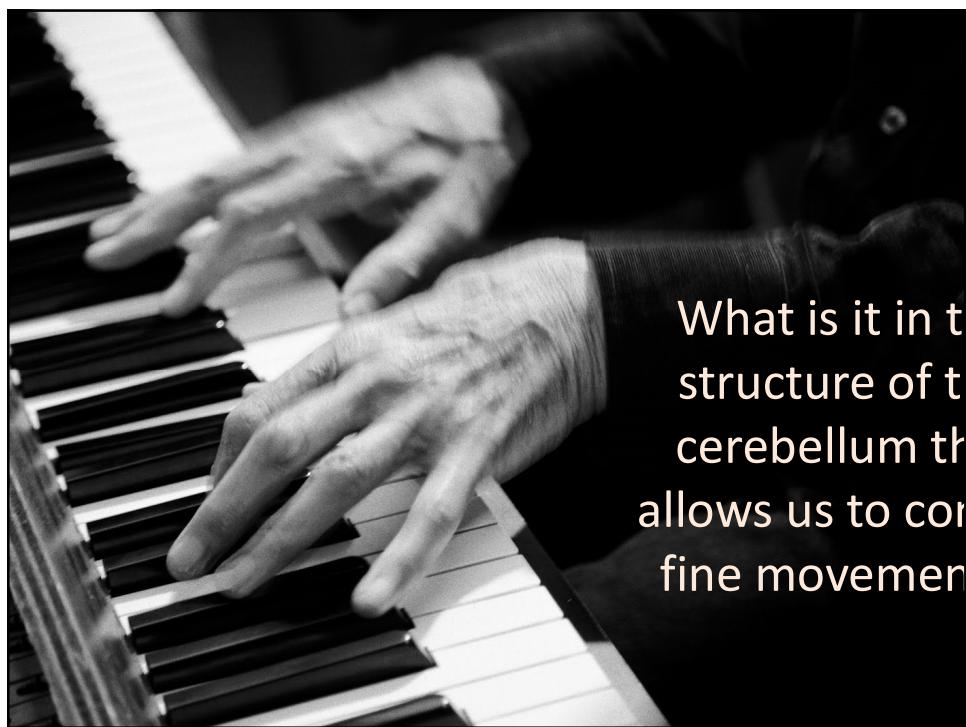




Cerebellum plays a function in posture, fine motor control, and programming.

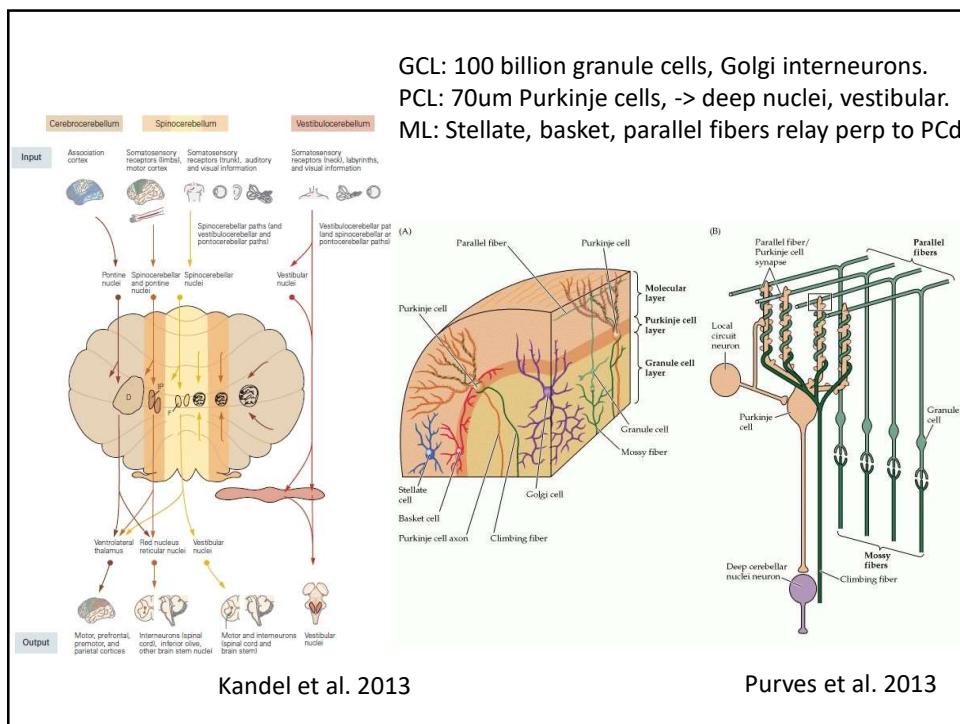
- 50% of cells in the brain.
- Cerebellar damage:
  - *Hypotonia* reduced resistance (pendulum).
  - *Astasia* inability to stand or walk (spread).
  - *Ataxia* irregular rhythmic movement (up-down).
  - *Intention tremor* antagonist muscle control error.

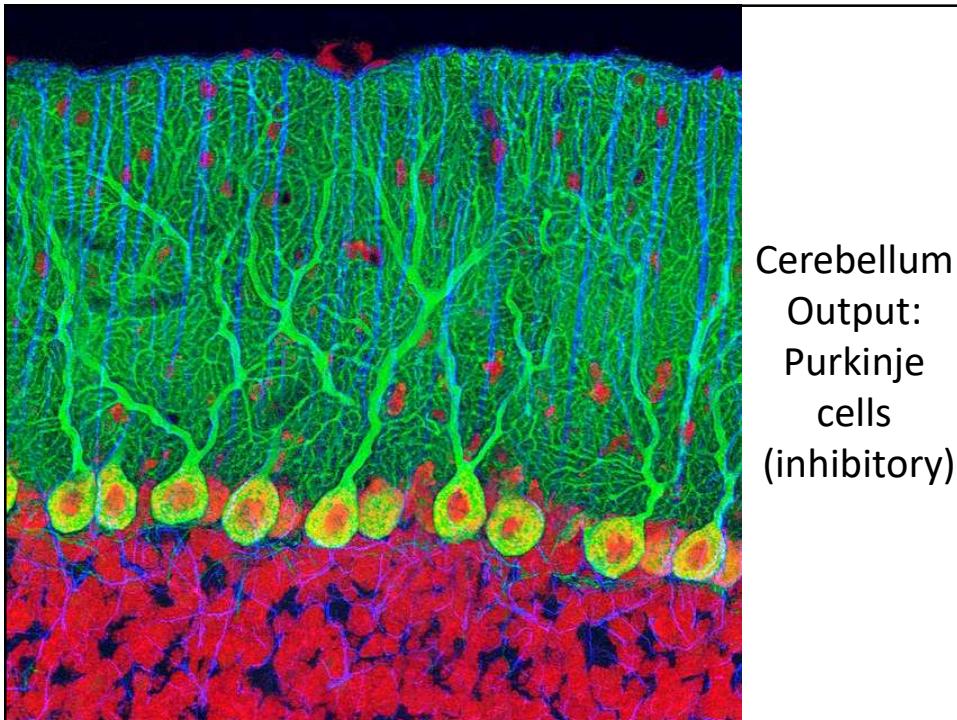
Intention tremor.



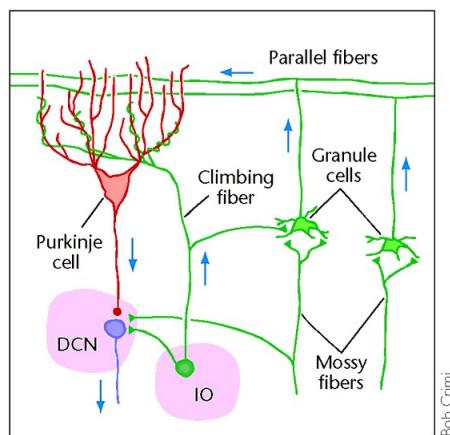
## Cerebellum is compartmentalized functionally.

- 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



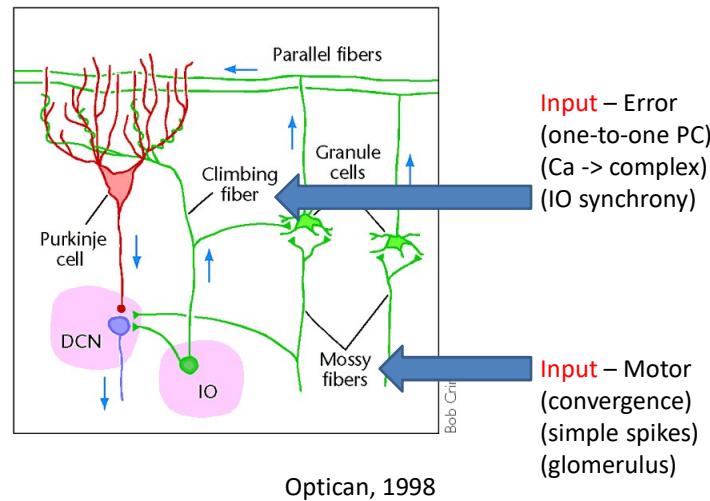
Optican, 1998

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

Purkinje Record  
Climbing fiber



Mossy fiber → Parallel fiber



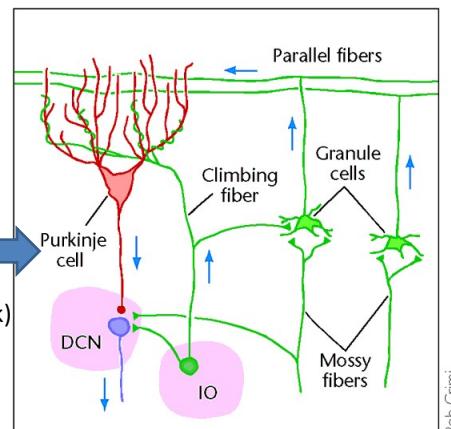
**Input** – Error  
(one-to-one PC)  
(Ca → complex)  
(IO synchrony)

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

Optican, 1998

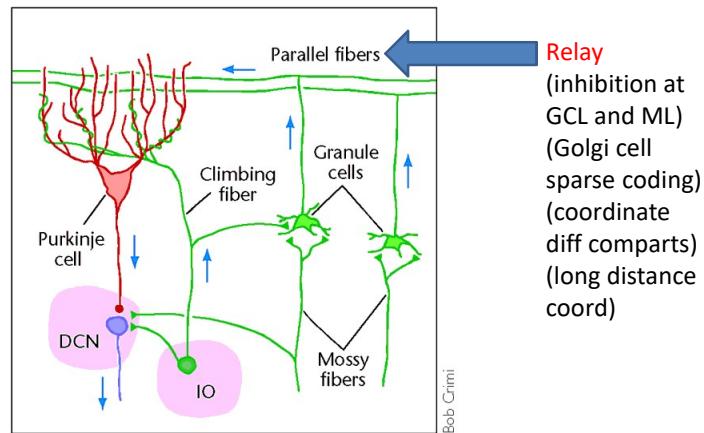
## Parallel fibers are axons of granule cells, project to Purkinje cells in molecular layer

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



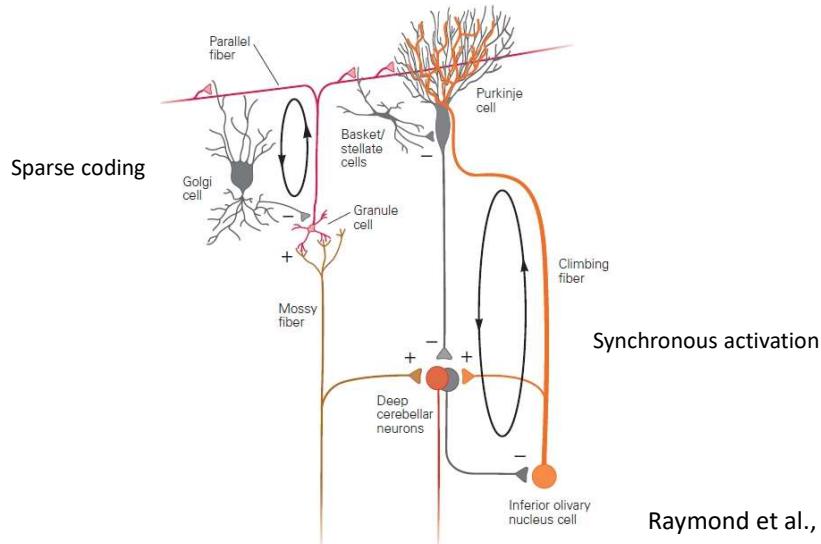
Optican, 1998

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.



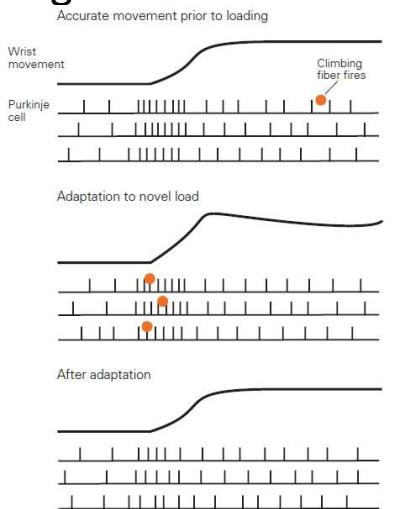
Raymond et al., 1996

## 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.

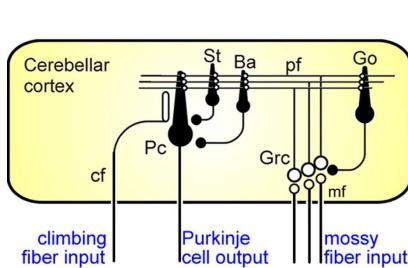
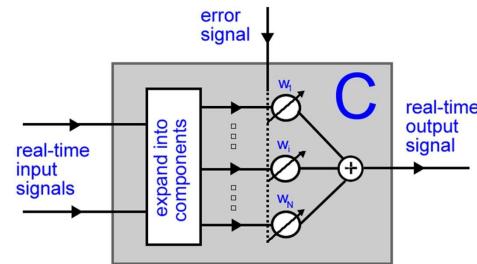
## One of multiple sites of cerebellar motor learning.

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



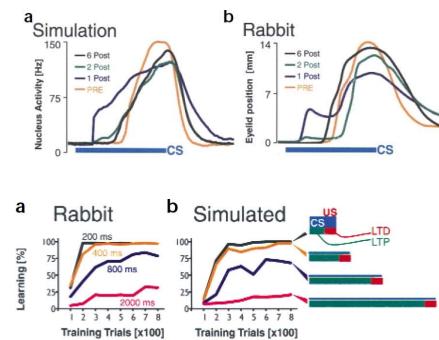
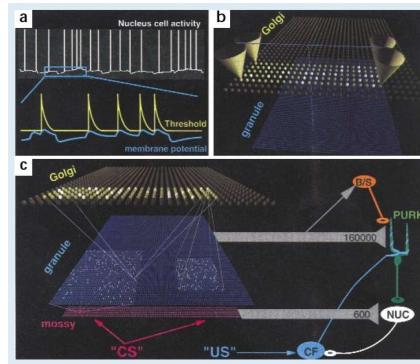
Gilbert, Thach, 1977

## 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**

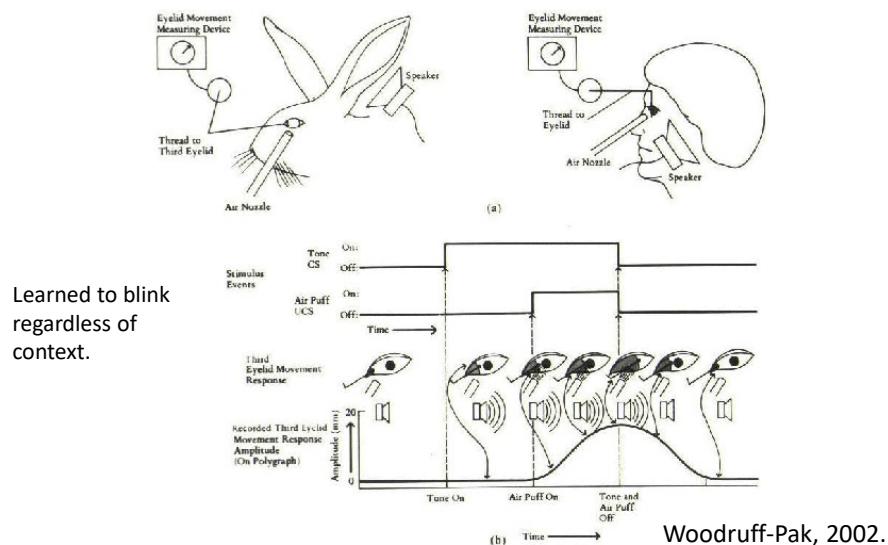
Lepora et al., 2010.

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

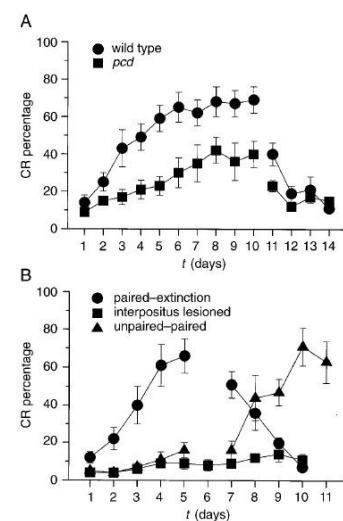
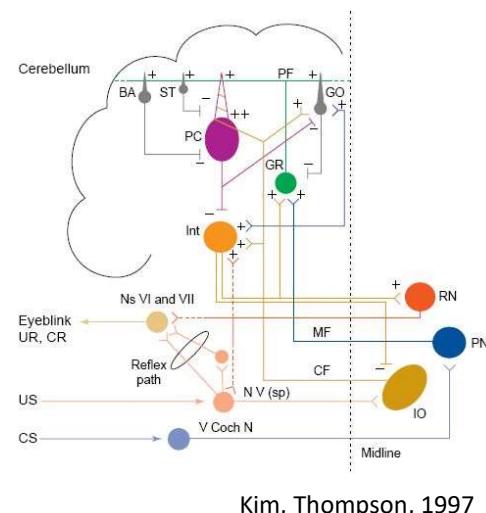


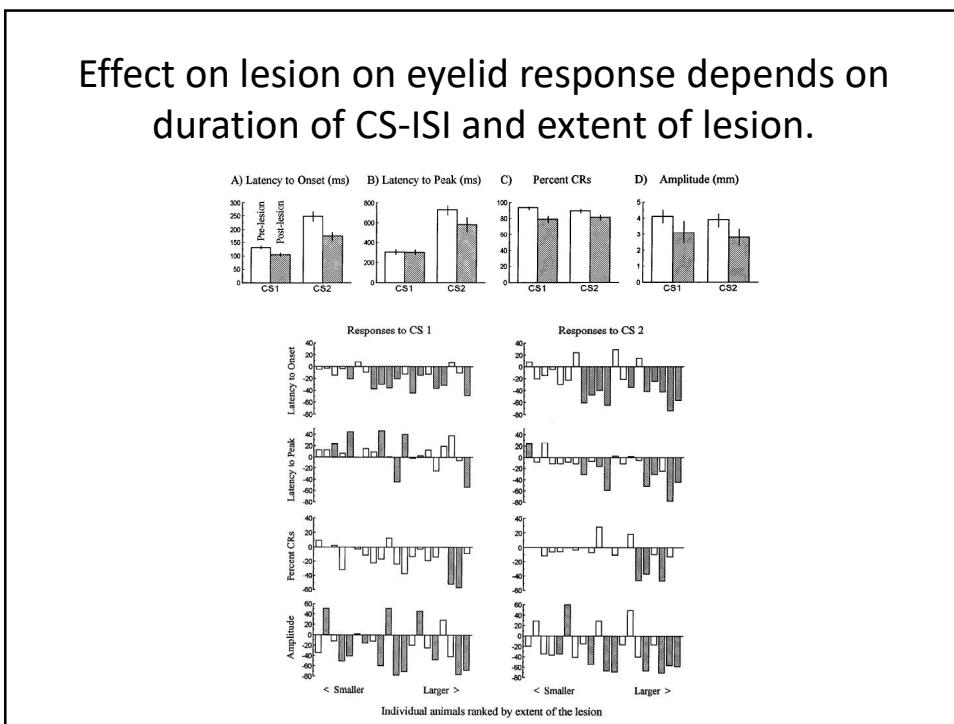
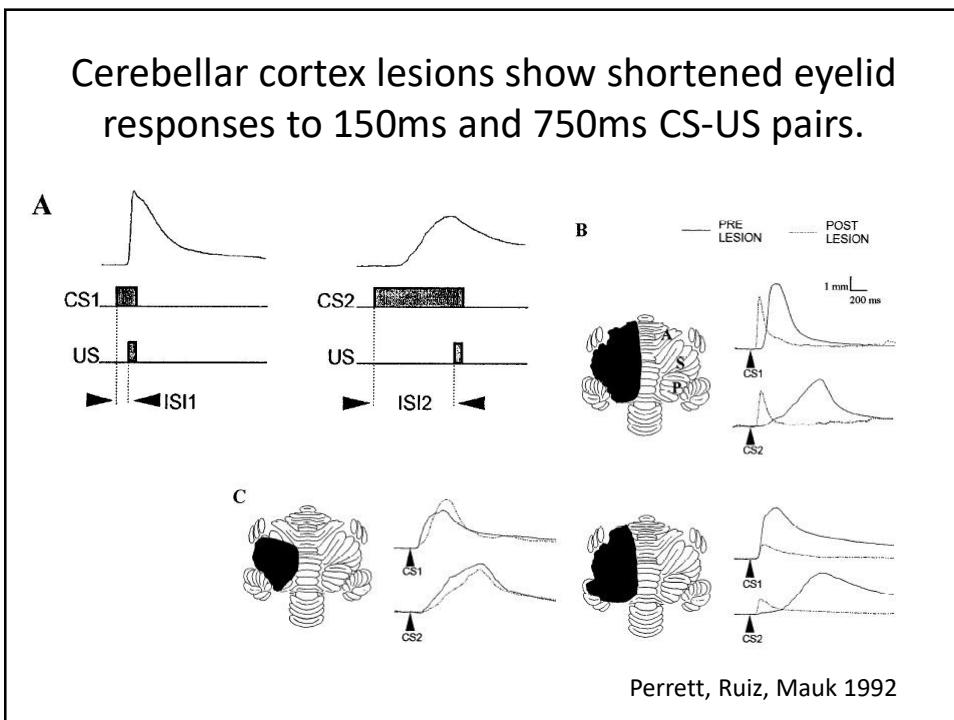
Medina, Mauk, 2000

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

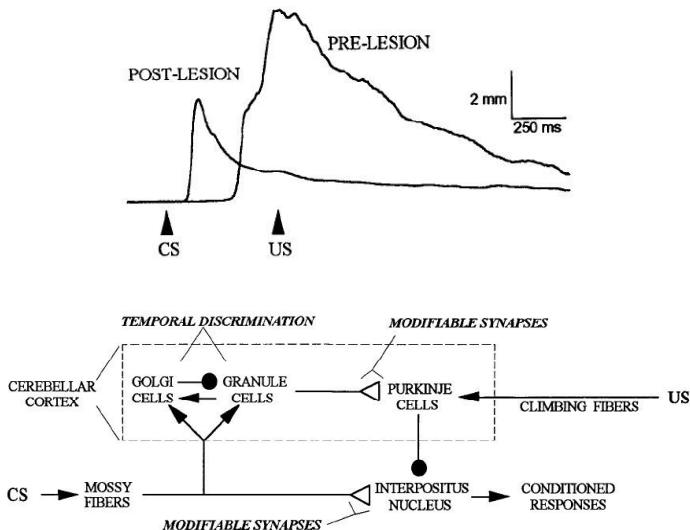


Cerebellar interpositus nuclei are necessary for learning of classical eyeblink conditioning.



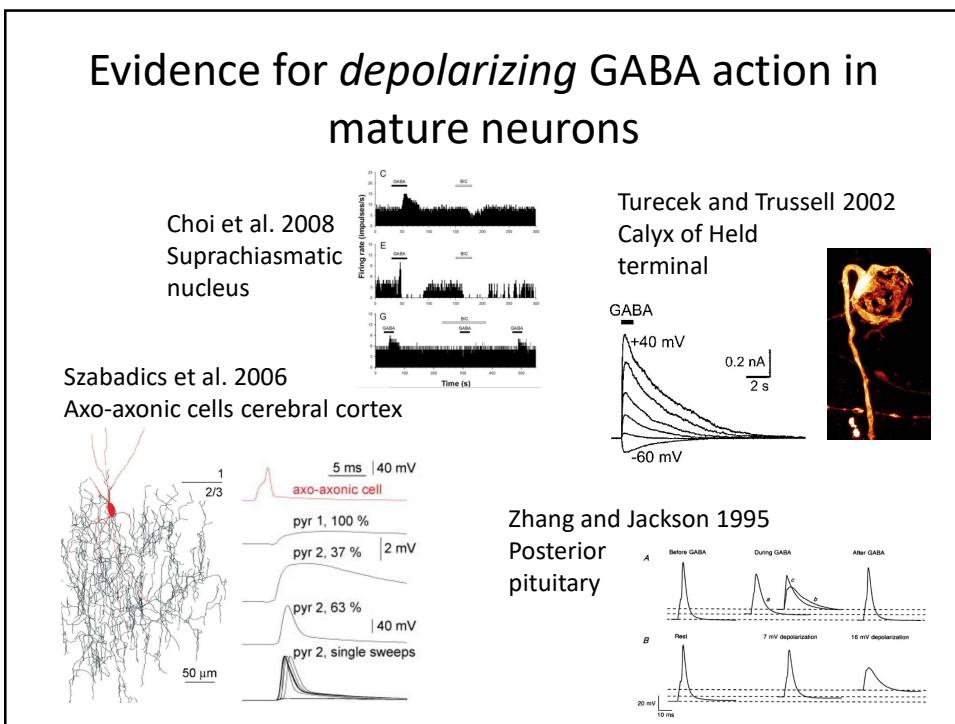
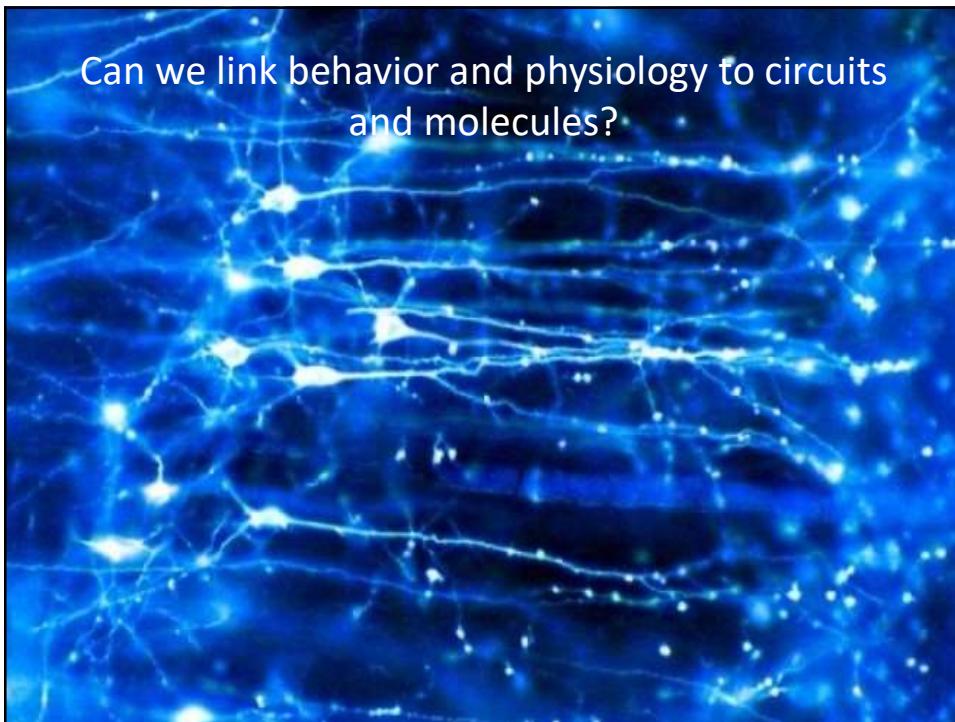


Single CS-ISI learning deficits are inconsistent with disruption of auditory discrimination.



## Summary of cerebellar action.

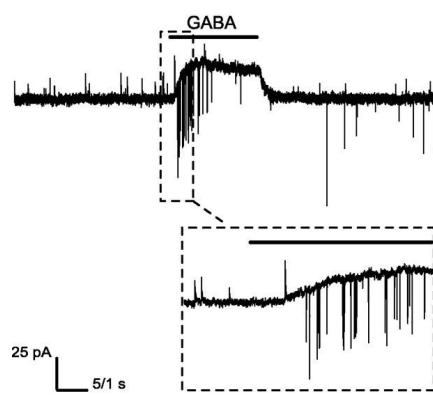
- The cerebellum is necessary for everyday movements like saccades (vermis) & pointing.
- Purkinje cells and deep nuclei cells fire during voluntary movements in feedforward control.
- Cerebellum has an internal model of limb structure that anticipates forces in movement.
- Altering strength of particular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



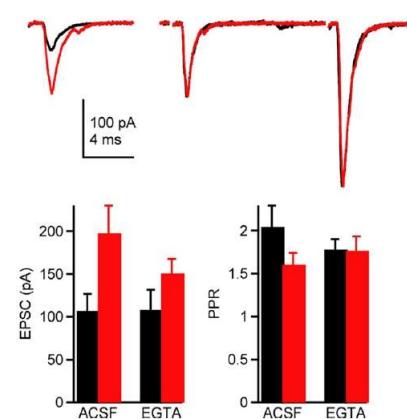
## Evidence for *excitatory GABA action in mature neurons*

- 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<sub>A</sub> agonist.

## GABA<sub>A</sub>R activation excites presynaptic input to Purkinje cells and MLIs

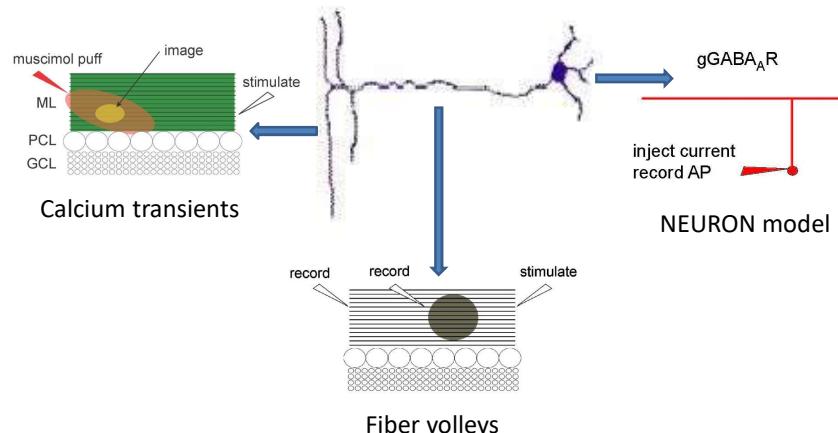


Stell, Marty 2007



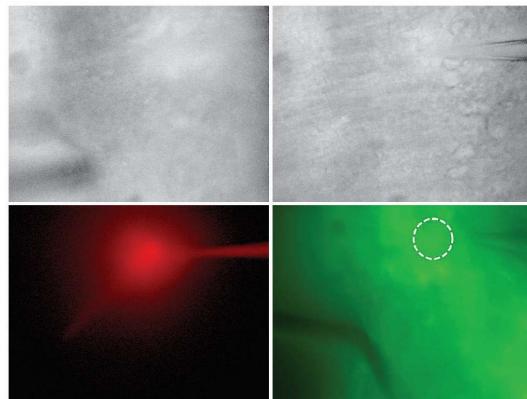
Pugh, Jahr 2011

## Where do we come from? Where are we going?

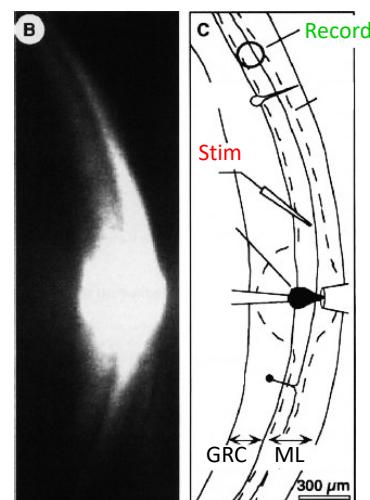


## Local perfusion of calcium indicator limited to molecular layer and parallel fibers

Oregon Green BAPTA-1 AM → transverse slice

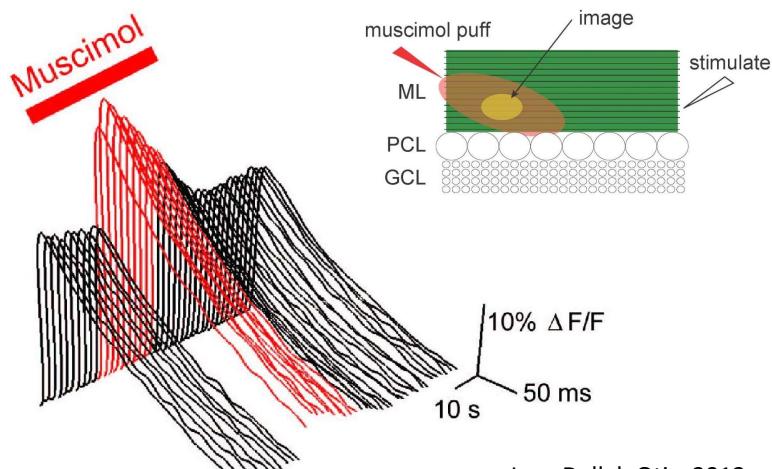


Luo, Dellal, Otis, 2012



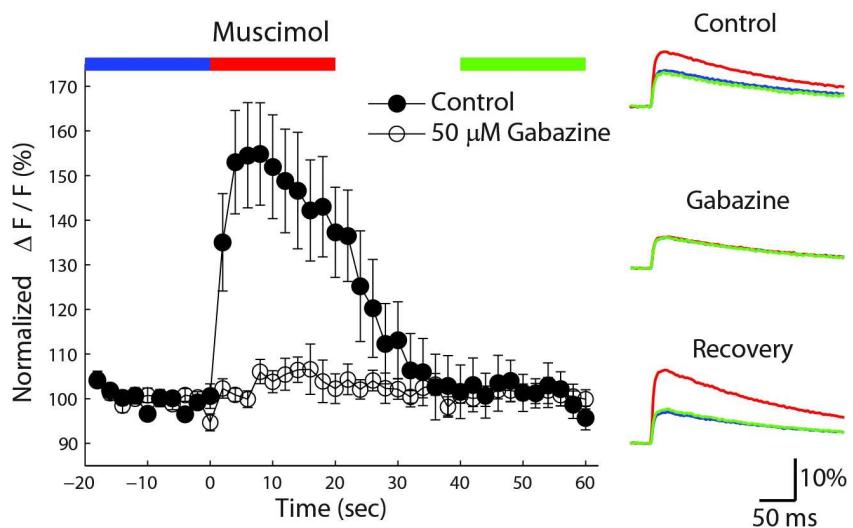
Regehr and Atluri, 1997

## Presynaptic calcium transients are potentiated by GABA<sub>A</sub>R agonist muscimol



Luo, Dellal, Otis, 2012

## Presynaptic calcium transients are potentiated by GABA<sub>A</sub>R agonist muscimol



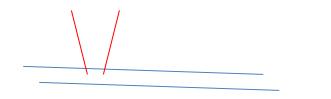
## Review Questions

- 1. Which of the following is NOT a disease caused by cerebellar dysfunction?
  - A. hypotonia: lack of muscle resistance
  - B. ataxic body movements
  - C. autism: verbal impairments and repetitive behavior
  - D. intention tremors
- 2. Which of the following forms the output of the cerebellar cortex circuit?
  - A. deep nuclei
  - B. parallel fibers
  - C. granule cells
  - D. Purkinje cells
- 3. We trained a rabbit to anticipate an airpuff (US) by blinking in response to a tone (CS). What happens if on the next day we present the same tone (CS) only (without US) in a new room that smells like pineapple but with lights dimmed?
  - A. the rabbit will cease to blink to the tone
  - B. the rabbit will continue to blink to the tone
  - C. the rabbit will not blink initially but will gradually regain blinking to the tone
  - D. the rabbit will move around when tone occurs but when she realizes there's no airpuff she will stop moving around

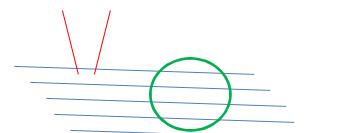
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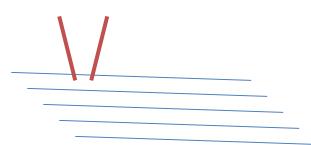
Is GABA-mediated excitation working at single parallel fibers? Or recruiting fibers?



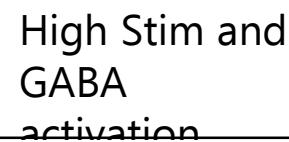
Low Stimulation



Low Stim and  
GABA  
activation

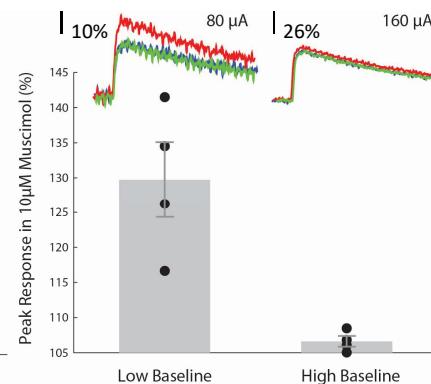
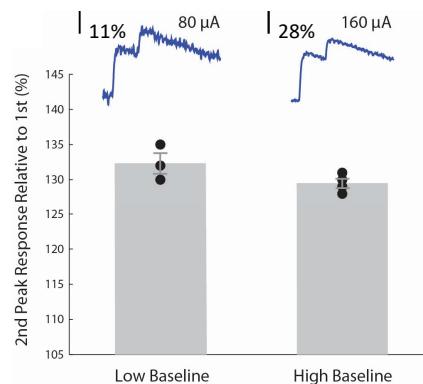


High Stimulation

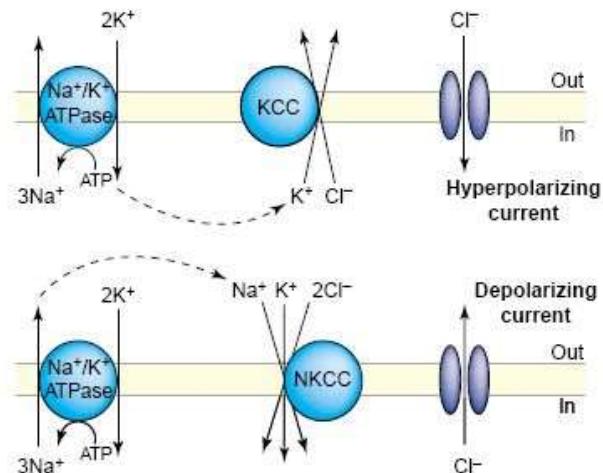


High Stim and  
GABA  
activation

$\text{GABA}_A$ R activation brings additional fibers closer to threshold for spike generation

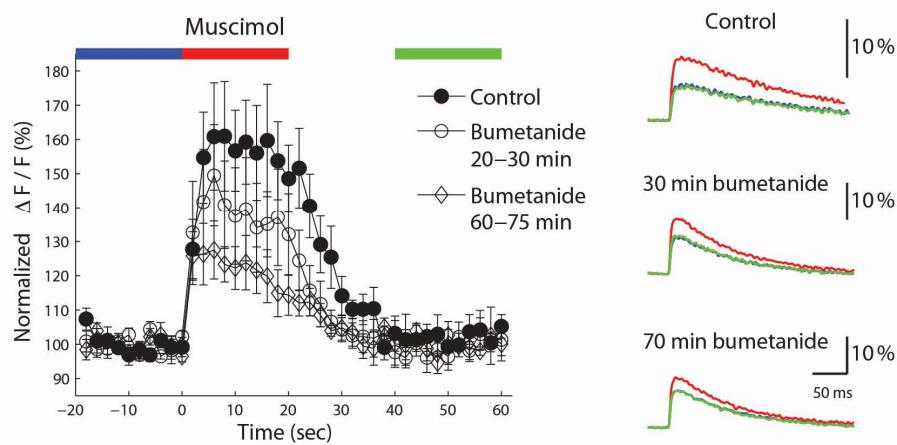


## NKCC1 transporter is the chloride accumulating transporter

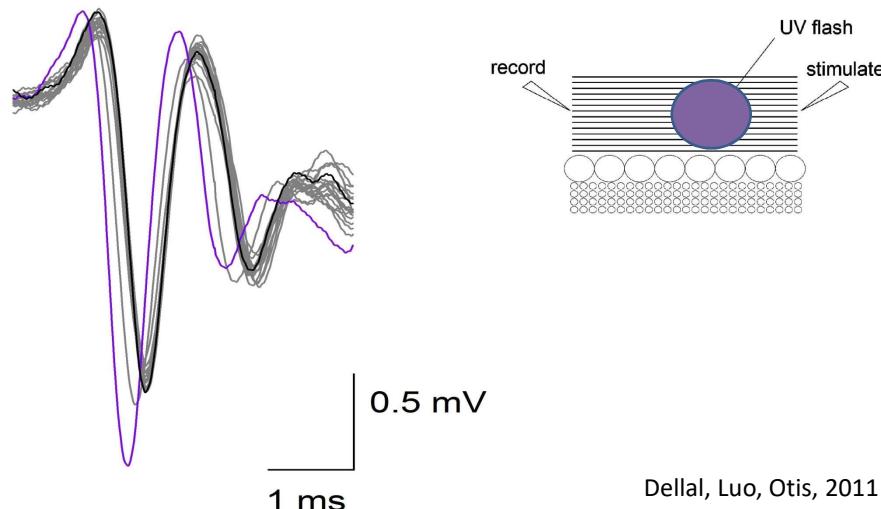


Payne et al. 2003

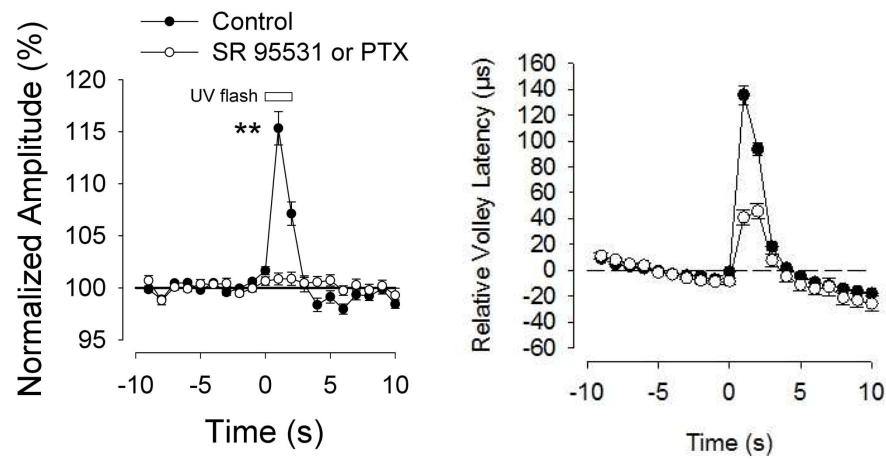
## Muscimol-induced increase in calcium transient depends on the chloride gradient



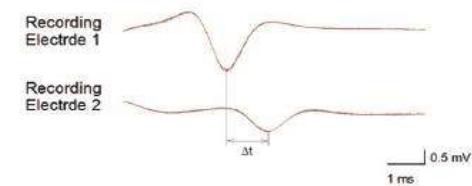
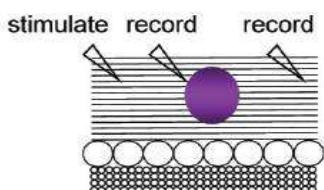
### Compound action potential (fiber volley) amplitude is increased by uncaging GABA



### GABA<sub>A</sub>R activation increases fiber volley amplitude and shortens latency

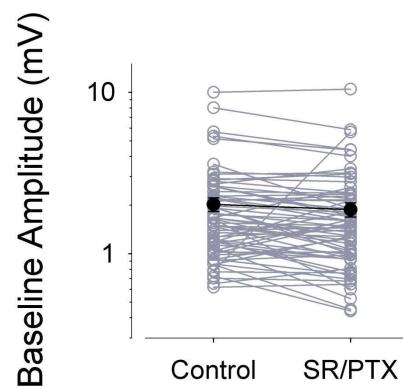
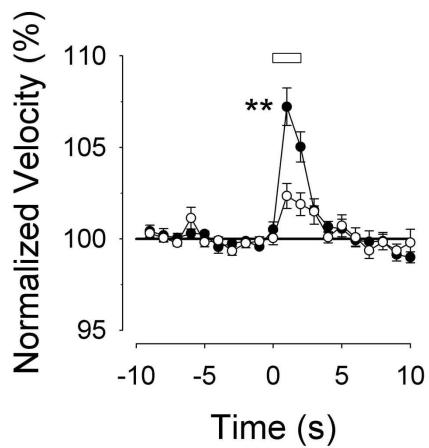


## Conduction velocity measurements using fiber volleys in a transverse slice

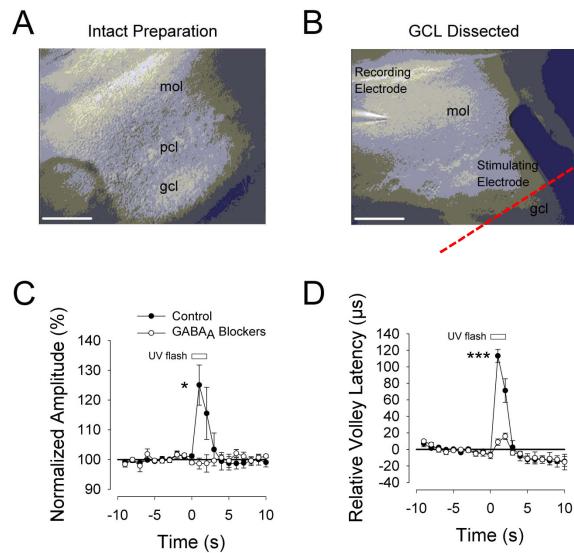


$$\text{Conduction Velocity} = (\text{Distance between recording electrodes}) / \Delta t$$

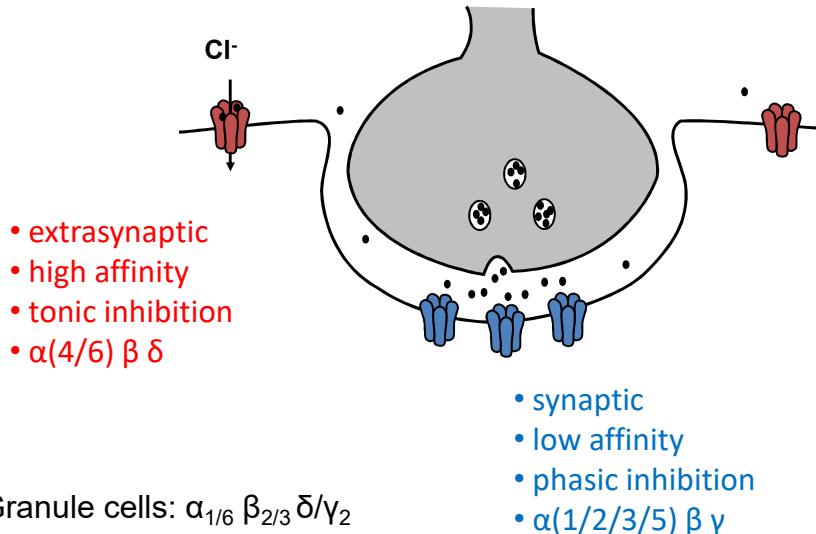
## GABA<sub>A</sub>R activation increases fiber volley conduction velocity



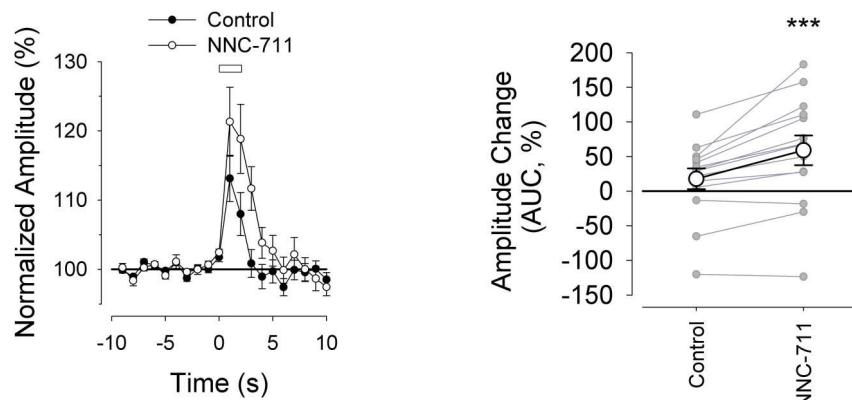
## GABA-mediated excitation of parallel fibers is independent of granule cell



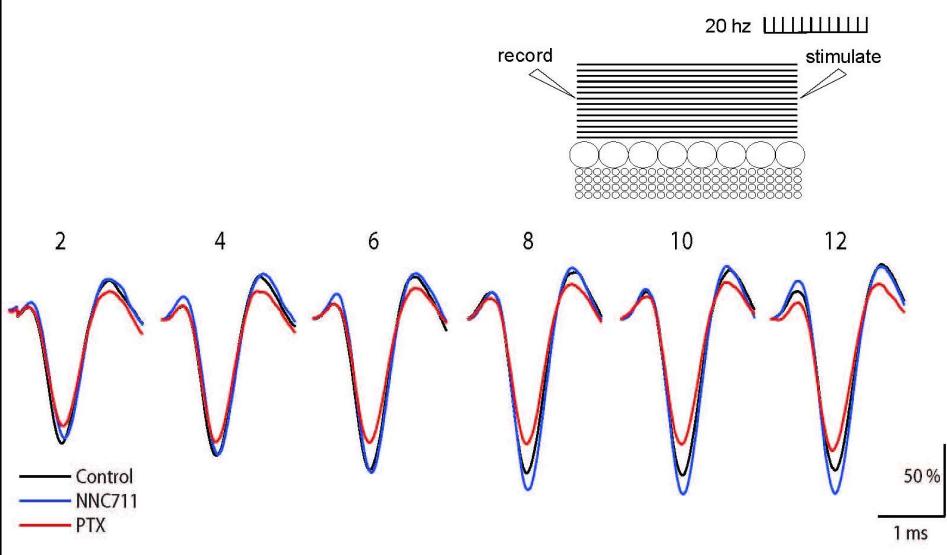
## GABA<sub>A</sub> receptors can be categorized into two major types



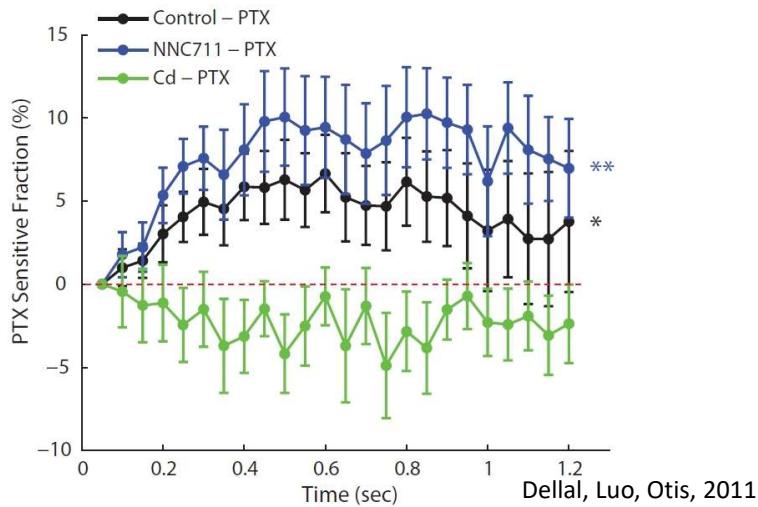
## Blocking GABA reuptake prolongs parallel fiber excitation



## Endogenous GABA is sufficient to increase parallel fiber excitability



## Endogenous GABA is sufficient to increase parallel fiber excitability

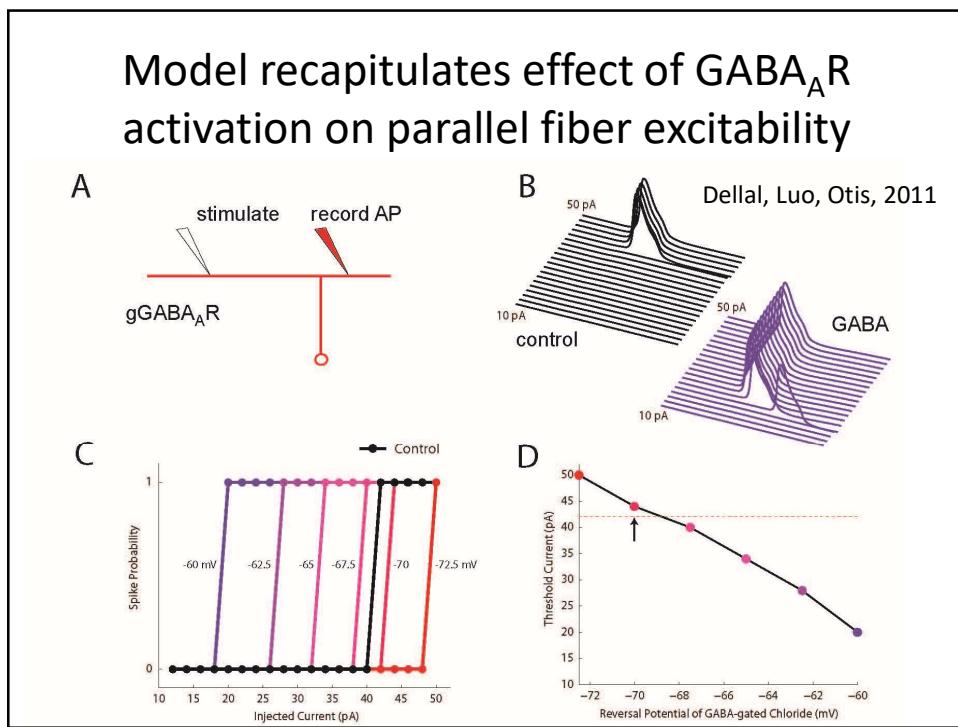
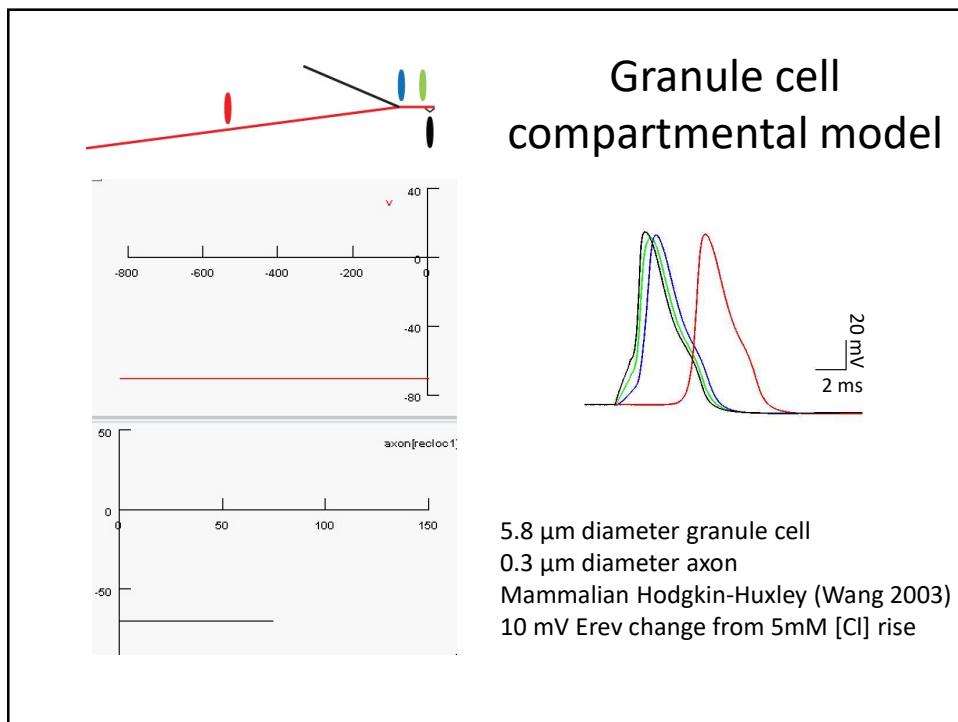


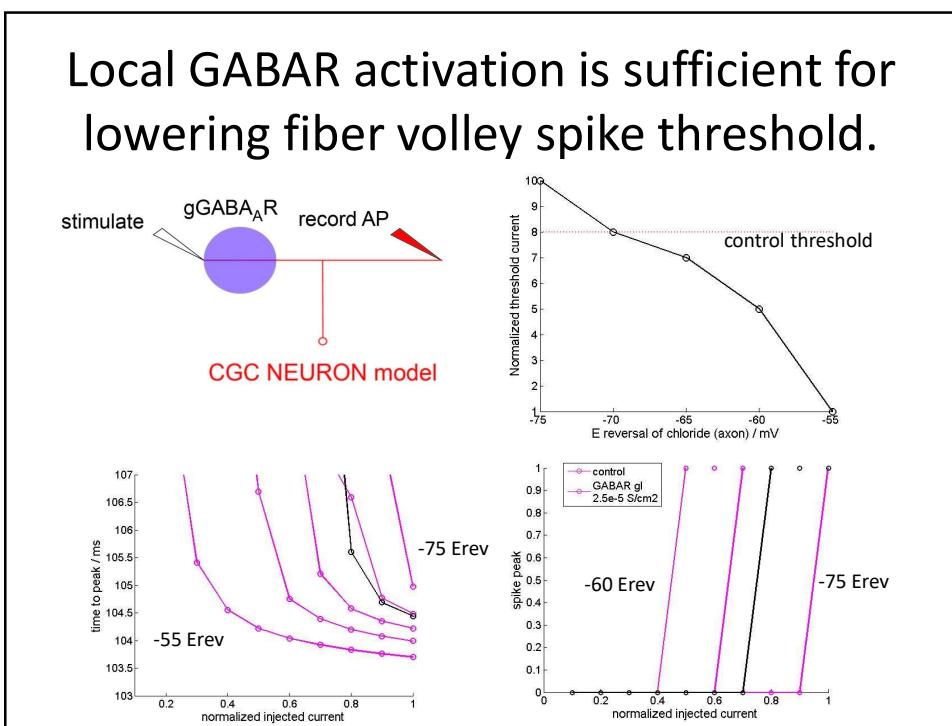
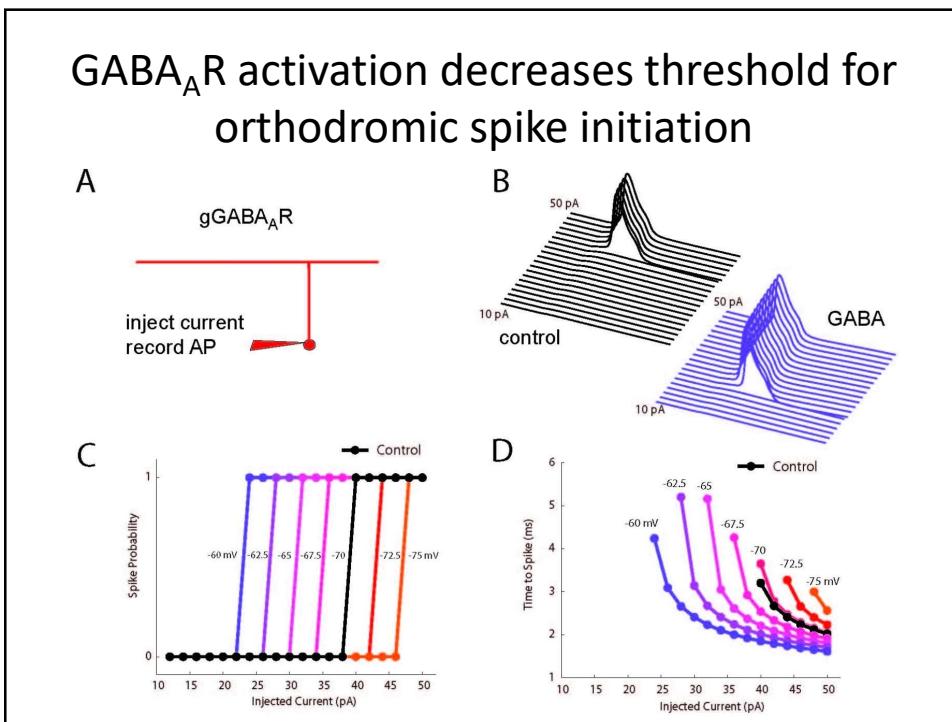
## Granule cell model.

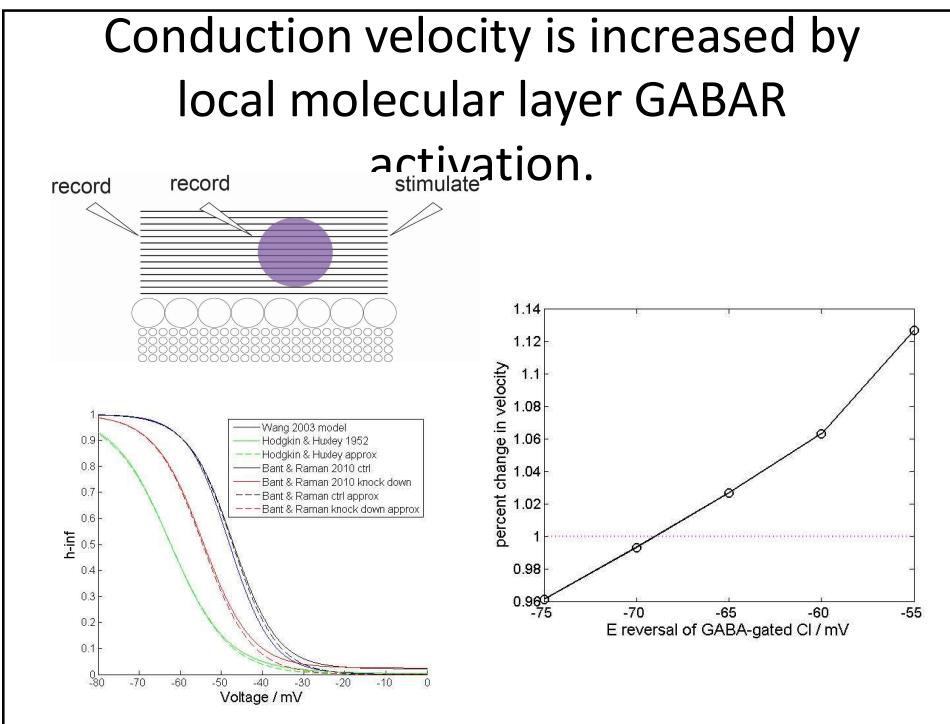
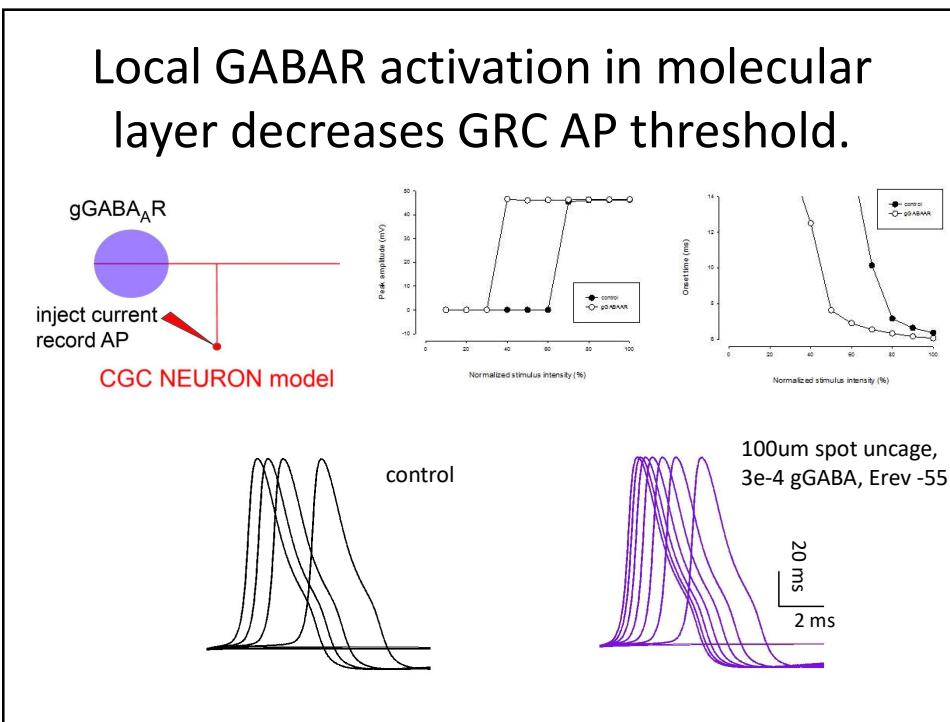
5.8 um diameter granule cell, 0.3 um diameter axon, 70 um ascending branch, 0.5 mm fiber after T-junction segment simulated.

Hodgkin-Huxley dynamics (from Walther), K-A channels, K-mixed-ion leak, chloride leak to maintain Erev-Cl, GABARs high conductance chloride leak.

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

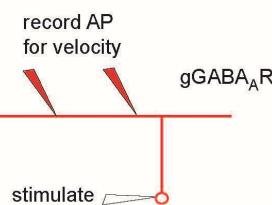




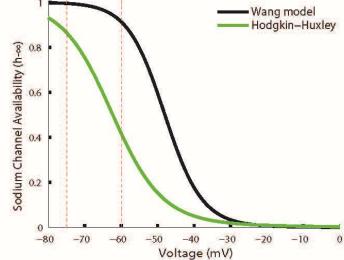


## GABA effect on conduction velocity depends on sodium channel inactivation

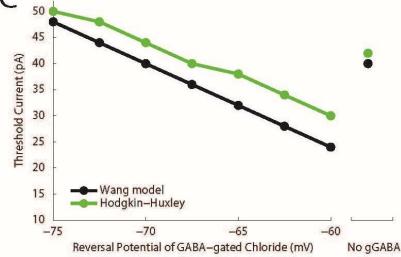
A



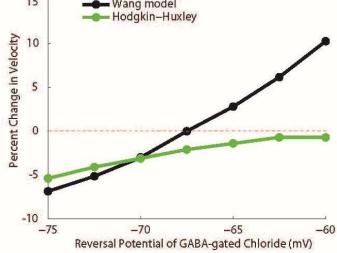
B



C

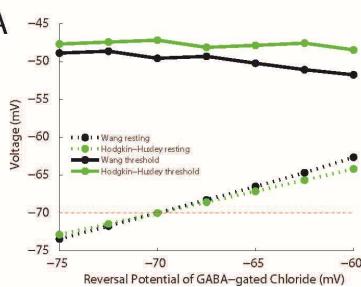


D

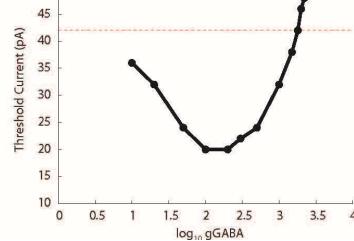


## $\text{GABA}_A\text{R}$ activation brings axon closer to threshold for spiking at low conductances.

A

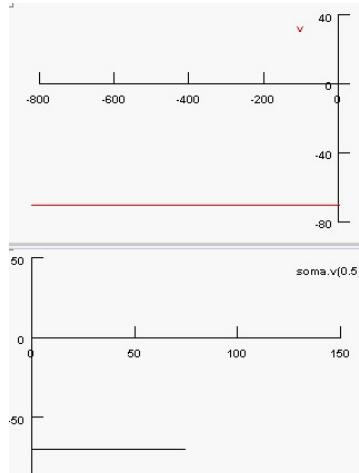


B

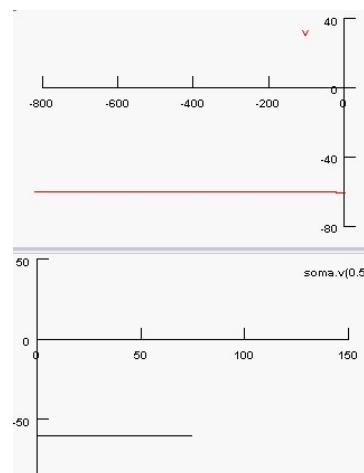


Spike failures (e.g. near the T) can occur near 100x the tonic conductance.

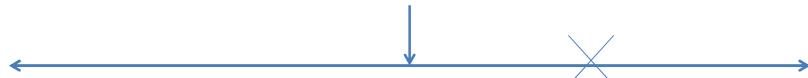
260x conductance, Erev -70mV.



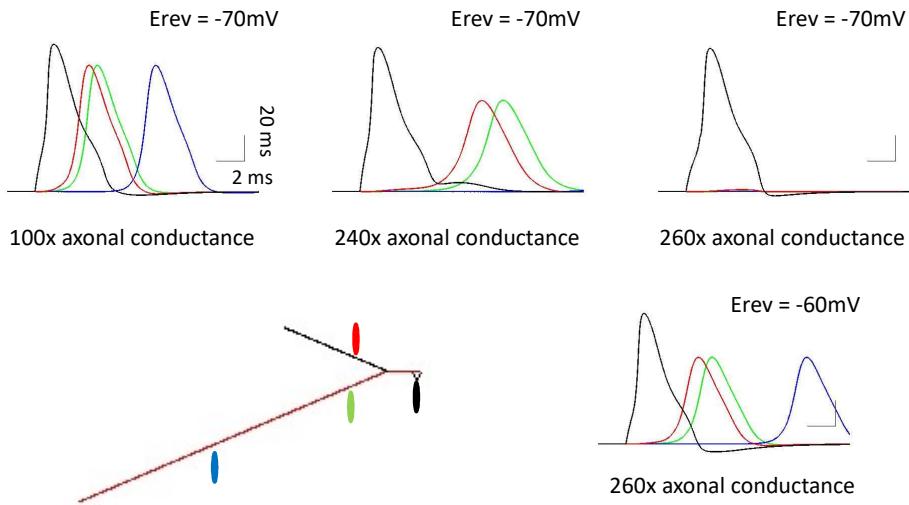
260x conductance, Erev -60mV.



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

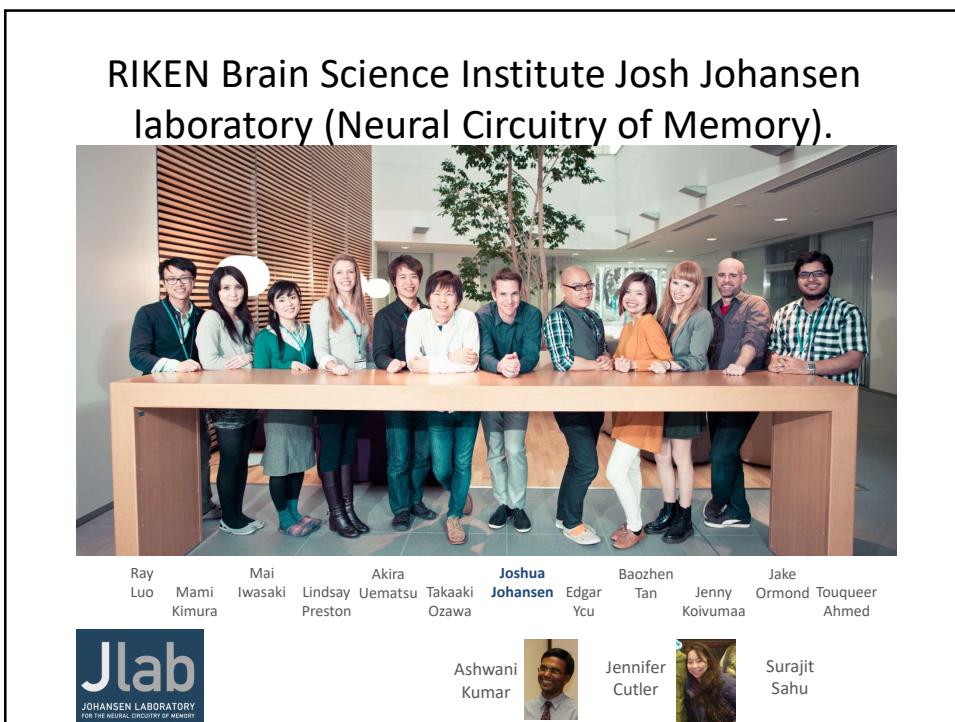


Spike failures (e.g. near the T) can occur near 100x the tonic conductance.



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





## Questions?



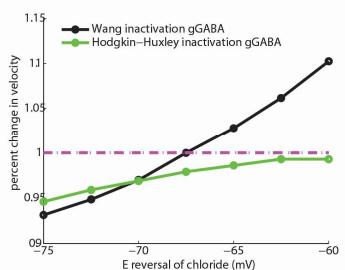
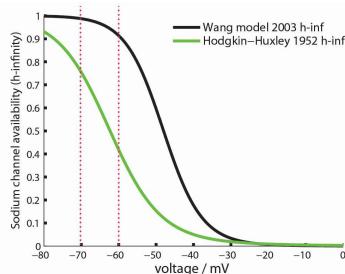
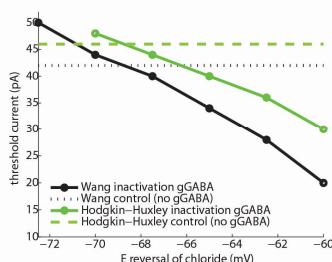
## Effect of GABAR on velocity depends on sodium channel inactivation.

J. Physiol. (1952) 117, 500–544

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

By A. L. HODGKIN AND A. F. HUXLEY  
From the Physiological Laboratory, University of Cambridge  
(Received 10 March 1952)

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



## GABA activation in ML decreases GRC AP threshold and initiation time.

