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Neuronal migration disorders: Heterotopic neocortical neurons in CA1 provide a bridge between the hippocampus and the neocortex

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ABSTRACT **Neuronal migration disorders have been involved in various pathologies, including epilepsy, but the properties of the neural networks underlying disorders have not been determined. In the present study, patch clamp recordings were made from intrahippocampal heterotopic as well as from neocortical and hippocampal neurons from brain slices of rats with prenatally methylazoxymethanol-induced cortical malformation. We report that heterotopic neurons have morphometrical parameters and cellular properties of neocortical supragranular neurons and are integrated in both neocortical and hippocampal networks. Thus, stimulation of the white matter induces both antidromic and orthodromic response in heterotopic and neocortical neurons. Stimulation of hippocampal afferents evokes a monosynaptic response in the majority of heterotopic neurons and a polysynaptic all-or-none epileptiform burst in the presence of bicuculline to block γ-aminobutyric acid type A inhibition. Furthermore, hippocampal paroxysmal activity generated by bath application of bicuculline can spread directly to the neocortex via the heterotopia in methylazoxymethanol-treated but not in naive rats. We conclude that heterotopias form a functional bridge between the limbic system and the neocortex, providing a substrate for pathological conditions.**

Migration of young postmitotic neurons from the ventricular zone to the cortical plate where they differentiate is a key event in cortical development. Neuronal migration disorders lead neurons to differentiate in an abnormal or heterotopic position (1). Periventricular and subcortical heterotopias long have been described in the brain of patients suffering from epilepsy (2–6). Moreover, discrete intracortical heterotopias also have been described in the brains of patients suffering from dyslexia (7) and schizophrenia (8). Together, these data suggest that neuronal migration disorders may constitute a morphological basis for these pathologies.

Despite their importance for the understanding of the physiopathological mechanisms of these disorders, the cellular properties and connections of heterotopic neurons are known poorly. In the present study, we have used the prenatal methylazoxymethanol (MAM) model that is associated with microcephaly (9, 10) and cortical disorganization with periventricular and intrahippocampal heterotopias (11–13). We report that intrahippocampal neocortical heterotopic neurons have bi-directional monosynaptic connections with the neocortex and are integrated in the hippocampal circuitry. They therefore provide a direct aberrant link between the hippocampus and the neocortex and a basis for disorders associated with cortical malformation. As an example for this, we report that paroxysmal activity generated in the hippocampus can directly propagate to the neocortex via the heterotopia.

MATERIALS AND METHODS

Animals. Pregnant Wistar rats were injected i.p. with 25 mg/kg of MAM (Sigma) dissolved in saline at embryonic day 14 (first gestation day as embryonic day 0). After normal delivery, rats were given food and water *ad libitum* and were housed according to Institut National de la Santé et de la Recherche Médicale guidelines for animal care.

Electrophysiology. Rats (3–7 weeks old) were anesthetized with ether and were decapitated, and their brains were removed. The telencephalon was dissected in ice-cold oxygenated artificial cerebrospinal fluid containing (in mM) 126 NaCl, 3.5 KCl, 1 $CaCl_2$, 2 $MgCl_2$, 1.2 NaH_2PO_4, 25 $NaHCO_3$, 11 glucose equilibrated with 95% 0_2, and 5% CO_2 (pH 7.4). Coronal hippocampo-neocortical slices (400 μm) were cut in chilled artificial cerebrospinal fluid by using a vibratome. After recovery at 20°C, slices were sectioned ventral to the hippocampus (a typical slice is shown in Fig. 2), were placed in a submerged recording chamber continuously superfused with artificial cerebrospinal fluid, then were stained with a drop of methylene blue to visualize the heterotopias. Blind patch clamp recordings in whole cell configuration were performed by using an Axopatch 200A (Axon Instruments, Foster City, CA) with microelectrodes (5–10 MΩ) containing (in mM) 120 K-Gluconate, 10KCl, 10 NaCl, 1 $CaCl_2$, 2MgATP, 0.5 GTP, 10 EGTA, 10 Hepes, and 1% biocytin, at pH 7.4. Stimulation was delivered with a bipolar electrode (0.5 mm) during 30–60 μs at 0.5–2 mA, 0.003 Hz. For the stimulation of the Schaffer collaterals and temporo-ammonic pathways, stimulating electrodes were positioned laterally in the stratum radiatum and medially in the stratum lacunosum respectively. Drugs were supplied by Tocris Neuramin (Bristol, U.K.). Data are expressed as mean ± SEM, and statistical significance was assessed ($P < 0.05$) by Student's t test.

Morphological Analysis. All recorded neurons were loaded with biocytin. After cryoprotection in 30% sucrose, slices were sectioned at 60 μm with a freezing microtome, were processed overnight with the ABC Elite kit (Vector Laboratories), and were revealed with diaminobenzidine as a chromogen. A neutral red counterstaining was performed to visualize the heterotopias.

Carbocyanine Tracing. MAM animals (2 weeks old) were perfused with 4% paraformaldehyde, and a small crystal of 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate (Molecular Probes) was inserted in the CA3 region. After a 1-month incubation, brains were sectioned 50 μm thick,

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Abbreviations: EPSC, excitatory postsynaptic current; EPSP, excitatory postsynaptic potential; MAM, methylazoxymethanol; WM, white matter.

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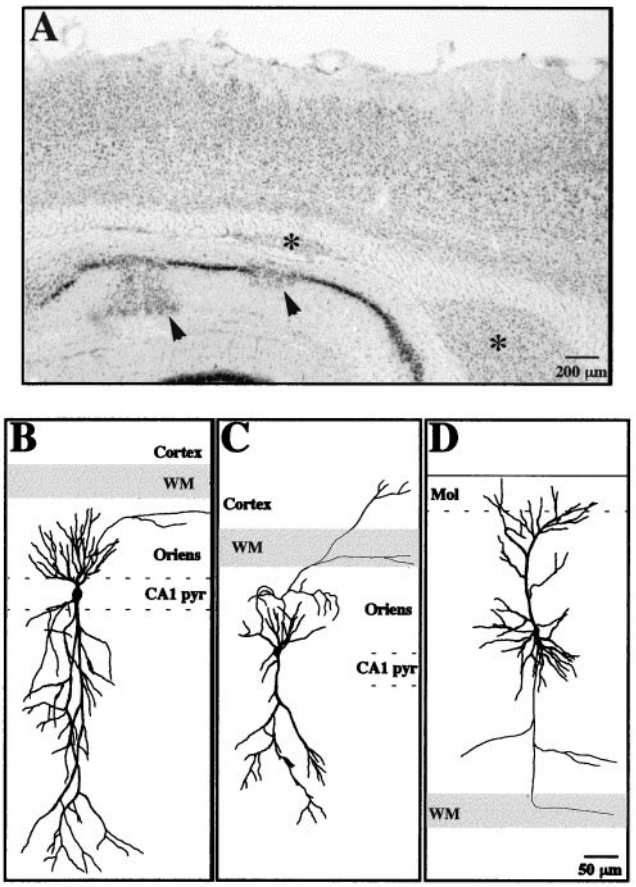

FIG. 1. Anatomical features of MAM cortex. (*A*) A longitudinal Nissl-stained section of an adult MAM rat showing cortical disorganization, WM heterotopias (star), and two types of CA1 heterotopias (arrowheads). Representative examples of biocytin-filled CA1 (*B*), heterotopic (*C*), and neocortical (*D*) neurons are shown.

were counterstained with bisbenzidine, were mounted, and were observed with an epifluorescence microscope.

RESULTS

In agreement with previous reports (12–14), we observed that prenatal treatment with MAM induces a diffuse cortical malformations in all of the offsets of a litter. MAM rats exhibit cortical thinning mainly affecting the supragranular layers and heterotopias in and below the white matter (WM) as well as in the CA1 region of the hippocampus (Fig. 1*A*). As described (15), WM heterotopias consistently were found rostral or lateral to the hippocampus. By contrast, CA1 heterotopias were found in the rostral portion of the hippocampus and were present in usually two brain slices per rat.

It has been reported that CA1 heterotopias share several developmental features with supragranular neocortex including similar neurogenesis period, neuronal phenotypes, and projections to the WM (14). To characterize the physiological properties of CA1 heterotopic neurons, we recorded from neurons in the CA1 pyramidal layer, in the CA1 heterotopia, and in the supragranular layers of the neocortex adjacent to the heterotopia. Nonpyramidal neurons, identified by their morphology and absence of spike frequency adaptation ($n = 3$ in the heterotopia, $n = 1$ in the neocortex), were excluded from analysis. The properties of recorded neurons are shown in Table 1. Biocytin filling showed that the overall shape of the dendritic tree were similar in these three populations (Fig. 1 *B–D*). However, morphometrical analysis revealed that neocortical neurons and CA1 heterotopic neurons had a smaller soma than CA1 pyramidal neurons (Table 1). In the 4 of 11 heterotopic neurons in which axonal filling was satisfactory, the axon was observed to run in the WM with collateral extending in the neocortex.

Therefore, the similarity in resting membrane potential, soma size, and axonal trajectory between supragranular neocortical and CA1 heterotopic neurons are in agreement with a previous description of CA1 heterotopias as neocortex in the hippocampus (14). We then addressed the following questions: Are CA1 heterotopic neocortical neurons integrated in the network to which they were committed: i.e., the neocortex? And are CA1 heterotopic neurons integrated in their environmental network: i.e., the hippocampus?

CA1 Heterotopias Are Integrated in the Neocortical Network. To determine whether CA1 heterotopic neurons were integrated in the neocortical network, we compared the response evoked in heterotopic and supragranular neurons by electrical stimulation of the WM that contains both afferent and efferent neocortical fibbers. WM stimulation evoked an excitatory postsynaptic current (EPSC) in all heterotopic ($n = 14$) and supragranular neocortical neurons ($n = 5$) but not in CA1 neurons ($n = 12$) (Fig. 2*A*). The mean response latency was, respectively, 3.3 ± 0.3 ms and 3.2 ± 0.2 ms, suggesting a monosynaptic response. The EPSC completely was blocked by bath application of the glutamatergic antagonists 6-cyano-7-dinitroquinoxaline-2,3-dione (10 μM) and D-2-amino-5-phosphopentanoate (50 μM), demonstrating that heterotopic neurons, like neocortical neurons, receive a glutamatergic input from the WM.

To determine whether heterotopic neurons also project to the neocortex, we used two types of experiments. We first tested whether WM stimulation evoked antidromic action potentials in heterotopic neurons. In the presence of 6-cyano-7-dinitroquinoxaline-2,3-dione/2-amino-5-phosphopentanoate to block glutamatergic responses, increased intensity of stimulation evoked in heterotopic neurons a spike ($n = 6$ of 8;

Table 1. Properties of heterotopic, necortical (layer II/III), and CA1 pyramidal neurons

	Heterotopic neurons	Supragranular necortical neurons	CA1 neurons
Length, μm	18.8 ± 1.2 (11) (12.5–24)	21.2 ± 1.9 (8) (18.3–24; $P = 0.13$)	27 ± 1.5(13) (16–37.6; $P = 0.0005$)
Width, μm	13.2 ± 0.7 (11) (10–17.6)	14.2 ± 0.9 (8) (10.5–17; $P = 0.41$)	13.9 ± 0.85 (13) (8.8–19.5; $P = 0.56$)
Area, μm^2	185 ± 17 (11) (118–270)	228 ± 19 (8) (150–286; $P = 0.12$)	297 ± 15 (13) (200–409; $P = 0.0001$)
RMP, mV	−74.4 ± 1 (45) (−65–−85)	−77.7 ± 1 (21) (−69–−85; $P = 0.1$)	−67.2 ± 1 (32) (−61–−78; $P = 0.0001$)
R_N, MΩ	155.8 ± 18 (11) (100–280)	163.6 ± 16 (8) (100–230; $P = 0.76$)	168.5 ± 18 (8) (120–250; $P = 0.0.63$)

n, the range value, and p are shown in parentheses. *P* = statistical difference compared to heterotopic neurons. RMP, resting membrane potential; R_N input resistance.

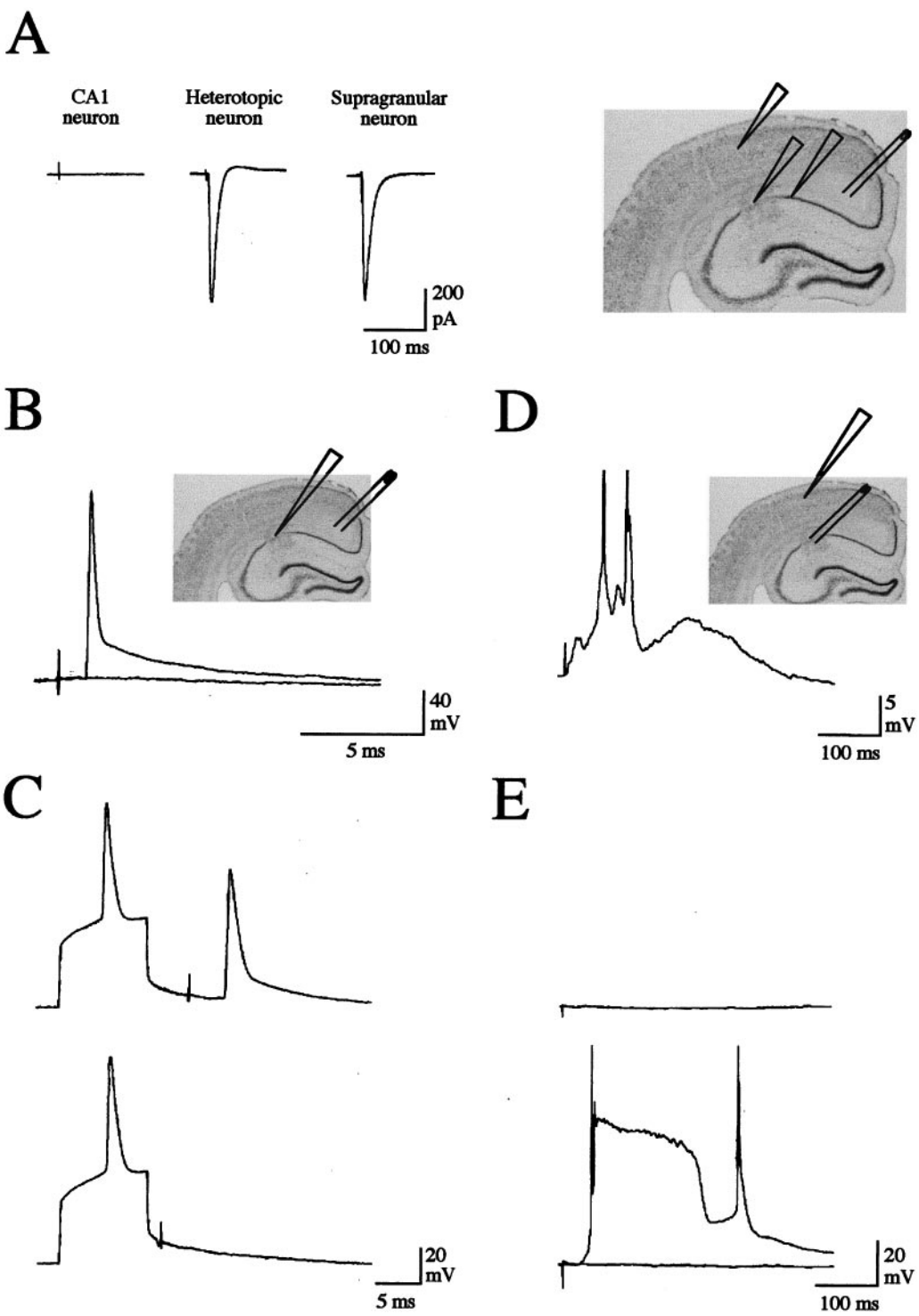

FIG. 2. Neocortical heterotopias are integrated within the neocortical circuitry. (*A*) Electrical stimulation of the WM evoked an EPSC in both heterotopic and supragranular neurons, but not in CA1 neurons. Holding potential (V_H) = −65 mV. (*B*) In the presence of 6-cyano-7-dinitroquinoxaline-2,3-dione and 2-amino-5-phosphopentanoate, electrical stimulation of the WM evoked an all-or-none action potential. This was not associated with an EPSP when stimulus intensity was reduced below the threshold for action potential generation. (*C*) An orthodromic action potential evoked by a depolarizing pulse collided with the stimulus-evoked action potential when the interspike delay (measured as the delay between the two action potential) was below 7 ms. Membrane potential (V_M) = −70 mV. (*D*) In control conditions, electrical stimulation of the heterotopia evoked a multiphasic EPSP with superimposed action potentials. This multiphasic EPSP was considered as a network-driven event because it was evoked in an all-or-none manner and its latency decreased with increasing stimulus intensity. V_M = −75 mV. (*E*) In other cells, stimulation of the heterotopia failed to induce any synaptic response in control conditions (upper trace). However, in presence of bicuculline (10 μM), an all-or-none epileptiform discharge was evoked (lower trace). V_M = −78 mV.

Fig. 2*B*) that we assume to be antidromic because (*i*) it was an all-or-none response that was not associated with an excitatory postsynaptic potential (EPSP) with subthreshold stimuli (n = 6); (*ii*) it was not modified by conditions that exhaust synaptic activity such as 5-Hz stimulation (n = 2, data not shown); and (*iii*) it collided with an orthodromic action potential generated by an intracellular current pulse (Fig. 2*C*) at interspike delay below 7 ms (5.5 ± 0.7 ms, n = 5). In agreement with their

reconstructed axons (Fig. 1*C*), these results show that heterotopic neurons send efferent projections to the subcortical WM. Second, we recorded synaptic response evoked in neocortical supragranular neurons by stimulation of the heterotopia. In 3 of 6 neurons, a response was recorded (Fig. 2*E*) that was similar to that evoked by stimulation of an adjacent, equidistant area of the neocortex ($n = 4$, data not shown). We hypothesized that the absence of response in three supragranular neurons could be caused by the tight control of γ-aminobutyric acid-mediated inhibition over the polysynaptic pathway (16). We then reproduced these experiments in the presence of the γ-aminobutyric acid type A receptor antagonist bicuculline (10 μM) to reveal latent excitatory connections. In the three neurons that did not respond under control conditions (Fig. 2*D*), an all-or-none burst of action potential lasting 551 ± 131 ms could be evoked (Fig. 2*F*). This activity was prevented by increasing the external concentration of Ca^{2+} and Mg^{2+} to 4 mM, conditions that block polysynaptic activity (17). This indicates that supragranular neocortical neurons receive an excitatory input from the heterotopia that we assume to be direct because: (*i*) the entorhinal cortex, which connects the hippocampus with the neocortex through the subiculum *in vivo*, was not in the coronal plan of the slice; and (*ii*) stimulation of the heterotopia did not evoke any response in the subiculum ($n = 2$) even in presence of bicuculline ($n = 4$; data not shown). We conclude that heterotopic neurons are integrated in the neocortical network because they receive functional projections from WM and send functional projections into the WM to the neocortex.

CA1 Heterotopias Are Integrated in the Hippocampal Network. To determine whether CA1 heterotopias also were integrated in the hippocampal network, we first used morphological techniques to examine whether heterotopic neurons, like CA1 neurons, are innervated by the Schaffer collaterals (from CA3 pyramidal neurons) and the temporo-ammonic pathway (from the entorhinal cortex). Morphological observation suggested that CA1 hippocampal afferents avoid the heterotopic core and that only few fibers penetrate in its ventral part (Fig. 3 *A* and *B*). However, the dendrites of heterotopic neurons arborize in the stratum radiatum and lacunosum (Fig. 3*C*), thus providing a morphological substrate for the innervation of heterotopic neurons by hippocampal afferents as described for the temporo-ammonic pathway (18).

To determine the functionality of these connections, we compared the response evoked in CA1 and heterotopias by stimulation to the Schaffer collaterals. As expected, all CA1 neurons responded by a 6-cyano-7-dinitroquinoxaline-2,3-dione/2-amino-5-phosphopentanoate-sensitive monosynaptic response, with a mean latency of 2.6 ± 0.2 ms ($n = 15$). The same stimulation evoked a monosynaptic response in 16 of 24 heterotopic neurons, with a mean latency of 3.2 ± 0.2 ms ($P = 0.07$) (Fig. 3*D*). When recorded at different potential, this response was an EPSC/inhibitory post synaptic current sequence in six cases, a pure EPSC in five cases, and a pure inhibitory post synaptic current in one case. Electrical stimulation of the temporo-ammonic pathway also evoked a monosynaptic response in all CA1 (mean latency of 3.3 ± 0.3 ms, $n = 5$) and heterotopic (mean latency of 2.88 ± 0.31 ms, $n = 5$, $P = 0.42$) neurons. This indicates that stimulation of both Schaffer collaterals and temporo-ammonic pathway evokes a similar response in CA1 and most heterotopic pyramidal neurons.

We hypothesized that heterotopic cells that did not respond in control conditions received a polysynaptic input that could

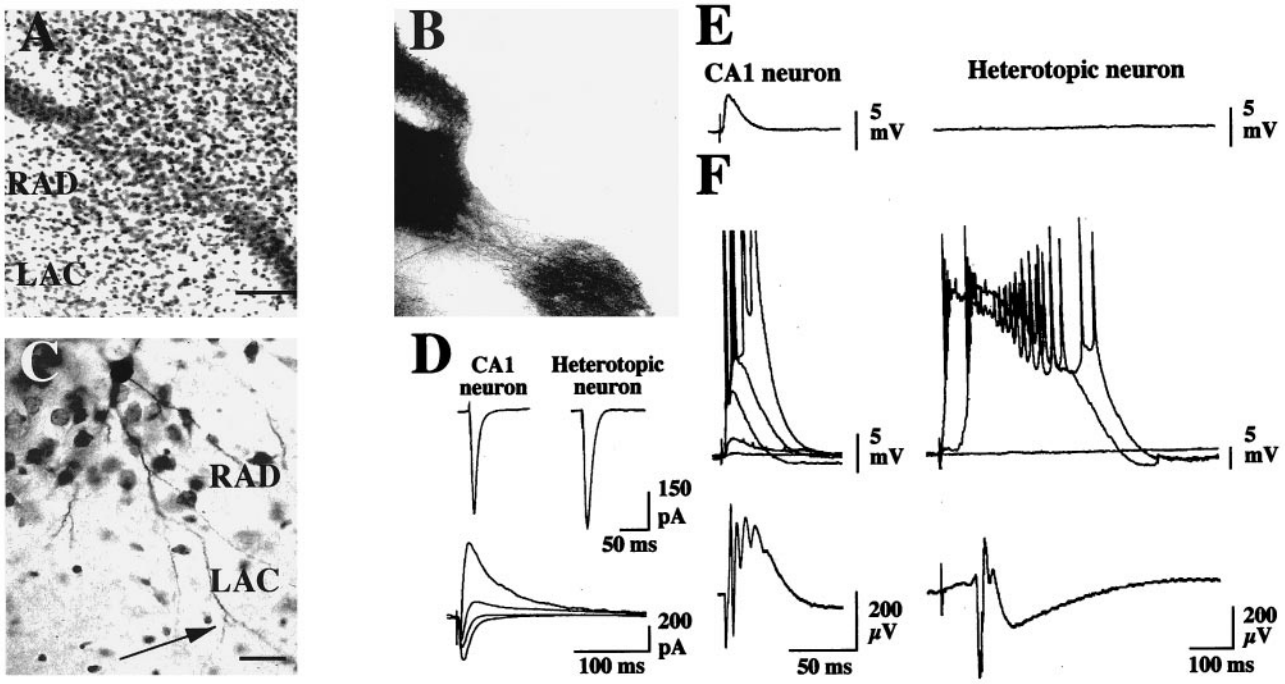

FIG. 3. Neocortical heterotopias receive hippocampal inputs. (*A*) Cytoarchitectonic staining of an heterotopia in a MAM brain in which a crystal of 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate was inserted in CA3. Star indicates the position of the cell depicted in *C*. Afferent fibbers from CA3 to CA1 that are found in RAD avoid the heterotopia (*B*) with only sparse fibbers coursing in the ventral part of the heterotopic core. (Bar = 50 μm.) (*C*) The dendrites of biocytin-filled heterotopic neurons that extend up to the stratum lacunosum are putative targets for CA3 fibbers avoiding the heterotopic core. (Bar = 20 μm.) (*D*) Electrical stimulation of the Schaffer collaterals evoked an EPSC in both CA1 and heterotopic neurons ($V_M = -65$ mV). When recorded at different holding potentials in heterotopic neurons, an EPSC/inhibitory post synaptic current sequence was observed in most cases (lower traces, from the most inward to the outward current, holding potentials were −70 mV, −60 mV, −50 mV, −40 mV). (*E*) Simultaneous whole cell patch clamp recordings of a pair of CA1 and heterotopic cells. Electrical stimulation of the Schaffer collaterals evoked an EPSP only in CA1 cell in control conditions ($V_M = -65$ mV). (*F*) Same cells as in *E*. In the presence of bicuculline (10 μM), the same stimulation evoked a graded burst of action potentials in the CA1 cell and an all-or-none paroxysmal depolarizing shift in the heterotopic cell (upper traces). The corresponding field potentials are shown in the lower part. The shape of the evoked field potential was constant from slice to slice when the extracellular electrode was situated in the continuity of the CA1 pyramidal layer (see Fig. 4*A*).

be revealed in the presence of bicuculline. Indeed, in the presence of 10 μM bicuculline, epileptiform discharges were evoked in all heterotopic and CA1 pyramidal neurons in response to stimulation of both Schaffer collaterals (Fig. 3 *E* and *F*) or temporo-ammonic pathway (data not shown). In CA1 neurons, graded bursts of action potentials were superimposed on an EPSP with a mean duration of 88 ± 5 ms (Fig. 3*F*, $n = 5$). In contrast, in heterotopic neurons, all-or-none paroxysmal depolarizing shifts with a mean duration of 566 ± 91 ms were recorded with superimposed action potentials (Fig. 3*F*, $n = 5$). These responses also could be recorded with extracellular electrodes (Fig. 3*F*), suggesting that they are network-driven synchronous discharge. Therefore, the heterotopias receive functional hippocampal inputs even if all heterotopic cells are not contacted individually by hippocampal afferents.

CA1 Heterotopias Form a Bridge Between the Hippocampus and the Neocortex. If heterotopic neurons receive CA1 hippocampal inputs and project to the neocortex, they may provide a direct link between the hippocampus and neocortex, structures that are not connected directly in naive rats. To examine possible functional disorders that may result from this aberrant connection, we studied whether hippocampal epileptiform activity could propagate to the neocortex via the heterotopia.

An example of such an experiment is illustrated on Fig. 4. In control conditions, stimulation of the dentate gyrus evoked a negative field potential in the CA3 region but not in the heterotopia or neocortex. In the presence of bath-applied bicuculline (10 μM), the same stimulation generated an epileptiform discharge in the CA3 region, which propagated first to the heterotopia and then to the neocortex (Fig. 4*A*). Similar results were obtained in 10 of 15 slices tested. Among these 10 slices, responses in the heterotopia and neocortex were abolished by knife-cutting the Schaffer collaterals in four of four slices (Fig. 4*A*). Therefore, stimulation of the dentate gyrus can evoke epileptiform activity in the neocortex of MAM rats. The following experiments were performed to demonstrate the role of heterotopia in the propagation of paroxysmal activity to the neocortex. When similar experiments were reproduced in slices of MAM rats without heterotopia, i.e., caudal slices, stimulation of the dentate gyrus failed to induce epileptiform activity in the neocortex ($n = 3$). In another set of experiments, bicuculline (100 μM) was applied locally within the heterotopia. In these conditions, Schaffer stimulation triggered paroxysmal activity in the heterotopia that propagated to the neocortex (Fig. 4*B*, $n = 4$ of 5 slices) but neither in CA1 nor in subicular regions ($n = 3$). We thus conclude that heterotopia form a functional bridge between the hippocampus and neocortex.

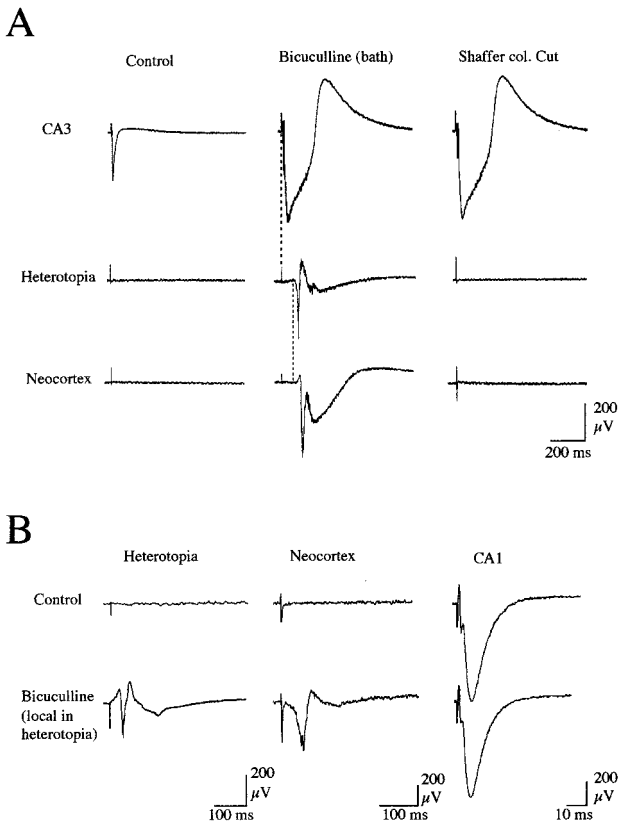

FIG. 4. Heterotopias allow the propagation of hippocampal paroxysmal activity to the neocortex. (*A*) In control conditions, electrical stimulation of the dentate gyrus evoked a negative field EPSP in the CA3 region but not in the heterotopia or in neocortex. When bicuculline was bath-applied, the same stimulation evoked an epileptiform discharge in the CA3 region, followed by an epileptiform discharge in the heterotopia and neocortex. Because it was difficult to determine the onset of the epileptiform discharge in the heterotopia, we can only estimate the delay between the epileptiform discharges recorded in the CA3 region and heterotopia (this delay ranges from 8 to 15 ms, with a mean of 7.8 ± 2 ms, $n = 6$). Except in one case, it was impossible to determine the delay between the epileptiform discharges recorded in the heterotopia and neocortex for the same reason. In this case, the delay was 2 ms. When the CA3 and CA1 regions were disconnected by a knife cut of the Schaffer collaterals, the same stimulation only evoked an epileptiform discharge in the CA3 region, with no synaptic response in the heterotopia and neocortex. (*B*) In control conditions, Schaffer collaterals stimulation evoked a negative field EPSP only in the hippocampal CA1 region adjacent to the heterotopia (upper traces). When bicuculline is ejected locally in the heterotopia, the same stimulation evoked a discharge in the heterotopia and neocortex whereas the field EPSP recorded in the CA1 region was not altered (lower traces). The discharges evoked in the heterotopia and neocortex were considered as network driven events because they were all-or-none and their latency was decreased with increased stimulus intensities.

DISCUSSION

We have shown that neocortical heterotopic neurons situated in the CA1 region of the hippocampus of MAM-treated rats have the same endogenous and connection properties as neocortical neurons while acquiring the same afferent connections as CA1 pyramidal neurons. The conservation of efferent projections by heterotopic neurons has been described in other models. For instance, heterotopically located neocortical layer 5 pyramidal neurons after prenatal MAM, irradiation, or ethanol treatment conserve their projection to the spinal cord (12, 19, 20). In contrast, what is interesting is our demonstration that neocortical heterotopias found in the hippocampus acquire the afferentiation pattern that are typical of their new neighbors while retaining their normal pattern of efferents despite their abnormal location. With this abnormal dual connectivity, MAM-induced hippocampal clusters of neocortical neurons form a short circuit linking the hippocampus with the neocortex. This abnormal pathway clearly seems capable of producing dramatic pathological consequences. One such consequence could be the increased behavioral sensitivity to kainic acid associated with a faster generalization of seizures in MAM-treated rats (21, 22). Because paroxysmal activity induced by kainic acid originates in limbic structures and then secondarily propagates to the neocortex (23), neocortical heterotopias are likely to be one cause of this faster propagation (24).

Of interest, bicuculline-induced epileptiform events were very different in CA1 and heterotopic neurons. Epileptiform discharges in CA1 neurons (Fig. 3*F*) consisted in a graded burst of action potentials similar to what has been described in the CA1 region of control animals (25, 26). In contrast, epilepti-

form discharges in heterotopic neurons was associated with a paroxysmal depolarization with superimposed action potentials. This all-or-none long lasting discharge also is observed in the control neocortex (27) but not in CA1 (28, 29) and is fairly suggestive of a high level of connectivity between heterotopic neurons.

In humans, gray matter heterotopias can be found in the WM of all regions, including the temporal lobe. Heterotopias are crossed by surrounding fibers in their borders (5, 30, 31). These fibers may, as hippocampal afferents do in the present model, provide aberrant connections linking unrelated brain structures. Moreover, abnormalities of the inhibitory nonpyramidal neurons have been reported in neocortical heterotopias (32) that could mimic the local failure of inhibition induced by bicuculline in our experiments. Human gray matter heterotopias thus could contribute to epileptogenesis by forming a disinhibited relay between normally unrelated cortical and subcortical regions.

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