# Electrical Compartmentalization in Dendritic Spines

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## Keywords

NMDA, computation, cortex, imaging, uncaging, network, emergent

## Abstract

Most excitatory inputs in the CNS contact dendritic spines, avoiding dendritic shafts, so spines must play a key role for neurons. Recent data suggest that, in addition to enhancing connectivity and isolating synaptic biochemistry, spines can behave as electrical compartments independent from their parent dendrites. It is becoming clear that, although spines experience voltages similar to those of dendrites during action potentials (APs), spines must sustain higher depolarizations than do dendritic shafts during excitatory postsynaptic potentials (EPSPs). Synaptic potentials are likely amplified at the spine head and then reduced as they invade the dendrite through the spine neck. These electrical changes, probably due to a combination of passive and active mechanisms, may prevent the saturation of dendrites by the joint activation of many inputs, influence dendritic integration, and contribute to rapid synaptic plasticity. The electrical properties of spines could enable neural circuits to harness a high connectivity, implementing a "synaptic democracy," where each input can be individually integrated, tallied, and modified in order to generate emergent functional states.

## Contents



## INTRODUCTION

Many neurons throughout different brain regions are covered with dendritic spines (Ramón y Cajal 1888), small dendritic appendages composed of a spine head (~<1 μm in diameter), which typically accommodates an excitatory synapse, and a thin spine neck (<0.1 μm thick and ~1 μm long) that connects the spine to the dendritic shaft (Gray 1959). Interestingly, most excitatory contacts choose to terminate on spines rather than on their adjacent dendritic shafts (Arellano et al. 2007, Harris & Kater 1994); spines must therefore play an important role in neuronal function because otherwise these inputs could directly contact the dendrites. Speculation about this special role that spines must play has centered on the potential functions of spines in enhancement of structural connectivity or in biochemical compartmentalization (Koch 1999, Peters & Kaiserman-Abramof 1969, Shepherd 1996, Swindale 1981, Yuste 2010). Indeed, spines are very small and extremely numerous and can be arranged in helicoidal patterns (O'Brien & Unwin 2006), as if they were systematically sampling the neighboring axons and helping the circuit become more distributed (Yuste 2011). Also, spines compartmentalize calcium and provide the biochemical isolation necessary for input-specific synaptic plasticity (Koch 1999, Yuste et al. 2000, Yuste & Denk 1995). Nevertheless, input-specific biochemical isolation can occur without spines (Goldberg et al. 2003, Soler-Llavina & Sabatini 2006), so spines are not strictly necessary to implement local biochemical domains, raising the issue that they could carry out a more specific function in the neuron.

As an alternative function, spines could be electrical compartments; i.e., their special morphology could enable synaptic inputs to generate and experience different membrane potential dynamics than if they were situated on the dendritic shaft. This idea was first proposed by Ramón y Cajal (1904), who suggested that spines could store electric energy, and has been endorsed by many investigators since then (Chang 1952, Jack et al. 1975, Llinás & Hillman 1969, Rall 1974, Rall & Rinzel 1971, Rall & Segev 1988, Segev & Rall 1988, Shepherd et al. 1985). According to this view, the main function of spines is electrical rather than structural or biochemical. This article reviews this hypothesis by first focusing on the computational models of the electrical properties of spines, then by reviewing recent data consistent with the idea that spines can indeed behave as electrical compartments, and finally by discussing potential biophysical mechanisms responsible for this process. I conclude by commenting on functional consequences of the electrical properties of spines, highlighting the role that spines could play in building widely distributed and plastic circuits as biological analogs of neural networks, computational systems where the functional states are represented by the emergent dynamics of activity of many or all the neurons.

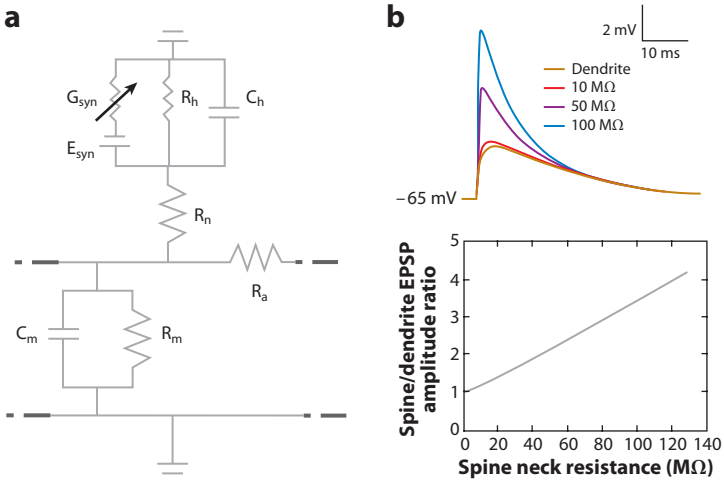


**Figure 1**

Passive electrical model of a dendritic spine. (*a*) Electrical circuit diagram of a passive spine with a synapse of conductance, $G_{syn}$, and reversal potential, $E_{syn}$. Cable parameters of the spine are represented by its input resistance ($R_h$), spine head capacitance ($C_h$), and neck resistance ($R_n$); adjacent dendrite is diagrammed by its axial resistance ($R_a$), membrane capacitance ($C_m$), and membrane resistance ($R_m$). (*b*) Numerical simulations demonstrate amplification of the excitatory postsynaptic potential (EPSP) at the spine head and subsequent reduction of EPSPs by spines, due to this cable structure. Note how increasing spine neck resistance results in larger EPSPs at the spine (*top*); the peak EPSP spine/dendrite voltage ratio is proportional to neck resistance (*bottom*). Adapted from Tsay & Yuste (2004).



## ELECTRICAL MODELS OF SPINES

Due of the dearth of experimental data from living spines, until very recently the discussion of the electrical properties of spines was based solely on theoretical models using either analytical calculations or numerical simulations. This ample literature, extending over many decades, unfortunately has not always been in agreement, probably because even simple cable models need to assume values for experimental variables that are not yet measured. For example, we still do not know the values of the parameters that determine the electrical behavior of spines, or even dendrites, such as their input resistance ($R_{sp}$ or $R_h$), membrane resistance ($R_m$), membrane capacitance ($C_m$, $C_{sp}$, or $C_h$), cytoplasmic or axial resistance ($R_a$), neck resistance ($R_{neck}$), spine synaptic conductance $G_{syn}$, or spine-reversal potential $E_{syn}$ (**Figure 1**). Even the spine membrane's basic structure, lipid composition, and precise complement of conductances still remain relatively unknown. For this reason, computational models of spines have been ahead of the experimental measurements and should be interpreted as the exploration of a spectrum of potential scenarios, rather than as the ground truth. The next paragraphs briefly summarize the highlights of some of these models, which are discussed in more detail elsewhere (Shepherd 1996, Tsay & Yuste 2004, Yuste 2010).

### Passive Models of Spines

Theoretical models of spines can be grouped into passive or active, depending on whether they incorporate voltage-dependent conductances. Passive models have used cable theory to explore the electrical consequences of the peculiar morphologies of spines, highlighting the electrical asymmetry created by a small spine connected to a large dendrite (Jack et al. 1975; Koch & Poggio 1983a,b; Llinás &

EPSP: excitatory postsynaptic potential

Hillman 1969; Rall 1970, 1978; Rall & Rinzel 1971) (**Figure 1**). The spine behaves as a sealed cable end with high input resistance ($R_{sp}$) and very small local capacitance ($C_{sp}$). Thus dendritic voltage pulses invade the spine without significant attenuation, whereas excitatory postsynaptic potentials (EPSPs) then attenuate as they propagate from the spine toward the dendrite. At the same time, the high spine input resistance can locally enhance the voltage of the EPSPs, when compared with EPSPs injected into the dendritic shaft. Finally, significant decreases in the driving force of the EPSP may occur, owing to the large effect that even small conductances can have on the ionic composition of the small volume of the spine. This driving force decrease could potentially even lead to the collapse of $Na^+$ gradients across the spine membrane.

In addition to an EPSP attenuation based on this cable impedance mismatch, the spine neck could also have a high electrical resistance ($R_{neck}$), which would further reduce the amplitude of synaptic inputs at the dendrite (Chang 1952, Jack et al. 1975, Llinás & Hillman 1969, Rall 1974, Rall & Rinzel 1971). Moreover, because the resistance of the spine neck should be proportional to its length, by altering their neck length, spines could potentially modulate the magnitude of this attenuation, thus controlling synaptic strength (Crick 1982, Rall 1978). It is still unknown what is the exact value of the spine neck resistance ($R_n$) or of its inverse, the neck conductance ($G_n$), whose ratio to the synaptic conductance determines the amount of electrical filtering. Initial estimates from passive models based on ultrastructural reconstructions and diffusional coupling suggested that $G_n$ ranges from 7 to 138 nanosiemens (nS) (Harris & Stevens 1988, Svoboda et al. 1996). These values are much higher than those reported for synaptic conductances (0.05–0.1 nS; see Bekkers et al. 1990), although synaptic conductances in spines may be underestimated because they rely on somatic voltage clamp measurements (Williams & Mitchell 2008). This large difference between spine and synaptic conductances has been used to predict a relatively modest filtering of EPSP by spines and to argue that spines are not electrical compartments, but solely chemical ones (Koch & Zador 1993, Svoboda et al. 1996, Wickens 1988). At the same time, as we argue below, spine neck resistance could be significant enough to partly isolate spine voltages from dendritic ones. A final prediction from passive cable models is that spines, by their sheer numbers, may add a significant amount of membrane to the dendrite (Wilson 1986). This could lower the input impedance of the neuron and increase its overall capacitance, altering the temporal dynamics of input integration (Jaslove 1992).

## INHIBITION IN SPINES

In addition to excitatory synapses, spines occasionally have symmetric (inhibitory) ones (Arellano et al. 2007, Jones & Powell 1969), which can originate from specific interneuron subtypes (DeFelipe et al. 1989). What is the function of this spine-specific inhibition? This inhibition probably curtails excitatory inputs, perhaps implementing logical gates (Shepherd & Brayton 1987). Moreover, extrasynaptic GABA receptors could be present on spines, even without an inhibitory synapse. In fact, a specific $GABA_A$ receptor ($\alpha4\beta\delta$) is present on many dendritic spines of mouse CA1 hippocampal pyramidal cells. These receptors are sensitive to low levels of ambient GABA (<1 μM) and could shunt the current necessary to activate NMDA receptors (Shen et al. 2010).

### Active Models of Spines

Passive cable models are only a first approximation to the physiological situation of the neuron because dendrites are active structures, endowed with voltage-dependent conductances (Llinás & Nicholson 1971, Stuart et al. 1999, Stuart & Sakmann 1994, Yuste & Tank 1996), and these conductances can override the effect of cable properties. For example, active conductances could allow spines to electrically isolate synaptic inputs (Diamond et al. 1970) and become electrogenic, particularly if the spine input resistance is high (Jack et al. 1975). If spines had sodium channels, they could act

as synaptic amplifiers (Coss & Perkel 1985, Perkel 1982, Perkel & Perkel 1985), generating dendritic action potentials (APs), which could spread to neighboring spines (**Figure 2**) perhaps in a saltatory fashion (Baer & Rinzel 1991; Miller et al. 1985; Rall & Segev 1987, 1988; Segev & Rall 1988; Shepherd et al. 1985; Tsay & Yuste 2002). Moreover, electrogenic spines could also implement logical operations: for example, AND gates, when two EPSPs occur simultaneously on two active spines; OR gates, when a single active spine can saturate the dendrite; and AND-NOT gates, when an EPSP and an inhibitory postsynaptic potential (IPSP) coincide at a different dendritic position (Koch et al. 1983, Shepherd & Brayton 1987).

## EVIDENCE OF ELECTRICAL COMPARTMENTALIZATION BY SPINES

Traditionally, the study of spines was purely anatomical, using fixed samples, because their small size makes them, even to this date, inaccessible to electrical recordings. However, the introduction of novel optical imaging techniques enabled for the first time functional measurements from living spines in vitro and in vivo. In particular, two-photon microscopy has allowed the imaging of calcium dynamics from spines under synaptic or AP stimulation, demonstrating that spines are invaded by backpropagating APs, are endowed with voltage-sensitive calcium channels (Yuste & Denk 1995) and, therefore, have active conductances (**Figure 3**).

Similar experiments revealed that spine *N*-methyl-D-aspartate receptors (NMDARs) flux significant amounts of calcium under minimal quantal synaptic stimulation (Koester & Sakmann 1998, Kovalchuk et al. 2000, Yuste et al. 1999), even when the somatic depolarization is very small [<1 millivolts (mV)] (**Figure 4**). These large calcium accumulations were unexpected because investigators assumed that NMDARs should be mostly blocked by $Mg^{2+}$ under these small depolarizations. Although some residual unblocked NMDARs may exist at rest, these data first suggested that the voltages generated by EPSPs at the spine could be significantly larger than those measured in the soma or at the dendrite.

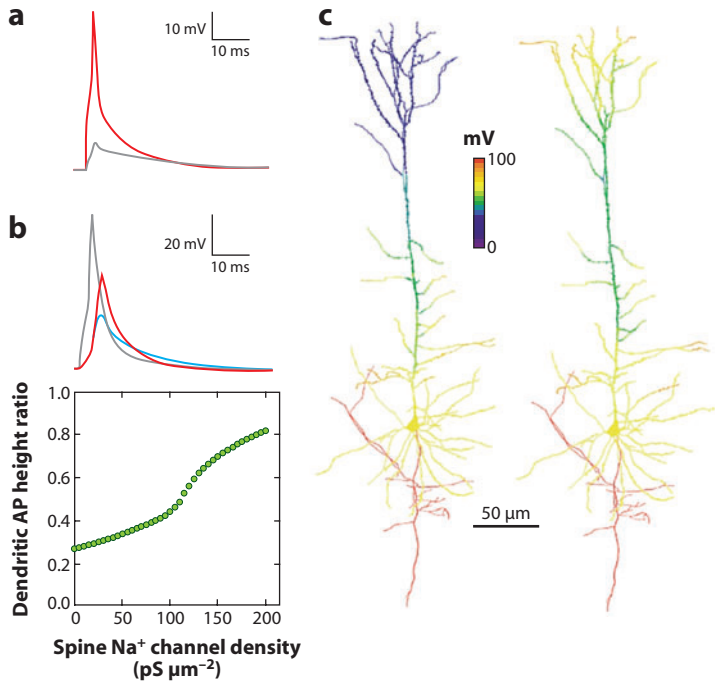


**Figure 2**

Active electrical models of spines. (*a*) Amplification of excitatory postsynaptic potentials (EPSPs) by spine sodium channels. Single-spine model with high sodium-channel densities in spines [~7,000 millisiemens per centimeter square ($mS/cm^2$)] elicits localized action-potential (AP) responses in the spine (*red*) but not in the dendrite (*gray*). For this to occur, spine neck resistances must provide some electrical decoupling (>100 MΩ). (*b*) Moderate sodium-channel densities in many spines increase the efficacy of backpropagation. Gray: AP at soma; blue: AP in apical dendrite (200 µm away), with weakly active spines (GNa = 40 $mS/cm^2$); red: AP in apical dendrite with more active spines (GNa = 200 $mS/cm^2$). (*c*) Peak voltage response to a backpropagating AP in a model with active spines. Backpropagation exhibits a decremental invasion of the apical tree when sodium-channel densities in spines are low (110 $mS/cm^2$) (*left*); but with higher densities in spines (200 $mS/cm^2$), a backpropagating AP fully invades the dendritic tree (*right*). Adapted from Tsay & Yuste 2004.

Two-photon glutamate uncaging produced further evidence that spines can behave as separate electrical compartments, by demonstrating that the somatic amplitude of the potentials generated by activating a spine was inversely proportional to the length of its spine neck (Araya et al. 2006b). Thus, whereas spines with short necks generated larger somatic potentials,

**AP:** action potential

**NMDAR:** *N*-methyl-D-aspartate receptor

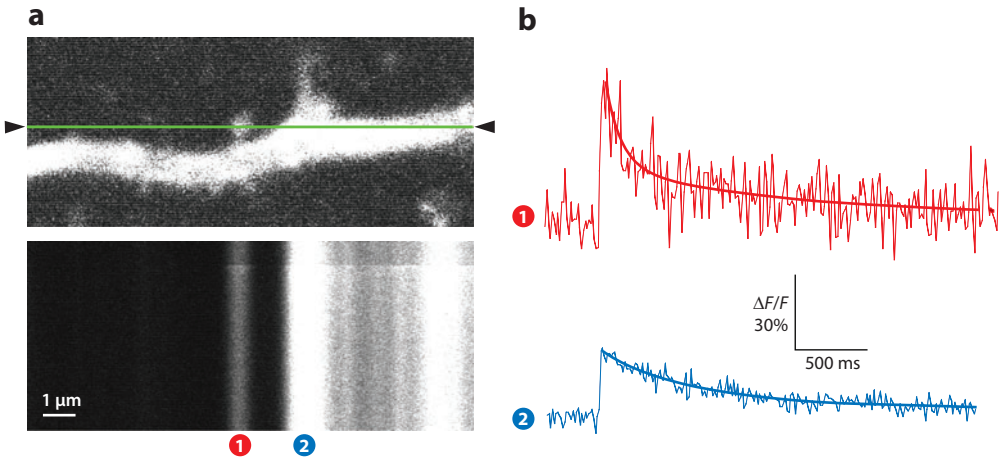


**Figure 3**

Imaging action potential (AP) invasion of spines. (*a*) Top: Two-photon image of a dendrite from a neocortical pyramidal neuron filled with a calcium indicator. Bottom: Line scan through a spine and nearby dendritic shaft (*between black arrowheads*) during invasion by a somatic AP. The backpropagating AP induces calcium accumulations in the spine (1) and dendritic shaft (2). (*b*) Kinetics of AP-triggered calcium accumulations in spine (1) and dendrite (2). Note the lack of significant delay between spine and dendrite accumulations, indicative of a local calcium influx at the spines triggered by the AP invasion. Adapted from Holthoff et al. 2002.



those with long necks generated smaller, or even undetectable, depolarizations (**Figure 5**). These data suggested the possibility that significant electrical reduction of synaptic potentials occurs at the spine neck. Although glutamate uncaging stimulates spines artificially, spines with longer necks also appear to have smaller postsynaptic potentials than do spines with shorter necks in physiological activation of synapses under minimal axonal stimulation (R. Araya, T. Vogels, and R. Yuste, submitted).

Additional support for electrical compartmentalization by spines comes from two-photon uncaging data that show that voltage-gated conductances can be differentially activated in a spine and its neighboring dendritic shaft, something that should not occur if both compartments were isopotential. Indeed, after glutamate uncaging on spines, calcium channels in the spine head activate differently than do those in the neighboring dendrite (Bloodgood et al. 2009). Moreover, the diffusional isolation generated by the spine neck can be regulated by neuronal activity and becomes significant enough to isolate the spine electrically (Bloodgood & Sabatini 2005). Also, bath application of the sodium-channel blocker TTX selectively blocks glutamate uncaging potentials generated on the spines but does not affect those in the neighboring dendritic shaft (Araya et al. 2007). These last experiments indicate that there must be sodium channels in spines and also that these channels can be activated independently from those in the neighboring dendrite. Moreover, the spine voltages reached after glutamate uncaging must be sufficiently high (>15 mV depolarizations) to activate sodium channels. Finally, a recent study, also using two-photon uncaging of glutamate, provides complementary evidence for electrical compartmentalization by spines (Harnett et al. 2012). Using calcium imaging, and assuming that the calcium influx is proportional to the local voltage, the authors estimate the ratio of spine to dendritic voltages during the uncaging potential by activating AMPA receptors (under blockade of NMDAR and sodium channels). They report up to a 45-fold amplification of the uncaging voltages in the spines, as compared with those in adjacent dendrites, as well as high spine neck resistances.

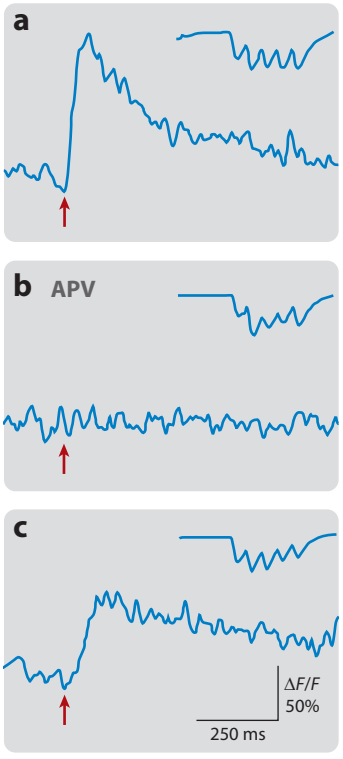


**Figure 4**

Activation of spine *N*-methyl-D-aspartate receptors (NMDARs) by subthreshold synaptic potentials. (*a*) Calcium accumulations in a spine in response to a train of EPSCs (*red arrow*) (*Inset*). (*b*) Identical stimulation in the presence of 100 μM APV, an NMDA receptor blocker. Calcium accumulations during EPSCs are completely blocked. (*c*) After washout of APV, the EPSC-induced calcium influx recovers. These results first suggested that the EPSP voltage is significantly higher in the spine than at the dendritic shaft or soma. Adapted from Yuste et al. 1999.

These results together indicate that spines may become electrical compartments when activated synaptically. However, this conclusion is still based on indirect evidence and should be supported by direct measurements of membrane potential in spines during EPSPs. Different types of voltage-imaging techniques (Peterka et al. 2011), either with fluorescence voltage-sensitive dyes (Cohen 1989) or with second-harmonic generation (SHG) chromophores (Lewis et al. 1999, Millard et al. 2005, Nemet et al. 2004), are enabling researchers to measure, for the first time, spine voltages. In a recent series of papers, investigators have directly demonstrated the invasion of backpropagated APs from dendrites into spine heads, revealing that the AP amplitude at the spine is similar to that of their parent dendritic shafts (Nuriya et al. 2006, Palmer & Stuart 2009, Holthoff et al. 2010, Acker et al. 2011) (**Figure 6**). Finally, voltage measurements under large-scale synaptic stimulation to dendrites indicate that some spines, but not all, can sustain substantially higher voltages than can their neighboring dendritic shafts (Palmer & Stuart 2009), although voltage measurements of "quantal" EPSP in individual spines still remain elusive.

## POTENTIAL MECHANISMS OF ELECTRICAL COMPARTMENTALIZATION

That spines and dendrites can sustain different membrane potentials, at least in some circumstances such as glutamate uncaging or synaptic activation, indicates that they can be electrically isolated. What are the mechanisms responsible for this electrical compartmentalization? They may comprise passive electrical properties of the spine, active conductances, or, perhaps more likely, a combination of both.

As mentioned above, passive electrical alteration of spine potentials could be due to the impedance mismatch between the spine and the dendrite, created by the spine's high resistance and low capacitance. The spine neck may act effectively as a diode, propagating dendritic voltages into the spine without decrement yet diminishing spine voltages as they invade the dendrite. This mechanism likely depends on the dendritic diameter: Spines on thinner dendrites would become more isopotential than would those on thicker dendrites. In addition, a passive filtering mechanism could occur if the spine neck resistance is high and directly reduces spine potentials, explaining the dependence of voltage reduction on the spine neck length (Araya et al. 2006b; **Figure 5**). Although simulations based on ultrastructural reconstructions

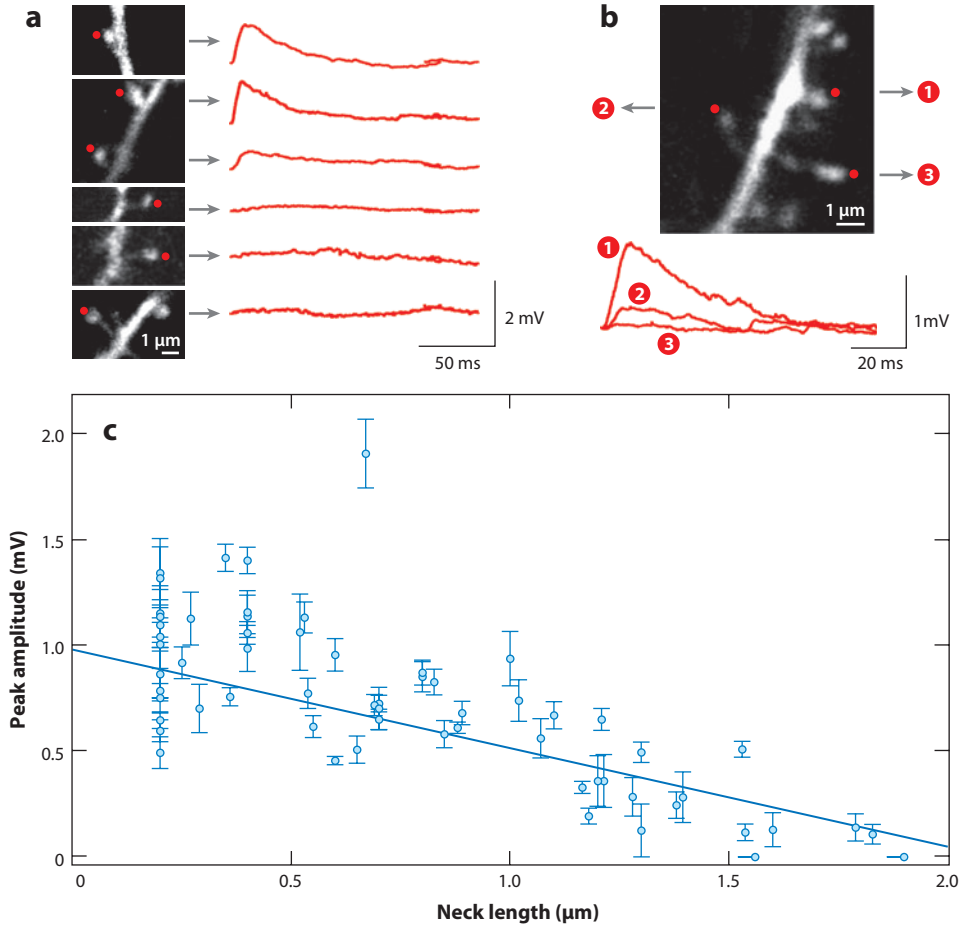


**Figure 5**

Effect of spine neck on spine potentials generated by two-photon glutamate uncaging. (*a*) Uncaging potentials from spines with short and long necks. Red dots indicate the site of uncaging, and red traces correspond to average uncaging potentials generated by different spines and measured at the soma. (*b*) Activation of three neighboring spines (1, 2, and 3) with different neck lengths. Note the large difference in their uncaging potentials at the soma. The shorter spine generates the stronger response, whereas activating the longer spine has no effect. Scale 1 µm. (*c*) Inverse correlation between uncaging potentials (peak amplitude) versus neck length. Line is linear regression of the data. Adapted from Araya et al. 2006a.

indicate that the spine neck resistance may not be significant to filter spine potentials (Harris & Stevens 1988, Koch & Zador 1993), calculations based on diffusional coupling vary widely (Bloodgood & Sabatini 2005, Svoboda et al. 1996); and some indicate Giga-Ohm neck resistances that could implement voltage filtering (Bloodgood & Sabatini 2005). Moreover, the spine neck, which is often depicted as a cylinder, is not a simple anatomical structure but often reveals constrictions where both membranes touch, as well as intracellular organelles that obstruct it (Arellano et al. 2007). The electrical consequences of these "pinches" and "plugs" are unknown but could significantly restrict ionic diffusion and transfer of electrical charges, particularly if the spine neck membrane lipids or proteins are charged and can screen ions.

Other mechanisms underlying the electrical compartmentalization in spines may derive

from the presence of active conductances in the spine head or in the neck. In fact, dendrites are full of active conductances (Stuart et al. 1999), and it seems unlikely that spines would exclude dendritic channels, particularly because spines can emerge in a matter of seconds (Dunaevsky et al. 1999, Engert & Bonhoeffer 1999, Fischer et al. 1998, Kwon & Sabatini 2011). Indeed, evidence for the existence of active conductances in spines is accumulating from structural techniques, proteomics, and functional imaging assays. In addition to glutamatergic and γ-amino-butyric-acid (GABA)-ergic receptors on postsynaptic membranes (Nusser et al. 1997, 1998), ultrastructural techniques have also revealed sodium- and calcium-channel subunits in the spine cytoplasm (Caldwell et al. 2000, Mills et al. 1994; although see Lorincz & Nusser 2010). Researchers have also found potassium and nonselective channels in spine heads and necks, including SK2, G protein–coupled inwardly rectifying potassium channel (GIRK), Kv4.2, and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (Allen et al. 2011, Kim et al. 2007, Lin et al. 2008, Lujan et al. 2009, Ngo-Anh et al. 2005, Wang et al. 2007). Moreover, because postsynaptic densities (PSDs) are restricted to spines (Gray 1959), their biochemical analysis should reveal the spine protein complement. Indeed, proteomics analysis of PSD fractions demonstrates a large diversity of receptors and conductances, including subunits from essentially all dendritic channel families, including sodium channels (Cheng et al. 2006, Grant et al. 2004, Husi et al. 2000, Li et al. 2004, Walikonis et al. 2000, Yoshimura et al. 2004).

In addition to these structural methods, functional evidence from two-photon imaging also supports the existence of active conductances in spines. Aside from revealing glutamate receptors (Koester & Sakmann 1998, Kovalchuk et al. 2000, Matsuzaki et al. 2004, Yuste et al. 1999, Yuste & Denk 1995), calcium imaging has also revealed several types of voltage-sensitive calcium channels (VSCCs) (Yuste & Denk 1995), including T-type, L-type, N-type, R-type, P/Q-type, and low-voltage-activated (LVA) $Ca^{2+}$ channels. (Bloodgood et al. 2009; Bloodgood & Sabatini 2007a,b; Sabatini et al. 2002; Sabatini & Svoboda 2000). Sodium imaging of spines under backpropagating APs has indicated that local sodium influx occurs in some spines (Rose et al. 1999), consistent with the specific effect of TTX on spine uncaging potentials (Araya et al. 2007) (**Figure 7**).

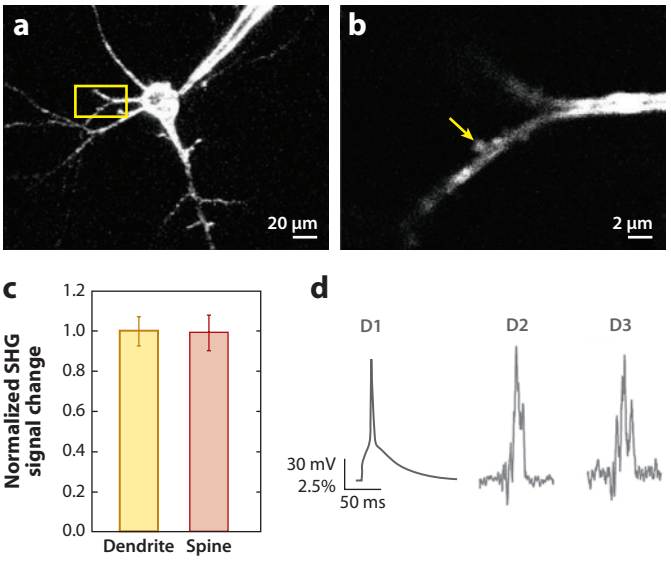


**Figure 6**

Imaging voltage in spines using second-harmonic generation (SHG). (*a*) SHG image of pyramidal neuron filled with the voltage-dependent SHG chromophore FM 4–64. (*b*) High-resolution image of a dendritic spine on the basal dendrite boxed in panel *a*. (*c*) Similar SHG voltage responses upon depolarizing voltage steps at spines and their parent dendrites. (*d*) SHG voltage measurements of spines during backpropagating APs. A single AP was initiated by current injection at the soma (D1), and SHG signals changes with similar amplitudes were measured at soma (D2) and dendritic spines (D3). Adapted from Nuriya et al. 2006.

## FUNCTIONAL CONSEQUENCES OF ELECTRICAL COMPARTMENTALIZATION OF SPINES

As discussed, mounting evidence indicates that spines are not always isopotential with the dendritic shaft and that spines must be significantly more depolarized than dendritic shafts when activated by synaptic inputs. The exact spine

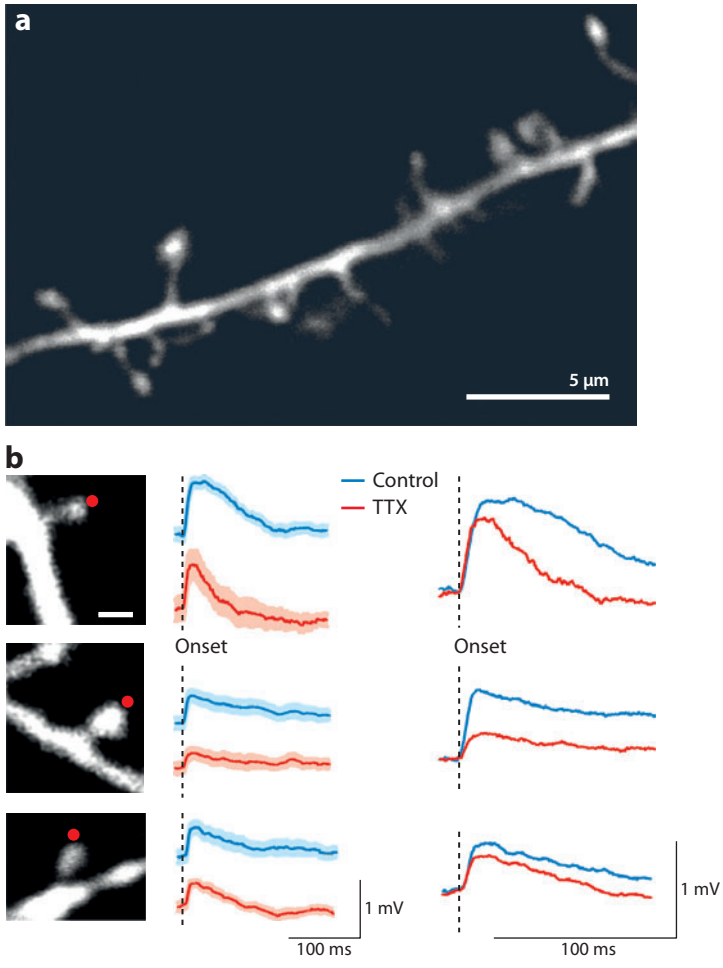


**Figure 7**

The sodium-channel blocker TTX reduces spine uncaging potentials. (*a*) Dendrite from a layer 5 pyramidal neuron, the spines of which were stimulated with two-photon glutamate uncaging. (*b*) Glutamate uncaging experiments. (*Left*) Red dots indicate the site of laser uncaging. (*Center*) Uncaging potentials under control conditions (*blue traces*) and in the presence of TTX (*red traces*). Dashed line indicates the time of uncaging onset. Thicker traces are an average of 10–15 depolarizations, and shaded areas illustrate standard error of the mean (SEM). (*Right*) Average uncaging potentials are superimposed. Note how TTX attenuates spine uncaging potentials. In similar experiments, TTX had no effect on uncaging potentials on dendritic shafts. Adapted from Araya et al. 2007.

voltage during uncaging activation or EPSPs could be as high as 20 mV, whereas at the dendritic shaft it is diminished to ~1 mV (Araya et al. 2006b, 2007; Harnett et al. 2012; Palmer & Stuart 2009). It seems paradoxical that once synaptic transmission is successful and activates postsynaptic glutamate receptors, its resulting depolarization becomes strongly curtailed. What could be the purpose of this reduction in synaptic potentials? Why would excitatory inputs need to be diminished as they traverse through the spine neck toward the dendritic shaft? In this section I briefly discuss the potential functional consequences of electrically isolating spines (see also Yuste 2010, 2011).

## Enhancement of Input Integration

One functional advantage of electrically isolating spines, regardless of how it occurs, could be the local amplification of synaptic currents. Passive or active mechanisms could enhance the effect of EPSP at the spine, so a similar presynaptic dose of a neurotransmitter could generate a larger postsynaptic depolarization than if there was no local amplification of EPSPs. This could be advantageous for the neuron, by economizing postsynaptic receptors and ensuring a more reliable activation of receptors and conductances. For example, an enhanced spine depolarization could release the $Mg^{2+}$ block of NMDA receptors (**Figure 4**), enable subthreshold calcium accumulations, and activate calcium, sodium, or potassium conductances (**Figures 3** and **7**). These processes could contribute to biochemical signaling and significantly shape postsynaptic depolarizations, thus providing potential mechanisms to modulate and modify it. For example, they could enable cooperative interaction between neighboring spines (Harnett et al. 2012).

But if the purpose of electrically isolating the spine is to amplify EPSPs, why then proceed to reduce the size of EPSPs as they invade the dendrite? One potential explanation of this paradox is that EPSP filtering prevents the electrical saturation of the neuron, a problem that must be particularly acute when neurons need to integrate thousands of inputs. Indeed, spines are normally found in neurons that receive large numbers of excitatory inputs, and electrically isolating spines could be a defense mechanism to prevent large conductance changes in the dendrite that could render it unexcitable, as in a shorted circuit (Llinás & Hillman 1969). Alternatively, spines could simply diminish the depolarization generated by each input so that more of them can be integrated before the neuron fires an AP. But if this is true, why not simply make synapses weaker directly, by reducing the number of glutamate receptors? Perhaps the initial amplification followed by filtering could permit the integration of more inputs without also increasing synaptic noise, because reducing the already very small number of receptors in each synapse could lead to excessive variability. Another advantage of using more receptors per synapse offers the possibility of encoding a large dynamic range of synaptic strengths. An alternative functional reason for EPSP amplitude reduction could be to devalue the additional electrical filtering caused by the dendritic tree, generating a dendrite where integration of the synapse would not matter; this process would help standardize the amplitude and kinetics of all EPSPs regardless of the synapse's position (Andersen et al. 1980, Gulledge et al. 2012, Konur et al. 2003, Magee & Cook 2000, Yuste 2011). Finally, an advantage of electrically isolating spines could be to enable the linear summation of EPSPs, as some models have predicted (Grunditz et al. 2008, Jack et al. 1975). In fact, excitatory inputs in spiny neurons are often integrated linearly (Cash & Yuste 1999); linear summation is found when glutamate uncaging stimulates neighboring spines but, interestingly, is not found when this stimulation is performed in the dendritic shafts (Araya et al. 2006a) (**Figure 8**). Altogether, a strategy with local amplification of EPSPs, followed by their attenuation and linear summation, would be of great functional advantage to the neuron, as a sort of biophysical homeostasis, if it needed to integrate a maximum number of inputs and add their values accurately without interference or cross talk between them. It makes perfect sense.

## Regulation of Synaptic Plasticity

An alternative functional advantage for the electrical compartmentalization of spines is that its regulation enables precise control of synaptic strength. This process could occur by modifying the amplification of EPSPs at the spine head, by altering the activation of spine conductances, or by altering the spine neck/dendritic shaft electrical coupling by either active or passive mechanisms.

The idea that changes in the spine neck control synaptic plasticity was proposed already in the first discussions of spine electrical properties (Chang 1952, Rall 1978). In fact, ample

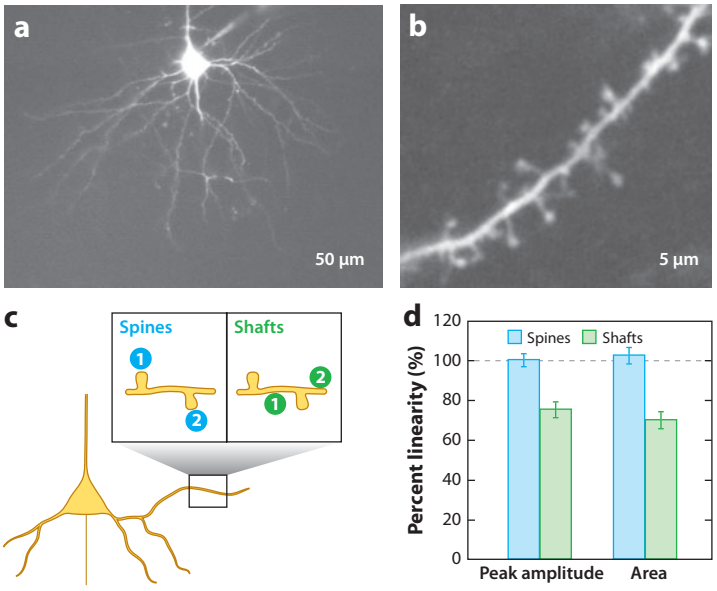


**Figure 8**

Linear summation of uncaging potentials on spines but not on dendritic shafts. (*a*) Layer 5 pyramidal cell filled with a fluorescence dye. (*b*) Basal dendrite selected for uncaging. (*c*) Protocol for testing input summation. Blue and red dots indicate the site of uncaging in spines or shaft locations, respectively. Uncaging was performed first at each spine or shaft location (1 or 2) and then simultaneously in both spines or both shaft locations (1 + 2). (*d*) Linearity of summation of uncaging potentials, measured as a ratio of the peak amplitude, or area, of the combined stimulation to the expected values calculated by summing the two independent stimulations. Note how summation of two spine potentials is linear, but summation of two shaft potentials is already reduced by 30%. A stronger shunting is expected if more shaft locations are stimulated, generating a short-circuited dendrite. Adapted from Araya et al. 2006b.

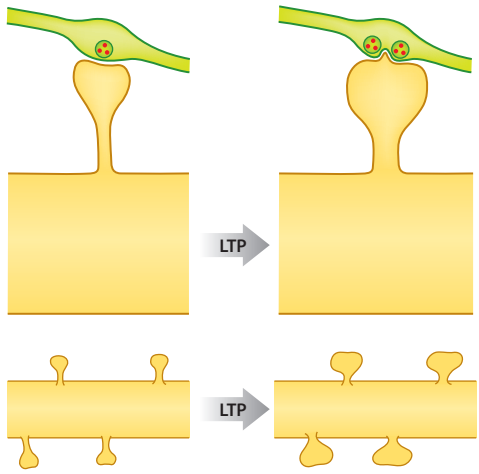


**Figure 9**

Changes in spine morphologies during synaptic plasticity. Representation of the Fifkova ultrastructural reconstructions. Long-term potentiation (LTP) results in larger spine heads and shorter and wider spine necks. Adapted from Yuste 2010.

experimental evidence shows that long-term synaptic plasticity is associated with morphological changes in spines, which could generate changes in electrical compartmentalization (Yuste & Bonhoeffer 2001). For example, LTP leads to increases in spine head size and to spine neck shortening and widening (Fifkova & Anderson 1981, Matsuzaki et al. 2004, Van Harreveld & Fifkova 1975) (**Figure 9**). This morphological plasticity could increase the number of glutamate receptors in the PSD and decrease the spine neck resistance, both mechanisms leading to larger EPSPs. Moreover, spines are constantly experiencing morphological plasticity in vitro and in vivo (Bonhoeffer & Yuste 2002). This "motility" is actin based (Fischer et al. 1998) and can lead to major changes in spine shapes, with elongation, shortening, or even complete disappearance of the spine neck in a matter of seconds (Dunaevsky et al. 1999) (**Figure 10**). This morphological plasticity likely has an effect on synaptic strength, perhaps due to changes in the electrical properties of spines. This scenario highlights the potential importance of the cell-biological mechanisms that control the tension, shape, and motility of cellular protrusions in the function of the neuron (Hall 1994).

## CONCLUSION: A SYNAPTIC DEMOCRACY FOR EMERGENT COMPUTATIONS

Spines are clearly electrical compartments, although the exact mechanisms and functional purpose of this are still unclear. This electrical compartmentalization may be advantageous for the neuron to integrate and better control the plasticity of large numbers of synaptic inputs. This could enable the circuit to function as a distributed neural network with a

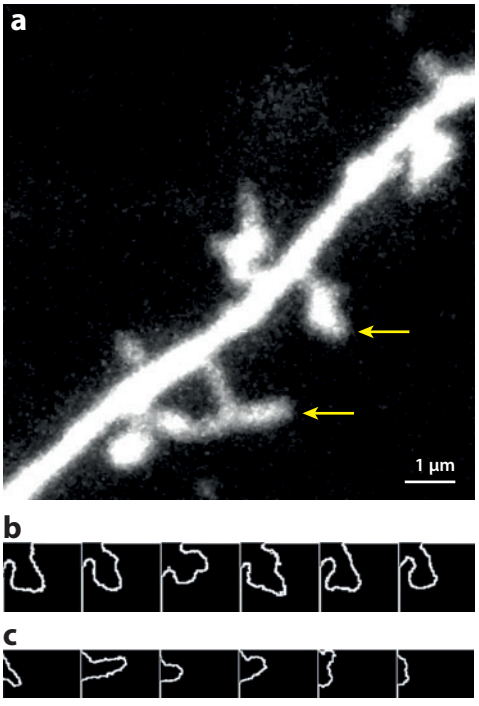


**Figure 10**

Spine motility. (*a*) Two-photon image of a pyramidal neuron from mouse visual cortex, labeled with green fluorescence protein (GFP). Diverse morphologies of dendritic protrusions can be observed. (*b*, *c*) Morphological changes in spines. Outlines of two spines (*yellow arrows in panel a*), shown at 2.5-min intervals. Note how the spines experience major changes in shape. Adapted from Konur & Yuste 2004a.

large synaptic matrix, where inputs would be integrated independently and linearly, as in a giant synaptic democracy (Yuste 2011). This view incorporates into a single functional framework traditional proposals for the function of spines, such as their role in the structural enhancement of connectivity or in the biochemical isolation necessary for input-specific synaptic plasticity (Chklovskii et al. 2002, Koch 1999, Peters & Kaiserman-Abramof 1969, Swindale 1981, Yuste 2010), because all these functions are actually necessary to create, and fully exploit, a distributed connectivity in the circuit (Yuste 2011). Spines being found in CNS circuits with large connectivity matrixes may not be coincidental because they may not be necessary for neurons that need to integrate few inputs, which can be accommodated in separate dendrites (Purves & Hume 1981).

Moreover, a distributed circuit could enable the brain to implement computational strategies where functional states are encoded at an emergent level of function, one based on the coordinated activity of many neurons, rather than at the single cell level. Indeed, the more distributed a circuit is, the less important the role that an individual neuron has. From this circuit-level viewpoint, spines would represent the anatomical signature of distributed neural networks, serving as their basic units of neuronal integration and plasticity and enabling them to function robustly. In fact, by ensuring the faithful integration and modification of all inputs, spines could greatly simplify and make more robust the function of these distributed circuits. Neural networks built with these simple elements, where each neuron adds input to lead to spiking, can implement Boolean logic (McCulloch & Pitts 1943), matrix multiplication, or vector remapping (Pellionisz & Llinas 1979) and perform relatively sophisticated computations such as associative memory (Hopfield 1982), optimization, or decision making (Hopfield & Tank 1986). It is fascinating to think that spines may illustrate an underlying simplicity hidden in the apparently complex morphological and functional design of neurons (Mead 1989).

## NEW TECHNIQUES TO STUDY DENDRITIC SPINES

New methods are suggested to be more important for science than new discoveries or even new ideas (Brenner 2002). Indeed, research on spines illustrates very clearly the critical dependence of science on the introduction of novel methods, from their first description by the application of then-novel Golgi stain (Ramón y Cajal 1888), to the demonstration that they serve as synaptic units by the introduction of electron microscopy (Gray 1959), to the

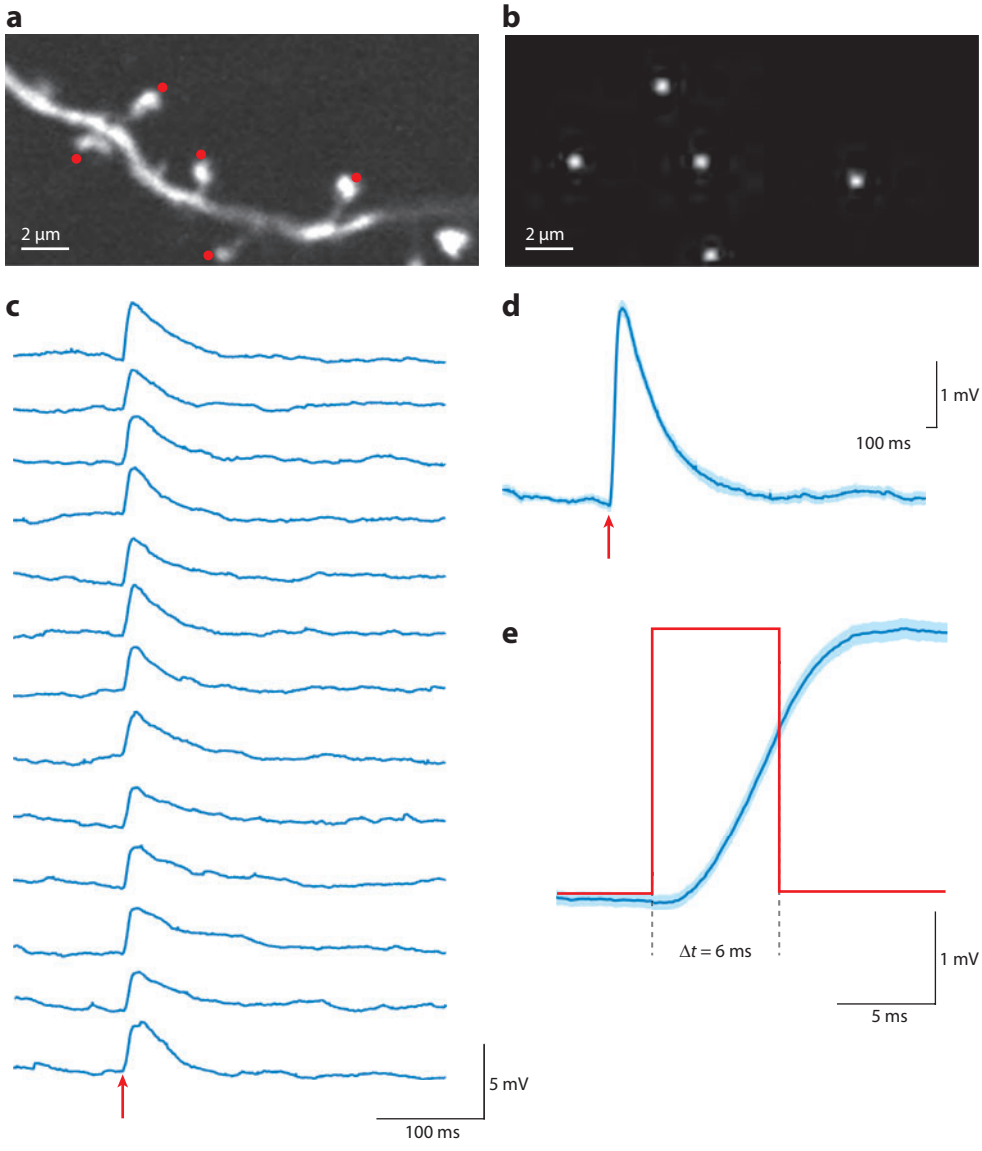


**Figure 11**

New techniques: holographic stimulation of groups of spines with a spatial light modulator (SLM). (*a*) Basal dendrite from a layer-5 pyramidal neuron in a mouse neocortical slice. Red dots indicate the sites chosen for simultaneous two-photon glutamate SLM uncaging. (*b*) Diffraction pattern of five uncaging spots next to the five spine heads, generated by sending to the SLM a Fourier transform of the image with the uncaging locations selected in panel *a*; (*c*) Whole-cell recording from the soma of the same cell during the experiment. Individual uncaging potentials generated after simultaneously uncaging glutamate (*red arrow*) next to the five spines shown in panels *a–d*. Average of the uncaging potentials shown in panel *c*. (*e*) Higher-resolution plot of response onset. Red trace represents the uncaging laser pulse. Blue trace is the average uncaging potential in panel *d*. Light blue areas in panels *d* and *e* are ± SEM. With SLM two-photon uncaging, one can "play the piano" with spines, activating them in an arbitrary spatiotemporal pattern. Adapted from Nikolenko et al. 2008.

## THE MYSTERY OF THE LONG SPINES

The possibility that EPSPs are electrically reduced in the spine neck as they arrive into the dendritic shaft has interesting implications for spines that have longer necks because those spines appear to generate no significant depolarization at the soma (Araya et al. 2006b). Are long spines electrically silent, as reserved connections? Perhaps their necks become shorter and wider during synaptic plasticity protocols (**Figure 9**), "plugging in" the presynaptic neuron they represent into the circuit and enabling fast circuit switching. Interestingly, human neurons have not only higher spine densities but also spines with characteristically long necks (Benavides-Piccione et al. 2002, 2012) (**Figure 12**). If long-necked spines are reserve connections, they could reflect a higher degree of synaptic connectivity and plasticity by our brains. Indeed, Ramón y Cajal himself pointed out that human neurons are particularly spiny, and part of his interest in spines was motivated by his lifelong quest to understand the physical basis of human intelligence (Ramón y Cajal 1904, 1923). Moreover, longer "humanized" spines can be induced in mice by manipulating human-specific gene paralogs (Charrier et al. 2012). Finally, spines with abnormally long necks are prominent in mental retardation patients (Purpura 1974) and could be related to cognitive impairments.

more recent discoveries of their biochemical compartmentalization and motility using two-photon microscopy (Yuste & Denk 1995). Thus, our understanding of spine function may be further advanced by a series of upcoming novel technologies: novel voltage-imaging methods to image spine voltages (Nuriya et al. 2006, Peterka et al. 2011), two-photon optogenetics activation of individual spines (Packer et al. 2012), holographic stimulation of multiple spines using spatial light modulator (SLM) uncaging (Nikolenko et al. 2008) (**Figure 11**), or stimulated-emission-depletion (STED) microscopy and other super-resolution techniques to image the fine structure of living spines (Nagerl et al. 2008).

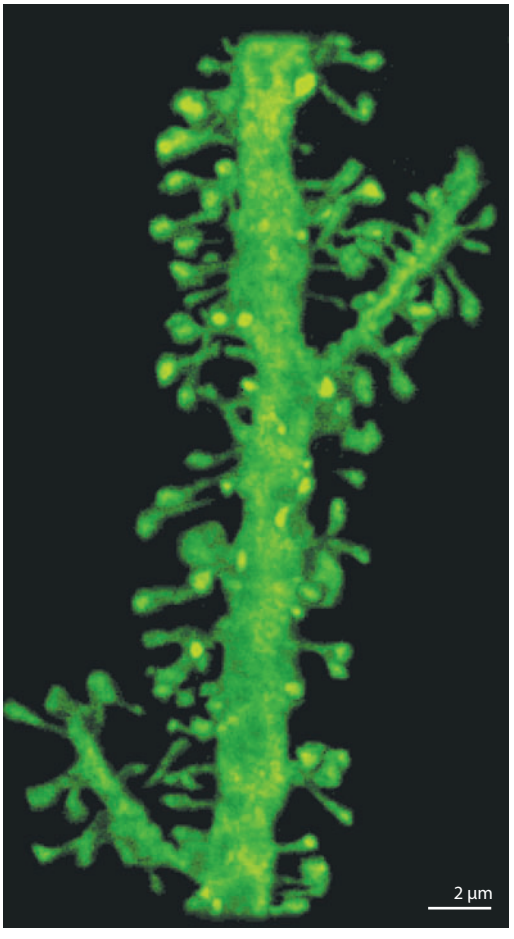


**Figure 12**

Long-necked spines in a human pyramidal neuron. Intracellularly injected layer-3 pyramidal neuron of a sample from a human cingulate cortex. Confocal image of an apical dendritic segment at ~100 µm from soma. Note the large density of spines and also the particularly long spine necks, both typical characteristics of human pyramidal neurons. Adapted from Yuste 2010. See also Benavides-Piccione et al. (2002, 2012).

**SUMMARY POINTS**

1. Dendritic spines can sustain membrane potential that differs from that of the dendrite.
2. This electrical compartmentalization could be due to passive and active biophysical mechanisms.
3. The electrical isolation of spines could help the neuron integrate and independently modulate the strength of large numbers of synaptic inputs and implement emergent-level computations.

## DISCLOSURE STATEMENT

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**Errata**

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