

Human Cortical Dendrites: Stretched to Perform Better?

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Most functional properties of human dendrites have been inferred from data obtained in model organisms. In this issue, Beaulieu-Laroche et al. record directly from human dendrites of cortical neurons and show that the considerably larger human neurons differ from rat neurons in the way they process synaptic signals.

Research in model organisms, primarily performed in rodents, provided major insights into the principles of dendritic function, such as the role of back-propagating action potentials and dendrite-generated regenerative events in synaptic integration and plasticity. Recently, accumulating evidence suggests that dendritic regenerative events are not only reliably observed during behavior, but also play essential roles in the induction of synaptic plasticity *in vivo* (Smith and Häusser, 2010, Bittner et al., 2015). However, the question remains: how helpful are these findings for understanding the human brain? From the seminal work of Rall and Rinzel (1973) and many computational and experimental studies that followed, we know that the electrical properties of the dendritic cables are fundamental determinants of synaptic integration. Human dendrites exceed rodent dendrites in diameter, length, and complexity. The difference in dendritic length alone has implications for the integration and propagation of dendritic signals. So far, however, most functional properties of human dendrites have been inferred from data obtained in model organisms and direct electrophysiological measurements from human neurons were missing. In this issue of *Cell*, Beaulieu-Laroche et al. (2018) record directly from human dendrites of layer 5 (L5) cortical neurons and compare their biophysical features to those of L5 rat neurons.

Their experiments reveal an unexpected difference. In the apical dendritic trunk of human neurons, the dendritic

input resistance increases with distance from the soma, while the rodent counterpart shows an opposite distance dependence of input resistance. What is the functional implication of this difference? In human neurons, an identical synaptic current at the same distance from the soma will result in a comparably larger local dendritic depolarization (Figure 1). At the same time, postsynaptic potentials undergo stronger voltage attenuation on their path to the axo-somatic region. As a direct result of the distance dependent difference in local input resistance, backward propagation of voltage from the soma to the apical dendrites in human neurons is enhanced (Figure 1). Thus, they compensate for the difference in absolute length. Their action potentials may reach the neuronal nexus region, which is hundreds of micrometers more distant, with comparable amplitude.

Ultimately, the decision of whether a neuron fires and participates in network activity is made at the axon initial segment where the threshold for action potential initiation is set. Given the strong voltage attenuation in human L5 neurons, synaptic potentials may not have sufficient influence on the axo-somatic membrane potential to cross this threshold. However, many neurons develop a compensatory mechanism. Their local ionic conductances support the generation of regenerative dendritic events. With dendritic recordings, Beaulieu-Laroche et al. observe these regenerative spikes in human dendrites. This direct experimental demonstration had been long awaited.

Surprisingly, dendritic spikes in human L5 neurons cause less local depolarization than in rats and attenuate much more strongly toward the soma (Figure 1). This limits their influence on neuronal output and increases the degree of compartmentalization of dendritic input.

What may be the mechanisms underlying higher dendritic input resistance and weaker dendritic spiking? Beaulieu-Laroche et al. hypothesize that the overall density of ion channels could be lower in human dendrites, representing a “stretched” version of the rodent counterpart. With an elegant application of model, prediction, and experimental testing, the authors present strong evidence in favor of this model. With dendritic patch-clamp recordings, they directly demonstrate a reduced density of dendritic hyperpolarization-activated cyclic-nucleotide-gated channels (HCNs; Figure 1). It seems plausible that a reduced channel density could account for the observed differences: first, a reduction of “leak” channels may account for the higher dendritic input resistance. Second, a reduced density of voltage-gated calcium and sodium channels could underlie the reduced dendritic depolarization by dendritic spikes. Third, the reduced recruitment of dendritic channels by back-propagating action potentials may lead to decreased burst firing of human L5 neurons.

These findings are somewhat surprising when seen in the light of a recent study challenging the view that the specific membrane capacitance of neuronal membranes settles at almost “universal”



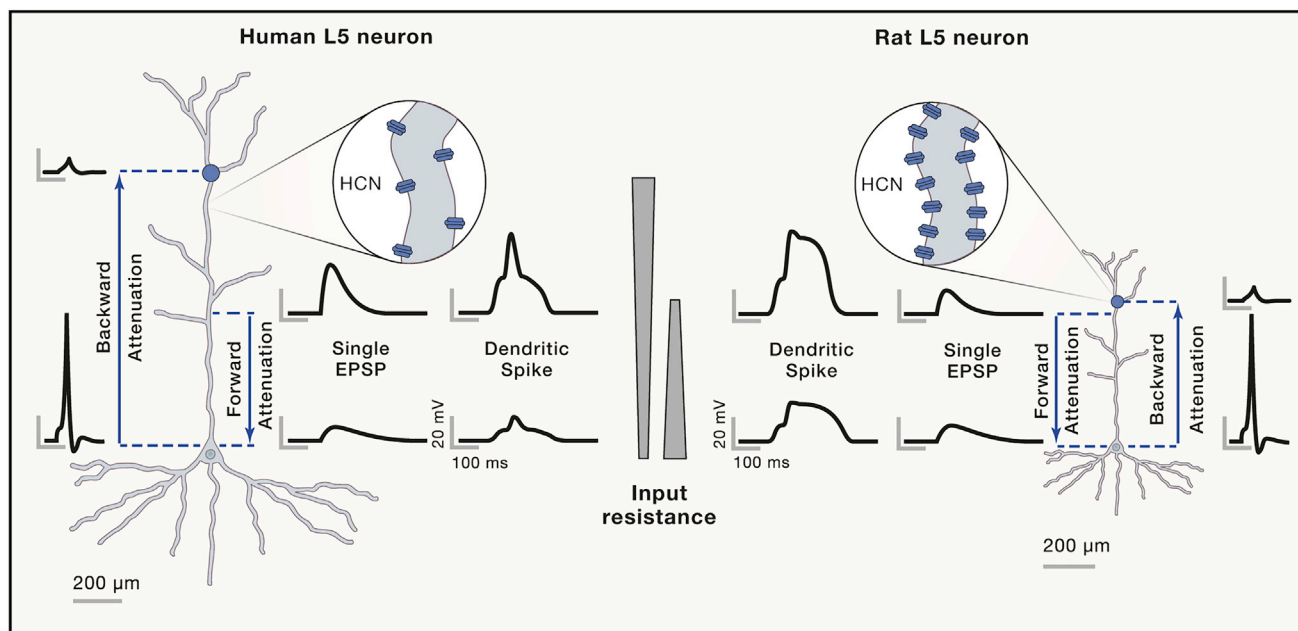


Figure 1. Human L5 Pyramidal Neurons Are Stretched Versions of Rat Neurons

Compared to rat dendrites, human L5 neuronal dendrites have a reduced density of ion channels, resulting in an opposite distance dependence of input resistance. This leads to more pronounced local depolarization at the synaptic input site but stronger forward attenuation. Further, it results in reduced backward attenuation of action potentials, compensating for the difference in absolute length. Finally, reduced density of dendritic calcium/sodium channels may underlie the weaker local depolarization by dendritic spikes.

values around 0.8–1 pF/cm² (Gentet et al., 2000). Eyal et al. (2016) observed a remarkably lower specific membrane capacitance of human L2/3 cortical neurons and predicted fundamentally different integrative properties. Beaulieu-Laroche et al. address this discrepancy directly using nucleated-patch recordings. They find neither a difference between rat and human L5 neurons nor uniquely low values of the specific membrane capacitance.

Is the compartmentalization of synaptic input a feature that enables human neurons to perform more complex computations? In order to potentiate, excitatory synapses need an associative signal. This signal could be back-propagating action potentials or dendritically generated spikes that lead to calcium/NMDA receptor activation. The high degree of input compartmentalization, together with the now experimentally uncovered ability of human apical dendrites to generate dendritic spikes, could allow for more compartmentalized induction of synaptic plasticity. Such a mechanism could be used to cluster synapses with correlated activity of presynaptic

neuronal ensembles on single-dendritic compartments (Losonczy et al., 2008; Häusser and Mel, 2003). However, Beaulieu-Laroche et al. also demonstrate that dendritic spikes in human neurons are weak and may be less-efficient triggers of plasticity. This decrease in dendritic excitability may be counteracted by increased synaptic strength in human neurons (Molnár et al., 2016). Finally, other factors that have to be considered when extrapolating from rodent data to human with respect to synaptic integration are differences in neuromodulation and short-term and/or long-term plasticity (Verhoog et al., 2013).

Overall, the work of Beaulieu-Laroche et al. demonstrates that the general principles of synaptic integration are preserved in both rat and human neocortical L5 neurons. However, the considerably larger human neurons clearly differ from rat neurons in the way they process synaptic signals. This finding emphasizes that while rodent data are well controlled and easier to obtain, human data may be required to build working models of human brain functions. Good models will be essential to understand how functional

differences on the single-cell level relate to higher cognitive abilities of humans.

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Mixed Palettes of Melanopsin Phototransduction

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Animal photoreceptors divide into two fundamental classes, ciliary and rhabdomeric. Jiang and colleagues demonstrate that this boundary is disregarded by the intrinsically photosensitive retinal ganglion cells of mammals. These neurons draw from phototransduction mechanisms of both classes, enriching the signals that they produce to drive a diversity of visual functions.

Animals use light to recognize objects, guide actions, regulate physiology, and tune development. These processes are triggered by photoreceptors of two basic classes. Ciliary photoreceptors include the familiar rods and cones of vertebrates, not to mention cells in the avian pineal gland and reptilian third eye. Their rhabdomeric counterparts are exemplified by photoreceptors of invertebrates like *Drosophila*, which detect light with remarkable sensitivity, dynamic range, and speed. These classes diverge in the G protein cascades that mediate phototransduction: a motif based on cyclic nucleotides signifies the former and phospholipase C (PLC) the latter (Yau and Hardie, 2009). In this issue of *Cell*, Jiang et al. (2018) present compelling evidence that this divide is bridged by the intrinsically photosensitive retinal ganglion cells (RGCs) (Do and Yau, 2010). These mammalian neurons appear capable of using both phototransduction motifs (Figure 1).

To capture light, intrinsically photosensitive RGCs express a visual pigment called melanopsin. Melanopsin phototransduction causes the membrane voltage to depolarize (becoming more

positive), evoking electrical spikes that are conveyed to dozens of brain areas. Intrinsically photosensitive RGCs are key mediators of functions that include regulation of the circadian clock, pupil response, sleep, and melatonin level. Ablating these cells spares visual perception but renders many aspects of physiology, such as the clock, completely insensitive to light. Conversely, when rods and cones are lost but intrinsically photosensitive RGCs remain, light regulates physiology even in the absence of visual awareness.

Intrinsically photosensitive RGCs are best understood in the mouse retina, where they are subdivided into several types (M1–M5) (Schmidt et al., 2011). Molecularly, the M1 type is the spitting image of a rhabdomeric photoreceptor. Its cascade uses G proteins of the q/11 family, PLCβ4, and TrpC6/TrpC7 ion channels; these are closely related to elements of *Drosophila* phototransduction. For the last decade, the other types have been assumed to be of the same mold because they also use melanopsin and depolarize to light.

Jiang et al. overturn this assumption to provide new insights into phototransduction. Their principal approach is to record the electrical responses generated by sin-

gle intrinsically photosensitive RGCs of different types using mice that lack genes for various signaling molecules. They find that light elevates cyclic nucleotides in M4s to gate ion channels—a decidedly ciliary event. Fittingly, early evidence of these particular channels (dubbed “HCN” for hyperpolarization-activated, cyclic-nucleotide-gated) was found in rods, though they do not mediate phototransduction there. Another surprise lies with the M2s. Unlike any other photoreceptor observed to date, these cells blend rhabdomeric and ciliary motifs. Intriguingly, it is speculated that the common ancestor of extant photoreceptors possessed a mixed nature (Yau and Hardie, 2009).

Impressive experiments are on display. For example, testing for an elevation of cyclic nucleotides within M4s is not trivial. Their small number (<0.01% of all retinal cells) makes biochemistry foreboding, and their photosensitivity is incompatible with fluorescent indicators. Jiang et al. met this challenge cleverly by expressing in M4s an ion channel that is opened specifically by cyclic nucleotides. They selected a channel that opens faster than the HCN channel, allowing its activity to be distinguished from the natural light

