determines the number of sodium spikes fired per event by individual cells (Maruta et al., 2007; Mathy et al., 2009) and may thereby mediate the direction and speed of learning in Purkinje cells (Mathy et al., 2009; Rasmussen et al., 2013). The phase of subthreshold oscillations in the inferior olive could be a determining factor for guiding climbing fiber-induced plasticity (Mathy et al., 2009; De Gruijl et al., 2012), indicating a possible role for a GABAergic reset of olivary oscillations in both motor timing and learning. In addition, inferior olive ensemble oscillation synchrony may determine the speed and direction of cerebellar learning (Bazzigaluppi et al., 2012; De Gruijl et al., 2012), which would emphasize the importance of correct segregation of inferior olive ensembles by GABAergic input from the cerebellum. As a result, cerebellar motor execution and motor learning hypotheses are now increasingly finding common ground. Spatiotemporal firing patterns of the olivocerebellum affect both motor execution and plasticity, and plasticity effects take place throughout the olivocerebellar system, apparently even down to the level of electrical synapses of the inferior olive (Lefler et al., 2014; Mathy et al., 2014; Turecek et al., 2014). We may not know the exact inner workings of the olivocerebellar system yet, let alone that of other loci in the CNS with chemical-electrical interacting synapses, but work done in the labs of Yarom, Häusser, and Welsh shows that we move toward that goal with leaps and bounds.

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# Active Dendrites under Parental Supervision

**Thomas G. Oertner**[1,*]
[1]Institute for Synaptic Physiology, Center for Molecular Neurobiology Hamburg, Falkenried 94, 20251 Hamburg, Germany
*Correspondence: thomas.oertner@zmnh.uni-hamburg.de
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**Pyramidal cell dendrites are able to produce a variety of active calcium signals in brain slices. In this issue of *Neuron*, Grienberger et al. (2014) investigate dendritic function in the hippocampus of live mice.**

Fluorescent $Ca^{2+}$ indicators have forever changed our view of how neurons work. Rather than passively propagating synaptic currents to the soma, a rich repertoire of active events has been discovered in pyramidal cell dendrites, including $Na^+$ spikes, $Ca^{2+}$ spikes, NMDA spikes, and wave-like $Ca^{2+}$ release events from intracellular $Ca^{2+}$ stores (Schiller et al., 2000; Nakamura et al., 1999). In the past, most calcium imaging studies have been conducted in brain slices, and some forms of dendritic calcium signaling can be observed only under quite specific stimulation conditions. Clearly, the spatial distribution of excitatory inputs, the degree and timing of inhibition, and the presence or absence of modulatory inputs all affect the frequency and extent of dendritic calcium signals.

In this issue of *Neuron*, Grienberger et al. (2014) investigate dendritic $Ca^{2+}$ signals in hippocampal pyramidal cells of live mice. As even two-photon microscopy cannot penetrate brain tissue deeper than about 1 mm, the authors removed a small portion of neocortex to gain optical access to the hippocampus. Individual pyramidal cells in CA1 were loaded with the high-affinity calcium dye OGB1 through a patch pipette. Two types of calcium signals occurred spontaneously in anesthetized mice, reflecting ongoing physiological activity: very small and localized calcium "blips" were associated with small somatic

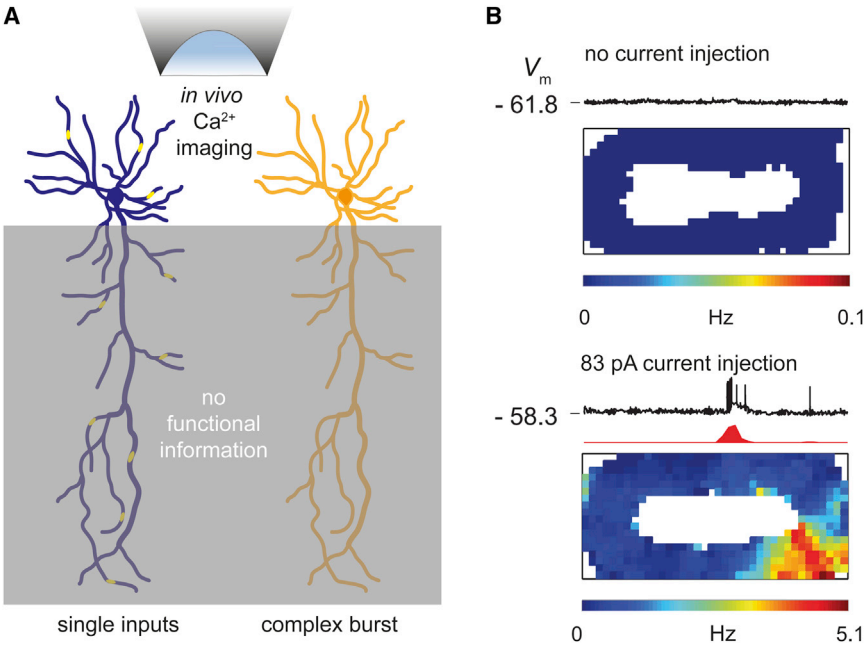


**Figure 1. Voltage-Dependent Input Amplification in CA1 Pyramidal Cells**
(A) Two types of dendritic $Ca^{2+}$ signals were observed by Grienberger et al. (2014), with multidendrite $Ca^{2+}$ spikes (right) occurring only at membrane potentials above −60 mV.
(B) Action potential rate map from a rat running counterclockwise on an oval track. CA1 pyramidal cell showing no place-dependent firing (top: whole-cell recording during single lap and color-coded rate map) develops clear place preference and complex burst firing upon injection of a small depolarizing current (bottom). Note membrane potential of −61.8 mV and −58.3 mV, respectively. Reproduced from Lee et al. (2012).

depolarizations and probably reflect the activity of individual excitatory synapses. The other type of event was very large, flooding all basal dendrites simultaneously with $Ca^{2+}$ (Figure 1A). These generalized calcium events were associated with complex spike bursts, a type of high-frequency discharge that is known to occur in CA1 pyramidal cells during behavior (Harris et al., 2001). Grienberger et al. (2014) used specific intracellular blockers to show that activation of postsynaptic NMDA receptors and voltage-dependent $Ca^{2+}$ channels is essential for the generation of complex spike bursts and pandendritic calcium spikes. Interestingly, the function of this dendritic amplifier was highly dependent on the cell's membrane potential: at potentials below −60 mV, no complex spike bursts were generated. In CA1 neurons that did not produce complex spike bursts spontaneously, a small constant current injection was sufficient to activate dendritic amplification and burst firing.

What is the physiological function of active dendritic amplification in the hippocampus? CA1 is famous for its "place cells," neurons that fire brief bursts of action potentials when the animal is crossing a specific position in its cage (O'Keefe and Dostrovsky, 1971). This position-sensitive firing, however, is seen only in a subset of CA1 pyramidal cells. Recently, it has been shown that a small sustained current injection can convert any CA1 cell into a place cell with its characteristic spatial tuning (Lee et al., 2012) (Figure 1B). Curiously, not even subthreshold depolarizations could be detected in the "quiescent" place cells in the absence of current injection. This was puzzling, as the observed spatial specificity must arise from appropriately tuned synaptic inputs that should leave a trace in the form of subthreshold excitatory postsynaptic potentials. Considering the new data from Grienberger et al. (2014), it seems that in the absence of dendritic amplification, spatially tuned synaptic inputs on distal dendrites completely lose their oomph on the way to the soma, preventing efficient summation and action potential generation. The cellular mechanisms investigated by Grienberger et al. (2014) might thus be responsible for the emergence of place cells in CA1.

Bursts of action potentials, as opposed to single spikes, are thought to signal events of special importance to the animal. NMDA receptors, as they integrate glutamate at individual synapses over 50–100 ms, can be thought of as specialized "burst sensors" in the synapse. In addition, their activation leads to prolonged depolarization of the postsynaptic neuron, which is essential for burst firing. Thus, NMDA receptors are poised to propagate bursts through the cortical network (Polsky et al., 2009). This role was postulated based on slice experiments and has now been nicely confirmed by patch-clamp recording in vivo (Grienberger et al., 2014).

In addition to acting as a voltage-dependent amplifier, the NMDA receptor is also distinguished by its very high permeability for $Ca^{2+}$. The massive dendritic $Ca^{2+}$ transients generated during complex burst firing could act as positive feedback signals, strengthening and stabilizing the synapses that causally contributed to burst initiation. Indeed, complex spike bursts enable the induction of LTP during 5 Hz stimulation, a frequency that is prominent in the hippocampus during active behavior and REM sleep (Thomas et al., 1998). In this context, it is interesting to note that in CA1 pyramidal cells, spike-timing-dependent plasticity protocols also require three postsynaptic spikes for reliable potentiation (Holbro et al., 2010; Frey et al., 2009). Pairing of synaptic input with a single spike has little effect on synaptic strength in these cells. Thus, it is possible that the generalized calcium transients observed by Grienberger et al. (2014) reflect the adjustment of synaptic weights on a cell-wide scale. While NMDA spikes alone are apparently not sufficient to induce LTP (Gordon et al., 2006), complex spike busts might, and it will be important to investigate the timing rules of such burst-timing-dependent plasticity.

A very interesting aspect of the new study is what was not observed: Grienberger et al. (2014) do not report any

regenerative $Ca^{2+}$ signals restricted to individual branches. The discovery of such local NMDA spikes in neocortical pyramidal cells generated a lot of interest as they could reflect specific dendritic computations performed by clusters of coactive synapses (Major et al., 2008). A recent in vivo imaging study on layer 2/3 pyramidal neurons provided clear evidence that local NMDA spikes occur in the apical tuft of these smaller neurons, most frequently after sensory stimulation (Palmer et al., 2014). In layer 2/3 neurons, local NMDA spikes strongly increase the probability of action potential generation after sensory input but are not associated with complex spike bursts. In CA1 pyramidal neurons, in contrast, even intense and focal stimulation triggers an NMDA spike only in the wake of a dendritic $Na^{+}$ spike (Ariav et al., 2003). In the intact hippocampus, coactive inputs might be widely distributed across the dendritic tree. Thus, both cellular properties of CA1 pyramidal cells and the sparse, distributed connectivity of the hippocampus could explain why local NMDA spikes were not observed in the basal dendrites. In addition, potential local NMDA spikes could be immediately masked by the generation of a global $Ca^{2+}$ spike. Indeed, Grienberger et al. (2014) report a strong dependence of global $Ca^{2+}$ events on voltage-gated $Ca^{2+}$ channels, while these channels contribute little to NMDA spikes in neocortical pyramidal cells (Major et al., 2008). It is also possible that NMDA spikes are generated in oblique or distal apical dendrites of CA1 cells, regions that are still out of reach for functional imaging in vivo (Figure 1A). Or they might occur during specific behavioral states, but not under anesthesia. The question of local dendritic amplification will certainly remain a subject of intense and technology-driven research. For example, NMDA trigger zones of $Ca^{2+}$ spikes might have been obscured due to saturation of OGB-1, and the latest generation of genetically encoded $Ca^{2+}$ indicators could help reveal differences between individual dendritic branches during complex spike bursts.

In summary, NMDA receptors act as gated coincidence detectors: dendritic amplification and telltale $Ca^{2+}$ transients can be switched "on" or "off" by small changes in membrane potential, which in turn is set by the integration of all excitatory and inhibitory inputs. In CA1, integrated synaptic activity seems to select a subset of pyramidal cells to function as place cells (Lee et al., 2012), which could explain why the stability of place fields is strongly dependent on task requirements and attention (Kentros et al., 2004). As a parent keeping control of their rowdy flock, CA1 pyramidal cells keep dendritic amplification under strict somatic voltage control (Grienberger et al., 2014). Neocortical pyramidal cells, on the other hand, seem to support a much more diverse repertoire of local and global signaling modes (Major et al., 2008). While it is reassuring that most phenomena that were originally discovered in slice preparations can now be observed in the intact animal, one has to keep in mind: not all pyramidal cells are created equal.

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