Evidence relating human verbal memory to hippocampal *N*-methyl-D-aspartate receptors

Thomas Grunwald*†, Heinz Beck*, Klaus Lehnertz*, Ingmar Blümcke‡, Nico Pezer*, Martin Kurthen*, Guillen Fernández*, Dirk Van Roost§, Hans J. Heinze¶, Marta Kutas‖, and Christian E. Elger*

Departments of *Epileptology, ‡Neuropathology, and §Neurosurgery, Bonn University Medical Center, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany; ¶Department of Neurology II, University of Magdeburg, Leipziger Strasse 44, 39120 Magdeburg, Germany; and ‖Cognitive Science and Neurosciences Departments, University of California, Mail Code 0515, 9500 Gilman Drive, La Jolla, CA 92093-0515

Edited by Michael I. Posner, Cornell University Medical College, New York, NY, and approved August 4, 1999 (received for review March 23, 1999)

Studies in rodents and nonhuman primates have linked the activity of *N*-methyl-D-aspartate (NMDA) receptors within the hippocampus to animals' performance on memory-related tasks. However, whether these receptors are similarly essential for human memory is still an open question. Here we present evidence suggesting that hippocampal NMDA receptors, most likely within the CA1 region, do participate in human verbal memory processes. Words elicit a negative event-related potential (ERP) peaking around 400 ms within the anterior mesial temporal lobe (AMTL-N400). Ketamine, an NMDA-receptor antagonist, reduces the amplitude of the AMTL-N400 (in contrast to other hippocampal potentials) on initial presentation, eliminates the typical AMTL-N400 amplitude reduction with repetition, and leads to significant memory impairment. Of the various hippocampal subfields, only the density of CA1 neurons correlates with the word-related ERPs that are reduced by ketamine. Altogether, our behavioral, anatomical, and electrophysiological results indicate that hippocampal NMDA receptors are involved in *human* memory.

Long-term potentiation (LTP) is a long-lasting increase in synaptic efficacy after high-frequency stimulation of afferent fibers. It depends on high levels of postsynaptic calcium. The primary source of the calcium influx during the induction of hippocampal LTP occurs through an ion channel that is coupled to the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor (1, 2). NMDA receptors are thus hypothesized to play a crucial role in the induction of associative LTP within the hippocampal CA1-region (3); this is viewed as a putative mechanism for Hebbian learning. This form of synaptic plasticity has been offered as a cellular model of memory processes in hippocampal slice preparations (4). Numerous studies in rodents and primates have linked hippocampal LTP with spatial learning and memory (5) although there are some contradictory results (6).

NMDA receptors are also abundant within the human hippocampus (14, 15). NMDA receptor antagonists block LTP induction in surgically resected specimens from the human temporal cortex (16). The human mesial temporal lobe system is considered essential for declarative memory (7, 8), contributing to both encoding and retrieval (9–13). Despite the suggestive findings of animal studies, however, the question of whether hippocampal NMDA receptors contribute to human memory processes remains unsettled.

The occasional need to place depth electrodes within the mesial temporal lobes during the presurgical evaluation of patients with pharmacoresistant temporal lobe epilepsy affords us the opportunity to record depth potentials directly from the human hippocampal formation. Analyses of limbic event-related potentials (ERPs) can contribute to the presurgical workup with respect to both the lateralization of the epileptogenic focus (17–19) and the prediction of surgical outcome (20, 21). Limbic ERPs also offer unique opportunities for investigating the relationship between hippocampal structures and their functions (22).

To examine whether hippocampal NMDA receptors are involved in human memory processes, we analyzed the influence of the noncompetitive NMDA receptor blocker ketamine on limbic ERPs and on verbal recognition memory performance. We used a continuous word-recognition paradigm wherein patients were asked to discriminate between words presented for the first time (new) and on repetition (old). Although AMTL-N400s potentials elicited in this task are generated in parahippocampal structures near the collateral sulcus (23) including rhinal areas (24), the hippocampus proper appears to contribute to their generation, at least in part (22).

Typically, AMTL-N400s to words are reduced in amplitude on repetition (25–27). Within the mesial temporal lobe, ERP repetition/recognition effects have also been observed for a positive potential peaking around 600 ms (25) and a late negative component (LNC) with a peak latency of about 700 ms within the hippocampus proper (28). Because the activity of NMDA receptors in the hippocampal CA1 region is important for spatial memory in rodents (29), we also looked for a specific association between ketamine-sensitive limbic ERPs and particular subfields within the human hippocampus.

Methods

Subjects. Ketamine effects were examined in 16 patients (8 women, age 30 ± 7 years). Twenty-five consecutive patients with Ammon's horn sclerosis (8 women, age 35 ± 10 years), two of whom had also entered the ketamine study, participated in ERP recordings for cell correlation studies. Three additional patients were excluded because their ERP recordings were contaminated by epileptiform potentials. All patients were evaluated for possible epilepsy surgery according to the Bonn protocol of presurgical workup (30). Depth electrodes were implanted because of the nonconclusive results of noninvasive studies. Informed consent was obtained from all patients, and the study was approved by the local institutional review board.

ERP Recording Methods and Data Analysis. In a visual word-recognition paradigm, 300 nouns (duration: 200 ms) were presented once every 1,800 ± 400 ms. Half of these were repeated after 3 ± 1 or 14 ± 4 intervening stimuli. Patients were asked to indicate whether an item was new or old by pressing one of two buttons. Because earlier studies have revealed no significant differences between AMTL-N400s to early and late repetitions, averages were collapsed over both lags for the present study (22). ERPs were recorded from bilateral depth electrodes implanted

This paper was submitted directly (Track II) to the PNAS office.

Abbreviations: LTP, long-term potentiation; AMTL, anterior mesial temporal lobe; ERP, event-related potential; NMDA, *N*-methyl-D-aspartate; LNC, late negative component; n.s., not significant.

†To whom reprint requests should be addressed. E-mail: thomas@jersey.meb.uni-bonn.de.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

stereotactically along the longitudinal axis of the hippocampus (31) and were referenced to extracranially linked mastoids. Additional subdural strip electrodes, with which limbic ERPs could not be recorded, were not considered for the present study. The silastic depth electrodes contained 10 contacts, each consisting of a nickel-chromium alloy. Their placements were verified by visual inspection of postimplant magnetic resonance images with reference to cross sections published by Duvernoy (32). ERP recordings during the word recognition task were performed twice. The second session occurred just before the removal of the depth electrodes. In this session, ERPs were recorded after intravenous administration of ketamine for analgesia in subanesthetic dosage (0.5 mg/kg). The word-recognition task was performed on a different set of words than were used in the first session, when the patients were oriented to time, place, and name, and when they could repeat at least five digits in a digit-span test. Depth-electroencephalogram recordings were amplified using a bandpass filter setting of 0.03 to 85 Hz (12 dB/octave) and, after 12-bit analog/digital conversion, were written continuously to a hard disk (sampling rate: 173 Hz per channel). Selective averaging was performed on 1,200-ms stimulus-locked epochs, including a 200-ms prestimulus baseline. We considered only recordings that were not contaminated by epileptiform potentials, and the averages included only correct-response trials. ERPs were quantified with respect to the prestimulus baseline as the mean amplitudes of the prominent negativity from 300 to 600 ms and from 600 to 900 ms after stimulus onset. Performance data and ERP measurements were subjected to repeated measures ANOVA (F test with Greenhouse–Geisser corrections for P values). When significant effects were found, posthoc t tests for paired samples were applied.

Neuronal Cell Counts. Ammon's horn sclerosis was defined as cell loss of the CA1, CA3, and CA4 segment of the Ammon's horn with relative sparing of dentate granule cells, severe gliosis, and axonal reorganization. After epilepsy surgery, this diagnosis was confirmed by two neuropathologists who independently evaluated paraffin-embedded coronal sections from different levels of the hippocampal longitudinal axis by using hematoxylin and eosin, Nissl, and combined hematoxylin-eosin-luxol-fast blue stains.

Neuronal cell densities were determined by using the monoclonal antibody NeuN directed against a neuronal nucleus-specific antigen, at a dilution of 1:500 (33). The slides were deparaffined with xylene and several rinses in 100% and 95% ethanol. Then they were incubated in 2% hydrogen peroxide, diluted in methanol for 15 min, rehydrated successively in 95%, 90%, 70%, and 50% ethanol, and rinsed in PBS. Sections were transferred into 0.01 M citrate buffer and boiled twice for 5 min in a microwave oven to improve the binding of the monoclonal antibodies and then transferred into PBS. Preincubation with 2% horse serum, 10% fetal calf serum, and 5% nonfat dry milk in PBS as a blocking reagent for unspecific immunoreactivity preceded incubation with the primary antibody overnight at 4°C in a humid chamber. Binding of primary antibody was detected by the avidin-biotin-complex peroxidase method by using 3,3′-diaminobenzidine as a chromogen. For semiautomatic imaging of the specimens, we used a Vanox microscope (Olympus, Hamburg, Germany) equipped with a CCD video camera and the IP Lab imaging analysis software (Signal Analytics, Vienna, VA). To determine the neuronal densities of pyramidal cells within CA1–4 and of dentate granule cells, NeuN labeled nuclei were tagged on the computer screen and the number of objects and respective regions of interest was calculated. Results of five adjacent regions of interest per hippocampal subfield were recorded, averaged, and expressed as mean cell number/mm^2. Bivariate correlations of these cell counts with mean amplitudes of ipsilateral ERPs were calculated by using Pearson correlation coefficients with Bonferroni corrections because of multiple comparisons.

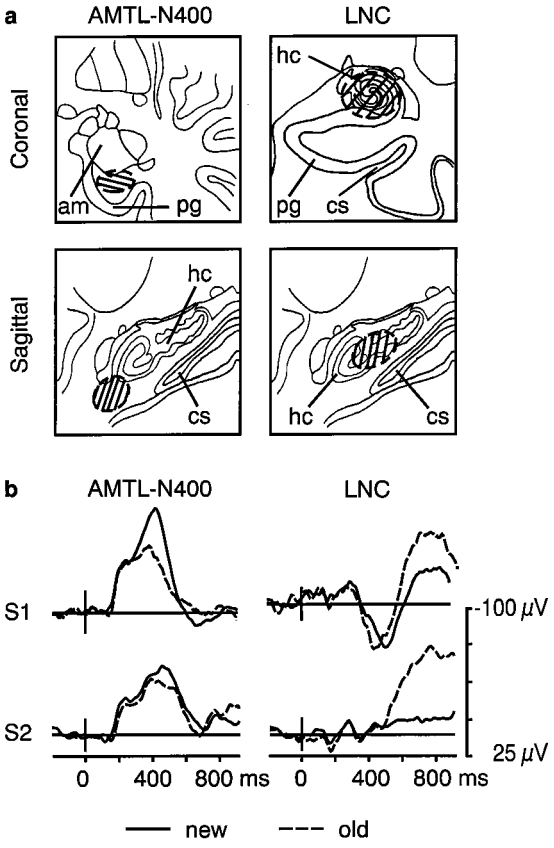

Fig. 1. Area of electrode locations at which limbic N400 potentials (AMTL-N400) and LNCs to words were recorded and examples of potentials from two patients. (*a*) Schematics of recording sites of AMTL-N400s and LNCs to words. Hatching spans the area of recording sites across all patients. am, amygdala; cs, collateral sulcus; hc, hippocampus; pg, parahippocampal gyrus. (*b*) Examples of ERPs from two patients (S1, S2) recorded within the nonepileptic temporal lobes. Solid line, initial presentations; dashed line, repetition.

Results

All patients were alert and attentive. However, ketamine lowered memory performance; that is, the patients recognized significantly fewer repeated words than they had in the experiment without ketamine (51.1 ± 20.2% vs. 65.4 ± 17.1%, $P < 0.01$). First presentations were identified as such equally well in both conditions [82.8 ± 17.1% vs. 81.2 ± 15.5%, not significant (n.s.)].

Words elicited well-defined AMTL-N400s (mean peak latency: 435 ± 53 ms) in the anterior mesial temporal lobe and LNCs (mean peak latency: 769 ± 85 ms) within the hippocampus proper (Fig. 1). Repeated measures ANOVA revealed a significant effect of ketamine on mean AMTL-N400 amplitudes ($F1, 15 = 15.17$, $P < 0.005$) and a significant interaction between ketamine and new-minus-old recognition effects ($F1, 15 = 5.15$, $P < 0.05$). Recognition effects were significant without ketamine ($F1, 15 = 14.57$, $P < 0.005$) but not after ketamine administration ($F1, 15 = 0.72$, n.s.; Fig. 2). Posthoc t tests for paired samples showed that ketamine significantly reduced MTL-N400 amplitudes to new words on both the epileptic (focal) and the contralateral side (focal: −23 ± 16 vs. −35 ± 20 μV, $P < 0.0005$; nonfocal: −31 ± 18 vs. −54 ± 18 μV, $P < 0.0005$). Mean AMTL-N400 amplitudes to old words were unaffected by ketamine administration (focal: −26 ± 15 vs. −31 ± 22 μV, n.s.;

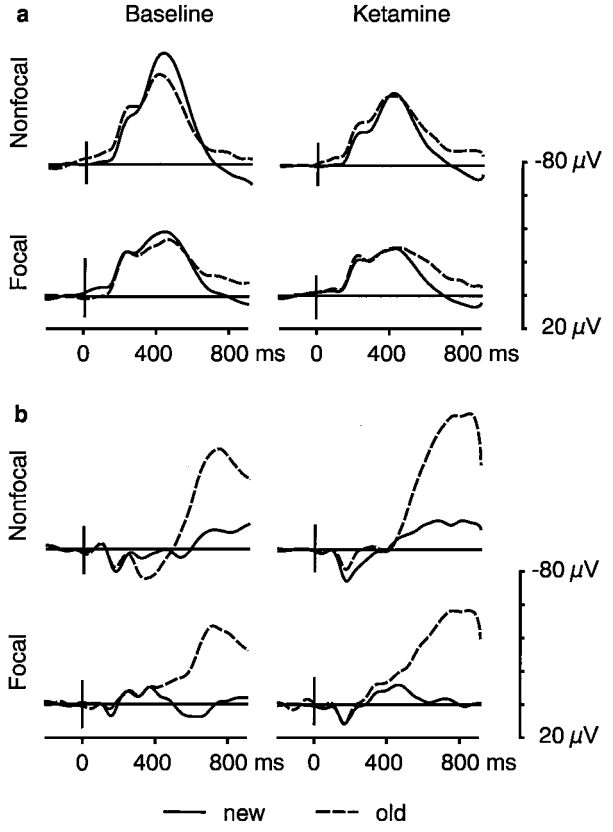

Fig. 2. ERPs averaged across patients. (*a*) AMTL-N400s were significantly affected by ketamine. Recognition effects were significant only without ketamine, not after intravenous administration of this NMDA-receptor antagonist. (*b*) Ketamine did not affect LNCs and LNC recognition effects. Focal, recordings from the epileptogenic temporal lobe; nonfocal, recordings from the contralateral side.

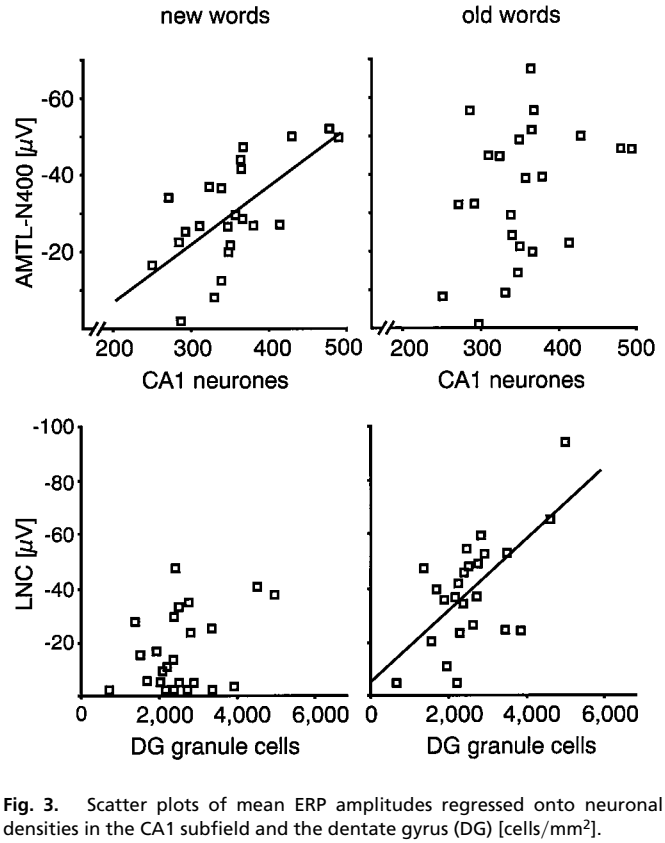

Fig. 3. Scatter plots of mean ERP amplitudes regressed onto neuronal densities in the CA1 subfield and the dentate gyrus (DG) [cells/mm^2].

nonfocal: -34 ± 18 vs. -42 ± 17 μV, n.s.). In contrast to the marked effect of ketamine on the AMTL-N400 repetition effect, LNCs were not affected (F1, 15 = 2.88, n.s.); there was a reliable LNC repetition/recognition effect both under the influence of ketamine (F1, 15 = 39.66, $P < 0.0005$) and without it (F1, 15 = 37.97, $P < 0.0005$).

Because it is not possible to perform controlled lesion experiments in humans, we examined the relationship between the graded neuronal loss in well-defined hippocampal subfields and limbic ERPs in temporal lobe epilepsy patients who underwent both hippocampectomy and invasive presurgical evaluation with depth electrodes. Cell correlation studies were performed in 25 consecutive patients in whom the diagnosis of Ammon's horn sclerosis was confirmed histopathologically. In all patients, limbic ERPs were recorded by using the word-recognition paradigm (described above) as part of their presurgical workup. After hippocampectomy, cell counts were determined for pyramidal neurons within the hippocampal subfields CA1–4 and for dentate granule cells. We found that the number of CA1 neurons correlated only with AMTL-N400s to new ($r = 0.65$, $P < 0.005$) but not old words ($r = 0.36$, n.s.; Table 1, Fig. 3). Moreover, the density of dentate granule cells correlated selectively with LNCs to old ($r = 0.62$, $P < 0.005$) but not new words ($r = 0.33$, n.s.). No other reliable correlations were obtained after Bonferroni correction for multiple comparisons.

Discussion

Studies in rodents and nonhuman primates have linked the activity of NMDA receptors within the hippocampus to the animals' performance in memory-related tasks. On the basis of these results, the activation of NMDA receptors has been hypothesized to be crucial for human memory. In search of evidence relating hippocampal NMDA receptors with human memory, we recorded depth ERPs from the hippocampal formation. We found that ketamine, an NMDA-receptor antago-

Table 1. Correlations between hippocampal cell counts and limbic ERPs

	r; *P*			
Subfield	AMTL-N400 (new)	AMTL-N400 (old)	LNC (new)	LNC (old)
CA1	0.65;*P*=0.001	0.36;n.s.	0.11;n.s.	−0.19; n.s.
CA2	−0.19; n.s.	0.03;n.s.	0.15;n.s.	0.43; n.s.*
CA3	−0.16; n.s.	0.12;n.s.	−0.10;n.s.	0.12; n.s.
CA4	−0.07; n.s.	0.14;n.s.	0.16;n.s.	0.48; n.s.*
Dentate gyrus	0.20; n.s.	0.36;n.s.	0.33;n.s.	0.62;*P*=0.001

Bivariate correlation coefficients (*r*) and levels of significance. *, $P = 0.05$; not significant after Bonferroni correction for multiple comparisons.

nist, significantly disturbed verbal recognition memory, diminished AMTL-N400 amplitudes to new words, and virtually eliminated the AMTL-N400 repetition/recognition effect. In contrast, LNC amplitudes and the associated LNC recognition effects were unaffected, indicating that ketamine did not simply attenuate all limbic ERPs. In sum, memory deficits induced by ketamine were selectively associated with smaller AMTL-N400s to words on their initial presentation and with the absence of the typical AMTL-N400 recognition effect.

AMTL-N400s were found only in electrode contacts located in rhinal areas anterior to the hippocampal head and not in posterior contacts within the hippocampus. This finding is consistent with previous reports of steep amplitude gradients and polarity inversions in immediately adjacent regions implicating local generation within mesial temporal lobe structures (23–25, 34, 35). We believe that ketamine affected hippocampal activity contributing to the generation of AMTL-N400s because neuronal loss within the hippocampus proper leads to a similar alteration in the AMTL-N400 recognition effect (22).

Exactly which psychological processes were influenced by ketamine is not so easy to determine because deficits in attention, memory span, and linguistic skills all can impair verbal recognition memory. Moreover, subanesthetic doses of ketamine have been observed to induce psychotic symptoms (36), influence degree of alertness, and impair perception (37), as well as lower free recall, recognition, and semantic and working memory performance (38–40). We used a digit span test to ensure that our patients were alert, attentive, and cooperative when the ERP recording began. Immediately after ketamine administration, patients' attention and/or immediate memory was affected; patients could repeat only one or two digits. However, their performance improved after a few minutes, and ERP recording did not begin until patients could repeat at least five digits, suggesting that their attention level was close to normal. Moreover, at that time no patient showed any signs of hallucinations, lowered vigilance, or language difficulties. Recognition memory performance thus may have been impaired because ketamine interfered with short-term memory, consistent with the possible role of NMDA receptors in this type of memory (41). However, given that ketamine specifically attenuated AMTL-N400s, which we previously found to be correlated with delayed verbal recall performance (42), it is likely that ketamine affected intermediate memory processes as well.

Correlating neuronal densities within the different hippocampal subregions with limbic ERPs elicited by words, we found two specific associations: (*i*) only the number of pyramidal cells within the CA1 subfield were linked to the amplitude of the ketamine-sensitive AMTL-N400s elicited by words on their initial presentation; and (*ii*) only the number of dentate gyrus granule cells correlated with the amplitude of the LNCs elicited by repeated words. We offer these correlations as evidence that the human hippocampus participates in both memory encoding and retrieval processes. This view is consistent with findings from functional imaging studies by using functional MRI (43) and positron emission tomography technology (44) of increased activity within the hippocampal system during both encoding and retrieval. Our data, however, cannot help adjudicate between the alternative positions on the distribution of the neuronal substrates of encoding and retrieval processes along the longitudinal axis of the hippocampal formation. In our patients, there were no electrodes situated in parahippocampal structures next to those intrahippocampal electrodes from which LNCs to old words were recorded. Therefore, we do not know whether new words elicit N400s only in the rostral or also in the caudal areas of the limbic system. Nonetheless, our findings extend earlier imaging studies inasmuch as they indicate different functional divisions even within the hippocampus proper: the various subfields contribute differentially to encoding and retrieval processes. In addition, the finding that ketamine-induced impairments of recognition memory were associated with attenuated limbic ERPs to new rather than to old words may suggest that ketamine interfered more with (possibly novelty-related) encoding processes.

Ketamine has effects on several receptor types, increases dopamine concentrations in striatal sites (45), and especially inhibits NMDA receptor-mediated acetylcholine release (46). Anticholinergic agents have been shown to increase amplitudes of limbic ERPs in the epileptogenic hippocampus (47). Whether the apparent increase of LNC amplitudes under ketamine in the present study reflects modulation of cholinergic activity cannot be determined by our data, because this effect was not significant. However, ketamine reduced rather than increased AMTL-N400 amplitudes. Moreover, during the test our patients exhibited no psychotic symptoms that are thought to be related to dopaminergic effects of ketamine (45). Therefore, it seems justifiable to hypothesize that the elimination of AMTL-N400 recognition effects may be attributed to NMDA-receptor antagonism, which is the most important neuropharmacological mechanism of ketamine. The hypothesis that memory processes associated with these effects rely on the activity of mesial temporal NMDA receptors is particularly interesting, because NMDA receptors are necessary for LTP with Hebbian characteristics at many central synapses. Pharmacological (3) and genetic (29) studies have identified this form of synaptic plasticity within the hippocampal CA1-region. In our investigations, it was only the number of CA1 neurons that were correlated with the limbic ERP potentials that seemed to tap aspects of verbal encoding and were reduced by ketamine. Taken together, we offer our findings as evidence relating human verbal memory processes to hippocampal NMDA receptors.

This specific link of ketamine-sensitive limbic ERPs with the CA1 subfield in humans is consistent with the recent finding that mice lacking the NMDAR1 receptor subunit show neither NMDA receptor-dependent LTP nor formation of place cells in the CA1 region and exhibit spatial memory deficits (47, 48). Our findings are also consistent with the reported correlations between verbal memory performance and AMTL-N400s to new words (21, 42) and neuronal densities in the CA1 subfield (50, 51). Impairment of NMDA receptor-mediated encoding processes may thus explain the significant memory deficits in human patients with bilateral lesions confined to the CA1 subfield (52, 53). In conclusion, by combining behavioral, electrophysiological, and pharmacological data from patients with temporal lobe epilepsy, we have demonstrated involvement of limbic NMDA receptors in human memory processes.

This study was supported by the Deutsche Forschungsgemeinschaft (project El 122/4–2 and Sonderforschungsbereich 400). M.K. is supported by grants MH52883 (National Institute of Mental Health), HD22614 (National Institute of Child Health and Human Development), and AG08313 (National Institute on Aging). We thank our colleagues J. Schramm, M.D., E. Behrens, M.D., and J. Zentner, M.D., who performed the implantation of depth electrodes and hippocampal resections. We also thank A. Wyler, M.D., for valuable comments on the manuscript.

1. Harris, E. W., Ganong, A. H. & Cotman, C. W. (1984) *Brain Res.* **323,** 132–137.
2. Jahr, C. E. & Stevens, C. F. (1987) *Nature (London)* **325,** 522–525.
3. Morris, R. G. M., Andersen, E., Lynch, G. S. & Baudry, M. (1986) *Nature (London)* **319,** 774–776.
4. Bliss, T. V. P. & Collingridge, G. L. (1993) *Nature (London)* **361,** 31–39.
5. Maren, S. & Baudry, M. (1995) *Neurobiol. Learn. Mem.* **63,** 1–18.
6. Saucier, D. & Cain, D. P. (1995) *Nature (London)* **378,** 186–189.
7. Squire, L. R. & Zola-Morgan, S. (1991) *Science* **253,** 1380–1386.
8. Eichenbaum, H, Otto, T. & Cohen, N. J. (1994) *Behav. Brain Sci.* **17,** 449–518.
9. Fernandez, G., Weyerts, H., Schrader-Bolsche, M., Tendolkar, I., Smid, H. G.,

Tempelmann, C., Hinrichs, H., Scheich, H., Elger, C. E., Mangun, G. R. *et al.* (1998) *J. Neurosci.* **18,** 1841–1847.
10. Maguire, E. A., Frackowiak, R. S. J. & Frith, C. D. (1997) *J. Neurosci.* **17,** 7103–7110.
11. Halgren, E., Wilson, C. L. & Stapleton, J. M. (1985) *Brain Cognit.* **4,** 287–295.
12. Stern, C. E., Corkin, S., Gonzáles, R. G., Guimaraes, A. R., Baker, J. R., Jennings, P. J., Carr, C. A., Sugiura, R. M., Vedantham, V. & Rosen, B. R. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 8660–8665.
13. Lepage, M., Habib, R. & Tulving, E. (1998) *Hippocampus* **8,** 313–322.
14. Blümcke, I., Beck, H., Scheffler, B., Hof, P. R., Morrison, J. H., Wolf, H. K., Schramm, J., Elger, C. E. & Wiestler, O. D. (1996) *Acta Neuropathol.* **92,** 576–587.
15. Scherzer, C. R., Landwehrmeyer, G. B., Kerner, J. A., Counihan, T. J., Kosinski, C. M., Standaert, D. G., Daggett, L. P., Velicelebi, G., Penney, J. B. & Young, A. B. (1998) *J. Comp. Neurol.* **390,** 75–90.
16. Chen, W. R., Lee, S., Kato, K., Spencer, D. D., Shepherd, G. M. & Williamson, A. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 8011–8015.
17. Meador, K. J., Loring, D. W., King, D. W., Gallagher, B. B., Gould, M. J., Flanigin, H. F. & Smith, J. R. (1987) *Neurology* **37,** 494–497.
18. Puce, A., Kalnins, R. M., Berkovic, S. F. & Bladin, P. F. (1989) *Ann. Neurol.* **26,** 377–385.
19. Grunwald, T., Beck, H., Lehnertz, K., Blümcke, I., Pezer, N., Kutas, K., Kurthen, M., Karakas, H. M., Van Roost, D., Wiestler, O. D., *et al.* (1999) *Eur. J. Neurosci.* **11,** 1899–1906.
20. Grunwald, T., Lehnertz, K., Pezer, N., Kurthen, M., Van Roost, D., Schramm, J. & Elger, C. E. (1999) *Epilepsia* **40,** 303–306.
21. Grunwald, T., Lehnertz, K., Helmstaedter, C., Kutas, M., Pezer, N., Kurthen, M., Van Roost, D. & Elger, C. E. (1998) *NeuroReport* **9,** 3375–3378.
22. Grunwald, T., Lehnertz, K., Heinze, H. J., Helmstaedter, C. & Elger, C. E. (1998) *Proc. Natl. Acad. Sci. USA* **95,** 3193–3197.
23. McCarthy, G., Nobre, A. C., Bentin, S. & Spencer, D. D. (1995) *J. Neurosci.* **15,** 1080–1089.
24. Halgren, E., Baudena, P., Heit, G., Clarke, M. & Marinkovic K. (1994) *J. Physiol. (Paris)* **88,** 1–50.
25. Smith, M. E., Stapleton, J. M. & Halgren, E. (1986) *Electroencephalogr. Clin. Neurophysiol.* **63,** 145–159.
26. Heit, G., Smith, M. E. & Halgren, E. (1990) *Brain* **113,** 1093–1112.
27. Nobre, A. C. & McCarthy, G. (1995) *J. Neurosci.* **15,** 1090–1098.
28. Grunwald, T., Elger, C. E., Lehnertz, K., Van Roost, D. & Heinze, H. J. (1995) *Electroencephalogr. Clin. Neurophysiol.* **95,** 53–62.
29. McHugh, T. J., Blum, K. I., Tsien, J. Z., Tonegawa, S. & Wilson, M. A. (1996) *Cell* **87,** 1339–1349.
30. Van Roost, D., Solymosi, L., Schramm, J., van Oosterwyck, B. & Elger, C. E. (1998) *Neurosurgery* **43,** 819–826.
31. Engel J., Jr. (1993) *Surgical Treatment of the Epilepsies* (Raven, New York), pp. 740–742.
32. Duvernoy, H. M. (1988) *The Human Hippocampus* (Bergmann, Munich).
33. Wolf, H. K, Buslei, R., Schmidt-Kastner, R., Schmidt-Kastner, P. K., Pietsch, T., Wiestler, O. D. & Bluemcke, I. (1996) *J. Histochem. Cytochem.* **44,** 1167–1171.
34. Puce, A., Andrewes, D. G., Berkovic, S. F. & Bladin, P. F. (1991) *Brain* **114,** 1647–1666.
35. Guillem, F., N′Kaoua, B., Rougier, A., Claverie, B. (1995) *Psychophysiology* **32,** 382–392.
36. Murman, D. L., Giordani, B., Mellow, A. M., Johanns, J. R., Little, R. J., Hariharan, M. & Foster, N. L. (1997) *Neurology* **49,** 153–161.
37. Sethna, N. F., Gracely, R., Bennett, G. J. & Max, M. B. (1998) *Anesth. Analg.* **86,** 1250–1256.
38. Malhotra, A. K., Pinals, D. A., Weingartner, H., Sirocco, K., Missar, C. D., Pickar, D. & Breier, A. (1996) *Neuropsychopharmacology* **14,** 301–307.
39. Malhotra, A. K., Pinals, D. A., Adler, C M., Elman, I., Pickar, D. & Breier, A. (1997) *Neuropsychopharmacology* **17,** 141–150.
40. Adler, C. M., Goldberg, T. E., Malhotra, A. K., Pickar, D. & Breier, A. (1998) *Biol. Psychiatry* **43,** 811–816.
41. Lisman, J. E., Fellous, J. M. & Wang, X. J. (1998) *Nat. Neurosci.* **1,** 273–275.
42. Elger, C. E., Grunwald, T., Lehnertz, K., Kutas, M., Helmstaedter, C., Brockhaus, A., Van Roost, D. & Heinze, H. J. (1997) *Neuropsychologia* **35,** 657–668.
43. Gabrieli, J. D. E., Brewer, J. B., Desmond, J. E. & Glover, G. H. (1997) *Science* **276,** 264–266.
44. Lepage, M., Habib, R. & Tulving, E. (1998) *Hippocampus* **8,** 313–322.
45. Breier, A., Adler, C. M., Weisenfeld, N., Su, T. P., Elamn, I., Picken, L., Malhotra, A. K. & Pickar, D. (1998) *Synapse* **29,** 142–147.
46. Feuerstein, T. J. (1994) *Anaesthesist* **43,** 48–51.
47. Meador, K. J., Loring, D. W., King, D. W., Gallagher, B. B., Gould, M. J., Smith, J. R. & Flanigin, H. F. (1988) *Int. J. Neurosci.* **38,** 407–414.
48. Tsien, J. Z., Huerta, P. T. & Tonegawa, S. (1996) *Cell* **87,** 1327–1338.
49. Wilson, M. A. & Tonegawa, S. (1997) *Trends Neurosci.* **20,** 102–106.
50. Sass, K. J., Silberfein, C. M., Platis, I., Westerveld, M., Buchanan, C. P., Delaney, R. C., Kim, J. H. & Spencer, D. D. (1995) *J. Int. Neuropsychol. Soc.* **1,** 554–560.
51. Baxendale, S. A., Van Paesschen, W., Thompson, P. J., Duncan, J. S., Harkness, W. F. & Shorvon, S. D. (1998) *Neuropsychiatry Neuropsychol. Behav. Neurol.* **11,** 12–21.
52. Zola-Morgan, S., Squire, L. R. & Amaral, D. G. (1986) *J. Neurosci.* **6,** 2950–2967.
53. Rempel-Clower, N. L., Zola, S. M., Squire, L. R. & Amaral, D. G. (1996) *J. Neurosci.* **16,** 5233–5255.