TN Journal Club: "A new cellular mechanism for coupling inputs arriving at different cortical layers" Larkum, Zhu and Sakmann. Nature vol 398, 1999

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Motivation

Some facts

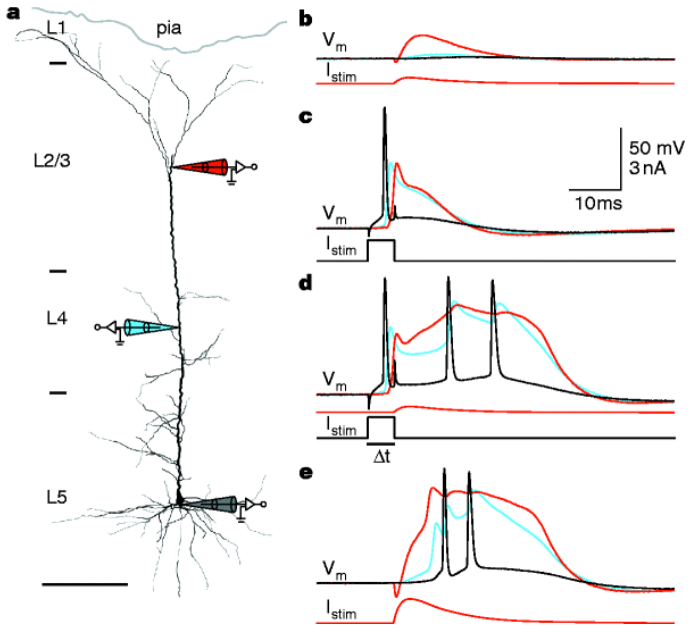
- layer V neocortical pyramidal cells are unusual:
  - their axons and dendrites extend into all layers.
  - the dendrites are long: an individual EPSP is greatly attenuated at the axon.
  - axonal and dendritic zone for initiation of action potentials (cf. Stuart et al)
  - dendritic APs are due to calcium currents and have a high threshold but can then initiate bursts of axon action potentials.

- seen: axonal sodium action potentials can back-propagate into the dendrite **GOAL**

- **To show that a back-propagating axonal action potential can initiate a calcium-dendritic action potential when it coincides with sub-threshold distal input.**

Coupling of a back-propagating action potential with a distal subthreshold current injection - proof of concept

a Setup: Soma grey, dendrites red, scale bar=200μm. **b** Distal input EPSP like current injection (lower red trace). Threshold not reached for either type of AP.**c** Threshold current injection into the soma evoked a backwards propagating AP.**d** Both inputs at once give rise to BAC firing. **e** Large dendritic input alone gives rise to BAC firing.



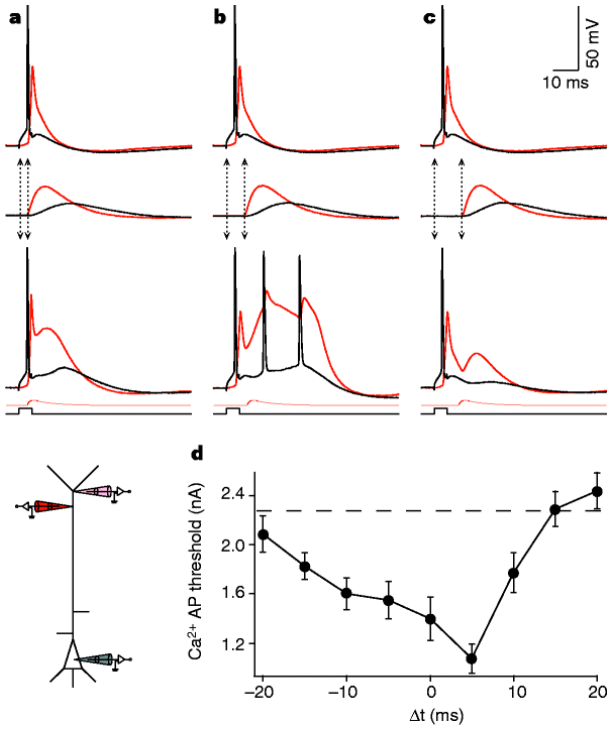
Precision of the spike timing required-milli second wide tuning

Back-propagating action potential activated Ca^{2+} spike (BAC) firing is possible (replicated in all 27 cells)

- It can cause enough de polarisation in the axonal initiation zone to initiate a burst of APs
- these (again) propagate backward (as well as forward) into the dendritic arbour

Precision of the spike timing required-milli second wide tuning

Inset: inject current at dendrite (EPSP like) and soma (AP inducing) with different time delays: **a** 3ms **b** 7ms **c** 11ms. Schematically indicated by top panels (somatic sodium AP 3ms ahead of dendritic). Bottom panels: True recordings-only **b** elicited a burst. **d** threshold as a function of time difference (solid) threshold without back-propagating AP (dashed)



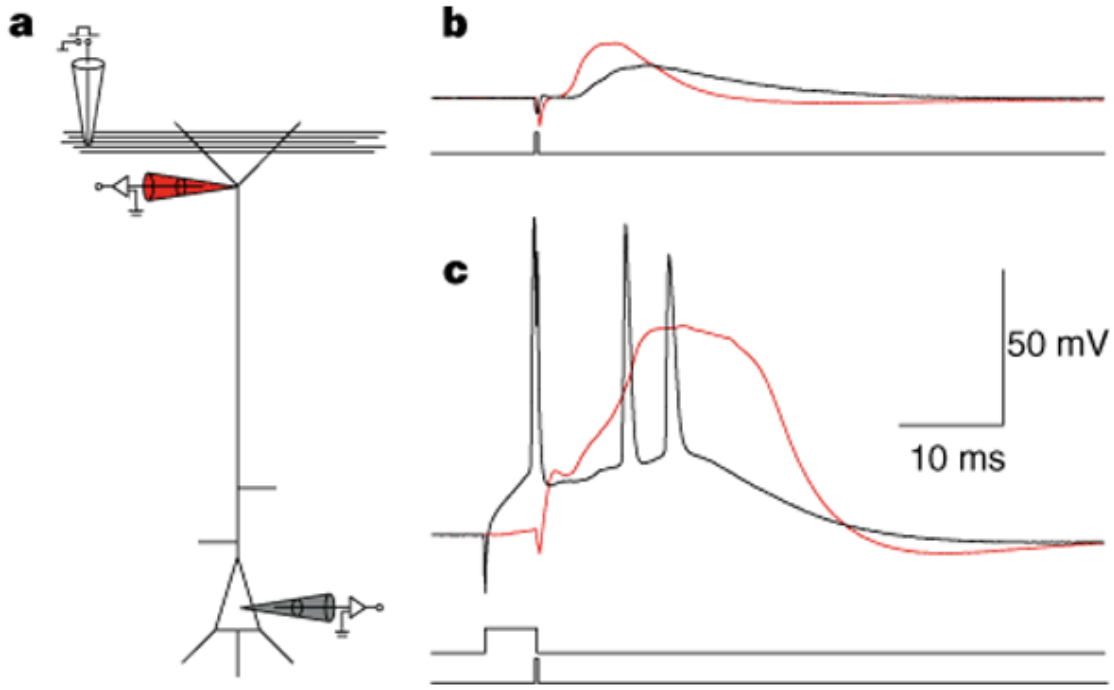
Precision of the spike timing required - milli second wide tuning

The generation of a Ca^{2+} action potential is

- greatly facilitated if the dendritic EPSP and axonal action potential are timed so that they coincide within a few ms
- (possibly) slightly depressed if the EPSP follows a back-propagating action potential 10-130ms later

Extracellularly evoked BAC-firing - can synaptic input generate BAC firing

a Setup: a bipolar electrode placed over layer 1 fibres $500\mu m$ from pyramidal cell (GABA antagonists required). **b** EPSPs at soma and dendrite (low attenuation implies synapses close to soma)**c** Preceding the extracellular stimulus with a retro-grade AP results in a Ca^{2+} AP.

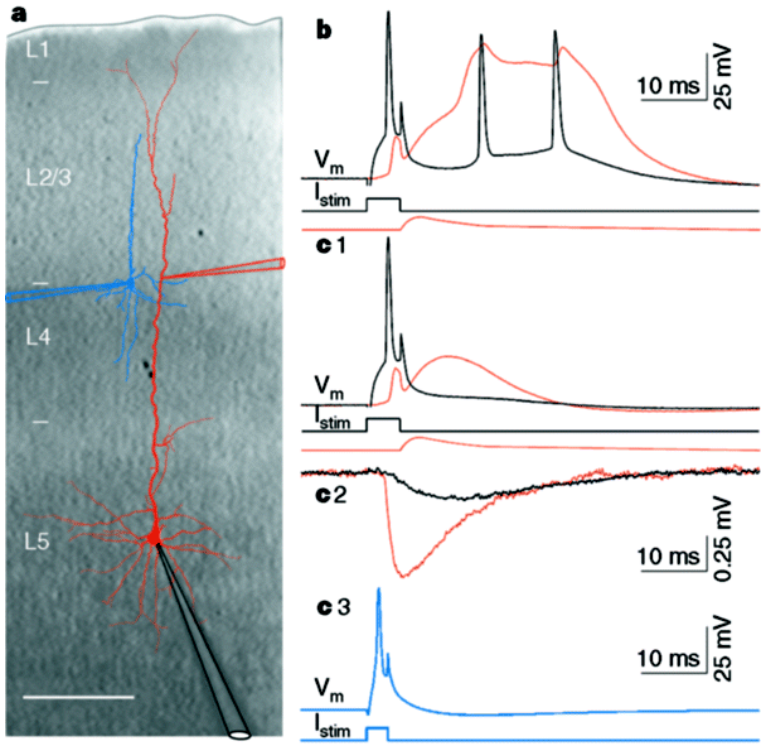


Extracellularly evoked BAC-firing - can synaptic input generate BAC firing

- Synaptic input can generate BAC firing
- GABA agonists required (increase in excitatory input)
- inhibition might selectively modulate the generation of the dendritic AP

Inhibition of BAC firing via interneurons

a Red: dendritic arbour of pyramidal neuron. Blue: inhibitory neuron connected to it. Pipettes shown symbolically.**b** As before current injected at the soma and then at the dendrites results in BAC firing **c1** 1 unitary inhibitory input blocked the bust but not the somatic AP. **c2** IPSPs **c3** AP in the presynaptic inhibitory neuron



Inhibition of BAC firing via interneurons

- unitary IPSPs can prevent the dendritic AP
- the action of inhibition was located at the dendritic initiation zone
- the inhibition is long lasting (up to approx 400ms)
- mechanism might be due to a shunt by GABA_A or GABA_B conductances
- may also involve the activation/deactivation of dendritic conductances

Conclusion

- Two regions of L5 pyramidal neurons can generate APs.
- one has a low threshold and integrates predominantly basal and apical dendrites and the other distal regions of the apical dendrite
- If threshold is reached in the axonal site, a backward propagating AP can lower the threshold at the dendritic site
- This is a new mechanism by which the main cortical output neurons can associate inputs arriving at upper and lower layers within a few ms resulting in a burst of APs.
- Inhibition acts as a 'general veto' on the busting and prevents continuous bursting