Electrophysiological connections between the hippocampus and entorhinal cortex in patients with complex partial seizures

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The electrophysiological properties of the neural pathways between the hippocampus and the entorhinal cortex were studied intraoperatively in 31 patients undergoing anterior temporal lobectomy for medically intractable complex partial seizures. The hippocampus, removed en bloc, was studied histologically and the pathology was correlated with the electrophysiological findings. In 29 of the patients, entorhinal stimulation evoked a characteristic positive-negative potential in the hippocampus. The entorhinal-evoked hippocampal response closely resembled, or was identical to, the spontaneously occurring hippocampal interictal spike discharge. In patients with Ammon's horn sclerosis in whom there was a major loss of neurons in the hippocampal subfields CA1, CA3, and CA4, the evoked responses were of simple morphology and long latency (mean 21.9 msec to the peak of the first potential). In patients with a ganglioglioma in whom the hippocampus was histologically normal, the evoked responses were of greater complexity and shorter latency (mean 11.8 msec). Stimulation at a single entorhinal site evoked similar waveforms at different hippocampal recording sites. Conversely, stimulation at different entorhinal sites evoked similar responses at a single hippocampal recording site. Stimulation of the hippocampus evoked a potential in the entorhinal cortex and, in some instances, in the amygdala, insula, and lateral temporal cortex. These connections may produce a positive feedback loop that favors seizure generation.

KEY WORDS: complex partial seizures · Ammon's horn sclerosis · epilepsy · hippocampus · entorhinal cortex · evoked responses

The hippocampus has the lowest seizure threshold of any major area of the brain, and most complex partial seizures originate in or are elaborated in the hippocampus. Depth electrode recordings show that hippocampal interictal spike discharges are present in most patients with intractable complex partial seizures. The neural circuits that generate the interictal hippocampal spike are not known. Stimulation of the afferent pathways to epileptogenic tissue can produce an epileptiform discharge, and therefore stimulation of afferent pathways to the hippocampus in patients with complex partial seizures might be expected to produce an interictal spike.

Studies in lower mammals have defined a trisynaptic pathway in the hippocampus that can be activated by stimulation of the entorhinal cortex (Fig. 1). Entorhinal synaptic input to the hippocampus is carried largely by the perforant path fibers that form excitatory synapses on the dentate granule neurons and the apical dendrites of hippocampal pyramidal neurons. The dentate granule neurons make excitatory connections with CA1 and CA4 pyramidal neurons via mossy fiber synapses. CA1 pyramidal neurons activate CA3 pyramidal neurons by way of Schaffer collateral projections. In lower mammals, this trisynaptic pathway is oriented in parallel beams, perpendicular to the long axis of the hippocampus, and has been reported to have a high degree of topographic specificity. The hippocampal formation has efferent connections with both subcortical and neocortical regions by way of the fornix and subiculum.

During anterior temporal lobectomy and hippocampectomy, the opportunity exists to study the physiology of the temporal lobe in man, including the physiological properties of the entorhinal-hippocampal projections. Previous studies have used depth electrodes to...
investigate the functional properties of these connections in man. In these studies, electrode location was determined radiographically. If similar studies are performed during surgery, the position of the electrodes can be verified with greater precision and their positions can be varied so that topographic relationships of projections between different areas can be studied and correlated with the histology of the hippocampus.

**Clinical Material and Methods**

**Patient Population**

Intraoperative electrocorticographic and evoked potential recordings were obtained from 31 patients who underwent anterior temporal lobectomy for medically intractable complex partial seizures. Seizure origin was determined by electroencephalographic/video monitoring of seizures using sphenoidal and, in 18 of the patients, depth electrodes. Patients were also evaluated with computerized tomography and/or magnetic resonance imaging, neuropsychological testing, and intracarotid Amytal (amobarbital) testing for language and memory localization.

**Surgical Procedure**

The surgery was performed under general anesthesia using nitrous oxide and isoflurane. In most cases, anesthetic gas concentrations were monitored with mass spectrophotography. While the recordings were being made, nitrous oxide concentrations were adjusted to between 5% and 10% and isoflurane to between 0.3% and 0.4%, and PaCO₂ was maintained at 24 to 27 torr. Blood pressure was carefully monitored for any change during the period of recording.

Anterior temporal lobectomy was performed in three stages. First, the anterior 4.5 to 5.5 cm of the lateral temporal lobe, from the superior temporal gyrus to the collateral fissure, was resected en bloc. The temporal horn of the lateral ventricle was opened and the alveus was exposed. The second stage consisted of en bloc microsurgical removal of the anterior 2 to 3 cm of the hippocampal formation and associated entorhinal cortex. In the third stage, the amygdala and uncus were dissected free of the pia and removed.

**Electrophysiological Methods**

Electrocorticographic recordings were made from the cerebral structures exposed at each of the three stages of the operation. The evoked potential data presented here were obtained after the first stage of the operation, during the course of recording from the exposed hippocampus and associated structures. Two platinum disc electrodes 1 mm in diameter and 1 mm apart, set into a leaflet of silicone rubber 1 mm thick, were used to stimulate the entorhinal and hippocampal surfaces. In some patients the subcortical white matter was stimulated with 100-μm thick stainless steel bipolar electrodes. The stimulation parameters were a rectangular pulse of 100-μsec duration, 1 to 12 mA in intensity, delivered at 0.1 to 20 Hz.

For the purposes of this study, the entorhinal cortex was defined as the anterior part of the parahippocampal gyrus (Fig. 1). The anterior, middle, and posterior regions of the entorhinal cortex were stimulated. The medial to lateral extent of the entorhinal cortex was explored with the stimulating electrodes at each of these sites. To verify that projections from the entorhinal cortex were responsible for the response recorded in the hippocampus following entorhinal stimulation, the perforant pathway in the white matter of the parahippocampal gyrus was directly stimulated with the stainless steel bipolar electrodes. When performed, this procedure uniformly evoked a response in the hippocampus similar to that evoked by placing the leaflet stimulating electrode on the surface of the entorhinal cortex.

Monopolar recordings from the surface of the hippocampus were made with a 1-mm platinum disc electrode embedded in a silicone leaflet. The reference and ground electrodes were placed on the temporalis mus-
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cle. In some patients, stainless steel wire electrodes 100 μm in diameter with three recording surfaces 1 mm apart were used to record from the depth of the hippocampus. These were used for both monopolar and bipolar recordings.

The topographic specificity of the entorhinal-hippocampal connections was evaluated by altering the stimulating and recording sites. Following stimulation at a fixed entorhinal site, recordings were made from three sites of the exposed hippocampus: the anterior portion of the pes hippocampi, and 1 and 2 cm behind the anterior pes. Conversely, the entorhinal cortex was stimulated at anterior, middle, and posterior sites (parallel to the three hippocampal sites), and the responses were recorded from a fixed hippocampal site. To ensure that the potentials recorded were generated in the hippocampus and were not volume-conducted from a remote source, potentials were recorded using the 100-μm electrodes from the depth of the hippocampus when referenced to the surface of the hippocampus, indicating local generation of evoked potentials. As a further test of the local generation of potentials, the recording electrode leaflet was inverted after recording the hippocampal potential so that the insulated side lay against the alveus and the electrode was in contact with the cerebrospinal fluid of the ventricle. No evoked potentials were recorded with the electrode in this position.

**Data Collection and Analysis**

Potentials were recorded with a Nicolet Pathfinder II with a bandpass filter setting of 0.5 to 3000 Hz.* Ten to 20 responses were usually averaged, but a smaller number of responses or a single response was often digitized. Potentials were also recorded on FM tape and subsequently digitized. In all patients, negative potentials were displayed as an upward deflection from the baseline. The waveform of the response recorded from the alvear surface of the hippocampus was classified as simple, intermediate, or complex according to the number of negative components that followed the initial positive component. A simple waveform had only one prominent negative component; an intermediate waveform had two prominent negative components; and a complex waveform had three or more negative components (see Fig. 3).

**Pathological Examination**

After fixation, the resected hippocampal and temporal tissue was embedded in paraffin and serially sectioned. The sections were stained with Nissl, hematoxylin and eosin, Luxol fast blue, phosphotungstic acid hematoxylin, or Beilschowsky silver stains, and examined with light microscopy. The criteria used to assess the specimens were those defined at the International Conference on the Surgical Treatment of Epilepsy.3 In 16 patients it was possible to make an unequivocal diagnosis of Ammon's horn sclerosis; a ganglioglioma was present in eight patients. In the other seven patients there were diffuse or nonspecific changes (including minimal neuronal loss in the hippocampus), ectopic neurons in the white matter of the temporal lobe and, in some patients, areas of microdysgenesis.

**Results**

**Characteristics of Hippocampal Potentials Evoked by Entorhinal Stimulation**

In 29 of the 31 patients, entorhinal stimulation produced a large potential (0.1 to 3 mV) recorded from the surface of the alveus. Small or negligible responses were evoked in the other two patients, possibly because a portion of the entorhinal cortex medial to the collateral fissure was removed during the first stage of the resection or, in one patient, because of infiltration of the hippocampus by a ganglioglioma. In 26 of the 29 patients, the response was characterized by an initial positive wave followed by a negative component. In the other three, there was an initial small-amplitude negative component that was followed by a positive-negative wave. The threshold for generating a response was between 1 and 4 mA. At threshold, the response consisted primarily of the initial positive wave (Fig. 2A). As the stimulus intensity was increased, the positive wave increased in amplitude and decreased in latency, and the negative potential became more prominent (Fig. 2B and C). In some patients, at higher stimulus intensities the waveform of the evoked response became more complex, consisting of a second positive component and more than one negative peak (Fig. 3C and D). At maximal stimulus intensity the latency to the peak of the positive potential for all 29 patients averaged 20.4 ± 2.0 msec (± standard error of the mean; Tables

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* Pathfinder II manufactured by Nicolet Biomedical Instruments, Madison, Wisconsin.
### TABLE 1
Findings in 16 patients with Ammon's horn sclerosis *

<table>
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<th>Case No.</th>
<th>Age at Surgery (yrs)</th>
<th>Side</th>
<th>Waveform Complexity</th>
<th>Latency to 1st Peak (msec)</th>
<th>Outcome Grade†</th>
<th>Follow-Up (mos)</th>
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<td>21.9 (± 2.7)</td>
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<td>43.4 (± 5.3)</td>
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*T Demographic characteristics, entorhinal-evoked hippocampal waveform complexity, and surgical outcome. See text for description of waveform complexity. SEM = standard error of the mean.
† I = > 95% reduction in seizures; II = 75%–95% reduction in seizures; III = 50%–75% reduction in seizures.

### TABLE 2
Findings in eight patients with a ganglioglioma *

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<tr>
<th>Case No.</th>
<th>Age at Surgery (yrs)</th>
<th>Side</th>
<th>Waveform Complexity</th>
<th>Latency to 1st Peak (msec)</th>
<th>Outcome Grade†</th>
<th>Follow-Up (mos)</th>
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<tr>
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<td></td>
<td>13.7 (± 3.9)</td>
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<td>32.5 (± 7.5)</td>
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</table>

*Tumor invasion of the parahippocampal gyrus.
§ Only an incomplete hippocampal specimen was available.
† I = > 95% reduction in seizures; II = 75%–95% reduction in seizures; IV = < 50% reduction in seizures.
‡ Mean latency of the six patients with a histologically normal hippocampus was 11.8 ± 4.1 msec.

**FIG. 3.** Examples of simple and complex hippocampal potentials evoked by entorhinal stimulation. A and B: Simple responses that consisted of a positive-negative waveform. Both of these patients had Ammon's horn sclerosis. Stimulus intensity was 8 mA. C and D: Complex responses in patients with a ganglioglioma and histologically normal hippocampus. These evoked potentials consisted of multiple components. Note the different time scale in D. Stimulus intensities were 12 and 8 mA for C and D, respectively.

1 to 3). The latency to the peak of the negative potential averaged 47.8 ± 4.8 msec.

The evoked response had a consistent amplitude at stimulation frequencies of 1 to 10 Hz. At stimulation frequencies between 10 and 20 Hz, the amplitude of the initial positive wave decreased and the negative component was obscured by the next stimulus. At stimulation frequencies of less than 1 Hz, the averaged hippocampal potential appeared to be of a lower amplitude than when evoked at 1 to 3 Hz.

The complexity and latency to the first peak of the entorhinal-evoked hippocampal potential were correlated with the underlying hippocampal pathology (Figs. 3 and 4, Tables 1 to 3). Patients with Ammon's horn sclerosis tended to have simple waveforms: of the 16 patients with Ammon's horn sclerosis, 11 had simple, four had intermediate, and one had a negligible evoked response. The mean latency to the first peak of the evoked response was 21.9 ± 2.7 msec for these patients.
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(Comment 1). Patients with a ganglioglioma without infiltration of the hippocampus tended to have more complex waveforms. Of the eight patients with a ganglioglioma, six did not have infiltration of the hippocampus and two had infiltration of the hippocampus (Comment 2). Of the two patients with infiltration, one had a simple and the other a negligible response. In the six patients with a ganglioglioma and a histologically normal hippocampus, the mean latency to the first peak of the evoked response was 11.8 ± 4.1 msec. The evoked response was complex in four patients and simple in the other two (Figs. 3C and D and 4B). One of the patients with a simple response had tumor infiltrating the entorhinal cortex; in the other patient, the hippocampal specimen was incomplete. The mean latency to the first peak for all of the patients with a ganglioglioma was 13.7 ± 3.9 msec. Of the seven patients with non-specific changes, four had simple, two intermediate, and one a complex response; the mean latency to the first peak was 24.1 ± 4.2 msec (Table 3). In general, the latency to the first peak was shortest in patients in whom the evoked response was most complex. The mean latency for complex waveforms was 9.1 ± 2.7 msec (five cases); for intermediate waveforms 16.2 ± 4.8 msec (six cases); and for simple waveforms 25.0 ± 2.1 msec (18 cases).

In 10 patients in whom spontaneously occurring hippocampal spikes were recorded using the same electrodes from which an evoked response was recorded, the waveform of the hippocampal response following entorhinal stimulation was similar, and in some cases identical, to the spontaneously occurring interictal hippocampal spike (Fig. 5). In the patient whose recordings are shown in Fig. 5A, there was also a spontaneously occurring entorhinal epileptiform discharge that appeared to be synchronous with or to precede the hippocampal spike. Our experience with recording simultaneously from the entorhinal cortex and hippocampus is limited; however, it is not known whether or not this relationship regularly occurs.

**Topographic Specificity of Entorhinal-Hippocampal Connections**

The topographic specificity of the hippocampal response to entorhinal stimulation was investigated in 12 patients. While recording was continued from a fixed hippocampal position, the stimulating electrode was moved to different positions on the entorhinal cortex. The paradigm used was first to stimulate the most anterior part of the entorhinal cortex, and then to stimulate sites 1 and 2 cm posterior to the most anterior position. Although the amplitudes and latencies varied, the recorded hippocampal waveforms were similar, regardless of the position of the stimulating electrode on the entorhinal cortex (Fig. 6).

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**TABLE 3**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Surgery (yrs)</th>
<th>Side</th>
<th>Waveform Complexity</th>
<th>Latency to 1st Peak (msec)</th>
<th>Outcome Grade†</th>
<th>Follow-Up (mos)</th>
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* Demographic characteristics, entorhinal-evoked hippocampal waveform complexity, and surgical outcome. See text for description of waveform complexity. SEM = standard error of the mean.
† I = > 95% reduction in seizures; III = 50%-75% reduction in seizures; IV = < 50% reduction in seizures.
FIG. 5. Relationship between spontaneous and evoked interictal responses. A: Recordings from Case 14, with Ammon's horn sclerosis. The upper and middle traces show simultaneously recorded spontaneous entorhinal and hippocampal spikes. The lower trace represents a single entorhinal-evoked hippocampal response (stimulus intensity of 4 mA). The evoked hippocampal response was identical to the spontaneously occurring hippocampal spike. The entorhinal trace was recorded with a surface electrode and the hippocampal traces were recorded with a 100-μM thick stainless steel electrode placed in the hippocampus. B: Recordings showing spontaneous (upper) and entorhinal-evoked (lower) hippocampal spikes in a patient with Ammon's horn sclerosis (Case 6). The waveforms were similar in both recordings.

The converse relationship was also studied: the entorhinal stimulating electrode position remained the same while the position of the hippocampal recording electrode was varied. Recordings were made from the pes anteriorly, and then from sites 1 and 2 cm posterior to the pes. The responses recorded at the pes and at a position 2 cm posterior to the pes were similar (Fig. 7).

Characteristics of Hippocampal Potentials Evoked by Stimulation of the Alveus

In five patients, the hippocampal potential evoked by stimulating the posterior portion of the exposed alveus was studied. Stimulation of the alveus would be expected to activate septal and commissural afferent input as well as to antidromically activate axons of the pyramidal and subicular neurons that exit via the fornix. The evoked potential recorded at a more anterior position on the alveus consisted of an initial negative component and a later positive component (Fig. 8). The latency to the peak of the initial negative component ranged from 5 to 25 msec among the five patients. The initial negative component may represent antidromic activation of the hippocampal pyramidal neurons.

Characteristics of Entorhinal, Amygdalar, and Lateral Temporal Cortical Potentials Evoked by Stimulation of the Hippocampus

In six patients, the hippocampal surface was stimulated and recordings were made from the entorhinal cortex. In some instances the hippocampal stimulus intensity that was effective for evoking a response was lower than that required to generate a hippocampal
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**Fig. 8.** Hippocampal response evoked by stimulating the alveus. Stimulus intensity was 8 mA for both traces. A: The response consisted of a short-latency negative potential followed by a positive potential. B: Response from another patient at a slower time scale.

response by entorhinal stimulation. Stimulation of the hippocampus produced entorhinal responses in two patients with Ammon's horn sclerosis; one with ganglioglioma and normal hippocampal histology; one with ganglioglioma infiltrating into CA4; and two with diffuse pathological changes. The entorhinal potential produced by hippocampal stimulation was characterized by a prominent negative potential that occurred 50 to 100 msec following the stimulus (Fig. 9). Preceding this negative potential there were smaller-amplitude positive-negative-positive or negative-positive potentials with a latency to the first peak of 5 to 20 msec.

In three of these patients responses were also recorded from the insular cortex, amygdala, and temporal neocortex following hippocampal stimulation.

**Clinical Outcome Related to Temporal Lobe Pathology**

Two-thirds of the 31 patients in this study had excellent outcomes, defined as greater than 95% reduction in seizure frequency. No surgical morbidity or postoperative complications occurred in the series. The best outcomes were in patients with Ammon's horn sclerosis, with 14 of 16 patients having an excellent outcome (Table 1); less favorable outcomes were associated with nonspecific pathological changes, with three of seven patients having an excellent outcome (Table 3). These results are comparable to those reported in other surgical series. An excellent outcome suggests that the tissue removed was involved in the generation or elaboration of the patient's seizures and that the pathways studied electrophysiologically played a role in seizure generation in these patients.

**Discussion**

This study characterizes the electrophysiological connections between the entorhinal cortex and the hippocampus in patients with complex partial seizures. The simplest evoked waveforms appeared in patients with Ammon's horn sclerosis, while the more complex waveforms were associated with more normal hippocampal histology. The generation of more complex waveforms in histologically normal hippocampi may be explained by the synaptic activation of a full complement of hippocampal regions (dentate granule neurons and CA3 and CA1 pyramidal neurons). In Ammon's horn sclerosis the simpler waveforms appear to be a product of a less complex ensemble of synaptic connections.

The specific neuronal generators of the components of the hippocampal response observed in this study have not yet been defined by current-source density analysis. Generalization from animal studies suggests that the positive component corresponds to a synaptic sink in the apical dendritic region of the pyramidal or granule neurons. The later negative component may represent a basilar dendritic synaptic sink or an inhibitory synaptic component. The latency of the negative component is compatible with recurrent inhibition. The latencies and waveforms of human entorhinal-evoked hippocampal potentials are remarkably similar to those which occur in rabbits and cats.
Further study of the laminar distribution of potentials within the hippocampus is required to identify the origin of the hippocampal response following entorhinal stimulation. Since the entorhinal-evoked response was similar or identical to the spontaneously occurring interictal spike, it appears likely that the interictal spike could be triggered by afferent activity entering the hippocampus via the perforant pathway.

A precise arrangement of entorhinal-hippocampal connections, which has been described in lower mammals, was not found in these patients. Instead, there appeared to be divergence of entorhinal activation of the hippocampus. Varying the placement of the stimulating electrode or the recording electrode by as much as 2 cm did not substantially alter the waveform of the entorhinal-evoked hippocampal potential. It is not known whether this is a normal feature of the human hippocampus or is the result of a loss of topographic specificity of projections in the epileptic cortex. Another possible substrate for the diffusion of the entorhinal-evoked hippocampal response is activation of the intra-hippocampal association pathway that runs in the long axis of the hippocampus, in a plane longitudinal to the septal-temporal axis. This pathway is believed to arise largely from CA$_2$ pyramidal neurons which are preserved to a greater degree than CA$_1$ or CA$_3$ pyramidal neurons in Ammon’s horn sclerosis.

The existence of feedback loops between the hippocampus and adjacent structures is suggested by the finding that stimulation of the hippocampus evoked a wide area of activation that included the entorhinal cortex, amygdala, insular cortex, and lateral temporal neocortex. These responses were robust and, in some instances, required only low current intensities of 1 to 2 mA. Anatomical and physiological studies in animals have demonstrated efferent pathways from hippocampal pyramidal neurons to both the subiculum and entorhinal cortex. Stimulation of the alvear surface of the hippocampus would be expected to activate hippocampal pyramidal neurons that could then activate the entorhinal cortex directly or activate subicular neurons which project to the entorhinal cortex. In two patients with severe neuronal loss in the CA$_1$ region, stimulation of the alveus produced an entorhinal potential. In these patients, it is possible that stimulation of the alveus antidromically activated subicular neurons to produce an entorhinal response. Alternatively, the few remaining CA$_1$ neurons may have been capable of exciting the subiculum which then activated the entorhinal cortex.

Another explanation for alvear stimulation producing a response in the entorhinal cortex is antidromic activation of the putative alvear pathway which has been reported to originate in the lateral entorhinal cortex and synapse on the basal dendrites of CA$_1$ pyramidal and subicular neurons. The existence of this pathway has not been documented in all studies. However, it is unlikely that the response that we observed, which had a latency of 50 to 100 msec, was an antidromic response mediated by an alvear pathway, if one existed in man. Instead, it is more likely that alvear stimulation activates the entorhinal cortex via pathways that originate in the hippocampus or subiculum.

Alvear stimulation was also observed to activate the amygdala, insular cortex, and lateral temporal cortex, either directly or via polysynaptic pathways. These observations are in keeping with known anatomical connections. In primates, the entorhinal cortex is an area of convergence and receives afferent input from many neocortical areas. The hippocampus also appears to be an area that receives a convergence of input and has a divergent output. These long feedback loops may be important in the generation of seizures and may help to explain the effectiveness of hippocampectomy in stopping seizures.

The results of the present study suggest possible techniques for preoperative evaluation that may predict the underlying pathology in patients with complex partial seizures. Stimulation of the entorhinal cortex through subdural strip electrodes and recording from the hippocampus with depth electrodes may provide a preoperative measurement of the complexity and excitability of the entorhinal-hippocampal connections and of the underlying hippocampal pathology.

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References

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