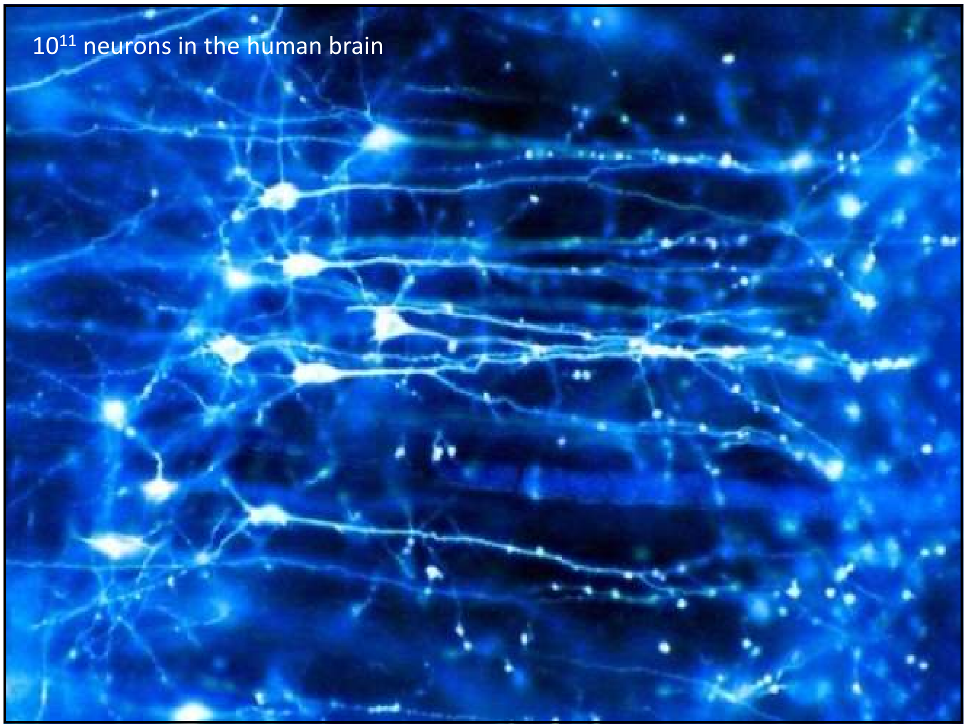
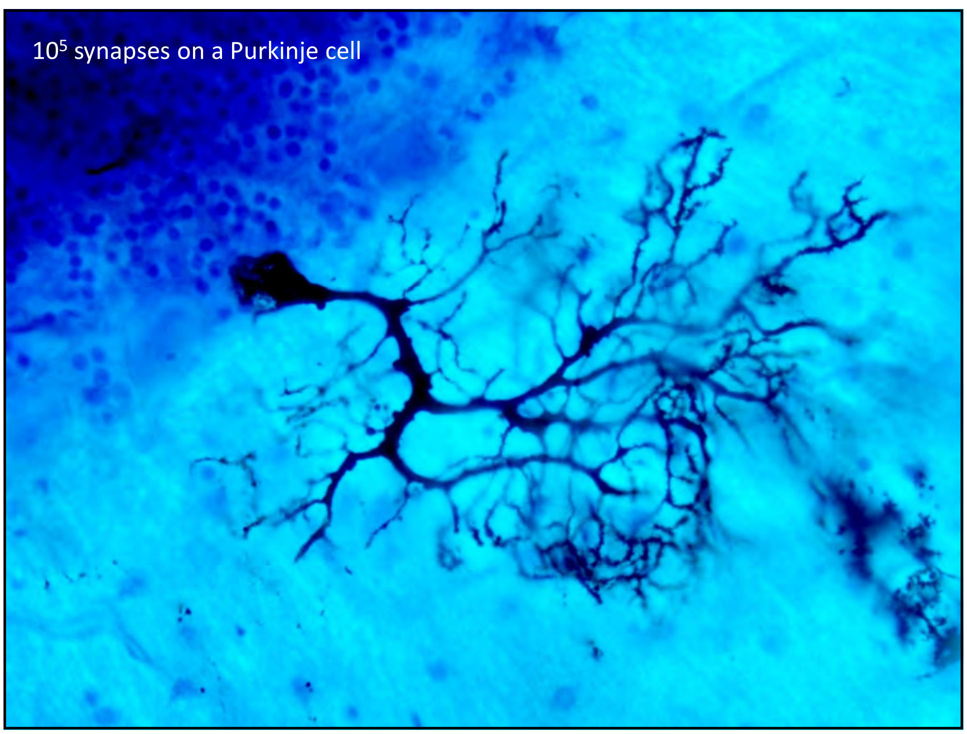
Playing Piano
(without the brain):
Movement and timing through cerebellar circuits.
Ray Luo
RIKEN BSI, UCLA

10^{10} people on Earth

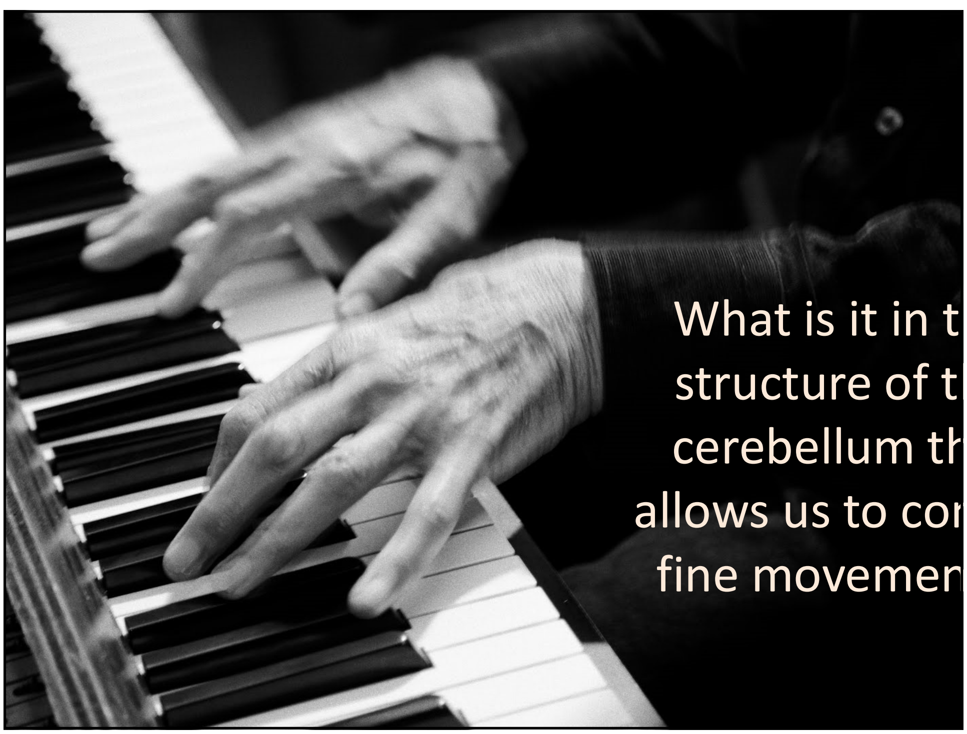

10^{11} neurons in the human brain


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.

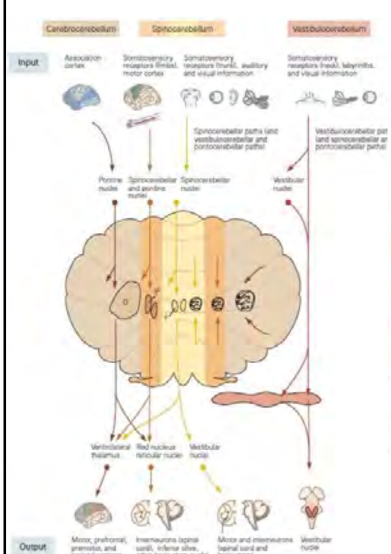
Intention tremor.



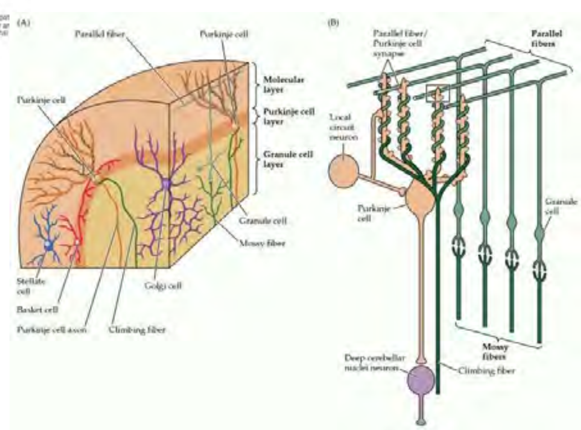
Cerebellum is compartmentalized functionally.

- Deep nuclei -> superior cerebellar peduncle.
- Vesticular input -> flocculonodular lobe -> vesticular 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.

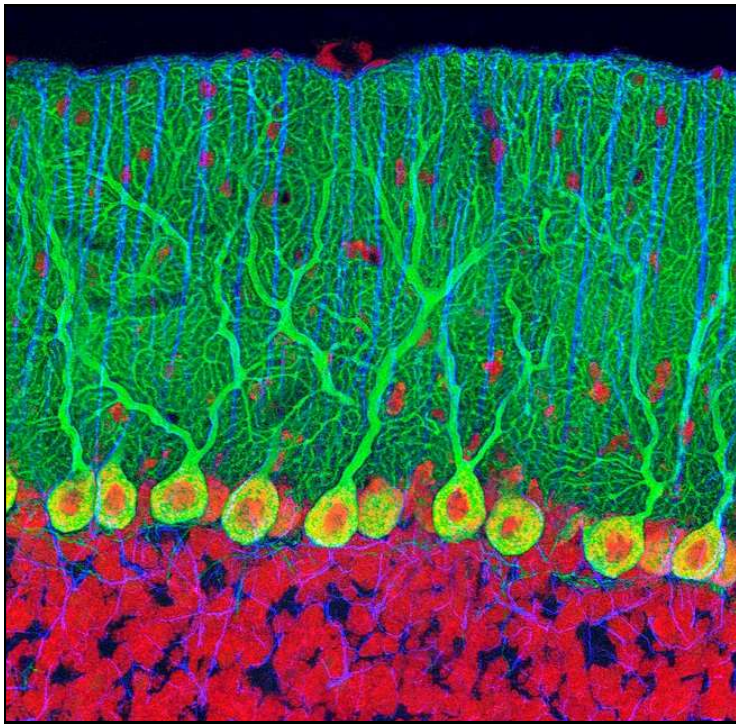
GCL: 100 billion granule cells, Golgi interneurons.
PCL: 70um Purkinje cells, -> deep nuclei, vestibular.
ML: Stellate, basket, parallel fibers relay perp to PCd



Kandel et al. 2013

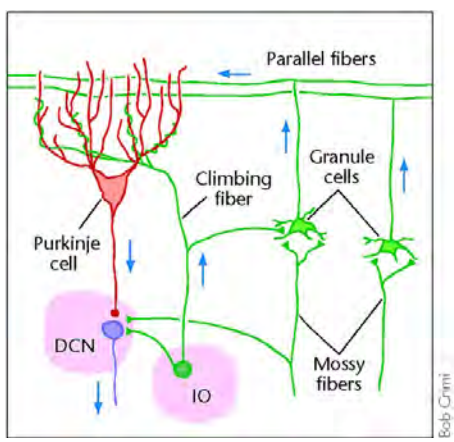


Purves et al. 2013



Cerebellum Output: Purkinje cells (inhibitory)

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



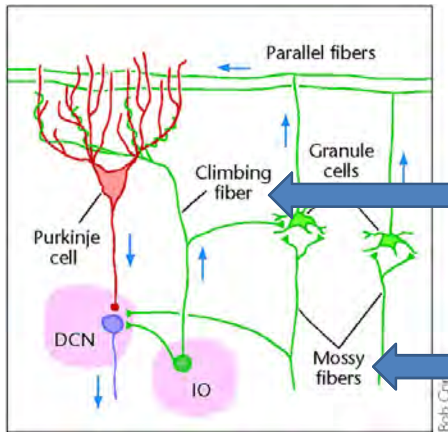
Optican, 1998

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

Purkinje Record

Climbing fiber

Mossy fiber ->
Parallel fiber



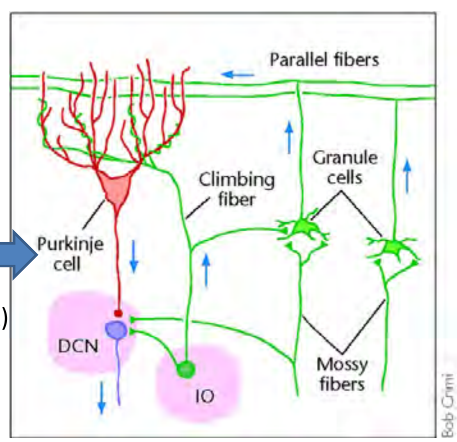
Input – Error
(one-to-one PC)
(Ca -> complex)
(IO synchrony)

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

Optican, 1998

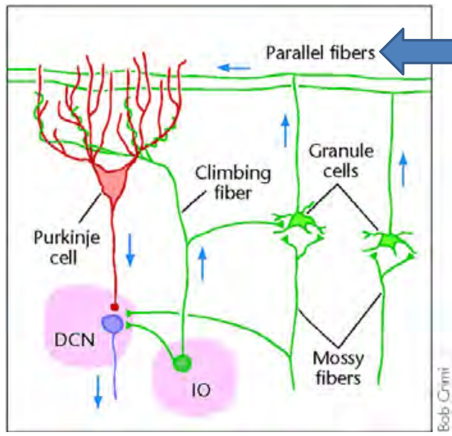
Parallel fibers are axons of granule cells, project to Purkinje cells in molecular layer

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



Optican, 1998

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

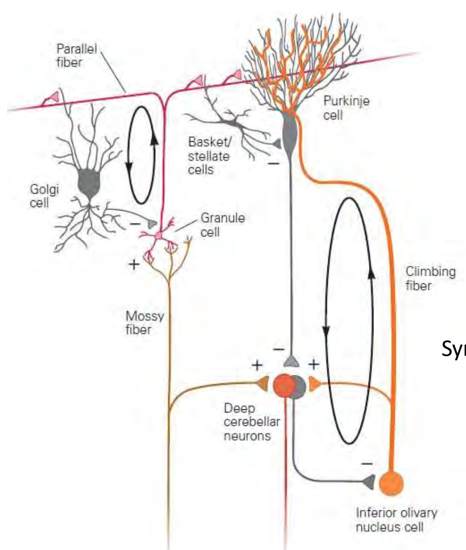


Relay
(inhibition at GCL and ML)
(Golgi cell sparse coding)
(coordinate diff comparts)
(long distance coord)

Optican, 1998

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

Sparse coding



Synchronous activation

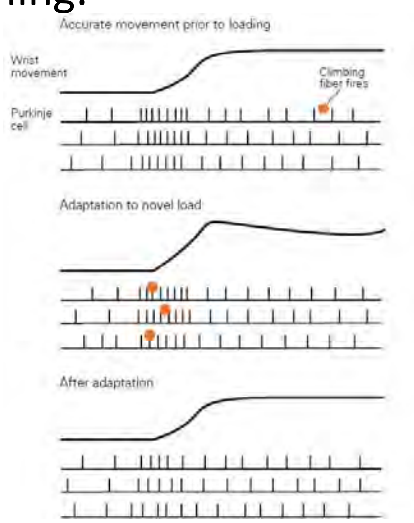
Raymond et al., 1996

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.

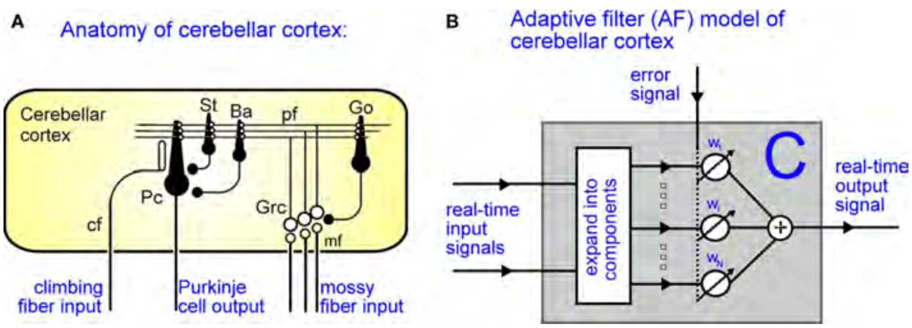
One of multiple sites of cerebellar motor learning.

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



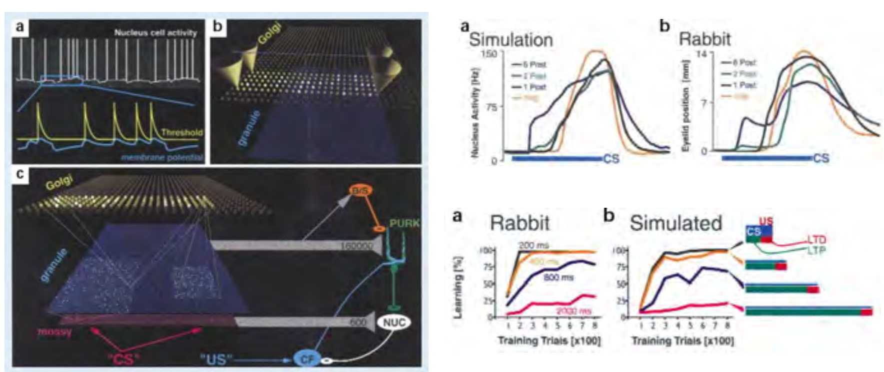
Gilbert, Thach, 1977

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



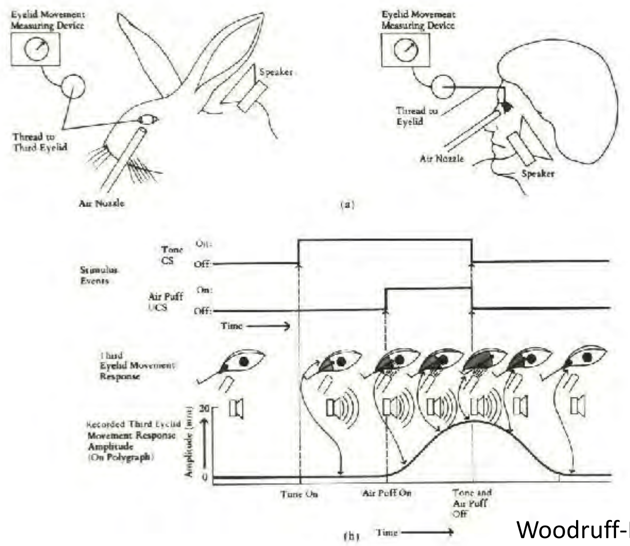
Lepora et al., 2010.

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



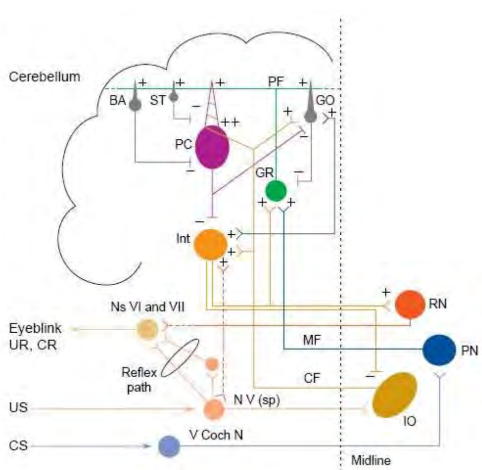
Medina, Mauk, 2000

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

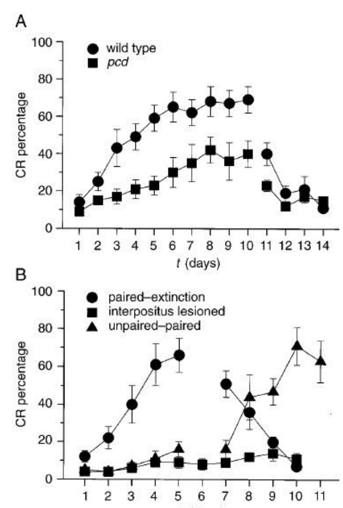


Woodruff-Pak, 2002.

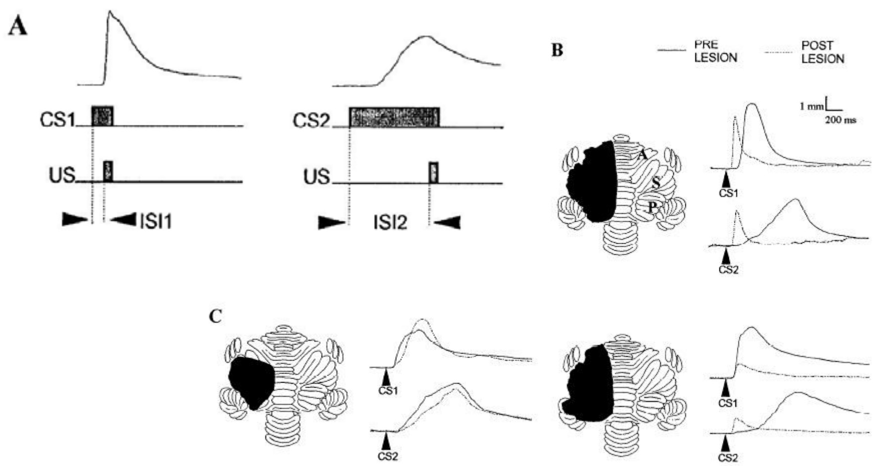
Cerebellar interpositus nuclei are necessary for learning of classical eyeblink conditioning.



Kim, Thompson, 1997

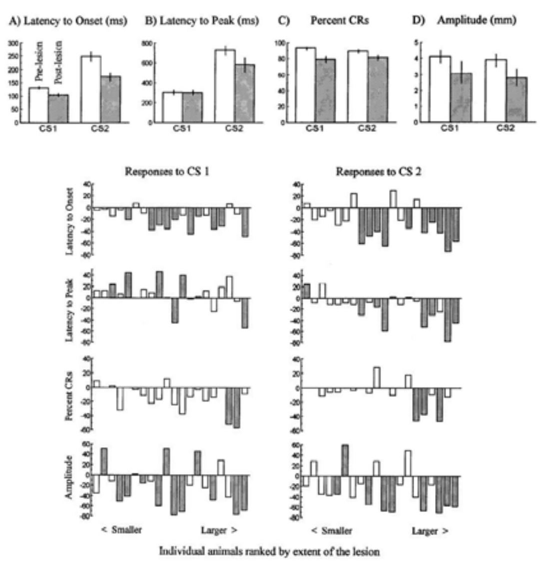


Cerebellar cortex lesions show shortened eyelid responses to 150ms and 750ms CS-US pairs.

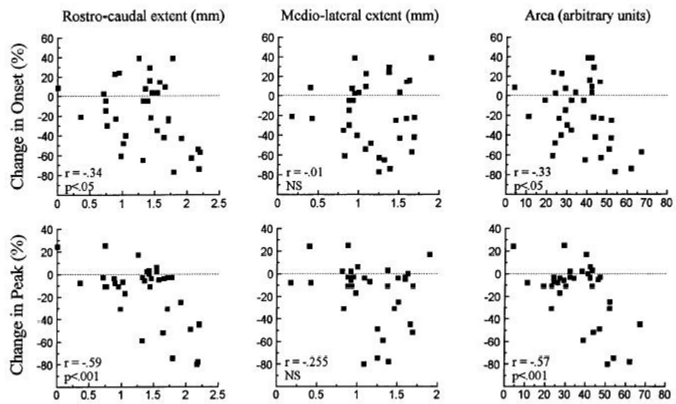


Perrett, Ruiz, Mauk 1992

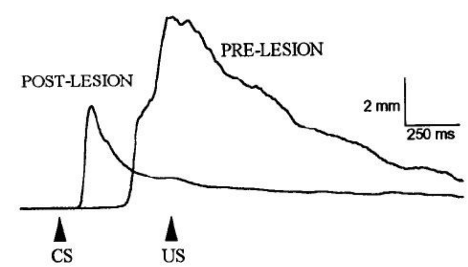
Effect on lesion on eyelid response depends on duration of CS-ISI and extent of lesion.

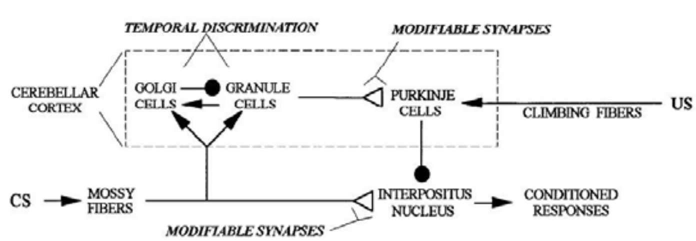


Lesion effects depend not on ML, but on RC extent of interpositus projecting parasagittal zone.



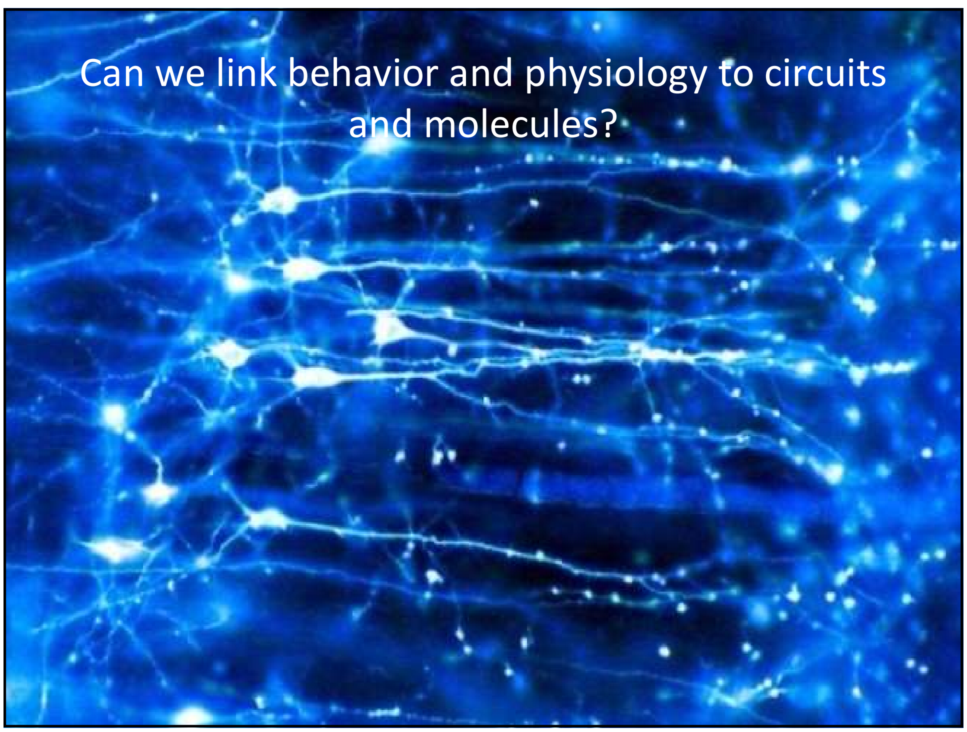
Single CS-ISI learning deficits are inconsistent with disruption of auditory discrimination.





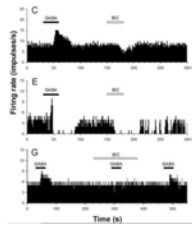
Summary of cerebellar action.

- 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).

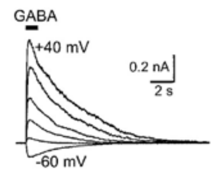


Evidence for *depolarizing* GABA action in mature neurons

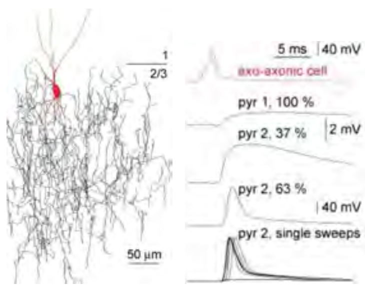
Choi et al. 2008
Suprachiasmatic
nucleus



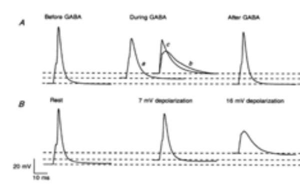
Turecek and Trussell 2002
Calyx of Held
terminal



Szabadics et al. 2006
Axo-axonic cells cerebral cortex



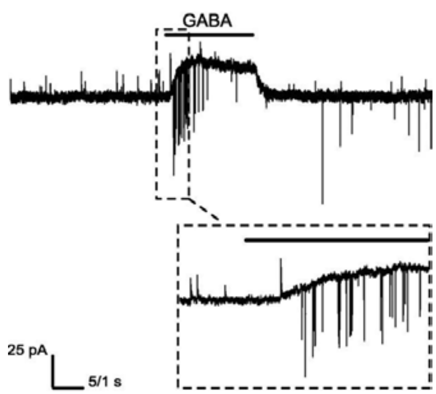
Zhang and Jackson 1995
Posterior
pituitary

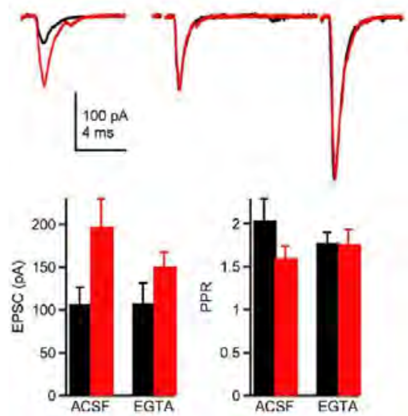


Evidence for *excitatory* GABA action in mature neurons

- 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

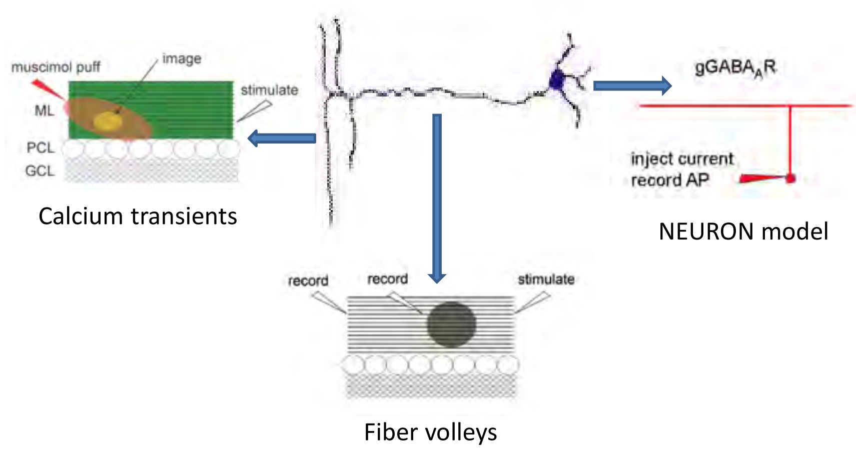




Stell, Marty 2007

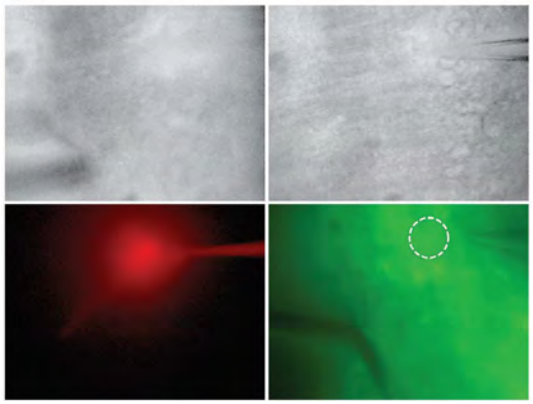
Pugh, Jahr 2011

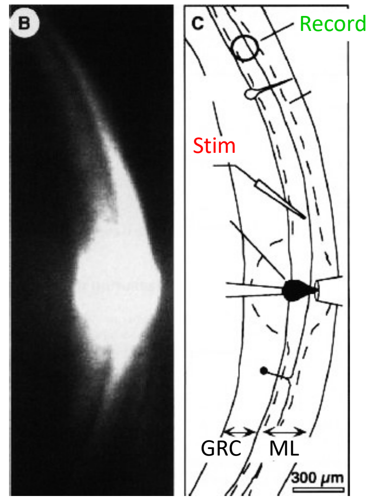
Where do we come from?
Where are we going?



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

Oregon Green BAPTA-1 AM -> transverse slice

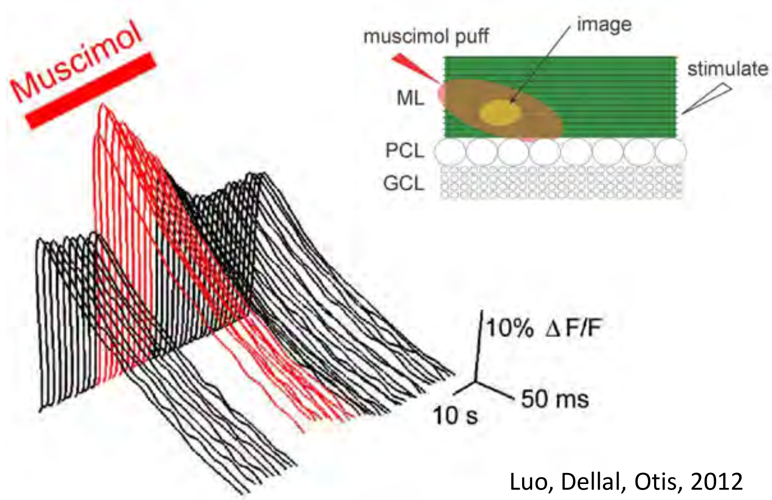




Luo, Dellal, Otis, 2012

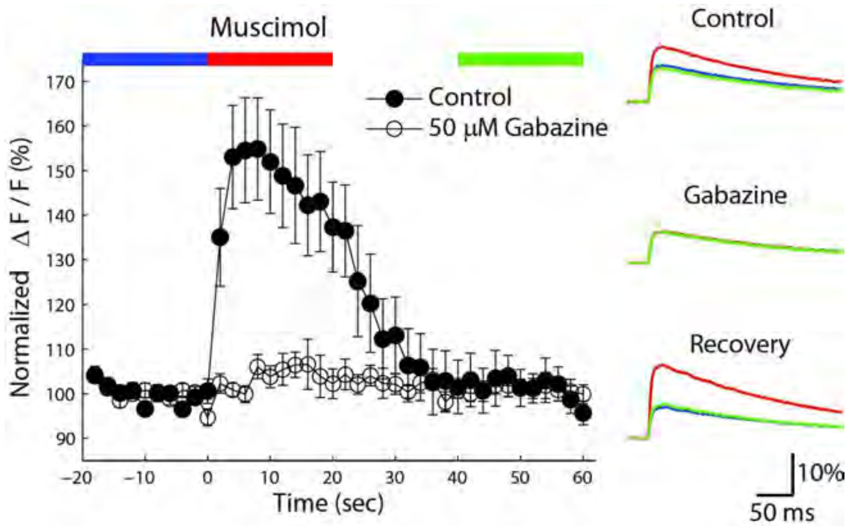
Regehr and Atluri, 1997

Presynaptic calcium transients are potentiated by $GABA_A$R agonist muscimol



Luo, Dellal, Otis, 2012

Presynaptic calcium transients are potentiated by $GABA_AR$ agonist muscimol



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

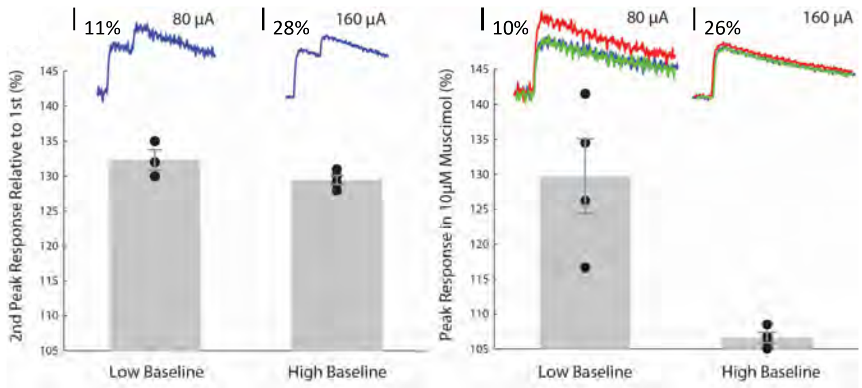
Low Stimulation

Low Stim and GABA activation

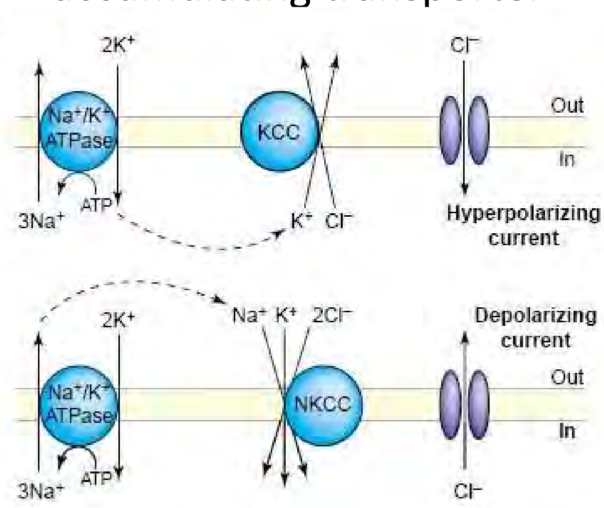
High Stimulation

High Stim and GABA activation

GABA$_A$R activation brings additional fibers closer to threshold for spike generation

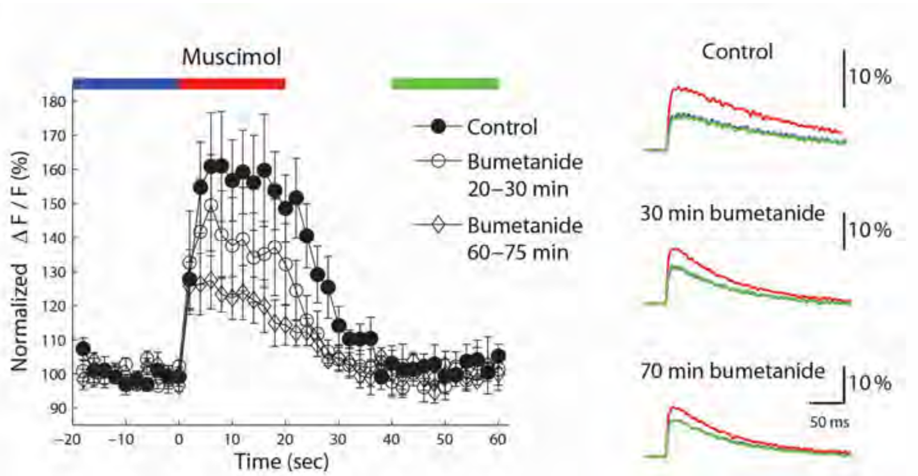


NKCC1 transporter is the chloride accumulating transporter

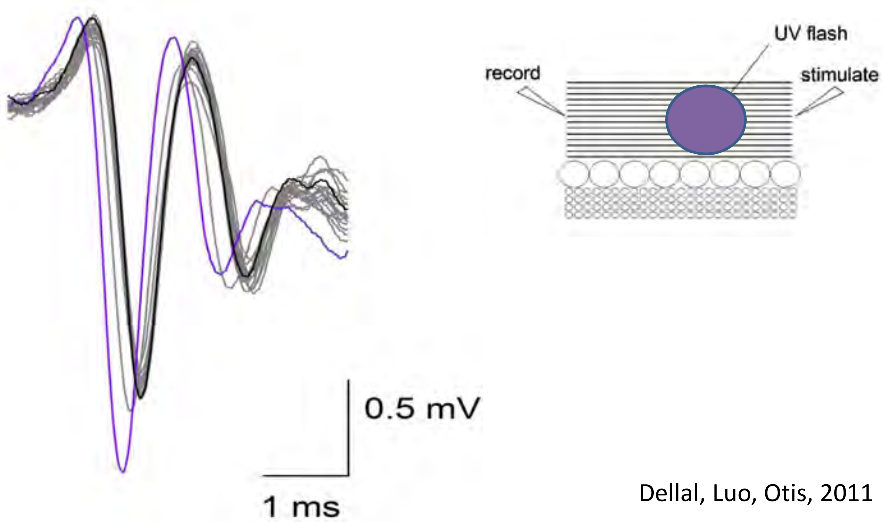


Payne et al. 2003

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

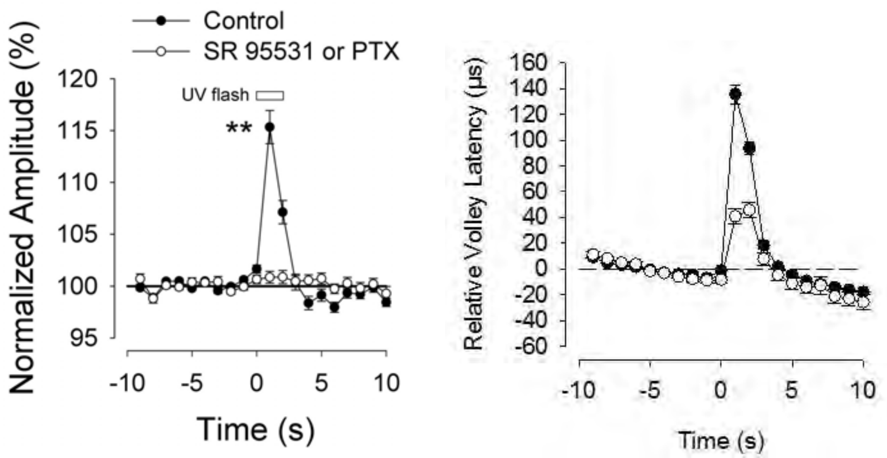


Compound action potential (fiber volley) amplitude is increased by uncaging GABA

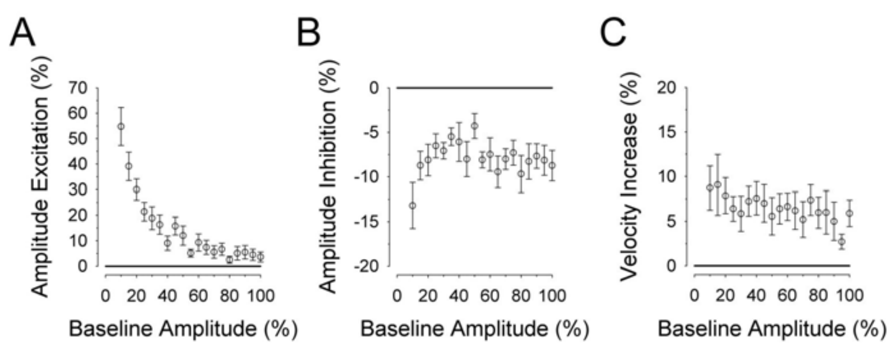


Dellal, Luo, Otis, 2011

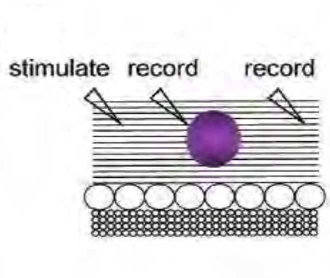
$GABA_AR$ activation increases fiber volley amplitude and shortens latency

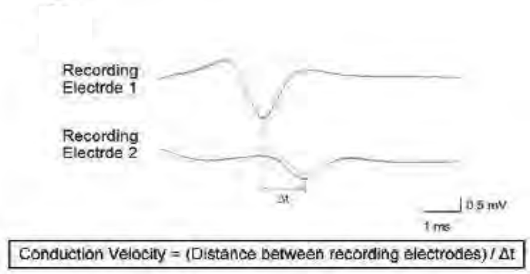


Stimulation variation on fiber volley shows recruitment of axons by GABA

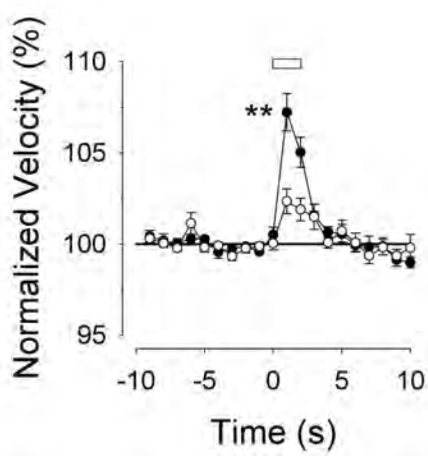


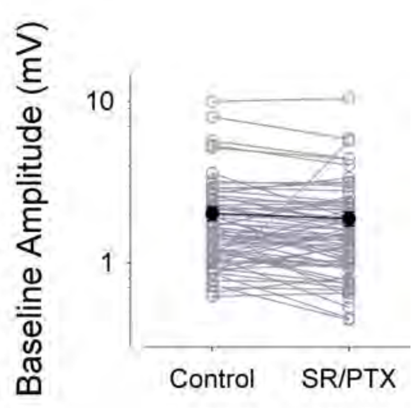
Conduction velocity measurements using fiber volleys in a transverse slice



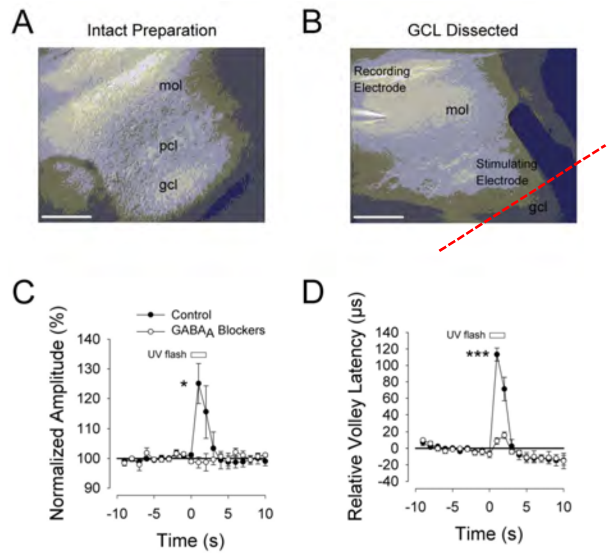


GABA$_A$R activation increases fiber volley conduction velocity

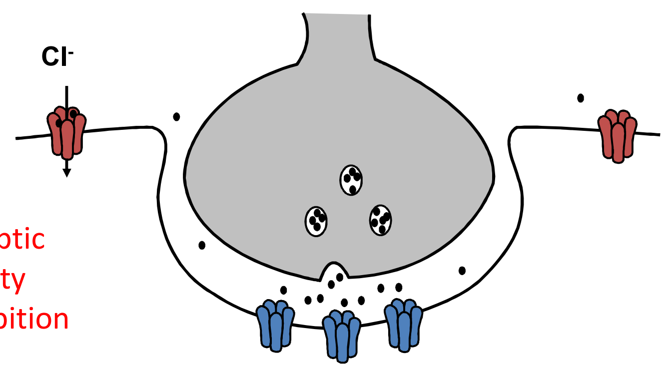




GABA-mediated excitation of parallel fibers is independent of granule cell



$GABA_A$ receptors can be categorized into two major types

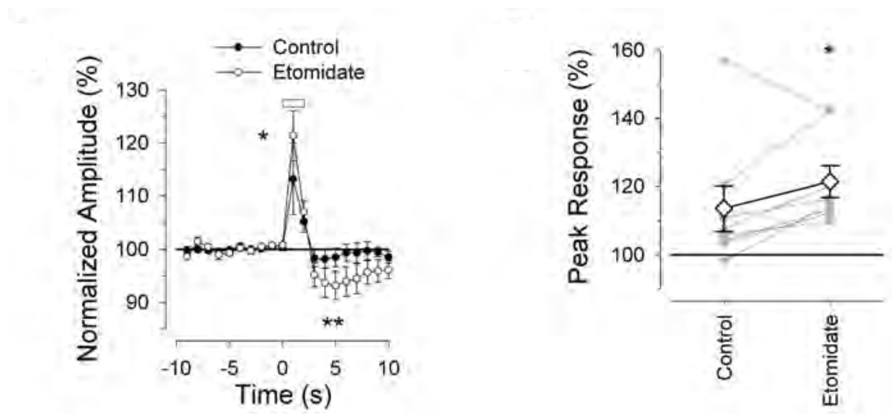


- extrasynaptic
- high affinity
- tonic inhibition
- α(4/6) β δ

- synaptic
- low affinity
- phasic inhibition
- α(1/2/3/5) β γ

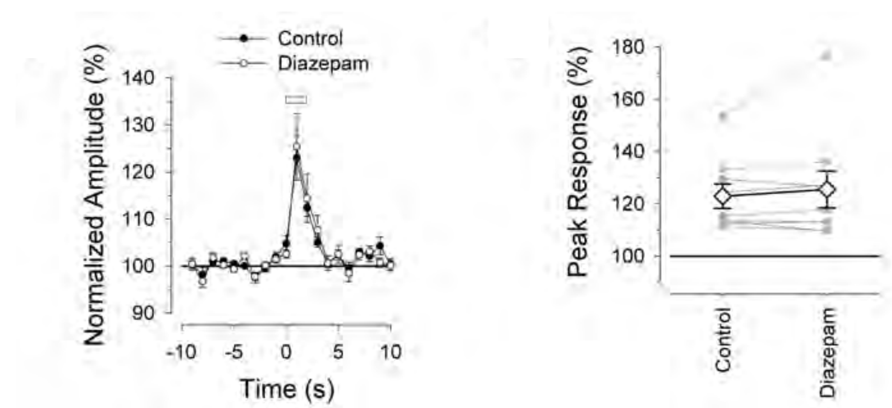
Granule cells: $\alpha_{1/6}\ \beta_{2/3}\ \delta/\gamma_2$

GABA$_A$R-mediated increase in excitability is sensitive to etomidate



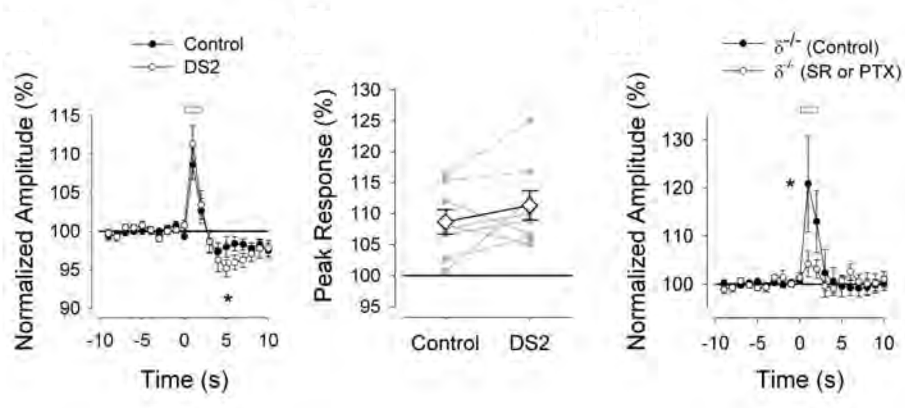
Sensitivity: β_2 or β_3 , independent of δ or γ

GABA$_A$R-mediated increase in excitability is unaffected by diazepam



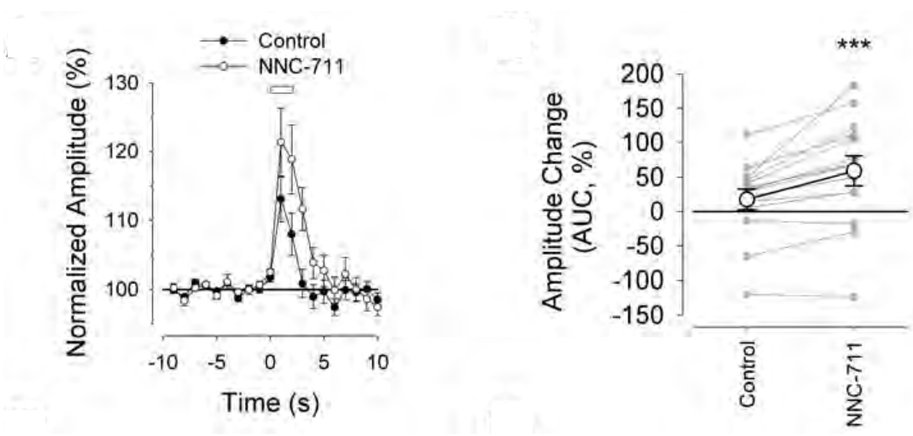
Sensitivity: lacking α_4 and α_6 , but contains γ

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

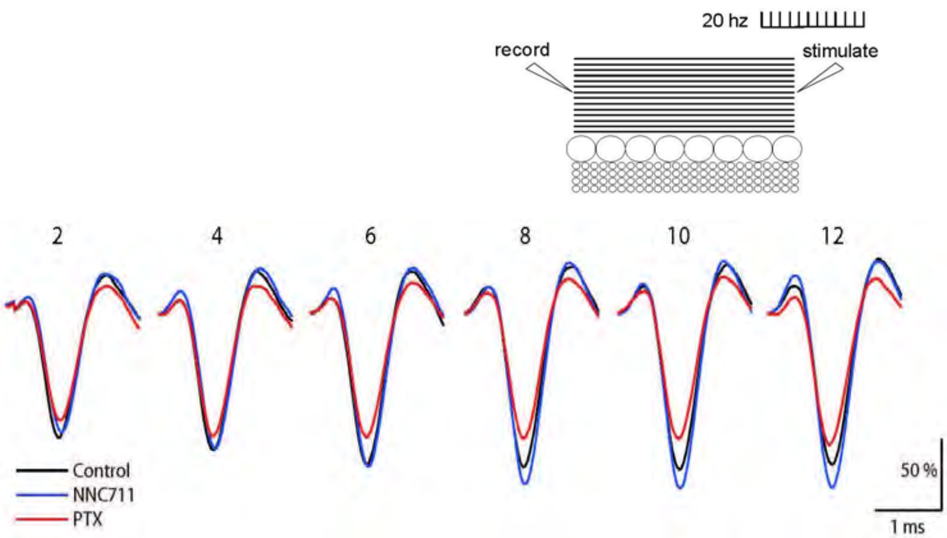


Sensitivity: δ

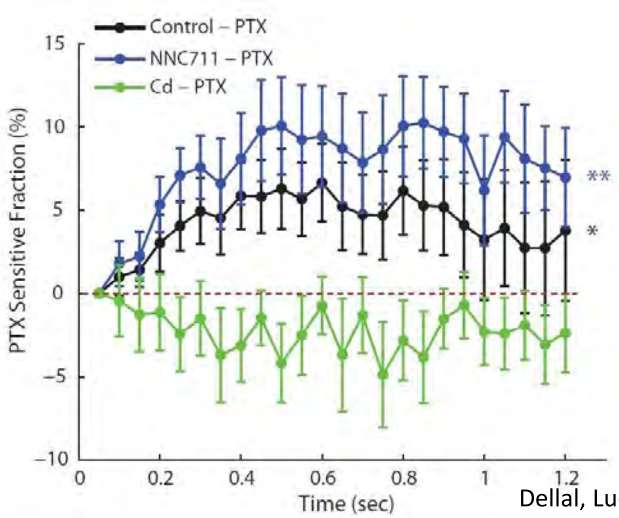
Blocking GABA reuptake prolongs parallel fiber excitation



Endogenous GABA is sufficient to increase parallel fiber excitability



Endogenous GABA is sufficient to increase parallel fiber excitability



Dellal, Luo, Otis, 2011

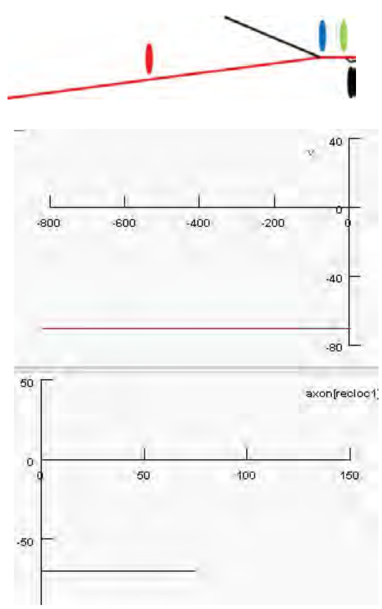
Granule cell model.

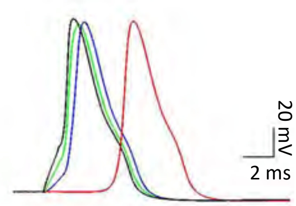
5.8 um diameter granule cell, 0.3 um diameter axon, 70 um ascending branch, 0.5 mm fiber after T-junction segment simulated.

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 -> [Cl] in = 15.8 mM).

Granule cell compartmental model

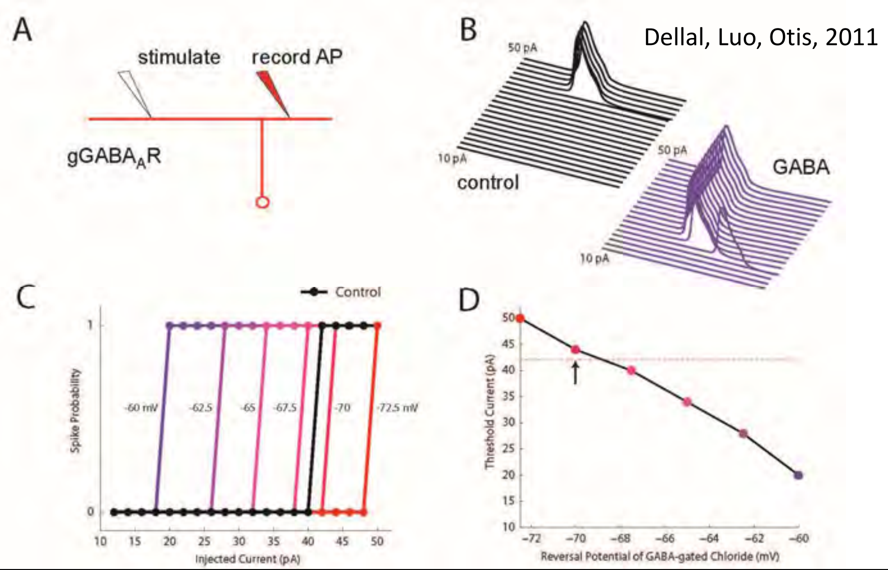




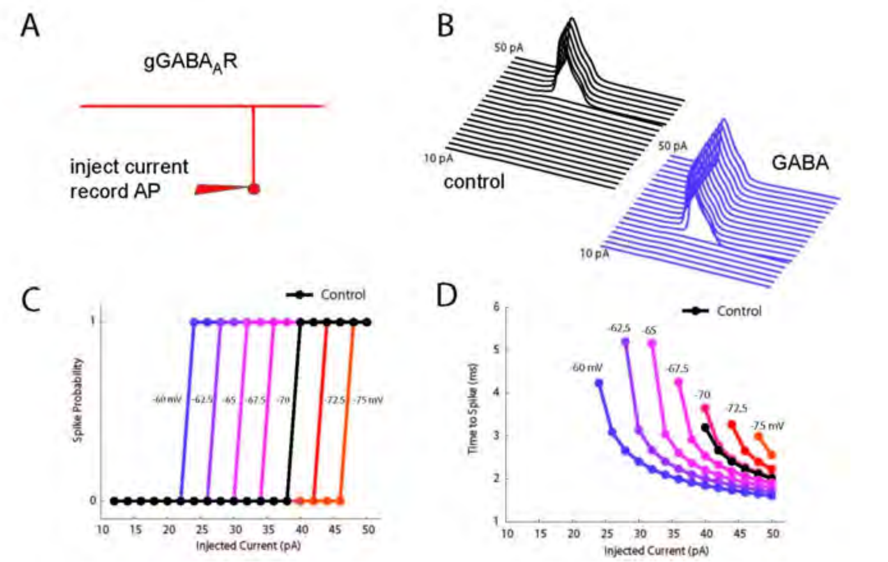
5.8 µm diameter granule cell
0.3 µm diameter axon
Mammalian Hodgkin-Huxley (Wang 2003)
10 mV Erev change from 5mM [Cl] rise

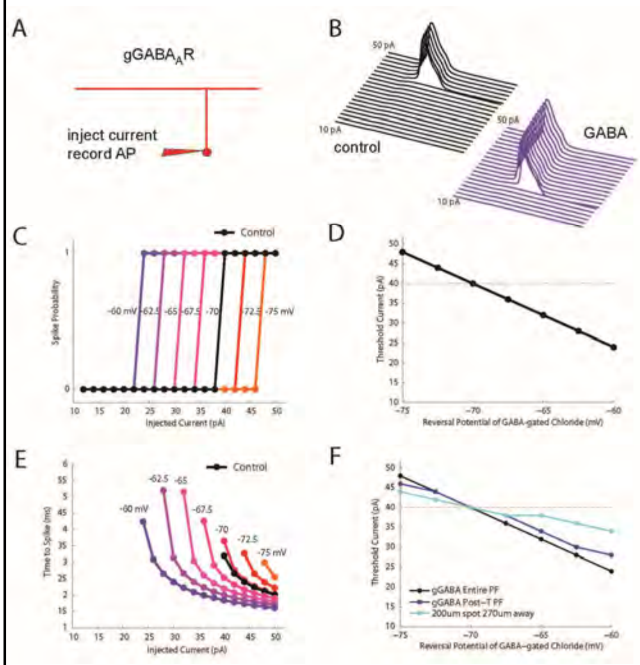
Model recapitulates effect of $GABA_AR$ activation on parallel fiber excitability

Dellal, Luo, Otis, 2011



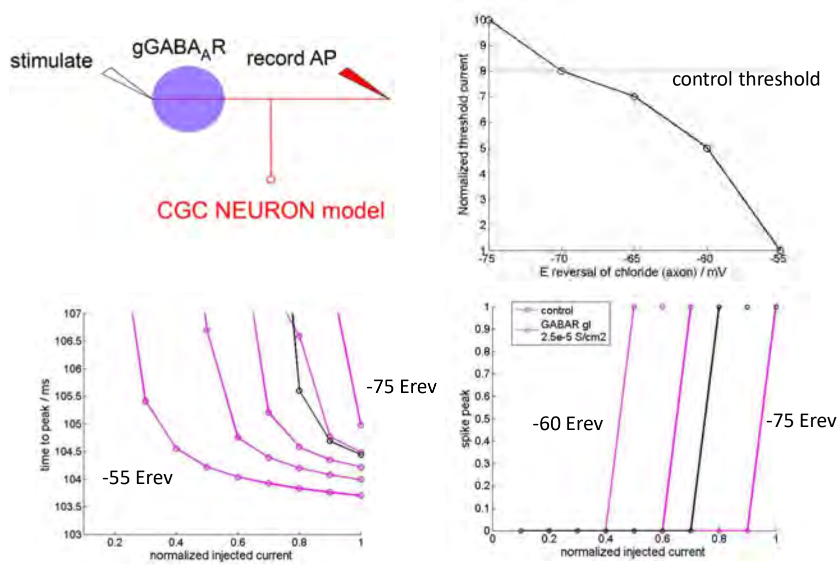
$GABA_AR$ activation decreases threshold for orthodromic spike initiation



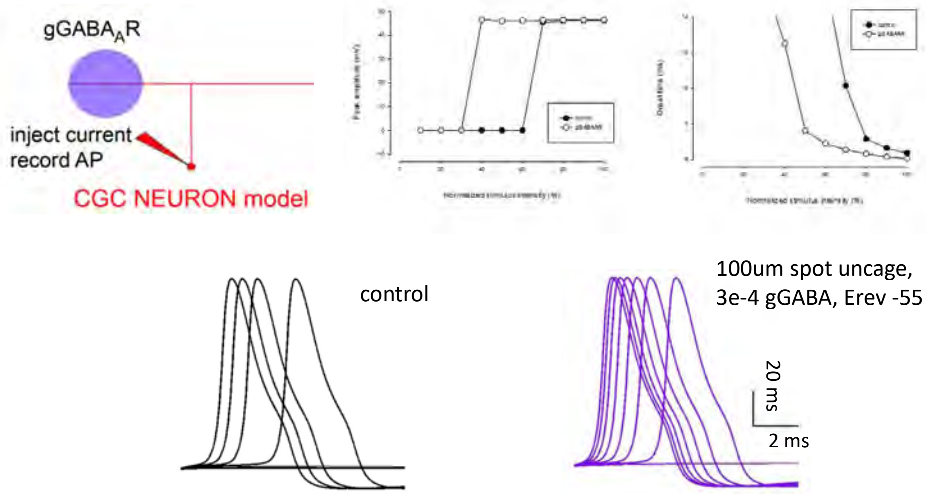


Effect on spike threshold at granule cell.

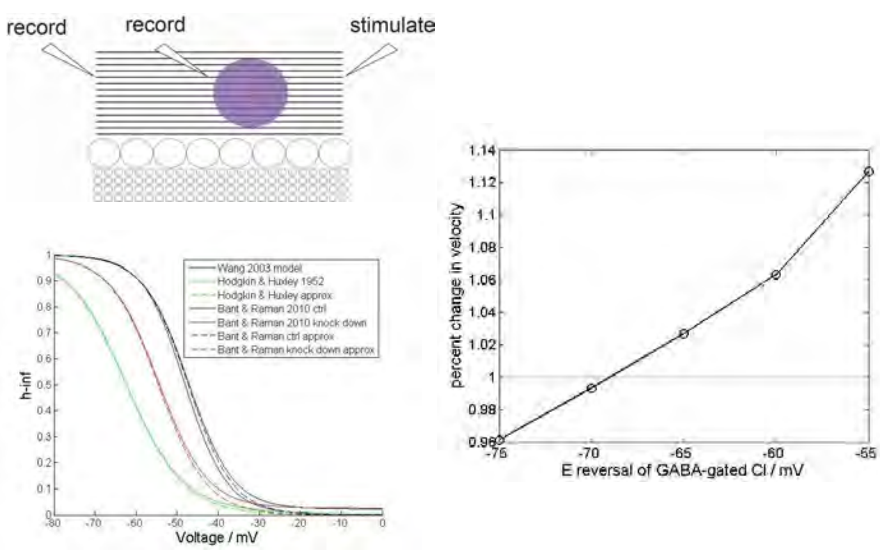
Local GABAR activation is sufficient for lowering fiber volley spike threshold.



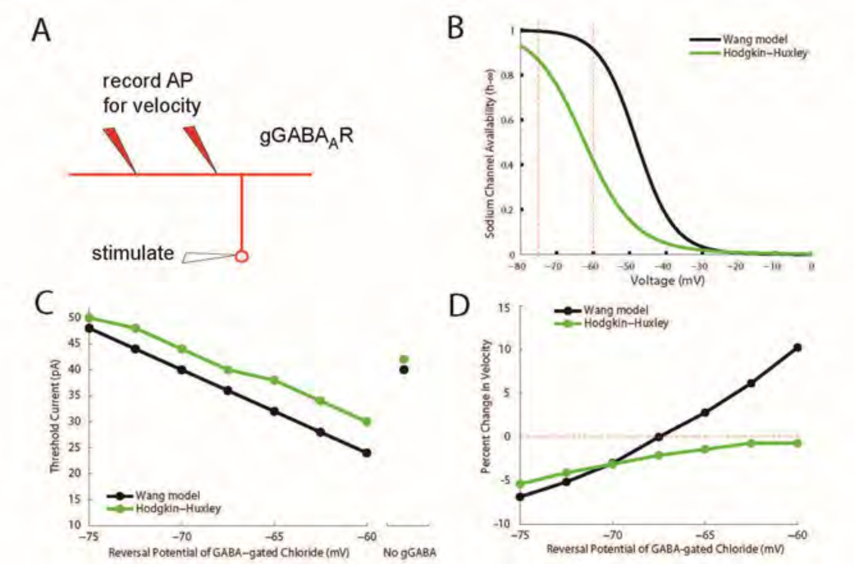
Local GABAR activation in molecular layer decreases GRC AP threshold.



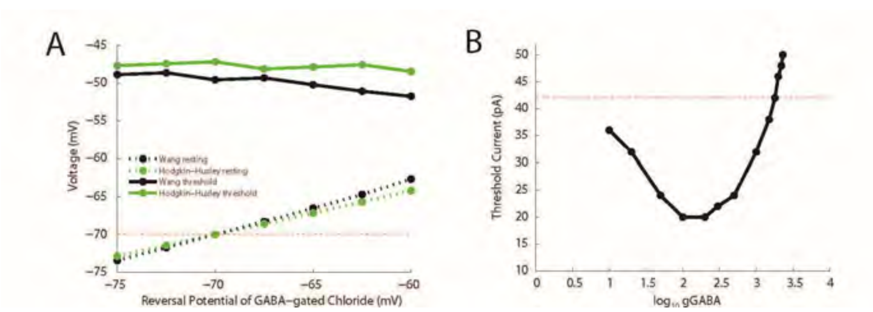
Conduction velocity is increased by local molecular layer GABAR activation.



GABA effect on conduction velocity depends on sodium channel inactivation

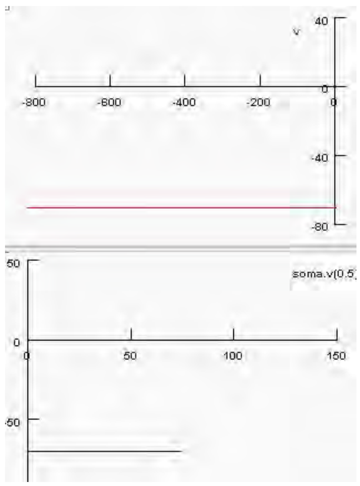


GABA$_A$R activation brings axon closer to threshold for spiking at low conductances.

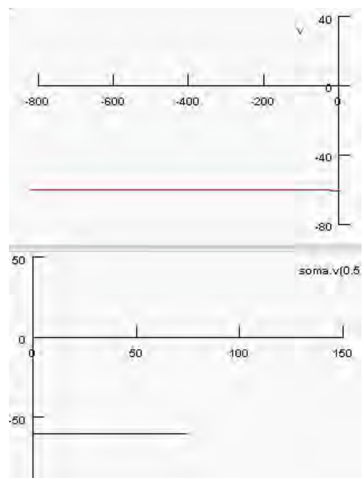


Spike failures (e.g. near the T) can occur near 100x the tonic conductance.

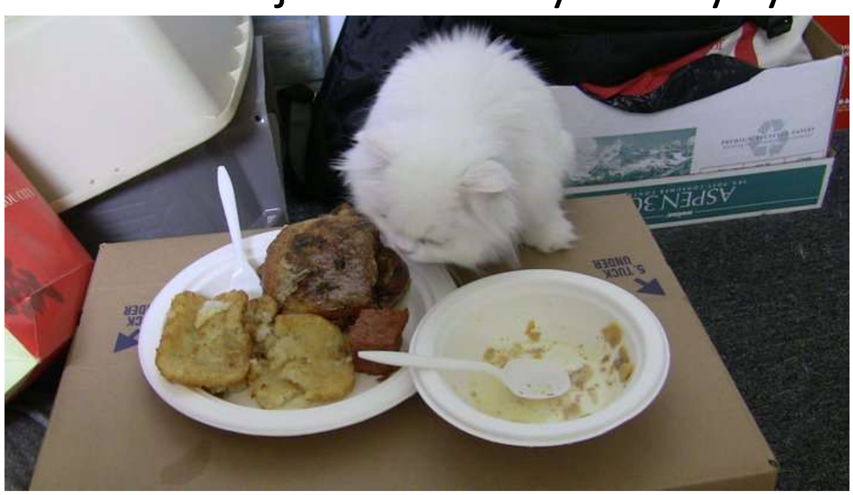
260x conductance, Erev -70mV.

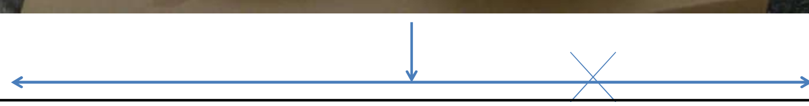


260x conductance, Erev -60mV.

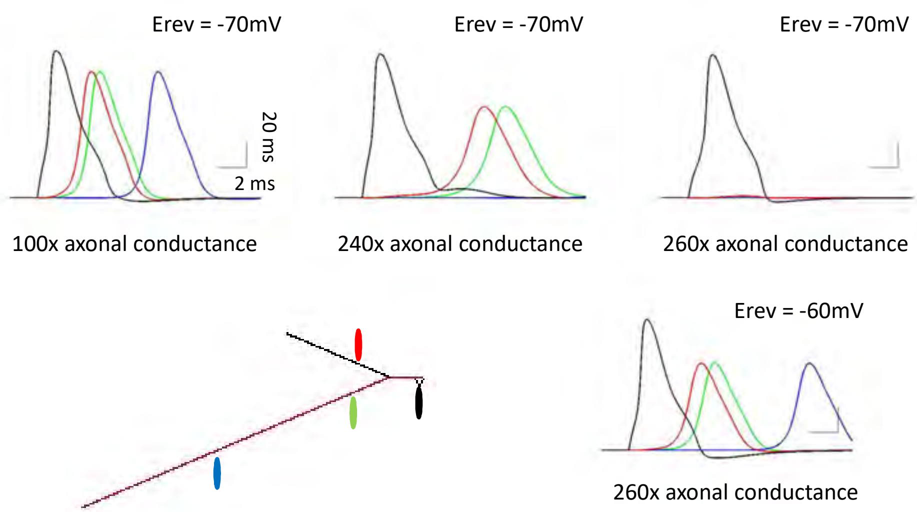


Can GABA excitation relieve spike failures at T-junction? My cat says yes.





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



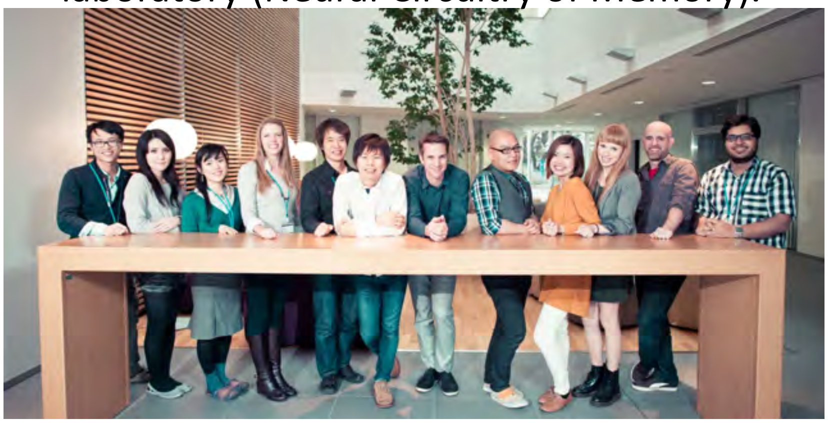
What it means to be fast? 10% increase from 200 µm/ms => 2 ms

What it means to be fast? Version 2.0 Fast Times

Acknowledgments (UCLA).

- Tom Otis
- Meera Pratap
- Shlomo Dellal
- Paul Mathews
- Jaione Maiz
- Joyce Wondolowski
- 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)
- Movses Karakossian
- Malte Rasch (Beijing)
- And You!

RIKEN Brain Science Institute Josh Johansen laboratory (Neural Circuitry of Memory).



Ray Luo, Mami Kimura, Mai Iwasaki, Lindsay Preston, Akira Uematsu, Takaaki Ozawa, **Joshua Johansen**, Edgar Ycu, Baozhen Tan, Jenny Koivumaa, Jake Ormond, Touqueer Ahmed

Jlab
JOHANSEN LABORATORY

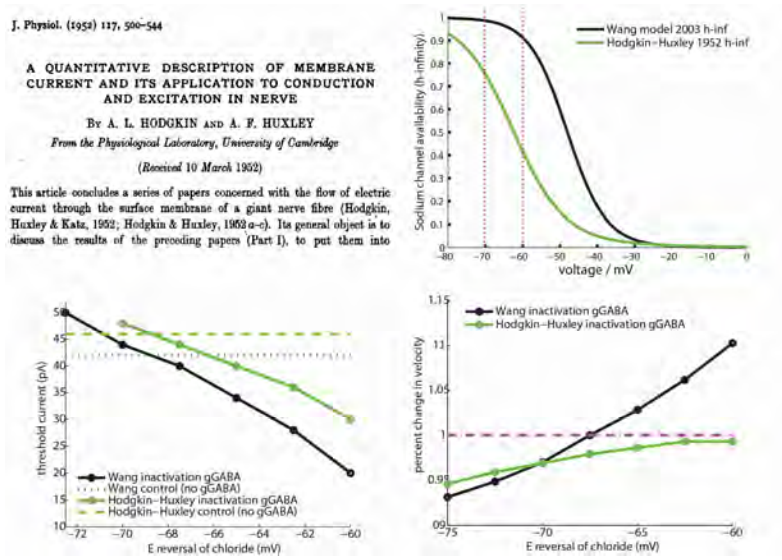
Ashwani Kumar

Jennifer Cutler

Surajit Sahu

Questions?

Effect of GABAR on velocity depends on sodium channel inactivation.



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