Supporting Information

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Fig. S1. Criteria for differentiating between synaptic responses evoked by mossy fibers and CA3 recurrent fibers. (*A*) Schematic of recording configuration. (*Insets*) Representative current traces evoked by paired-pulse stimulation with a 50-ms interval. (*B*) Pooled data. Mossy fiber stimulation always resulted in paired-pulse facilitation (1.96 ± 0.3 ; P < 0.001), whereas CA3 recurrent fiber stimulation induced either paired-pulse facilitation or depression (1.2 ± 0.2 ; P = 0.15) (1). In addition, the latency of evoked responses is longer when stimulating mossy fibers ($6.8 \pm 0.3 \text{ ms}$; P < 0.001) (2) versus CA3 recurrent fibers ($2.3 \pm 0.4 \text{ ms}$; P < 0.001) (3). (C) DCG-IV (2μ M), an mGlu2 agonist that blocks glutamate release from mossy fiber but not CA3 pyramidal cell terminals (4), reduced mossy fiber responses by 88.2 $\pm 2.1\%$ (P < 0.001) and CA3 responses by 14.6 $\pm 5\%$ (P > 0.74). (D) Pooled data for DCG-IV experiments.

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Fig. S2. Characterization of excitatory postsynaptic potential (EPSP)-dependent long-term potentiation (LTP). (*A*) Data from a representative cell with a resting potential of -65 mV showing the time course of potentiation both during and after the pairing protocol in an experiment in which the entire recording was performed in current-clamp mode. (*B*) Traces from time points indicated in *A*. (C and *D*) Action potentials were never observed during the pairing protocol. (*E*) Mossy fiber EPSP-dependent LTP is maintained with intact GABA_A receptor-mediated inhibition. In the absence of GABA_A-receptor antagonists, EPSPs recorded during the pairing protocol are followed by IPSPs. (*F*) Pooled data for LTP with GABA_A receptor-mediated inhibition intact (35.8 \pm 9.8%; n = 6; P < 0.001).



Fig. 53. (*A*) Experimental configuration to examine whether LTP is input-specific. (*B*) Pathway independence was determined for two extracellularly stimulated CA3 inputs by selecting one pathway that was facilitating $(1.9 \pm 0.4; n = 4; P < 0.001)$ and one pathway that was depressing $(0.8 \pm 0.03; n = 4; P < 0.01)$. After determining the paired-pulse ratio for pathways 1 and 2, the absence of paired-pulse modulation in the cross-pathway configuration establishes independence of the two pathways $(1.1 \pm 0.09; n = 4)$ (1). (C) The subtreshold pairing protocol applied at time 0 induced LTP in the paired (black) pathway (54.2 \pm 9.8%; n = 4; P < 0.001), but not in the unpaired (green) pathway $(-14.7\% \pm 8.5\%; n = 4; P < 0.03)$. To rule out dysfunction in the unpotentiated pathway, a standard spike-timing-dependent plasticity protocol applied at time 40 min showed that the unpotentiated input underwent LTP (58 \pm 6.2%; n = 4; P < 0.001), whereas the previously potentiated pathway was not further potentiated $(-3.6 \pm 7.7\%; n = 4; P = 0.5)$. (*D*) Representative traces from the experiment shown in C.

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Fig. 54. (A–C) Examples of data from three cells. The left column depicts all 60 traces during pairing, demonstrating that action potentials are not elicited during the LTP protocol. The middle and right columns show that scaling responses to the amplitude of the evoked CA3 recurrent EPSP segregates the summed events into linear and supralinear responses.



Fig. S5. Induction of a supralinear response depends on the activation of NMDA receptors. (A) Raw data recorded from a CA3 pyramidal cell showing supralinear responses in several trials. (B and C) Supralinear responses are suppressed when NMDA receptors are blocked with AP-5 (B) or MK-801 (C). (D) Pooled data for experiments with NMDA receptor antagonists.



Fig. 56. (A) Activation of a single CA3 recurrent axon by recording from two synaptically connected CA3 pyramidal cells. (B) Repetitive pairing (60 times at 0.1 Hz) of the CA3 recurrent response evoked by stimulating a single axon, followed after 10 ms by a mossy fiber-evoked subthreshold response, did not result in synaptic potentiation (n = 4).



Fig. 57. Characterization of supralinear responses. (*A*) The supralinear summation of synaptic responses does not require calcium spikes. A dendritic recording from the cell shown in Fig. 3*B* reveals that a much stronger stimulation than that needed to induce an NMDA spike is required to evoke a calcium plateau response. (*B*) In the presence of intracellular QX-314 (500 μ M), which blocks sodium channels (1) and reduces calcium currents (2), a calcium plateau no longer can be evoked, but the supralinear NMDA response is maintained. (*C*) Summary data illustrating the mean amplitude of supralinear events recorded in the apical dendrite under various timing and pharmacologic conditions.

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Fig. S8. Comparison of evoked responses recorded in the soma and a first-order apical dendritic branch. (*A*) Configuration of recording and stimulating electrodes. (*B*) Passive membrane properties of the somatic and dendritic compartments. (*C*) Individual traces recorded in the soma and dendrite of the cell from Fig. 3*D* showing distant-dependent attenuation of supralinear responses in the soma. (*Inset*) image of a CA3 pyramidal cell during simultaneous recording from the first-order apical dendritic branch (right electrode) and soma (left electrode). (Scale bar: 20 µm.)

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