Figures and figure supplements

Unique membrane properties and enhanced signal processing in human neocortical neurons

Guy Eyal et al

Figure 1. Exceptionally low specific membrane capacitance, $C_m$, for L2/3 human pyramidal cells predicted using detailed neuron models. (a) Experimental transient voltage response (upper black trace, Exp.) to a brief somatic depolarizing current pulse (2 ms, 200 pA). The corresponding 3D reconstructed HL2/3 cell from which this voltage transient was obtained is shown in the inset. Color traces depict theoretical transients resulting from injecting the experimental current into the compartmental model of that cell (see Materials and methods). The corresponding cable parameters ($C_m$, $R_m$, $R_a$) are shown for each theoretical transient. Excellent fit was obtained only with $C_m$ value near 0.5 $\mu$F/cm$^2$ (green trace), which is half the conventional value of around 1 $\mu$F/cm$^2$, obtained for a variety of neuron types, including cortical neurons of other species. (b) Model parameters with low $C_m$ (green traces in a) also match the experimental responses (black) to stimuli of different strength and signs ($-$200 pA, $-$100 pA, $-$50 pA, 50 pA, 50 pA, 100 pA, 200 pA). (c1–c5) Five additional human L2/3 neurons taken from our human neuron database (depth from pia is provided above each cell). (d1–d5) The experimental transient voltage response for the neurons in c1–c5 (black traces), and models fit to the transients (overlapping color traces). In all models, $C_m$ ranged between 0.30 $\mu$F/cm$^2$ and 0.52 $\mu$F/cm$^2$. Patient history for these six cells is described in Table 2.

DOI: 10.7554/eLife.16553.002
Figure 1—figure supplement 1. Estimates for passive properties of human L2/3 neurons. (a1–a3) Model values for the best fits shown in Figure 1 for the three passive parameters \( C_m \), \( R_a \), \( R_m \). Colors match the model colors as in Figure 1. Bar shows the mean value. (b) Root Mean Square Distance of best fits when \( C_m \) value was constrained (x-axis) in the optimization procedure. For these simulations, the other passive parameters (\( R_a \), \( R_m \)) were free parameters. Note that the smallest RMSD is obtained with \( C_m = 0.5 \) \( \mu F/cm^2 \). (c) and (d) Similar to (b), but when \( R_m \) or \( R_a \) were constrained. Note the shallow dependence of the RMSD on \( R_a \).

DOI: 10.7554/eLife.16553.003
Figure 1—figure supplement 2. Cable properties for mouse L2/3 pyramidal cells from the temporal cortex. (a1–a4) Four L2/3 neurons from three mice reconstructed in 3D. (b1–b4) Black traces, experimental voltage traces recorded in the four corresponding neurons shown in a1–a4. Color traces, best fitted theoretical transients resulting from injecting the experimental current into the compartmental model of that cell. The corresponding cable parameters ($R_m$, $C_m$, $R_a$) are shown on the right.

DOI: 10.7554/eLife.16553.004
Figure 1—figure supplement 3. Estimating passive parameters for human L2/3 pyramidal cells when incorporating Ih channels into the model. (a1) The best fit between experimental transient (black) and theoretical transient (green) for the passive model (no Ih) for the cell shown in Figure 1a. The corresponding cable parameters are shown in the inset. (a2) Zoom in into the first few ms of the transients shown in a1. (b1), (b2), and (c1), (c2); similar to a1, a2 but with somatic Ih density of 0.1 mS/cm$^2$ and 0.2 mS/cm$^2$ respectively, and increased Ih density in the apical tree as in Eq. (4). The theoretical transient is depicted in blue. Note the increase in RMSD and the discrepancy between the experimental and the theoretical transients at the first few ms in both b2 and c2. (d1), (d2) similar to c1, c2 but when $C_m$ was constrained at 0.5 μF/cm$^2$. Note the large discrepancy in the tail of the transient d1 but the excellent match between the model and the experiments in its first few ms.

DOI: 10.7554/eLife.16553.005
**Figure 2.** Nucleated-patch measurement of the specific membrane capacitance in HL2/3 neurons directly validated model prediction for the low $C_m$ value in these cells. (a) Differential Interference Contrast (DIC) image of a human L2/3 pyramidal neuron in an acute brain slice of human temporal cortex targeted for whole-cell patch clamp recording. (b) Nucleated soma patch pulled from the neuron in a. (c) Top trace: Current response of the nucleated patch shown in a to a $-5$ mV hyperpolarizing step (middle trace). Bottom trace: magnification of the green box in the top trace, showing mono-exponential fit (green line) to the capacitive current from which the total membrane capacitance was extracted. This capacitance was then divided by the surface area of the patch, providing the specific membrane capacitance (see Materials and methods). (d) Summary plot of the specific membrane capacitance from human and mouse. Triangles, $C_m$ values from the nucleated patches. Circles, $C_m$ values obtained from fitting model to experimental transients (as in Figure 1 and Figure 1—figure supplement 2); human (red, $n = 11$, see details in Table 2), mouse (blue, $n = 11$). $p$-val = 0.0021 using students t-test following the KS test for normality.

DOI: 10.7554/eLife.16553.007
**Figure 3.** Functional implications of the low $C_m$ value in human L2/3 cortical neurons for signal processing.  

(a) The neuron model shown in Figure 1a, receiving an excitatory synaptic input on distal apical dendritic spine (top trace) and on a distal basal dendritic spine (lower traces). The model cell has either $C_m = 0.45 \mu F/cm^2$ (red traces) or $C_m = 0.9 \mu F/cm^2$ (blue traces), while the other cable parameters ($R_a = 203 \Omega cm$, $R_m = 38,907 \Omega cm^2$) were kept fixed. Excitatory synapses were activated on the head of the modeled dendritic spine (inset, scale bar is 5 µm; see Materials and methods). Note the larger and faster somatic EPSP for the red case.  

(b) For the cell model shown in a, significantly smaller number of excitatory spinous synapses were required for initiation of a somatic spike when $C_m = 0.45 \mu F/cm^2$. Synapses were simultaneously activated and distributed randomly over the dendritic tree (see Materials and methods).  

(c) Top, schematics of soma and axon of the cell modeled in a, the axon had a diameter of 1 µm. Bottom, the velocity ($\theta$) of the axonal spike, measured at 1 mm from the soma, is significantly increased (by about 65%) with $C_m = 0.45 \mu F/cm^2$ (red spike); the amplitude of the propagated axonal spike is also slightly increased in this case.

DOI: 10.7554/eLife.16553.008
Figure 3—figure supplement 1. The functional implications of the low $C_m$ value for the case where the membrane time constant, $\tau_m$, is kept fixed by a corresponding change in $R_m$ for both $C_m = 0.45 \mu F/cm^2$ and $C_m = 0.9 \mu F/cm^2$. (a) As in Figure 3a, but here when $C_m = 0.9 \mu F/cm^2$ and $R_m$ is halved ($R_m = 19,453 \Omega cm^2$). This resulted in smaller differences in the dendritic delay as compared to the case shown in Figure 3a, with more strongly attenuated EPSPs. (b) As in Figure 3b, but here, due to the smaller EPSPs when $C_m = 0.9 \mu F/cm^2$, more excitatory inputs are required in order to initiate a somatic spike. (c) Conduction velocity is determined mostly by the axon’s diameter, the axial resistivity, $R_a$, and the membrane capacitance, $C_m$ (Jack et al., 1975). Consequently, halving $R_m$ had very small effect on spike propagation velocity (less than 1% change between the black traces shown here compared to the blue traces in Figure 3c).

$\theta = 0.51 \text{ m/s} ; \theta = 0.31 \text{ m/s}$
Figure 4. High resolution reconstruction of spines from HL2/3 dendrites. Top. Three examples of confocal images of basal dendritic branches from post mortem tissue. Bottom. The 3D images were segregated to spines (red) and shafts (white) that were later reconstructed in 3D. The dendritic shaft area and total spines area were calculated from the reconstructions and resulted in a F value for each branch (Equation 2). Scale bar is 5 μm.
DOI: 10.7554/eLife.16553.010