

A photograph of a person with long hair playing a piano. The image is overlaid with a yellow banner containing the title 'Playing Piano' in red, a purple banner with the subtitle '(without the brain): Movement and timing through cerebellar circuits.' in white, and the name 'Ray Luo' and affiliation 'RIKEN BSI, UCLA' in white text in the bottom right corner.

Playing Piano
(without the brain):
Movement and timing through cerebellar circuits.

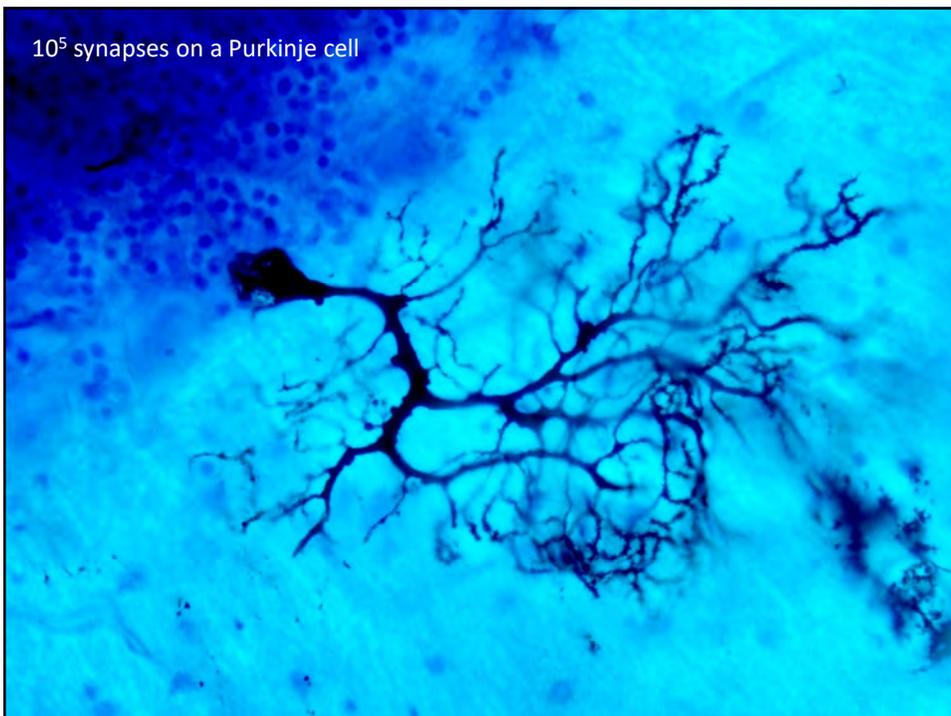
Ray Luo
RIKEN BSI, UCLA



10^{11} neurons in the human brain



10^5 synapses on a Purkinje cell

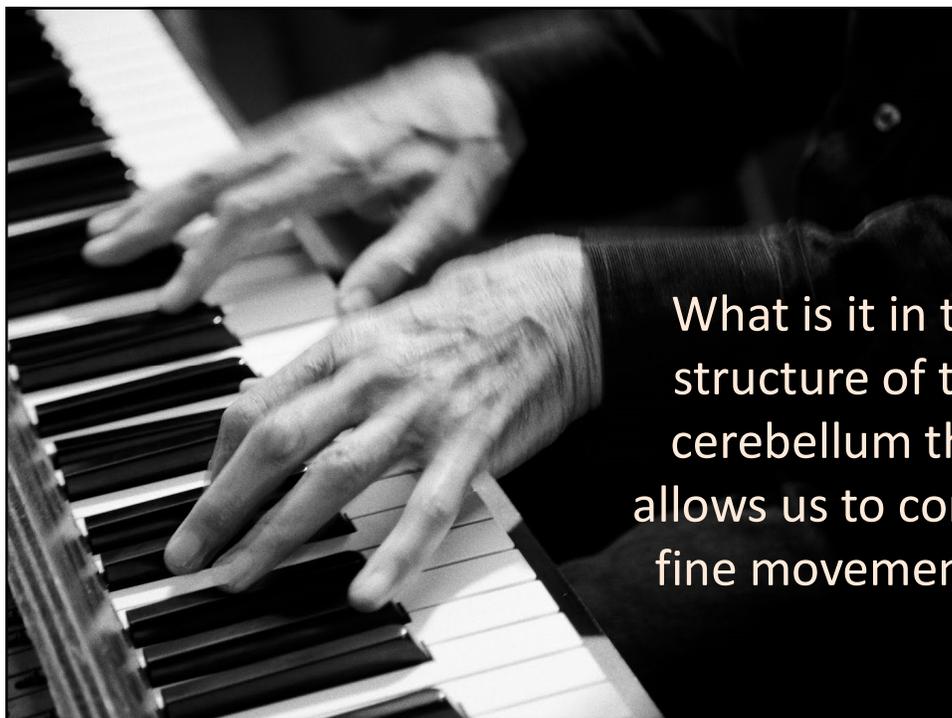




Cerebellum plays a function in posture, fine motor control, and programming.

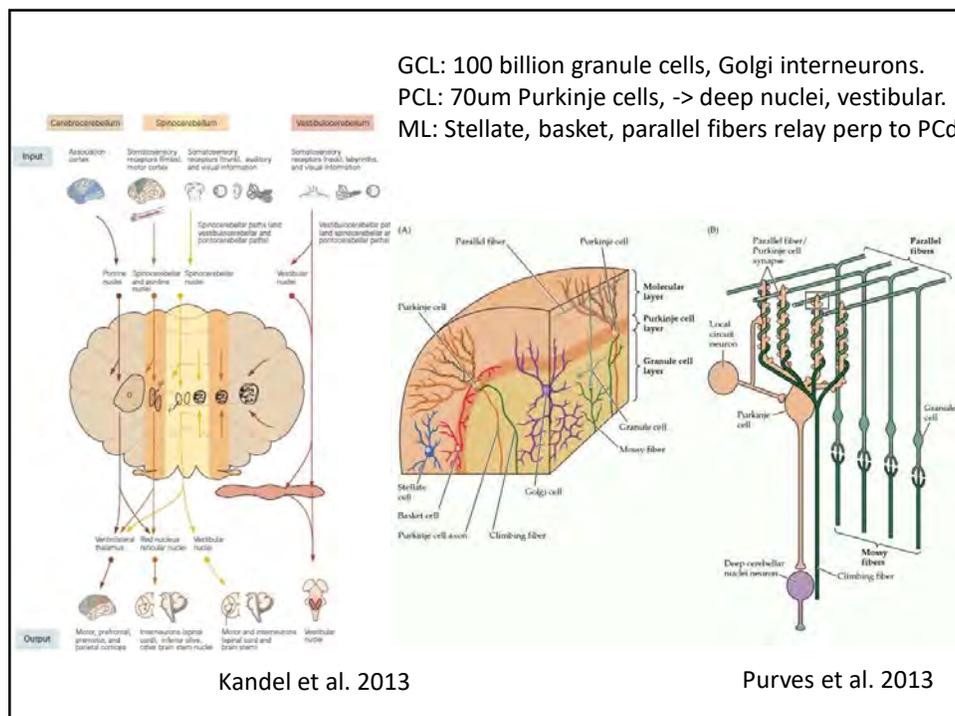
- 50% of cells in the brain.
- Cerebellar damage:
 - *Hypotonia* reduced resistance (pendulum).
 - *Astasia* inability to stand or walk (spread).
 - *Ataxia* irregular rhythmic movement (up-down).
 - *Intention tremor* antagonist muscle control error.

Intention tremor.



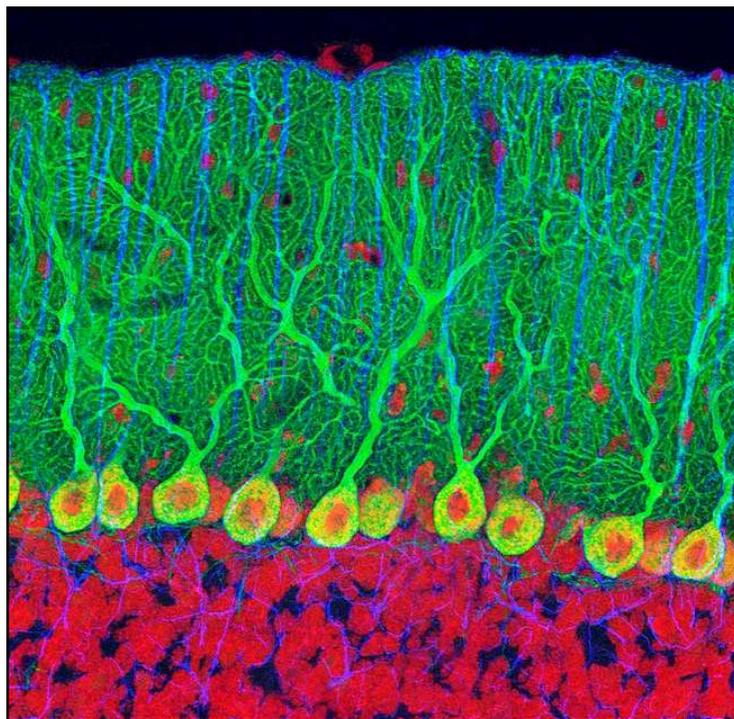
Cerebellum is compartmentalized functionally.

- Deep nuclei -> superior cerebellar peduncle.
- Vestibular 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.



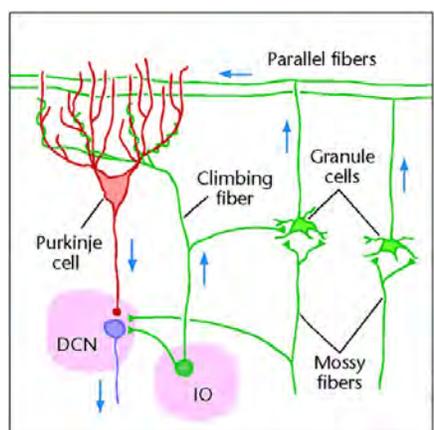
Kandel et al. 2013

Purves et al. 2013



Cerebellum
Output:
Purkinje
cells
(inhibitory)

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



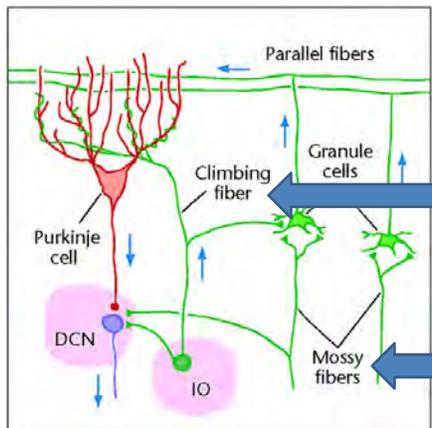
Optican, 1998

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

Purkinje Record
Climbing fiber



Mossy fiber ->
Parallel fiber



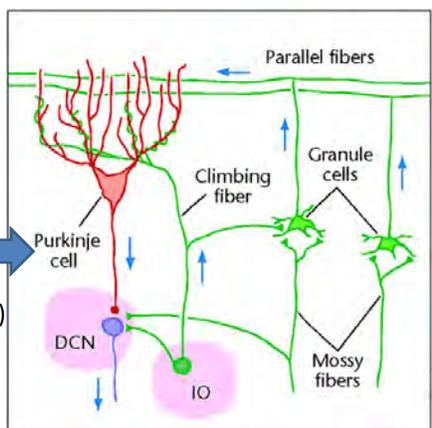
Input – Error
(one-to-one PC)
(Ca -> complex)
(IO synchrony)

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

Optican, 1998

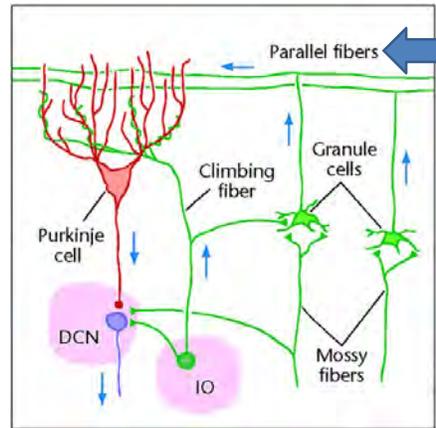
Parallel fibers are axons of granule cells, project to Purkinje cells in molecular layer

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



Optican, 1998

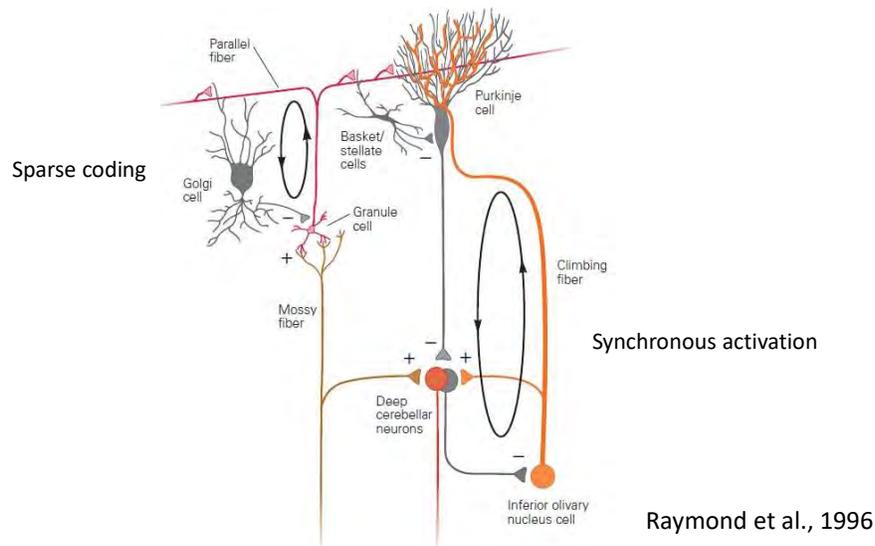
Parallel fibers are axons of granule cells, project to Purkinje cells in molecular layer



Relay
(inhibition at GCL and ML)
(Golgi cell sparse coding)
(coordinate diff compartments)
(long distance coord)

Optican, 1998

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



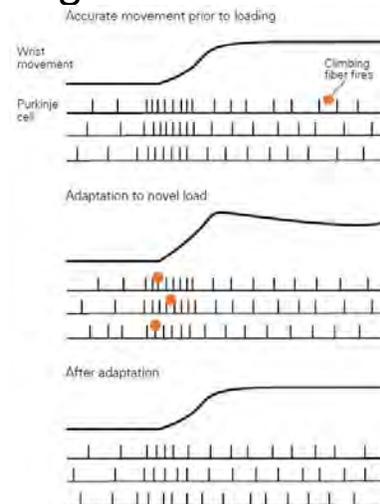
Raymond et al., 1996

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.

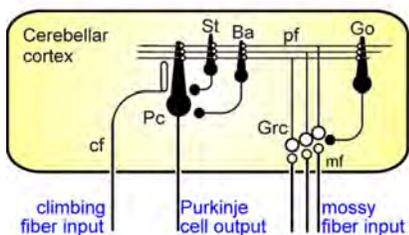
- Climbing fiber (CF) induced long term depression LTD of parallel fiber to Purkinje synapses.
- Motor system as cerebellum implemented internal (inverse dynamics) model.



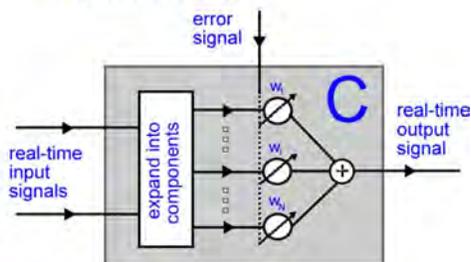
Gilbert, Thach, 1977

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

A Anatomy of cerebellar cortex:

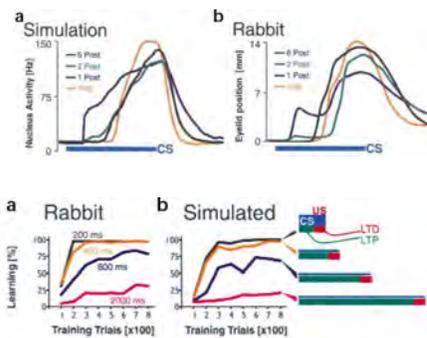
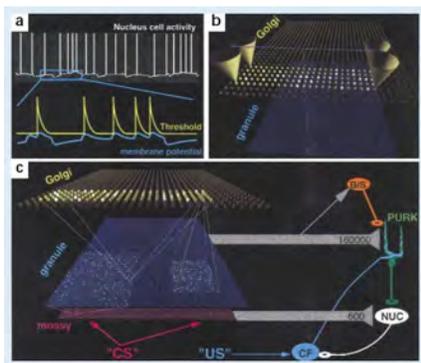


B Adaptive filter (AF) model of cerebellar cortex



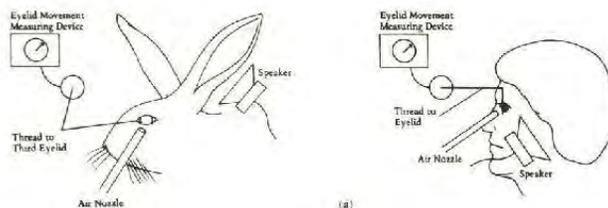
Lepora et al., 2010.

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

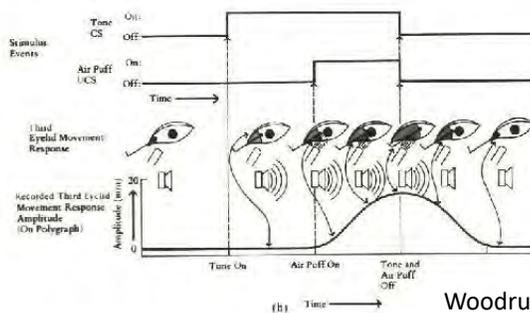


Medina, Mauk, 2000

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

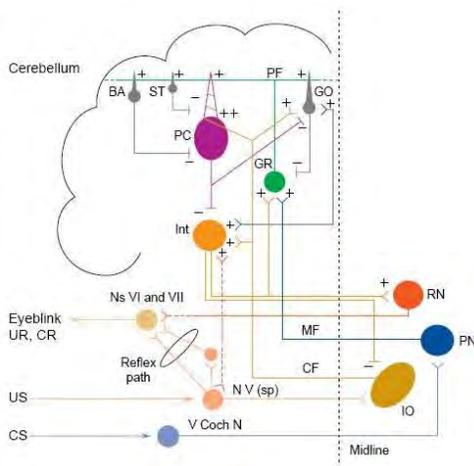


Learned to blink regardless of context.

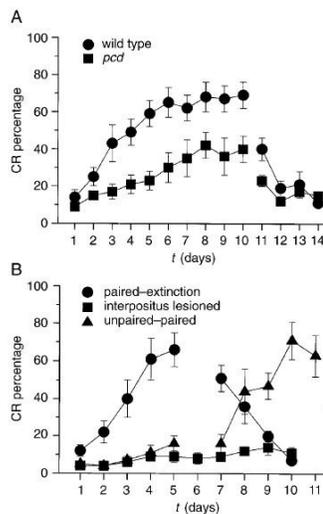


Woodruff-Pak, 2002.

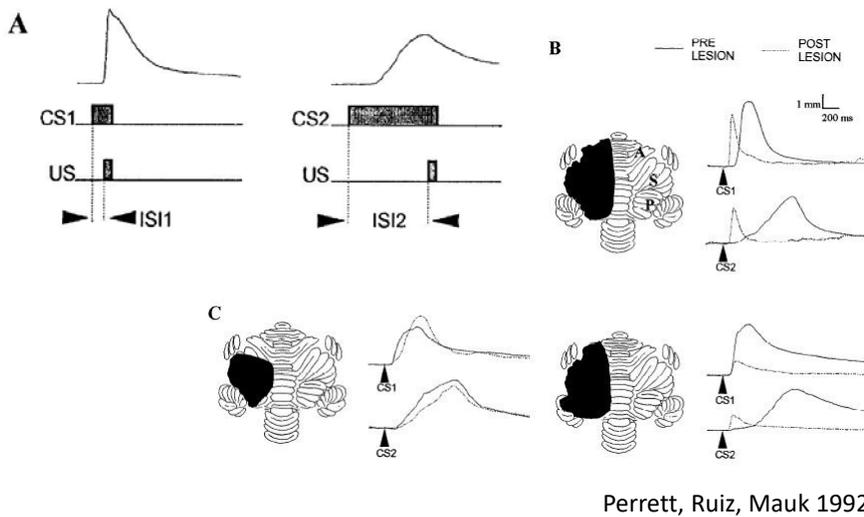
Cerebellar interpositus nuclei are necessary for learning of classical eyblink conditioning.



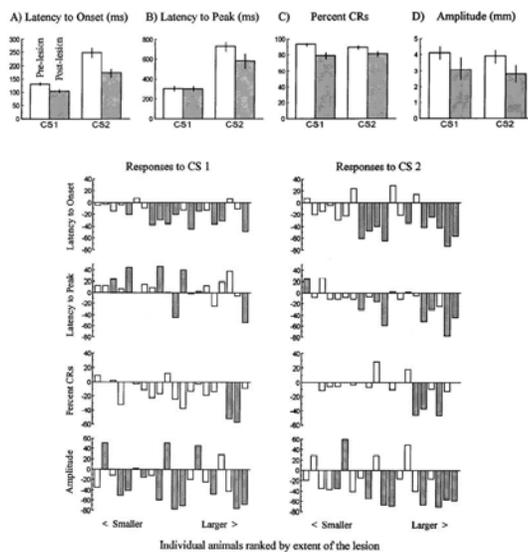
Kim, Thompson, 1997



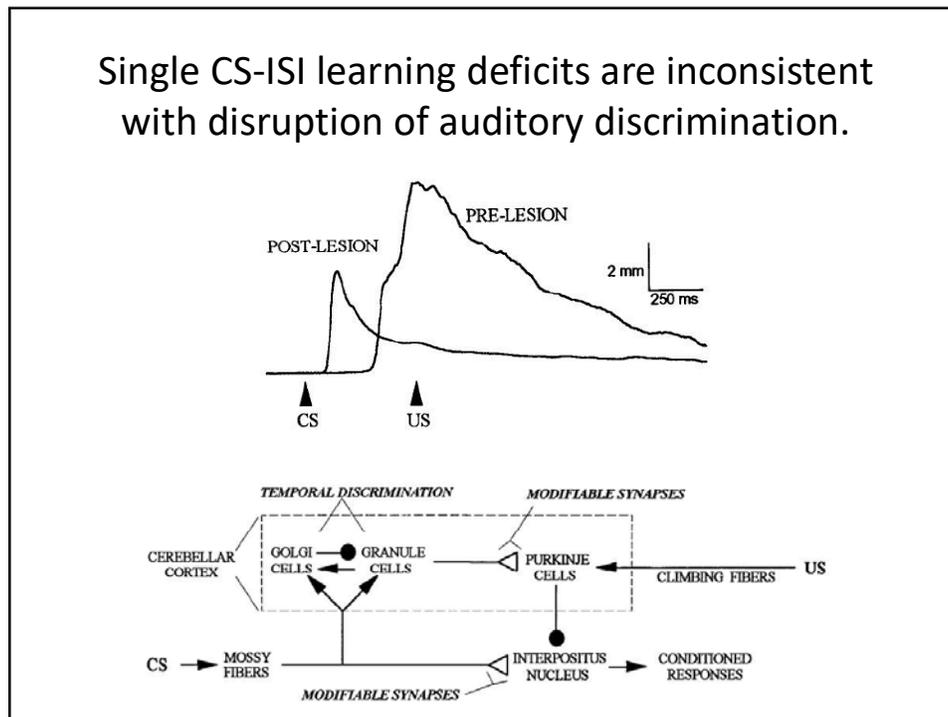
Cerebellar cortex lesions show shortened eyelid responses to 150ms and 750ms CS-US pairs.



Effect on lesion on eyelid response depends on duration of CS-ISI and extent of lesion.

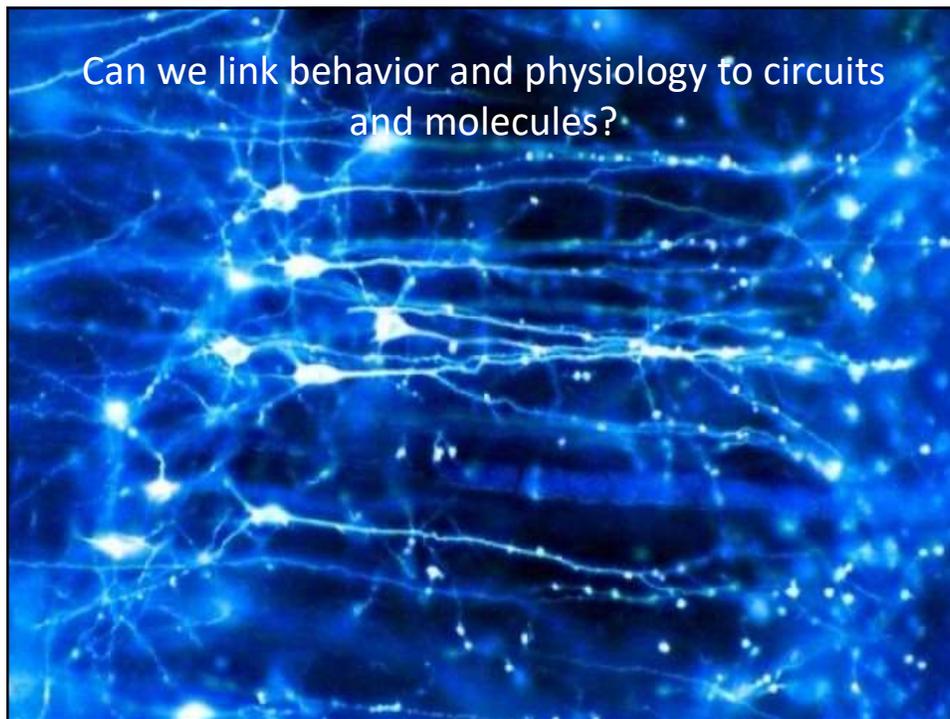


Single CS-ISI learning deficits are inconsistent with disruption of auditory discrimination.



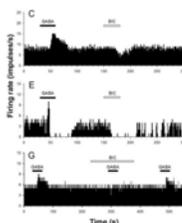
Summary of cerebellar action.

- 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).

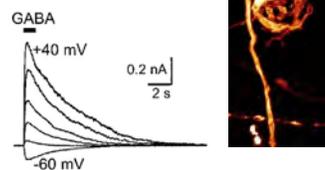


Evidence for *depolarizing* GABA action in mature neurons

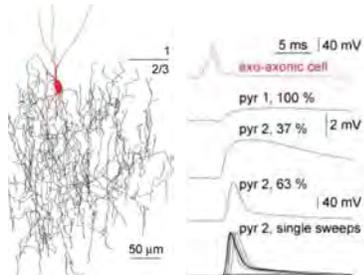
Choi et al. 2008
Suprachiasmatic nucleus



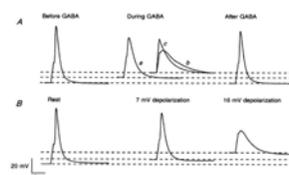
Turecek and Trussell 2002
Calyx of Held terminal



Szabadics et al. 2006
Axo-axonic cells cerebral cortex



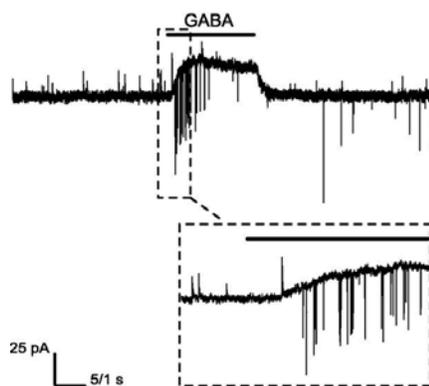
Zhang and Jackson 1995
Posterior pituitary



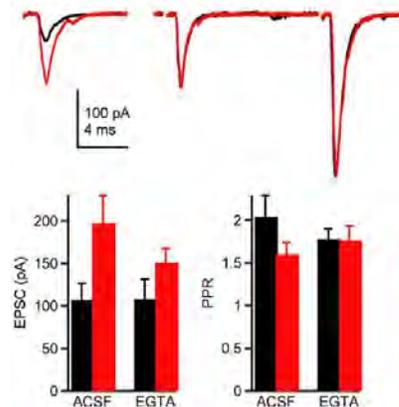
Evidence for *excitatory* GABA action in mature neurons

- 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

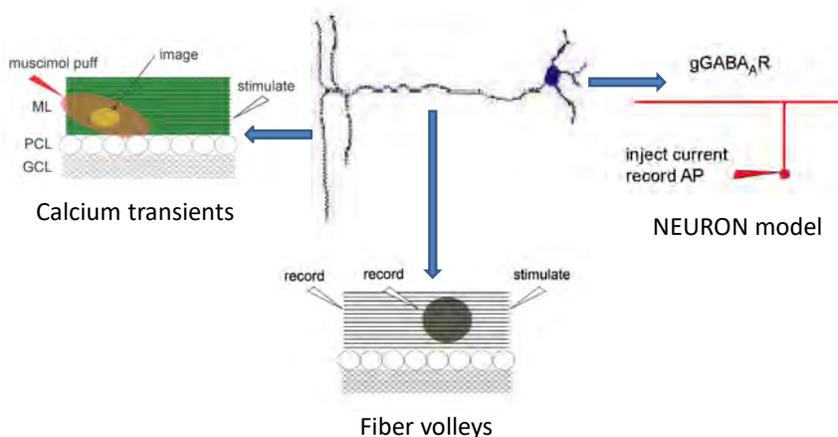


Stell, Marty 2007



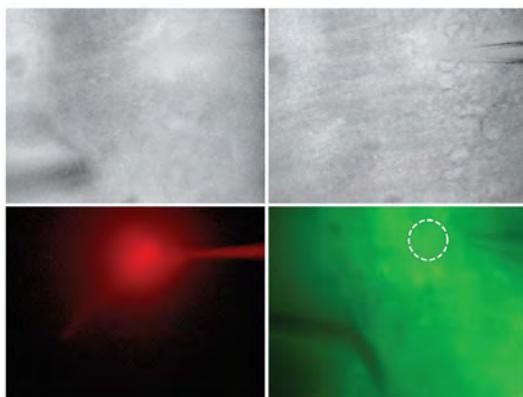
Pugh, Jahr 2011

Where do we come from? Where are we going?

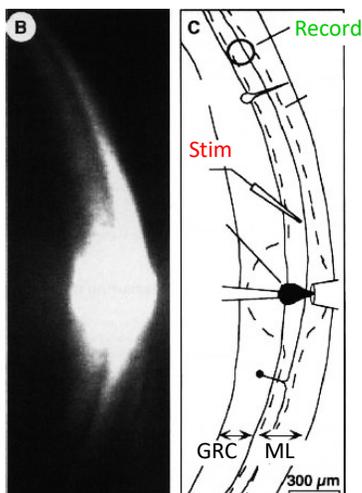


Local perfusion of calcium indicator limited to molecular layer and parallel fibers

Oregon Green BAPTA-1 AM -> transverse slice

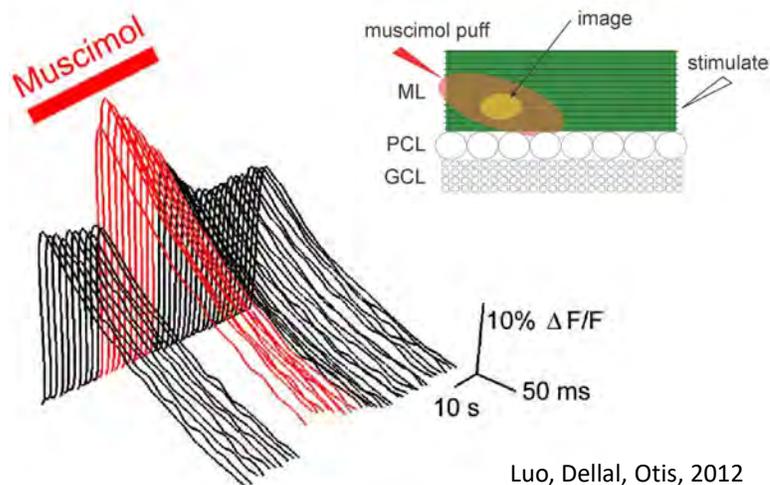


Luo, Dellal, Otis, 2012

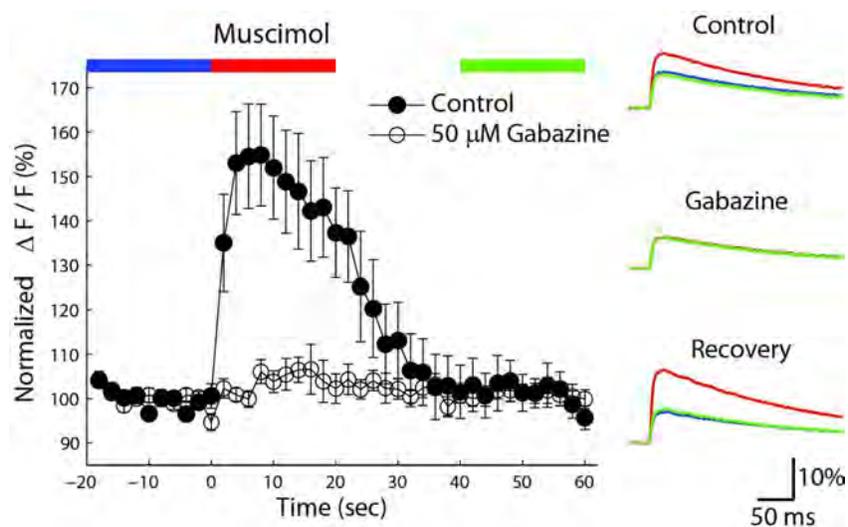


Regehr and Atluri, 1997

Presynaptic calcium transients are potentiated by GABA_AR agonist muscimol



Presynaptic calcium transients are potentiated by GABA_AR agonist muscimol



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 blink 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

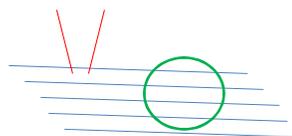
Review Questions

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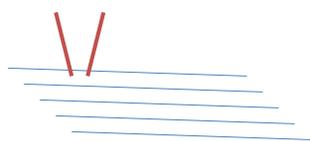
Is GABA-mediated excitation working at single parallel fibers? Or recruiting fibers?



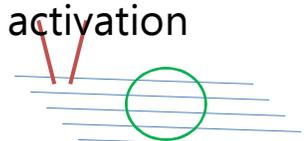
Low Stimulation



Low Stim and GABA activation

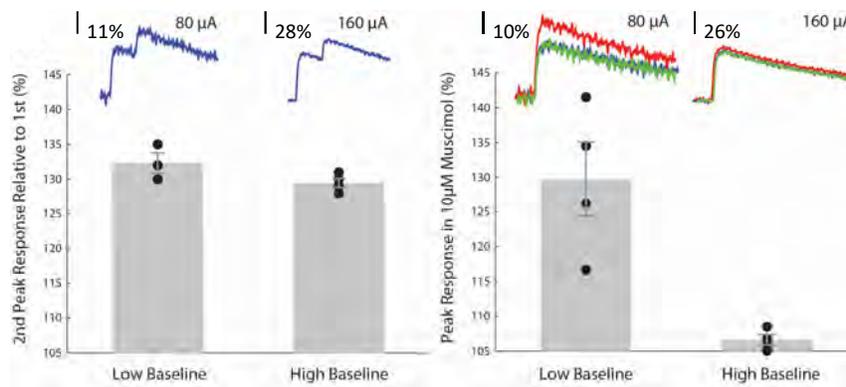


High Stimulation

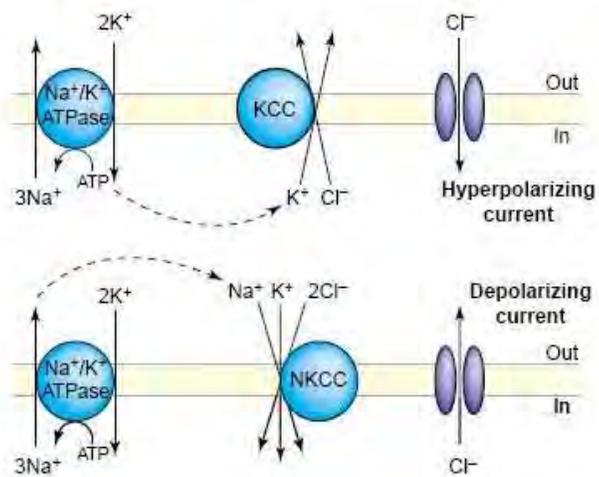


High Stim and GABA activation

GABA_AR activation brings additional fibers closer to threshold for spike generation

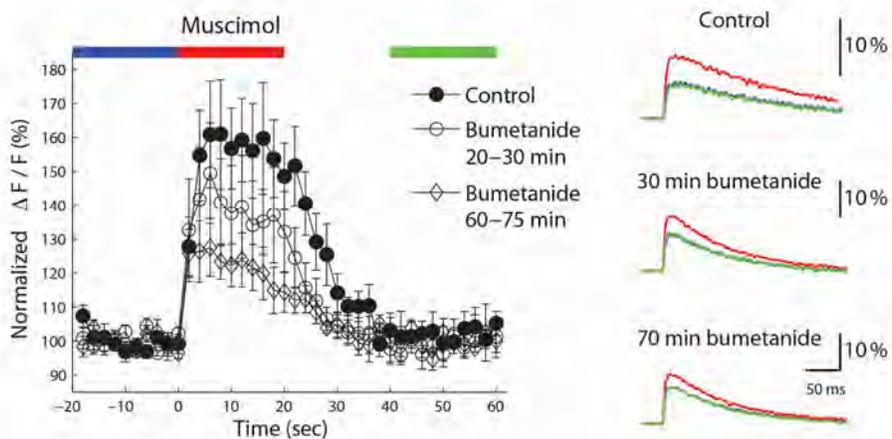


NKCC1 transporter is the chloride accumulating transporter

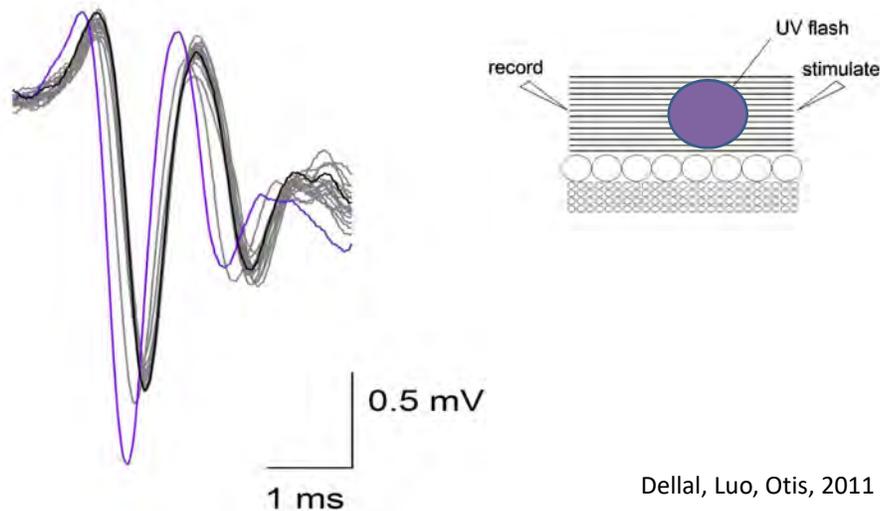


Payne et al. 2003

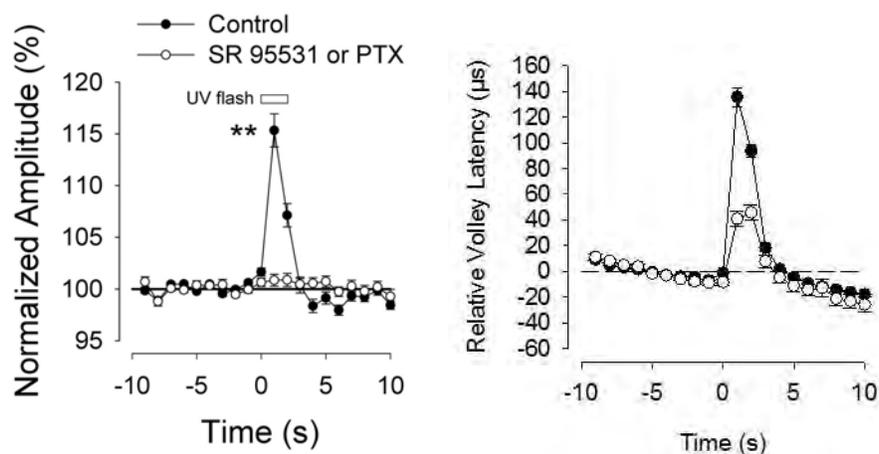
Muscimol-induced increase in calcium transient depends on the chloride gradient



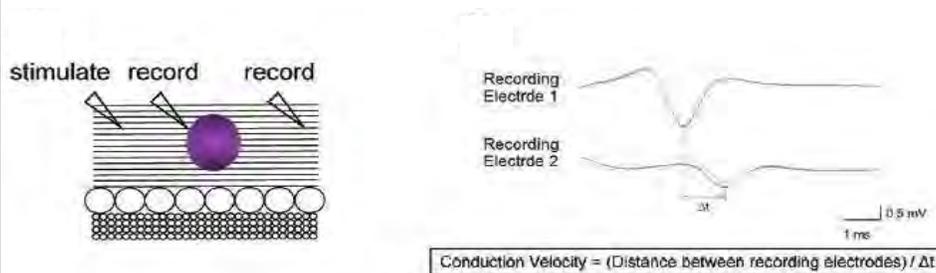
Compound action potential (fiber volley) amplitude is increased by uncaging GABA



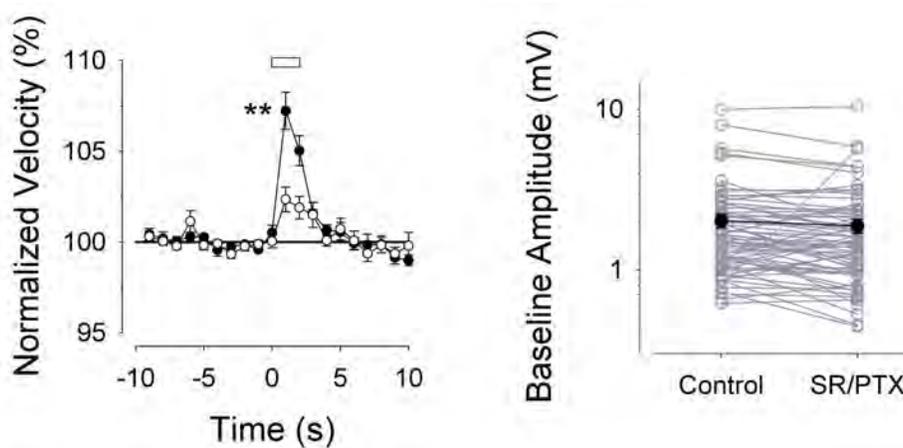
GABA_AR activation increases fiber volley amplitude and shortens latency



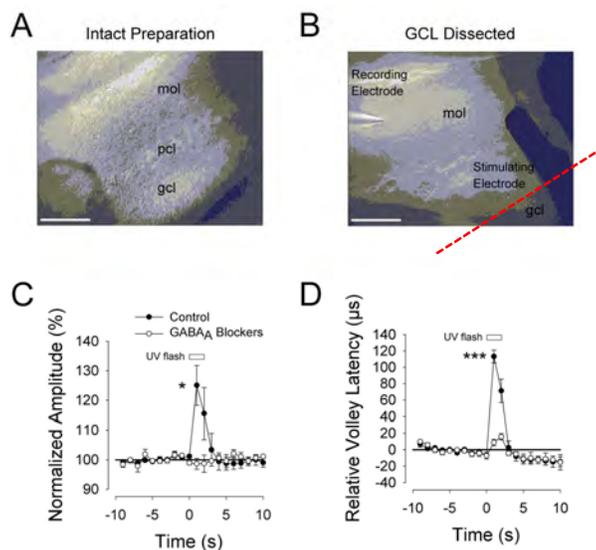
Conduction velocity measurements using fiber volleys in a transverse slice



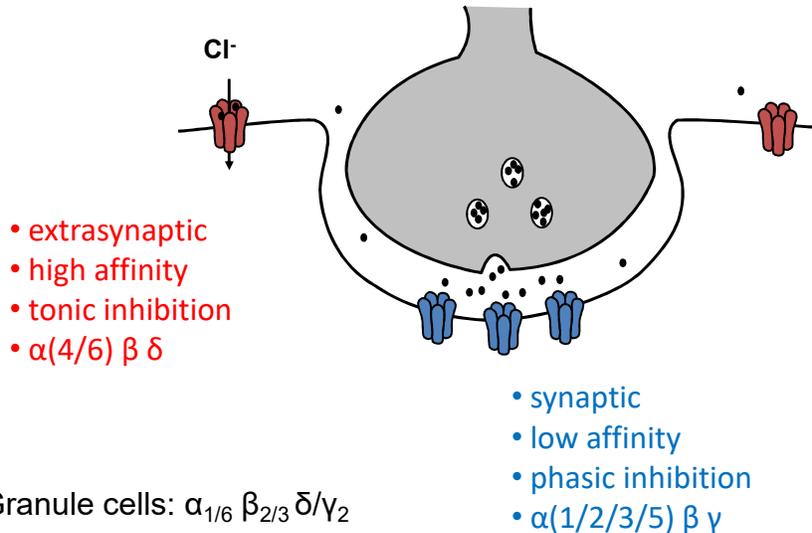
GABA_AR activation increases fiber volley conduction velocity



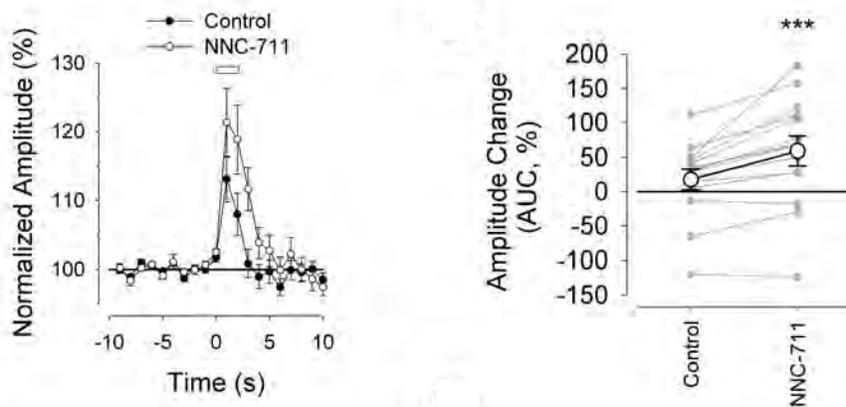
GABA-mediated excitation of parallel fibers is independent of granule cell



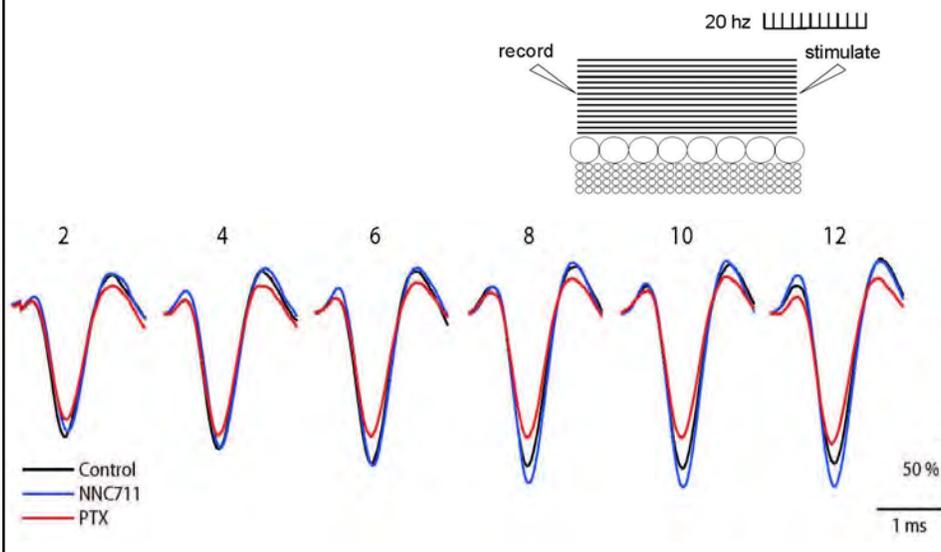
GABA_A receptors can be categorized into two major types



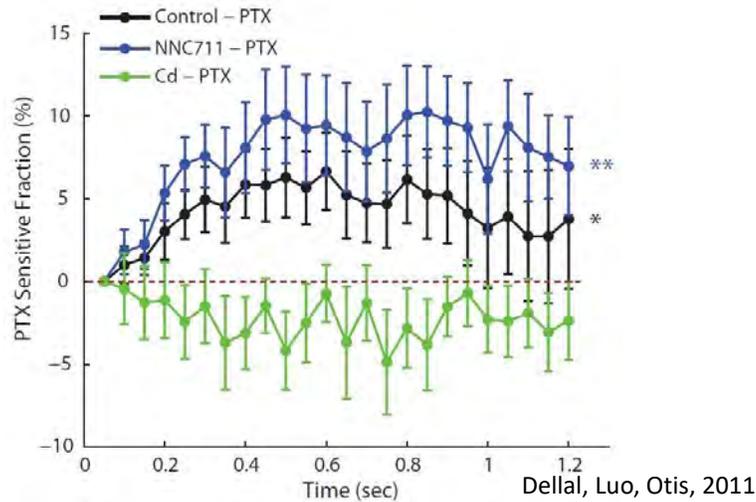
Blocking GABA reuptake prolongs parallel fiber excitation



Endogenous GABA is sufficient to increase parallel fiber excitability



Endogenous GABA is sufficient to increase parallel fiber excitability

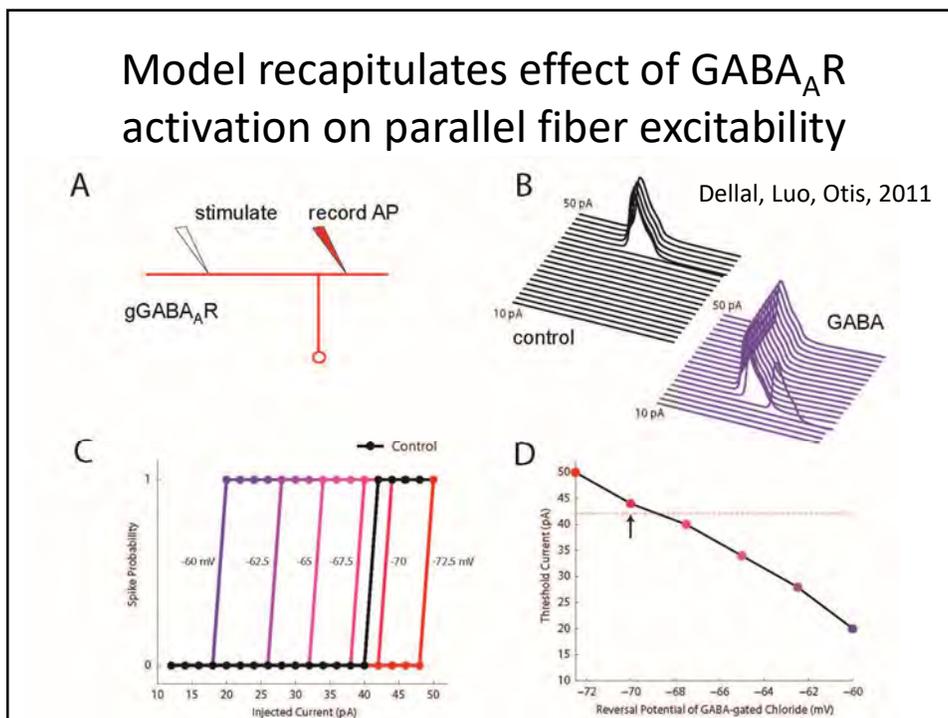
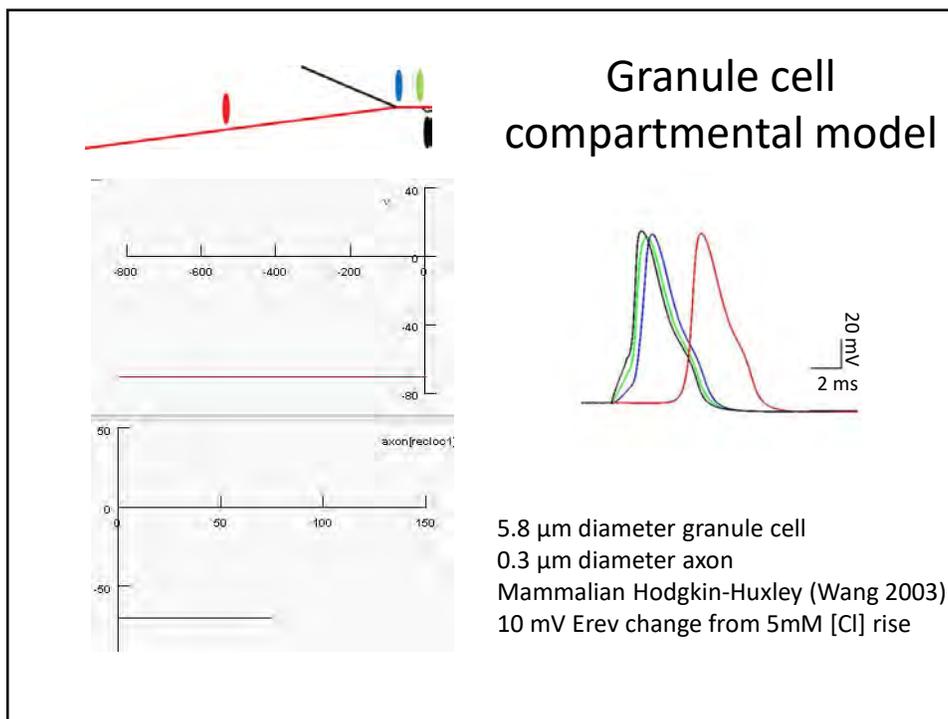


Granule cell model.

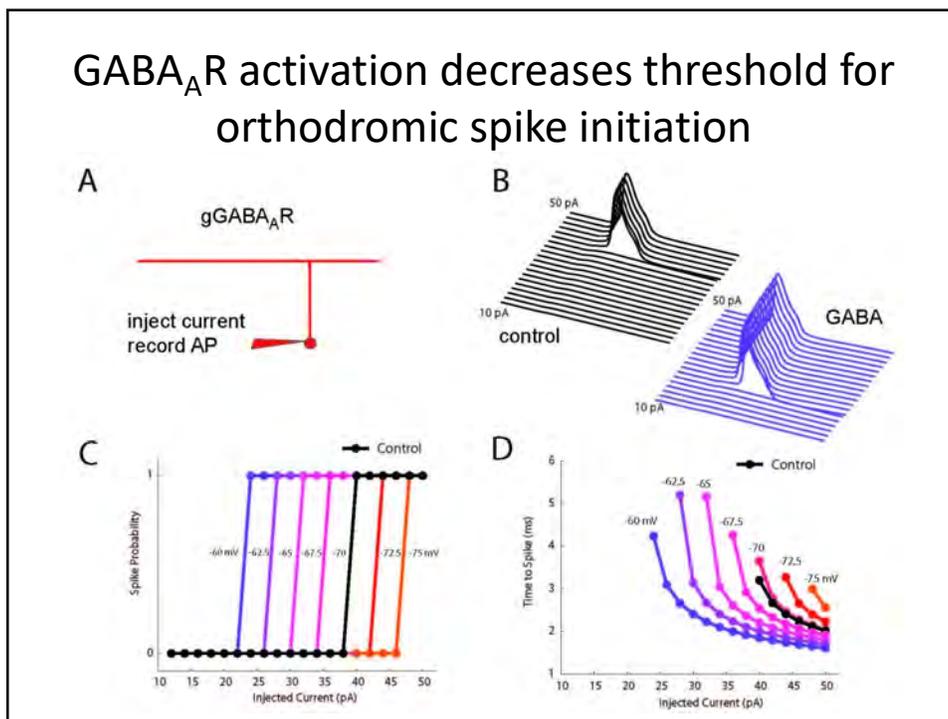
5.8 μm diameter granule cell, 0.3 μm diameter axon, 70 μm ascending branch, 0.5 mm fiber after T-junction segment simulated.

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

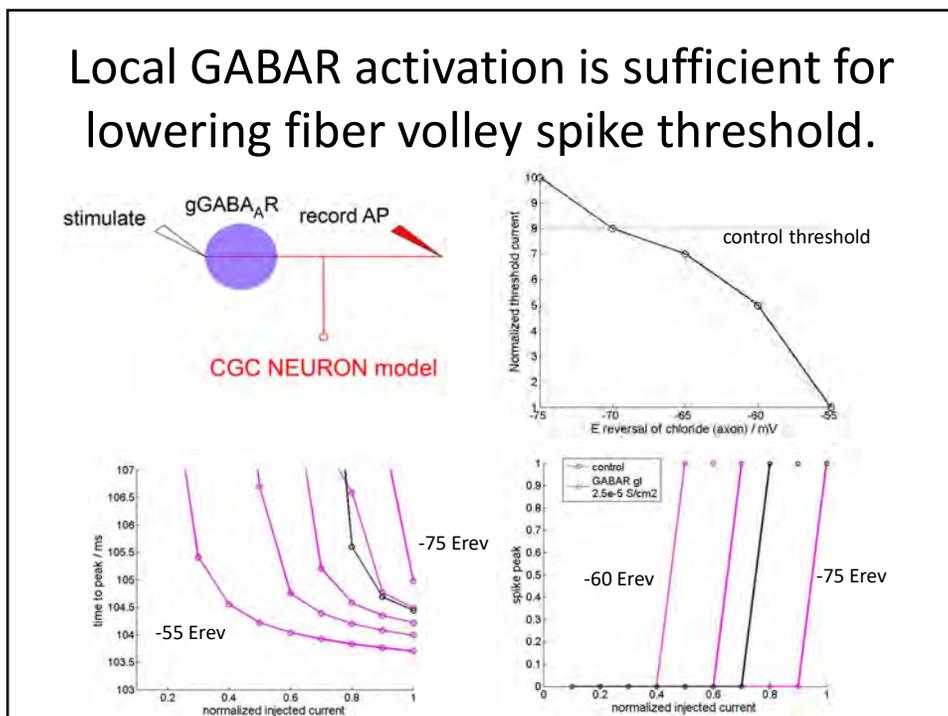
At 303 K, $[\text{Cl}]_{\text{out}} = 130 \text{ mM}$, a change in reversal potential for $[\text{Cl}]$ of 5 mV results from $[\text{Cl}]_{\text{in}}$ rise from 10.8 to 13 mM (10 mV \rightarrow $[\text{Cl}]_{\text{in}} = 15.8 \text{ mM}$).



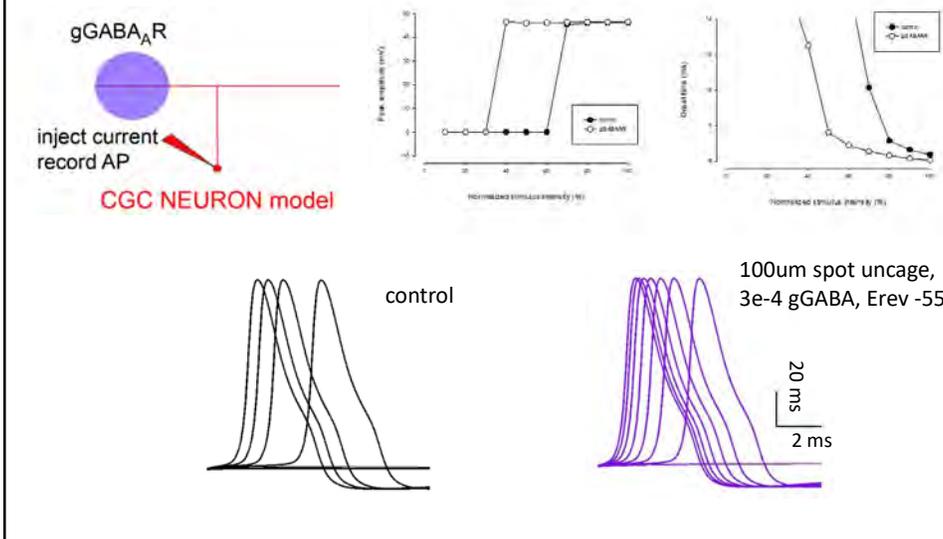
GABA_AR activation decreases threshold for orthodromic spike initiation



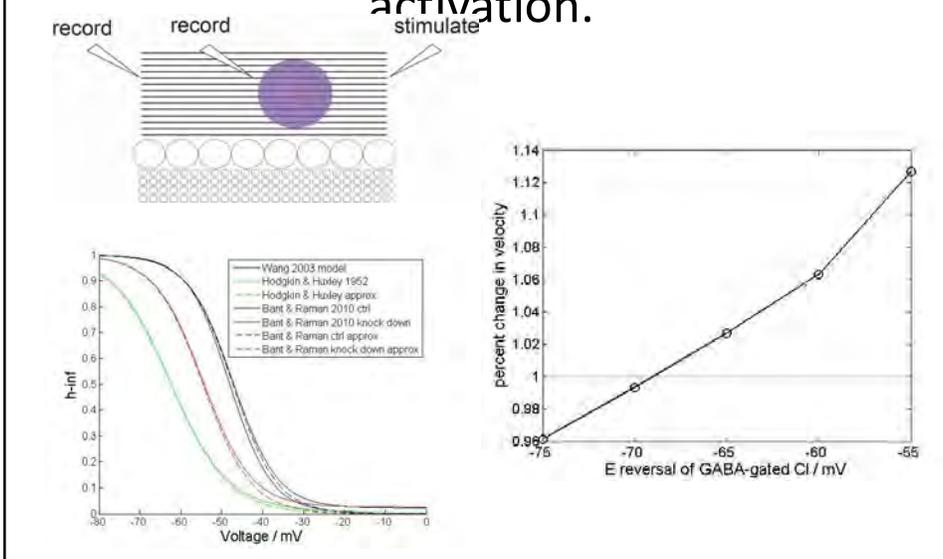
Local GABAR activation is sufficient for lowering fiber volley spike threshold.



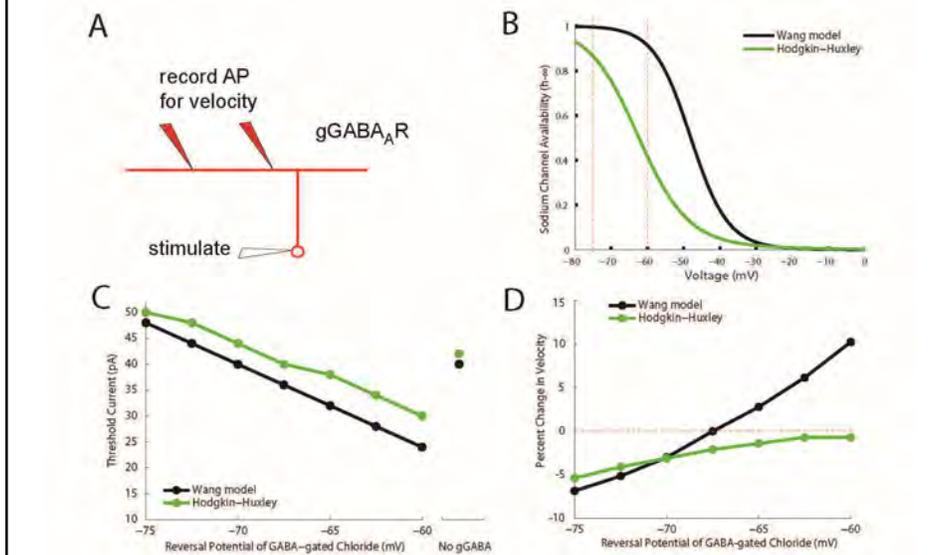
Local GABAR activation in molecular layer decreases GRC AP threshold.



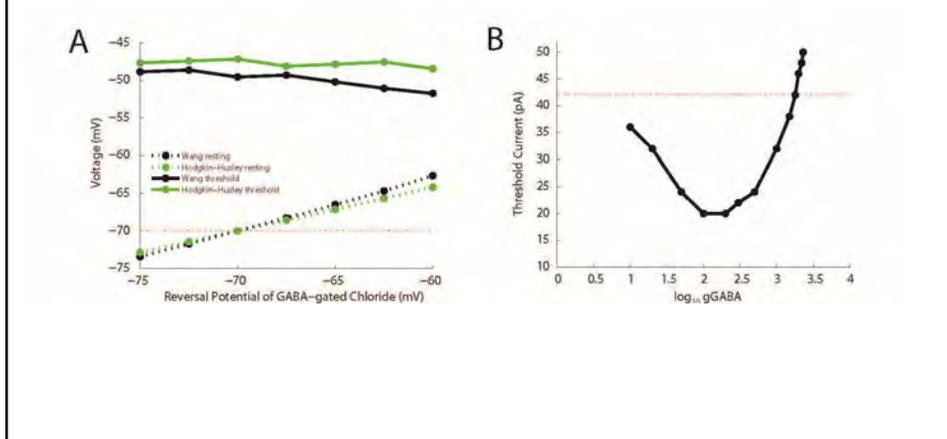
Conduction velocity is increased by local molecular layer GABAR activation.



GABA effect on conduction velocity depends on sodium channel inactivation

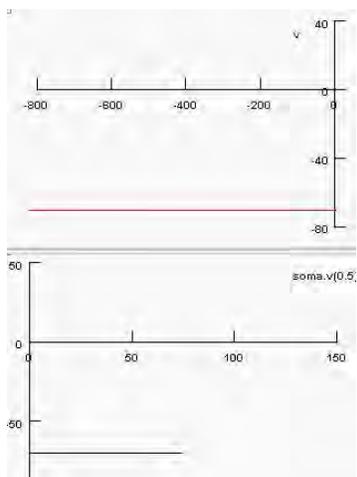


GABA_AR activation brings axon closer to threshold for spiking at low conductances.

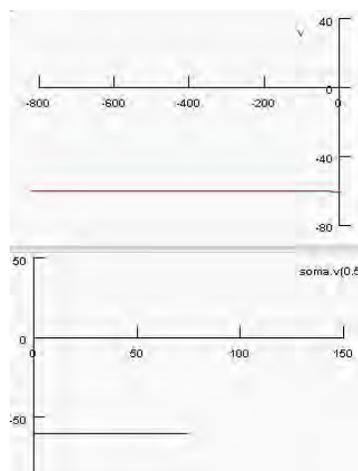


Spike failures (e.g. near the T) can occur near 100x the tonic conductance.

260x conductance, Erev -70mV.



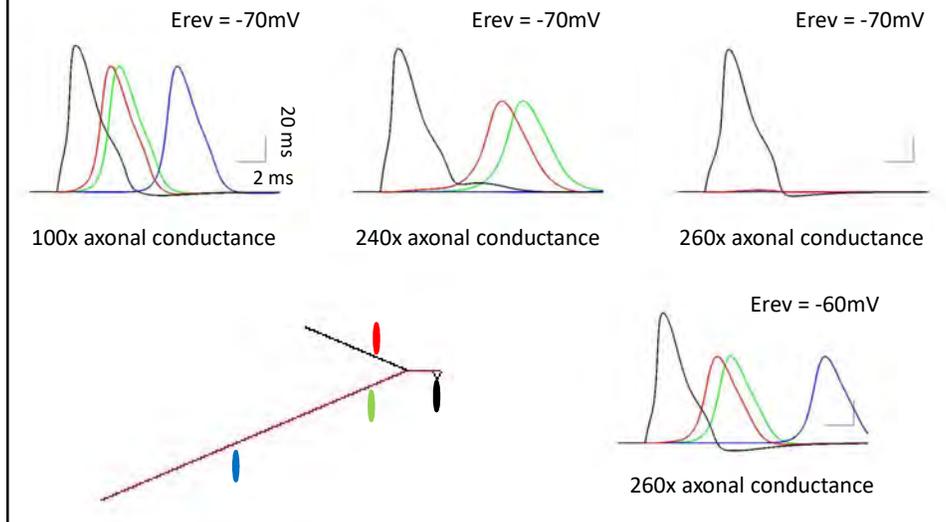
260x conductance, Erev -60mV.



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 ms



Acknowledgments (UCLA).

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- **Meera Pratap**
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- **Ka Hung Lee**
- **Matthew Shtrahman**
- **Martin Wallner**
- **Alex Reeves**
- **Vivy Tran**
- **MOM!**
- **Felix Schweizer**
- **Dean Buonomano**
- **Julio Vergara**
- **Xiao-Jing Wang (Yale)**
- **Walter Akemann (RIKEN)**
- **Moses Karakossian**
- **Malte Rasch (Beijing)**
- **And You!**

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						Ashwani Kumar	Jennifer Cutler			Surajit Sahu	





Questions?



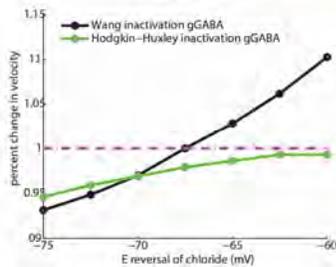
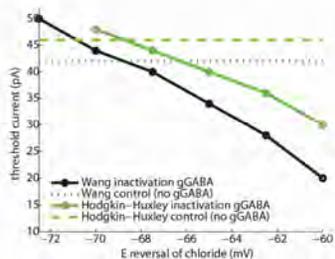
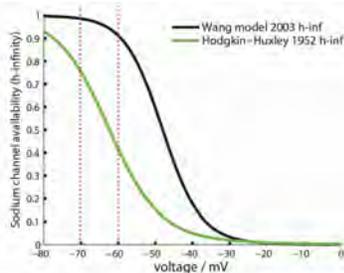
Effect of GABAR on velocity depends on sodium channel inactivation.

J. Physiol. (1952) 117, 500-544

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

By A. L. HODGKIN AND A. F. HUXLEY
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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, 1962 a-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.

