampectomy (Johnson, 1988). Thus, the hippocampal P300 does not or only to a minor degree contribute to the P300 signal at the scalp.

Recordings with electrodes implanted in the hippocampus of patients with pharmacoresistant temporal lobe epilepsy (TLE) offer the rare opportunity to measure

hippocampal activity directly, both with high temporal resolution and excellent signal-to-noise ratio. Previous studies with intracranial electrodes in the human hippocampus have shown that words elicit two different ERP components: the P600, which is a positivity between ~ 300 and 800 ms, and a late negative component (LNC), which is a negativity between ~ 600 and 1400 ms. Both components are larger for old than for new words and, therefore, are assumed to reflect memory processes (Smith *et al.*, 1986; Grunwald *et al.*, 2003). Usually, the P600 old-new effect is maximal between 300 to 600 ms (Grunwald *et al.*, 2003). The intracranial P600 is labelled with reference to the surface nomenclature (Guillem *et al.*, 1995), but actually peaks around 450 ms in response to old words and around 550 ms in response to new words.

During encoding, the P600 amplitude to new words increased with successful memory formation (Fernández *et al.*, 1999; Fernández *et al.*, 2002). In contrast to the P600 old-new effect, this subsequent memory effect (with a more positive P600 to new words that are later remembered than for new words that are later forgotten) is a long lasting effect measurable till up to 2000 ms after stimulus onset (Fernández *et al.*, 1999; Fernández *et al.*, 2002). Beside its relevance for the encoding of verbal material, the P600 is also sensitive to general semantic association processes (Vannucci *et al.*, 2003; Klaver *et al.*, 2005; Dietl *et al.*, 2005).

During encoding, there was no subsequent memory effect for the LNC (Fernández *et al.*, 1999), but the LNC for successfully recognized old words differed significantly from the LNC for new words (Grunwald *et al.*, 2003). This old-new effect on the LNC was larger in an intentional recognition task than in an incidental one (Grunwald *et al.*, 2003). Thus, the LNC probably reflects successful retrieval processes. Although it could be assumed that P600 and LNC should be larger for verbal material on the left side and for pictorial material on the right side, no significant hemispheric differences have been found in previous studies (Grunwald *et al.*, 1995; Vannucci *et al.*, 2003; Klaver *et al.*, 2005).

Until now, no systematic evaluation of the spatial distribution of invasive ERP memory effects along the hippocampus axis has been undertaken, although such an analysis offers the possibility to dissociate encoding and retrieval processes with a high temporal and spatial resolution and to test previous hypotheses about a functional separation within the hippocampus. For example, if encoding is supported by the anterior and retrieval by the posterior part of the hippocampus (Lepage *et al.*, 1998), then the subsequent memory effect should be larger in the anterior hippocampus and the LNC old-new effect larger in the posterior hippocampus. In the current study we examined P600 and LNC old-new effects as well as the subsequent memory effects along the longitudinal axis of the hippocampus in order to assess functional separations within the hippocampus in memory processes. We further tested for hemispheric differences.

Methods

Subjects

We investigated patients with pharmacoresistant unilateral TLE, who were implanted with bilateral depth electrodes along the longitudinal axis of the hippocampus during presurgical evaluation. Only recordings from the nonepileptic temporal lobe and only patients with at least one electrode located in the hippocampal head or three electrodes in the hippocampal body were included. Patients with demonstrated atypical language dominance were excluded, but language dominance (Wada-test or fMRI) was not tested in all cases. All but one patient were right handed. In the left handed patient, fMRI language testing indicated typical left hemispheric language lateralization. Thus, 27 patients (10 females; 13 left, 14 right TLE) were included in the study (see Table 1 for patients´ characteristics). Patients ranged in age from 18 to 61 years (mean 42 yrs) and in duration of their epilepsy from 4 to 57 years (mean 26 yrs).

TABLE 1. Patients´ characteristics and performance in the continuous word recognition paradigm as well as an overview of available electrodes.

Patients´ characteristics						available electr.
Subject	non-focal side	Sex	age	duration of epilepsy	Pathology of focal side	
1	L	m	37	33	HS	HH
2	L	f	46	37	HS	HH
3	R	m	45	25	HS	HH
4	R	f	57	30	HS	HH
5	R	m	54	43	HS	HH 2
6	L	f	37	4	HS	HH,HB
7	L	f	40	38	HS	HH,HB
8	L	m	43	30	HS	HH,HB
9	L	m	46	20	HS	HH,HB
10	R	m	61	57	HS	HH,HB
11	L	m	50	34	HS + temporal lobe dysplasia	HH,HB 1
12	L	m	45	29	Parieto-occipital astrocytoma	HH,HB 1
13	L	m	34	4	HS + temporal lobe tumor	HH,HB 2
14	L	f	41	14	HS	HB
15	L	m	42	34	HS	HB
16	R	m	38	13	HS	HB
17	R	m	40	35	HS	HB
18	R	f	44	43	HS	HB
19	R	f	28	24	Amygdala -ganglioglioma	HB
20	R	f	38	9	Temporal blurring of the grey-white matter junction	HB
21	R	m	22	10	No clear lesion	HB
22	R	m	55	9	Occipito-temporal cavernoma	HB
23	L	m	47	39	Temporal arteriovenous malformation	HB
24	R	m	57	17	Temporal necrosis	HB
25	R	f	25	18	Temporal blurring of the grey-white matter junction	HB
26	L	m	38	26	HS	HB 1
27	L	f	18	16	Temporal dysplasia	HB 1

R= right, L= left; m= male, f= female; HS= hippocampal sclerosis
HH= hippocampal head electrode, HB= hippocampal body electrode
1= excluded from subsequent memory analysis; 2= completely excluded

All participants had normal or corrected-to-normal vision. MRI scans or histological examinations demonstrated hippocampal sclerosis in 18 patients, extrahippocampal lesions without signs of hippocampal sclerosis in 8 patients and no clear lesion in one patient. All but two patients underwent subsequent epilepsy surgery after implantation (16 selective amygdalo-hippocampectomies, 5 temporal two-thirds

resections, 4 lesionectomies). The test paradigm is part of the routine presurgical workup in patients with hippocampal depth electrodes. The study was approved by the ethics committee of the University of Bonn.

Paradigms

For a continuous word-recognition paradigm, 300 frequent German nouns were selected (mean word frequency was 50 per 1 million words according to the CELEX lexical database, version 2.5). 150 stimuli were only presented once, whereas the other 150 words were shown with one repetition. This repetition occurred in 50% of the trials after a short lag of 3 to 6 words and in 50% after a long lag of 10 to 30 words. In line with a previous study (Grunwald *et al.*, 1998), the analyses of our own ERP data separated for short and long lags did not reveal any essential impact of the applied lag on the reported effects. For clarity, only the analysis of ERPs for the both lags collapsed is provided. 450 words were presented consecutively with a duration of 300 ms per word. The length of the interstimulus interval was randomised around ~ 2000 ms, but was increased in adjustment of the subject abilities in some cases (on average, the interval was 2155 ± 416 ms long). After each word, subjects had to indicate by pressing one of two buttons whether it was new or already presented before. 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 monitor approximately 80 to 100 cm away. The words were presented in white color on a black background with an height of ~1,5° and a width of ~3 to 9° visual angle, depending on word length. Recordings were occasionally repeated on the following day, if performance was bad or ERPs were contaminated by spikes or sharp waves.

Explored brain structures and recording sites

ERPs were recorded from bilateral depth electrodes implanted stereotactically along the longitudinal axis of the hippocampus. Each catheter-like, 1 mm thick depth electrode contained 10 cylindrical platinum electrodes of 2.5 mm every 4 mm. Ideally, the first three of these ten electrodes are 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. There were variabilities in placement of the electrodes across patients in the anterior-posterior and also inferior-superior direction. Therefore, numbers of patients varied for different analyses. Electrodes were grouped in hippocampal head and hippocampal body electrodes (Fig. 1), according to the anatomy atlas of Duvernoy (1988). The first hippocampal body electrode was defined as the first position where the fimbria was visible and the uncus had disappeared.

Recordings

Electrophysiological data were recorded with the digital EPAS system (Schwarzer, Munich, Germany) and its implemented Harmonie EEG software (Stellate, Quebec, Canada). EEG was measured against left and right mastoids with a sampling rate of 200 Hz or 1000 Hz. 1000 Hz recorded data were re-sampled to 200 Hz. For the analysis of old-new effects, segments were averaged for correctly identified first presentations (“new”) and correctly identified repetitions (“old”). For the subsequent memory analysis, segments were averaged for first presentations which were later successfully recognized (“rem”) and first presentations which were later forgotten and not recognized when repeated (“forg”).

All EEG segments had a duration of 1,700-ms with a 200-ms prestimulus period as baseline. Data were highpass filtered at 0.1 Hz with a slope of 12 dB/octave and lowpass filtered at 12 Hz with a slope of 12 dB/octave. Amplitudes were measured relative to the mean amplitude of the 200 ms pre-stimulus baseline. An automated artifact rejection was implemented using Matlab 7.1 (Mathworks, Natick, MA). For each segment, the standard deviation of the data points as well as the standard deviation of the gradients (the increase or decrease between two successive data point) were determined. A segment was rejected if any data point or gradient deviated more than four standard-deviations from the mean. Thus, segments with abnormally high amplitudes as well as abrupt rises or falls were eliminated. On average, 10.7 % of trials were removed based on these criteria.

Electrode selection

To study old-new as well as subsequent memory effects in different parts of the hippocampus, one electrode in the hippocampal head and three electrodes in the hippocampal body were selected. The hippocampal head ("HH") electrode is defined as the most anterior electrode in the hippocampal head. In the hippocampal body, the most anterior ("ant HB"), the most posterior ("post HB") and a medial hippocampal body electrode ("med HB") were selected. The medial hippocampal body electrode was either the electrode that was located exactly in the middle of the anterior and posterior hippocampal body electrodes, or, if this was not possible, the mean average of two medial electrodes. See Figure 1 for an example of the anatomical location of contact labels.

Because the first electrodes were often located in the subiculum and not in the hippocampal head, there were less subjects with electrodes in the hippocampal head than with electrodes in the hippocampal body. In order to keep the number of subjects included in the analysis sufficiently high, the data of hippocampal head electrodes and of hippocampal body electrodes were analysed separately.

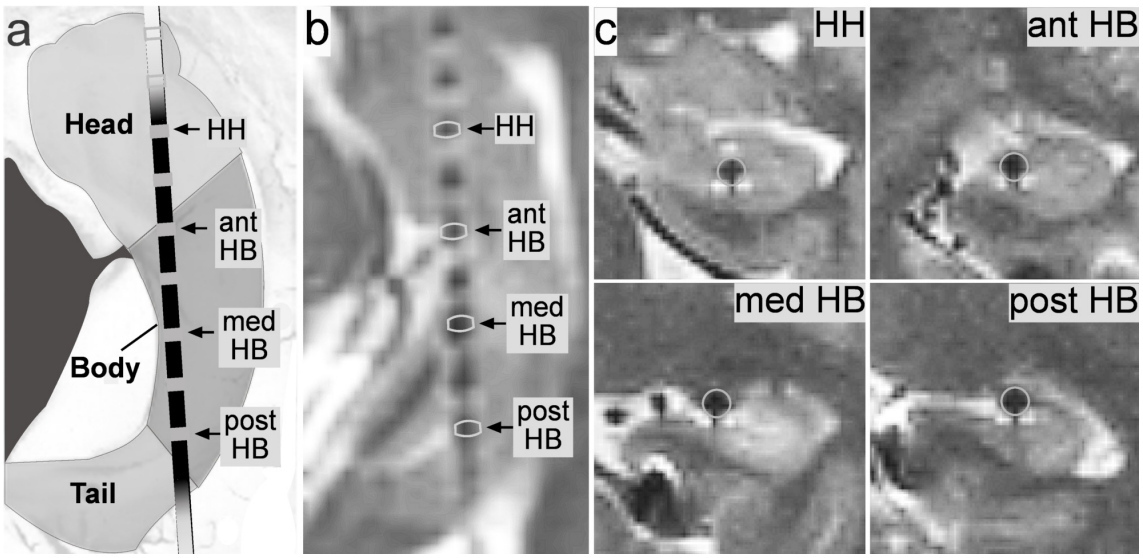

FIGURE 1. Location of hippocampal electrodes and exemplary MRI data (patient 11). The selected hippocampal head electrode (HH), anterior hippocampal body electrode (ant HB), medial hippocampal body electrode (med HB) and posterior hippocampal body electrode (post HB): (a) in a schematic overview, (b) in the axial slice, (c) in coronal slices. The two electrodes visible in the axial slice anterior to HH are located in the amygdala

Data analysis

For the old-new effect, the mean amplitudes of three time windows were analysed. The time window between 350 - 550 ms was chosen to measure the P600 old-new effect. We selected this time window because the P600 in response to new words shows a broader and more shallow progression than for old words. Therefore, the P600 old-new effect is best measured in the time window before the steep P600 to old words crosses the smaller and more shallow P600 to new words. The time windows between 600 - 900 ms and 900 - 1200 ms were chosen to measure the early and late LNC. To assess the subsequent memory effect, we analysed the "rem" and "forg" trials in the time window between 400 - 900 ms. This longer time window as compared to the P600 old-new effect was selected because the subsequent memory effect covers later parts of the P600 as well.

For the evaluation of old-new or subsequent memory effects in the hippocampal head, we applied paired t-tests. The number of patients with electrodes in the

hippocampal head was too low for hemispheric evaluations (8 with left hemispheric and 3 with right hemispheric HH electrodes). For the hippocampal body, we were interested in differential memory effects along the hippocampal axis. For each memory effect (old-new, subsequent memory) separate analyses of variance (ANOVAs) were calculated.

Old-new effects were evaluated in a two-way repeated-measures ANOVA with old-new (old vs. new) and position (anterior, medial, posterior electrode in the hippocampal body) as within-subjects factors and hemisphere as between-subject factor. An interaction between old-new effect and position would be expected if an old-new effect systematically varied along the longitudinal axis of the hippocampal body. For the analysis of subsequent memory effects, an analogue ANOVA was calculated with subsequent memory (rem vs. forg) and position as within-subject factor and hemisphere as between-subject factor. For the direct comparison of hippocampal head and anterior hippocampal body electrodes, an ANOVA was calculated for the subgroup of patients who had electrodes in both regions, with position (hippocampal head vs. anterior hippocampal body) and old-new or subsequent memory as within-subject factors. The Greenhouse-Geisser correction was used when necessary, and is indicated by citation of ε-values. Within the ANOVAs, the effects of position were tested for linearity. When significant effects were found, post-hoc t-tests for paired samples were applied.

Results

Behavioral Data

On average, 86.6% (± 13.1) of the new words and 65.1% (± 22.7) of the old words were correctly categorized. This performance was significantly different from chance (new words: $t(26) = 34.407$, $p < 0.001$; old words: $t(26) = 14.917$, $p < 0.001$) and did not differ between patients with left and right focal hemisphere or between male and female patients (all t values < 0.700, n.s.). Also, reaction times for correct responses did not differ between new and old words (new words: 840 ± 192 ms; old words: 878 ± 156 ms, paired t-test: $t(26) = 1.440$, n.s.).

ERPs in the hippocampal head

Old-new effects

For the analysis of old-new effects, 11 patients with at least one electrode in the hippocampal head were included. Data for 2 other patients were excluded because the morphology of the ERPs was not comparable to the other patients. In the hippocampal head, the P600 elicited by old words was more positive than was the P600 to new words ($t(10) = 3.359$, $p < 0.01$). The early LNC to old and new words did not differ ($t(10) = 0.239$, n.s.). In the late LNC time window, new words were significantly more negative than old words ($t(10) = 3.923$, $p < 0.005$; Fig.2a top panel).

Subsequent memory effect

For this analysis, two more patients were excluded because performance was extremely good, which left too few "forgotten" trials for a reliable calculation of ERPs. In the nine patients analysed, no significant subsequent memory effect was observed in the hippocampal head ($t(8) = 1.671$, n.s; Fig.2b top panel).

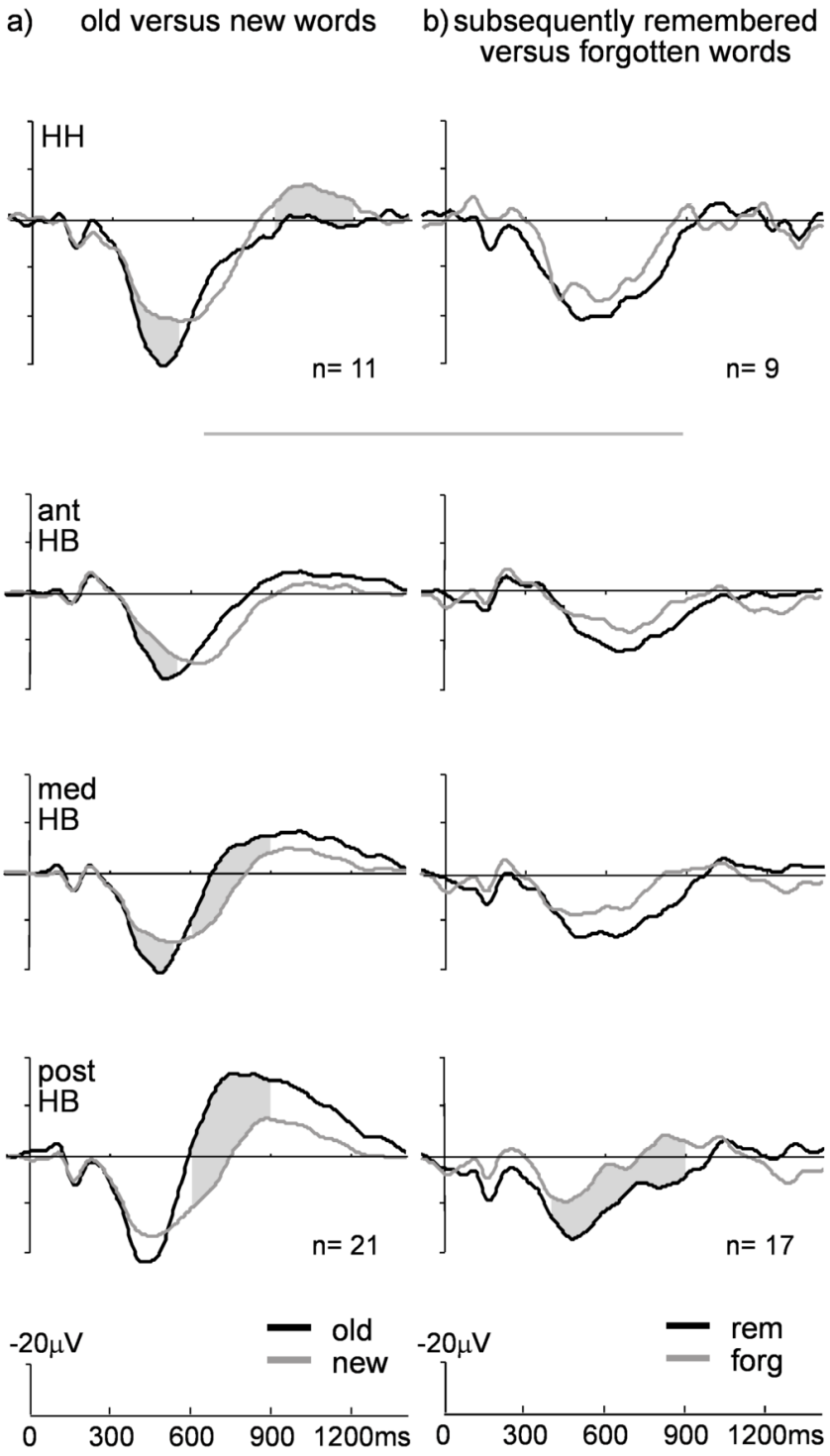

FIGURE 2. ERPs to (a) correctly recognized old versus new words and to (b) subsequently remembered (rem) versus forgotten (forg) words for hippocampal head (HH) and three hippocampal body (HB) electrodes. Significant differences in mean amplitude between old and new or later remembered and later forgotten are grey shaded. Negative values are plotted upwards.

ERPs in the hippocampal body

Old-new effects

For the analysis of old-new effects, 21 patients with at least three electrodes in the hippocampal body were included. Data of one patient were not evaluated because of unusual ERPs.

For the P600, the overall old-new effect reached significance ($F(1,19) = 7.148$, $p < 0.05$), with larger P600 mean amplitudes for old than new words. No significant effects of position or interaction between position and old-new effect were observed (see Fig. 2a for ERPs). In paired t-tests for ERPs at each electrode separately, the old-new effects at the anterior and medial, but not at the posterior electrode reached significance (anterior: $t(20) = 3.248$, $p < 0.005$; medial: $t(20) = 2.694$, $p < 0.05$; posterior: $t(20) = 1.610$, n.s.).

There was a more negative LNC for old words than for new words at all electrodes ($F(1,19) = 7.158$, $p < 0.05$). This old-new effect interacted with position, and was largest at the most posterior electrodes (linear effect: $F(1,19) = 9.021$, $p < 0.01$), as also reflected in the p-values of paired t-tests at each of the three electrode positions (anterior: $t(20) = 1.662$, n.s.; medial: $t(20) = 2.199$, $p < 0.05$; posterior: $t(20) = 3.345$, $p < 0.005$; Fig. 3a and 3c). Independent of the old-new effect, mean amplitudes of the early LNC were overall largest at the most posterior electrodes in the hippocampal body (main effect of position: $F(1,19) = 18.411$, $p < 0.001$). This was also true for the late LNC ($F(1,19) = 13.027$, $p < 0.005$), but there was no significant old-new effect or interaction between old-new effect and position in the late time window.

Subsequent memory effect

For the subsequent memory analysis, four patients were not included because they had forgotten too few words. Beside a general subsequent memory effect with more positive amplitudes between 400-900 ms for subsequently remembered words at all

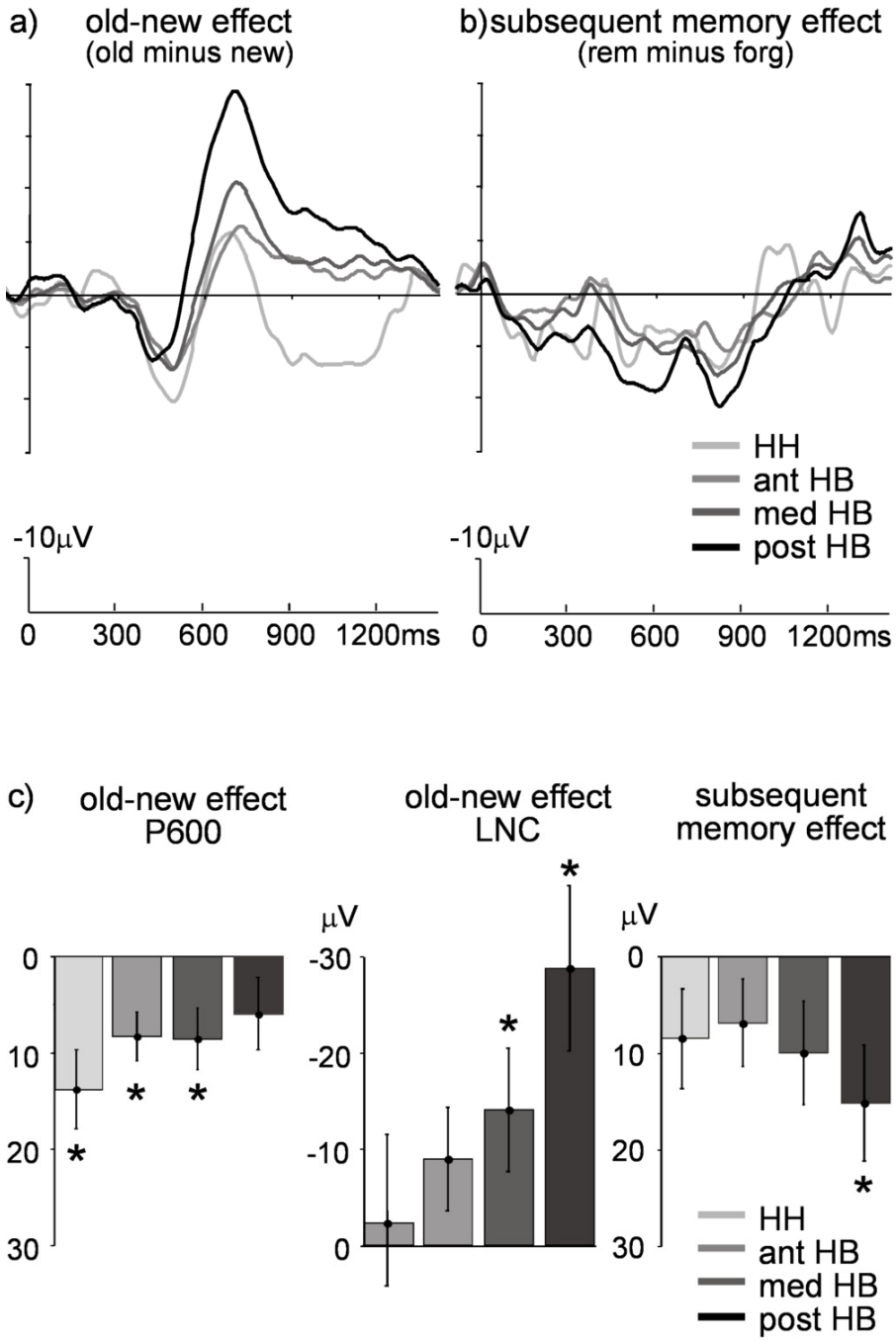

FIGURE 3. ERP difference waves (a) old minus new, (b) subsequently remembered minus forgotten, (c) the mean differences reflecting the P600 old-new effect, the early LNC old-new effect as well as the subsequent memory effect for hippocampal head (HH), anterior (ant HB), medial (med HB) and posterior (post HB) hippocampal body. Negative values are plotted upwards.

electrodes ($F(1,15) = 4.729$, $p < 0.05$), we also observed a linear increase of the subsequent memory effect with a more posterior position ($F(1,15) = 4.541$, $p = 0.05$; Fig. 3b). Post-hoc tests showed that there was no subsequent memory effect for the anterior and medial hippocampal body ($t(16) = 1.532$, n.s. and $t(16) = 1.890$, n.s.), but there was one for the posterior hippocampal body ($t(16) = 2.562$, $p < 0.05$; Fig. 3c).

Hemispheric differences

A significant effect of hemisphere was only observed for the P600 ($F(1,19) = 7.896$, $p < 0.05$; Fig. 4), which was larger on the left than right side. No interactions of hemisphere with old-new (Fig. 4a) or subsequent memory effect (Fig. 4b) and no interaction of hemisphere with position were found for any ERP component.

Hippocampal head versus hippocampal body

For all patients with hippocampal head electrodes, an anterior hippocampal body electrode was also available. 11 patients were included in the old-new analysis and 9 patients were included in the subsequent memory analysis. Concerning the P600 and LNC old-new data, no significant effects of position nor interactions between position and old-new effect were observed ($F(1,10) < 0.9$). Of note, the old-new effect of the P600 was virtually the same at both electrodes for those patients (HH: 13.9 µV ± 13.7; anterior HB: 14.8 µV ± 14.2). Also the subsequent memory effect did not differ significantly between the hippcampal head and anterior hippocampal body electrode (interaction $F(1,8) < 1.2$, n.s.).

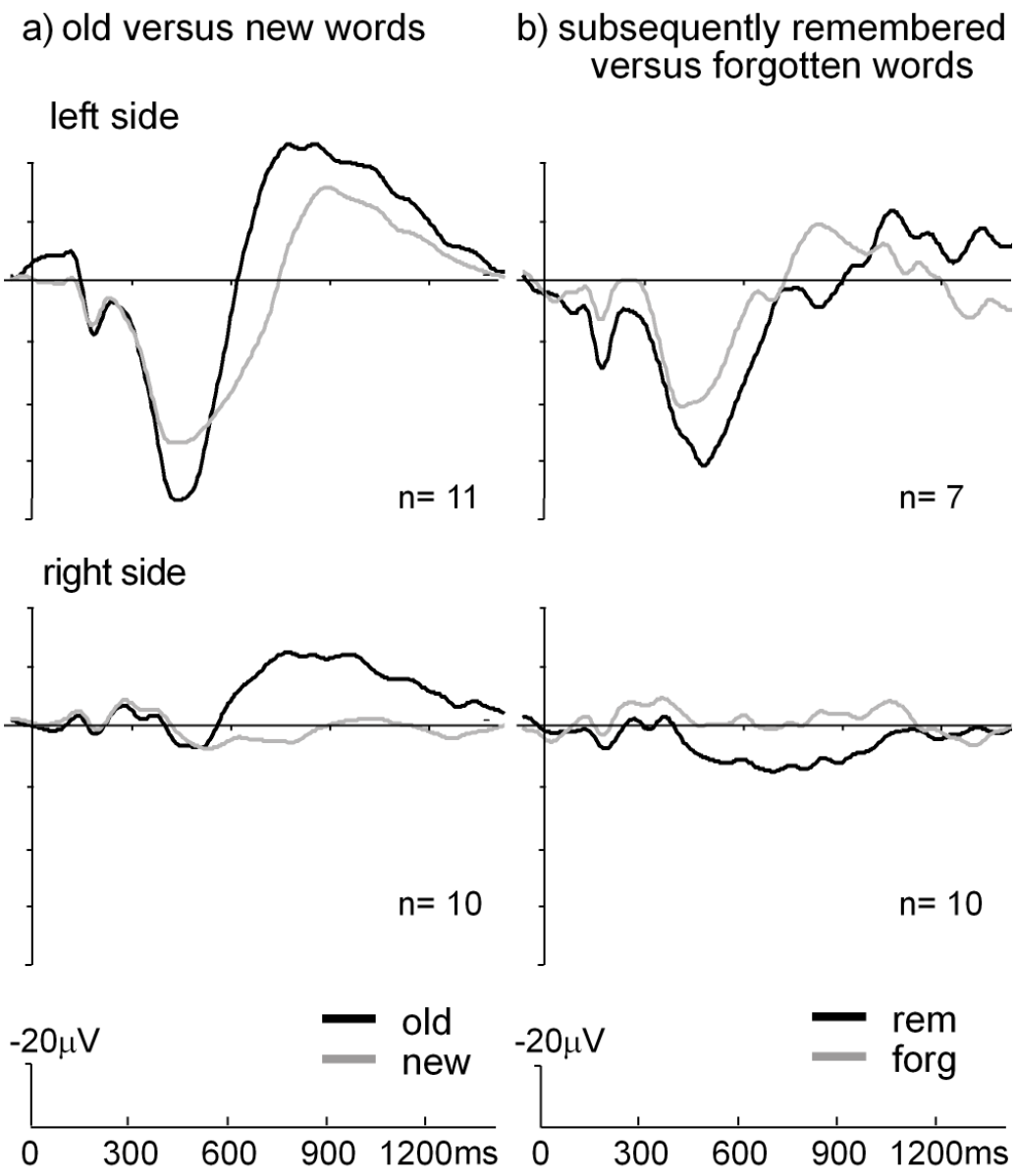

FIGURE 4. **Left versus right hemisphere: (a) ERPs for correctly recognized old versus new words for the posterior hippocampal body electrode, (b) ERPs for subsequently remembered versus forgotten words for the posterior hippocampal body electrode. Negative values are plotted upwards.**

Discussion

The aim of the present study was to evaluate systematically the distribution of old-new and subsequent memory effects along the longitudinal axis of the hippocampus. We found a linear increase for the early LNC old-new effect, as well as for the subsequent memory effect: Both effects were larger the further posterior the electrode was located in the hippocampus. The P600 old-new effect was equally significant in the hippocampal head and body. Hemispheric differences were observed for the P600, which was significantly larger on the left as compared to the right side; the old-new and subsequent memory effect did not differ between hemispheres. For the late LNC we found an inverted old-new ("novelty") effect in the hippocampal head.

Retrieval and the hippocampus

The comparison between words that were correctly recognized as new words and words that were correctly recognized as old words ("old-new effect") can be used to explore successful recognition. The LNC old-new effect between 600 and 900 ms was assumed to reflect successful retrieval processes (Grunwald *et al.*, 2003). In this time window (the "early" LNC), we observed a linear increase of the old-new effect along the hippocampal axis – with no old-new effect in the hippocampal head and anterior hippocampal body, but moderately sized effects in the medial and large effect in the posterior hippocampal body.

Our finding is in line with the majority of fMRI and PET studies showing, that the posterior hippocampus is more involved in memory retrieval than its more anterior parts (Lepage *et al.*, 1998; Stark and Squire, 2000; Daselaar *et al.*, 2006; Henson *et al.*, 1999). To our knowledge, there are no studies showing a predominantly anterior hippocampal involvement during retrieval of single items. The anterior hippocampus might be more important in relational memory, since Giovanello *et al.* (2004) found greater anterior hippocampal activity during retrieval of associations than during retrieval of single items.

As we did not collect confidence ratings in the behavioural task, we were not able to separate decisions based on recollection from those based on familiarity. Many studies propose that recollection activates the hippocampus more than does familiarity (Strange *et al.*, 1999; Yonelinas *et al.*, 2005; Daselaar *et al.*, 2006). However, we were able to show strong hippocampal activity in the present study. If we intermixed recollection-based trials (with high activity) with familiarity-based trials and correct responses by chance (with smaller or no retrieval related activity), this might have affected the overall signal, but should not change the interpretation of differences along the longitudinal axis of the hippocampus.

Encoding and the hippocampus

A suitable method to probe successful encoding is a comparison between stimuli that are later remembered and those that are later forgotten. In the hippocampus, subsequently recalled words are accompanied by a more positive ERP component than subsequently forgotten words (Fernández *et al.*, 1999; Fernández *et al.*, 2002). As for the retrieval success-related LNC, we also found a linear increase of this subsequent memory effect along the hippocampal body. Thus, we assume that successful encoding is also subserved by the posterior part of the hippocampal body. This assumption is in line with several event-related fMRI studies showing that posterior parts of the hippocampus exhibited larger activity than anterior parts for subsequently remembered words (Fernández *et al.*, 1998; Reber *et al.*, 2002a; Greicius *et al.*, 2003). But at least one event-related study claimed a predominant involvement of the anterior hippocampus in encoding (Kensinger *et al.*, 2003).

Aside from these event-related fMRI studies specifically testing successful encoding, many other fMRI studies examined encoding in blocked designs, thus comparing blocks with an encoding task to blocks with a control task. Here, most of these studies also indicated a posterior focus for encoding (see Schacter and Wagner, 1999 and Henson, 2005 for reviews), but especially PET studies often reported anterior

hippocampal activity during encoding (Lepage *et al.*, 1998). It remains unclear whether these PET and fMRI inconsistencies are based on differences in methodology (e.g., fMRI susceptibility artefacts can result in a loss of anterior hippocampal BOLD signal; Ojemann *et al.*, 1997; Greicius *et al.*, 2003), or on differences in behavioural procedure (see Schacter and Wagner, 1999 for review). Generally, the use of blocked designs is somewhat problematic as encoding is analysed without considering the success of encoding. Thus, effects of novelty detection, semantic encoding processes and actual successful encoding are intermixed in these designs.

Furthermore, in most studies, analyses were not designed to directly compare anterior and posterior hippocampal activation, which would require a direct ROI-based comparison (Constable *et al.*, 1998). By applying such a ROI-based comparison, Greicius *et al*. (2003) observed larger posterior than anterior hippocampal activation in their event-related design. Reber *et al*. (2002b) reported a similar finding, but in their study the difference did not reach significance, possibly due to the small sample size (n = 5).

Cameron *et al*. (2001) investigated successful encoding in an associative learning task by recordings from microelectrodes in the hippocampus. The authors reported that neurons in the anterior hippocampus responded selectively to the successful learning of associations. Unfortunately, their study design did not allow a comparison of anterior and posterior electrodes, and the authors did not specify how they defined the anteriority of electrodes. However, even the finding of encoding sensitive neurons in anterior regions of the hippocampus is not necessarily contradictory to our results. The increasing subsequent memory effect along the hippocampus found in our study might reflect an increasing number of neurons along the hippocampus axis involved in successful encoding. Another possibility is that associative learning results in more anterior hippocampal activation, while single item learning is mediated more by posterior hippocampus, as proposed by Schacter and Wagner (1999).

Semantic association processes and the hippocampus

Aside from the subsequent memory effect, we also observed a P600 old-new effect reflecting larger activation in response to old than new words in hippocampal head and body. Thus, the P600 is influenced by two spatially and temporally distinguishable effects: By successful encoding with larger effects in the posterior than in the anterior hippocampal body, and by a short lasting effect of word repetition, with an equal distribution in the hippocampal head and body.

Encoding is an important feature of the hippocampus, but before a stimulus can be encoded, it must be activated in the semantic lexicon, which is likely mediated by the frontal lobes (Poldrack *et al.*, 1999; Fletcher *et al.*, 2000). Addis and McAndrews (2006) presented triads of words with either no, two or all three words being semantically associated. The authors observed larger inferior frontal cortex activity when less associations were provided and larger left hippocampal activity when more associations were provided. Thus, it was supposed that the inferior frontal cortex is responsible for providing semantic associations, while the hippocampus binds the provided associations during encoding.

We propose that the P600 represents an index of these provided associations. This would be in line with the previous findings, revealing a larger P600 for real than unreal objects (Vannucci *et al.*, 2003), for famous than nonfamous faces (Dietl *et al.*, 2005) and for concrete words with high imageability than for abstract words (Klaver *et al.*, 2005). If a word was previously encoded, the associations are more easily reactivated and more associations are accessible to the hippocampus, explaining a larger P600 for old words (Grunwald *et al.*, 2003). Since the P600 old-new effect was not significantly different between hippocampal head and anterior hippocampal body nor along the hippocampal body, these semantic association processes might be mediated by extended hippocampal networks.

Hemispheric differences

The mean amplitudes of the P600 between 350 and 550 ms were significantly larger on the left than on the right side for new and old words, whereas the left-right comparison for new words between 400 and 900 ms was not significant. There were no significant differences concerning old-new effects or the subsequent memory effect. This suggests that the left hemisphere is more involved in semantic association processes than the right hemisphere, but that both hemispheres are equally involved in memory encoding and retrieval.

The larger involvement of the left hippocampus in association processes is in line with the Addis and McAndrews study (2006), where also larger left hippocampal activity was observed when more associations were provided in a word association learning task. However, previous studies did not find hemispheric differences of the P600 in the continuous word recognition paradigm (Grunwald *et al.*, 1995; Klaver *et al.*, 2005) or in an object recognition task (Vannucci *et al.*, 2003).

Several studies reported left hemispheric activity to word stimuli during encoding (Strange *et al.*, 2002) or retrieval (Eldridge *et al.*, 2000; Fliessbach *et al.*, 2006), underlining the dominant role of the left hemisphere in verbal processing. In the current study, the LNC old-new effect reflecting successful retrieval, as well as the subsequent memory effect reflecting successful encoding, were observable to a comparable extent on the left and right side. Other studies revealed also bilateral hippocampal activity during encoding (Fernández *et al.*, 1998; Cameron *et al.*, 2001) and retrieval of verbal material (Yonelinas *et al.*, 2005). Beside other factors, it might depend on task characteristics, whether the language-dominant hemisphere exhibits a larger hippocampal activation during a verbal memory task or not. Overall, both the lack of hemispheric differences in memory functions in the current study, as well as the found hemispheric differences should be interpreted with some caution, as the left and right hemispheric ERPs were obtained in different subjects.

Novelty and the hippocampus

In the hippocampal head, a late negativity ("the late LNC") was shown to be larger for new than old words, thus reflecting a novelty effect. This finding of an "inverted" LNC old-new effect was unexpected and not shown with intracranial recordings before. However, it is supported by various fMRI studies (Tulving *et al.*, 1996; Dolan and Fletcher, 1997; Strange *et al.*, 1999; Strange and Dolan, 2001; Daselaar *et al.*, 2006) that especially anterior regions of the hippocampus are sensitive to stimulus novelty. In this context, it should be noted, that the N400 component, recorded in the rhinal cortex, is also larger for new than old words between 300 and 600 ms, and thus also sensitive to novelty (Grunwald *et al.*, 1995). A role of the hippocampus in novelty detection is in line with the finding that the integrity of the hippocampus is critical for the novelty detection in the rhinal cortex. For instance, hippocampal sclerosis decreases the rhinal AMTL-N400 to new but not to old words (Grunwald *et al.*, 1998) and the rhinal AMTL-N400 to new words is correlated with neuronal density in the CA1 subfield of the hippocampus (Grunwald *et al.*, 1999a).

Local generation of the ERPs

The LNC and P600 are most likely generated locally in the hippocampus. Previous studies have shown that the distribution and polarity of the P600 varied greatly between MTL structures like the amygdala, hippocampus and parahippocampal gyrus, and that the polarity inverted over short distances within the hippocampus (Smith *et al.*, 1986). This suggests that the potentials are generated by local synapses and do not reflect activity from distant sources (Halgren *et al.*, 1980). Although we did not observe polarity inversions within the hippocampus, both the P600 and LNC were detectable within the hippocampus, but not immediately outside of it: neither in the rhinal or parahippocampal cortex, the amygdala nor posterior to the hippocampus. Neurons in the hippocampus are arranged cylindrically (Amaral and Insausti, 1990), producing a radially symmetric closed field (Klee and Rall, 1977).

Hippocampal activity is thus shielded towards the outside, and the LNC component, as well as the P600, are most likely generated locally (Fernández *et al.*, 2002). Furthermore, due to the laminated structure of the hippocampus, synaptic current flows in the hippocampus tend to summate rather than to cancel out, providing a basis for large hippocampal ERPs (Smith *et al.*, 1986).

Limitations of the study

For clinical considerations, the exact location and number of the electrodes in the hippocampus is of minor relevance. This variability of electrode location has some impact on our study design and the interpretation of the data: (1) Only a low number of patients had electrodes in the hippocampal head *and* more than two electrodes in the hippocampal body. Thus, a statistical comparison of ERPs obtained at the hippocampal head and body was possible only in a subset of patients and, therefore, was statistically less sensitive than the analysis within the hippocampal body. However, the results of both analyses did not conflict in any aspect. Thus, there is no reason to assume that the inclusion of a larger number of patients with hippocampal head electrodes would have affected our major findings. (2) The hippocampal head electrodes as well as the anterior hippocampal body electrodes were chosen strictly according to the MRI images. In contrast, the medial and posterior hippocampal body electrodes were defined based on their relative positions, because the number of electrodes in the hippocampus body considerably varied in our sample. We decided to include all subjects with 3 to 5 hippocampal body electrodes in order to include as many subjects as possible and, thus, to provide a data basis, as reliable as possible. The inclusion of a larger number of patients with 5 electrodes in the hippocampus body might have resulted in more pronounced findings, but would have extended the temporal scope of the study tremendously. (3) The hippocampal tail is extremely rarely penetrated by electrodes. Therefore, it was not possible to study the functions of this region.

Also other factors might have influenced our findings. All our subjects were epileptic patients, and it is yet difficult to assess the impact of the epileptic focus on brain functions. However, it appears rather unlikely that the epileptic focus affects the component localization along the hippocampus of the non-focal hemisphere. Epilepsy should also be taken into account for the interpretation of hemispheric differences, as the hemispheric dominance in epilepsy patients might be affected by cortical plasticity and secondary effects, as e.g. crowding (Strauss *et al.*, 1990; Helmstaedter *et al.*, 2004). As already outlined, the current findings concerning hemispheric differences are limited by the fact that it was not possible to compare left and right hemispheres of the same subjects (because in each case one hemisphere was affected by the epileptic focus).

Finally, in the continuous word recognition paradigm items have to be encoded and retrieved at the same time. Although the chosen contrasts (old-new effect as reflecting successful retrieval, and subsequent memory effect as reflecting successful encoding) theoretically correct for this impreciseness, a task with separate phases of encoding and retrieval might be better suited to dissociate these two functions.

Conclusion: Memory in the medial temporal lobe

In a continuous word recognition paradigm, ERP effects previously associated with successful encoding and successful retrieval were larger more posterior in the hippocampal body. Therefore, we assume that similar posterior hippocampal neuronal networks are activated during encoding and retrieval of single items. ERP effects likely reflecting novelty detection were more pronounced in the hippocampal head, while effects presumably reflecting semantic association processes did not differ between anterior and posterior parts. Thus, although novelty detection, semantic association processes and successful encoding are closely related processes (Strange *et al.*, 2005), the results of our study suggest a regional dissociation.

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8 Studie III

Phase-locking within human mediotemporal lobe predicts memory formation

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Abstract

Lesion and imaging studies have demonstrated that encoding of declarative memories, i.e. consciously accessible events and facts, is supported by processes within the rhinal cortex and the hippocampus, two substructures of the mediotemporal lobe (MTL). Successful memory formation has, for instance, been shown to be accompanied by the rhinal N400 component, followed by a hippocampal positivity, as well as by transient rhinal-hippocampal phase synchronization. However, it has been an open question, which mediotemporal electroencephalogram (EEG) measures predict memory formation most accurately. Therefore, we analyzed and compared the association of different mediotemporal EEG measures with successful memory formation. EEG characteristics were extracted from intracranial rhinal and hippocampal depth recordings in 31 epilepsy patients performing a continuous word recognition paradigm. Classical event-related potential measures, rhinal-hippocampal synchronization, as well as inter-trial phase-locking and power changes within rhinal cortex and hippocampus were evaluated. We found that inter-trial phase-locking is superior to other EEG measures in predicting subsequent memory. This means that memory formation critically depends on how temporally precise the phase of the EEG responses within the MTL is locked to stimulus onset. In particular, early rhinal and hippocampal phase-locking in the alpha/beta range reaching its maximum already between 100 and 300 ms after stimulus onset appears to be a precursor of successful memory formation. Our data indicate that the precise chronology of early mediotemporal processes is crucial for declarative memory encoding.

Abbreviations: EEG = electroencephalogram; MEG = magnetoencephalogram; MTL = mediotemporal lobe; MRI = magnetic resonance imaging.

Introduction

Lesion and imaging studies have demonstrated that encoding of declarative memories, i.e. consciously accessible events and facts, depends on processes within the rhinal cortex and the hippocampus, two substructures of the mediotemporal lobe (MTL) (e.g. Eichenbaum, 2000; Squire *et al.*, 2004). Successful memory formation has, for instance, been shown to be associated with different mediotemporal event-related potential (ERP) components and electroencephalogram (EEG) measures: the rhinal N400 component and a later hippocampal positivity (Grunwald *et al.*, 1999c; Fernández *et al.*, 1999, 2002), rhinal-hippocampal phase synchronization in the gamma and low frequency range (Fell *et al.*, 2001; 2003), rhinal and hippocampal inter-trial phase-locking (Mormann *et al.*, 2005), as well as an increase of hippocampal power in the upper gamma range and a decrease mainly in the alpha and beta range (Sederberg *et al.*, 2007). All these measures carry different information. Phase synchronization characterizes the coupling between two brain regions as given by the variability of phase differences across trials. Inter-trial phase-locking specifies the phase stability at a certain brain region, i.e. how temporally precise the phase of an EEG response is locked to stimulus onset. Phase-locking and power changes are complementary aspects, which differentially contribute to averaged ERPs depending on the cognitive task (e.g. Fell *et al.*, 2004; Klimesch *et al.*, 2004; Makeig *et al.*, 2004; Mazaheri and Jensen, 2006). However, it has been yet an open question, which mediotemporal EEG measures predict memory formation best.

Therefore, we aimed to analyze a variety of EEG measures for the same memory task performed by a large patient group. Intracranial EEG was recorded from 31 patients with pharmacoresistant temporal lobe epilepsies during a continuous word recognition experiment. Data from this experiment are routinely used for the planning of resective surgery. Multicontact depth electrodes had been implanted stereotactically along the longitudinal axis of each MTL (Van Roost *et al.*, 1998) during presurgical evaluation because the seizure onset zone could not be precisely

determined with noninvasive investigations. Presurgical evaluation revealed unilateral pathologies for all patients included in the present study. To reduce the possibility of introducing uncontrolled variables brought about by the epileptic process, only those EEG recordings were analyzed that were taken from the MTL contralateral to the zone of seizure origin (Grunwald *et al.*, 1995; Puce *et al.*, 1989). We aimed at comparing both different types (groups) of EEG measures, which possibly correspond to different neural mechanisms, as well as different individual measures with respect to the ability to predict successful memory formation. For this purpose, we evaluated EEG responses to subsequently remembered and forgotten words by quantifying event-related potential components, frequency band-specific rhinal-hippocampal synchronization, inter-trial phase-locking and power changes. For these groups of measures, EEG characteristics were selected based on a priori hypotheses, if available. In addition, we analyzed characteristics, which showed a strong subsequent memory effect.

Materials and methods

Patients

All patients suffered from pharmacoresistant unilateral temporal lobe epilepsies and were implanted with bilateral depth electrodes along the longitudinal axis of the hippocampus during presurgical evaluation. 31 patients (14 females) with at least one electrode in the rhinal cortex and one electrode in the hippocampus were included in the study. Patients ranged in age from 16 to 61 years (mean 40 yrs) and in duration of their epilepsy from 4 to 57 years (mean 23 yrs). At the time of the recordings, all patients received anticonvulsive medication (plasma levels within the therapeutic range). All participants were right-handed and had normal or corrected-to-normal vision. MRI scans or post-surgical histological examinations demonstrated unilateral hippocampal sclerosis in 16 patients (left: 5; right: 11), unilateral extra-hippocampal lesions without signs of hippocampal sclerosis in 9 patients (left: 3;

right: 6), unilateral hippocampal sclerosis with additional extrahippocampal lesions on the same side in 3 patients (left: 2; right: 1) and no clear lesion in 3 patients. All but two patients underwent subsequent epilepsy surgery after implantation (17 selective amygdalo-hippocampectomies, 7 temporal two-thirds resections, 5 lesionectomies). The word recognition test was conducted as part of the presurgical routine in patients with hippocampal depth electrodes. Informed consent for the intracranial EEG recordings and the use of the data for research purposes was obtained by all patients. The study was approved by the ethics committee of the University of Bonn.

Experimental paradigm

For a continuous word-recognition paradigm, 300 frequent German nouns were selected (mean word frequency was 50 per 1 million words according to the CELEX lexical database, version 2.5). 150 stimuli were only presented once, whereas the other 150 words were shown with one repetition. This repetition occurred in 50% of the trials after a short lag of 3 to 6 words and in 50% after a long lag of 10 to 30 words. Thus, 450 words were presented consecutively with a duration of 300 ms per word. The length of the interstimulus interval was adjusted to the subjects' abilities (assessed from the responses in a few pilot trials) and was either short (1600 ± 200 ms; n = 6), medial (2000 ± 200 ms; n = 16) or long (2700 ± 200 ms; n = 9).

After each word, subjects had to indicate by pressing one of two buttons whether it was new (left button) or already presented before (right button). Subjects used their left and right forefingers for pressing the buttons. 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 monitor at a distance of approximately 80 to 100 cm away. The words were presented in white color on a black background with an height of ~1,5° and a width of ~3 to 9° visual angle, depending on word length. Recordings were occasionally repeated with a parallel version of the recognition task on the following day, if performance was bad or ERPs were contaminated by spikes

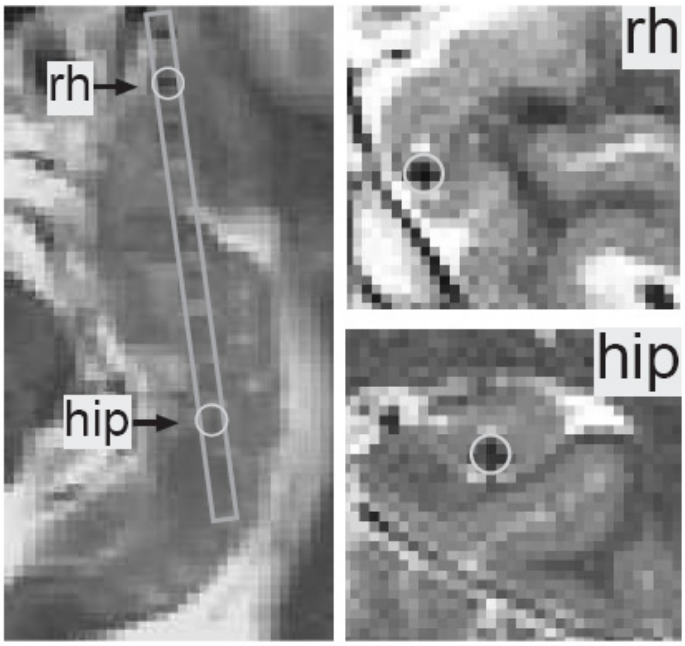

Fig. 1: Exemplary MRI images of one patient showing the selected rhinal (rh) and hippocampal electrode contact (hip) in axial (left) and coronal slices (right).

or sharp waves. Performance was considered bad if there was a small amount (<30 correctly recognized "old" or "new" words) of evaluable trials. Throughout, data of the second recordings were used for the analyses in these cases.

EEG recording

Depth electroencephalograms were referenced to linked mastoids, bandpass-filtered (0.01 Hz (6dB/octave) to 70 Hz (12dB/octave)), and recorded with a sampling rate of 200 Hz. Electrode contact placement was ascertained by examining MRIs acquired in the sagittal, axial and coronal planes and adjusted to the longitudinal axis of the hippocampus. Electrode contacts were localized based on the individual MRIs and comparison with standardized anatomical atlases (e.g. Duvernoy, 1988; see also figure 1). Only EEG recordings from the non-pathological MTL were analyzed. EEG data obtained from the non-pathological MTL in patients with a unilateral seizure origin have been shown to be qualitatively similar to the invasive EEGs recorded in

healthy monkeys (Paller *et al.*, 1992). The rhinal electrode was defined as the electrode located within the anterior parahippocampal gyrus (based on the MRI data) with the largest N400 mean amplitude (new words) between 200 and 600 ms (e.g. Grunwald *et al.*, 1999c). Because our methods cannot clearly separate perirhinal and entorhinal generators, we use the term rhinal cortex without intending to indicate an integrated rhinal processing stage. The hippocampal electrode was defined as the electrode located within the hippocampus (based on the MRI data) with the largest mean amplitude (new words) of the positive component between 300 and 1500 ms (e.g. Fernández *et al.*, 1999). EEG measures from right and left hemisphere were combined for statistical analyses and figures, because lateralization of verbal memory in MTL epilepsy patients is variable due to functional shifts (e.g. Helmstaedter *et al.*, 2006).

Artifact rejection

An automated artifact rejection was implemented using MATLAB (Mathworks, MATLAB 7.1). For each segment, the standard deviation of the data points as well as the standard deviation of the gradients (the increase or decrease between two successive data points) were determined. A segment was rejected if any data point or gradient deviated more than five standard deviations from the mean. Thus, segments with abnormally high amplitudes as well as abrupt rises or falls were eliminated. For the oscillation analyses, always segments of both electrodes (rhinal and hippocampal) were rejected, if one segment of either position had to be removed. On average, 14 % of trials were removed based on these criteria. The data from four patients, which still exhibited artifacts (observed by visual inspection) after applying the automated rejection procedure were discarded from further analysis.

Classical ERP measures

We analysed the EEG responses to the first presentation of words shown with one repetition. Responses were classified into remembered (REM) or forgotten (FORG)

depending on whether the word was subsequently (i.e. at the second presentation) correctly identified or not. For the evaluation of classical ERP measures, EEG responses were filtered with a low cut-off of 0.1 Hz (12 dB/oct) and a high cut-off of 12 Hz (48 dB/oct) (Ludowig *et al.*, 2008). Event-related potentials were averaged for the interval [-200 ms; 1400 ms] and baseline-corrected with respect to the prestimulus interval [-200 ms; 0 ms]. The peak amplitudes of the rhinal N400 and the hippocampal P600, as well as the mean amplitudes in the intervals [300 ms; 600 ms] (rhinal cortex) and [400 ms; 900 ms] (hippocampus) were chosen as ERP measures.

Analysis of power, phase-locking and synchronization changes

EEG responses were filtered in the frequency range from 1 Hz to 49 Hz (1 Hz steps) by continuous wavelet transforms implementing Morlet wavelets with a bandwith parameter $f_0/\sigma_f = 5$, i.e. roughly speaking wavelets of five cycles length (e.g. Lachaux *et al.*, 1999). The complex 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. In order to avoid edge effects, EEG responses were segmented from –1200 ms to 2400 ms with respect to stimulus onset, and after wavelet-transform 1000 ms at both sides were discarded. Based on the wavelet transformed signals $w_{j,k}$ the phases $\varphi_{j,k}$ ($\varphi_{j,k} = \arctan(Im(w_{j,k})/Re(w_{j,k}))$), the phase differences between rhinal cortex and hippocampus $\Delta\varphi_{j,k} = \varphi_{j,k}(RH) - \varphi_{j,k}(HI)$, and the power values $P_{j,k}$ ($P_{j,k} = Re(w_{j,k})^2+Im(w_{j,k})^2$) were extracted for each time point j of each trial k. The calculation of inter-trial phase locking and phase synchronization values was done by a procedure suitable for the evaluation of small and unequal trial numbers (e.g. Fell *et al.*, 2004). Distributions of phases (phase locking) and rhinal-hippocampal phase differences (synchronization) across trials were calculated separately for "remembered" and "forgotten" trials. For this purpose, the phase domain was divided into 8 boxes of 45° covering the range from -180° to +180°. Distribution probabilities X_i were calculated for each box i and each time point j. Phase locking

values PL_j (as well as phase synchronization values) were then evaluated based on a normalised entropy measure: $PL_j = 1 + \sum_{i=1}^{8} X_{i,j} * \log X_{i,j} / \log (8)$. A large phase locking or synchronization value indicates that phases or phase differences are not uniformely distributed, but exhibit phase accumulations. To allow a finer phase resolution, calculations were iterated for 45 shifts of the boxes about 1°. Finally, the phase locking and synchronization values resulted from the averages of these iterations. We did not contrast synchronization values against trial-shuffeled surrogates (Lachaux *et al.* 1999), i.e. our synchronization estimates include synchronization caused by stimulus-locked activity within rhinal cortex and hippocampus, which overlaps in the frequency and time domain.

Power, phase locking and synchronization values were averaged for non-overlapping successive time windows of 100 ms duration from -200 to 1400 ms (16 windows in total). Afterwards, values corresponding to the time windows between -100 and 1400 ms were divided by the prestimulus time window from -200 to -100 ms separately for each subject and each filter frequency. We chose this prestimulus interval as a baseline so that the variation of normalized power, phase locking and synchronization could be demonstrated for the prestimulus interval between -100 and 0 ms. Power, phase locking and synchronization values were transformed into a dB scale ($10*\log_{10}$) only for graphical depiction.

Statistical analyses

To evaluate the capability of the different EEG measures to predict successful memory formation paired t-tests for the individual measures, MANOVAs for groups of measures and parametric discriminant analyses using pooled covariance matrices were performed (SAS procedure DISCRIM). Into a first discriminant analysis (DISCRIM1) the changes with respect to baseline for subsequently remembered and forgotten words were entered. This discriminant analysis quantifies the ability of a certain measure, to identify the class (remembered, forgotten) to which an average

response belongs, when only the response for this class (and not the response for the other class) is given. Furthermore, a stepwise discriminant analysis with a significance level of p = 0.05 for entering and staying in the model was performed. For a second discriminant analysis (DISCRIM2) the changes were normalized to the average change across the classes (remembered, forgotten). This discriminant analysis quantifies the capability to identify responses corresponding to later remembered or forgotten words, when the responses for both classes are given.

Results

Behavioral Data

On average, 66.7±21.3% of presented words were later successfully remembered. Performance did not differ between patients with left and right focal hemisphere (t_{30} = 0.518, p = 0.61) or between male and female patients (t_{30} = 0.875, p = 0.39). Reaction times did also not differ between subsequently remembered and forgotten words (remembered: 878 ± 161 ms; forgotten: 882 ± 232 ms, paired t-test: t_{30} = 0.175, p = 0.86).

Qualitative EEG effects

Figure 2 shows the ERP responses for later remembered and forgotten words. In accordance with previous data, the rhinal N400 and the hippocampal P600 component are increased for later remembered compared to forgotten words. Figures 3-5 depict the differences in synchronization, phase-locking and power between the responses to later remembered versus forgotten words. The synchronization, phase-locking and power changes are displayed separately for remembered and forgotten words in figures 6 and 7. Consistent with our prior findings, we observed an early increase of rhinal-hippocampal gamma synchronization and a later decrease (Fell *et*

al., 2001), as well as a synchronization increase in the delta and theta range (Fell *et al.*, 2003). These effects are in the order of ± 0.4 dB (equivalent to around ± 10%). The most pronounced subsequent memory effects in the range of ± 1.5 dB (equivalent to around ± 40%), however, were observed for rhinal and hippocampal phase-locking. In accordance to prior data related to the continuous recognition task (Mormann *et al.*, 2006), rhinal phase-locking mainly occurred in the delta, theta and alpha/beta range. A phase-locking decrease was observed for the lower gamma range. Hippocampal phase-locking was detected in the delta, alpha/beta and gamma range. In contrast to the rhinal recordings, a decrease of hippocampal phase-locking occurred in the theta range. Finally, memory related rhinal and hippocampal power changes were observed in the order of ± 0.6 dB (equivalent to around ± 15%). Within rhinal cortex, an early broad-band decrease of power in the alpha/beta/gamma range was detected. Within the hippocampus, an increase of delta power, as well as an increase of upper gamma power and a decrease of power mainly in the alpha/beta range were found. The latter effects are in accordance with the findings of Sederberg and colleagues (2007).

Selection of the EEG measures

Based on the apriori hypotheses and the observed subsequent memory effects five different groups of measures were composed: classical ERP components, rhinal-hippocampal synchronization, rhinal phase-locking, hippocampal phase locking, rhinal and hippocampal power. For each group four measures were selected, which are listed in table 1 (see also figures 2-5). Besides measures based on apriori hypotheses (e.g. gamma and theta synchronization), those with the largest remembered vs. forgotten differences were chosen under the condition that they had an extension of at least 10 time (100 ms) * frequency (1 Hz) voxels.

Statistical evaluation of subsequent memory effects

When comparing baseline related changes for remembered versus forgotten responses by paired two-tailed t-tests (see table 2), nine of the twenty EEG measures yielded a significant effect ($p < 0.05$). The clearly largest effects were reached by three phase-locking measures: rhinal alpha/beta phase-locking (difference between average changes with respect to baseline for remembered and forgotten words (rem.-forg.): 70.7%, $p < 0.0001$), as well as hippocampal delta (rem.-forg.: 39.6%, $p < 0.001$) and alpha/beta (rem.-forg.: 36.6%, $p = 0.001$) phase-locking. Indeed, a stepwise discriminant analysis included into the best model two of those measures (rhinal alpha/beta and hippocampal delta phase-locking) plus hippocampal gamma phase-locking (rem.-forg.: 8.8%, $p = 0.107$) and the rhinal-hippocampal gamma synchronization increase (rem.-forg.: 9.1%, $p = 0.090$), in the following order: 1) ↑ Rhinal alpha/beta phase-locking; 2) ↑ Rhinal-hippocampal gamma synchronization; 3) ↑ Hippocampal delta phase-locking; 4) ↑ Hippocampal gamma phase-locking. Also MANOVAs for the different groups of measures (see table 3) produced the by far most significant effects for phase-locking within rhinal cortex ($p = 0.0002$) and within the hippocampus ($p = 0.0003$). However, the best model selected by stepwise discriminant analysis yielded a superior MANOVA effect of $p < 10^{-5}$. The only group for which no significant effect or trend was detected are the classical ERP measures.

The discriminant analysis without normalization across classes (DISCRIM1; see methods) yielded error rates of 22.2% for the prediction of subsequent memory based on the rhinal or the hippocampal phase-locking measures (see table 3). For the best model the prediction error amounted to 18.5%. The highest error rate (40.7%) was observed for the classical ERP measures. For rhinal-hippocampal synchronization and the phase-locking measures, prediction of later forgetting was better then prediction of later remembering (e.g. error rate of 14.8% versus 29.6% for rhinal phase-locking). For the classical ERP measures and power changes, the opposite was

the case. Finally, the discriminant analysis with normalization across classes (DISCRIM2) revealed considerably lower error rates: 22.2 % for the classical ERP measures, 7.4% for rhinal-phase locking and 3.7% for the best model. This means that knowledge of responses for both classes significantly improves the prediction of subsequent memory.

Individual discriminant analyses for those EEG measures, which showed a significant remembered/forgotten effect or trend ($p < 0.1$) for the paired t-tests, are depicted in table 4. Discriminant analysis without normalization across classes yielded lowest error rates (31.5 %) for rhinal and hippocampal alpha/beta phase-locking. Discriminant analysis with normalization across classes revealed lowest error rates (14.8 %) for rhinal alpha/beta and hippocampal delta phase-locking, as well as for hippocampal alpha/beta power reduction. We furthermore analysed, whether concurrent rhinal and hippocampal alpha/beta phase-locking is predictive for memory formation by entering the product between both measures as discriminant variable (see table 4). Indeed, this measure yielded even lower error rates than rhinal phase-locking alone (24.1% and 11.1%, respectively).

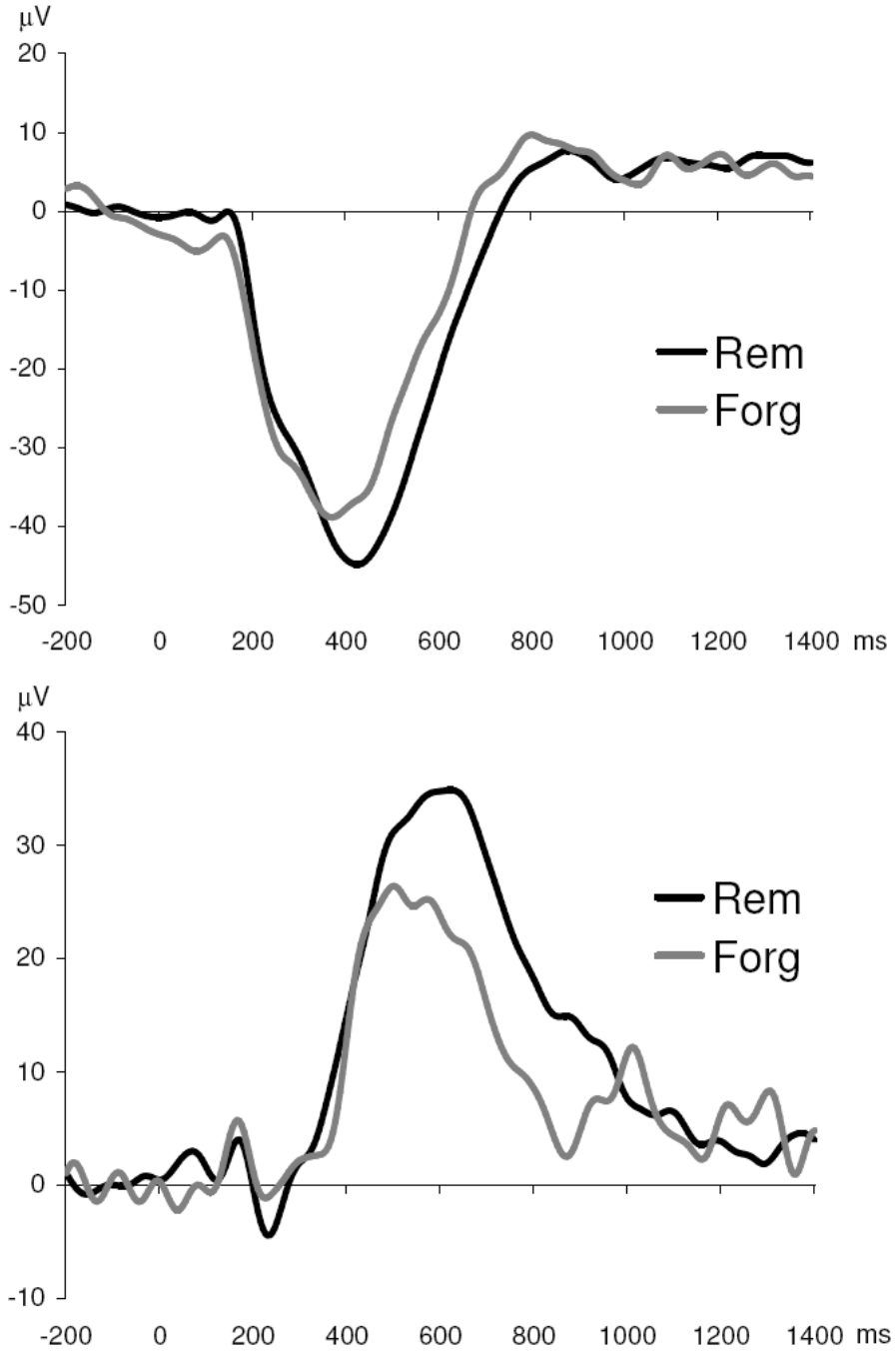

Fig. 2: ERPs after presentation of new words recorded during the continuous recognition experiment. ERPs were averaged separately for a) words that were correctly recognized when presented for the second time (i.e. remembered); b) words that were later not recognized (i.e. forgotten). Above: ERPs recorded from rhinal cortex. Below: ERPs recorded from the hippocampus.

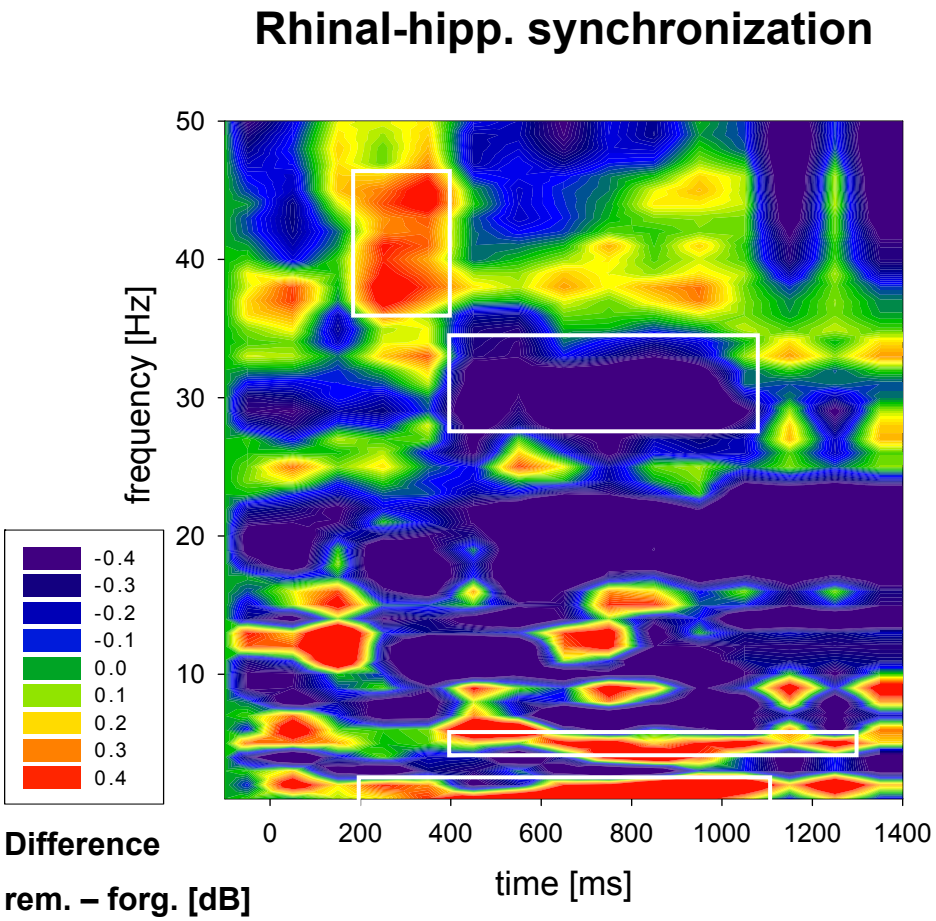

Fig. 3: Difference of changes in rhinal-hippocampal synchronization for remembered versus forgotten words. The plots show color-coded differences of synchronization values, which have been normalized with respect to a prestimulus baseline [-200 to 100 ms] and have been transformed into a dB scale ($10*\log_{10}$). Frequencies between 1 and 49 Hz are represented in y direction while time relative to word presentation is depicted in x direction. EEG measures selected for statistical analysis are indicated by white boxes.

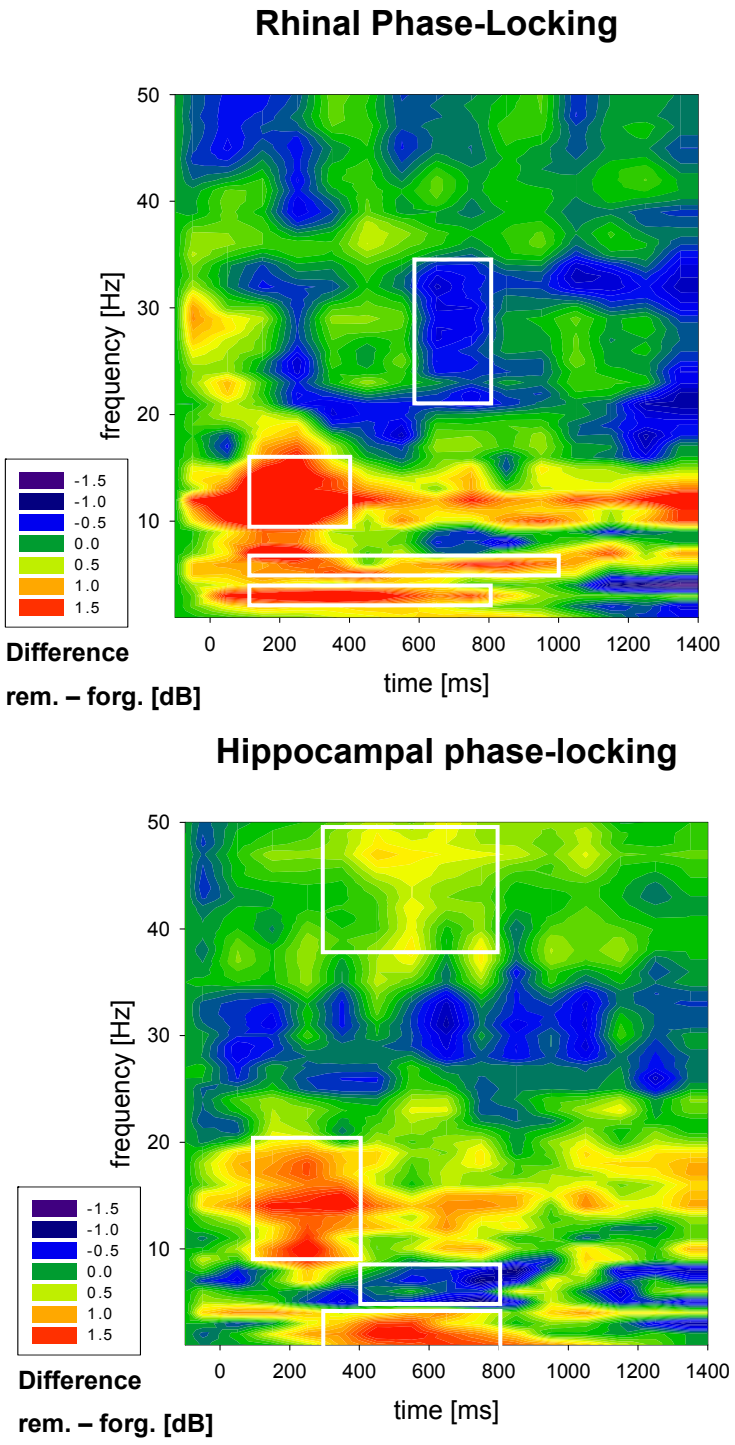

Fig. 4: Difference of phase-locking changes for remembered versus forgotten words (for details see legend of fig. 2).

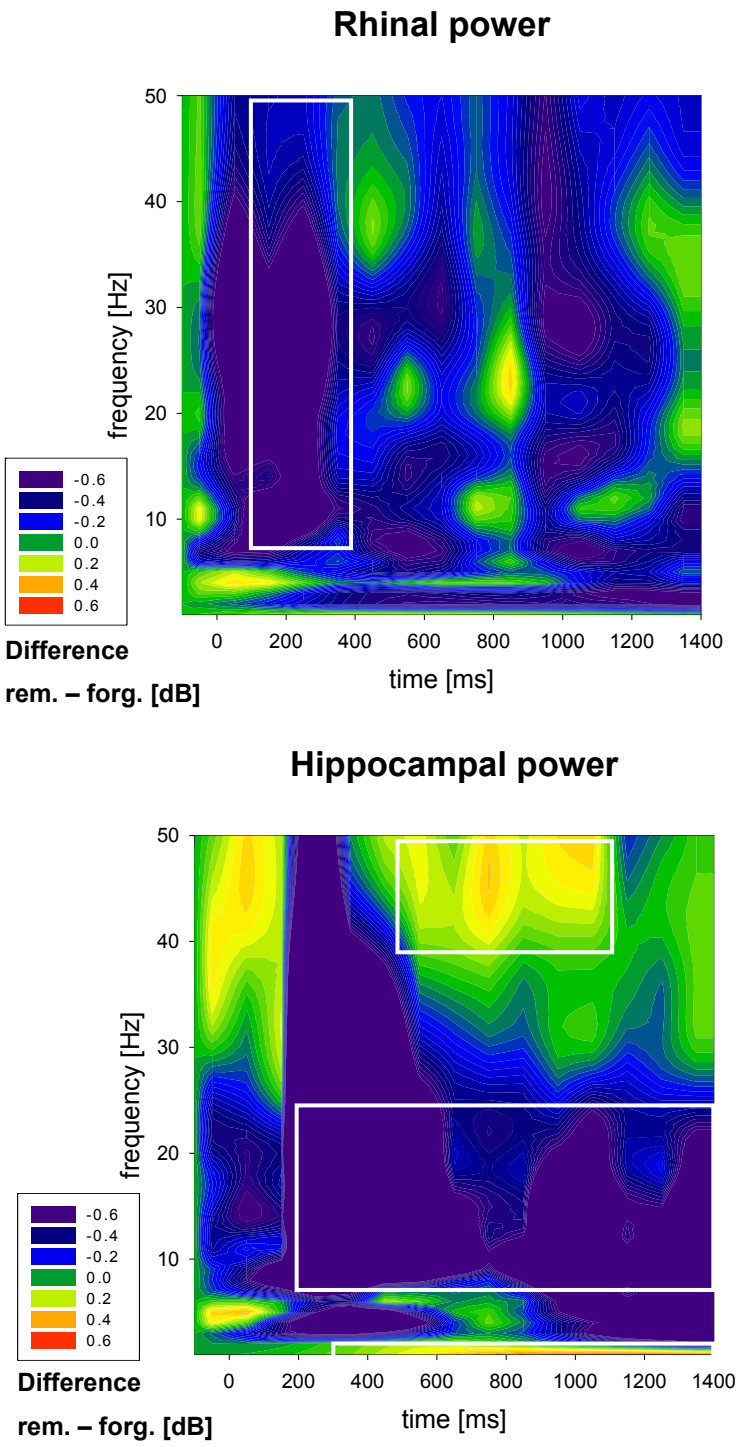

Fig. 5: Difference of power changes for remembered versus forgotten words (for details see legend of fig. 2).

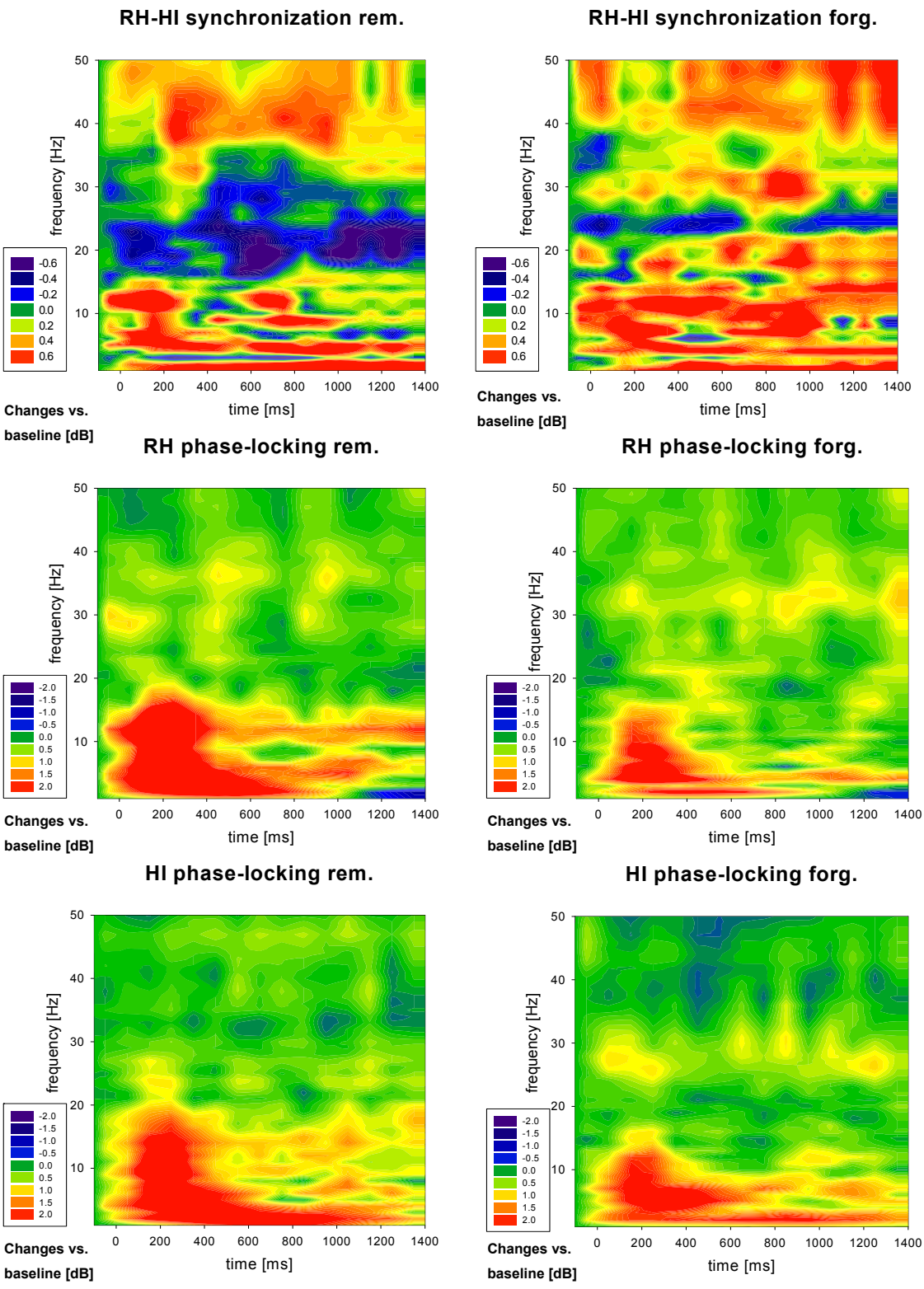

Fig. 6: Changes of rhinal-hippocampal synchronization, as well as rhinal and hippocampal phase-locking separately for remembered (left) and forgotten (right) words (for details see legend of fig. 2).

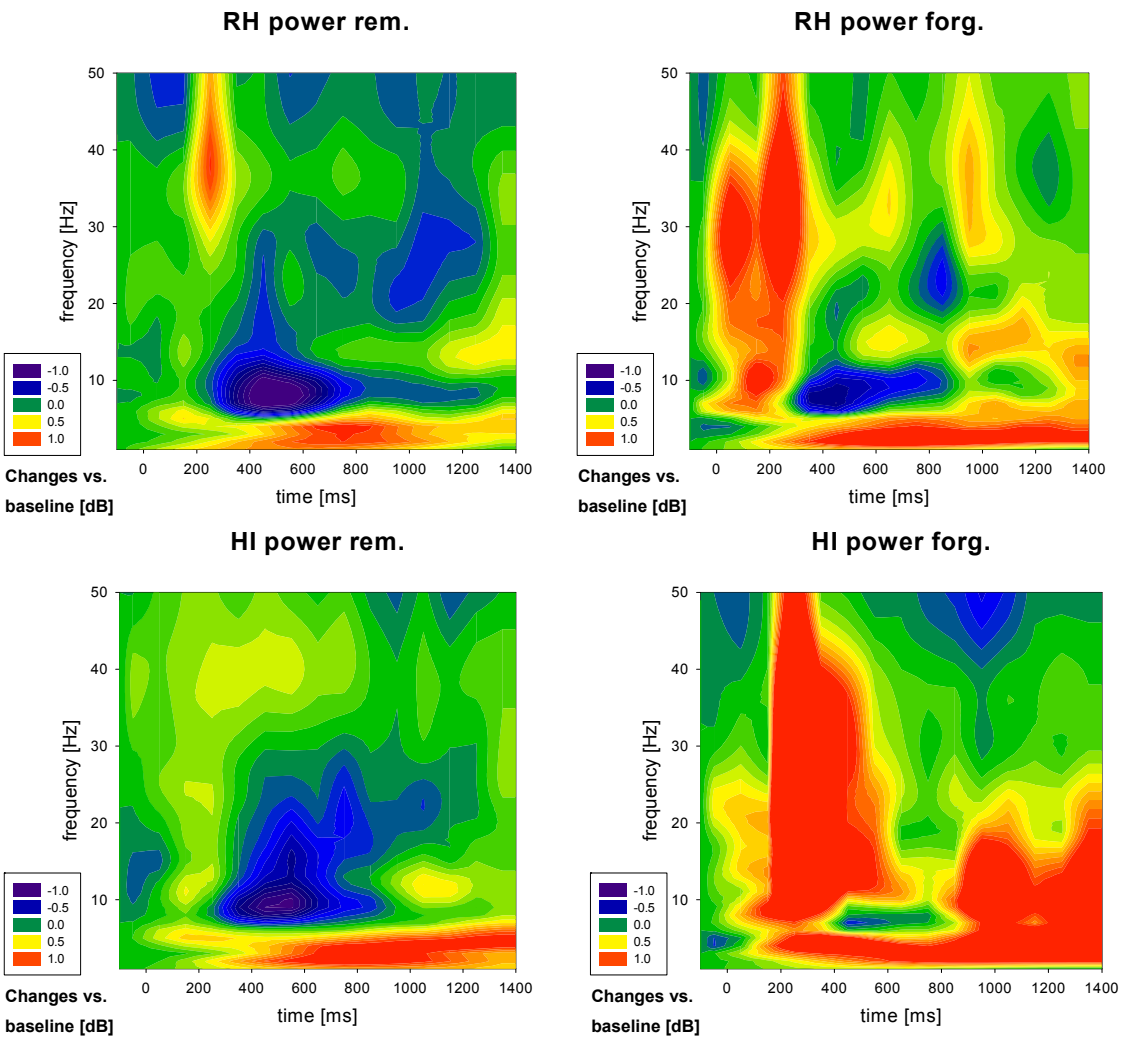

Fig. 7: Changes of rhinal and hippocampal power separately for remembered (left) and forgotten (right) words (for details see legend of fig. 2).

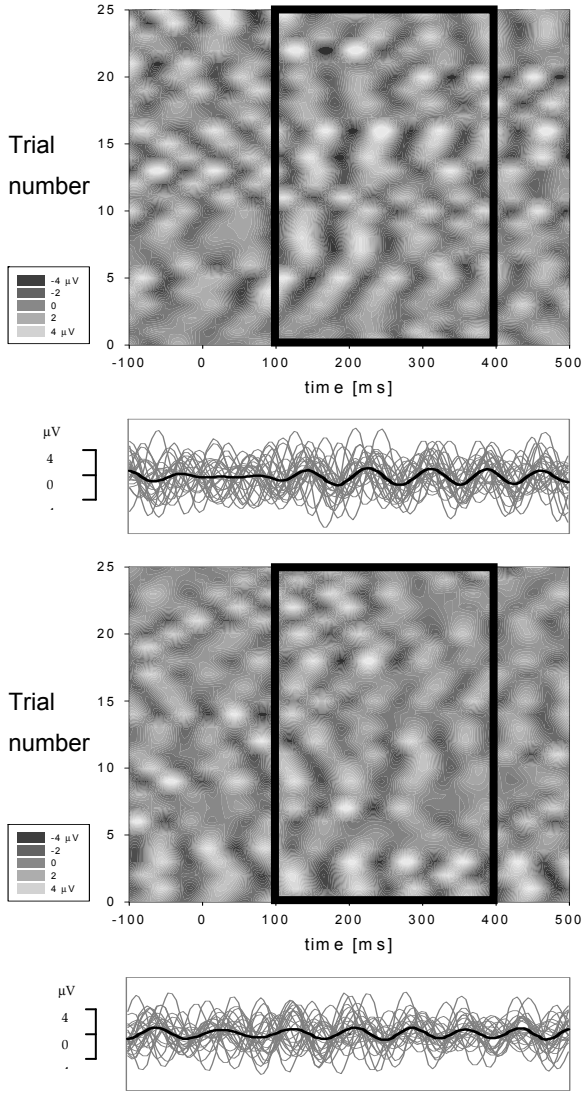

Fig. 8: Illustration of rhinal alpha/beta phase-locking for one patient. Rhinal recordings were filtered in the frequency range between 12 and 14 Hz (Butterworth Filter, 48db/octave). On the y-axis the first 25 trials corresponding to later remembered (above) and later forgotten words (below) are depicted. Time with respect to word presentation is depicted on the x-axis. EEG voltage is coded by a gray scale (black: max. negative voltage; white: max. positive voltage). Alpha/beta phase-locking is reflected by the alignment of peaks and throughs in the vertical direction. Below the gray-scale plots the same trials are depicted as superimposed waveforms (gray) and averages (black).

Discussion

In the present study we evaluated the capability of several groups of mediotemporal EEG measures to differentiate between subsequently remembered and forgotten words: amplitudes of ERP components, rhinal-hippocampal phase-synchronization, as well as intertrial phase-locking and power changes. In accordance to prior investigations, we observed a memory-related increase of the rhinal N400 component and the later hippocampal positivity (Fernández *et al.*, 1999, 2002), an enhanced rhinal-hippocampal phase synchronization in the gamma and the low frequency range (Fell *et al.*, 2001; 2003), as well as a hippocampal power increase in the upper gamma range and a power decrease in the alpha and beta range (Sederberg *et al.*, 2007).

The best predictors of subsequent memory, however, were the phase-locking characteristics, most notably rhinal phase-locking in the alpha/beta range. This finding represents an important advance over previous reports. Figure 8 illustrates the rhinal alpha/beta phase-locking effect for one patient. For trials corresponding to remembered (above) compared to forgotten words (below) a stronger alignment of peaks and troughs in the vertical direction is observable. Generally, the memory-related phase-locking effects seem to exhibit a very early onset already within 100 ms after word presentation. Of course, one has to account for the temporal resolution of the wavelet-transform, which may be estimated as the half width at half maximum of the Gaussian envelope of the Morlet wavelet (e.g. Baudin *et al.*, 1994), yielding, for instance, 94 ms for 10 Hz, or 67 ms for 14 Hz. Still, this means that the rhinal phase-locking effect may already start around 100 ms and reaches its maximum in the time window between 100 and 300 ms after stimulus onset. This phase-locking increase reflects the precise onset of an alpha/beta oscillation contributing to the rising edge of the rhinal N400 component. The early timing suggests that mediotemporal phase-locking may be initiated by an attentional top-down process mediated directly by the thalamus (LaBerge, 1997). This process may prepare for the arrival of detailed

stimulus information from higher-order visual areas, which is not to be expected before 200 ms after word presentation (e.g. Nobre *et al.*, 1994). Our findings are reminiscent of the reported reset of human neocortical oscillations in the theta/alpha/beta range during a working memory task (Rizzuto *et al.* 2003).

It may be speculated that the concurrence of rhinal and hippocampal alpha/beta phase-locking has a significant impact on neurons receiving information from both the rhinal cortex and the hippocampus, for instance neurons in the subiculum (e.g. Behr *et al.* 1998). This effect may be qualitatively similar to the impact of rhinal-hippocampal synchronization. Actually, there is a circumscribed memory-related increase of rhinal-hippocampal synchronization between 10 and 14 Hz and 100 and 200 ms (figure 3), which may correspond to the concurrent rhinal and hippocampal alpha/beta phase locking. Moreover, we observed the lowest discrimination error rates for the variable resulting from the product of rhinal and hippocampal phase-locking. For this variable, discrimination accuracy was even better than for rhinal phase-locking alone. This finding yields strong evidence for the idea that concurrent rhinal and hippocampal alpha-beta phase-locking is crucial for successful memory formation.

Interestingly, the rhinal phase-locking increase in the alpha/beta range is accompanied by a broad-band decrease of rhinal power in the alpha, beta and gamma range. This power decrease, which similarly occurs within the hippocampus, may be related to a shut down of ongoing neural activity in order to prepare for incoming sensory information. Moreover, our data suggest that the phase-locking increase results from a phase-reset of ongoing oscillations and not from additive stimulus-locked activity, although the evidence is not conclusive (e.g. Hanslmayr *et al.*, 2007). As a consequence, the subsequent memory effects for the rhinal N400 peak and the mean N400 amplitude are rather small, in spite of the strong and concentrated phase-locking effect (which, in principle, should particularly boost the N400 peak amplitude). This result underlines the need for a separation of phase-locking and

power changes, because both aspects contribute to cognitive ERPs and may dissociate between conditions (e.g. Fell *et al.*, 2007).

Actually, the ERP and phase synchronization effects observed in the present investigation are smaller than those found in previous studies (e.g. a memory-related gamma synchronization increase of up to 14% compared to up to 30% in Fell *et al.*, 2001). There may be two major reasons for this outcome: First of all, encoding-related activations in item recognition paradigms are typically less pronounced than activations observed in free recall paradigms (e.g. Staresina and Davachi, 2006). Second, the task of encoding new words is overlaid with the task of recognizing previously presented words in the continuous recognition paradigm, which may have partly clouded the encoding related effects. Furthermore, subsequent memory effects in the continuous word recognition paradigm have been shown to vary considerably along the longitudinal axis of the hippocampus (Ludowig *et al.*, 2008). For the present study, we selected electrode contacts based on the largest memory-related ERP components across conditions (remembered, forgotten), in order to minimize the bias towards a certain group of measures.

The best model as selected by a stepwise discriminant analysis, besides three phase-locking measures (rhinal alpha/beta and hippocampal delta and gamma phase-locking), included the rhinal-hippocampal synchronization increase in the gamma range. This means that the four measures contain independent information, which maximizes predictive power. In particular, hippocampal phase-locking in the gamma range and rhinal-hippocampal gamma synchronization appear to represent EEG characteristics that are not redundant. Indeed, Pearson's correlation between both measures is rather small ($r = -0.11$; n.s.). On the other hand, there is a significant correlation between rhinal and hippocampal alpha/beta phase-locking ($r = 0.36$; $p < 0.05$). Consequently, hippocampal alpha/beta phase-locking was not included into the best model, in spite of its highly significant capability to distinguish between responses corresponding to later remembered and forgotten words.

While discriminant analyses without normalization across classes yielded error rates around 20% for the prediction of subsequent memory based on the phase-locking measures or based on the best model, prediction errors of only 7.4% for rhinal phase-locking and of 3.7% for the best model were reached with discriminant analyses including normalization across classes. This result is probably caused by the fact that the average level of the phase-locking responses for both, later remembered and forgotten words varies considerably across subjects. For instance, for rhinal alpha/beta phase-locking the standard errors corresponding to remembered (15.4%) and forgotten (8.1%) items are larger than the standard errors for the difference between both classes (6.8%). Accounting for this variability by normalizing across classes, which practically implies a prediction based on knowledge of responses for both, later remembered and forgotten words, results in a much higher prediction accuracy. Interestingly, prediction of later forgetting is better than prediction of remembering for the phase-locking and synchronization measures, i.e. it seems easier to determine when memory formation fails than when it succeeds.

It is yet an open question how the increased mediotemporal phase-locking may be functionally interpreted. Generally, an enhancement of phase-locking indicates that the timing of stimulus processing related to oscillations within a certain frequency band exhibits less inter-trial variability. It has been suggested that slow EEG waves provide a threshold controlling the excitability of cortical networks (Elbert and Rockstroh, 1987; Schupp *et al.*, 1994). Indeed, it has been shown that, for instance, the phase of theta oscillations modulates the amplitude of gamma activity (e.g. Chrobak and Buzsáki, 1998; Canolty *et al.*, 2006; Mormann *et al.*, 2005), which is probably closely related to the strength of neural firing (e.g. Mukamel *et al.*, 2005). Such a mechanism may contribute to the so-called hippocampal phase coding, i.e. to the coding of neural memory representations by the phase of a low frequency oscillation (e.g. Jensen and Lisman, 2005). In this sense, the increased mediotemporal phase-locking may support a phase representation of to be memorized material.

More generally, precise timing of the phase of EEG responses may reflect inhibition or facilitation of neural firing occurring exactly at the right time point within the required sequence of neural processing. It is, for instance, conceivable that the early mediotemporal phase-reset in the alpha-beta range triggers rhinal-hippocampal phase synchronization and prepares for the later increase of hippocampal gamma activity. Our findings furthermore underline the role of alpha-phase dynamics in memory processes, which has previously been shown for surface EEG and MEG data (e.g. Herrmann *et al.*, 2004; Klimesch *et al.*, 2004; Palva and Palva 2007). To summarize, our data demonstrate that memory encoding crucially depends on the precise chronology of early processes within the MTL.

Acknowledgements

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Table 1:

Overview of EEG measures selected for statistical analysis.

ERP components	Time range [ms]	Frequency range [Hz]
Rhinal N4	Peak	-
Hippocampal P6	Peak	-
Rhinal N4 area	300 – 600	-
Hippocampal P6 area	400 – 900	-
Synchronization		
Delta ↑	200 - 1100	1 - 2
Theta ↑	400 - 1300	5
Gamma ↓	400 - 1100	28 - 34
Gamma ↑	200 - 400	37 - 46
Phase-Locking (RH)		
Delta ↑	100 - 800	2 - 3
Theta ↑	100 - 1000	5 - 6
AlphaBeta ↑	100 - 400	10 - 16
Gamma ↓	600 - 800	21 - 34
Phase-Locking (HI)		
Delta ↑	300 - 800	1 - 4
Theta ↓	400 - 800	5 - 8
AlphaBeta ↑	100 - 400	9 - 20
Gamma ↑	300 - 800	38 - 49
Power		
RH: AlphaBetaGamma ↓	100 - 400	8 - 49
HI: Delta ↑	300 - 1400	1
HI: AlphaBeta ↓	200 - 1400	8 - 24
HI: Gamma ↑	500 - 1100	39 - 49

Table 2:

Average changes with respect to baseline for the selected measures. P-values indicate significance levels for paired two-tailed t-tests comparing changes corresponding to subsequently remembered and forgotten responses.

	Remembered		Forgotten		Paired t-test
	Mean	SEM	Mean	SEM	p-value
ERP components [μV]					
Rhinal N4	-53.21	6.38	-49.44	6.19	n.s. (0.103)
Hippocampal P6	54.99	9.06	50.20	8.27	n.s. (0.267)
Rhinal N4 mean	-36.59	4.63	-29.52	4.63	0.038
Hippocampal P6 mean	25.60	6.62	16.63	5.39	0.048
Synchronization [%]					
Delta ↑	35.10	9.94	20.79	7.45	n.s. (0.153)
Theta ↑	19.17	9.87	9.31	9.09	n.s. (0.409)
Gamma ↓	-1.64	3.98	9.04	4.73	0.035
Gamma ↑	13.96	4.58	4.85	2.75	n.s. (0.090)
RH Phase-Locking [%]					
Delta ↑	93.48	16.72	45.30	12.53	0.014
Theta ↑	77.89	13.61	40.42	9.64	0.026
AlphaBeta ↑	103.53	15.38	32.80	8.14	< 0.0001
Gamma ↓	1.49	4.08	13.38	3.65	0.028
HI Phase-Locking [%]					
Delta ↑	78.64	9.99	39.07	8.50	< 0.001
Theta ↓	29.38	7.76	42.21	10.78	n.s. (0.361)
AlphaBeta ↑	59.91	9.56	23.29	6.23	0.001
Gamma ↑	6.66	4.46	-2.10	3.13	n.s. (0.107)
Power [%]					
RH:AlphaBetaGamma ↓	4.34	1.40	19.66	10.69	n.s. (0.160)
HI: Delta ↑	14.79	3.83	4.78	4.86	n.s. (0.162)
HI: AlphaBeta ↓	-1.97	2.56	34.26	18.82	n.s. (0.065)
HI: Gamma ↑	3.22	2.23	-1.27	2.23	n.s. (0.104)

Table 3:

Statistical separation of EEG responses corresponding to subsequently remembered and forgotten words. Results of MANOVAs and discriminant analyses for the different groups of EEG measures are shown.

	MANOVA $F_{4,49}$	p-value	DISCRIM1 Error rate % mean		DISCRIM2 Error rate %
			rem.	forg.	
ERP components	0.980	0.427	33.3	40.7 48.2	22.2
Synchronization	2.326	0.069	37.0	35.2 33.3	25.9
Phase-Locking (RH)	6.640	0.0002	29.6	22.2 14.8	7.4
Phase-Locking (HI)	6.489	0.0003	25.9	22.2 18.5	18.5
Power	2.070	0.099	29.6	35.2 40.7	29.6
Best four	10.607	< 0.00001	18.5	18.5 18.5	3.7

Table 4:

Statistical separation of EEG responses corresponding to subsequently remembered and forgotten words: discriminant analyses for those individual EEG measures, which showed a significant remembered/forgotten effect or trend ($p < 0.1$) for the paired t-tests, as well as for the variable "rhinal alpha/beta phase-locking * hippocampal alpha/beta phase-locking".

	DISCRIM1 **Error rate %** **mean** **rem.** **forg.**	**DISCRIM2** **Error rate %**
ERP components		
Rhinal N4 mean	48.2 48.2 48.2	25.9
Hippocampal P6 mean	44.4 51.9 37.0	40.7
Synchronization		
Gamma↓	38.9 37.0 40.7	25.9
Gamma↑	38.9 44.4 33.3	40.7
RH Phase-Locking		
Delta↑	42.6 51.9 33.3	29.6
Theta↑	37.0 40.7 33.3	40.7
AlphaBeta↑	31.5 44.4 18.5	14.8
Gamma↓	38.9 40.7 37.0	37.0
HI Phase-Locking		
Delta↑	35.2 40.7 29.6	14.8
AlphaBeta↑	31.5 37.0 26.0	22.2
Power		
HI: AlphaBeta↓	37.0 11.1 63.0	14.8
RH Ph.-L. AlphaBeta **x HI Ph.-L.** AlphaBeta	24.1 40.7 0.07	11.1

9 Studie IV

Active suppression in the mediotemporal lobe contributes to the directed forgetting effect

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Abstract

The aim of the present study was to investigate whether forgetting is merely the result of weak memory traces 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 is 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.

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 and 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 *et al.*, 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 *et al.*, 2003; Reber *et al.*, 2002b).

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 the memory trace. Alternatively, forgetting might be attained by additional 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 *et al.*, 1996), a recent fMRI study indicated that inhibition during directed forgetting is mediated by medial and superior frontal areas (Wylie *et al.*, 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 *et al.*, 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, 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 and 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 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 exellent temporal resolution, intracranial recordings offer the rare opportunity to measure neural activity directly within the critical structure.

In our study, ERPs elicited by TBR and TBF cues in a single-item cueing-paradigm were examined to test the two models. In a subsequent recognition test, all TBR and TBF words as well as new words were presented. Patients had to decide whether

each word was new or already presented before (irrespective of cue). Recognition-performance was taken into account as an indicator for the success of the instruction.

We predicted different ERP patterns for each model: selective rehearsal should result in larger amplitudes in response to the TBR than to the TBF cues. Since more elaborated rehearsal of words usually leads to a more successful encoding in the MTL, the model further predicts that TBR cues belonging to the later successfully recognized words result in larger ERPs than those belonging to the later forgotten words. In contrast, active suppression of memory encoding should be triggered by TBF cues only. Thus, memory suppression might result in smaller ERPs in response to the TBF as compared to the TBR cues in MTL areas relevant for memory encoding. Further, ERPs should be smaller for successful than unsuccessful suppression.

On the other hand, if substructures of the MTL are involved in the active suppression of memory traces, brain potentials from electrodes placed within these areas should display larger amplitudes for TBF than TBR cues, especially for the succesfull suppression of words subsequently not recognized as familiar. Table 1 provides an overview of expected effects based on the two models.

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 versus not recognized) would give evidence for the underlying process.

With regard to the recognition of the studied words, more intense rehearsal of TBR cued words as well as active suppression of the encoding of TBF cued words should lead to a deeper encoding of TBR than TBF cued words. Since ERPs in the hippocampus were previously shown to be sensitive to depth of encoding (Grunwald *et al.*, 2003), we expected to see a larger hippocampal old-new effect for the ERPs of recognized TBR than TBF cued words.

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
↑	... be increased
↑↑	... be increased strongly
↓	... be decreased
↓↓	... be decreased strongly

Materials and Methods

Subjects

We investigated 24 patients with pharmacoresistant temporal lobe epilepsy. 12 patients (9 females; 9 with left, 3 with right TLE) were included in the study. The other 12 patients had to be excluded due to poor memory performance (n = 5), non-compliance with the instruction (n = 6), or due to technical malfunction (n = 1). This might explain why the paradigm was too difficult for almost half of the patients. Included patients ranged in age from 28 to 56 years (mean age = 43 yrs) and in duration of their epilepsy from 2 to 28 years (mean epilepsy duration = 13 yrs). All participants had normal or corrected-to-normal vision and were right-handed. MRI scans or post-operative histological examinations demonstrated hippocampal sclerosis in 8 patients (3 with additional temporopolar blurring of the gray-white matter junction; 1 with bilateral hippocampal sclerosis), temporopolar blurring of the gray-white matter junction without hippocampal sclerosis in 1 patient and no clear lesion in 3 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.

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 to 100 cm away. In the study phase, we presented 50 individual words. 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 cue). All patients participated in 4 - 5 blocks of study phase, free recall, and recognition, with each block lasting approximately 15 minutes.

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 *et al.*, 1995), as well as the word length (range: 4-7 letters). The assignment to the TBR, TBF, and new words was randomized across patients.

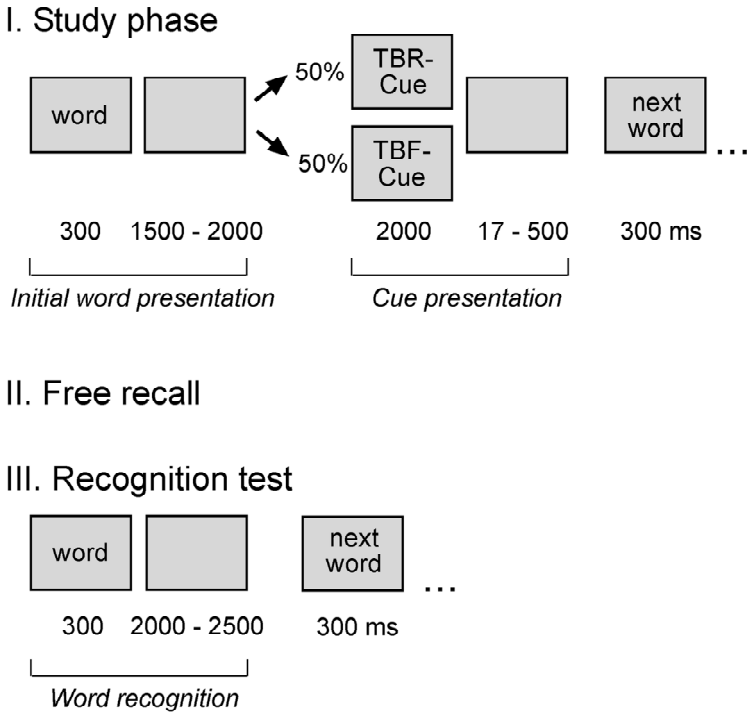

FIGURE 1. Study paradigm. 50 words were presented, each either followed by the cued instruction that this word is to-be-remembered (TBR) or to-be-forgotten (TBF). During free recall, only TBR cued words had to be listed. In the recognition part, subjects were supposed to recognize previously presented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

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.

EEG segments with duration of 2,200 ms, including a 200 ms prestimulus 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 prestimulus period.

An automated artifact rejection was implemented by using MATLAB 7.5 (Math-works). 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") and correctly identified old words presented in the study phase as TBR or TBF cued words ("TBR hits" or "TBF hits").

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. Within patients with bilateral implants only recordings of the non-focal hemisphere were subsequently analyzed. Only from two patients with unilateral implants, data from the focal-side entered the analysis after verification that brain potentials were comparable in size and shape to those obtained from the non-focal sides of bilateral 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, figure 1, for the anatomical location of electrodes along the MTL). 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 hippocampal body due to the poor signal quality in the hippocampal head electrodes. In one patient, the electrode array was shifted towards the anterior, thus only an anterior and 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.

Data analysis

Behavioral measures (reaction times and accuracy for TBR hits, TBF hits and 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. For each time window and each electrode position, these mean amplitudes were submitted to separate paired t-tests and repeated measures ANOVAs.

For the evaluation of subsequent memory effects during initial word encoding (W-R versus W-F), we applied paired t-tests. Effects of cue-presentation were evaluated in a two-way repeated-measures ANOVA with CUE (TBR vs. TBF) and subsequent memory (SUBSM: R vs. F) as within-subjects factors. A Greenhouse-Geisser correction was applied when necessary. When significant effects were found, post-hoc t-tests for paired samples were applied. 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), as well as for the differences between TBR hits and TBF hits.

Results

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 versus 904 ± 136 ms; $t_{11} = 3.36$, $p < 0.005$). False alarms (new-responses to old 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 mention TBR and not TBF cued words during free recall.

ERPs in the study phase

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.

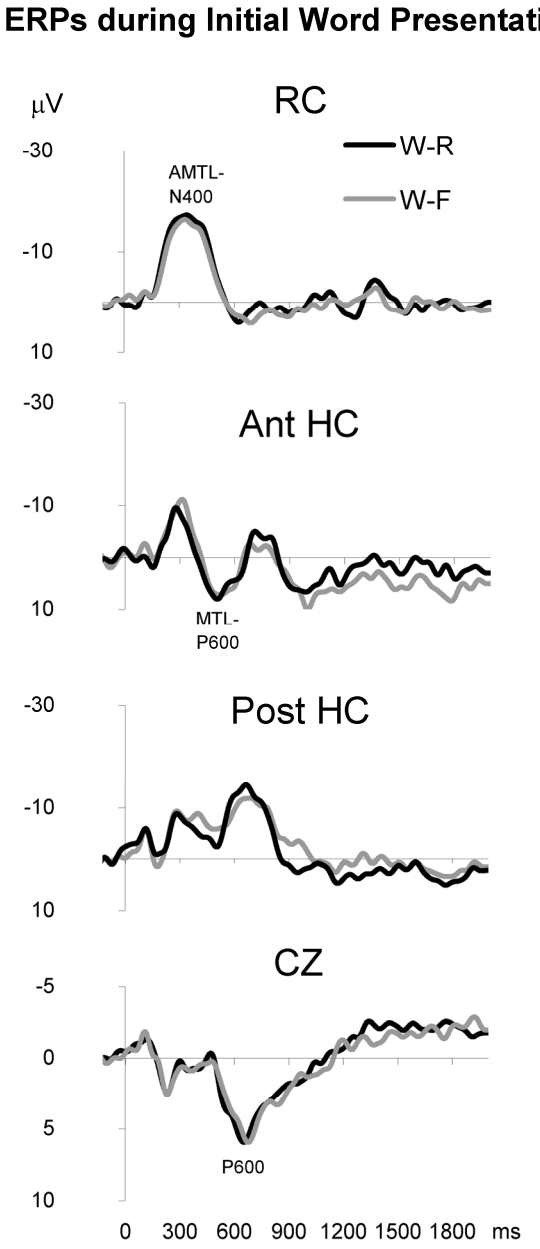

FIGURE 2. ERPs during initial word encoding separated for subsequently remembered words (W-R) and subsequently forgotten words (W-F). Shown are the ERPs of the rhinal cortex electrode (RC), the anterior hippocampal electrode (Ant HC), the posterior hippocampal electrode (Post HC) as well as Cz. Negative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

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 (Figure 3). This was reflected by the significant main effects of CUE within the three time windows between 600 and 1500 ms (300 – 600 ms: $F_{1,10} = 15.21$, $p < 0.005$; 600 – 900 ms: $F_{1,10} = 12.09$, $p < 0.01$; 900 – 1200 ms: $F_{1,10} = 17.44$, $p < 0.005$). Neither a main effect of SUBSM nor a SUBSM x CUE interaction effect were observed for the RC recording.

In the anterior hippocampus, both kinds of instruction elicited a large negativity between 200 and 900 ms. This response was smaller for TBF-F trials than for the other conditions, as reflected by significant interactions between CUE and SUBSM in the time window 600 to 900 ms ($F_{1,10} = 8.01$, $p < 0.05$). Post-hoc paired t-tests revealed significant differences between TBF-R and TBF-F trials ($t_{10} = 2.54$, $p < 0.05$). In the later time window from 1200 to 1500 ms, an interaction between CUE and SUBSM was found ($F_{1,10} = 5.24$, $p < 0.05$), reflecting more negative ERPs for TBR-F and TBF-R trials than for TBR-R and TBF-F trials. However, post-hoc paired t-tests revealed no significant differences.

In the posterior hippocampus, the interaction between CUE and SUBSM between 600 and 900 ms was also significant ($F_{1,9} > 6.00$, $p < 0.05$), but post-hoc paired t-tests did not reveal significant results. Note, that for one patient no data of the posterior hippocampus were available.

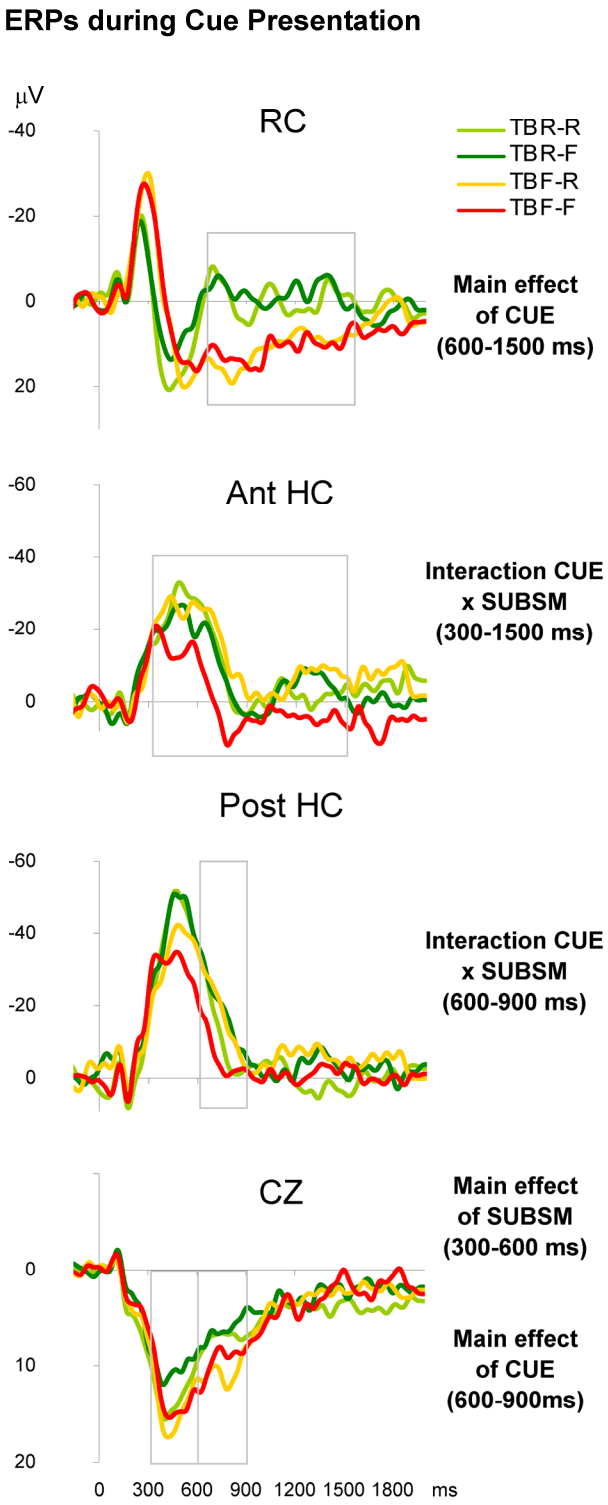

FIGURE 3. **ERPs in response to TBR cues and TBF cues, separated for cues belonging to subsequently remembered (-R) versus subsequently forgotten words (-F). Negative values are plotted upwards. Shown are the ERPs of the electrodes RC, ant HC, post HC as well as Cz. Significant results of the ANOVA statistics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

At the scalp (Cz electrode), a broad positive component (lasting from 200 to 1500 ms) was observed. In the early time window between 300 and 600 ms, its mean amplitude was larger for cues of subsequently remembered than for cues of subsequently forgotten words (SUBSM main effect: $F_{1,8} = 32.94$, $p < 0.001$). In the time window 600 to 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. There was no SUBSM x CUE interaction for any of the time-windows for the Cz-electrode.

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: $t_{11} = 2.29$, $p < 0.05$). The rhinal ERPs of TBR and TBF hits 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: $t_{10} = 3.31$, $p < 0.01$). Hippocampal ERPs to recognized TBF and correctly classified new words did not differ. 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 ($t_9 = 5.40$, $p < 0.001$).

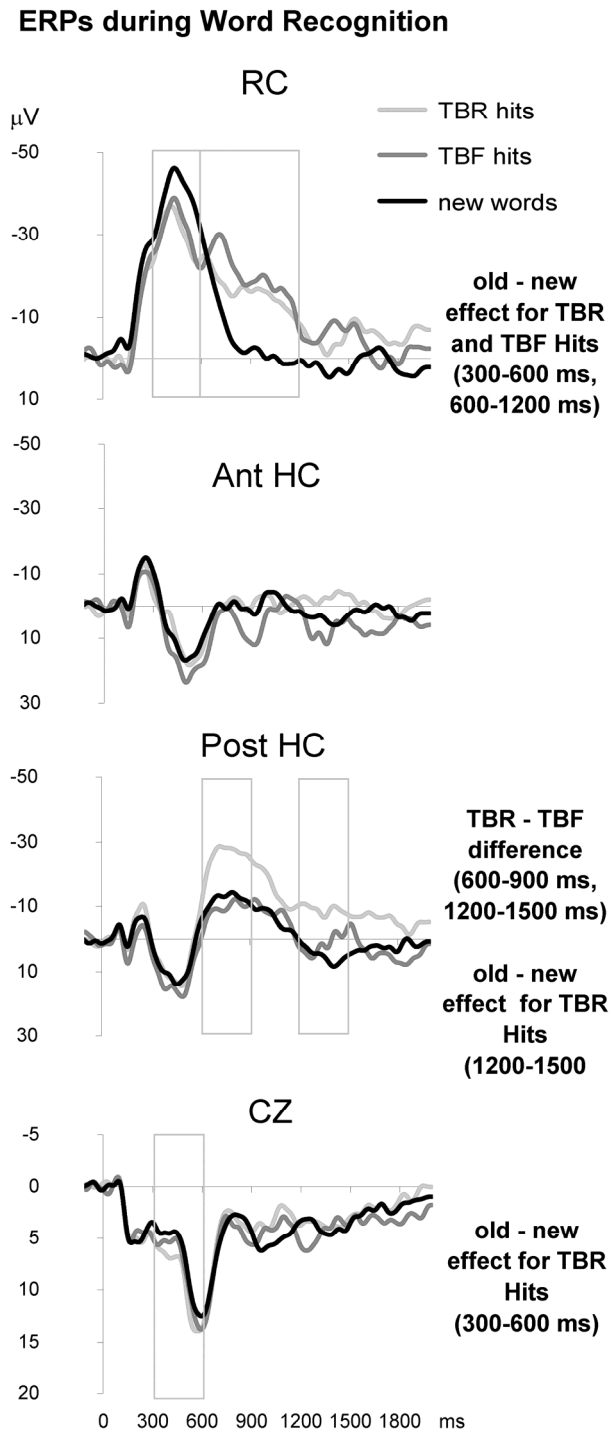

FIGURE 4. ERPs during word recognition separated for TBR hits, TBF hits and new words. Shown are the ERPs of the electrodes RC, ant HC, post HC as well as Cz. Negative values are plotted upwards. Significant results of the paired t-tests are indicated by frames that cover the particular time window and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

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, word recognition).

Initial word presentation

Each trial started with the presentation of a word item. Based on previous studies (Smith *et al.*, 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 (Fernández *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 only be involved in initial word encoding to a small extent, 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 *et al.*, 2000a).

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.

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.*, 2002b; Wylie *et al.*, 2008), one could assume that the MTL is not involved in selective rehearsal following TBR cues. Theoretically, the TBF cue might also be followed by rehearsal processes, however not by rehearsal of the current word, but of the previously presented TBR cued words. Therefore, it might be possible that the MTL is indeed involved in word rehearsal, but that the MTL processes following TBR and TBF are too similar to be separable 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.*, 2002b; 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.*, 2002b). Therefore, it can be speculated that we missed the effect, since our sample in this analysis comprised the data of 9 right and only 2 left hemispheric electrodes.

At Cz, a broad positive component (presumably a scalp-P300 component) was observed with 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 *et al.* study, who also found a larger P300 for subsequently remembered words (2000a).

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 evidence 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, 1995a), we consider the positivity in response to cues as an MTL-P300 component. ERP analyses

showed a significant interaction between CUE and SUBSM for anterior and posterior hippocampal electrodes. TBF-F cues were associated with a smaller MTL-P300 than TBF-R cues. 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.

The hippocampus is regarded as one generator (together with a larger assembly of temporal/ parietal brain areas) of the scalp P3b (Bledowski, 2004; Halgren, 1995a). While the scalp P3b has been generally associated with context updating (Donchin and Coles, 1988), the hippocampal P300 was also suggested to be associated with memory processes (Halgren, 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). 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 analysis of rhinal ERPs also 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. Anatomical studies have indicated that associational connections within the perirhinal, parahippocampal, and entorhinal areas enable integration of unimodal and polymodal inputs, such that only highly integrated information reaches the hippocampus. The rhinal cortex (especially the entorhinal part) integrates but also rejects neocortical input and thus operates as a sensory filter (Lavenex and Amaral, 2000). Ablating the rhinal cortex in monkeys has for example been shown to have equivalent effects to that of removing the entire hippocampus, also suggesting that the rhinal cortex is an important interface between the neocortex and the hippocampus (Murray and Mishkin, 1998). The long lasting positivity, which we

observed in response to the TBF cue, might therefore reflect inhibition of information transmission between the rhinal cortex and hippocampus. Since no interaction with subsequent memory was shown, the rhinal cortex might mediate the intention to forget, while the success of this intention depends on other structures such as the hippocampus or frontal cortex. It can be speculated that the rhinal cortex is directly integrated in frontal inhibition networks. In a previous study, a larger activity for TBF than TBR cues was observed in the parahippocampal gyrus (Wylie *et al.*, 2008), which might be based on similar mechanisms as our rhinal cortex activity.

At Cz, findings were similar to those in the rhinal cortex. We observed a 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 positivity has been observed for Nogo than for Go trials and interpreted in terms of inhibition (Eimer, 1993; Falkenstein *et al.*, 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 *et al.*, 2000b).

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 are 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 ("old-new effect"), 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 *et al.*, 2005) as well as single-unit studies (Brown and 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.

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.* (2000b), 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 and Bagheri, 1985; Ullsperger *et al.*, 2000b). Such a process, impeding the recognition of TBF cued words, should have resulted in larger old-new effects for TBF than TBR hits, reflecting the effort of overcoming the inhibition (Ullsperger *et al.*, 2000b). Our results provide no indication for retrieval inhibition in the MTL or scalp recordings.

Limitations of the study

The interpretation of results of intracranial studies with epilepsy patients is always constrained by the possibility that the epilepsy disease impairs brain processing. Additionally, many patients had to be excluded due to problems with the rather demanding paradigm. However, those patients coping with the task showed scalp ERPs that were comparable in size to previous studies with healthy subjects (Paz-Caballero *et al.*, 2004) as well as pronounced directed forgetting effects. Naturally, the decision to insert depth electrodes as well as their placement has been made solely on clinical grounds. Hence several cortical areas which would be of great interest in the context of directed forgetting are out of limits with the present approach. These criticisms notwithstanding, intracranial recordings offer the unique possibility to assess cognitive functions with high anatomical and temporal precision (Münte *et al.*, 2008).

Conclusion

The present investigation used depth recorded 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 is actively 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 and Pare, 2004). Thus, it can be speculated that the frontal cortex suppresses hippocampal encoding via the rhinal cortex.

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Die hier vorgelegte Dissertation habe ich eigenständig und ohne unerlaubte Hilfsmittel angefertigt. Die Dissertation wurde in der vorliegenden oder in ähnlicher Form bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Eva Ludowig

Eigene Veröffentlichungen

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