Neuronal Diversity and Temporal Dynamics: The Unity of Hippocampal Circuit Operations

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In the cerebral cortex, diverse types of neurons form intricate circuits and cooperate in time for the processing and storage of information. Recent advances reveal a spatiotemporal division of labor in cortical circuits, as exemplified in the CA1 hippocampal area. In particular, distinct GABAergic (γ-aminobutyric acid–releasing) cell types subdivide the surface of pyramidal cells and act in discrete time windows, either on the same or on different subcellular compartments. They also interact with glutamatergic pyramidal cell inputs in a domain-specific manner and support synaptic temporal dynamics, network oscillations, selection of cell assemblies, and the implementation of brain states. The spatiotemporal specializations in cortical circuits reveal that cellular diversity and temporal dynamics coemerged during evolution, providing a basis for cognitive behavior.

The cerebral cortex of mammals has a large diversity of cells operating in intricate circuits. This cellular diversity endows the cerebral cortex with the capacity to perform complex biological processes such as the subjective representation and interpretation of the world, encoding and retrieval of emotionally colored memories, understanding and empathizing with other individuals, and scientifically investigating the universe (including the mind). We argue here that time is the key metric to all cortical operations. Temporal demands drive selection for computational sophistication and also drive the evolution of neuronal diversity. In turn, cellular diversity serves the temporal organization of cortical functions in the coordination of the activity of different subcellular domains of a single neuron as well as neuronal populations.

The exploration of different cells started in the late 19th century, enduringly represented by Ramon y Cajal's insights into connectivity through Golgi impregnation, which revealed the processes of single neurons (1). To the embarrassment of thousands of neuroscientists trying to explain cortical events through specific circuits today, we still lack the basic knowledge of how many types of neuron exist and how cells are interconnected. The CA1 area of the hippocampus constitutes one of the simplest and most examined cortical areas where recent progress has been made in explaining neuronal diversity and the temporal activity of distinct cells. Here, excitatory pyramidal cells encode representations of spatial (2) and other episodic memories (3) and provide glutamatergic output to other cortical as well as subcortical areas. Although few differences have

been noted in CA1 pyramidal cells, they (Fig. 1, neuron types 22 to 24) represent at least three distinct types (fig. S1) targeting more than 10 extrahippocampal brain areas (4). The variety of areas targeted by each individual cell remains to be established.

The relatively uniform pyramidal cells are supported by a rich diversity of GABAergic interneurons that provide general inhibition and also temporally regulate pyramidal cell activity. Interneurons are recognized on the basis of firing patterns, molecular expression profiles, and their innervations of distinct subcellular domains of pyramidal cells (Fig. 1). The GABAergic interneuron types are not unique to the CA1 area; similar neurons are present in most other areas of the hippocampus and the isocortex (5). Furthermore, these GABAergic interneurons can be found in mouse, rat, cat, monkey, and the human cortex. Why has such a highly structured neuronal machinery evolved and been preserved throughout evolution? Why do GABAergic interneurons, rather than glutamatergic principal cells, show the largest cellular diversity? We explore three answers to these questions and discuss how the dynamic timing of synaptic action between different types of interneuron and pyramidal cells supports distinct brain states and cognitive processing.

The Soma, Axon-Initial Segment, and Distinct Dendritic Domains of Pyramidal Cells Receive GABAergic Innervations Differentiated in Time

A CA1 pyramidal cell receives about 30,000 synaptic inputs and emits several types of dendrite to provide a framework for their integration. The cell body integrates inputs from the dendrites and receives only GABAergic synapses, as does the axon-initial segment, which contributes to action potential generation. The small, oblique dendrites emerging from one or two large

apical dendrites and the basal dendrites receive glutamatergic input mainly from the hippocampal CA3 area, local axon collaterals, and the amygdala. The apical dendritic tuft is innervated mainly by glutamatergic inputs from the entorhinal cortex and the thalamus. All dendrites also receive local GABAergic inputs from interneurons. Such a compartmentalized structure of pyramidal cells allows spatially segregated activities at the same time. Interestingly, different types of parvalbumin (PV)–expressing, GABAergic interneuron also innervate distinct subcellular domains: Axo-axonic cells (Fig. 1, type 1) innervate exclusively the axon-initial segment of pyramidal cells; basket cells (Fig. 1, type 2) innervate the cell bodies and proximal dendrites; bistratified cells (Fig. 1, type 5) innervate the basal and oblique dendrites co-aligned with the CA3 glutamatergic input; and oriens–lacunosum moleculare (O-LM) interneurons (Fig. 1, type 7) target the apical dendritic tuft aligned with the entorhinal cortical input.

Indications that interneurons might contribute differentially to the temporal coordination of pyramidal cells came from in vitro recordings in brain slices of rats. Perisomatic innervating interneurons modulate the probability of sodium spikes, and some dendritic GABAergic innervation interferes with Ca^{2+}-dependent spike generation (6). Furthermore, differences in the short-term plasticity of glutamatergic synapses onto distinct interneurons (7–10) may lead to a temporally distinct and spatially distributed recurrent inhibition in perisomatic or dendritic domains of pyramidal cells (11). In the somatosensory cortex, the firing frequency of perisomatic- and dendrite-targeting interneurons may differentially entrain the output of postsynaptic pyramidal cells (12). The dissection of cellular properties in vitro has provided stimulating possibilities of how distinct types of interneuron might act. It remains a challenge to explain how these concepts relate to the information flow when the neurons are embedded in ongoing network activity.

A temporally distinct contribution of interneurons in the intact rat brain was indicated by diverse firing patterns of putative and unidentified interneurons during network oscillations (13). Network oscillations in the cerebral cortex indicate highly coordinated neuronal activity (14) over large areas. For example, theta oscillations (4 to 10 Hz) highlight the online state of the hippocampus and related structures. Theta waves together with gamma oscillations (30 to 80 Hz) occur during spatial navigation, memory tasks, and rapid-eye-movement sleep. In contrast, sharp wave-associated ripples (100 to 200 Hz) occur during resting, consummatory behavior, and slow-wave sleep, supporting offline replay and consolidation of previous experiences (15, 16). The spike timing of putative interneurons can be referenced to the network events (13). The recording of identified interneurons in anesthetized rats demonstrated that interneurons belonging to distinct classes defined by their axonal target domain

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on the pyramidal cell do indeed fire action potentials at distinct times (Fig. 2).

During ripple oscillations, basket (*17*) and bistratified cells (*18*) strongly increase their firing rate and discharge in a manner phase-coupled to the oscillatory cycles. In contrast, axo-axonic cells fire sometimes before the ripple episode but are silenced during and after it, and O-LM cell firing is suppressed during ripples (*19*). Because these different interneurons innervate distinct domains of pyramidal cells, they imprint a spatiotemporal GABAergic conductance matrix onto the pyramidal cells. This GABAergic fingerprint changes its pattern during different brain states. During theta oscillations, O-LM cells (*19*) become very active and, in cooperation with bistratified cells (*18*), modulate the dendrites of pyramidal cells one-quarter of a theta cycle after PV-expressing basket cells (*20*) discharge; PV-expressing basket cells in turn fire later than axo-axonic cells (*19*). Also, during gamma oscillations, distinct types of interneuron contribute differentially to the temporal modulation of pyramidal cell subcellular domains (Fig. 2) (*21–23*). Firing of basket (*24*) and axo-axonic cells (*23*) is moderately

coupled to the ascending phase of extracellular gamma oscillations in the pyramidal cell layer. In contrast, spike timing of bistratified cells is most tightly correlated to field gamma, whereas O-LM cells do not contribute (*23*) to the synchronization of pyramidal cells to network gamma oscillations in the CA1 area.

In summary, the different classes of interneurons that have been tested fire action potentials, and presumably release GABA, at different time points to distinct subcellular domains of pyramidal cells. Therefore, GABA cannot be provided by the axon of a single type of neuron; instead, independently firing cell classes are required to support the distributed computations of pyramidal cells.

The Same Domain of Pyramidal Cells Receives Differentially Timed GABAergic Input from Distinct Sources

In addition to PV-expressing cells, cholecystokinin (CCK)–expressing GABAergic interneurons also innervate pyramidal cells (Fig. 1) at the soma and proximal dendrites (types 3 and 4), at the apical dendrites (type 9), at dendrites receiving glutamatergic CA3 input (type 8), and

at the apical tuft (type 10). These CCK-expressing cells receive specific inputs from modulatory brainstem nuclei (*25*) and fire different spike trains in vitro (*26*); their asynchronous GABA release causes longer-lasting inhibition in pyramidal cells (*27*); and their inhibitory effect is attenuated by postsynaptic pyramidal cells via cannabinoid receptors (*28*). Electrical stimulation of presynaptic fibers in vitro indicated that CCK-expressing cells may be particularly suited for integrating excitation from multiple afferents (*29*).

In vivo recordings of identified CCK-expressing cells in anesthetized rats (*30*) showed that CCK- and PV-expressing interneurons fire at distinct times (Fig. 2). During theta oscillations, CCK-expressing cells fire at a phase when CA1 pyramidal cells start firing as the rat enters a spatial location, the place field of the cell. During gamma oscillations, CCK-expressing cells fire just before CA1 pyramidal cells (*23*). Because active pyramidal cells can selectively reduce the inhibition from CCK-expressing cells via retrograde cannabinoid receptor activation, the unique spike timing and molecular design of these GABAergic cells are well suited to increase the contrast in
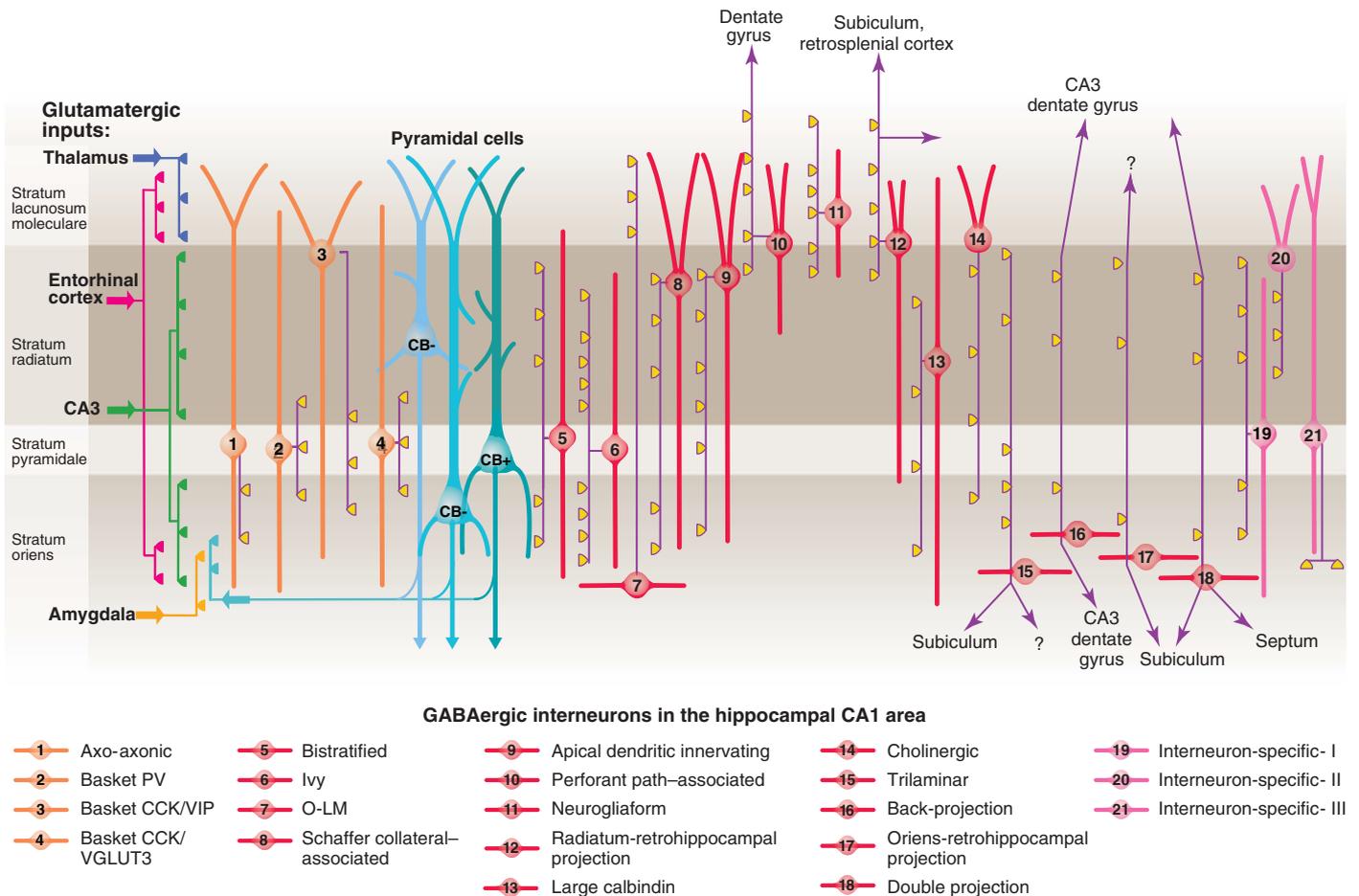
Fig. 1. Three types of pyramidal cell are accompanied by at least 21 classes of interneuron in the hippocampal CA1 area. The main termination of five glutamatergic inputs are indicated on the left. The somata and dendrites of interneurons innervating pyramidal cells (blue) are orange, and those innervating mainly other interneurons are pink. Axons are purple; the main synaptic terminations are yellow. Note the association of the output synapses of different interneuron types with the perisomatic region (left) and either the Schaffer collateral/commissural or the entorhinal pathway termination zones (right), respectively. VIP, vasoactive intestinal polypeptide; VGLUT, vesicular glutamate transporter; O-LM, oriens lacunosum moleculare.

Fig. 2. Spatiotemporal interaction between pyramidal cells and several classes of interneuron during network oscillations, shown as a schematic summary of the main synaptic connections of pyramidal cells (P), PV-expressing basket, axo-axonic, bistratified, O-LM, and three classes of CCK-expressing interneurons. The firing probability histograms show that interneurons innervating different domains of pyramidal cells fire with distinct temporal patterns during theta and ripple oscillations, and their spike timing is coupled to field gamma oscillations to differing degrees. The same somatic and dendritic domains receive differentially timed input from several types of GABAergic interneuron (*18*, *19*, *23*, *30*). ACh, acetylcholine.

the firing of strongly active (disinhibited via CB1 receptors) and weakly active or inactive (still inhibited by CCK interneurons) pyramidal cells, supporting the implementation of sparse coding in cell assemblies. The sum of PV- and CCK-expressing basket cell activity, together with axo-axonic cell firing, is maximal when pyramidal cell firing is minimal during theta oscillations. The different spike timing of CCK- and PV-expressing interneurons is likely to be generated by synaptic inputs from distinct sources, thus demonstrating the cooperation of temporal and spatial organization.

In addition, the dendrites of pyramidal cells are also innervated by GABAergic neurogliaform cells, which provide slow GABA$_A$ receptor–mediated (*31*, *32*) and also GABA$_B$ receptor–mediated inhibition (*33*, *34*). Neurogliaform cells (type 11) innervate the apical dendritic tuft of CA1 pyramidal cells co-aligned with the entorhinal input, whereas a related cell type, the Ivy cell (type 6), innervates more proximal pyramidal cell dendrites aligned with the CA3 input (Fig. 1). The spatially complementary axonal termination of Ivy and neurogliaform cells is mirrored by distinct spike timing in vivo (*35*, *36*). Ivy cells expressing nitric oxide synthase and neuropeptide Y, but neither PV nor CCK, represent the most numerous class of interneuron described so far. They evoke slow GABAergic inhibition in pyramidal cells, and through neuropeptide Y signaling

they are likely to modulate glutamate release from terminals of CA3 pyramidal cells, which, in contrast to perforant path terminals, express a high level of Y2 receptor (*37*). Ivy cells, together with neurogliaform cells, are a major source of nitric oxide, probably released by their extraordinarily dense axons. They modulate pre- and postsynaptic excitability at slower time scales and more diffusely than do other interneurons providing homeostasis to the network.

How the different firing patterns of distinct GABAergic neurons are generated remains largely unknown. For example, since the discovery of axo-axonic cells in 1983 (*38*), only one glutamatergic input from CA1 pyramidal cells has been published (*39*); all other excitatory and inhibitory inputs remain inferential predictions. Potential candidates for governing the activation of interneurons include differential glutamatergic and subcortical innervation (*40*, *41*), selective GABAergic and electrical coupling between interneurons, cell type–specific modulatory regulation (*42*), cell type–specific expression of distinct receptors and channels (*43*–*46*), or differential input from interneurons (Fig. 1, types 19 to 21), which apparently innervate exclusively other interneurons (*47*, *48*). Little is known about the activity of the latter cell types in vivo. Interestingly, the only subcellular pyramidal cell domain that receives GABAergic input from a single source is the axon-initial seg-

ment, which highlights the unique place of axo-axonic cells in the cortex of mammals.

The Coordination of Network States Across Cortical Areas Is Supported by GABAergic Projection Neurons

Many distributed areas of the cerebral cortex participate in each cognitive process. Coordination is supported by shared subcortical pathways and by inter-areal pyramidal cell projections terminating on both pyramidal cells and local GABAergic interneurons. In addition, GABAergic corticocortical connections are also present [e.g., (*49*)], including those in the temporal lobe (*50*). Some neurons (Fig. 1, type 16) project to neighboring hippocampal subfields (*51*) and/or to the medial septum (type 18) (*52*), a key structure regulating network states. Recording and labeling GABAergic neurons in vivo revealed a variety of GABAergic projection neurons (*50*). Hippocamposeptal neurons (type 18) also send thick, myelinated axons to the subiculum and other retrohippocampal areas; other GABAergic cells (types 15 and 17) project only to retrohippocampal areas, parallel with glutamatergic CA1 pyramidal cells. Because these projection cells fire rhythmically during sharp wave-associated ripple and gamma oscillations, they contribute to temporal organization across the septohippocampal-subicular circuit. In addition, other GABAergic projection neurons (Fig. 1, type 12) emit long-

Fig. 3. In vivo spike timing of a GABAergic CA1 neuron projecting to the subiculum (Sub), presubiculum (PrS), retrosplenial cortex (RSG), and indusium griseum (IG). (**A**) The soma, dendrites (red), and axons (yellow) in coronal plains as indicated in (B). CC, corpus callosum. (**B**) Representation in the sagittal plane, showing the rostrocaudal extent of the cell. The soma is located at the border of the stratum radiatum and lacunosum moleculare. The axon, traced over 5 mm, runs toward caudal regions through the subiculum and presubiculum, then bifurcates into further caudal and rostral branches. Shaded areas represent boutons in the reconstructed sections. (**C** to **G**) Soma and dendrites are complete; the axon is shown from selected sections [blocks in (B)]; note few local collaterals within the hippocampus. The axon innervates the molecular layer in the subiculum and the retrosplenial granular cortex. (**H**) Electron micrograph of a neurobiotin-filled bouton making a type II synapse (arrow) with a dendritic shaft in the subiculum. (**I**) In vivo firing patterns show that the cell fires at the descending phase of extracellular theta oscillations (filter, direct current to 220 Hz) recorded from a second electrode in the pyramidal layer. During ripple episodes (right upper, 90 to 140 Hz band pass), there is no increase in firing. Scale bars, 100 μm [(C) to (G)], 0.2 μm (H). Calibrations in (I): theta, 0.2 mV; ripples, 0.05 mV, 0.1 s; spikes, 0.5 mV.

range myelinated axons that arborize in the molecular layers of subiculum, presubiculum, and retrosplenial cortex (50). Their rhythmic firing during theta oscillations indicates a contribution to the temporal organization of this brain state across the targeted areas (Fig. 3).

In summary, information between cortical areas is transmitted via axonal projections of glutamatergic pyramidal cells, but they alone may not produce the required high degree of temporal precision between brain regions. Together with common subcortical state-modulating inputs, the cortical long-range GABAergic projections could prime and reset activity in specific neurons of the target areas before the information arrives via glutamatergic fibers from pyramidal cells. The neuronal diversity of GABAergic projection neurons differing in target area and temporal activity increases computational powers between related cortical areas.

Dynamic Cooperation of Pyramidal Cells and Specific GABAergic Interneurons in Cell Assemblies

The diversity of subcellular domain-specific GABAergic interneurons, combinatorial input to the very same subcellular domain, and differentiated projections to long-range target areas provide a basis for dynamic, rather than clock-like, regulation of pyramidal cell networks. Without this cooperative temporal framework, the glutamatergic connections would lose meaning. Indeed, the stimulation of a single putative interneuron in the barrel cortex can affect behavioral responses (53), and hippocampal interneurons actively participate in recognition memory (54). Although many interneurons fire at high rates during theta oscillations, some cells also show increased firing when the animal is in a particular location (55, 56), a hallmark of pyramidal place cells (2). Like pyramidal cells, some interneurons also fire at progressively earlier phases of the theta cycles when the rat passes through fields of increased firing (57–59). Together with the observation that CCK-expressing and axo-axonic cells fire only during and before some of the ripple episodes (19, 30), this indicates that some GABAergic interneurons contribute to the dynamic selection and control of cell assemblies. Such an interneuron contribution is not reflected in linear flowcharts of synfire chains, in which interneurons simply inhibit pyramidal cells that are not part of that assembly or delay the firing of pyramidal cells, which fire later in the chain.

As GABAergic interneurons innervate thousands of nearby pyramidal cells, a hard-wiring that includes GABAergic connections is unlikely, given the large number of representations involving the same pyramidal cell (60). The effect of domain-specific GABAergic inputs is more likely dependent on the state of the receiving pyramidal cells or the domains on a single pyramidal cell. For example, axo-axonic cells might depolarize the axon-initial segment depending on the membrane potential, momentary internal chloride concentra-

tion, and recent history of ion channels in the postsynaptic membrane (61), whereas cross-correlation of firing patterns in vivo (Fig. 2) suggests that axo-axonic cells, on average, inhibit CA1 pyramidal cells. The GABAergic input to a dendrite might shunt other inputs, de-inactivate voltage-gated cation channels through hyperpolarization, reset the phase of intrinsic dendritic oscillations, or gate the incoming excitation in a winner-take-all manner, according to the recent history of that dendrite. Such state-dependent effects, together with the powerful combinatorial GABAergic inputs from independently regulated cell classes, enable the nonlinear emergence of cell assemblies.

Conclusion

Recording the spike timing of identified neurons has revealed that the large diversity of cortical neurons is accompanied by an equally sophisticated temporal differentiation of their activity. Indeed, the existence of one can only be explained and understood by the other. The in vivo firing patterns also indicate that a classification of GABAergic interneurons based on axonal target specificity and molecular expression profile correctly groups cells according to their temporal contribution to network activity. It remains to be seen whether the differential expression of calbindin by CA1 pyramidal cells is also accompanied by different temporal (62) and axonal target specialization and by a distinct contribution to cognitive operations. Defining all neuronal populations, their molecular expression profile (63), synaptic connections, and temporal activity, together with changing the activity of selected cell types or connections (64), will explain cortical circuits and how defects in timing cause cortical pathologies (65–68).

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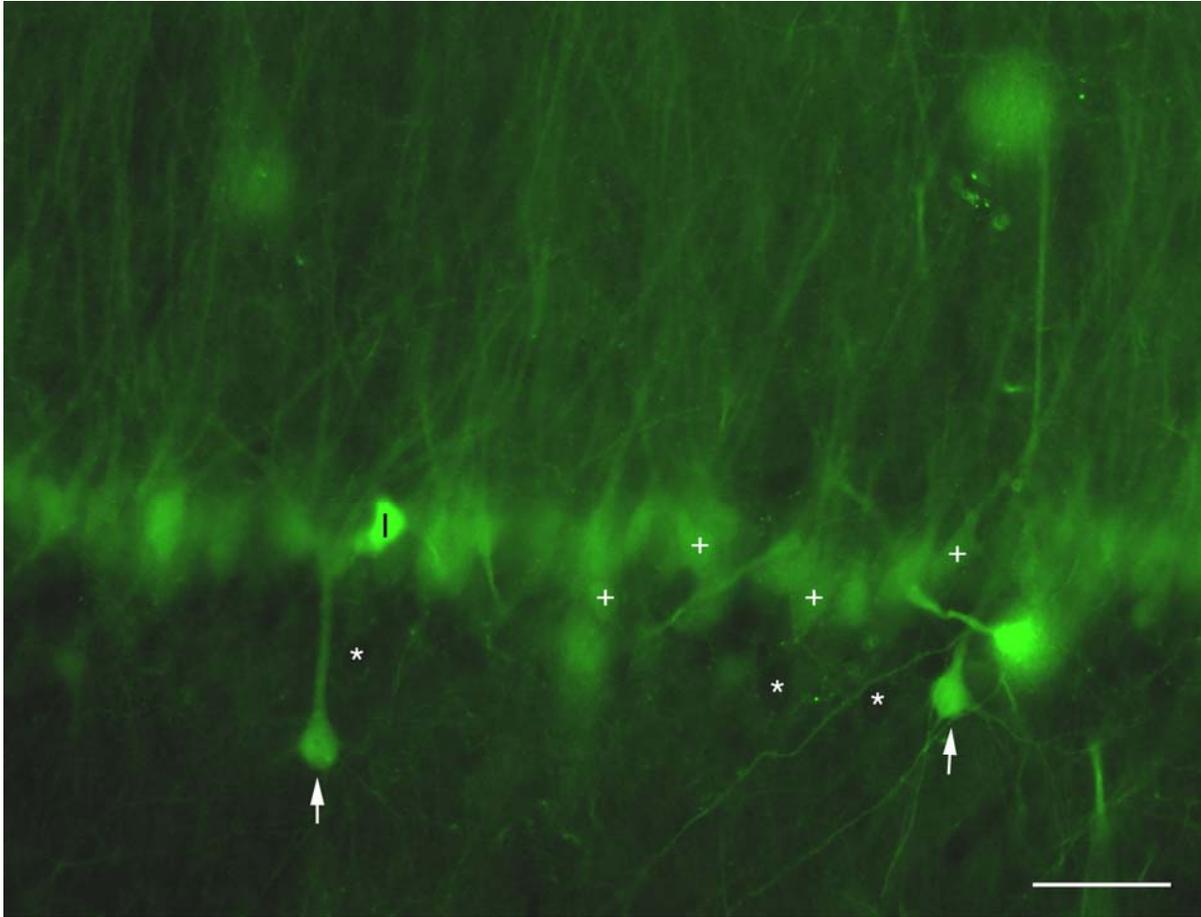
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Fig. S1.

Immunolabeling for calbindin reveals at least 2 types of pyramidal cell (*1*). Tightly packed cells close to str. radiatum are calbindin-immunopositive (crosses), whereas deeper cells closer to str. oriens are immunonegative (asterisks). There are also occasional large strongly immunopositive cells, mostly, but not exclusively in deep str. pyramidale (arrows), the connections of which are unknown. In addition, there are interneurons (I) strongly-immunopositive for calbindin. A third type of pyramidal cell (not shown) present in str. radiatum (*2-4*) as well as in str. pyramidale is immunonegative for calbindin and projects to the accessory olfactory bulb (*5*). Scale bar: 50 µm.

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