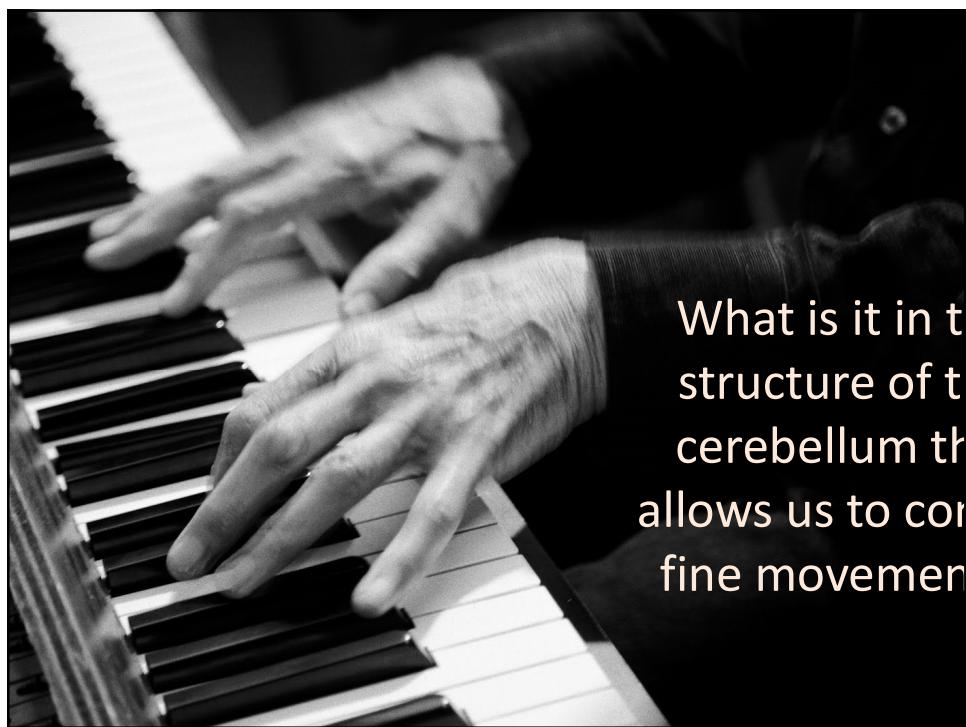




Cerebellum plays a function in posture, fine motor control, and programming.

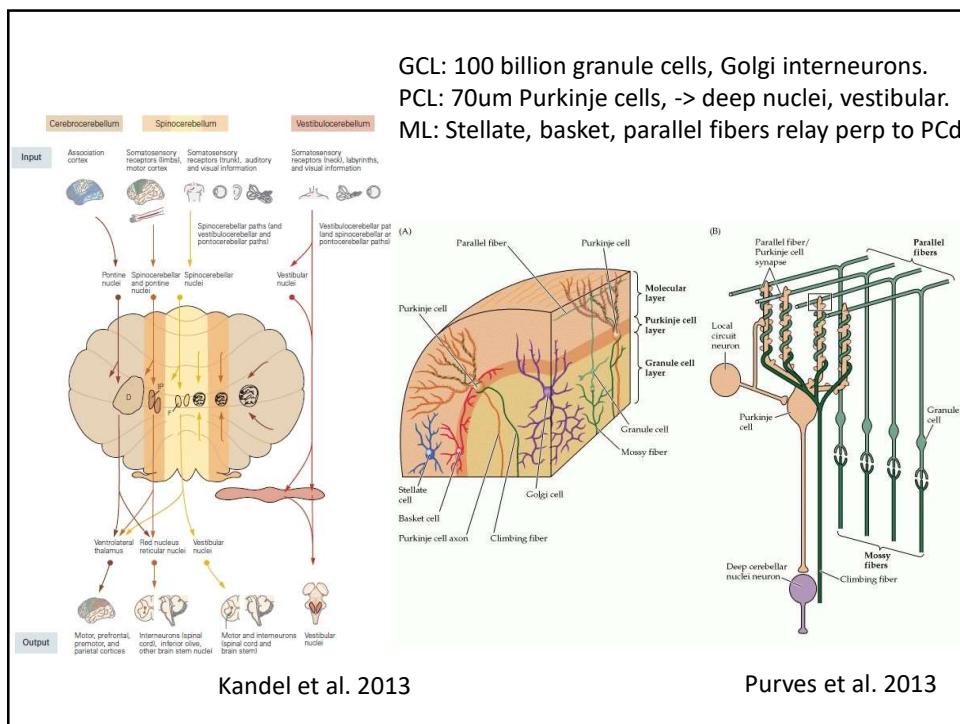
- 50% of cells in the brain.
- Cerebellar damage:
 - *Hypotonia* reduced resistance (pendulum).
 - *Astasia* inability to stand or walk (spread).
 - *Ataxia* irregular rhythmic movement (up-down).
 - *Intention tremor* antagonist muscle control error.

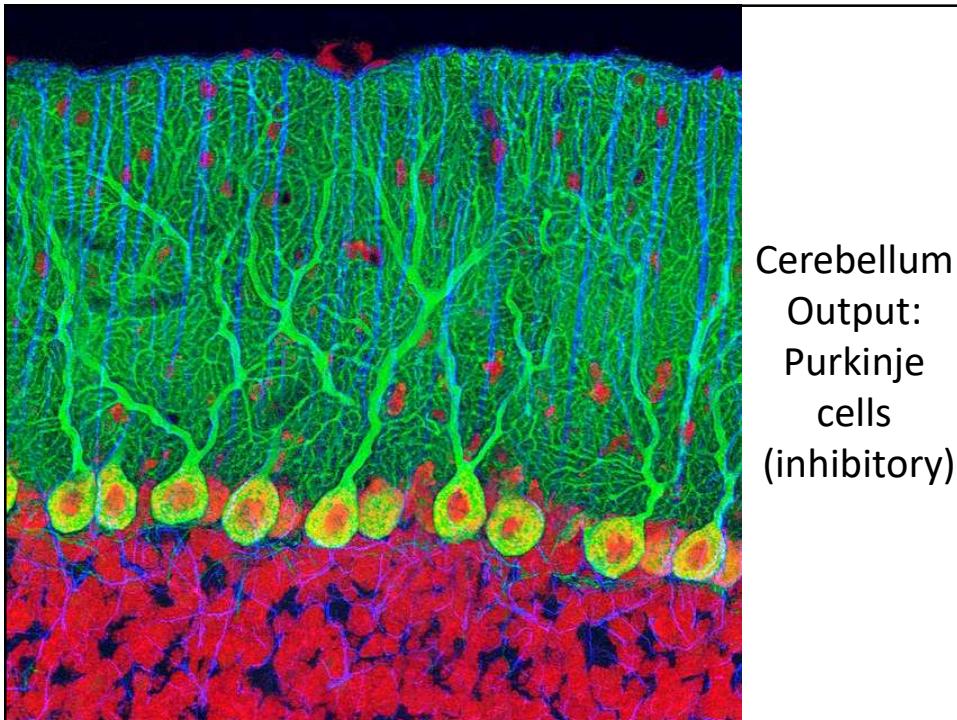
Intention tremor.



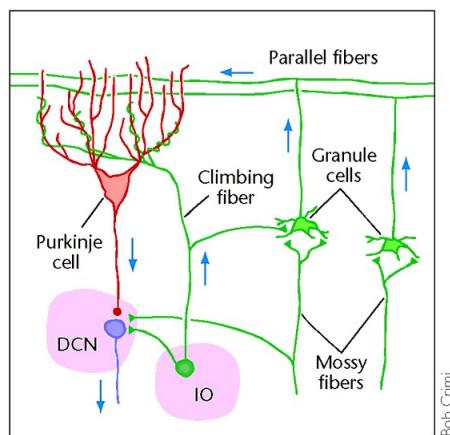
Cerebellum is compartmentalized functionally.

- Deep nuclei -> superior cerebellar peduncle.
- Vesticular input -> flocculonodular lobe -> vestibular nuclei (smooth eye track pursuit).
- Spinal chord -> vermis fastigial nucleus -> red nucleus descending tract (dorsal tract passive feedback, ventral tract active efference copy, ipsilateral, deep nuclei somatotopic).
- Cortical areas -> pons -> **lateral cerebellum** -> dentate -> motor prefrontal cortices.





Parallel fibers are axons of granule cells,
project to Purkinje cells in molecular layer



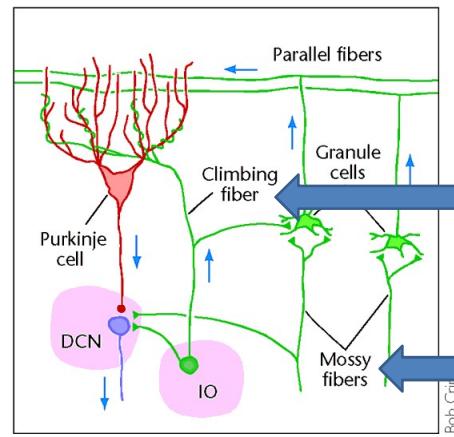
Optican, 1998

Parallel fibers are axons of granule cells, project to Purkinje cells in molecular layer

Purkinje Record
Climbing fiber



Mossy fiber → Parallel fiber



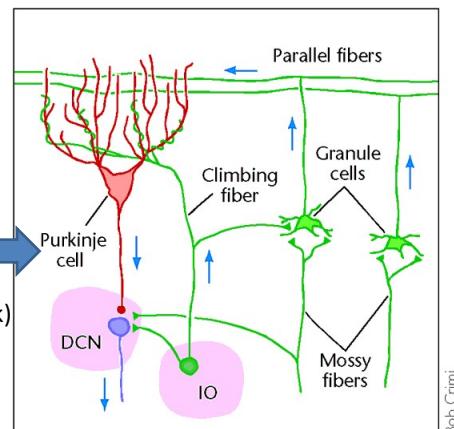
Input – Error
(one-to-one PC)
(Ca → complex)
(IO synchrony)

Input – Motor
(convergence)
(simple spikes)
(glomerulus)

Optican, 1998

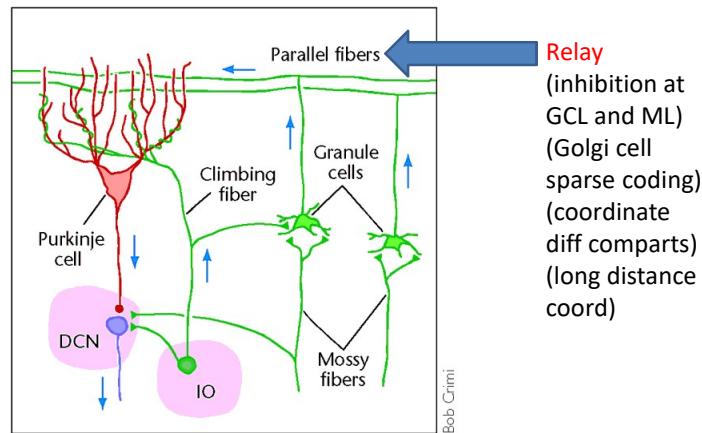
Parallel fibers are axons of granule cells, project to Purkinje cells in molecular layer

Output
(inhibit mod)
(negative feedback)
(IO gap junctions)



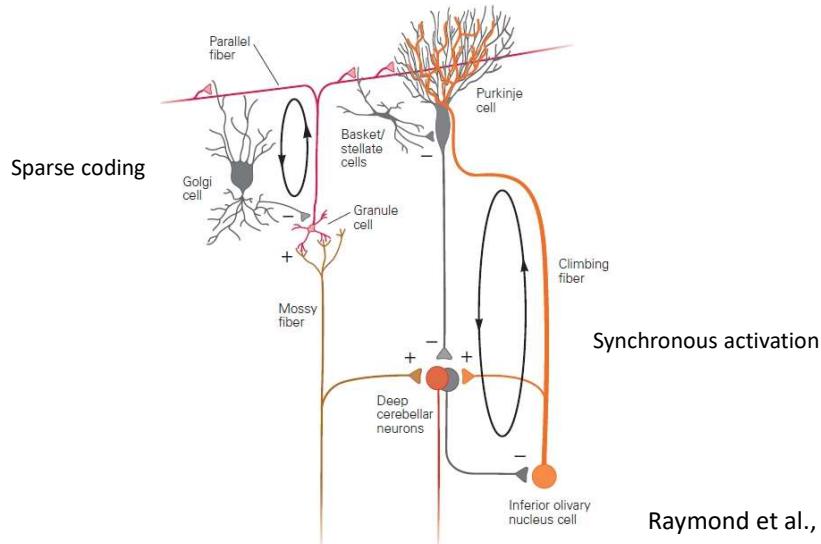
Optican, 1998

Parallel fibers are axons of granule cells,
project to Purkinje cells in molecular layer



Optican, 1998

Both excitatory and inhibitory connections converge at cerebellar cortex and deep nuclei.



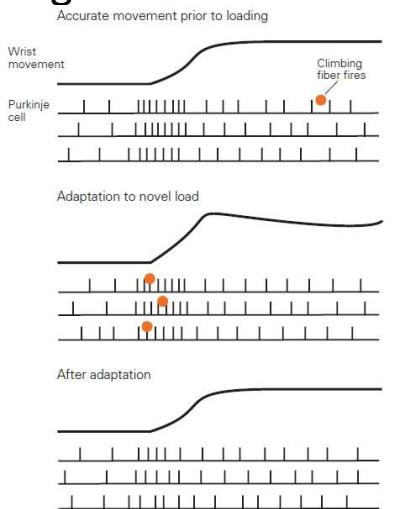
Raymond et al., 1996

Cognitive functions of cerebellum.

- Lateral lesions interfere with (subjective) serial timing (duration and speed judgments), not only irregular tapping.
- Right lateral cerebellar activation in word association vs reading aloud task.
- Greater activation when solving peg puzzle vs simply moving pegs in a board.
- Anticipatory postural adjustments require efference copy of intended movement.

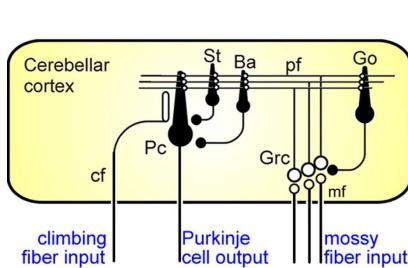
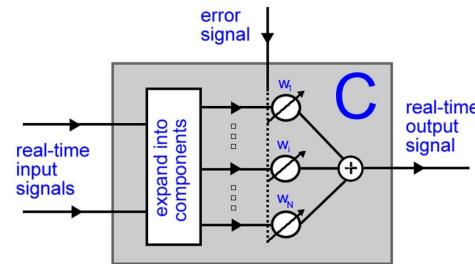
One of multiple sites of cerebellar motor learning.

- Climbing fiber (CF) induced long term depression LTD of parallel fiber to Purkinje synapses.
- Motor system as cerebellum implemented internal (inverse dynamics) model.



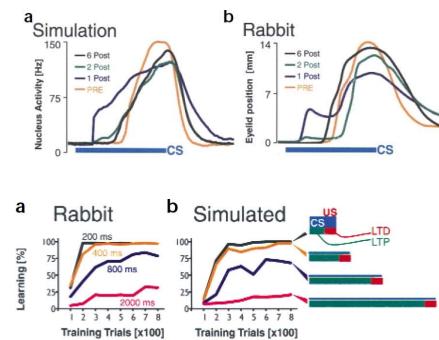
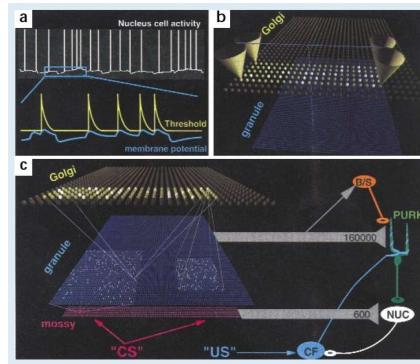
Gilbert, Thach, 1977

Cerebellar cortex can be thought of as an adaptive filter (Marr-Albus-Ito).

A Anatomy of cerebellar cortex:**B Adaptive filter (AF) model of cerebellar cortex**

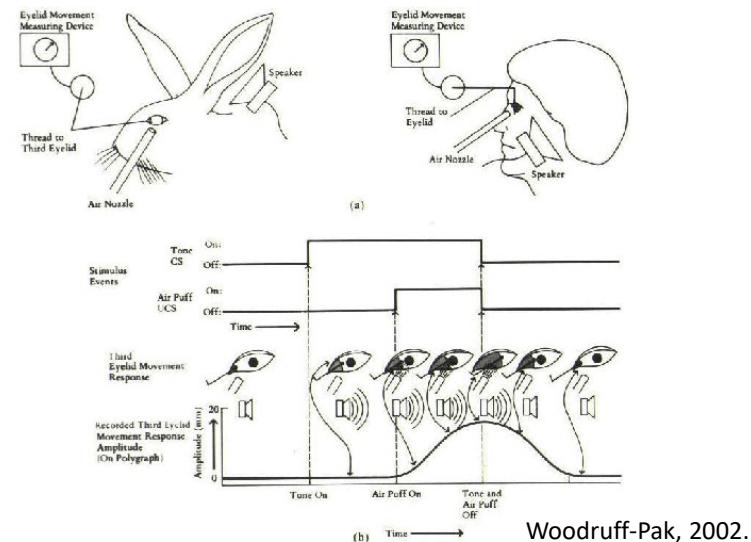
Lepora et al., 2010.

Computational simulation (10,000 grc, 20 PC) of cerebellar circuits recapitulate behavior.

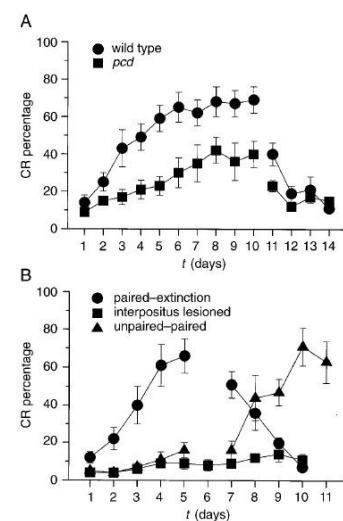
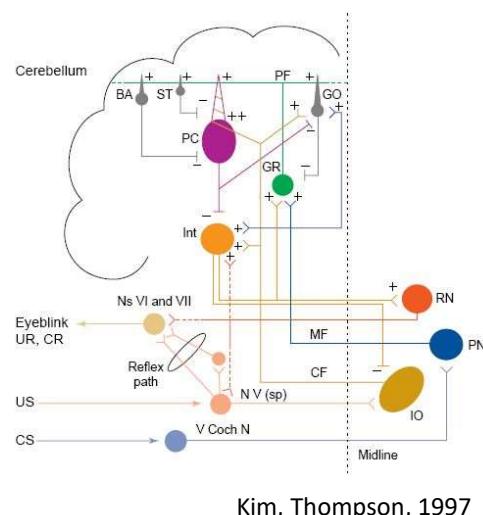


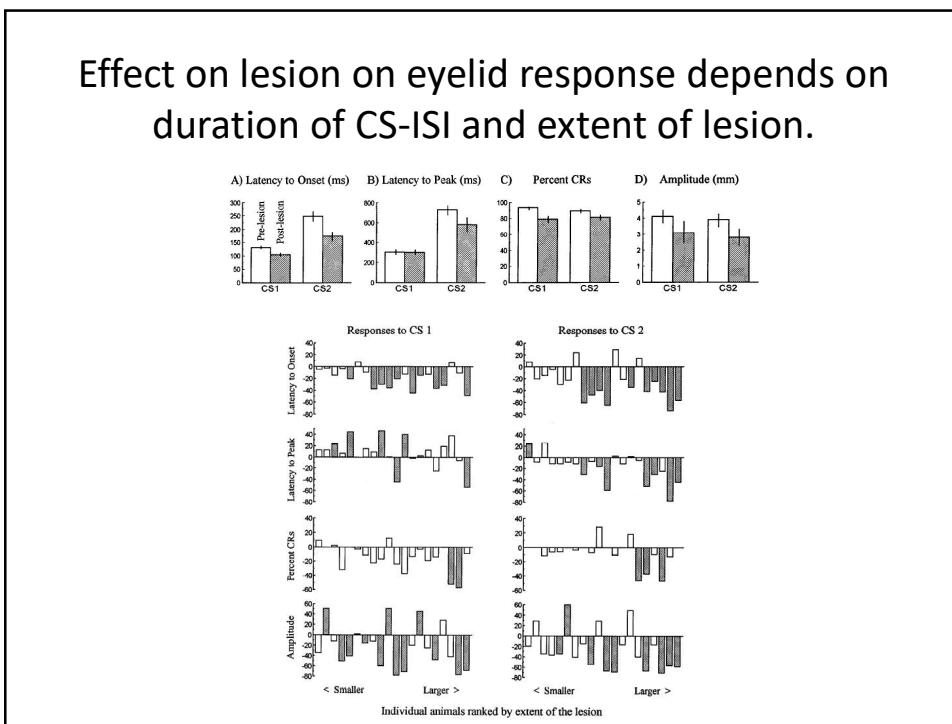
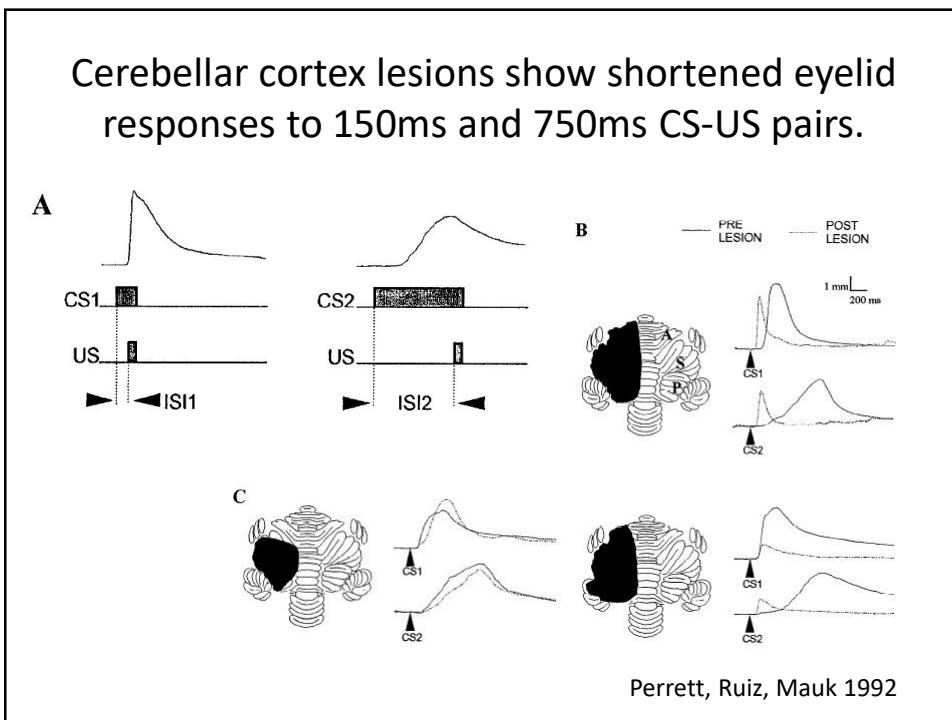
Medina, Mauk, 2000

Eyeblink conditioning repeatedly pairs tone CS to air puff US, to enable learning of blink CR.

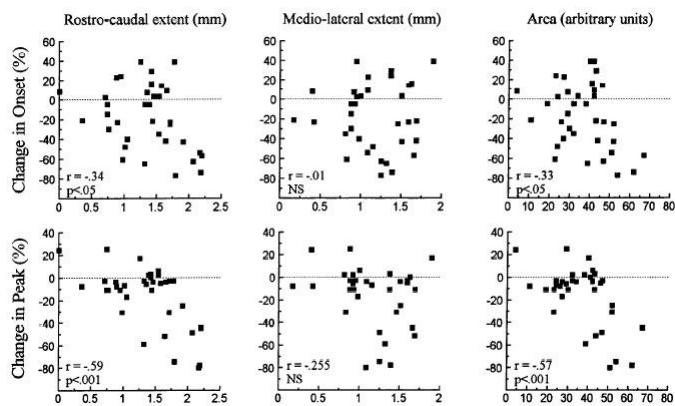


Cerebellar interpositus nuclei are necessary for learning of classical eyeblink conditioning.

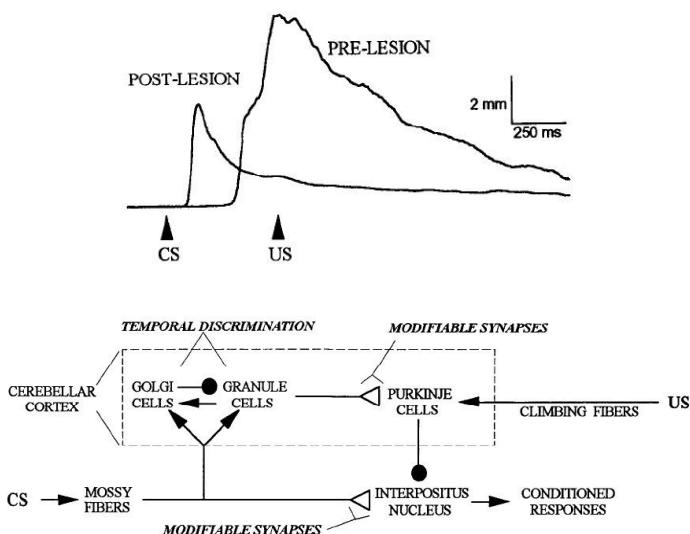




Lesion effects depend not on ML, but on RC extent of interpositus projecting parasagittal zone.



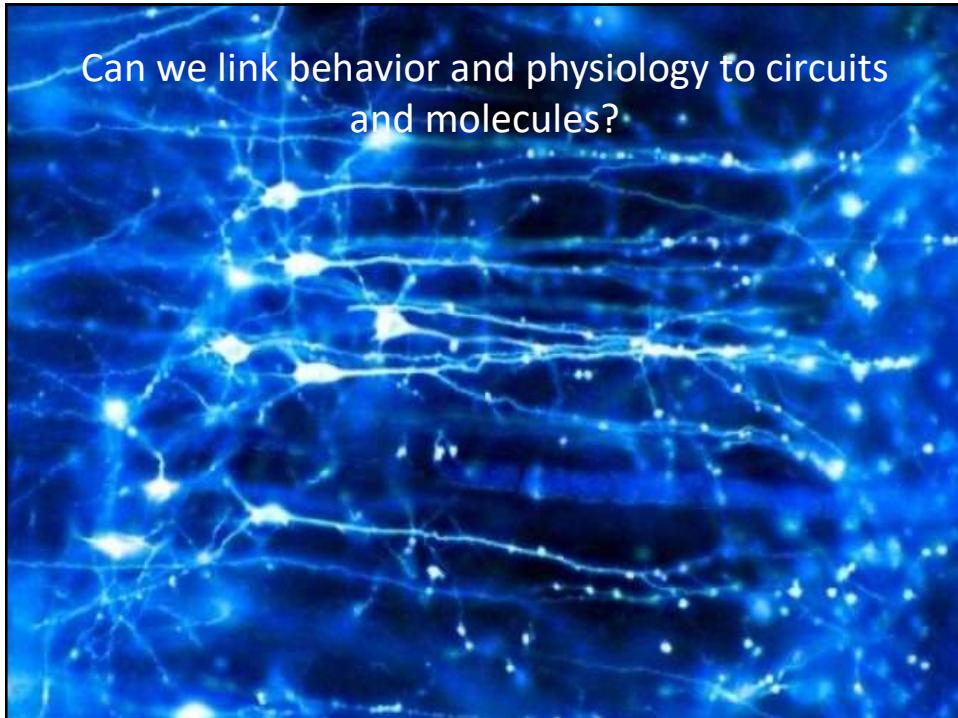
Single CS-ISI learning deficits are inconsistent with disruption of auditory discrimination.



Summary of cerebellar action.

- The cerebellum is necessary for everyday movements like saccades (vermis) & pointing.
- Purkinje cells and deep nuclei cells fire during voluntary movements in feedforward control.
- Cerebellum has an internal model of limb structure that anticipates forces in movement.
- Altering strength of particular parallel fiber to Purkinje cell synapses reduces motor error, and may allow for accurate learning (piano).

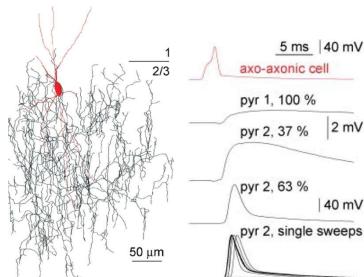
Can we link behavior and physiology to circuits and molecules?



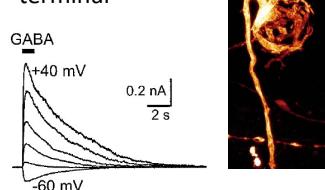
Evidence for depolarizing GABA action in mature neurons

Choi et al. 2008
Suprachiasmatic nucleus

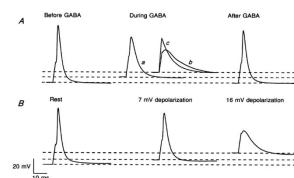
Szabadics et al. 2006
Axo-axonic cells cerebral cortex



Turecek and Trussell 2002
Calyx of Held terminal



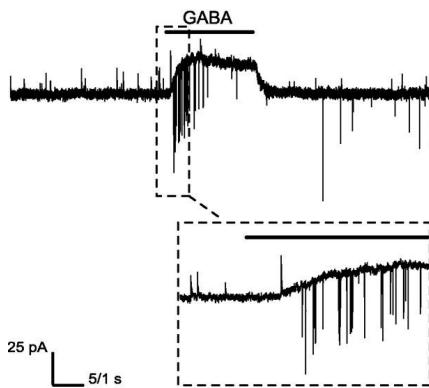
Zhang and Jackson 1995
Posterior pituitary



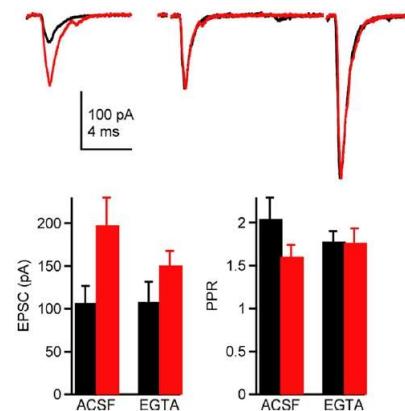
Evidence for excitatory GABA action in mature neurons

- Turecek & Trussell 2002, excitatory glycine and GABA currents at calyx of Held MNTB.
- Szabadics et al. 2006, excitatory action of GABA released by axo-axonic cortical cells, absence of KCC2 transporter in axons.
- Stell et al. 2007, bursts of EPSCs recorded in Purkinje cells and molecular layer interneurons evoked by GABA_A agonist.

GABA_AR activation excites presynaptic input to Purkinje cells and MLIs

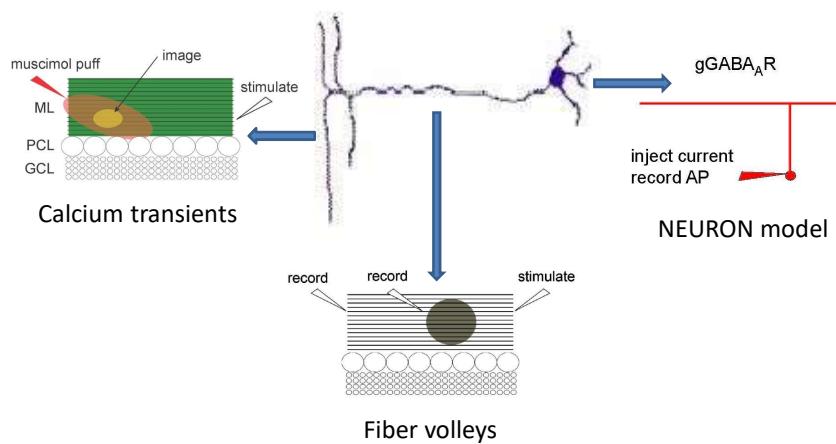


Stell, Marty 2007



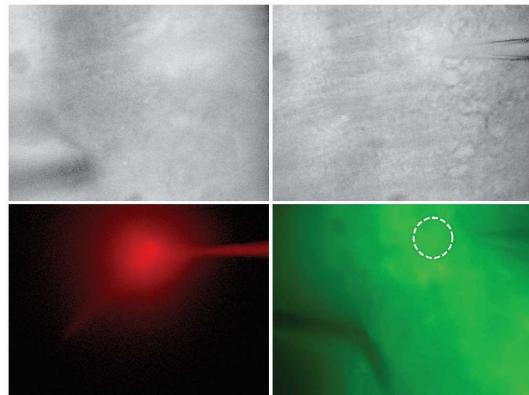
Pugh, Jahr 2011

Where do we come from? Where are we going?

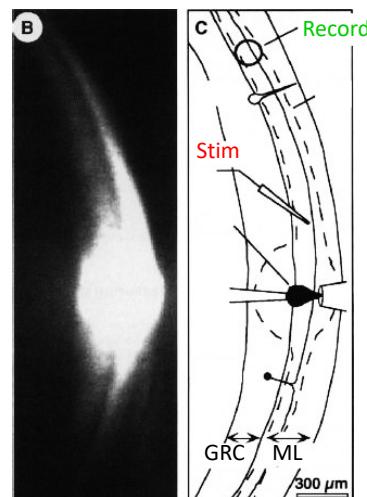


Local perfusion of calcium indicator limited to molecular layer and parallel fibers

Oregon Green BAPTA-1 AM → transverse slice

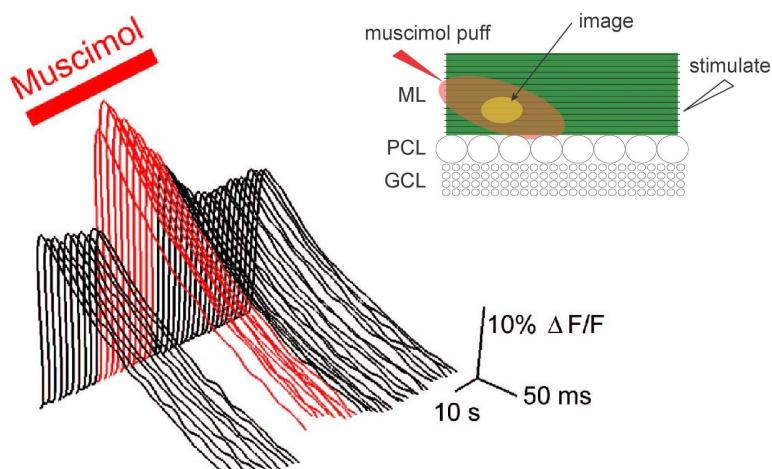


Luo, Dellal, Otis, 2012

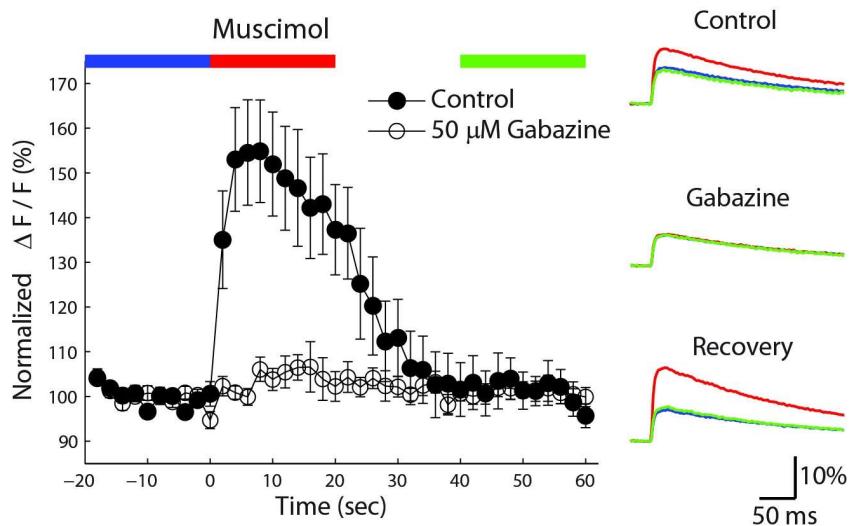


Regehr and Atluri, 1997

Presynaptic calcium transients are potentiated by GABA_AR agonist muscimol



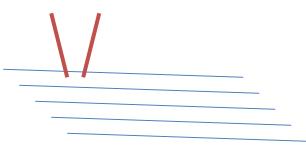
Presynaptic calcium transients are potentiated by GABA_AR agonist muscimol



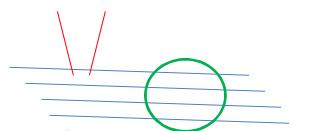
Is GABA-mediated excitation working at single parallel fibers? Or recruiting fibers?



Low Stimulation



High Stimulation

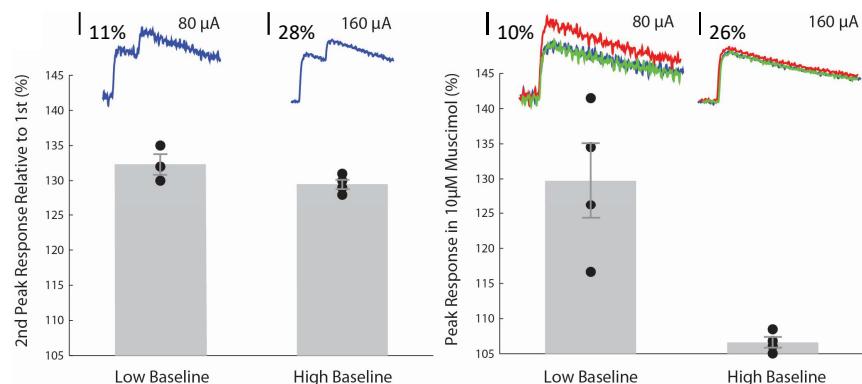


Low Stim and
GABA
activation

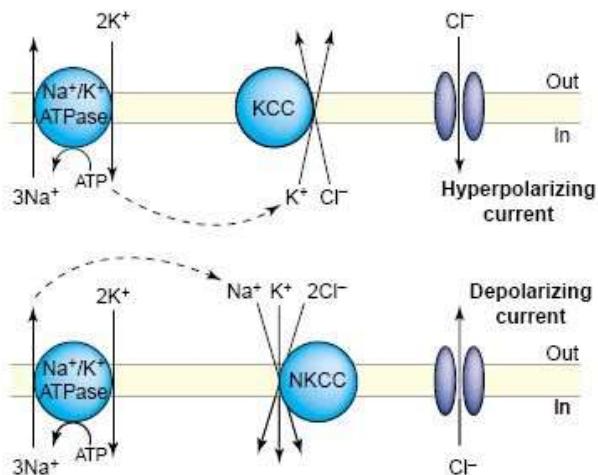


High Stim and
GABA
activation

GABA_AR activation brings additional fibers closer to threshold for spike generation

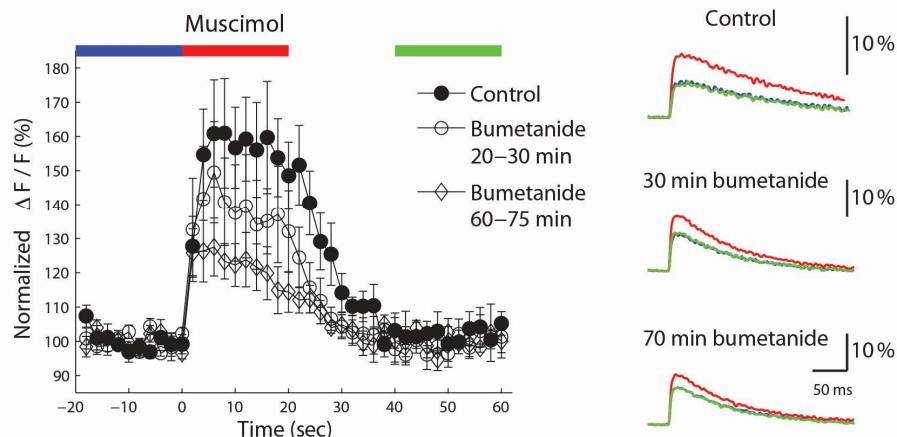


NKCC1 transporter is the chloride accumulating transporter

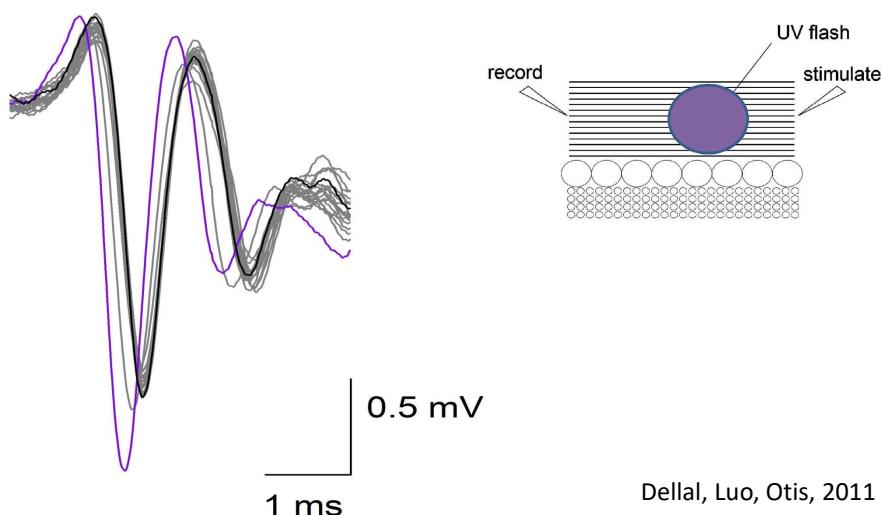


Payne et al. 2003

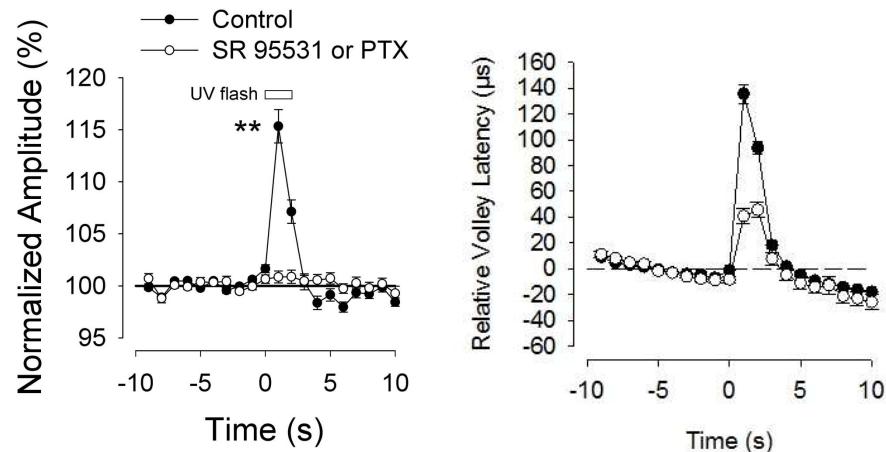
Muscimol-induced increase in calcium transient depends on the chloride gradient



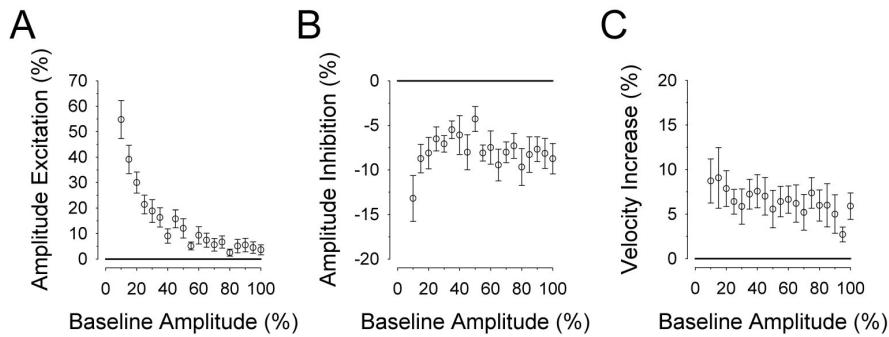
Compound action potential (fiber volley) amplitude is increased by uncaging GABA



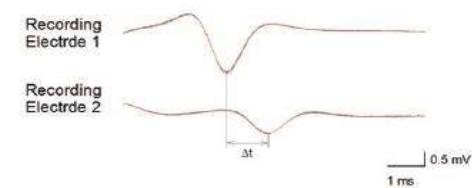
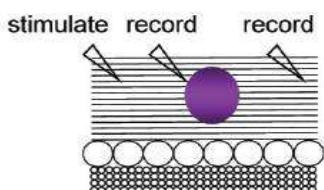
GABA_AR activation increases fiber volley amplitude and shortens latency



Stimulation variation on fiber volley shows recruitment of axons by GABA

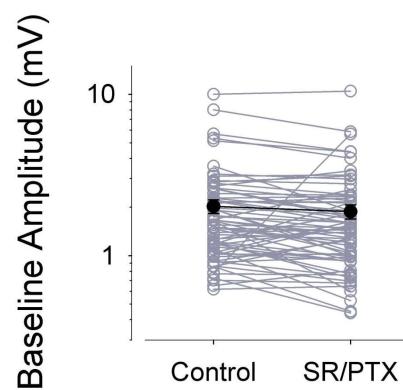
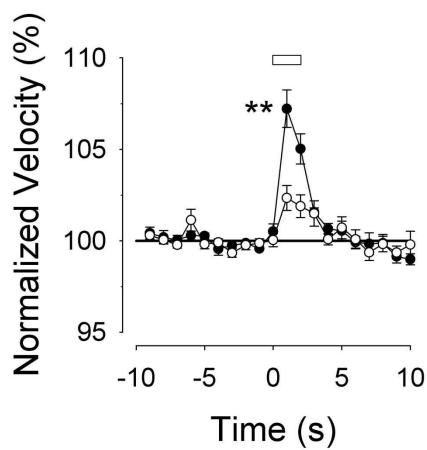


Conduction velocity measurements using fiber volleys in a transverse slice

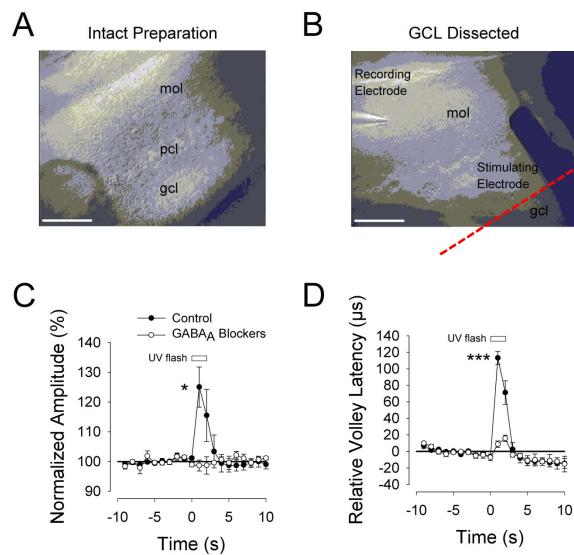


$$\text{Conduction Velocity} = (\text{Distance between recording electrodes}) / \Delta t$$

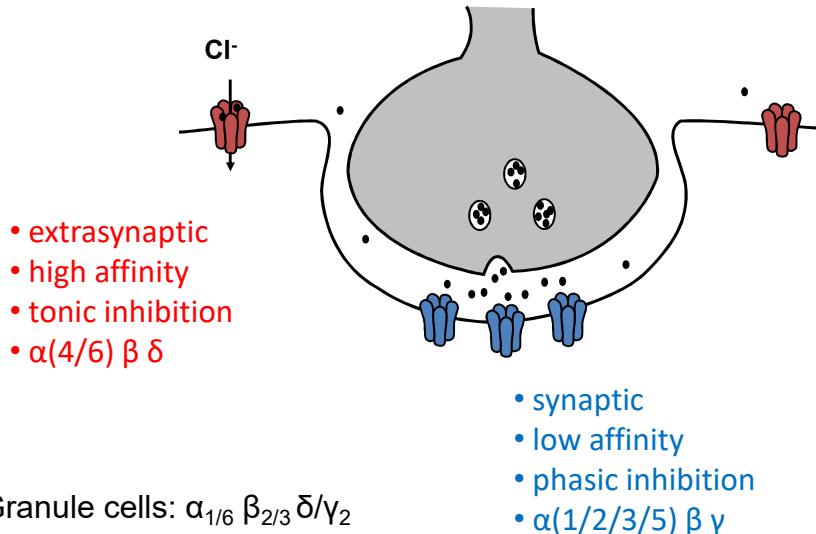
GABA_AR activation increases fiber volley conduction velocity



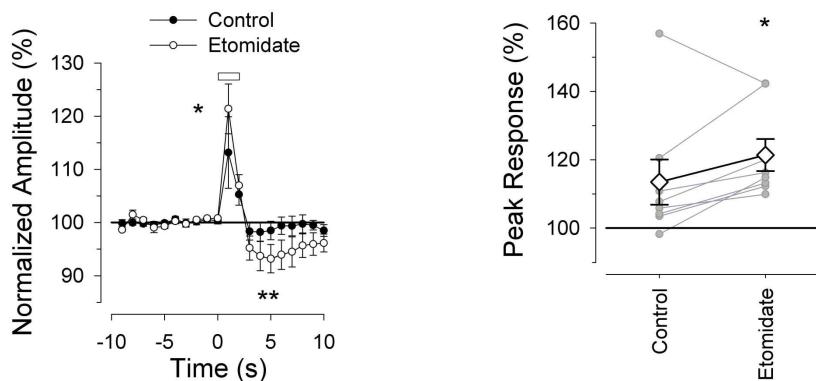
GABA-mediated excitation of parallel fibers is independent of granule cell



GABA_A receptors can be categorized into two major types

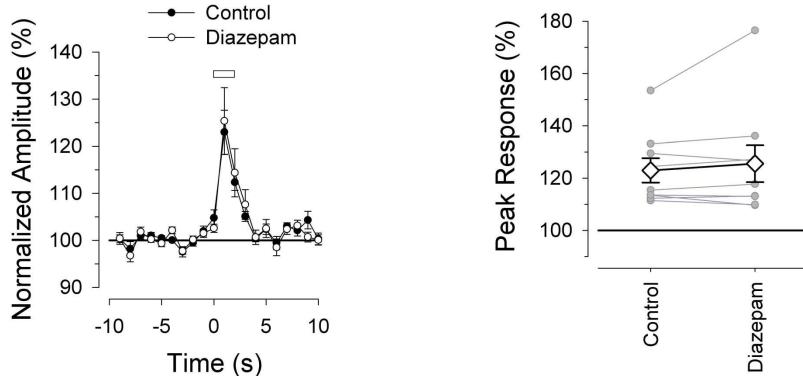


GABA_AR-mediated increase in excitability is sensitive to etomidate



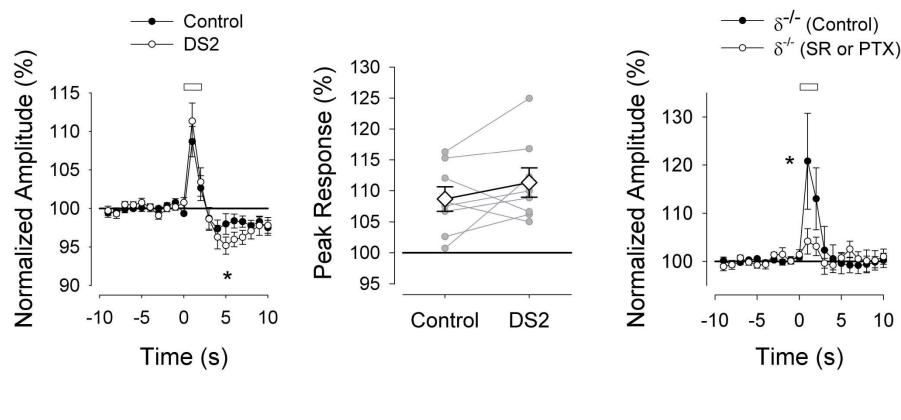
Sensitivity: β_2 or β_3 , independent of δ or γ

GABA_AR-mediated increase in excitability is unaffected by diazepam



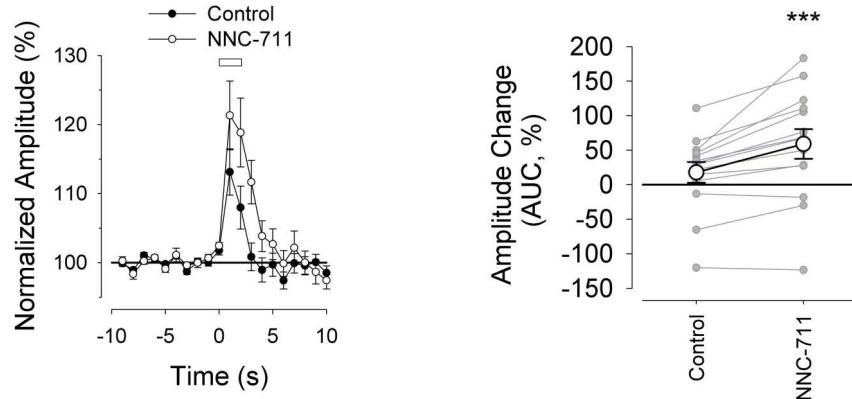
Sensitivity: lacking α_4 and α_6 , but contains γ

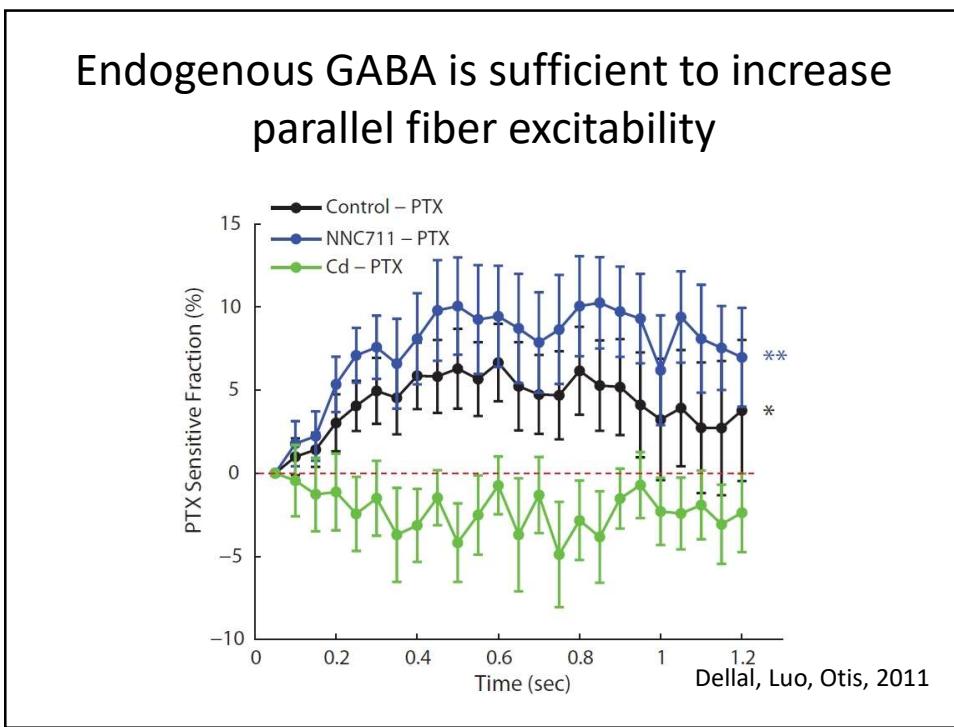
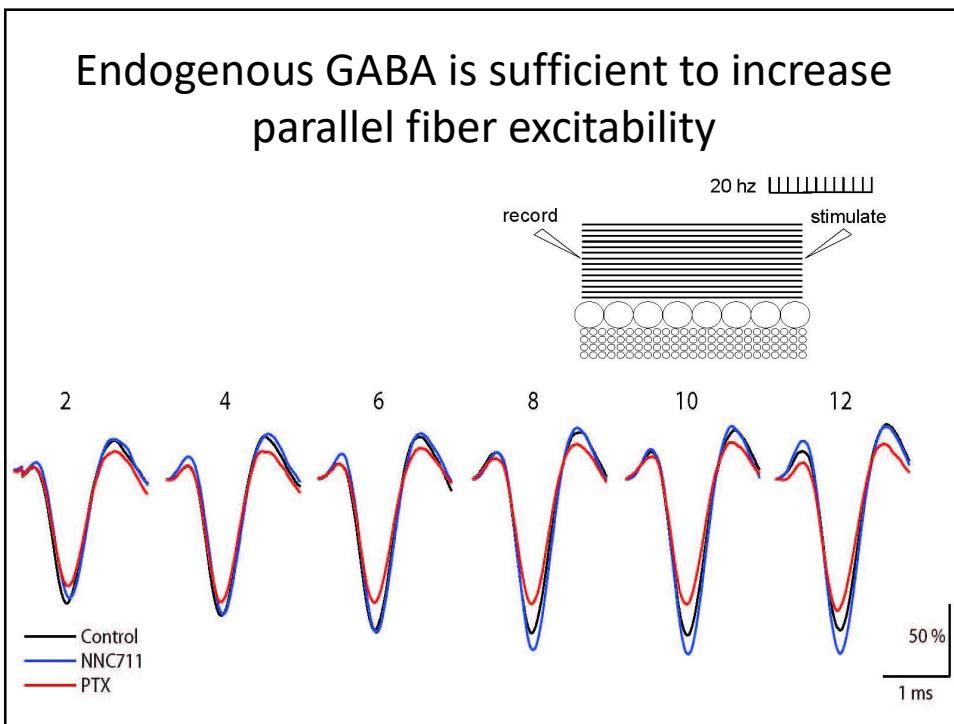
The δ subunit is not required for GABA_AR-mediated increase in excitability



Sensitivity: δ

Blocking GABA reuptake prolongs parallel fiber excitation





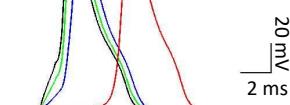
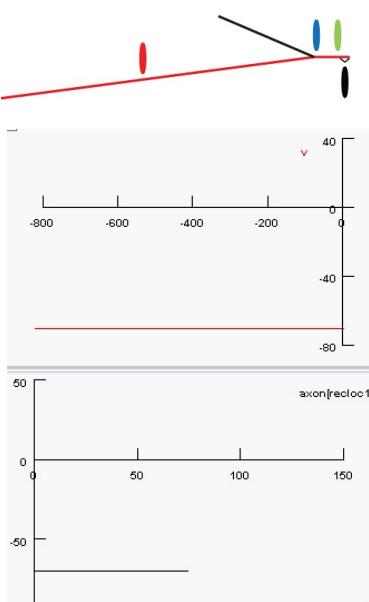
Granule cell model.

5.8 μm diameter granule cell, 0.3 μm diameter axon, 70 μm ascending branch, 0.5 mm fiber after T-junction segment simulated.

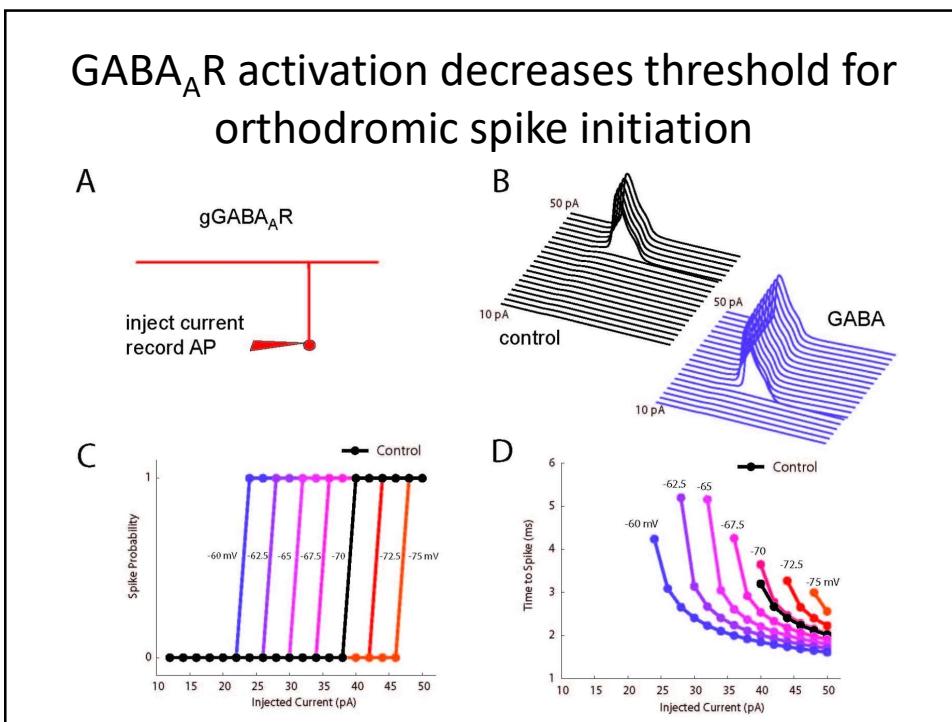
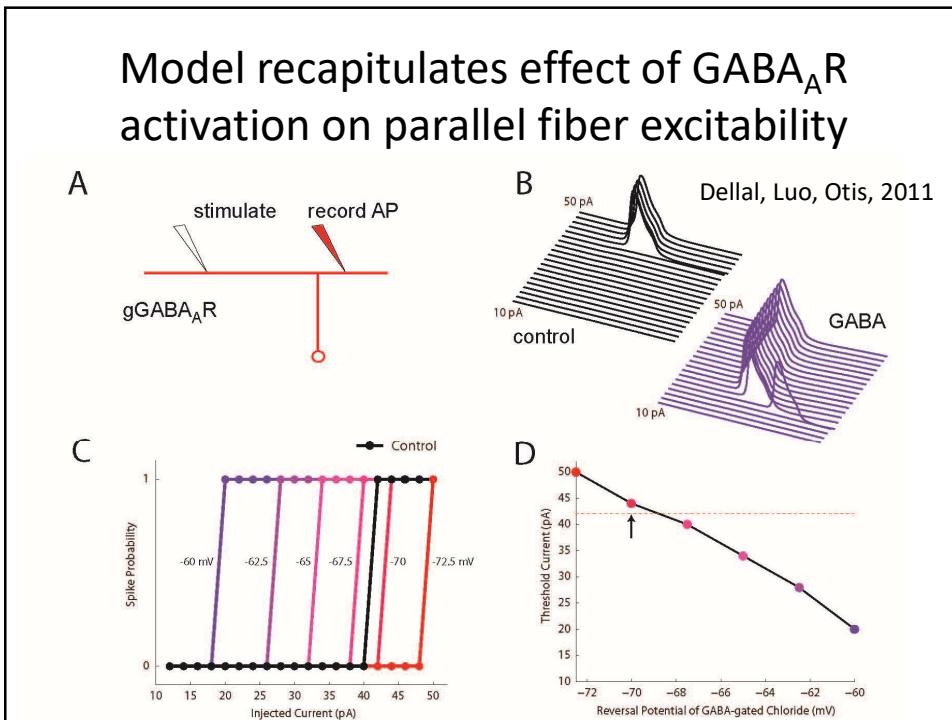
Hodgkin-Huxley dynamics (from Walther), K-A channels, K-mixed-ion leak, chloride leak to maintain $E_{\text{rev}}-\text{Cl}$, GABARs high conductance chloride leak.

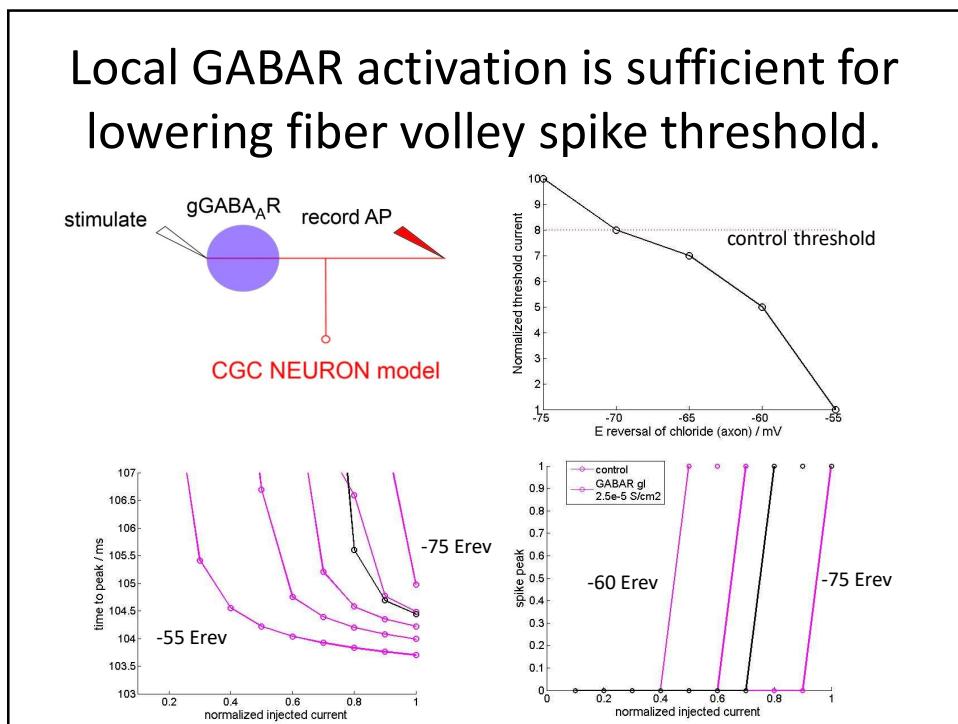
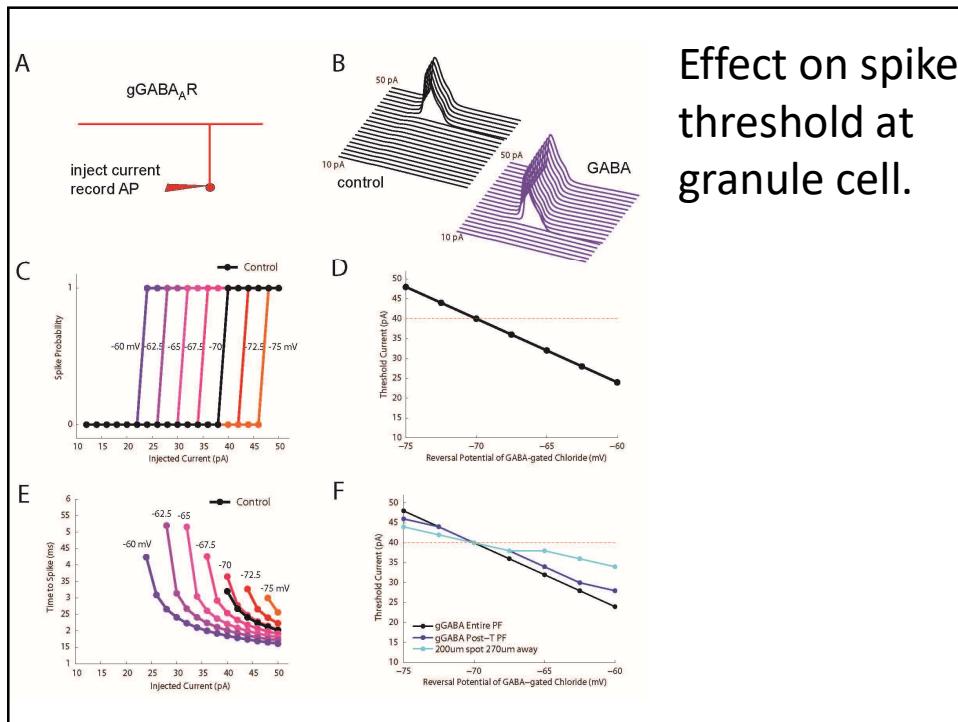
At 303 K, $[\text{Cl}]_{\text{out}} = 130 \text{ mM}$, a change in reversal potential for $[\text{Cl}]$ of 5 mV results from $[\text{Cl}]$ in rise from 10.8 to 13 mM (10 mV \rightarrow $[\text{Cl}]_{\text{in}} = 15.8 \text{ mM}$).

Granule cell compartmental model

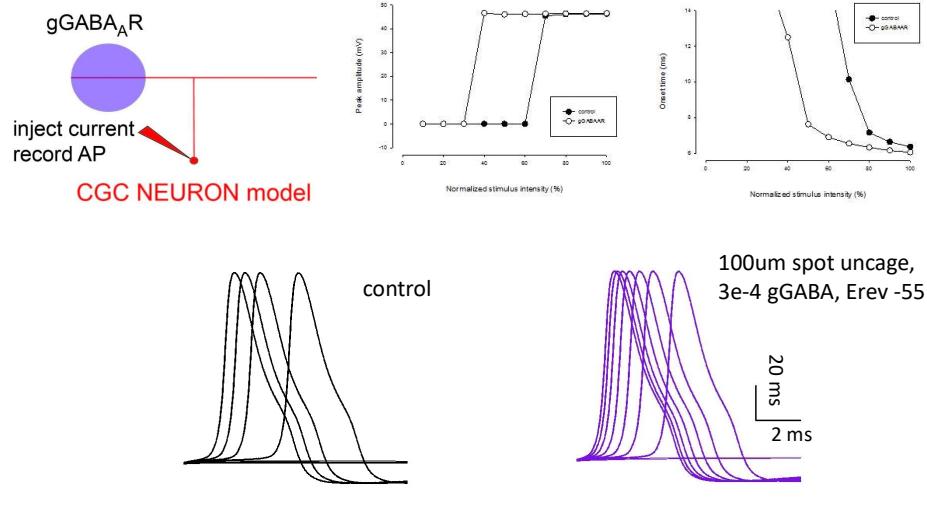


5.8 μm diameter granule cell
0.3 μm diameter axon
Mammalian Hodgkin-Huxley (Wang 2003)
10 mV E_{rev} change from 5 mM $[\text{Cl}]$ rise

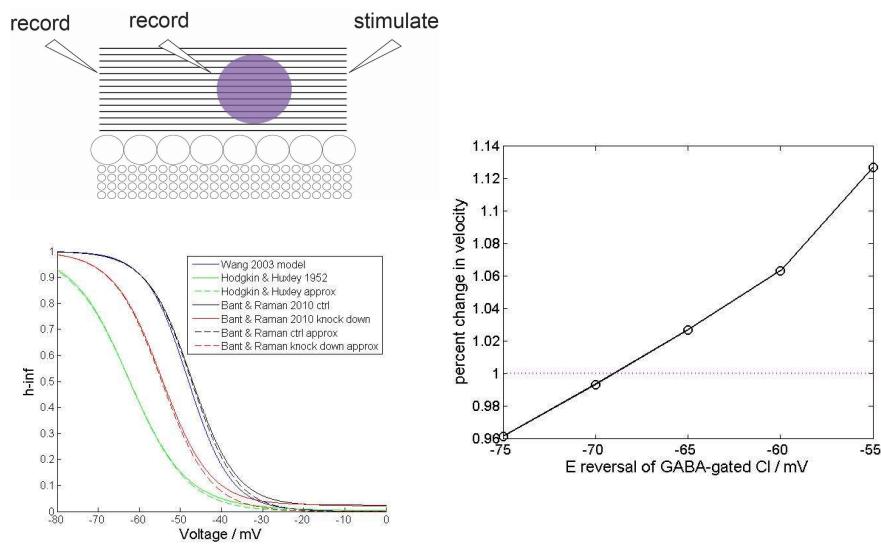




Local GABA_AR activation in molecular layer decreases GRC AP threshold.

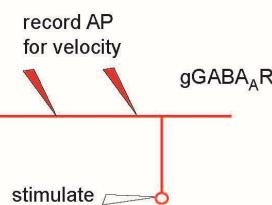


Conduction velocity is increased by local molecular layer GABA_AR activation.

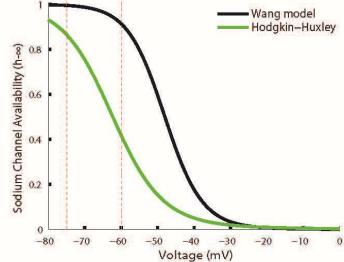


GABA effect on conduction velocity depends on sodium channel inactivation

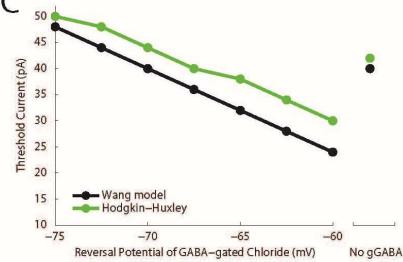
A



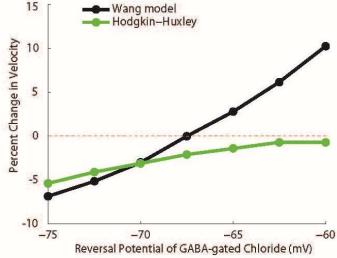
B



C

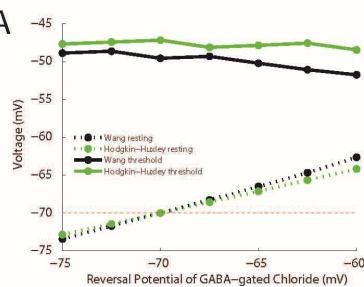


D

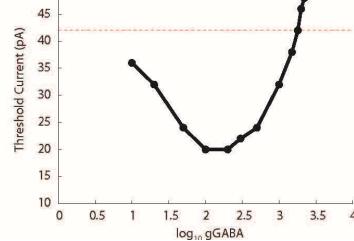


GABA_AR activation brings axon closer to threshold for spiking at low conductances.

A

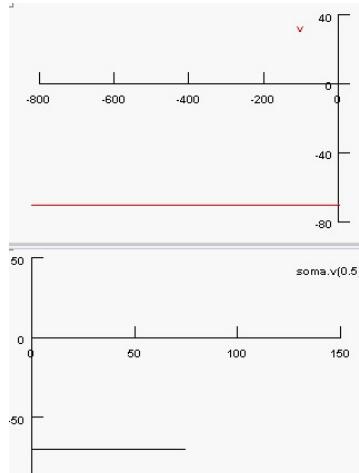


B

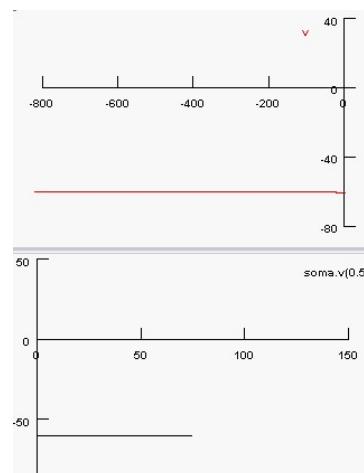


Spike failures (e.g. near the T) can occur near 100x the tonic conductance.

260x conductance, Erev -70mV.



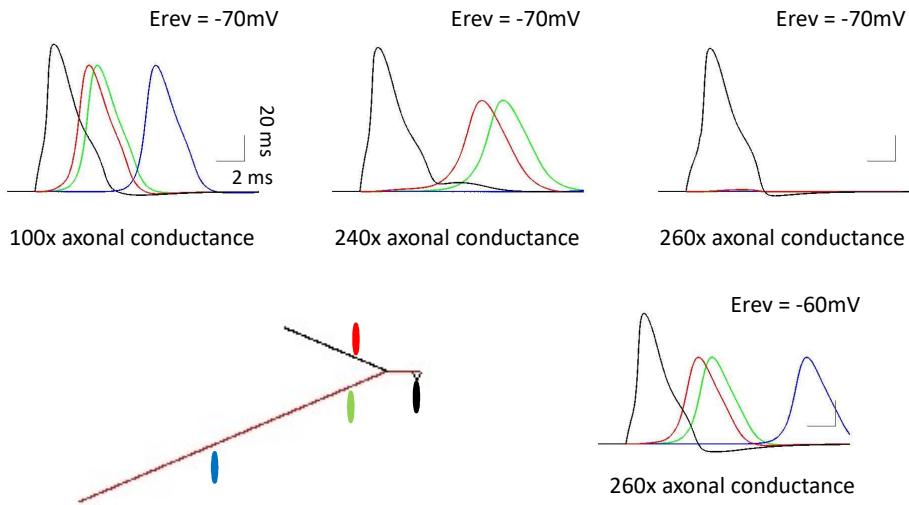
260x conductance, Erev -60mV.



Can GABA excitation relieve spike failures at T-junction? My cat says yes.



Spike failures (e.g. near the T) can occur near 100x the tonic conductance.



What it means to be fast? 10% increase from $200 \mu\text{m}/\text{ms} \Rightarrow 2 \text{ ms}$



What it means to be fast? Version 2.0 Fast Times



Acknowledgments (UCLA).

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- **Alex Reeves**
- **Vivy Tran**
- **MOM!**
- **Felix Schweizer**
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Ycu

Baozhen
Tan
Jenny
Koivumaa

Jake

Ormond

Touqueer

Ahmed



Ashwani
Kumar

Jennifer
Cutler

Surajit
Sahu

Questions?



Effect of GABAR on velocity depends on sodium channel inactivation.

J. Physiol. (1952) 117, 500–544

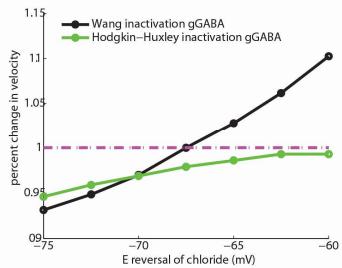
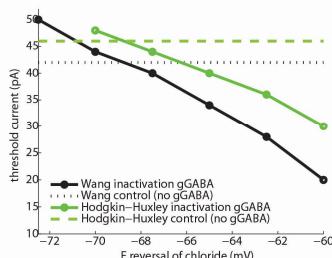
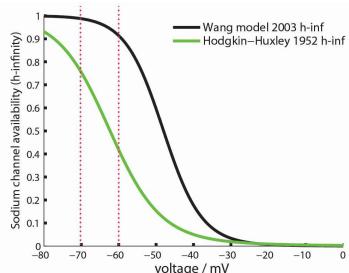
A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

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This article concludes a series of papers concerned with the flow of electric current through the surface membrane of a giant nerve fibre (Hodgkin & Huxley & Katz, 1952; Hodgkin & Huxley, 1952a-c). Its general object is to discuss the results of the preceding papers (Part I), to put them into



GABAR activation in ML decreases GRC AP threshold and initiation time.

