Big Biology Questions

- Why does L5 TT both produce behavior and pool objects?
- Why does L5 TT receive direct VPM input?
- What is the role of bursting?
- What is the role of thalamic burst/tonic mode?
- What can L5 do?
- Does L5 make no sense without other layers?
- What role does burst/tonic mode have in primary sensory thalamus and elsewhere?

Speculation Toolset

- Output layer minicolumns are for attribute context so can pool equivalent contexts into objects.
- Disambiguation of possibilities in learning, starting with assumptions or random connectivity.
- Bursting = predicted input.
- Second-scale integration by short term depression.
- Temporal context reset (sequence context, possible objects, etc.) by becoming silent.
- RA/phase coding for speed invariance.
- Sequences as part of object representation.
- L5 TT responds with long duration EPSPs, and L2/3 might decide which responses are sustained. So L5a could do the same because longer latency than L5b, like L2/3.
- L5a activity might increase during behavior not because it responds to it, but because it causes it (-> L5b/striatum).
- Maybe if a cell's segments have access to overlapping sets of inputs (because each axon targets multiple segments), it responds to different things similarly. E.g. in temporal memory, allows partial invariance to sequence context because the same SP item has overlapping active cells in different sequence contexts.
- Maybe NMDA spikes being long duration signals helps provide the sustained signal for plateau potentials.
- L2/3 has a map of whisking setpoint-centric space, so it converts from orientation-dependent input to orientation-invariant.
- Burst as change in perception or predicted input.

Random Ideas (clean this out)

- Does L5 only target m-type thalamus i.e. thalamus which doesn't -> L4?
- If SOM causes only one tuft segment to be able to respond, then the only way to generate a plateau potential with non-primary tuft input is by a bAP, since one tuft NMDA spike is insufficient w/o another NMDA spike, an EPSP, or a bAP.

- Maybe SOM cells limit tuft spiking to single segments not by inhibiting all but one, but rather by preventing spread between branches.
- Maybe just as somatic input substantially reduces the apical threshold, basal plateau does the same. It causes similar firing rates to weak somatic input.
- Maybe competition for predictions (e.g. with SOM FDDI if bursting = predicted firing or by firing at low rates when predicted) can help deal with SM thinking it recognizes the sequence after it starts in the middle, because it causes there to be different predictions generated by unpredicted entirely activated minicolumns versus predicted minicolumns. Or might help with other issues e.g. not knowing the place in the sequence when portions repeat.
    - E.g. when the sequence is recognized, it acts as apical input, causing low frequency firing of predicted cells, whereas basal predictions alone do not cause any firing. So low frequency firing depends on the sequence. Example sequence: ABCBCD, with only ABC known. When it gets to the second B, minicolumns burst, but current SM thinks it recognizes the second C's sequence context because the prediction is still made since the predictor cells are on, just in bursting minicolumns. So it learns multiple predictions for C in this sequence, B and D. It also has to relearn sequence context for C once B learns the sequence context.
    - To deal with that issue, don't make the prediction from the bursting minicolumns for the second B. But still need to make some predictions from bursting minicolumns for the start of the sequence.
    - So bursting minicolumns merely narrow down the possible contexts, i.e. they make multiple predictions in each predicted minicolumn. As the sequence plays, each time the same element appears, the context for that element is narrowed down. Essentially, instead of finding full sequence context, it finds the context of all prior elements, and the chaining effect results from those prior elements being in context of their prior elements.
    - To do so, SOM gradually facilitates, increasing sparsity of apical activation.
    - Basal predictions are like normal SM, but each minicolumn's apical predictions are for all contexts that minicolumn can appear in for the sequence. Basal isn't an issue for repeated elements because after an NMDA spike, that segment's NMDARs are depressed for a while, so the same transition won't use the same segments if it repeats during the sequence.
    - Maybe this can learn sets and sequences.
    -

L5 Dendritic Integration Summary

Perisomatic Zone

The soma, proximal 100 um apical, and proximal 50 um basal evoke RS for suprathreshold input, increasing FR with input strength [A, B, C].

Plateau Zone - Suprathreshold

Besides the perisomatic zone (and perhaps non-primary tuft and distal oblique), the dendrite supports plateau potentials, which have fixed amplitude [A, B, C]. Plateau potentials usually cause RS, but plateaus in the primary tuft and basal dendrite have a weak to negligible impact on firing rate [A, B, C]. Plateau RS is roughly 40 hz for more proximal sites, and less for distal sites [B]. It can sustain firing after stimulation ends, and it does so longer for stronger dendritic or somatic stimulation [A].

Basal dendrites evoke small plateaus, although they likely sum from separate entire basal dendrites. However, the total voltage evoked probably only evokes 10 hz firing [B].

Plateau Zone - Subthreshold

Below burst threshold (and presumably above a lower threshold), apical up to primary tuft and proximal oblique evoke RS which increases FR with input strength, up to 20 hz at more proximal locations [B]. However, [A] did not find this for the apical dendrite, nor did [C] for 510 um apical.

Pre-Plateau Response

The basal dendrite rapidly evokes a plateau, but not the other parts of the plateau zone [B]. One more more calcium transients and bursts precede the plateau [B]. It repetitively bursts, and stronger input causes it to transition or rapidly switch to plateau RS sooner, possibly with an initial plateau burst [A, B, C]. At threshold, it might never switch from bursting [A].

The bursts have large ISIs because of large AHPs, and there is also sometimes an AHP between the transient and plateau [A, B].

Distal Tuft Zone

Most apical studies are based on the initiation zone, but the non-primary tuft is different, although thickness might be a better classifier than branch order [E]. Although distal tuft occasionally produces calcium spikes for current injection, it does not for synaptic stimulation [E]. Instead, the distal tuft primarily has NMDA spikes and weak regenerative sodium spikes [E]. The distal tuft spike attenuates a lot, at least for widely separated branches, and it attenuates a half or a third at the main bifurcation [E].

A single distal tuft NMDA spike isn't sufficient for the initiation zone's calcium spike, but if another branch has an EPSP or there is a little initiation zone depolarization, it is suprathreshold [E]. Only about 10 active synapses on a branch are required for an NMDA spike at the most distal branches, but more at more proximal branches [E].

Injection to the primary tuft or main bifurcation causes a calcium spike which propagates well to the quaternary tuft [E].

Burst/Plateau Threshold

[C] found that the threshold for firing at all increases distally along the apical dendrite, whereas [B] found that more proximal sites have higher plateau thresholds.

Apical Trunk/Tuft-Somatic Integration

Even if apical is subthreshold alone, it can evoke a burst if even subthreshold somatic injection is added [A]. However, this is likely because the two inputs together evoke firing and thus a bAP.

When somatic injection is barely subthreshold, even slight apical initiation zone injection causes it to fire RS [C]. For stronger apical injection, FR increases linearly with strength, and bursts beyond a threshold (although singlets also can occur, even without plateaus, probably because of noisy injection) [C]. Above burst threshold, FR increases more rapidly with strength [C]. For very strong injection RS and plateaus occur [C].

Even with weak apical initiation zone injection, the somatic threshold for firing at all is reduced a lot, and the firing rate increases with somatic injection current more quickly than without apical injection [C]. The threshold reduces more for stronger apical input, whereas the slope of FR for somatic input is increased without much difference for different apical input currents [C].

When a bAP occurs, the apical trunk produces a calcium signal, but the tuft only does so if there is coincident synaptic input [D]. When this occurs on a branch, it propagates along the length of the branch, meaning at least a 30 um stretch, and possibly the entire tuft [D].

Tuft calcium signals are unreliable during firing, but occur throughout the tuft at the same time [D]. This unreliability is because a calcium signal requires a bAP coincident with synaptic input for tuft calcium signals, whereas the apical trunk reliably produces a calcium signal for a bAP [D].

Apical-Basal Integration

A basal plateau will sum with an apical plateau [B].

Apical Trunk Multisite Integration

When two plateaus occur on the apical dendrite, only the more proximal one is seen at the soma [B]. If there are two currents subthreshold for plateaus on the apical dendrite, they can sum at the soma or summate to produce the proximal plateau [B].

Burst Mechanisms

The first spike in a burst drives the rest of that burst because of the bAP it sends triggering a delayed depolarization, which isn't the same thing as a calcium transient [A]. Rather, a spike during the transient causes a DD and a burst [A].

Sources:

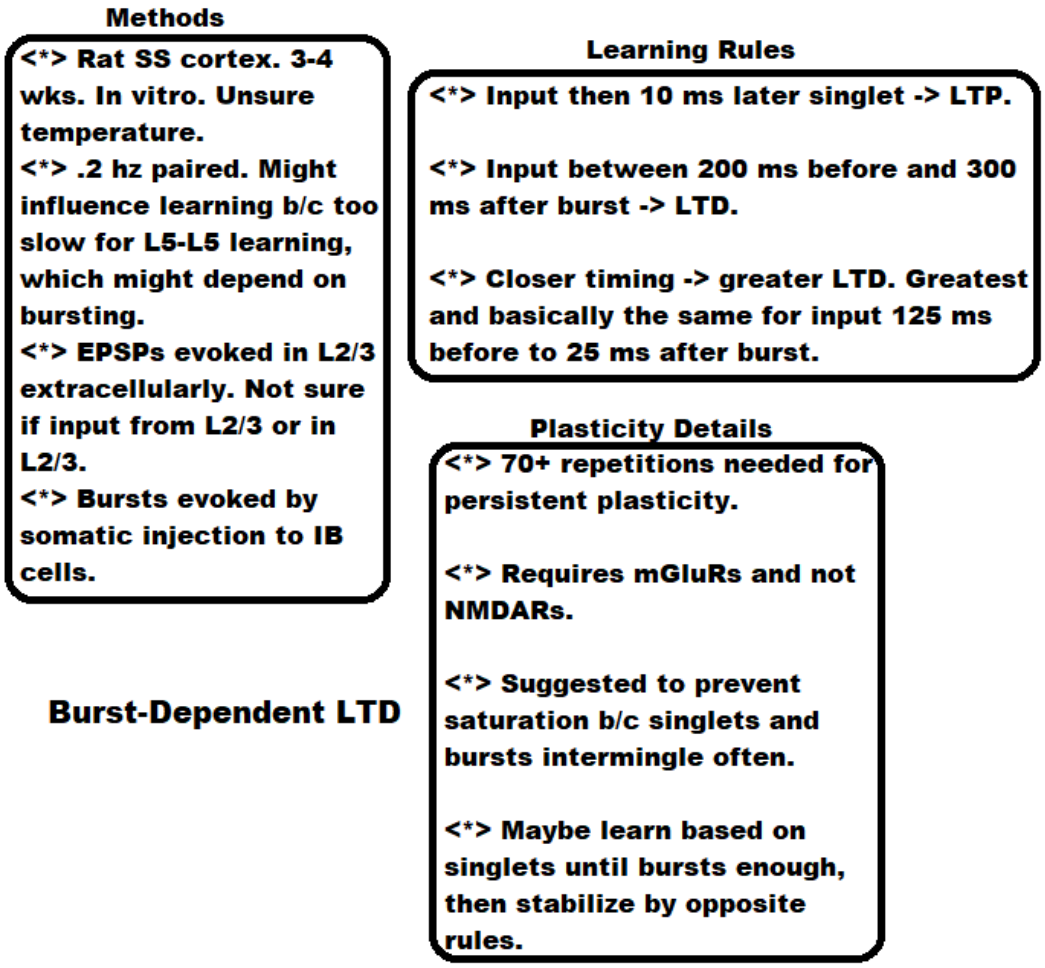
A: Peter Schwindt and Wayne Crill, 1999
B: J. C. Oakley, P. C. Schwindt, and W. E. Crill, 2001
C: Matthew E. Larkum, Walter Senn, and Hans-R. Lüscher, 2004
D: Daniel N. Hill, Zsuzsanna Varga, Hongbo Jia, Bert Sakmann, and Arthur Konnerth, 2013
E: Matthew Larkum, Thomas Nevian, Maya Sandler, Alon Polsky, and Jackie Schiller, 2009

Branch-specific dendritic Ca2+ spikes cause persistent synaptic plasticity (Joseph Cichon and Wen-Biao Gan, 2015)

Mouse M1 Tuft

Misc	Responsivity	Learning	Role of Inhibition	Ideas
*Running forwards/ backwards, which involved learning. *In barrel cortex, calcium spikes instead occur throughout the tuft. *Spine calcium transient = NMDA response to a single input.	*Each distal branch calcium spikes for 1/40 tasks. Converges towards nexus. *During training by running, 8x spine calcium transients compared to rest. *1/2 responsive spines are within 300 ms of the calcium spike, likely much less. *The others are distributed in the many seconds beforehand.	*Spine transients up to 5 seconds before branch calcium spike ->depotentiate amplitude. *Concurrent and maybe a little beforehand -> potentiate. *Calcium imaging. Can't determine rules for afterwards. *Training increases the number of transients.	*Inactivated SOM cells. *Doesn't increase number of calcium spikes. *But 4x as many branches to spike for both tasks. *Learning rules and responsivity lead to overall depotentiation for erronous branch spikes. Learning a task interferes with the prior learning.	*Do SOM cells inhibit in a branch and task-specific manner? *Check the study which said 2 NMDA spikes is sufficient for bursting. Does that mean influence on bursting and learning are separate? *More transients during running b/c disinhibition? Motor input?

Firing Mode-Dependent Synaptic Plasticity in Rat Neocortical Pyramidal Neurons (Barbara Birtoli and Daniel Ulrich, 2004)



Cellular mechanisms of burst firing-mediated long-term depression in rat neocortical pyramidal cells (Antonny Czarnecki, Barbara Birtoli, Daniel Ulrich, 2007)

- Follow up with similar methods. Juvenile rats. 3-4 weeks, like last study.
- -20 ms burst then +10 ms singlet still -> LTD, similar amount to the burst alone.
- Another study found LTP is shifted towards LTD by longer calcium influx, mirroring the singlet LTP, doublet no change, and burst LTD.
- Another study (maybe on basal dendrites, which this study might also be) found NMDAR-mediated LTP caused by bursts, possibly because of different EPSP amplitude or site.

Plasticity Compartments in Basal Dendrites of Neocortical Pyramidal Neurons (Urit Gordon, Alon Polsky, and Jackie Schiller, 2006)

- Slice. L5 and L2/3 but same results for both. Calcium imaging, but the temporal imprecision is okay for this study.

- Main Results - Distal Basal:
    - NMDAR + BDNF -> local EPSPs potentiate, even without somatic spiking. Other tested conditions failed.
    - If the 50 ms EPSP starts between 25 ms before and 125 ms after the NMDA spike starts, LTP.
- Minor:
    - Proximal basal LTP depends on somatic spiking.
    - On distal basal, no LTD when BDNF is present.
    - Distal basal EPSPs are typically ~50 ms. Since that's long but correct, make sure other studies use the correct duration. The same issue might apply to apical.
- Caveats:
    - They didn't test an NMDA spike paired with a bAP without BDNF, so that might be another way to induce LTP.
- Further Research:
    - Cites some sources about BDNF release.
    - Other studies found BDNF causes calcium transients in spines and dendritic depolarization, but this study argues not because NMDA spike evokes large calcium response.
    - The authors frame negative timing plasticity as associating to feedback input, which explains the longer plasticity window. But that can only be part of the story, since the NMDA spike results from input.

Surround Integration Organizes a Spatial Map during Active Sensation (Scott R. Pluta, Evan H. Lyall, Greg I. Telian, Elena Ryapolova-Webb, and Hillel Adesnik, 2017)

- A mechanism to convert from whisker-centric space to scanned space-centric.
- Input from surround whiskers modulates the response to the PW.
- L2/3 has a map of scanned space, which is absent with a single intact whisker. Is it in terms of RFs being scanned-space centric, or is there an actual map in each column?
- Tracked a single PW.
- The PW only contacts the bar when in a central zone.
- L5 recorded cells were RS, but I'm guessing there aren't IB cells while awake.
- The PW drives L4 responses in its corresponding column, but not other columns.
- When the bar is in the forward position of the zone scanned by the PW, leaving surround whiskers intact reduces the response in L4 of the PW column, to on average ¼ of the population response. When the bar is in the backward position of that zone, leaving them intact instead increases the population response slightly, to 1.25x.
- Leaving the SWs intact shifts the scanned space RFs of almost all PW column L4 cells, on average backward ~a couple mm. That seems pretty small because whiskers are ~30 mm long, although maybe not depending on how wide the whisking arc is.

- L2/3 and L5 in the PW column often respond to whisking contact outside the zone swept by the PW.
- When they trimmed the SWs, they trimmed all whiskers except the PW.
- Leaving SWs intact -> when pole in forward part of the PW scanned zone, reduced on average. When in backward part, enhanced on average. However, not as homogeneously as L4. Most cells' RFs are shifted backward by SWs intact, but some are shifted forward. On average, a little bit smaller shift than for L4. I'm guessing the difference is because of RF sizes.
- In L5, SWs intact primarily enhances responses to the bar when in the backwards area in the scanned area. But it's a lot messier, probably because of broad L5 RFs. The shift is ~½ that for L2/3.
- VPM responses might've shifted a bit, but it's hard to tell.
- Removing the PW while leaving the SWs intact reduced L5 touch-evoked firing rates, but didn't change their spatial preferences. 95% of L5 cells retained touch-evoked firing rate responses, so I guess L5 ST cells have multi-whisker responses, unless they only selected L5 TT cells.
- In visual cortex L2/3, orientation tunings of nearby neurons have little correlation. This is referred to as salt and pepper. They tested whether L2/3 of vS1 is the same with respect to scanned space (which isn't the same as orientation tuning, because that's position), or a continuous map.
- Mapped the spatial preferences for L2/3 in an area encompassing several barrels.
- They find a continuous map of scanned space in L2/3. Specifically, rostrocaudal (forward/back) position is mapped along the vS1 row axis (which I'm guessing is the same axis as forward/back).
- L2/3 but not L5 were recorded by calcium imaging.
- The map of scanned space is whisker set point-centric, since it changes when whisking set point changes. Keep in mind they only studied the map in L2/3 and didn't check for one in L5.
- The map is smoother when whisking amplitude is smaller (i.e. when it runs faster, so I wonder if that changes other things like frequency). So the map seems to have a lot of variances.
- Suppression of L4 by forward whiskers and enhancement by backward whiskers might cause it to primarily respond only for the first whisker to contact the surface. I wonder if the reason they say this could lead to the map is that e.g. the second forward whisker is only suppressed by the 1st forward whisker, but enhanced by all backward whiskers, creating a gradient of responses.

Deconstructing the Cortical Column in the Barrel Cortex (Kevin Fox, 2018)

- A review.

- Misc:
    - L5 ST projects stronger to superficial than L5 TT.
    - Septal columns (receive POm) -> M1 and S2 whereas VPM-receiving barrel columns -> S2. So dorsal/ventral might arise in S1. Septal/barrel cells also code different things and adapt differently. Check the cited studies because I'm not sure what it means by adapt.
    - Septal/barrel columns are separate systems, so be careful of other studies pooling them.
- Whisker RFs:
    - Barrel/septal L5a/b (possibly except barrel L5a) respond to surround whiskers similarly to the principal whisker, gradually descending average spike response for more distant whiskers.
    - L5 RS excitatory input is mostly within the column and the inhibitory input is both within the column and neighboring columns.
    - Compared to RS, L5 IB cells have more excitatory input from neighboring columns, stronger L6 input from the same column and other columns, and much weaker inhibitory input than RS. Maybe the inhibition difference is for the difference in sparsity/baseline FRs.
    - Since L5 IB cells receive more excitatory input from other columns and less inhibition than RS, explains why multi-whisker.
- Deflection Responses:
    - VPM -> L4/5b PW response w/ 10 ms latency.
    - Response radiates to nearby barrels likely intracortically.
    - L2/3 contributes to L5b PW response, but the latency means it might sustain responses rather than initiate them. Following deflection, L5 IB can have 50 ms EPSPs and fire 30 ms after stimulus onset, so L2/3 can influence the PW response.
    - L5a/b and septa/barrel PW response is shorter latency than the SW response. So should check whether L4 drives that PW response of L5 ST rather than POm or just POm.
- Multiwhisker Integration:
    - L2/3 PW responses are enhanced by stimulation of other whiskers because of intracortical signals. Facilitation is best when the 2 deflections are 1 ms apart but can occur for up to 14 ms apart. It might only be in septal L2/3.
    - That mechanism fits detecting sweeping a surface, and it is direction-selective in a manner which allows creating a continuous map of scanned space. See Pluta et al., 2017. The direction selectivity might not arise in L2/3.
    - That L2/3 enhancement mechanism could also hypothetically detect sweep direction. I wonder if it's related to sequence memory because it enhances

responses to upcoming sensory input, although perhaps not in a predictively learned fashion.

- Deprivation Plasticity:
    - Deprivation of a whisker row -> L5 RS depresses PW response and mostly unchanged short latency SW response. L5 IB mostly unchanged PW response and potentiates SW response by LTP. These changes are because of changes in excitatory input. The RS depression isn't by LTP molecular mechanisms.
    - The RS short latency potentiation is likely of VPM input. What about L4 input?

Long-range recruitment of Martinotti cells causes surround suppression and promotes saliency in an attractor network model (Pradeep Krishnamurthy, Gilad Silberberg, and Anders Lansner, 2015)

- A modelling study, but makes some interesting inferences.
- MCs are at least somewhat orientation-selective.
- Motor cortex -> VIP cells (with no intermediates locally), and those activates cells target SOM cells strongest.
- VIP disinhibition occurs in V1, auditory cortex, and somatosensory cortex.
- The VIP circuit is activated by acetylcholine during locomotion and whisking, but also during auditory fear conditioning. Maybe learning is what activates it, not exactly behavior. Or attention.
- This study is related to attention, but SOM cells target distal apical and they used single compartment cells.
- In their model, because of facilitating synapses, a larger input activates SOM cells better than a small input. I'm guessing it's sigmoidal.
- Cholinergic cortical input might not just be diffuse/slow, but also millisecond scale inputs/topography.
- VIP inhibition of SOM cells is present while awake, but absent under anesthesia, in multiple studies.
- In V1, most cells active during locomotion without visual stimuli were VIP cells, which are activated in V1 during locomotion. Locomotion increases V1 py cell gain without changing orientation selectivities. SOM cells are inhibited during locomotion. Therefore, this suggests a circuit which increases gain during locomotion. Cholinergic release and therefore probably VIP disinhibition is proportional to locomotion speed.

Functional Local Input to Layer 5 Pyramidal Neurons in the Rat Visual Cortex (Amir Zarrinpar and Edward M. Callaway, 2016)
-check citations, e.g. for somatosensory 3 L5 types.

- Rat V1. 3-4 weeks (juvenile). Room temp slices.

- To determine how many inputs are shared, photostimulation generates asynchronous APs. So synchronous postsynaptic EPSPs imply shared input. This method has many potential issues.
- Rat somatosensory has 3 L5 types: short, tall simple, and tall complex.
    - Short: apical ends before L1. Projects to superficial layers in the same column and maybe neighboring columns. Also projects contralaterally. RS.
    - Tall simple: tuft in L1. Project to superficial layers with a lot of lateral extent, and project contralaterally.
    - Tall complex: extensive tuft. Axon almost only in deep layers. Projects to SC and thalamus. SC, even though somatosensory.
- V1 L5 subtypes: SH (short), TR (tall RS), and TB (tall bursting).
- Only measured somatic EPSPs.
- All cell types exist through the depth of L5.
- TB cell fast ADP -> later AHP.
- SH: 39% input from L4, 35% from L5, 19% L2/3, 9% L6.
- TR: 47% L5, 27% L4, 12% L2/3, 14% L6.
- TB: 48% L5, 26% L4, 12% L2/3, 14% L6. So the inputs to tall are virtually the same in terms of layer.
- Out of 42 L5 cell pairs, only 1 was connected. This contradicts another study, likely because that study used P12-P20.
- Check correlation probability (CP) for cell pairs. X means either of the other 2 types.
- TR-TR CP for L5 input: .08. Means 8% chance that when cell A receive an EPSP from photostimulation, cell B received a synchronous EPSP. 4 ms bins.
- TR-X (i.e. TB or SH) CP for input from L5: .02.
- TR-TR CP for L6 input: .05
- L6 TR-X CP: .006
- L5 TB-TB: .07
- L5 TB-X: .032
- L6 TB-TB: also .032
- L6 TB-X: .02
- L4 TB-TB: .05
- L4 TB-X: .02
- L5 TR-TB: .03
- L6 tall matched (TB-TB or TR-TR): .04.
- L6 tall unmatched: .01
- L4 tall matched: .05
- L4 tall unmatched: .02
- SH-SH CP was lower than TR-TR and TB-TB.
- L5 SH-SH: .02

- L5 SH-X: .03
- L5 TB-SH: .06
- L5 TR-SH: .01
- So TB-SH share 5x more input than TR-SH.
- According to another study, TR cells synapse onto TR and TB with similar probability, ~10%, whereas TB -> TR 1%.
- Maybe the L4 input to L5 TB is the V1 version of VPM -> L5 TT in barrel cortex.

Encoding and Decoding Bursts by NMDA Spikes in Basal Dendrites of Layer 5 Pyramidal Neurons (Alon Polsky, Bartlett Mel, and Jackie Schiller, 2009)
-check which parts are simulation

- Slice: P20-P40. Anesthesia: P30-P40. Calcium imaging.
- Defined bursts as 2 or more spikes in a 50 ms window. So not really bursts.
- Abstract:
- Basal NMDA spikes mediate detection and initiation of bursts.
- High frequency inputs facilitate compared to low frequency inputs.
- The facilitation is not by temporal summation of voltage. Rather, based on glutamate bound to NMDARs from prior input.
- NMDA spikes trigger output bursts.
- Intro:
- Prolonged somatic depolarization caused by NMDARs is suited for generating bursts.
- Results:
- ISI Dependence of NMDA Spike Initiation:
- Electrically stimulated synapses on thin basal dendrite. In the image, it appears ~400 um from the soma.
- Delivered 2 pulses.
- ISI 10-20 ms -> NMDA spikes at lower intensities and occurs on 2nd pulse. At 200+ ms ISI, 1.6x intensity required and occurs on the first input pulse.
- When subthreshold for NMDA spike at high frequency (20 ms ISI), 1.2x facilitation (i.e. paired pulse ratio of 1.2), similar to AMPAR-only facilitation.
- When the 2nd pulse is suprathreshold for NMDA spike at 20 ms ISI, much greater paired pulse ratio, ~4. Lower PPR at larger ISI but still ~2.5x at 100 ms. Didn't test between 100 and 200 ms.
- When even the 1st pulse is suprathreshold for NMDA spike, 2nd pulse instead depressed. Depressed meaning the response had lower average amplitude and lower probability of NMDA spike. If the NMDA spike occurs, does it depress? Did they test a wide range of ISIs? They at least tested an ISI of 500 ms. This PPR in this case remains depressed for ~1 second.
- Temporal summation with long stimulus trains:

- Used 10 pulse trains.
- For 50 hz, evoked a plateau potential which outlasted the stimulation by 300 ms, although it starts decaying soon after stimulation ends.
- Stimulation intensity required to evoke NMDA spikes was lowest for the ISIs of 100 ms or less, although they didn't test anything from 101 to 199 ms.
- For ISI 10-20 ms, lowest threshold for NMDA spike rarely for 1st input, ~30% of the time for 2nd input, and ~50% of the time for 3rd input.
- For ISI 50-100 ms, ~25% of the time lowest threshold for 1st input, ~30% for 2nd input, and ~50% for 3rd input.
- Keep in mind that presynaptic depression/facilitation might have a role, so lowest threshold time might not always be when it responds.
- For ISI 200-1000 ms, lowest threshold is always for the first input. The threshold for generating an NMDA spike (at the optimal spike number) is on average 1.6x higher than for ISIs of 10-100 ms.
- Response of basal dendrites under in vivo-like conditions:
- In vivo -> up/down states.
- Recorded spontaneous L5 activity and used the patterns as input. Applied that input in slices. To mimic up/down state, somatic depolarization with the same pattern. Note that this isn't necessarily a good way to mimic it because up/down state involves dendritic depolarization.
- I don't think they could've mimicked the synaptic stimulation intensities, just the patterns.
- Down state condition:
- Short ISI in vivo patterns -> NMDA spikes, but with shorter temporal integration window than in normal slice paired pulse (~70 ms).
- It appears that when a triplet caused 2 NMDA spikes in a row with 2nd/3rd inputs ISI ~20 ms, the 2nd NMDA spike is greater than the 1st.
- During down state condition, even with NMDA spikes, usually subthreshold for somatic AP.
- Up state condition:
- NMDA spikes reliably triggered APs.
- High frequency input is the main drive of somatic APs.
- >75% high frequency input bursts (meaning ISI <20 ms) evoked somatic firing.
- Only 6% of inputs with ISI >200 ms evoked somatic firing.
- 65% of outputs were bursts (in terms of ISI).
- Based on the figure, somatic AP probability decreases fairly linearly with ISI. ~75% for 20 ms, ~60% for 40 ms, ~20% for 70 ms, and less than 20% for greater ISIs up to 1000 ms tested.
- The output ISI distribution peaks around 15 ms.

- For input ISI <50 ms, roughly equal probabilities of 0 (~35%), 1 (~20%), and 2 (~35%) output APs, and ~10% 3 APs.
- Responsivity was similar for cells IB and RS cells.
- They selected in vivo patterns, so I'm not sure if the results are biased.
- One possible mechanism of facilitation is prolonged depolarization helping remove Mg from NMDARs. Another possibility is glutamate still bound to NMDARs, because on the second pulse more NMDARs have bound glutamate.
- The first possibility would suggest facilitation for voltage spread, whereas the second would suggest segment-specific facilitation. I'm not entirely sure whether it's segment specific or synapse specific or something else.
- They provide evidence that the second possibility is correct and not the first one. I'm not completely convinced the first possibility plays no role, but the second possibility seems to probably play a role.
- Discussion:
- NMDA spike is a regenerative event, and enough must be open to reach the spike threshold. It's a conductance threshold, maybe not a voltage threshold.
- NMDA response depresses starting ~500 ms after an NMDA spike.
- Basal dendrites use localized (segment) summation.
- Whereas apically initiated bursts depend more on a voltage threshold for calcium channels, basal initiated bursts depend on enough NMDARs activity rather than voltage, which depends on input frequency. I wonder if apical dendrites are actually the same, since there are NMDARs which contribute to the initiation zone voltage.

Multibranch activity in basal and tuft dendrites during firing of layer 5 cortical neurons in vivo (Daniel N. Hill, Zsuzsanna Varga, Hongbo Jia, Bert Sakmann, and Arthur Konnerth, 2013)

- L5 motor cortex. Two photon calcium imaging. Anesthesia.
- During firing, calcium signals in basal are linear to FR (spike count? Something else?), and tuft calcium signals are unreliable during firing. The calcium signals are throughout all branches in both tuft and basal.
- bAPs only caused tuft calcium signals during the up state, suggesting that synaptic input is required to do so. bAPs caused apical trunk and basal calcium responses in both up and down state. What about multiple high frequency bAPs?
- Unlike in the tuft, in the basal dendrite the calcium signal increased for more bAPs.
- The bAP-associated calcium responses are propagated along the length of the branch, so the entire branch tends to have a calcium response or not. Doesn't necessarily mean the entire tuft etc. responds.
- In basal dendrite and apical trunk, the amplitude of the calcium signal greater for more spikes in a burst/singlet, but this relationship isn't true for the tuft. Perhaps this is because the calcium response requires synaptic input.

- For both tuft and basal, calcium transients during firing are synchronous throughout all branches within a region of interest (so e.g. latency could change that). The amplitudes are basically the same, too. Does that mean all branches respond, or just the branches that respond are synced? This suggests that individual branches are not responsible for generating APs. But aren't these responses just bAPs if the imaged branches didn't drive firing? Also, if bAP-triggered calcium responses are larger than synaptically-driven calcium responses, they would've been noticed.

Cortical Sensory Responses Are Enhanced by the Higher-Order Thalamus (Rebecca A. Mease, Markus Metz, and Alexander Groh, 2016)

- vS1 L5. Anesthesia. Only tested whisker-responsive cells.
- Optogenetically stimulated POm boutons. The responses are stronger for stronger stimulation than used.
- POm stimulation and deflection were both brief. Tens of ms.
- Early phase: 0-200 ms after stimulation begins. Late phase: 200-800 ms after stimulation begins.
- POm stimulation alone relative to no stimulation enhanced early phase response in a small fraction of both L5a and L5b cells, and none were enhanced in the late phase.
- POm + deflection (synchronous) relative to deflection alone early phase spike responses:
    - 7/9 L5a enhanced to average 1.5x, and 1 suppressed to .7x.
    - 7/12 L5b enhanced to average 1.7x, and 3 suppressed to average .7x.
- " late phase:
    - 7/9 L5a enhanced to average 1.7x.
    - 7/12 L5b enhanced to average 2.6x, and 4 suppressed to average .7x. So although enhanced more strongly than L5a, more are suppressed.
- When varied timing between POm and deflection to ±75 spike responses:
    - These notes apply to both early and late phase.
    - Many cells had different responses for different timings.
    - Most L5b changes are enhancement and some are suppression. Few L5a changes are suppression.
    - Keep in mind the relative timings don't indicate the temporal separation between the end of the first and start of the second.
- When recorded the soma in response to POm:
    - Responses to bouton activation usually monosynaptic because ~5 ms latency. Some L5a and L5b cells also had polysynaptic responses.
    - The POm-triggered depolarizations often outlasted photostimulation and often caused plateau potentials, which appear to last ~100 ms and sometimes longer. They can start after photostimulation ends and occur in both L5a and L5b cells, and can occur for POm alone as well as POm + deflection.
    - Spiking doesn't appear to occur during the plateau potentials, at least not often.

    - The plateau potentials decay rather than stopping suddenly.
    - When tested varied delays between POm/deflection, similar results to those described in this section and to the results for spiking for varied delays.
- According to another study, POm activates mGluRs on L5 cells, which have responses for hundreds of ms.
- In L2/3, POm-evoked plateau potentials require NMDARs.
- Besides NMDARs and mGluRs, another hypothetical way for POm to evoke the sustained L5 activity is by L5b->POm->L5b loop.

Cortical Sensory Responses Are Enhanced by the Higher-Order Thalamus (Rebecca A. Mease, Markus Metz, and Alexander Groh, 2016)

- vS1 L5. Anesthesia. Only tested whisker-responsive cells.
- Optogenetically stimulated POm boutons. The responses are stronger for stronger stimulation than used.
- POm stimulation and deflection were both brief. Tens of ms.
- Early phase: 0-200 ms after stimulation begins. Late phase: 200-800 ms after stimulation begins.
- POm stimulation alone relative to no stimulation enhanced early phase response in a small fraction of both L5a and L5b cells, and none were enhanced in the late phase.
- POm + deflection (synchronous) relative to deflection alone early phase spike responses:
    - 7/9 L5a enhanced to average 1.5x, and 1 suppressed to .7x.
    - 7/12 L5b enhanced to average 1.7x, and 3 suppressed to average .7x.
- " late phase:
    - 7/9 L5a enhanced to average 1.7x.
    - 7/12 L5b enhanced to average 2.6x, and 4 suppressed to average .7x. So although enhanced more strongly than L5a, more are suppressed.
    - It's interesting that 7/9 and 7/12 were for both early and late phase. Maybe the same cells are enhanced/suppressed the same way in early and late phase.
- When varied timing between POm and deflection to +-~75 ms early phase spike responses:
    - Many cells had different responses for different timings.
    - Most L5b changes are enhancement and some are suppression. Few L5a changes are suppression.
    - So there doesn't seem to be anything special going on except the fact that they can integrate responses when the end of one is before the start of the other up to ~20 ms and maybe more.
- " late phase:
    - Same description as early phase.

- The lack of common suppression is unexpected given POm projecting to L1, where there are inhibitory cells. However, stronger inhibition when awake is still possible for a few reasons, and inhibition might just be always active during anesthesia.
- When recorded the soma in response to POm:
    - Responses to bouton activation usually monosynaptic because ~5 ms latency. Some L5a and L5b cells also had polysynaptic responses.
    - Inhibitory responses weren't seen.
    - The POm-triggered depolarizations often outlasted photostimulation and often caused plateau potentials, which appear to last ~100 ms and sometimes longer. They can start after photostimulation ends and occur in both L5a and L5b cells, and can occur for POm alone as well as POm + deflection.
    - Spiking doesn't usually occur during the plateau potentials, and might not even be the cause of the two spiking cells.
    - The plateau potentials decay rather than stopping suddenly.
    - When tested varied delays between POm/deflection, similar results to those described in this section and to the results for spiking for varied delays.
- According to another study, POm activates mGluRs on L5 cells, which have responses for 100s of ms.
- In L2/3, POm-evoked plateau potentials are caused by or at least require NMDARs.
- Besides NMDARs and mGluRs, another possible way for POm to evoke the sustained L5 activity is by L5b->POm->L5b loop. Untested.
- Pulvinar inactivation almost completely suppresses V1 visual responses, so POm might serve a similar role.
- Pulvinar is involved in salience/attention.

Control of somatosensory cortical processing by thalamic posterior medial nucleus: A new role of thalamus in cortical function (Carlos Castejon, Natali Barros-Zulaica, and Angel Nunez, 2016)

- By targets in L1, POm controls magnitude/duration of deep and superficial layer responses to whiskers.
- Blocking L1 GABA or P/Q type calcium channels stops this.
- POm also controls S2 sensory responses (by the same mechanism?) and S1 L5 activity modulates this.

Properties of basal dendrites of layer 5 pyramidal neurons: a direct patch-clamp recording study (Thomas Nevian, Matthew E Larkum, Alon Polsky, and Jackie Schiller, 2007)

- Because EPSP amplitude increases distally on basal, somatic signal is fairly location independent.
- Sodium and NMDA spikes but not calcium spikes for ¾ of length.

- Two modes of integration. Subthreshold location-independent and local amplification of clustered (both temporally and spatially) input.
- Voltage sensitive dyes and calcium imaging have problems which led to conflicting results about amplitude of basal bAPs.
- Modelling studies rely on properties of dendrites/synaptic inputs which are uncertain.
- Studied bAPs up to 140 um from the soma.
- bAPs attenuated with a length constant of ~140 um. This makes attenuation similar to apical normalized to overall dendrite length. This might just be normalized for apical up to branch point.
- Length constant doesn't have a meaning I can understand. Just use it for comparisons with apical.
- Apical and basal bAPs are low latency, just a few ms, based on their velocities.
- Basal bAP is mediated by voltage gated sodium channels, and I'm guessing for apical, too. So maybe sodium spikes in apical tuft are primarily for the bAP.
- The calcium transient evoked by basal bAP didn't change amplitude along the the basal dendrite, even though voltage attenuated somewhat. This might be because the bAP half width increased distally.
- Whereas bAPs are boosted for distal apical by a dendritic depolarization, they aren't for distal basal. They tested this by recording at ~50% of the total length, so 500 um for apical and 100 um for basal, and for basal same results for injection at various distances/intensities, 20 um to 300 um.
- An EPSP (synaptically evoked) on the basal dendrite attenuates to the soma with length constant 50 um. This was with TTX. Normalized to length, this is nearly the same as for apical, but non-primary tuft probably not included in all these comparisons.
- Somatic (synaptic) EPSPs spread back in the other direction much better. Normalized for length, similar for apical and basal.
- Attenuation still exists with sustained injection, but not as much attenuation than for synaptically evoked EPSPs. For dendrite to soma, 250 um length constant for steady state versus 50 um for EPSP.
- Unlike apical, Ih in basal is similar to the soma.
- Although EPSP amplitude at location of origin depends on basal distance, it isn't as dependent for EPSP amplitude at the soma. From 50 to 100 um, almost location independent. For 0 to 50 um, it decreases a bit with distance. They say it decreases for terminal basal, but I don't see that in the figure. It appears to decrease somewhat from 50 um to terminal. This was with synaptic stimulation.
- Didn't examine or use cited info about distal basal terminal branches nor tuft except in simulation sometimes.

- With EPSP-like injection, caused local dendritic spike which attenuated 6x to soma. These spikes are caused by voltage gated sodium channels but not VG calcium channels. Distance 40-90 um. Initiated in ~½ of cases. Attenuated much less from soma to dendrite.
- Couldn't evoke basal calcium spikes like those in apical. Also unlike apical, high frequency somatically evoked firing didn't cause a basal calcium regenerative event (just the normal bAP-evoked calcium transients), up to 140 um from soma, although it did evoke an ADP like high frequency APs evoke at the soma, which likely spread from soma to basal.
- 500 ms basal injection up to 140 um never converted it from RS to bursting.
- With extracellular synaptic stimulation on distal basal (50 to 120 um), above threshold, caused NMDA spikes. Beyond threshold, further increases broadened the NMDA spikes (which are evoked by 2 pulses at 50 hz), without increasing amplitude much. These NMDA attenuated ~5.5x to soma versus 22x for subthreshold EPSPs. The NMDA spikes at tested intensities don't last 100 ms like I thought, but more like 50 ms for the strongest stimulation.
- Another study found that the most distal basal has calcium influx caused by burst bAPs.

Calcium Spikes in Basal Dendrites of Layer 5 Pyramidal Neurons during Action Potential Bursts (Björn M. Kampa and Greg J. Stuart, 2006)

- 3-4 week rat slice.
- Calcium and voltage imaging of fine basal L5 dendrites.
- 100+ hz bursts caused supralinear distal calcium but not supralinear for proximal.
- Single bAPs attenuate a lot, in contrast with this supralinear burst calcium.
- A-type potassium channels regulate the backpropagation. They cause the single bAP attenuation.
- EPSPs paired with bursts are effective for activating NMDARs.
- Single bAPs or non-burst RS (for five spikes) caused similar proximal/distal calcium signals, whereas burst bAPs caused larger distal than proximal. The difference between burst and single starts at ~130 um but is much greater more distally. Most measurements were less than 200 um, but a few were 250 um.
- The distal calcium signal is greater for five APs at 100 hz than 80 hz, but ~double that at 133 hz and higher tested frequencies.
- The increase for triplet versus singlet is greatest for for 3rd AP compared to the singlet, using voltage sensitive dyes.
- Although single bAPs caused similar proximal/distal calcium signals, they argue the voltage attenuates distally.
- Calcium channels in the dendrite are responsible for the difference for bursting in terms of voltage. I'm not sure the calcium channels are on the basal dendrite, since they

blocked all calcium channels. Doing so reduced the voltage signal of the 3rd AP in the triplet to be the same as the first, at distal locations i.e. >130 um.

- I'm not convinced the AP bursts propagate better by activating voltage sensitive calcium channels in the basal dendrite. They might be in the apical dendrite.
- A-type potassium channels are sensitive to 4-AP. D-type potassium channels are also blocked at sufficiently high concentrations (but they dealt with that, so it's A-type channels that are responsible).
- A-type potassium channels limit AP backpropagation at least in apical and oblique dendrites.
- When blocked A-type potassium channels, to prevent epileptic discharges, also blocked AMPARs, NMDARs, and GABAARs. That could be an issue, although maybe not with injection.
- 4-AP usually causes burst firing, so they evoked singlets with a depolarizing and then hyperpolarizing signal.
- 4-AP didn't change the calcium signal for proximal sites, both for bursts and singlets. For distal sites, increased calcium signal for both bursts and singlets.
- A-type potassium channels are fast inactivating.
- Without direct evidence, since can't tell which compartment channels are blocked on, I don't think it's certain that they directly do so on basal dendrites. The same goes for studies on apical.
- Without 4-AP, TTX only slightly singlet AP-evoked calcium signals on distal basal but reduced it a lot on proximal apical (apical isn't a typo). With 4-AP, the distal basal calcium signals were instead reduced with TTX relative to 4-AP alone. Therefore, voltage gated sodium channels are recruited by singlet bAPs only with A-type potassium channels blocked. Furthermore, A-type potassium channels appeared to inactivate during bursts, strengthening this conclusion.
- Burst bAPs might relieve NMDARs from the voltage-dependent magnesium blockage. When paired a burst (3 APs at 200 hz) with an EPSP 10 ms after the 2nd AP, the EPSP and bAPs sum supralinearly, with somewhat greater supralinearity >150 um versus <150 um. The supralinearity was blocked by NMDAR blocker.
- According to another study, L5 distal apical dendrites have small to negligible calcium signals for singlet bAPs, but large signals for burst bAPs.
- This study argues that single bAPs attenuate distally based on things like bAP rise time and latency. I'm not convinced, though. It might not even matter functionally, because the threshold for responses and input types might also change distally. It does matter for interpreting results, though.
- Another study contradicted this study's arguing for attenuating distally single bAPs for L5. This might be because that study used room temperature or differences in how distally they recorded.

- Basal dendrites have high voltage gated calcium channels, as well as nickel-sensitive low voltage gated calcium channels (=T-type), according to one study. According to another study, mainly P/Q type calcium channels. Another: L-type channels, at least any that exist, are only somatic and proximal dendritic. These studies are all on L5.
- bAP attenuation etc. is relevant to STDP because it signals the somatic output. With bAP attenuation, if that actually happens, it might fail to relieve NMDAR magnesium blockage.
- In a study on L2/3, AP burst -> dendritic calcium spike -> relieves magnesium blockage much better than singlets. This study found a similar result.
- In a study which used mature rats, AP bursts were required for basal NMDAR activation, whereas in a couple studies on juvenile rats, singlets were sufficient for basal NMDAR activation. Therefore, singlet bAPs might attenuate better in juveniles.

https://en.wikipedia.org/wiki/Neural_backpropagation

- bAPs are both by active and passive spread.
- bAPs could hypothetically cause a feedback loop because they activate dendrites which could trigger another AP in response. A-type K+ channels prevent this.
- A-type K+ channels return the cell to resting potential following an AP. Because of their high density in dendrites, they prevent dendrites activated by synaptic input from directly generating an AP.
- Increasing A-type K+ channel distally causes bAP attenuation.

Inhibition of the slow afterhyperpolarization restores the classical spike timing-dependent plasticity rule obeyed in layer 2/3 pyramidal cells of the prefrontal cortex (Zaitsev, Aleksey V ; Anwyl, Roger, 2012)

- On L2/3, but could be useful for explaining the strange L5 tuft learning rules.
- On proximal synapses of rat PFC L2/3.
- Output then input -> LTD, but input then output also -> LTD.
- When the K+ mediated calcium-dependent slow afterhyperpolarization was impaired, normal STDP.
- Even though the proximal location and L2/3 are different from L5 tuft, K+ mediated and calcium dependent slow AHP seem maybe similar to L5 post-burst long refractory period.

A Novel Form of Local Plasticity in Tuft Dendrites of Neocortical Somatosensory Layer 5 Pyramidal Neurons (Maya Sandler, Yoav Shulman, and Jackie Schiller, 2016)

- .1 hz input to tuft underwent LTP.
- Also increased excitability of the stimulated segment. Caused more efficient back-spread of somatic APs and dendritic calcium spikes into the segment.

- Didn't occur in basal.
- Required Kv4.2 potassium channel and NMDAR channel activation.
- Tuft EPSPs contribute little to the apical calcium initiation zone.
- I wonder if this reflects the low number of synapses required for the tuft to activate. It might not occur much in vivo because .1 hz -> low chance of synchronous inputs.
- How does the current compare to the control .1 hz condition of other studies?

Learning Rules for Spike Timing-Dependent Plasticity Depend on Dendritic Synapse Location (Johannes J. Letzkus, Björn M. Kampa, and Greg J. Stuart, 2006)

- Synapses from L2/3 to L5.
- Low frequency positive timed input -> LTD at distal synapses. Proximally, LTD, but LTP for bursting output.

Backpropagation of Physiological Spike Trains in Neocortical Pyramidal Neurons: Implications for Temporal Coding in Dendrites (Stephen R. Williams and Greg J. Stuart, 2000)

- Seems like an early study on bursting.
- Burst-like bAPs propagate much better into the apical dendrite than regular spiking with the same average FR.
- Dendritic hyperpolarization reduces this difference between RS and bursting bAPs. Dendritic depolarization enhances single bAPs a lot, similar to how burst-like bAPs enhance.
- Blocking distal sodium channels -> greatly reduced burst bAPs but not singlet bAPs. Also true for calcium channels.

Intracortical augmenting responses in networks of reduced compartmental models of tufted layer 5 cells (Fadi N. Karamehand Steve G. Massaquoi, 2009)

- A model, but might cite some very useful results from other studies.
- Augmenting responses (AR) result from repetitive input.
- AR initiation was controlled by low threshold calcium, involving rebound firing.
- AR strength was controlled by Ih, which regulated bursting and helped respond similarly to especially strong stimuli.
- AR was more pronounced with coincident input to basal and distal apical.
- GABAB controlled AR strength and frequency range.

Calcium Dynamics in Basal Dendrites of Layer 5A and 5B Pyramidal Neurons Is Tuned to the Cell-Type Specific Physiological Action Potential Discharge (Patrik Krieger, Christiaan P. J. de Kock, and Andreas Frick, 2017)

- Compare L5 ST and L5 TT bAP propagation into basal based on calcium.

- A single burst of bAPs causes calcium signals for TT but not ST.
- Whisker-evoked AP patterns were very different for the two, but evoked a similar calcium signal for both.

Brief Bursts Self-Inhibit and Correlate the Pyramidal Network (Thomas K. Berger, Gilad Silberberg, Rodrigo Perin, and Henry Markram, 2010)

- On martinotti-mediated frequency-dependent disynaptic inhibition.
- Synchronous bursts in just 4 cells can cause this to all cells in a cortical column. Because a small number of interneurons mediate this, the inhibition is similar in terms of membrane potential fluctuations. This causes synchronous spiking of py cells.
- The somatic inhibition is integrated in a manner electrically isolated from integration of excitation between the py cells.

Origins of Cortical Layer V Surround Receptive Fields in the Rat Barrel Cortex (Nicholas Wright and Kevin Fox, 2010)

- About L5a/L5b barrel/septa responses to principal/surround whiskers and the sources of those responses.
- Barrel L5b cells had less phasic inhibition from sensory input than L5a cells.
- Thalamic input to L5 ("direct" so maybe with lateral L5 connectivity removed) didn't evoke responses without input from superficial layers.
- Probably quick to take notes on and useful for determining details of the L5 TT/ST circuits.

Regular Spiking and Intrinsic Bursting Pyramidal Cells Show Orthogonal Forms of Experience-Dependent Plasticity in Layer V of Barrel Cortex (Vincent Jacob, Leopoldo Petreanu, Nick Wright, Karel Svoboda, and Kevin Fox, 2011)

- Compares L5 IB/RS plasticity following whisker deprivation. Even if that's not useful on its own, that could help support connectivity findings and synapse-specific plasticity. Also, gain rules are important because this is the only way available to determine them.
- Info on L2/3 -> L5 including sensory deprivation plasticity.
- Sources regarding L5b RS vs. IB morphology/connectivity. Useful b/c sublayer specific.
- Argues that RS = slender and IB = TT.
- Also makes a lot of inferences about various details of the circuits which might be hard to make with other methods.

Emergent Properties of Tactile Scenes Selectively Activate Barrel Cortex Neurons (Vincent Jacob, Julie Le Cam, Vale´rie Ego-Stengel, and Daniel E. Shulz, 2008)

- Includes info on determining the direction an object sweeps across the whiskers by integrating info from each whisker.

- This topic could help integrate object ID with sequence tracking, since the sequence of deflections might help ID the shape. It's also useful for hypothesizing about shape ID.
- For this to be useful, need to compare it to another sensory modality.

Segregated Excitatory-Inhibitory Recurrent Subnetworks in Layer 5 of the Rat Frontal Cortex (Morishima M, Kobayashi K, Kato S, Kobayashi K, and Kawaguchi Y, 1991)

- L5 frontal cortex corticopontine and crossed corticostriatal.
- How SOM subtypes and PV cells connect with them.

Target and temporal pattern selection at neocortical synapses (A.M. Thomson, A.P. Bannister, A. Mercer, and O.T. Morris, 2002)

- Burst input rapidly depresses at most spiny cells. Does it depress especially strongly?
- Facilitating inputs to interneurons don't respond to low frequency input much, but respond well to sustained firing.
- L5 -> L3 mainly targets interneurons. So does L5a not target L2/3 py cells?

Cell type specific connections from primary motor to primary somatosensory cortex (Amanda K Kinnischtzke, 2013)

- M1 -> S1 strongest in L1 and deep layers.
- Pyramidal, fast spiking, and SOM cells all receive high probability M1 input.
- A subpopulation of L5/6 py cells receive especially strong M1 input.
- Details of connections.

Translaminar Inhibitory Cells Recruited by Layer 6 Corticothalamic Neurons Suppress Visual Cortex (Dante S. Bortone, Shawn R. Olsen, and Massimo Scanziani, 2014)

- A subpopulation of L6 excitatory cells, with CT output, cause widespread inhibition of all layers by activating deep layer FS cells whose axons target all layers.
- Maybe this explains the extremely sparse L6 activity of one CT subtype.

Calcium Dynamics in Basal Dendrites of Layer 5A and 5B Pyramidal Neurons Is Tuned to the Cell-Type Specific Physiological Action Potential Discharge (Patrik Krieger, Christiaan P. J. de Kock, and Andreas Frick, 2017)

- Compares basal dendrites of L5a/b cells. Calcium imaging.
- 3 APs cause a calcium response in TT cells but not ST cells.
- With (longer?) in-vivo AP patterns, similar calcium response in TT/ST proximal dendrites, but only in TT it decays with distance.
- Whisker-evoked AP patterns are very different for them, yet evoke similar calcium responses.

Emergent Properties of Tactile Scenes Selectively Activate Barrel Cortex Neurons (Vincent Jacob, Julie Le Cam, Valérie Ego-Stengel, and Daniel E. Shulz, 2008)

- Cells are selective for the direction that whisker deflections move along the whisker pad.
- Mechanisms.
- Global vs. local direction.

Whisker row deprivation affects the flow of sensory information through rat barrel cortex (Vincent Jacob, Akinori Mitani, Taro Toyoizumi, and Kevin Fox, 2017)

- Whisker trimming. Could provide some useful constraints because how responses can change depends on what causes those responses.
- Info from reattached trimmed whiskers to L2/3 and L5 IB is delayed and reduced.
- Info from spared whiskers to L4/L5 RS is increased and lower latency. For L5 RS, this is partially because of increased low latency excitatory input (from L4?)
- Frames the changes in latency as showing thalamic vs. intracortical input.
- Mechanisms of deprivation plasticity.
- Cites a lot of interesting info.

The subcellular organization of neocortical excitatory connections (Petreanu L, Mao T, Sternson SM, and Svoboda K, 2009)

- Connectivity to specific parts of cells.
- Input to L3/L5 dendrites in L1 from thalamus/motor cortex conveys whisker movement/position.

Correlation between intrinsic firing patterns and thalamocortical synaptic responses of neurons in mouse barrel cortex (A Agmon and BW Connors, 1992)

- Divided L5 RS into two types, with different laminar distributions and adaptation patterns. I wonder if that shows short vs. ST in vS1.
- Considers latencies from thalamic stimulation greater than 5 ms to be polysynaptic. So there's disagreement with the study that considered 10 ms monosynaptic. Could probably resolve that disagreement based on EPSP rise times, since slowly rising -> probably not significant until later.
- In deep layers the putatively monosynaptic EPSPs are almost always followed by IPSPs, whereas in superficial layers EPSPs aren't always followed by IPSPs.

Monosynaptic connections between pairs of spiny stellate cells in layer 4 and pyramidal cells in layer 5A indicate that lemniscal and paralemniscal afferent pathways converge in the infragranular somatosensory cortex (Feldmeyer D, Roth A, and Sakmann B, 2005)

- Cell pairs forming L4 -> L5a are primarily near or at the border between barrel and septum. The overlap of L4 axons with L5a dendrites is also consistent with that.
- L4 -> L5a is high reliability and low weight. Weakly depressing, meaning .8 paired pulse ratio at 10 hz.
- Details of L4 -> L5a.

Hebbian and Homeostatic Plasticity Mechanisms in Regular Spiking and Intrinsic Bursting Cells of Cortical Layer 5 (Stuart David Greenhill, Adam Ranson, and Kevin Fox, 2015)

- L5 RS/IB hebbian and homeostatic plasticity.
- IB cells had faster depression and homeostatic rebound.
- Only IB cells had input-specific conventional LTP.

Laminar Analysis of Excitatory Local Circuits in Vibrissal Motor and Sensory Cortical Areas (B. M. Hooks, S. Andrew Hires, Ying-Xin Zhang, Daniel Huber, Leopoldo Petreanu, Karel Svoboda, and Gordon M. G. Shepherd, 2011)

- Compares intralaminar connectivity strengths in S1, S2, and M1. Could help show which circuits are canonical.

Persistently active, pacemaker-like neurons in neocortex (Morgane Le Bon-Jego and Rafael Yuste, 2007)

- Two types of cells are active when synapses are suppressed, one of which is L5 martinotti. The other is a type of py cell in L2/3 and L5, which doesn't seem to be L5 TT. Comparing the provided info to L5 ST and L5 short will probably work.
- Framed as like CPGs. I wonder if that relates to L5 ST possibly modulating to sync targets with whisking.
- The L5 martinotti cell pacemaker activity is very regular. Project to L1 and L4, and dendrites mostly in L5.

Quantitative morphologic classification of layer 5 neurons from mouse primary visual cortex (Tsiola A, Hamzei-Sichani F, Peterlin Z, and Yuste R, 2001)

- 5 subtypes of V1 L5 cells.

Beyond Columnar Organization: Cell Type- and Target Layer-Specific Principles of Horizontal Axon Projection Patterns in Rat Vibrissal Cortex (Rajeevan T. Narayanan, Robert Egger, Andrew S. Johnson, Huibert D. Mansvelder, Bert Sakmann, Christiaan P.J. de Kock, and Marcel Oberlaender, 2015)

- Inter-columnar connectivity of each cell type is different along whisker rows versus whisker arcs.

- This could provide constraints because, if a connection is missing along either the row or arc, it probably isn't essential. Or the differences are because the row contacts the object sequentially whereas position in the arc is more for vertical location.
- Superficial/deep mirror arc/row somehow.

Sensory experience restructures thalamocortical axons during adulthood (Oberlaender M, Ramirez A, and Bruno RM, 2012)

- Whisker trimming -> thalamocortical axon length reduces but density of synapses on the axon.
- Maybe that's how map plasticity works.

Thalamocortical input onto layer 5 pyramidal neurons measured using quantitative large-scale array tomography (Jong-Cheol Rah, Erhan Bas, Jennifer Colonell, Yuriy Mishchenko, Bill Karsh, Richard D. Fetter, Eugene W. Myers, Dmitri B. Chklovskii, Karel Svoboda, Timothy D. Harris, and John T. R. Isaac, 2013)

- Subcellular location-specific connectivity.
- TC synapses on L5 are clustered. So is it dendritic segment processing, unlike normal spatial pooling?

Layer-specific intracolumnar and transcolumnar functional connectivity of layer V pyramidal cells in rat barrel cortex (Schubert D, Staiger JF, Cho N, Kötter R, Zilles K, and Luhmann HJ, 2001)

- Excitatory and inhibitory intra/transcolumnar input to L5 IB/RS.
- L5 IB receives L4 input. Maybe L5 IB includes L5 ST.

Synaptic mechanisms underlying functional dichotomy between intrinsic-bursting and regular-spiking neurons in auditory cortical layer 5 (Sun YJ, Kim YJ, Ibrahim LA, Tao HW, and Zhang LI, 2013)

- Auditory cortex L5 IB/RS.
- IB cells have broad frequency tuning because of broad long-duration excitatory input and more narrowly tuned inhibitory input.
- So maybe L5 TT cells are broadly tuned because of their weak (~= narrowly tuned) inhibitory input.
- RS cells are sharply tuned similar to L4.
- Inputs to L5 are temporally prolonged, which may contribute to broad tuning.
- They suggest IB cell broad tuning is for generalized subcortical control/plasticity. That might make sense.
    - Important: IB cells project to the thalamus, so maybe their role is in cortical mapping if they determine how S2 activates by broad POm control.

    - And that even makes sense for generating behavior, since a muscle movement is rather broad compared to e.g. sensory features, and each muscle is like a column, or even broader since many muscles move a bunch of columns' sensory patches.
    - Also, behavior is linked to coordinate frames, so it makes sense for the same cells to generate behavior (coordinate frame changes) and control maps.
    - If L5 also recognizes objects, that's still consistent because allocentric coordinate frames depend on the object. The coordinate system might even be the object if it's unique to the object.
    - Even if behavior changes the object, still consistent with a role in mapping because that changes the allocentric map.
    - In the where pathway, behavior changes the egocentric object position and therefore the map.
    - Should distinguish map of features (where each feature is in the coordinate system), coordinate system, and column mapping.
    - Maybe by changing the map (e.g. shifting RFs), it produces an allocentric map which updates how it responds to each sensor based on behavior/the object.
    - Behavior changes how each column contacts the object, so it makes sense to control mapping on a column scale, by causing cells in a column to respond to another column's sensory patch. E.g. a whisker contacts a surface, and then behavior moves the adjacent whisker to contact the surface, so the whisker which just contacted the surface and the whisker which is about to contact the surface should respond in the same way as when they contact.
    - Maybe since remapping in L5 is pretty messy and only on average full remapping, there's something else going on.

Receptive Field Properties of the Macaque Second Somatosensory Cortex: Nonlinear Mechanisms Underlying the Representation of Orientation Within a Finger Pad (Pramodsingh H. Thakur, Paul J. Fitzgerald, John W. Lane, and Steven S. Hsiao, 2006)

- A prior study found orientation tuning to the fingertips, invariant to which fingertip.
- This study is about details of that.
- It seems to frame features in terms of orientation.

Supralinear increase of recurrent inhibition during sparse activity in the somatosensory cortex (Christoph Kapfer, Lindsey L Glickfeld, Bassam V Atallah, and Massimo Scanziani, 2007)

- A single L2/3 py cell can generate widespread SOM inhibition. Specifically, SOM cells in L2/3 and L5.
- However, the inhibition increases supralinearly with the number of active py cells.

- Tested L2/3 py cells within 50 um of each other, in different directions, meaning possible cell A -> cell B. Not exactly connections because could be indirect. In 12% of directions, a 10 AP train of 100+ hz in cell A -> hyperpolarization in cell B. On average, the hyperpolarization began between the 4th of 5th APs in the train. GABAA, and not GABAB.
- So that's longer than a burst, but keep in mind they recorded the soma.
- When a cell elicited the inhibition in a neighboring py cell, there was a ~40% chance of also doing so in another tested neighbor, ~twice as likely as inhibiting a random neighboring cell. They interpret this to mean that disynaptic inhibition inhibits ~40% of neighboring cell.
- Direct connections between the py cells had a 10% chance of 1-way and a ~2.5% chance of 2-way. So it doesn't seem particularly reciprocal within a 50 um range. When cells were connected, the odds that the presynaptic cell evoked inhibition postsynaptically, at least at 100+ hz, was virtually the same as the random chance of evoking inhibition for another cell, although this did result in an EPSP-IPSP sequence and it appears not to happen right away as would be expected for PV inhibition.
- It's interesting that they detect the IPSP even though SOM cells target distal apical, at least for L5.
- When two py cells were both activated, the odds of generating inhibition were much higher, about double that expected without supralinear increase. 13% -> 48%. The strength of inhibition might also increase. Also, inhibition now began on average between the 2nd and 3rd spikes in the 2-cell 100-125 hz train.
- Divided interneurons (that send to and must also receive from L2/3 py cells) into those receiving depressing input and those receiving facilitating input. Membrane potential of the depressing group peaked early in the train, on average between the 1st and 2nd input spikes, whereas that of the facilitating group was higher at each consecutive spike, at least up to 10 spikes. However, these cells were also adapting to a constant current, although that might be over the course of 2 seconds, although it still appears to adapt noticeably during just 200 ms.
- The facilitating-input interneurons which both receive from and project to L2/3 py cells were in L2/3 and L5. The depressing-input ones were only in L2/3. All of those facilitating cells were SOM+ and none of the depressing ones.
- The SOM cells but not the depressing cells are the ones responsible for the L2/3 py cell disynaptic inhibition.
- Even though L2/3 py -> depressing cell -> L2/3 py, a single py cell isn't sufficient to activate them. Two pyramidal cells caused inhibition of a third py cell via depressing cells 2% of the time, so still not responsible.

- The depressing-input cells (specifically, the fast spiking type, meaning non-adapting) were more densely connected with the py cells than were the SOM cells. Very roughly 50% chance in both directions.
- The results suggest that a single py cell only activates a somewhat small fraction of SOM cells because of not reaching threshold, not because of connectivity, because of the supralinear increase.
- SOM cells have a long membrane time constant, 26 ms, allowing them to integrate longer periods. That's not much different from py cells, but it means the burst input doesn't have to be entirely synchronous. Membrane time constant is how long it takes to decay to 37% above resting voltage.

Disynaptic Inhibition between Neocortical Pyramidal Cells Mediated by Martinotti Cells
(Gilad Silberberg and Henry Markram, 2007)

- FDDI between neighboring L5 cells
- Inhibition between 2 cells is more than 2x as likely as direct excitation. But is that inhibition via SOM cells?
- The inhibition increases with FR and firing duration.
- The inhibition is on the apical dendrite and tuft, and didn't test basal.
- Only examined TT L5 cells.
- Recorded cells were within 100 um horizontally of each other.
- Connections between L5 py cells depress strongly.
- 12% of pairs had monosynaptic excitation and 27% had disynaptic inhibition.
- If a pair has disynaptic inhibition, it still has the same chance of monosynaptic excitation.
- The disynaptic inhibition is not at the start of the AP train at least when 1 py cell is activated, so by SOM cells.
- Used 70 hz trains of 15 APs. Results in peak inhibition measured from the soma of .8 mV. Latency of peak response from start of the train was 94 to 410 ms, average 241 ms. This is for 15 APs, so the average latency comes after the train ends.
- In an example pair with both disynaptic inhibition and monosynaptic excitation, the overall signal at the soma is excitatory, and remains that way but decreases with each spike, and then once the train ends the signal is inhibitory for ~80 ms.
- The magnitude and probability of inhibition increase proportionally with the firing rate of the py cell. Tested 30 to 70 hz. When changed from 70 hz to 50 hz, the peak inhibition amplitude is cut in half. The probability of inhibition increases with AP number. On average, inhibition begins between the 4th and 5th APs.
- FDDI is rare below 20 hz.
- GABAA, not GABAB.

- Inhibition reversal potential of -57 mV. When comparing this to the study on sometimes excitatory inhibition in L1, the chloride concentration is 10 mM and reversal potential is less negative at higher concentrations.
- However, contradicting that reversal potential, most responses at resting membrane potential were hyperpolarizing, as well as at least some responses at more negative potentials. The effective soma-measured reversal potential is -79 mV on average, but it varies from -113 mV to -58 mV.
- The contradiction is because the membrane potential is held at the soma, whereas the inhibition is dendritic, and also because the -57 mV was derived by somatic inhibition. Dendrites are less affected by somatically held potential.
- Recorded apical dendrite, not basal.
- The dendritic input affects the other results because the latencies and rise times are shorter and amplitudes greater than at the soma.
- Those differences are opposite for the excitatory connections because those are mostly basal.
- Morphologically, the intermediate cells are martinotti cells. They only checked for interneurons (as well as py cells) all within 100 um of each other, so they are at least L5 martinotti cells, assuming 100 um doesn't bring it out of the same layer. Not completely sure, though, because last time 100 um was just the lateral distance.
- The martinotti cells have an axon ascending to L1. They adapt and have an initial burst, at least for step somatic injection. They do not appear to burst for synaptic input.
- I'm not sure, but it looks like the martinotti -> L5 py synapses are on the entire apical dendrite except maybe the shaft, so including oblique, 1st order tuft, etc.
- SOM cell inputs had a long duration of membrane potential summation. Increased presynaptic latency -> reduced SOM cell spike latency from train onset.
- More presynaptic APs sometimes caused multiple SOM discharges. It appears in the example that it fires, then it needs a lot of APs to fire again (at least as many as required to fire the first time, but it varies and can require more).
- On average, from resting potential, the latency for the SOM cell to fire from 70 hz input train initiation is 150 ms on average, so 10 APs on average. Minimum 3 APs. For the same py/SOM cell pair, the discharge onset varies.
- SOM -> py synapses were depressing. Average reversal potential of -88 mV soma holding potential. Synapses are on apical, oblique, and tuft, and all of those receive a reasonably high % of the synapses. They don't appear to be on the trunk.
- When tested for a single SOM/py/py circuit, when the SOM cell was silenced, disynaptic inhibition still occurred, so multiple SOM cells are at least sometimes involved. Also, the inhibition IPSP at the soma is .5 mV on average for a single SOM cell being activated , whereas it's more (.8 mV average) when FDDI is via a py cell.

- Each SOM cell targets targeted py cells with on average 12 synapses. Based on the examples, I doubt a single SOM cell can silence all but one distal tuft segment, but individual SOM cells can probably silence a large fraction.
- Each py cell targets targeted SOM cells with on average 8 synapses. On average 135 um from the SOM soma, ranging from 22 to 337 um. Targets the 1st to 6th order branches, and unevenly distributed onto descending dendrites i.e. below the SOM soma.
- 33% of disynaptic connections were reciprocal, at least for neighboring py cells. Neighboring probably means within 100 um laterally.
- 68% of neighboring py cells contact the same SOM cell, and a given SOM cell contacts 79% of neighboring py cells.
- Compared to the disynaptic inhibition, single SOM cell -> py cell responses are 22% to 98% as strong, average 65%. Keep in mind this might be misleading because recording the soma might reflect supralinear summation in the py cell.
- When a py cell -> SOM -> other py cell, 77% of the time the presynaptic py cell is also inhibited. So I guess regardless of the presynaptic cell, the SOM cell inhibits ~78% of neighboring py cells. Keep in mind there may also be inhibition of more distant py cells.
- 5% of all cortical cells are martinotti cells. Therefore, the prominence of the FDDI circuit is because of high connectivity with py cells.
- Each SOM cell's axon has ~3000 boutons, 90% of which are on py cells. This is based on a study not restricted to L5. Therefore, this study estimates each SOM cell targets a few hundred py cells. Therefore, they operate primarily on a subcolumnar scale. I'm not so sure though, because SOM cells also have wide axon and dendrite arbors.
- SOM cells preferentially target nearby py cells because of the ascending axons. So maybe those wide axons arbors e.g. inhibit PV cells.
- According to the study, more distal pyramidal cells probably only receive SOM input on the tuft in L1.
- Disynaptic connectivity between py cells drops 10x when the somas are greater than 50 um apart, although the tuft dendrite could still easily be targeted because that's based on soma recording. Therefore, FDDI is primarily within the dimensions of minicolumns or a bit bigger, except possible for tuft dendrites. I can't find access to the source for 50 um and it's a bit vague whether it means FDDI or just general disynaptic connectivity, so I'm not sure. Also, there are probably way less than a few hundred cells in a minicolumn, although perhaps most of those cells are contacted on the tuft.
- I'm guessing the depressing synaptic output from SOM cells doesn't matter, because of their apparently low FRs.
- SOM cell axons ascend to L1, where they spread laterally.
- Cites that disynaptic inhibition wasn't observed in the L5 cells which project to the other hemisphere.

Distinct behavioural and network correlates of two interneuron types in prefrontal cortex (D. Kvitsiani, S. Ranade, B. Hangya, H. Taniguchi, J. Z. Huang, and A. Kepecs, 2013)

- PFC, specifically anterior cingulate cortex. Awake.
- A subtype of SOM cell responds at reward approach, whereas PV cells respond at reward leaving and encode stay duration.
- PV cells fired in millisecond synchrony whereas SOM cell inhibition in terms of py cell firing was weaker/more variable compared to PV cells. SOM cells are not synchronized at least so much as PV cells.
- Whether to stay or leave is a function of anterior cingulate cortex.
- ⅓ of SOM cells had narrower spikes and FRs of ~16 hz, whereas the others have wider spikes and FRs of ~4 hz. The FRs are during behavior, so maybe not reliable if they change depending on what the animal is doing.
- PV cells briefly inhibit nearby cells, whereas SOM cells inhibit longer and more variably, in terms of target cell FRs.
- Task: 2 platforms. Running to one -> reward at the other platform. Reward size while approaching reward platform cued by auditory signal.
- 11/14 PV cells had increased FR while leaving the reward platform and around that time.
- 9/10 narrow spiking SOM cells reduced their firing rates upong reward zone entry and had reduced FRs at least the next 1.5 seconds. Wide spiking SOM cells instead increased their FRs around the time of entry, but it appears too variable to say that's why the average FRs increased.
- I don't trust the results. The correlations appear too variable and there are alternative explanations.

Dendritic encoding of sensory stimuli controlled by deep cortical interneurons (Masanori Murayama, Enrique Pérez-Garci, Thomas Nevian, Tobias Bock, Walter Senn, and Matthew E. Larkum, 2009)

- Awake and anesthetized, mostly the latter. L5. Appears to be on the scale of multiple nearby cells, not individual apical dendrites.
- The strength of sensory stimulus (air puff on skin) is encoded by the overall L5 cell dendritic calcium signal. This was under anesthesia.
- The slope of the stimulus-response is controlled by certain interneurons activated primarily by synapses in L5.
- Tuft activity via interneurons blocks dendritic calcium spikes in neighboring py cells. Specifically, at least the initiation of those calcium spikes.
- Blocking GABAB receptors had little influence, although possibly a very small one.
- TTX into L5, which prevents firing and thus bAPs, increased the calcium signal a lot. Based on other additional evidence, that's because of inhibiting martinotti cells.

- FDDI severely reduced the calcium signal. Maybe they mean that of particular cells. Stimulus-response function for calcium response is linear, except without GABAA.
- The disynaptically evoked apical inhibition was able to inhibit current injection to the calcium initiation zone, and it did so in an all or none fashion. So I guess the idea of inhibiting particular tuft segments is probably wrong, although it's hard to compare two different locations of excitation.,
- Disynaptically evoked apical inhibition also reduced (to average 1/5th) the calcium signal evoked by high frequency bAPs. In the example, 70 hz firing didn't create an apical calcium signal in the cell, whereas 80 hz did. (So maybe there's a critical frequency for bAPs). That was abolished by disynaptic inhibition. Keep in mind this is a sample size of just 1 cell.
- So even if FDDI inhibits selected tuft segments, it at least inhibits bAPs, perhaps including bursts.
- Inhibition of dendritic calcium spikes is all or none, as are the calcium spikes themselves.

Top-down Dendritic Input Increases the Gain of Layer 5 Pyramidal Neurons (Matthew E. Larkum, Walter Senn, and Hans-R. Lüscher, 2004)

- Slice. A little below body temperature.
- bAP and EPSP coincidence window of ~25 ms.
- For apical injection, once strong enough to general APs, quickly (perhaps immediately, i.e. no more voltage increase required) high average FR (~20 hz), but it still rises more with stronger injection.
- The apical (appears 1st order tuft) has a much higher threshold than the soma to begin firing, and double the proximal apical shaft. Somatic injection causes a linear rise in average FR, compared to the threshold-like initiation zone injection response. Beyond the threshold, average FR ~20 hz, but can achieve that with somatic injection.
- The dendritic injection causes APs in bursts, at least mostly. The threshold for dendritic injection is 1.1 nA. I'm guessing the variability in whether or not it bursts is because of when it switches from burst to RS, so it probably always bursts initially.
- .25 nA into the soma, which is just subthreshold, causes it to actually fire faster for more dendritic input (but check if that involves bursting), linearly up to ~12 hz, and then upon passing a threshold of .85 nA (compared to the threshold of 1.1 nA before, although that appears to cause a more rapid rise) -> increases more rapidly, but still linearly. These are probably just one cell tests.
- It bursts at least sometimes once it passes that .85 nA threshold, but not below it even tho FR increases with dendritic input at the initiation zone. The bursting might only occur initially, and then mix of RS and bursts.
- Keep in mind that this influence of the apical dendrite on the singlet FR might just be a result of using near-threshold somatic current, or martinotti cells not acting properly.

- With constant subthreshold apical initiation zone input, the threshold of somatic input for firing decreases. Once it reaches that threshold, it appears to increase with roughly the same slope for the different subthreshold apical input strengths, and the slope is higher than for somatic injection alone. The shift in threshold is linearly related to the strength of apical input. So weak initiation zone input can enhance singlet firing.
- Weak dendritic input helps firing greatly.
- Some of the results weakly contradict apical input influencing singlet output. But the voltage ranges they chose in the noise-using experiment might be why. Still, sample sizes are low, so need to confirm the results elsewhere. Also, I'm going to select articles which confirm this result for notes, so need to compare methods etc. with sources which don't confirm this result. Don't just base it on how many articles confirm it or don't.
- 1000 pA = 1 nA.
- Should verify this, but the authors say that weak dendritic input changes the firing pattern of moderate somatic input to burst, whereas weak somatic input produces firing more easily for moderate dendritic input. Does that make sense, and is there a grey area between those two regimes?
- How does the temporal coincidence window for the bAP/dendritic input fit into this scheme? If the input is strong but not in that window, does it increase FR? It's probably like apical input without somatic input, but maybe not, since subthreshold -> no bAPs, yet that somatic input still matters.

Dendritic Calcium Spikes in Layer 5 Pyramidal Neurons Amplify and Limit Transmission of Ligand-Gated Dendritic Current to Soma (J. C. Oakley, P. C. Schwindt, and W. E. Crill, 2001)

- Slice. L5. Were only able to find RS cells.
- Glutamate iontophoresis (seems to mean introducing glutamate with an electric current which moves the glutamate) on dendrite caused FR to increase linearly with iontophoresis current until a threshold where calcium response caused a sudden increase in FR, after which point the FR increased no further. It stopped increasing FR because increased glutamate couldn't change the plateau potential's amplitude.
- Similar patterns occured when iontophoresis was on distal apical, oblique, and basal, but not on proximal apical. How similar and do they all evoke bursting? What about proximal vs. distal basal? Apical initiation zone vs. distal tuft?
- On the soma and proximal apical, iontophoresis caused FR increasing with current linearly, without plateaus.
- Plateaus at the soma attenuate with more distal iontophoresis (meaning distal in terms of compartment?), and currents sum at the soma if plateaus are evoked at separate dendritic compartments (?), and subthreshold currents at the same dendrite (compartment?) sum at the soma. Two plateaus generated on the same dendrite (meaning compartment?) -> only

the proximal plateau is seen at the soma, although I'm not convinced but they clearly don't sum much. Two slightly subthreshold currents on the same dendrite can create a plateau at the soma by summing.

- Plateaus prevent current from distal ligand gated channels from reaching the soma. What is the implication of this? Isn't the response the same, because plateau potential amplitude is fixed? Or are more distal plateau potentials more powerful? Does it vary with oblique/basal/apical?
- The apical dendrite can evoke both short and long duration calcium spikes. Only the long duration is called a plateau, whereas the short duration might be called a calcium transient.
- Sufficiently long dendritic depolarization evokes an initial short calcium spike and then a long calcium spike. The short calcium spike is ~100 ms and repolarizes even though depolarization continues. The long calcium spike (plateau) continues as long as the depolarization continues and then ends.
- This study focuses on the plateau, because it allows reaching a steady state response. But wouldn't that focus on something biologically unrealistic or rare? Does this mean most articles on plateaus show something unrealistic?
- Used constant somatic current injection when studying dendrites with glutamate. In cells which could fire without that somatic injection, the responses to dendritic glutamate were the same qualitatively.
- >200 um from the soma on apical, weaker glutamate evoked RS. Increasing the glutamate to a threshold -> initial epoch of bursting followed by RS. During that bursting epoch, bursts of 2-4 spikes each followed by large hyperpolarizing afterpotential. Increasing glutamate above that threshold -> shortened epoch of bursting and less bursts, switching to RS sooner during the continuous glutamate. There is always at least 1 initial burst. Increases in glutamate don't increase RS FR once above bursting threshold, but it does increase FR below burst threshold, up to ~20 hz before the burst threshold. RS above the threshold is faster than 20 hz, ~45 hz. RS doesn't appear to change FR over time with constant glutamate. It appears to begin very very roughly ~300 ms after bursting begins, possibly more and certainly sometimes less, depending on glutamate strength.
- Somatic-only (or on the 1st 100 um of apical) glutamate -> RS only, increasing FR with glutamate iontophoresis current linearly. FRs of 50 hz are attainable, possibly higher. The maximum possible FR is higher than the max possible late RS FR for dendritic.
- Beyond apical plateau threshold, increasing glutamate doesn't increase amplitude, but it does decrease latency. There's always a delay for even somatic RS with iontophoresis, so I worry that the decreased latency is simply because the current moved the glutamate to the cell faster.

- However, they take this latency change as an explanation for why increased glutamate decreases burst duration, since they assert that the RS occurs during the plateau. Their reasoning is that RS doesn't increase FR with greater current (suprathreshold for bursting), and, likewise, the plateau doesn't increase amplitude. That appears to be correct, since there is an initial calcium spike which repolarizes before the plateau. Note that this was measured at the soma, so I wonder where the early calcium spike initiates.
- So far, the apical glutamate was applied at ~230 um and ~330 um from the soma, at least for 2 example cells. Is that in the initiation zone?
- Calcium channels are required for plateaus, but sometimes blocking sodium channels or NMDARs can also stop the plateau.
- Plateau amplitude measured at the soma decreases linearly with distance of iontophoresis from the soma, suggesting attenuation of the plateau with distance from the soma. Likewise, the jump in RS FR (i.e. subthreshold FR vs. post-burst threshold RS FR) decreases with distance from the soma, likely because of that attenuation.
- I worry that, if plateaus are normally initiated in the same place, these results are wrong or irrelevant, especially those about attenuation. Using glutamate does activate synapses, though.
- The jump in frequency ranges from ~20 hz (~100 um) to ~5 hz (~750 um). Decreases by ~2 hz per 100 um.
- Another study found evidence for attenuation of the initial transient calcium spike, so they both attenuate. That study found that it depends on K+ channels, at least for the transient.
- Is the post-burst hyperpolarization the same as the repolarization after the initial calcium spike? Is there one calcium spike per burst? Since it was measured at the soma, is there actually just one continuous calcium plateau but initial post-burst hyperpolarization at the soma? Is the transient because of NMDARs?
- Couldn't test the fine branches of the tuft.
- Tested on the tuft ~730 um from soma, ~200 um from primary branch point. This was able to evoke a calcium transient followed by a plateau. 14/15 sites beyond the primary branch point were able to produce plateaus, measured at the soma.
- 7/9 apical oblique sites generated plateaus. In the example, plateau was generate on oblique which branched off apical trunk at 60 um from soma, 20 um along that oblique.
- Within 100 um of the soma on the apical trunk didn't evoke plateaus.
- 7/8 basal sites evoked plateaus at the soma. All basal cites evoked a smaller somatic plateau compared to the same distance on basal. No basal sites evoked an initial calcium transient spike. Plateaus could be evoked closer than apical, 50 to 100 um as minimums. (Or is 50-100 um just how much closer they can be evoked compared to apical?)
- Plateau potential on basal, oblique, and apical never grew larger once the iontophoresis was suprathreshold for the plateau.

- At basal and distal apical (i.e. primary tuft), plateaus were too small to evoke firing by themselves.With somatic input which alone causes firing at a low frequency, both basal and distal apical increase RS FR with increasing glutamate, but only by up to ~5 hz before reaching plateau threshold and thereby jumping then not increasing FR. For distal apical, ~8-12 hz depending on glutamate strength and then jumps to ~18 hz. For basal, ~12-14 hz and then ~17 hz. For oblique, which didn't involve somatic injection, ~12-22 hz and then ~35 hz.
- Basal doesn't jump much once passing the plateau threshold likely because the plateau amplitude is fairly small.
- Oblique and distal apical (primary tuft) appear to generate the initial transient, but not basal.
- Basal never generated an initial sodium spike burst.
- Basal sites < 50 um cannot generate plateaus nor frequency jumps like happens at plateau threshold.
- When a plateau is evoked at a distal apical site and a more proximal apical site, with appropriate timing offsets, the plateau of the proximal blocks the somatically-recorded distal calcium transient. This was with TTX.
- I wonder if transients = NMDA spikes and the calcium plateau is beyond the NMDAR calcium reversal concentration.
- When proximal is turned off and distal continues, it decays down to the distal-alone plateau potential.
- The proximal only blocks the distal for plateaus (guessing just the proximal must be a plateau). When both are subthreshold for plateaus, they summate at the soma.
- When the distal is suprathreshold for plateau and proximal subthreshold, the response is still similar to proximal suprathreshold alone.
- Also, even if both are subthreshold, they can summate to produce the proximal suprathreshold response. This relates to the response for spatially distributed depolarizations.
- Sufficiently proximal basal -> no jump in RS FR, and FR just linear increases with glutamate strength. Same for sufficiently proximal apical.
- Cannot evoke RS FR jumps on proximal 50 um of basal nor proximal 100 um of apical.
- Does it burst multiple times during the transient? It seems that the plateau often takes ~200 or more ms after the transient peaks to begin.
- Transients require voltage gated calcium channels, like plateaus.
- The plateau collapses when glutamate is no longer being applied, so it requires fairly continuous stimulation. So maybe the weird tuft learning rules are because of this, i.e. associate to inputs which cause it to continue firing after the burst.

- In another study on L5 basal dendrites, glutamate evoked dendritic spikes (not plateaus), but probably because the evoked depolarization was brief unlike in this study. But that study is about NMDA spikes, so I'm not sure.
- In that study, the dendritic spikes were blocked by calcium channel blocker (cd2+), and by TTX, but they can be evoked in the presence of both with strong enough glutamate but not with NMDAR blocker.
- Calcium transients are regenerative. What about plateaus? They cause additional current beyond a threshold, but are they considered regenerative?
- On the apical dendrite, regenerative potentials required voltage gated calcium channels, but it's still possible that sufficient glutamate activates NMDA-based regenerative current with voltage gated calcium channel blocker.
- Similar to how this study found a greater FR jump upon more proximal plateau initiation, another study found a greater jump for more proximal calcium transients.
- Calcium transients and plateaus have similar amplitude, and the proximal blocking distal effect likely applies to them, at least for proximal plateaus blocking distal transients at the soma.
- Based on the summation of subthreshold distal/more proximal apical, causing plateau as if initiated at the proximal site, and because more proximal sites have higher plateau threshold, they think with uniform excitation, stronger excitation -> more proximal initiation site -> stronger somatic plateau -> uniform excitation level is reflected in somatically measured plateau level and therefore FR.
- But if it can evoke a distal calcium plateau, it probably evokes a more proximal plateau because the voltage rise is large. Still, whether or not there is subthreshold proximal input matters. Maybe it cannot burst for non-initiation zone tuft input, but can with additional subthreshold initiation zone input.
- The apical dendrite probably cannot drive plateau RS greater than 50 hz, except in combination with input to other compartments including oblique. They also didn't test non-primary tuft.
- The all or none plateau mechanism allows preventing excessive FR without inhibitory control for the studied inputs.

Mechanisms Underlying Burst and Regular Spiking Evoked by Dendritic Depolarization in Layer 5 Cortical Pyramidal Neurons (Peter Schwindt and Wayne Crill, 1999)

- Slice. Likely only TT L5 cells. Not sure though, because they just say they're likely large cells, and that's based on low input resistance.
- Some of these notes are cited by this study from another study, with similar methods but some differences.
- Apical dendrites. Long lasting glutamate iontophoresis.

- The weakest glutamate that evoked firing usually caused repetitive bursting, separated by long hyperpolarizations. Stronger glutamate -> initial bursting then RS, and stronger -> initial bursting switches more quickly to RS. Plateau during that RS.
- Many of the results are similar to J. C. Oakley, P. C. Schwindt, and W. E. Crill, 2001.
- Dendrite below threshold to evoke APs alone but above a lower threshold -> somatic EPSP causes bursting.
- The burst (or all of them?) are driven by an all or none delayed depolarization initiated in the dendrite which was calcium dependent. NMDARs or voltage gated calcium channels?
- It says the delayed depolarization was triggered along with the first sodium spike in the burst. Does that mean the 1st spike in the burst isn't special? Or does that first spike reflect a normal somatic spike caused by the somatic current alone?
- Duration of plateau is increased by stronger dendritic depolarization. Is that because it lasts longer once input stops, or because it converts from burst to RS faster?
- Plateau initiation causes termination of bursting.
- RS during the plateau has constant frequency. I wonder if that's why L5 TT cells don't adapt. Do they adapt for other causes of RS?
- If more proximal has higher threshold than distal to cause a plateau for the strength of its synapses, maybe normally proximal alone -> bursting because can never be suprathreshold for plateau alone -> signal up the hierarchy -> distal input -> switches to RS now that the signal has been sent and integrated. And maybe SOM causes it to stop bursting if it doesn't get a signal back soon enough. But do L5 ST cells synapse on the initiation zone a lot?
- In IB L5 cells, which initially burst for somatic injection, most cells switch to RS after the initial burst.
- In a prior study by the authors, with long lasting dendritic depolarization when preventing APs, calcium dependent dendritic spikes only occured at depolarization onset. In contrast, when APs were allowed, repetitive bursts occurred as long as depolarization continued. So repetitive bursting seemed to require bAPs.
- Most cells responded to somatic depolarization with rapidly adapting RS. Half as many responded with an initial burst followed by RS which continued with the current, which lasts a total of 1 second. Need to check the cited source because this seems too simplified.
- At barely suprathreshold dendritic depolarization (repetitive bursting), bursts rode on delayed depolarizations.
- With the strongest glutamate iontophoresis, only one or two initial bursts before RS.
- It looks like there might be a transition between bursting and subsequent RS, with less spikes per burst and smaller ISIs & smaller inter-burst hyperpolarizations.
- I worry that with iontophoresis, the signal increases over time because of accumulating glutamate near the receptors.
- Most data was from iontophoresis 370 to 500 um from the soma.

- When iontophoresis was tested less than 150 to 200 um from the soma, only evoked RS, no bursting.
- A subthreshold dendritic depolarization + a subthreshold somatic depolarization evoked repetitive burst firing, and could also be controlled to evoke an initial burst followed by RS even though both are subthreshold. Was the burst by subthreshold backwards spread or by subthreshold spread to the soma? Did it involve a normal regular AP? Also, I'm not convinced by this because the soma-alone subthreshold depolarization appears to increase over time, which might mimic influences of the plateau potential or the possible pre-potential build up voltage.
- In 3 of 12 cells, somatic nor dendritic input alone could evoke bursting, but somatic + dendritic could evoke bursting. For these cells, dendritic input alone evoked RS and had to be strong. For subthreshold somatic + subthreshold dendritic, repetitive bursting, and increasing either one to be suprathreshold -> RS after initial burst. Do they mean suprathreshold like when they are each activated alone? That might suggest the mechanism.
- If it is suprathreshold for bursting then switching to RS, could inhibition by SOM cells switch it to repetitive bursting?
- Neither calcium spikes nor the dendritic depolarization directly cause the bursting.
- Used a brief somatic current and a subthreshold dendritic depolarization. When the somatic current pulse was suprathreshold, triggered a single AP followed by a large afterhyperpolarization, when injected at resting potential i.e. without dendritic depolarization. During dendritic iontophoresis, somatic voltage gradually increases and peaks at the end of iontophoresis or maybe a little afterwards, and that rise must reach a sufficient level. When the current pulse was at the peak, evoked a burst and then AHP, but only with sufficient dendritic depolarization (although still subthreshold). Otherwise, just the singlet and AHP. The AHP might be because there was also weak dendritic iontophoresis, which I'm guessing is the case.
- The first singlet in the burst is followed by a all or none delayed depolarization which drives the rest of the spikes in the burst.
- The DD (delayed depolarization) was caused by a bAP-triggered dendritic spike, and required dendritic depolarization. After the DD, AHP. A DD is also responsible for each burst during repetitive bursting, and the initial AP in each causes the DD.
- Blocking voltage gated calcium channels with Cd2+ didn't abolish the bursts. They had more spikes each, were longer duration, and repolarized less between intraburst spikes. Also, a somatic current pulse that normally evoked a singlet now evoked a burst.
- They think this is because of reduction of calcium-dependent K+ currents, which seems likely to me because of the change in repolarization. Also, the burst likely resulted from another mechanism because the DD was eliminated.

- The plateau and RS last longer after iontophoresis ends for stronger iontophoresis. Is this just because of more glutamate still around to bind, or does it also happen with injection? The difference is up to at least a few hundred ms. Somatic depolarization also contributes to a longer plateau.
- The transient before the plateau does not require firing.
- Firing is RS during the plateau because each spike is followed by an AHP rather than a DD. They suggest it's because calcium channels are already active fully for the plateau, but it can burst during the transient (which has similar voltage to the plateau) so probably not, unless voltage of the transient is partially because of something that doesn't contribute to plateau voltage, e.g. sodium.
- A spike during the transient before the plateau causes a DD and a burst, so they aren't the same thing.
- Plateaus don't require NMDARs.
- Because the plateau and transient have similar amplitudes, maybe the transients/conversion to plateau is an automatic mechanism.
- The transient and the plateau both are abolished by Cd2+, and also by TTX.

Synaptic efficacy and reliability of excitatory connections between the principal neurones of the input (layer 4) and output layer (layer 5) of the neocortex (Dirk Feldmeyer and Bert Sakmann, 2000)

- Barrel cortex. On L5 -> L5 connections. Seems to be a review. Doesn't distinguish TT/ST/short.
- 60% of contacts are basal (on average 80 um from the soma), 30% oblique (on average 150 um from the soma), and 10% tertiary tuft. Compared to L4-L4 connections, roughly doubled EPSP rise and decay times. 3 ms rise time and 40 ms decay time.
- The majority of synapses are onto cells with somata 50-150 um away from the projecting cell's soma. There are few at other distances, including 0-50 um.

Effect of Common Anesthetics on Dendritic Properties in Layer 5 Neocortical Pyramidal Neurons (Sarah Potez and Matthew E. Larkum, 2008)

- Lots of data here about influencing various properties.
- Slices: S1 P35-P56. Recorded at 32 celsius.
- Anesthesia: P28-P70
- Covers urethane (U), pentobarbital (P), and ketamine/xylazine mixed (K/X).
- U and P in vitro suppressed dendritic calcium spikes (~35%), whereas K/X enhanced them (~100%).
- None of them altered propagation of calcium spikes (or do they mean somatic spikes?)
- Under anesthesia, they had the same effects as in vitro, and there was also suppression of dendritic excitability.

- P primarily increases GABAA receptor activity.
- U and K block NMDARs.
- Evoked dendritic calcium signals by evoking high firing frequency somatically.
- Long duration initiation zone injection caused a calcium signal and repetitive bursting. There appears to be one calcium spike per burst, so perhaps the calcium signal is from burst bAPs.
- K/X increases dendritic calcium spikes in terms of duration, and number.
- P increased the dendritic regenerative threshold (+60%), whereas K/X decreased it (-15%).
- All them have little impact on calcium spike amplitude.
- When evoked an artificial burst by repeated somatic pulses, the apical initiation zone voltage was larger for the 3rd bAP, and the 2nd bAP was also larger than the 1st.
- Control critical frequency was ~85 hz.
- U and P increased critical frequency (threshold for the somatic ADP) and decreased ADP amplitude, suggesting inhibiting calcium spiking. Critical frequency increases ~20 hz for U and ~15 hz for P, roughly.
- K/X decreased critical frequency. It decreases ~20 hz, roughly.
- bAP amplitude/half width weren't influenced significantly, but small sample size and they might change a bit, especially K/X increases half width 30% (like it increases calcium spike duration).
- 10% ADP amplitude decrease for U, and 55% for P. Increased 150% for K/X.
- The anesthesia concentrations were larger than normal.
- Urethane generally had smaller somatic effects than the other tested anesthetics.
- P caused missing single spikes during sustained somatic injection. It also increased threshold for somatic spiking by 80%.
- P caused 4x frequency adaptation.
- K/X increased the proportion of bursts for somatic injection and tripled adaptation.
- K/X increased somatic injection threshold.
- In vivo increased the CF compared to in vitro, by ~10 hz maybe, possibly because of inhibition being less active in slice than in vivo. The K/X decrease in vitro wasn't apparent in vivo.
- Another study found that P can cause cells to switch from RS to IB.
- X enhances Ih

<u>Notes on Old Sources</u>

Enhanced dendritic activity in awake rats (Masanori Murayama and Matthew E. Larkum, 2009)

- Rat S1. P30-P45. Recorded L5 apical calcium with periscope technique, which has potential issues.
- Somatosensory stimulation -> a fast calcium response component during the first ~100-200 ms, and a slow component which lasts seconds.
- During anesthesia, the fast component was smaller than when awake, whether or not the stimulation evoked a responsive movement of the stimulated limb. No movement under anesthesia.
- The slow component was also larger when awake. It was even larger when awake and moved in response.
- Inhibition of calcium in the apical dendrite is stronger with anesthesia.
- The slow component was larger for more forceful responsive movements. The correlation is better for the area rather than the peak of slow component.
- Keep in mind the movement can last e.g. 2 seconds. In that example, the slow component peaks at the end of the movement (but with a smaller peak for each peak in muscle movement) and then decays for ~2 seconds. Without the movement, the calcium signal peaks at the start of stimulation (although perhaps first 100 ms) then decays.
- 2 second decay is pretty extreme. Given the pattern of a small peak for each movement peak and higher peak each time, I'm pretty sure it is not temporally precise, i.e. the signal decays over time.

Synaptic Integration in Tuft Dendrites of Layer 5 Pyramidal Neurons: A New Unifying Principle (Matthew Larkum, Thomas Nevian, Maya Sandler, Alon Polsky, and Jackie Schiller, 2009)

- Slice. P27-56 rat L5.
- Apical recording is typically from thick dendrites, and these recordings suggest calcium spikes. But thin apical dendrites are different.
- Distal tuft means near or beyond the L1/2 border.
- Glutamate uncaging or extracellular stimulation of thin distal tuft:
    - NMDA spikes and weak sodium spikes, and no voltage-gated calcium channel spikes. Distal tuft injection caused calcium spikes 1/10 times, though.
    - Local spikes attenuate to 10% at other distal tuft branches, at least those separated by the primary bifurcation.
    - Attenuates to ~1/2.25 at primary bifurcation, so it still contributes some.
    - A single NMDA spike isn't enough to cause initiation zone calcium spike. Two NMDA spikes on different branches or an NMDA spike and an EPSP are required, or an NMDA spike and small initiation zone depolarization.
    - With a distal NMDA spike, need 260 pA at initiation zone, compared to 820 pA otherwise.

    - In simulation, the most distal tuft dendrites only required ~9 synapses for NMDA spikes.
- Distal tuft injection: (maybe doesn't activate NMDARs)
    - Local regenerative sodium spikes. Attenuates to ~⅓ at apical trunk initiation zone.
    - Secondary tuft threshold: 1000 ± 500 pA.
    - Tertiary+ tuft threshold: 740 ± 240 pA.
- Main bifurcation/primary tuft injection:
    - Calcium spikes. Propagates well, including to quaternary tuft.
    - Threshold 1000 pA ± 350 pA
    - NMDARs probably not tested by injection.
- Branch thickness rather than branch order might be the best classification. For injection, ~1.6 um or thinner -> sodium spikes only, whereas ~3 um or thicker -> calcium spikes only.
- Some distances from soma:
    - Near main branch point: 660 +- 110 um.
    - Secondary tuft: 775 +- 100 um.
    - Tertiary/quaternary tuft: 860 +- 60 um.
- Ih has a large influence on tuft compartmentalization. Hyperpolarization-activated current, which is active at resting potential, causes leaking excitation. Blocking it increases NMDA spike amplitude both locally and at the main bifurcation.

Quantitative analysis of firing properties of pyramidal neurons from layer 5 of rat sensorimotor cortex (Peter Schwindt, Jennifer A. O'Brien, and Wayne Crill, 1997)

- L5 rat sensorimotor cortex slice. P21-31. 31-34 degrees.
- Examined differences between IB/RS cells.
- The recorded cells had tonic firing for sustained injection. Most cells had the same tonic firing properties regardless of initial response.
- However, a group of high resistance cells had different tonic firing properties. With slowly increasing current injection, relationship between FR and instantaneous current strength was similar to the relationship for injection which doesn't change strength over time.
- Low resistance cells had 3 types of initial responses: fast adaptation (55%), high threshold burst (25%), and low threshold bursts (10%).
- High resistance cells slowly adapted FR.
- Slowly adapting, fast adapting, and high threshold bursting cells showed no adaptation near threshold for repetitive firing.
- FA and HTB cells had doublet ("two-spike") adaptation before a stable tonic FR, for currents up to 1.6x threshold for firing.

- HTB cells required 2.1x threshold current to burst, whereas LTB cells burst at firing threshold.
- In most cells, initial FR increased monotonically with current strength.
- The response to quickly ramping current suggests FR during adaptation or bursting encodes rate of change in current strength.
- Transient and tonic firing properties are stable over at least long periods of time.
- Different firing properties of large/small cells might be more important than the burst/nonburst properties of large cells.
- This study compares responses found for current injection with findings of studies using iontophoresis.
- Laminar location of IB cells can vary by species (but be careful that they aren't just using different regions). Based on the citations, in guinea pig sensorimotor cortex: L4/5a only. Mouse somatosensory cortex: L5/6 border and not L2/3/4. Rat somatosensory and visual cortex: L5b and not L5a nor L2/3.
- Used large microelectrodes to bias recordings to larger cells (because of the lower electrode resistance and lower resistance of large cells), and placed electrodes in L5b. Most recorded cells were large cells. Large cells have lower input resistance.
- Recorded an area with both sensory and motor roles.
- Tonic firing properties of large cells are similar even if have different initial responses, and differ from the tonic firing properties of small cells.
- Stained 15/68 recorded cells. All were in L5b and had apical reaching L1.
- Evoked repetitive firing using 1-2 second sustained current. All cells fired for the duration of that current if sufficient amplitude. The tonic portion of all responses had average FR increase for stronger injection. Minimum steady firing rate 5-16 hz.
- Max current was 3 nA across all cells. For individual cells, .8 to 3 nA was max current.
- The tonic firing rate was fit well by two lines for ~½ of recorded cells. The first line has greater slope (FR to nA) than the line beyond an amplitude.
- 54% of cells were FA (fast adapting). No bursting for any tested current. FA means tonic firing rate begins after just one ISI during continuous injection. The first ISI is a tiny bit smaller than the rest, which are all nearly equal.
- Does fast/slow adapting in general mean how quickly it reaches a stable FR, not how much firing slows down over time?
- FA: The first ISI is pretty similar to the other ISIs for current injection below ~1 nA (so no adaption, although a tiny bit is noticeable at 40 hz), but beyond that, first ISI decreases more quickly with injection strength than the other ISIs. For the example cell, this divergence occurs at ~60 hz. At ~80 hz tonic FR, the first ISI corresponds to an FR of ~120 hz for the example cell.
- HTB (high threshold bursting): 28% of recorded cells (keep in mind the bias towards large cells). This means they can have an initial burst. For HTBs, threshold for bursting

~2x threshold for firing. Half of HTBs had initial 2 spike burst, and half had triplet+. Besides the longer ISI after the initial burst, similar properties to FA cells. The first ISI for an example initial-doublet-above-threshold HTB cell decreases more quickly than the other ISIs until a point beyond which it decreases much more quickly. The other HTBs were similar to the example cell but can have triplets+.

- All HTBs had burst FR which increased with current injection amplitude linearly (although flattens out eventually because of FR saturation).
- Included doublets as bursts. Defined bursts as a spike cluster with ISIs lower than the following ISI.
- LTBs (low threshold bursting): 10% of recorded cells. Initial burst at firing threshold. Some have doublets and some have more. Longer post-burst ISI, which becomes more similar to the tonic ISIs at higher injection amplitudes. Some have burst ISI decreasing for stronger injection, and some don't for the initial ISI because that ISI reflects saturated firing rate (but if the subsequent ISIs aren't saturated they decrease with injection amplitude).
- A very small fraction (2/68) of cells had repetitive bursting. At firing threshold, they burst repetitively for at least 2 seconds and probably more. An increase beyond threshold (which appears to be ~.2 nA) of just .05 nA causes the example cell to burst a two or three times and then switch to RS. Increasing another .075 nA causes the example cell to burst just once before RS, and the same pattern for all tested higher currents.
- 7% (5/68) cells were SA (slowly adapting). Greater input resistance than the other groups pooled. They also had lower threshold for firing, whereas the other groups didn't have significant differences between each other in firing threshold. ~½ the current threshold (.27 nA versus .58 nA). Unlike between the other groups, SA cells had significantly different tonic current/FR slope for the primary range (meaning the slightly greater initial slope below a particular FR). 88 hz/nA for SA cells versus 36 hz/nA for the other cells pooled. Does input resistance influence the current delivered synaptically?
- During stronger current injection, SA cells adapt over many ISIs. They do not adapt for firing threshold current, although the example cell appears to adapt just above threshold. Although they can take many spikes to adapt, they eventually stabilize FR.
- During the early adapting ISIs, FR increases with injection amplitude with steeper slope below a threshold, at least in the example where it occurs at .7 nA. The steady state FR does not have this change in slope.
- Firing rates for SA cells are generally quite high. Near 0 at threshold (or more likely on the order of 5-15 hz) but at ~1.5x threshold (.4 nA), the first ISI corresponds to 75 hz, although the other ISIs are much longer. At .6 nA, first ISI 125 hz, second 100 hz, third ~60 hz hz, 4th ~50 hz, and steady state ~40 hz. This seems like a lot of adaptation total, but at 1.3 nA it only adapts from extremely rapid (~250 hz) to ~150 hz after a few spikes and then adapts to ~100 hz steady state after ~175 ms.

- In that example cell graph, it appears to reach steady state after ~150 ms (give or take maybe 50 ms) regardless of the firing rate. So it probably adapts over time more so than for each spike, conceptually.
- SA average second ISI is .8x the steady state ISI.
- When tested whether response class changes over many minutes (on the order of 45 minutes), none changed. They only used one or two for most classes, although they tested 15 FA cells.
- Because constant amplitude depolarization is probably rare in vivo, tested ramping current.
- In a cell tested for ramping current, first ISI decreased with ramp slope. Fires more quickly over the entire ~1 second ramp for greater ramp slope. Unlike with constant current, there was slow adaptation of sorts. When a ramp then constant current, constant current FR was greater for faster ramp. This indirectly detected adaptation appears pretty minor, though, even over the course of a second.
- However, the ISIs towards the end of the ramp period are smaller than the ISIs during the subsequent constant current period. For ramping over 200 ms, ~50 hz towards the end of ramp and ~40 hz during constant amplitude. Also, ISI appears smaller during ramp of greater slope. They only tested down to 100 ms ramp duration for this cell. Only one ISI occured for that duration, for an ISI of 55 hz then during constant still ~40 hz. So I guess less than 100 ms ramp probably isn't important because too few ISIs.
- That one ISI behavior prevented them from testing more rapid ramps, ranging from 10 nA/s to 40 nA/s depending on the cell.
- The one tested LTB cell fired a burst as its initial response only for slopes of at least 5 nA/s. Even though it normally bursts at firing threshold, for slower ramps it only has RS. Besides the initial response, RS throughout the ramp duration.
- I wonder if LTB responses are because of the sudden increase in depolarization caused in normal injection.
- The one tested HTB cell didn't fire an initial burst for all slopes (tested up to 25 nA/s). I guess that makes sense, because it wouldn't be at threshold early. But that also means it won't suddenly switch to bursting once ramping past that threshold.
- Didn't test ramps for any SA cells, and most tested were FA cells.
- Tested fast ramps (up to 500 nA/s). To create adaption, only used final steady currents sufficient to create adaptation when injected without a preceding ramp. One ISI occurs during the ramp, which may be longer than the ramp if sufficient slope. That ISI depended on ramp rate, not final amplitude.
- I think it makes sense for the initial ISI or initial burst to represent change because of the switch from bursting to RS for apical input. Even if the initial ISI isn't a burst, there's still an initial fast FR. Maybe initial fast FR -> faster ramping postsynaptic signals because of temporal summation -> the signal passes from cell to cell.

- Maybe the signals to thalamus which cause tonic mode aren't exactly predictions, but rather to suppress signals of change. E.g. if it's the same object and the region is just representing the object, different views of that object don't reflect external change of the internally represented thing.
- The small cells had slightly wider spikes.
- When dyed cells to check laminar location and whether apical reaches L1, dyed all groups except SA cells. All dyed cells had primary bifurcation 400-600 um from soma.
- According to another studies, IB cells have larger cell body, thicker apical, more basal and oblique branches, and larger tuft than RS cells. These characteristics were also seen in FA cells (how are they deciding what cell class the citations are about? FA cells are RS). SA RS cells in those studies had smaller somata, thinner apical dendrites, and fewer dendritic branches.
- In another study, corticotectal and corticopontine cells were repetitive bursters, and those projection types might be rare in this region, so the scarcity of repetitive bursting cells might be because of projection types. I wonder if this makes repetitive bursters another actual class.
- According to some other studies, triplet+ bursts are unique to L5, and bursting in other layers is only doublets. However, those doublets in other layers might just be an initial short ISI like those found in this study. Also, this study didn't find differences for two versus three+ spike bursts (except burst duration).
- With short ramps, it wasn't firing but rather excess firing rate above tonic FR that increased linearly with slope.
- Bursting with constant current amplitude just evokes rapid firing followed by a period without firing, but possibly a better interpretation for synaptic interactions is that the longer ISI reflects a period of reduced excitability. (They discuss this interpretation).
- Or maybe the right interpretation includes spike rate coding, since it will spike sooner during that post-burst AHP for stronger input.
- They suggest the role of burst firing/adaptation would be more clear for input pulses than continuous injection. FA cells might respond better to fast input pulse frequencies and bursters might respond better to slower input pulse frequencies depending on the number of spikes in the burst. Is that because a slower input frequency aligns better with the end of the AHP (whereas it would have to be at least twice as fast to align properly)?
- According to a couple other studies, bursting is abolished when bursters are constantly depolarized (I assume subthreshold, so before the suprathreshold input, since otherwise this study did that too with 1+ second injection). This study supports that conclusion based on the ramp responses of HTBs and the initial-only bursts.
- Betz cells (not in this region) adapt even more slowly than the SA cells found in this study. According to another study, this slow adaptation occurs because of slow activation of calcium/sodium-dependent K+ channels which cause slow AHPs. (Are those like

post-burst AHPs? Maybe post-burst AHPs aren't exactly tied to bursts.) In Betz cells, slowly ramping -> sufficient time for that K+ activity so cannot reach the FR for suddenly beginning steady current. In another study, FA RS cells lacked a slow AHP following repetitive firing. This is consistent with the idea that the examined large cells have less slow K+ conductance than Betz cells and therefore adapt much more rapidly.

- They argue the tonic response properties are more important than the transient responses when most cells are somewhat depolarized, and transient responses only important when operating at resting membrane potentials. Maybe the right way to think about it is, there is only transient input reflecting sensory input, and the transient/tonic responses are controlled not by time but by tonic depolarization level.
- In another study by mostly the same authors, apical glutamate iontophoresis can evoke repetitive bursting even for cells which don't burst for somatic injection. Therefore, they argue there might not be a distinction between bursting and non-bursting. But didn't burst/non-bursting not change over many minutes?
- Glutamate iontophoresis is like continuous asynchronous synaptic input. "Insofar" so I'm not sure if that's exact.
- When they tested repetitive firing properties for apical iontophoresis and somatic injection, no difference in bursting for iontophoresis based on burster/nonburster for somatic injection except all bursters had an initial burst for iontophoresis but not nonbursters.
- According to another study, somatic bursters burst because of non-inactivating sodium current acting as the underlying depolarization. In the iontophoresis study, they found that non-inactivating current for apical. But still possible that somatic bursters don't need dendritic spikes to burst.

Target-specific differences in somatodendritic morphology of layer V pyramidal neurons in rat motor cortex (Wen-Jun Gao and Ze-Hui Zheng, 2004)

- Rat motor cortex slice L5. Multiple motor regions.
- Corticospinal: large, deep L5, largest dendritic arbours. Apical is thick, spiny, and the trunk branches in L3 for many cells
- Corticostriatal: small, superficial L5, slender apical shafts which are spiny.
- Corticothalamic: Superficial L5 and L6 (so they might pool them which is an issue). Small or medium. Slender apical shifts which mostly lacked spines.
- Tested projections using parafascicular nucleus (Pf). Doesn't seem to be a sensory nucleus.
- Keep in mind all of the subcortical areas from which they labeled projecting cells are probably subsets.
- PT (meaning corticospinal) cells were primarily in M1. PT cells were also labelled in medial agranular cortex (possible analog of supplemental motor cortex) and S2.

- Corticostriatal cells were primarily in PFC and motor cortex. In PFC, they were in ipsilateral L2-6, whereas in M1, they were in ipsilateral L5a mostly and also some in bilateral L3c (deep L3).
- Corticothalamic cells in M1 were in L5a and L6 contralaterally (bilaterally?)
- PT cells never projected to the other subcortical areas, but corticostriatal and corticothalamic cells were sometimes doubly labelled.
- It seems like CT and corticostriatal cells in L5 are very similar.
- Both CT and corticostriatal apical dendrites usually didn't have branched trunks and had thinner trunks than PT cells. This is at least true for L5 cells.
- For all three types, oblique branches came off the trunk in L5 and L3.
- Basal dendrites of CT cells are more similar to those of PT cells than corticostriatal cells.
- In the apical midsection trunk/proximal oblique, corticostriatal and PT cells had spines but were sparse to absent on CT cells (~50% were spine free). 2/15 CT cells were spine dense, though.
- For all three classes, the most proximal apical and basal were spine free. The first ~20 um of the primary basal for all three classes. For PTN, first 60 um of apical was spine free; 20 um for corticostriatal; 35 um for CT.
- On all three classes apical shaft, spine density increased and peaked midway from the soma to tuft then gradually decreased distally (but never reaches 0).
- In all three types, oblique dendrites were covered with spines, with lower density towards L1 and no real drop in density proximal to shaft.
- On all three classes for basal, spine density increases distally, peaks around 75 um, then drops reaching 0 at 150 um for corticostriatal and 200 um for the other two.
- PTN and corticostriatal had more basal spines than CT. Seems to be a small difference.
- For all three populations, spine-sparse cells had reduced primary branch oblique spine densities.
- They didn't find short cells maybe because of the methods.
- Only a small percentage were doubly labelled, so I worry that the lack of PT double labelling is because of sparse labelling.
- Slow conducting PT cells are spiny whereas fast conducting PT cells lack spines. PT cells in this study were only slow conducting.

A Slow Fraction of Mg2+ Unblock of NMDA Receptors Limits Their Contribution to Spike Generation in Cortical Pyramidal Neurons (Mariana Vargas-Caballero and Hugh P. C. Robinson, 2003)

- Rat P8-P14. Room temp or 31-35 degrees but doesn't seem to make a difference. L2/3.
- NMDAR Mg2+ unblock has a fast component and a slow component. Block by hyperpolarization (to -70 mV) is very fast.
- It might depend on subunit type, e.g. combo of different types may cause fast and slow.

- A postsynaptic sodium AP isn't fit to unblock but the rise phase of a slow calcium AP is.
- NMDARs contribute to membrane excitability because of the depolarization -> unblock feedback loop.
- Slow unblock reduces response to sudden/transient depolarizations because end soon. Depends on how slow though.
- Full unblock requires depolarizations lasting just several ms. Not sodium APs but calcium APs work
- Lots of math etc. I don't know.
- Many studies don't use bio concentration of mg2+.
- The fast part is too slow to contribute to the upstroke of a sodium AP, but they still react, they just don't contribute to the excitability.
- They mean the upstroke both for calcium and sodium APs because then they contribute to the AP in terms of excitability (since the unblock is like a feedback loop). And they seem to mean activated by input not by the AP (but unblock depends on postsynaptic voltage).
- Stable voltage unblocks much more than the rise of a single fast AP.
- This is relevant to learning because I'm guessing the bAP unblock is involved in learning. Should research that. Also, there's a difference in what they contribute to in terms of excitability and what they would respond during, since the excitability contribution is just rise phase.
- When membrane potential is subthreshold, membrane depolarization unblocks NMDARs at least somewhat. So I worry that constant subthreshold membrane depolarization means they respond to sodium APs.
- Calcium spike appears to mean the dendritic voltage response to a burst. It appears to last about 20 ms.
- It seems they used TTX. That's an issue. The cells didn't exactly fire, but instead AP waveforms were injected.
- A dendritic sodium spikelet was smaller/slower than the somatic sodium spike. It looks like NMDARs responded to this including with the slow component.

A new cellular mechanism for coupling inputs arriving at different cortical layers (Matthew E. Larkum, J. Julius Zhu, and Bert Sakmann, 1999)

- L5. P28-58. Slice. 34-35 degrees. Dendritic injection is EPSP shaped.
- With a bAP, calcium spike/burst required half the current in distal apical. Based on the required current possibly less than 10 synaptic inputs in distal apical are required.
- Measured threshold at 5 ms intervals relative to bAP. Minimum at +5 ms after somatic injection (and presumably a bAP). For lower (tested to -20 ms) still lower than without bAP but gets closer. At +10 ms still lower than without bAP but for 20+ the threshold is higher than w/o bAP, tested to 130 ms, though just a little higher threshold than without bAP for all those times. Injected at apex.

- I'm guessing the bAP is a bit delayed relative to the somatic injection.
- I wonder if that is b/c of a slow AHP, even though no burst just singlet. It's just a little over threshold, so a low amplitude AHP would work.
- I wonder if the threshold increase for bAPs up to 130 ms ago builds up with more APs. How does it work when there are multiple bAPs? Maybe it helps detect changes/firing onset.
- Keep in mind EPSP time course influences timings. But when stimulated L1, similar rise time at apex. Duration?
- Without bAP, threshold 2.3 nA.
- Synaptic input:
    - When excited L1 fibers (and maybe e.g. L2/3 b/c stimulating electrode) at 500 um away laterally, bAP caused BAC firing in 3/10
    - The calcium AP was smaller to nonexistent w/ GABA in the other 7/10 cells. I.e. they had to add GABA antagonist.
    - When L1 was activated in one case (at least) small difference in soma/dendrite EPSP size, so they assume synapses on the soma too. But maybe synaptic input on tuft travels to soma better than injection. Or maybe iontophoresis actually activates synapses elsewhere.
- Activating the interneuron only impacted the bAP when coincident with the bAP, yet they could block calcium spikes well ahead of time. So unless these two results are based on different interneurons, that's strange because it means the influence lingers yet still doesn't impact the bAP. I'm guessing up to 400 ms is only for some interneurons, so probably nothing weird.
- When evoked an EPSP probably from a cell synapsing on dendrie (located in L3 or upper L4), only impacted bAP when coincident. Abolished calcium spike and burst.
- Long depolarization causing bursts or input trains from that inhibitory cell can block APs up to 150 ms in advance. Both did that? Do they mean bursts in the interneurons
- Calcium AP can be isolated from soma i.e. not trigger burst by hyperpolarizing somatic injection or using <4ms dendritic injections (hyperpolarizing?) was there a particular sequence b/c they say there was still a bAP? Their goal is to show inhibition acted at the initiation zone. I think it could also be elsewhere on apical.
- Hyperpolarizing or depolarizing the soma and/or dendrite immediately before the calcium AP didn't influence threshold so inhibition not by voltage dependent mechanism. Therefore possibly by GABAA/B shunt or influencing or turning on/off membrane conductances, and because means not voltage dependent, might not influence sodium spiking. I worry that this is just because of delayed initiation or because slow regenerative means inhibition immediately beforehand doesn't influence it.
- The effect of inhibition can last 100s of ms. 400 ms when blocked excitatory input.so it isn't temporally precise and more like a general block ca aps

- They say apical oblique generates singlets i.e. is part of the singlet zone but no citations.

Burst generation in rat pyramidal neurones by regenerative potentials elicited in a restricted part of the basilar dendritic tree (Bogdan A. Milojkovic, Mihailo S. Radojicic, Patricia S. Goldman-Rakic, and Srdjan D. Antic, 2004)

- L5 rat PFC slice. Voltage sensitive dyes for distal basal. P21-42. 29-34 degrees.
- Brief glutamate iontophoresis localized stimulation to basal caused sustain plateau potential measured at soma and bursting.
- L5 large cells mainly connect on basal.
- In slices containing only L5/6 (so no apical), still up/down states.
- They argue basal and proximal oblique are suited for recurrence and therefore up/down and persistence/working memory
- In vivo, background firing -> synaptic integration usually alongside somatic APs (probably mean that in a loose sense b/c FRs can be low and bAP integration window is limited) so bAPs common. Do cells just fire at baseline FR or does it actually represent something?
- The response to iontophoresis on basal resembled up state so likely responsible. Similar platea amplitude, plateau duration, and number/frequency of APs. Maybe this means oscillatory control e.g. by SOM cells matters for plateau duration and maybe a plateau is a timestep.
- The plateau appears to begin immediately after the brief glutamate and lasts ~500 ms. I'm not sure there is 100 hz bursting, and FR appears slow, but large time scale so hard to tell. Might be initial burst
- 5 ms glutamate pulses. 60 to 100 um from soma. Caused somatic plateau 12-23 mV on which APs rode. Lasts about 400 ms.
- When instead 100 to 145 um, plateau amplitude ~11 mv and no riding sodium APs.
- More distal sites (on average proximal cite 80 um and distal 120 um) less able to cause reaching AP threshold. Distal site: 12 mV 350 ms .1 spikes average. Prox: 18 mV 335 ms 3.9 spikes.
- They think same amplitude at both distances and attenuate to soma.
- Proximal/distal both caused quick plateau onset.
- Glutamate diffusing to the soma was a concern. Didn't cause plateaus, but when not near dendrite and 50 um from soma, produced mini postsynaptic signals
- It could easily diffuse on the dendrites, I think.
- Next used VSDs. When glutamate caused soma burst, the targeted dendrite had fast rising plateau on which bAPs rode.
- At the soma, the first AP appears to occur around when the platea reaches peak (or earlier, but its a quick rise) and there appears to be an initial doublet AP followed without a larger ISI by roughly 40-50 hz firing.

- On the targeted dendrite the plateau has a delay from iontophoresis but rises at same time as soma. It starts with a spike wider than a normal bAP and as long as the doublet so I think maybe a DD. The plateau lasts around 200 ms then drops over maybe 50 ms to baseline and then drops even further over 50 ms. the non-target dendrites don't have the plateau or possible DD but have bAPs including the doublet, and have the decrease starting at the plateau end which actually immediately goes below pre-ionto. B/c the drop has a bump i think it's maybe not AHP.
- The recorded dendrite ROIs were overall 55 to 140 um but each is a range of distance.
- Actually the non-target dendrites had plateaus but quite small amplitude compared to the target.
- When blocked APs by hyperpolarizing soma the dendritic plateau 100-500 ms, fast onset, and fast end. In 2 of 5 cells initial small spikelet at dendrite but not soma. The plateau end might be much quicker but still descends over a little time.
- VSDs cannot show absolute voltage
- The bAPs during plateau increase amplitude relative to plateau to 1.5x but little increase at initiation site because already fairly large plateau voltage signal. bAPs are brief.
- Maybe the spikelet relates to the possible DD and initial burst
- ROIs on the same target dendrite but proximal to target segment have smaller plateau amplitudes so attenuation.
- Below plateau threshold increased iontophoresis strength increases membrane potential response but beyond threshold no change. During the plateau one or two APs. This was 135 um. Just-threshold plateau around 100 ms. Increasing ionto increased duration but not amplitude. Because more glutamate to bind over time?
- Even when ionto was weak enough to barely produce a response there was still that late drop so I think it might be b/c of the methods.
- I'm guessing glutamate binds over around 75 ms because of the slowness of subthreshold response. Or maybe it's b/c of VSD time.
- To test whether delivered glutamate biological scale stimulated synapses extracellularly. Plateau evoked was about 150 ms +- 60. In 3/6 neurons one or two bAPs occured in the plateau. In the other 3 no APs. In an example, synapses at around 170 um. Plateau in target dendrite but not soma or other dendrites. At soma small initial spikelet, and slow EPSP component overlapping with fast IPSP component. At dendrite fast initial spikelet and 110 ms plateau. Attenuated to soma fully.
- Long lasting somatic plateaus weren't possible with single shock. Can it only evoke somatic spikes?
- Ionto is likely to cause more prolonged glutamate.
- When used shock trains, 140-590 ms soma plateau. Used 3 pulses of 50 hz. Evoked an initial doublet starting on 2nd pulse and ending before 3rd, then two more spikes then long spikeless plateau. In some cells failed to evoke APs.

- I worry about polysynaptic effects.
- 2/7 fired none and 5/7 fired 3-6 per plateau.
- Maybe SOM cells control plateau duration by facilitating during plateau RS. If a plateau is a time step, end when there is a change in what is represented. And maybe chunk sequences in this manner into just a few transitions, bridging between in some other way. Or phase precession so represent long sequences each time step.
- B/c voltage gated, NMDARs might've contributed to the plateau.
- Proximal basal doesn't support plateaus is why the signal at soma is weak. I wonder if it would be a strong signal with proximal basal input. Maybe bAPs or subthreshold somatic input operate by bridging the non-plateau proximal dendritic zone.
- I wonder if plateau potentials are for working memory. Maybe if sensory cortex lacks strong basal plateaus it's because apical feedback is higher order and so fits working memory.

Mechanisms and consequences of action potential burst firing in rat neocortical pyramidal neurons (Stephen R. Williams and Greg J. Stuarty, 1999)

- Rat L5 slice. 3-5 weeks.
- Postsynaptic depression occurs during burst, but a TTX sensitive voltage dependent process counteracts that when postsynaptic membrane potential >-60 mv. Wouldn't it usually be over -60 mV?
- I wonder if L5 is uniquely IB because initiates up states
- According to some studies IB cells burst by activation of persistent sodium current. I wonder if that resolves burst during plateau initially but RS despite calcium after.
- This study frames persistent sodium vs dendritic calcium based bursting as contradictory or in opposition.
- Below 100 hz (or maybe lower b/c "<<", check citations) synapses between L5 cells depress.
- Extracellularly evoked synaptic input w/ electrode in L2/3. This caused singlet in some and 2-6 spike burst in others. This is at extracellular voltage threshold. Keep in mind might activate neurons in L2/3. Cells were same type (IB/RS) for somatic injection. RS had singlet or < 10 hz FR and IB cells bursted riding on depolarizing envelope. IB cells had higher threshold. .28 vs .45 nA. 9/61 were weak bursters and 26/61 were strong bursters. Weak bursters initial 2-3 spike burst then RS whereas strong had repeated bursting throughout injection duration.
- Weak burst threshold .29 nA and strong .5 nA.
- Replaced calcium with magnesium (maybe issue for nmdars). Reduced average APs per burst. Also nickel did so.
- Replacing calcium reduced AP repolarization but wasn't' by nickel sensitive channels. Maybe calcium sensitive K+ channels? Or Mg2+ impact?

- TTX (eliminates bAPs). On apical over 150 um, reduced spikes per burst (remember, this can include converting to singlets, so I worry that it actually either has no influence or changes to singlet) more proximally interfered with 1st AP in the burst so didn't check reduction.
- Nickel to basal reduced spikes per burst a little (3.5->2) but not significant.
- Bursting (or switching to bursting) increased over time for apical over 150 um w/ sustained dendritic input because bAP duration increased. In others, burst at threshold. VG calcium channels do this by lengthening bAP shoulder. This suggests slowly activating/inactivating channels
- At postsynaptic membrane potentials near threshold burst spikes facilitate because of VG channels. More APs in the burst amplify/summate more. Is -60 mV near threshold or is facilitation only near threshold, as opposed to counteracting depression?
- Hyperpolarized membrane potential -> depressed 2nd EPSP. How hyperpolarized?
- Burst firing causes a large calcium signal in apical but not in tuft. Check the citation.
- They suggest the slow change is inactivating k+ channels
- The facilitation is likely by persistent sodium channels.

Apical dendrites of the neocortex: correlation between sodium- and calcium-dependent spiking and pyramidal cell morphology (Han G. Kim and Barry W. Connors, 1993)

- Recorded apical trunks at 100-430 um, usually in L4.
- Possibly because of the difference in apical shaft width, group 2 was on average recorded further from the soma than group 1. Average 220 vs 330 um, with a lot of variation.
- Seems they recorded from the same electrode as injected through.
- In unclassified somata (n = 4), 1 uM TTX blocked spikes for somatic injection-recording. However, it left an initial depolarization which was greater for stronger injection and was transient (<100 ms, possibly the right duration for a burst). This was blocked by replacing Ca2+ with Mg2+.
- Group 1:
    - Morphology:
        - Fewer oblique dendrites (5.5)
        - Thinner apical trunk (2 um)
    - Dendritic injection response:
        - Lower amplitude/broader sodium-dependent fast dendritic APs than G2. Lower amplitude for more distal injection-recording, tested up to 300 um.
        - Sometimes has an initial burst of two or more spikes. So might be bAPs.
        - Suprathreshold dendritic injection-recording causes adapting RS. The dendritic spikes are sodium-dependent and shaped like somatic spikes but somewhat broader. Lower amplitude for more distal injection-recording. There might be an initial burst above a higher threshold.

        - 1 uM TTX eliminated most dendritic APs. It left fairly irregular very low amplitude regenerative spikes. This was eliminated by substituting Mg2+ for Ca2+.
        - No plateaus, but probably only tested to 700 pA.
- Group 2:
    - Morphology:
        - More oblique dendrites (12)
        - Thicker apical trunk (2.5 um)
    - Dendritic injection response:
        - Clustered sodium-dependent dendritic spikes and higher threshold slow spikes/plateaus with riding variable amplitude faster dendritic spikes.
        - Spike amplitude not correlated with recording distance from soma, at least for the initial fast spike.
        - Only 4/12 supported plateau potentials (probably tested up to 700 pA).
        - Plateaus sometimes lasted as long as the current and sometimes stopped early for the same cells, possibly depending on injection strength. Sometimes, the plateau only lasts ~40 ms, but it can last hundreds of ms.
        - Always starts with a fast spike (maybe sometimes multiple) immediately before the plateau.
        - 1 uM TTX blocked fast spikes and left a large slow high threshold calcium spike. Higher threshold than without the fast spike/TTX. I think it might be higher threshold simply because the shorter duration lower threshold plateau can't be evoked. Maybe the shorter duration lower threshold one is evoked by a bAP.
        - Inhibiting calcium current with Co2+ (2 mM) creates dendritic spike patterns similar to those of G1 cells. Maybe this explains results of studies at lower temperatures.
        - With a low concentration of calcium channel blocker (10 uM Cd2+), the plateau still appears bursty but has some added large ~30 ms dips. I wonder if low temperature is the cause of large AHPs.
- L1 extracellular stimulation response at dendritic shaft:
    - Same for both groups.
    - All or none fast and slow spikes. The slow spike lasts on the order of 20-60 ms. Can be single riding/initial spike or burst for both groups, or just a fast spike with no slow spike.
    - When the dendrite was hyperpolarized, the slow spike was blocked but not the fast spike. Only tested for a G2 cell.
    - The slow spiker is higher threshold of extracellular stimulation than the fast spike.
- Both groups had ~5 primary basal dendrites.

- They suggest a lower threshold more distally. I wonder if G1/G2 both have an initiation zone, and injection didn't cause a plateau in G1 because of attenuation distally.
- Oblique dendrites might've played a role in the results because close to injection site.
- Keep in mind fast spikes for L1 activation might be local sodium spikes, not bAPs.
- Because of the attenuation, group 1 dendrites likely have lower sodium channel density.
- I wonder if the G1 difference between injection and L1 excitation is because of e.g. NMDARs.
- The results suggest G2 cells have larger calcium currents in apical than G1 cells.

Anatomy and physiology of the thick-tufted layer 5 pyramidal neuron (Srikanth Ramaswamy and Henry Markram, 2015)

- It doesn't always distinguish by L5 cell type, and thick refers to the size of the apical tuft, not the shaft. Not all of these notes are specifically about L5.
- Taking notes on single cell integration for now.
- TTL5 soma shapes have been classified as round, oval, or triangular, but they are mostly triangular P14+.
- P28 seems to be when cells are adult cells. Slow changes after.
- In rodent PFC, there is a complex and a simple variant of TTL5. In medial PFC, complex is the more common one.
- TTL5 projects to superficial layers, but only sparsely to py cells (but also target interneurons).
- Rat somatosensory corticothalamic and corticotrigeminal TTL5 cells were both non-adapting and had an initial doublet for injected current. Corticostriatal L5 cells had an initial singlet and adapting spike train.
- This review seems to include ST cells as TT at least sometimes.
- Apical inhibition is primarily on terminal tufts.
- At P14, the dendritic regenerative potential often outlasts the somatic AP.
- At P28, tuft injection can elicit either singlets or a burst. Suprathreshold sustained injection causes a plateau potential and bursting. Regenerative potentials are longer at P28 than before. At P28-42, the signal from apical to soma attenuates more than before.
- Regenerative potentials are weak and elicit somatic APs less reliably at P28 than P42.
- Thick tufted means the tuft itself is wide, not the apical shaft. So it includes what I consider ST (thin apical shaft)
- Dendrites have A-type and persistent K+ channels, transient and persistent Na+ channels, HCN (hyperpolarization-activated cation) channels, and small and large conductance calcium-dependent K+ channels.
- HCN channels are responsible for Ih and If
- A-type K+ channels increase distally along apical. So they help define a distal low threshold regenerative potential zone.

- A-type and persistent K+ channels compartmentalize the tuft.
- Transient Na+ channels are uniform density along apical. They are responsible for sustaining bAPs and for local dendritic spikes.
- Persistent Na+ channels are also uniform density along apical, and they amplify synaptic current in apical.
- HCN channels are responsible for the depolarizing Ih activated by hyperpolarization. Responsible for dendritic excitability. (Actually, Ih might be hyperpolarizing, but there seems to be a contradiction).
- There are T, L, N, R, and P (so all) VG Ca2+ channels.
- Small and large conductance K+ channels (respectively SK and BK) are constant density along apical. Activation reduces Ca2+ spikes. A bit unclear, but seems to be saying BK channels don't influence the time window for calcium spikes which result from bursts.
- EPSPs cause a transient increase in calcium because of T-type channels.
- bAPs in proximal apical cause a calcium transient.
- Above ~100 hz causes a regenerative calcium spike in both basal and apical.
- Local calcium spikes are generated by synaptic input coincident with a bAP. This is suppressed by GABAB.
- Distal apical input coincident with a bAP -> BAC -> burst.
- Basal attenuates massively to soma from 140 um. EPSPs spread from soma to basal with little attenuation.
- Local calcium, sodium, and NMDA spikes in dendrite.
- Synaptically evoked basal potentials are NMDA spikes and usually are followed by large calcium influx. Basal dendrites use localized processing, as do distal tuft segments.
- Respond to somatic injection with adapting RS or bursting.
- The axon initial segment has P/Q and N type calcium channels
- Bursts are generated by activation of calcium channels
- At least below 100 hz, connections between them depress in a frequency-dependent manner. Check the citations because might not be entirely correct. Might mean long term plasticity.
- Persistent Na+ channels in node of ranvier contribute to burst generation.
- Most synaptic connections between TTL5 cells are on secondary/tertiary basal ~80-120 um, although there are synapses elsewhere. The densities of synapses on primary/secondary/tertiary basal are similar.
- In juvenile animals, connections between TTL5 cells undergo short term depression. In medial PFC, they facilitate. In rodent PFC, they are depressing when young but become more facilitating with age. In mature rodent somatosensory cortex, connections between TTL5 cells are mainly facilitating. Check that study because ctrl+f found nothing.
- For depressing connections between TTL5 cells, past a threshold frequency, the postsynaptic response is inversely proportional to the frequency.

- Small basket cells inhibit TTL5 cells with facilitating synapses, contrary to most inhibitory synapses being depressing.
- Neurogliaform cells form both GABAA and GABAB synapses on TTL5 cells.
- In developing TTL5 cells, for connections between them, unitary EPSP amplitude average 1.3 mV and decay time constant of 40 ms.
- Unitary EPSPs in TTL5 connections are voltage dependent in developing cortex. Above -60 mV, greater amplitude and decay time constant. This could be because of increased flow through NMDARs, blockage of Ih (so is Ih hyperpolarizing?), activating T-type calcium channels, or persistent sodium channels. At hyperpolarized potentials, synaptic transmission is mainly via AMPARs, whereas also by NMDARs at more depolarized potentials.
- On the apical dendrite, there are receptor hot spots. Stimulating them contributes to both Na+ and Ca2+ spikes.
- There are kainate receptors (based on a quick search, have a role in plasticity and synaptic transmission.)
- In L2/3, py cells can inhibit each other by directly activating nerve terminals of inhibitory cells, without causing interneurons to fire.
- Martinotti cells activate GABAB. (Need to research this because might be by GABA spillover).
- Py cells in L2b and middle L3 -> TTL5 oblique.
- L4 spiny stellate cells -> L5a in a precise topographical manner, although might innervate dendrites of L5b cells rather than L5a cells there.
- Bipolar, bitufted, and double bouquet cells target mainly proximal apical and basal.
- Supragranular neurogliaform cells target distal dendrites with GABAB
- VPM targets proximal TTL5 dendrites.
- The martinotti circuit has been suggested to synchronize cells or control dynamic range.
- Martinotti disynaptic inhibition is only GABAA, not GABAB. (That doesn't rule out GABAB in other situations).
- Neurogliaform cells in L1 directly inhibit TTL5 tufts, as well as interneurons.
- In developing rat, TTL5 cells are more often bidirectionally connected than unidirectionally.
- bAPs trigger plasticity when they coincide with or miss EPSPs.
- In classical STDP, timing of pre/postsynaptic APs induce LTP by depolarizing/unblocking NMDARs.
- When bAPs fail to invade the dendrite, sufficient somatic depolarization (evoking a burst or by current injection) can salvage the bAP.
- Bursts might be required for STDP, although that result might instead reflect the need for dendritic depolarization for STDP. Induction of STDP on basal and apical can be blocked by blocking VG Ca2+ channels.

- At proximal TTL5 synapses, pairing AP trains and EPSPs led to LTP, whereas LTD distally. Distal LTD resulted even without postsynaptic APs, but was converted to LTP by bAPs combined with sufficient dendritic injection.
- For L2/3 -> TTL5, pairing input with postsynaptic burst at positive timing led to proximal synapse LTP and distal synapse LTD. Negative timing caused the opposite for both proximal and distal.
- On basal dendrites, proximal plasticity occurs based on the cell's global activity, whereas on distal basal, an NMDA spike causes local plasticity.
- Acetylcholine reduces the rate of short term depression between TTL5 cells. It also reduces IPSPS and increases EPSPs, increases calcium spikes, and allows basal dendrite-only input to generate bursts.
- Neuropolypeptide Y inhibits burst-triggered distal dendrite calcium influx in distal apical, thereby suppressing the LTD which normally results.

Potassium Channels Control the Interaction between Active Dendritic Integration Compartments in Layer 5 Cortical Pyramidal Neurons (Mark T. Harnett, Ning-Long Xu, Jeffrey C. Magee, and Stephen R.Williams, 2013)

- vS1 L5b.
- Based on wikipedia, K+ channels activate during depolarization to repolarize the cell. Rapidly inactivating ones sometimes cannot contribute to repolarization if there was another recent depolarization.
- Nexus = distal 200 um of apical trunk.
- Sub- and supra-threshold refer to threshold for evoking a local dendritic spike.
- Nexus to soma:
    - Subthreshold injection: attenuates linearly with distance towards soma, to 10% at the soma.
- Nexus to tuft:
    - Local spike is short duration and can cause a burst or singlet. With Kv blocker, RS following the initial burst because of long duration VG Ca2+ plateau.
    - Subthreshold and suprathreshold: attenuates distally, but by 50% at most at least for subthreshold.
    - Kv blocker removes the suprathreshold attenuation.
- Tuft to nexus:
    - Suprathreshold injection -> short duration Na+ spike. Uncaging evokes a local NMDA spike which makes some contribution to the nexus, but not a large contribution and doesn't make a functional difference besides that modest contribution.
    - Subthreshold and suprathreshold injection attenuates distally, very weakly from proximal tuft and very strongly from distal.
    - Kv blocker does not remove the subthreshold attenuation.

    - Kv blocker converts the injection Na+ spike into a locally initiated plateau potential which spreads into the nexus. Lasts as long as injection locally, but gradually decreases at nexus.
- Kv channels:
    - At soma, Kv channels don't inactivate much. Kv channels on proximal and distal apical trunk had a large transient component.
    - Rapidly inactivating Kv channels take around ten ms to inactivate.
    - The tuft has a uniform amplitude of transient/sustained Kv.
- Soma-Apical Integration:
    - Caused ongoing activity with EPSP-shaped somatic injection barrage -> RS.
    - Pairing the somatic stimulation with EPSP injection barrage to nexus -> RS with FR increasing linearly with nexus injection strength. Kv blocker -> sustained nexus electrogenesis which increases FR a lot.
    - DC soma + DC tuft injection causes the same firing as DC soma alone.
    - DC soma + DC nexus -> RS, possibly with initial burst.
    - Paired with DC somatic injection, DC subthreshold trunk or DC subthreshold tuft injection didn't impact firing. Pairing trunk/tuft together with soma caused large repetitive plateaus/bursts. Even though continuous injection, the plateaus are repetitive, last tens of ms, and start at the start of each burst, for the displayed injection strength. The tuft/nexus potential duration was controlled by tuft injection strength. E.g. 350 ms for .6 nA, 50 ms for .2 nA.
- During awake whisking an object, large amplitude calcium signals throughout the tuft (or at least ROI) of a sparse subset of cells were found by this study. (L5/6 cells expressed the calcium indicator).
- A previous study (Xu et al., 2012) found that L5b cells have that signal by integrating intracolumnar and long range motor input.
- Applying Kv blocker to the surface of the cortex increased the occurrence and amplitude of those signals.
- Kv inactivation is voltage dependent. If there is widespread apical depolarization during behavior, would explain results of Xu et al., 2012.

Retrograde tracing with recombinant rabies virus reveals correlations between projection targets and dendritic architecture in layer 5 of mouse barrel cortex (DeLaine D. Larsen, Ian R. Wickersham, and Edward M. Callaway, 2008)

- vS1 L5 cell types: tall-tufted (TT), tall-simple (TS), short (SH).
- Tall-tufted -> thalamus and superior colliculus.
- SH/TS -> L2/3, but not TT.
- TS -> superficial layers with lateral spread but SH -> superficial in a more columnar fashion.

- SH and TS both project contralaterally.
- SH apical only reaches L2/3 and has few branches in L2/3.
- TS superficial projection is patchy.
- Based on the small number of axonal reconstructions, there isn't a huge difference in lateral spread of SH/TS. Unless they weren't fully reconstructed.

Monosynaptic Connections between Pairs of L5A Pyramidal Neurons in Columns of Juvenile Rat Somatosensory Cortex (Andreas Frick, Dirk Feldmeyer, Moritz Helmstaedter, and Bert Sakmann, 2008)

- P18-P20.
- L5a cells preferentially connect proximally.
- Very low synaptic failure rate.
- EPSP amplitude has fairly low CV, but varies 30x between synapses. Because of synaptic location?
- Depression from 2 to 100 hz. (That's all they tested)
- A single L5a cell targets ~240 py cells in its column in the same layer (L5 or L5a?)
- L5a projects to motor cortex and S2.
- Short term depression was based on trains of 3 to 5 APs with ISIs 10 to 500 ms.
- 23/27 connections between L5a cells were unidirectional.
- Connections between L5a cells were completely blocked by AMPAR and NMDAR blockers.
- The axons project to both superficial and deep layers up to several columns away. Not sure exactly which sublayers.
- Somata of connected pairs were located at the lateral border of the barrel column (the soma are nearby/in same column). Tend to cluster vertically. Cell bodies of presynaptic cells were closer to L4/5a border than the postsynaptic cells.
- 70% of dendrite in home column and 90% in home + neighboring columns.
- Basal dendrite mostly confined to L5 and lower L4.
- The axon projects towards L1 vertically, and into same/neighboring columns in L2/3/4/5.
- ⅔ of synaptic connections between L5a are basal and ⅓ are oblique. They do not connect on the tuft (n = 6 synaptically connected pairs). From the presynaptic soma to the postsynaptic contact, 10 to 265 um averaging 110 um. For basal dendrites, average 85 um. For oblique, average 150 um.
- PPR both between EPSP 1/2 and EPSP 2/3 was .82. ISI = 100 ms.
- EPSP decay time constant 18 ms.
- Based on the figure, at 10 ms ISI, PPR between EPSP 1 and 2 is .5, between 1 and 3 is .3, and between 1 and 5 is .1. At 20 ms ISI, .6, .45, .25. 50 ms ISI, .7, .5, .45. 100 ms ISI, .7, .6, .5.
- Between 100 and 500 ms ISI, similar depression to ISI 100 ms for the tested 5 AP trains.
- Same-column input from L2/3, L5b, and especially L5a.

- L5a projects to L5a, L5b, and L2/3.
- A single L5a cell connects to an estimated 270 other L5a cells (not limited to same column). The estimate is pretty rough. It might only be for neighboring/same columns.
- L4 -> L5a has similar PPR to L5a -> L5a at 10 hz, but has ~½ sent voltage. Somewhat fewer average synaptic contacts. L4 -> L5a is ⅔ on apical.
- Both L4 -> L5a and L5a -> L5a connections tend towards vertical clustering along the lateral barrel column walls.

Spatiotemporally graded NMDA spike/plateau potentials in basal dendrites of neocortical pyramidal neurons (Guy Major, Alon Polsky, Winfried Denk, Jackie Schiller, and David W. Tank, 2008)

- Abstract:
    - Clustered glutamatergic stimulation (i.e. over a 20-40 um segment) on terminal basal branches can elicit an NMDA spike/plateau. However, terminal segments are usually 100-200 um long, so they might act as multiple subunits. They test that.
    - Used iontophoresis and uncaging on terminal L5 basal somatosensory rat slice.
    - Distal sent ~3 mV to soma vs ~23 mV for proximal. Meaning proximal on the terminal branch?
    - At all locations, NMDAR conductance dominated spikes/plateaus. Large calcium transients accompanied the spike/plateau in a ~10-40 um zone around the stimulation site. Smaller calcium transients extended to the dendritic tip.
    - Spike/plateau duration increased with glutamate and depolarization (meaning?). The large calcium transient zone grew with spike/plateau duration.
    - The minimum (i.e. just above NMDA spike threshold) NMDA glutamate threshold and large Ca2+ transient zone half width increased from distal to proximal locations (meaning? Says some small distances.)
    - Depolarization reduced glutamate threshold.
- Introduction:
    - Because terminal segments are long, they have been suggested to act as sliding subunit detecting clustered input (so I guess so long as clustered, summate locally), or string or cascade (meaning?) of multiple subunits or more complex temporal integrator. Cites sources about each possibility.
    - Fast local sodium spikes last a few ms max. Slower spikes evoked on thin branches (not restricted to basal and citations include hippocampus) last 20 to hundreds of ms.
    - In L5 and L2/3, basal dendrite spikes/plateaus require NMDARs, although Na+ and Ca2+ channels can reduce threshold.
    - NMDA spikes evoked by focal stimulation are caused primarily by a zone up to a few tens of um from the stimulation site.

    - Two stimulating electrodes summate supralinearly if within ~40 um. So the study suggested a sliding integration window. In that study, the distal site was fixed and the proximal site was moved, though.
    - More proximal basal spikes/plateaus have larger somatic amplitude. Hasn't been tested along entire length of a single basal dendrite.
    - In hippocampal apical tuft/oblique (but relevant to cortex b/c shows possible issues with methods), calcium blocker and calcium imaging suggested all or none plateau throughout the dendritic compartment, rather than local subunit-specific.
        - But didn't test whether or not VG Ca2+ channels simply lowered the threshold (didn't test reinitiation), and NMDAR blocker blocked the plateau, so it might be NMDA dominated.
        - This study's inspection of their data suggests a high calcium zone around the input site, suggesting a localized zone. So I wonder if L5 apical plateaus are actually NMDA spikes.
    - With fast two photon glutamate uncaging in hippocampus, fast local sodium spike and can also have a slower NMDAR-dependent component.
    - To determine whether subunits along a branch interact, tested voltage dependence. I worry that the interaction instead depends on channel state e.g. NMDAR unblock.
- Methods:
    - For somatic recording, rat P23-41 somatosensory slice. Recorded at 35-37 degrees.
    - Somatic recordings were from large L5 cells.
    - Cells with peak input resistance at -72 mV of >35 were excluded from the amplitude-distance analysis. Generally similar results, but larger spike/plateau amplitudes.
    - Two photon calcium imaging.
    - In earlier experiments, found that cells with high affinity calcium indicator Calcium Green-1, subthreshold responses were associated with fluorescence signal transients, but suprathreshold spike/plateau signals reached elevated levels that were constant for long periods, indicating severe indicator saturation. This obscured the difference in calcium at different sites.
    - So are long duration plateaus just because of saturated indicator? Or even plateaus being so flat?
    - Used low affinity indicator to reduce calcium buffering and reduce signal slowing/saturation.
    - Glutamate ionto: double barreled electrodes with glutamate in one barrel and a fluorescent indicator in the other. Within a couple um of the basal dendrite. Used

5 ms current pulse into the glutamate barrel, usually less than 300 nA. Large L5 cells.
    - For glutamate uncaging, rat P25-33.
- Results:
    - Ionto onto terminal basal with small (up to a few tens of nA) pulses evoked EPSP-shaped responses at soma. Larger amplitude for larger ionto amplitude.
    - Above an ionto threshold, typically 30-200 nA, sudden jump in somatic voltage because of dendritic spike/plateau. Fast onset and fast offset, with a slowly declining portion for longer duration cases.
    - The spike/plateau was associated with a large localized calcium transient restricted near the stimulation site. In a few cases when another dendrite was close by or within 10-20 um of branch points, stronger stimulation also activated the neighboring dendrite or parent branch, causing a further jump in somatic amplitude. These two dendrite responses were excluded from analysis.
    - When the ionto electrode or uncaging spot is slowly withdrawn from the dendrite, responses decrease over distance. The glutamate cloud ejected from the electrode activates NMDARs up to 10-25 um away.
    - In the example, spike/plateau amplitude at the soma grew proximally a lot (example was from 240 um to 60 um and grew 7x). Similar numbers elsewhere elsewhere, tested 50 to 240 um. The change is exponential decay from proximal to distal. Limited analysis to slow spikes 50-100 ms. Length constant 87 um (95% confidence 80-100 um). Similar results with uncaging, except length constant around 77 um (67-91 um)
    - Soma depolarized -> larger amplitude plateau/spike.
    - Just subthreshold EPSPs (technically EPSP-like events evoked by ionto) had similar decay from soma to suprathreshold plateau/spike. 96 um length constant, confidence interval 80-120 um.
    - Glutamate threshold reduced distally.
    - Divided responses into 50-100 um and 100-200 um. NMDA dominated responses for both groups, at least for threshold measured as just-subthreshold EPSP at soma and amplitude measured at soma. I worry that the threshold is actually changed because the just subthreshold response at the soma would be reduced if there is less active propagation.
    - Because of low density Ca2+ channels, there is a lower amplitude calcium zone distal up to the dendrite tip from the input site. The high amplitude calcium zone is around the input site, extending 20 um proximally and has delayed rise more proximally up to that 20 um. Distally, it drops over ~35 um then levels off. It lasts ~75-160 ms (but much long at places where indicator was saturated).

- The spike/plateau is mostly all or none at a given location in terms of amplitude, but increasing glutamate/depolarization increases duration.
- The calcium transient is longer than somatic voltage even without indicator saturation, and in the figure it does not start falling until the end of the spike for just suprathreshold. Just suprathreshold in the figure, it lasts ~30 ms. Based on the responses to ionto strength, either synaptic activation strength increases somatic NMDA spike duration somewhat or ionto increases the duration somewhat (maybe linearly) because of the method itself.
- Linear correlation between high calcium zone size and plateau/spike fluorescence duration. So I worry it's a result of using calcium imaging.
- High calcium zone half widths (i.e. size/distance from input site, not duration) fell distally. No consistent correlation between location and NMDA spike duration.
- Depolarization/hyperpolarization linearly changes glutamate threshold. This is a sharp threshold, not just an additive/subtractive influence on the voltage which reaches the soma.
- When a plateau propagates more proximally, each mV that reaches a potential plateau initiation site is predicted to reduce the threshold 4%.
- Because the steep voltage drop towards soma suggests non-regenerative propagation, the spikes cannot be mediated by non-synaptic VG channels or it would propagate more strongly. VG channels still can have roles, e.g. reducing threshold number of activated synapses to reduce NMDA spike duration, and they might have roles during network activity e.g. for bAPs or more rapidly rising glutamate stimulation which favors AMPA activity over NMDA activity.
- The high calcium zone might reflect active NMDARs, i.e. binding glutamate from the cloud.
- Gives an explanation for the low calcium zone.
- In simulation, when a distal input is followed tens of ms later by proximal input, lower proximal threshold than for the other order. It is also possible in simulation to generate a chain of activation from distal to proximal, reducing threshold.
- I wonder what the time scale is like. Perhaps this effect could allow prediction farther in the further than an NMDA spike lasts.
- Voltage plateaus can be flat for ionto.
- Strong brief ionto can evoke a voltage plateau/firing lasting hundreds of ms.
- It is possible that the long responses is because of prolonged glutamate clearance. But the model and the slow NMDA deactivation suggest otherwise.
- In models, a sufficient number of glutamate bound NMDARs -> responds to depolarization by activating, for a period of time. Don't have access to supplemental figures right now so check that.

    - I worry that even though duration increases with depolarization, that's just because it stays suprathreshold longer because glutamate can decline more.

Control of somatosensory cortical processing by thalamic posterior medial nucleus: A new role of thalamus in cortical function (Carlos Castejon, Natali Barros-Zulaica, and Angel Nuñez, 2016)

- Rat. Anesthesia.
- POm controls magnitude/duration of sensory responses.
- Blocking L1 GABA or blocking P/Q type calcium channels in L1 prevents the modulation caused by POm.
- POm has more multi-whisker RFs than VPM.
- Many things have been reported about what POm encodes (e.g. whisking regardless of touch, temporal frequency of whisking, roles in motor-related temporal processing, etc.) but it is still debated.
- Inputs from brainstem and L5 converge on at least some of the same neurons in POm.
- 70% of POm cells and 80% of SpVi cells had responses which lasted the duration of whisker deflection. The responses end pretty much when the sensory stimulation ends.
- Brief electrical stimulation of POm -> spike response latencies (both supragranular and subgranular) 5-50 ms (or maybe that's just a broad range meant to convey that it's monosynaptic). Subgranular on average 23 ms, and 16 ms in supragranular.
- One potential issue with stimulating POm is it could antidromically activate CT cells. This would be indicated by lack of neural fatigue and low response variability. It was ruled out.
- Tested brief electrical POm stimulation 500 ms before whisker stimulus. Also tested it just before whisker stimulus. The latter decreased magnitude/duration of responses, rather than increasing it like I'd expect. The influence was mainly on the response component from ~20 ms to ~70 ms after the stimulus, leaving the component from ~10 to ~20 ms less influenced. It seems "just before" means 500 ms before stimulus, but make sure. Similar impact to superficial and deep.
- ~85% of deep cells decreased response for that, from average 2 spikes per stimulus to average 1.5. Onset sensory response latency stayed average 13 ms whereas offset latency changed from average 60 ms to 45 ms.
- The first component (onset to 20 ms) wasn't changed, whereas the second response had half the spike count. Same for both deep/superficial.
- POm alone evoked some spiking lasting up to 150 ms in deep layers and 50 ms in superficial (how long is the stimulus pulse and evoked firing?)
- I'm pretty sure the 500 ms is correct. POm pulse is brief.
- Inactivating POm enhanced cortical responses in 67% deep cells and 86% superficial. Sensory evoked spikes were increased from 2 to 2.25 spikes per stimulus in deep layers

and similar in superficial. The first component was not influenced, as expected. Response offset latency increased a bit. More spontaneous activity.

- Tested intervals between POm stimulation and sensory stimulation of 50-1000 ms (POm always before sensory). In deep layers, no interval changes the early component, whereas spikes in the first component were reduced at all intervals for superficial (doesn't this contradict the result for 500 ms?) Both deep and superficial had reduced responses for the second component. In superficial, changes weren't found for intervals over 700 ms, whereas there were found for the largest interval tested for deep layers. Based on the figure, it might've just passed below significance at 1000 ms for the first component, but the second component has a clear change.
- Based on the figure, tested 50, 200, 500, 700, and 1000 ms. Unlike for superficial, for deep layers, for 50 ms, the total response only changes ~10%, although the second component reduces 45%. I'm guessing this is because of leftover POm spike responses.
- Response duration/magnitude decreased further with stronger POm stimulation.
- Blocked GABAA in L1. Baseline FRs increased.
- P/Q type VG Ca2+ channels are expressed on PV cells are contribute to PV cell inhibition of py cells. When blocked L1 P/Q channels, sensory response magnitude and duration increased both deep/superficial. Somewhat larger effect in second component.
- When tested the L1 GABAA block along with POm stimulation 500 ms before whisker stimulation, response magnitude/duration wasn't influenced in superficial/deep. The same occured when blocked P/Q channels (by application to surface, so L1) instead of GABAA.
- Tested L1 electrical stimulation 150 ms before sensory stimulation. Decreased response duration/magnitude. Larger impact in second response component, i.e. no early component impact, for deep but for superficial both components were impacted.
- I don't think they have a set definition for second response component, but seems to be fairly short first component and they say the change in influence in sudden.
- For the L1 stimulation, response offset latency decreased somewhat.
- Not taking full notes on the S2 experiments. S1 L5 alone evoked strong S2 responses, but stimulating S1 L5 150 ms before sensory decreased S2 responses (both first and second components, more so the second). The influence was blocked by silencing POm, both the direct spike response and the 150 ms time separation decreased sensory response.
- They activated L5b, based on the figure.
- Maybe the air pulse durations were brief enough to treat as noise.
- Maybe compare spontaneous FRs. If POm's influence is to bias towards a particular voltage, could help explain the contradiction.
- Should research L1 interneurons with P/Q channels (probably PV cells).
- In other studies, activating L1 at lower intensities mostly influences L1/2, whereas higher intensities influences all layers. This study used lower intensity.

- L1 stimulation can antidromically activate martinotti cells with their vertically oriented axons, impacting other layers.
- In two studies, the L5/6 border depth ranged somewhere within 1400-1600 um. This study recorded deep layers at 900-1500 um, so mainly L5. When they divided L5 into L5a and L5b, similar POm modulation.
- In a study on another region, matrix thalamus activates L1 interneurons directly and activates them more than they activate L2/3 py cells. The activated interneurons could then truncate responses in other layers. Window of opportunity for sensory responses.
- In another study, SpVi and L5 converge on single POm cells and summate supralinearly.
- Another study found that when L1 electrical stimulation was paired with whisker stimulation, the sensory response was primarily enhanced for intervals <10 ms and primarily suppressed for intervals >10 ms (both + and - intervals?)
- The mechanism could be involved in controlling temporal integration or resetting cortical responses to prepare for the next stimulus, and these possibilities relate to the roles of POm in sensorimotor integration e.g. whisking phase-selective responses.
- NMDA-triggered APs tend to be longer latency than non-NMDA triggered firing, so the second component might be the NMDA-triggered spiking. Check the study. Is it completely silenced by APV? Are they just sustained responses or do new cells fire?
- Maybe the window for integrating POm/sensory to generate the mGluR response is the same window as before inhibition. In that study, the stimuli might've only been separated 20 ms between start/end of the two stimuli, so might be consistent.
- Another study found that POm mediates NMDA-based APs.
- Inactivating POm removed the second component S2 sensory response, but not the first component, so the first component probably results from VPM, although extralemniscal. Too short latency to be S1 -> S2.

Stereotyped Position of Local Synaptic Targets in Neocortex (James Kozloski, Farid Hamzei-Sichani, Rafael Yuste, 2014)

- Mouse V1. When scanning this, remember CT = corticotectal.
- Activated L5 corticotectal cells and looked for cells which fire as a result.
- Cells which fired as a result were pyramidal, fusiform, some large triangular, and a small number of small triangular with sparse dendrites.
- Pyramidal followers had basal dendrites extending 300 um into L6. Broad spikes and adapting firing rate (adapted to 50% after 800 ms pulse). They receive depressing input from corticotectal cells, and the synapses are on proximal basal and apical collaterals. Proximal basal seems to include <50 um but also a couple hundred um (92 +- 55 um.) and at least some have apical reaching L1.
- Not taking full notes on the other follower types. Facilitating EPSPs to fusiform followers and facilitating and LTS. They resemble some martinotti cells and some bitufted cells.

Large triangular followers also receive facilitating input. The small triangular follower is FS.
- No corticotectal followers were found, but small sample sizes.
- Fusiform followers were always ~50 um from the trigger and below the trigger, forming a semicircle (the semicircle shape is up/down, so the lowest is 50 um below the trigger soma and the highest is a little above the same depth as the trigger).
- Triangular followers were ~65 um above the trigger.
- Pyramidal followers were in a long horizontal band at the same depth as the triggers.

Synaptic Microcircuits in the Barrel Cortex (Gabriele Radnikow, Guanxiao Qi, and Dirk Feldmeyer, 2015)
- Chapter of a book.
- vS1.
- VPM -> lower L3, L4, L5b, and L6a. Other layers have nearly no VPM boutons.
- POm -> mainly L5a and L1, with some boutons in L2, L5b, and L6a, and septal L4. Based on the figure, also small number in L3 and barrel L4.
- L6b receives no VPM/POm input (except maybe a tiny bit of VPM input) and L2 receives very little VPM/POm input.
- In L4, star pyramids -> subgranular more than stellate cells do. Some projections from L4 to L5a are to multiple columns.
- L4 projects to L5b and L6a in the same column.
- L4 -> L5a py cells mainly on basal but also on tuft. Check the citation because if it's based on somatic EPSPs, would bias away from tuft inputs.
- L4 targets L5b on proximal.
- L4 spiny -> L5a and L5b py with connection ratios of ~10%. This is just a bit less than L4 stellate -> L2/3 connection ratio. Does that mean a given L4 cell projects to 10% of L5a and L5b cells? They say the L4 connectivity ratio of 10-15% to L2/3 is large because the axon travels a long distance in L2/3, so maybe the connectivity ratio means how many potential boutons are formed. Seems to be the standard.
- L2/3 -> L5 in multiple columns.
- Septal L2 py cells receive stronger L5a py input than septal L3 py cells.
- L2/3 py vertically -> L5a py and L5b py, and also to L5 py in multiple columns
- Connectivity ratio and strength can be altered by e.g. sensory deprivation.
- L2/3 -> L5 where it arborizes extensively. Low initial amplitude and facilitation.
- For this note, I'm also using the source. An L2/3 cell -> two reciprocally connected L5 cells 22% of the time (68 pairs; 15 pairs had input to both cells and 12 had input to one cell). When those L5 cells aren't reciprocally connected, just 2% (340 pairs; 7 double and 100 single connections). For L5 -> L2/3, opposite effect. 7.4% chance both L2/3 cells receive input if they aren't reciprocally connected (148 pairs; 11 double and 30 single connections). If they are reciprocally connected, 2% (106 pairs; 2 double and 35 single

connections). The study used L5 TT cells and somatic recordings. I'm not sure the requirement is reciprocal connectivity; it seems to include unidirectional. Cell pairs were within 100 um of each other. Tested L2/3 cells vertical from the midpoint between the two L5 somata. Same for L5. Didn't find a distance-dependent connectivity for the L5 cells within 100 um. Tested with 5 APs 20 hz train.

- As opposed to thick and slender tufted L5 cells, untufted L5 cells exist in both L5a and L5b, although low density.
- L5 ST TC input is almost only from POm. L5 TT TC input is primarily from VPM and there might be some POm input, possibly partially in L1.
- L5 short cells project strongly to L3 (ambiguous about L2), and much more weakly to L5/6.
- Provides sources on L5 short cells in other regions. Citations 89-92. Also see 87, 88, and 66.
- L5 ST -> L1 and L2/3 extensively. Projects throughout the barrel field both along rows and arcs (meaning the entire barrel field is accessible or to all columns or just referring to both along rows/arcs??)
- L5a ST -> vM1.
- 60% of the L5b TT axon is in L5b. Lower length axon in supragranular layers than the other two L5 cell types.
- Instead of the third cell being short, it's called untufted. I assume they're the same so I'm replacing the name.
- Different L5b cell subtypes differ in gene expression profiles. So probably should take the RS/IB division more seriously.
- I worry that the reported connectivity strengths are just based on connectivity ratios, which is influenced by bouton density/number of axons and seems like a bad measure of connectivity.
- L5a intracortical synaptic input is mostly from L2, L3, and L4. Respective connectivity ratios of 10%, 6%, and 12%. The strongest input is from the same layer. Somas within ~50-100 um have 20% connectivity ratios. 15% of connections are reciprocal.
- L5a cells mostly connect on basal but also on tuft. Somewhat high release probability.
- Synaptically connected L5a cell somata are often below the barrel borders (i.e. septal) and tend towards vertical clustering.
- L5a -> L2 with 2% connectivity ratio and L3 with 4% connectivity ratio, whereas L5b -> L2 with 1% and L3 with 2% (and a shorter total axon length). But it says that reflects the different axon density. Does that mean the connectivity ratio doesn't = % of potential synapses or is it just saying that those are similar results?
- Actually, connectivity ratio means the % of connections between tested cells. So far, unless otherwise stated, restricted to the same barrel column.

- L5b cells have connectivity ratio of 5-10%. Lower connectivity probability than for L5a-L5a, but L5b-L5b connections each have a larger average number of synaptic contacts, and higher synaptic EPSP amplitude, roughly double, although I'm not sure how the release probabilities compare. .45 for L5b-L5b vs. "relatively high" for L5a-L5a.
- L5b cells with different projection targets might form separate subnetworks. Maybe reciprocal L5b connections result from connecting preferentially to cells with the same target, rather than true subnetworks as I think of them.
- ST L5a phase locking of L2/3 membrane potential hypothesis.
- During exploratory behavior e.g. for object localization, VPM afferents and L5a cells activate almost simultaneously (I'm guessing by touch because that's what activates VPM). This suggests coincidence detection if L5a cells -> L5b tuft.
- L5b -> POm has large efficacy but depresses, so hypothesis of two modes, one where the pathway is depressed by high spontaneous activity and therefore requires coincident input from multiple L5b cells, and one where the pathway is effective. During active whisking, spontaneous activity is low. I kind of disagree with this hypothesis, unless lateral activity causes more global spontaneous activity, since the depresses is synapse-specific.
- Maybe this helps deal with varying sparsity, since if the representation is dense, it shouldn't generate a dense thalamic response. If L5b cells don't activate too synchronously, then the initial response isn't too dense either.
- Short (called untufted) L5 cells have connection probabilities of only 3%. Lower release probability than between ST and TT cells, but .4 so I'm guessing no facilitation. Similar average EPSP amplitude to the connections between TT cells and ST cells. They mainly connect on basal. It might be different for SH cells which don't project contralaterally since they weren't tested, if they exist.
- An L2/3 cell -> two L5 cells with higher probability if those L5 cells are reciprocally connectected. Two L2/3 cells both -> and L5 cell with lower probability if those L2/3 cells are reciprocally connected. Based on the cited study, 22% of L5 cell pairs receive input from the same L2/3 cell when those L5 cells are connected (reciprocally?) versus 2% when they are not connected. For the 22%, 68 pairs had input to both cells and 12 had input to one cell, so it seems like a massively increased chance of the other cell receiving input if the other receives input. Compared to random connectivity, both L5 cells receive input with 4.5x likelihood if they are connected compared to random chance, and a little below random connectivity chance if they aren't connected (reciprocally?) For L5 -> L2/3, both L2/3 cells receive input from the L5 cell 7.5% of the time when the L2/3 cells aren't (reciprocally?) connected and 2% when the L2/3 cells are connected.
- Info on L6.
- Based on the main citation this is using for connectivity, L6 doesn't target L5a/L5b much at all (just one or two connections out of many). But that study found similar input connectivity rations for L6 -> all other layers.

- L6a CC cells -> L5b 7% connectivity ratio. Not sure about the methods i.e. whether or not it was restricted to the same column or etc.
- Some L4 SOM cells receive VPM input, which facilitates and has low initial probability. These L4 SOM cells include LTS and adapting cells.
- Some L4 SOM cells project to L1.
- Info on interneurons.
- A fairly high fraction of L5a interneurons are SOM+ (there are also SOM+ interneurons in L5b of unstated density).
- FS PV+ L5b cells depress TC inputs so they might stop or functionally stop firing soon after sustained TC input starts.
- L5b SOM+ interneurons don't synapse onto distal apical, unlike most other SOM+ cells. Receive TC input. They target L4 spiny cells in the same column. So they're similar to L4 SOM+ cells. They have facilitating input, so spike frequency dependent. Brief thalamocortical stimulation doesn't activate them. Seems they used broad thalamic stimulation (ventrobasal thalamus).
- L5b SOM+ cells might activate after FR PV+ L5b cells inactivate. Something like this is required, or else inactivation of the PV cells would lead to excessive excitation. So later in the response, SOM+ cells are the main source of inhibition. The switch from L5b PV+ to SOM+ dominant inhibition would occur for stimulation frequencies ~10-20 hz, which is similar to whisking frequency. However, L4 SOM+ cells disinhibit by inhibiting L4 FS PV+ cells. I wonder if that's actually functionally equivalent, i.e. they just do that to cause PV+ cells to inactivate, since they also inhibit excitatory cells in L4. Unless that disinhibition was shown directly.
- Actually, there might be distal apical-targeting L5b SOM+ cells. That information is just for a subtype, but might extend to other L5b SOM cell types.
- Martinotti cells which participate in the possible FDDI circuit target apical tuft and oblique. Besides FDDI, they could also synchronize membrane potentials because of their high connectivity (input and output).
- CT L6a cells activate both L4 and L5a FS cells. CT L6a also -> L5a SOM+ cells weakly and facilitating.
- L6 SOM LTS cells receive VPM input. Weaker EPSPs than other targets in L6, and facilitating.

POm Thalamocortical Input Drives Layer-Specific Microcircuits in Somatosensory Cortex (Audette NJ, Urban-Ciecko J, Matsushita M, and Barth AL, 2017)

- ➢ POm stimulation suppresses SOM cell spontaneous activity, for both superficial and deep layers.
- ➢ POm activation evokes short latency responses in deep layers, synchronized (truncated?) by feedforward inhibition from PV cells.

- ➢ In superficial layers, POm activation evokes weaker/delayed and more prolonged responses and there is slow inhibition from GABAergic cells expressing 5HT3a receptor (VIP cells?)
- ➢ SOM cells in both deep and superficial layers do not receive direct POm input.

Topography of connections between primary somatosensory cortex and posterior complex in rat: a multiple fluorescent tracer study (Mara Fabri and Harold Burton, 1990)

- ➢ POm might receive different sensory information than VPM with a higher sensory stimulation threshold.

Time-dependent, layer-specific modulation of sensory responses mediated by neocortical layer 1 (Dan Shlosberg, Yael Amitai, and Rony Azouz, 2006)

- S1.
- Blocking L1 increases whisker-evoked response magnitude.
- When L1 stimulation is paired with whisker stimulation, sensory response is enhanced for intervals <10 ms and suppression for intervals >10 ms.
- Resulted in time-dependent directional tuning.
- The suppression is mainly because of shunting inhibition.
- TTX (blocks both excitatory and inhibitory signals) to L1 increased whisker sensory responses, whereas DNQX (AMPAR blocker) to L1 had no influence.
- Activating L1 at sufficiently high electrical strength -> L5 response. If this is the source Castejon et al. cited, I'm not sure L1 stimulation activates L4/6. Used a lower intensity for the rest of the study.
- The time-dependent changes are for both superficial and deep layers. The longer tested intervals were 10 to 50 ms.
- The influence of timing on whisker deflection angle selectivity might just be a change in the degree of selectivity. Seems to be the case. And the enhanced response is less selective, so I'm not sure this is a real mechanism.
- Tested activating L1 and white matter. For >10 ms separation, for L5 at least, sublinear summation, whereas <10 ms -> supralinear.
- Based on a quick search, shunting inhibition means inhibition adjacent to excitatory synapses which through electrical mechanisms I can't understand reduces the response to those synapses. It's more complex when the resting potential isn't the same as the reversal potential. But according to another part of the wiki article, it probably doesn't divide the response. But it doesn't matter to me whether it is a dividing effect or just subtracting from the influence of any locally suprathreshold responses.
- Synaptic shunting is responsible for most of the sublinearity of the summation.
- Keep in mind e.g. the size of dendritic arbors of different cell types has a large influence on the impact of extracellular stimulation.

Thalamic circuitry and thalamocortical synchrony (Edward G. Jones, 2002)

- Seems to be a review or similar.
- When a thalamic relay cell is held at -55 mV, a weak electrical pulse to CT fibers causes a small EPSP but truncated by a large IPSP from RTN lasting 100 ms with both GABAA and GABAB components. As the cell recovers from inhibition, low threshold calcium current deinactivates leading to a burst. This sends a signal to RTN, specifically a stepwise EPSP which increases amplitude for each AP in the relay cell burst. This inhibits the relay cell again, and the cycle continues the same way. 7-14 hz cycle.
- Because the signals are sent to RTN from relay cell TC collaterals and because of the distribution of those collaterals, the 7-14 hz oscillation/burst cycle spreads through the thalamus.
- I wonder if the time it takes for relay cells to switch between modes is because of RTN inhibition. It could be both that and calcium channel deinactivation kinetics.
- I guess that is a potential timing signal, like Jeff Hawkins suggested. Also, depressing CT synapses might make it track timing from the start of the signal. But the issue is whether or not it works at more depolarized potentials and what typical resting potentials are, and whether or not a sensory input or L5 CT input could drive it even though the potential isn't help hyperpolarized. Also, how does the signal represent timing if cells which activate the repetitive bursting after longer delays also receive sensory/CT inputs.
- The cortex might synchronize those oscillations. Those oscillations in vivo might begin around the same time throughout the thalamus, I'm guessing because sensory input doesn't just activate one cell.
- For this to work, the author says the disynaptic inhibition from cortex to relay cells must be more powerful than the excitation. But I guess it depends on which of the three CT fiber types.
- When relay cells and RTN cells are both at more depolarized membrane potentials (-45 mV vs -55 mV for the prior condition for repetitive bursting), relay cells oscillate potential at 20-80 hz. This is because of high threshold Ca2+ channels in dendrites. It is usually subthreshold for spiking, but they fire at that frequency intermittently when there are volleys of CT input above 10 hz. Further above 10 hz, each EPSP evokes more spikes likely because of facilitation, frequency dependent NMDAR responsivity, and activation of high threshold Ca2+ channels in distal dendrites.
- High frequency CT fiber activation is effective for activating mGluRs.
- L6 CT to higher order thalamic nuclei might only be in rodents.
- In V1, L5 -> pulvinar-lateral posterior complex. In A1, L5 -> dorsal and magnocellular nuclei of the medial geniculate complex.
- Parvalbumin+ relay cells (core-type) exist in both primary sensory thalamus and motor relay nuclei, as well as certain nuclei of the pulvinar and some intralaminar nuclei. Calbindin+ (matrix-type) are throughout dorsal thalamus.

- ➢ Core-type cells usually form dense clusters associated with dense afferent fiber terminations, which are themselves PV+.
- ➢ In the dorsal lateral geniculate nucleus, PV cells are only in the parvocellular and magnocellular layers, whereas calbindin cells are concentrated in the S-layers and the interlaminar plexuses between the principal layers, but also exist in the other layers.
- ➢ Nuclei/parts of nuclei with high calbindin density receive different sensory inputs than those with high PV density. The sensory input is also more diffuse and less directly connected to sensory receptors. These are just trends, and there seems to be a lot of variety in the type of sensory input.

Synaptic Connections between Layer 5B Pyramidal Neurons in Mouse Somatosensory Cortex Are Independent of Apical Dendrite Bundling (Patrik Krieger, Thomas Kuner, and Bert Sakmann, 2007)

- ➢ vS1 L5b cell apical bundles are thought to be part of minicolumn architecture.
- ➢ Those in the same cluster (which bundle their apical dendrites) didn't receive more correlated synaptic input than adjacent clusters.
- ➢ IB and RS cells were in the same cluster. In another study, some clusters had IB+RS and some had only RS (but could be because of methods so check the source.)
- ➢ Correlation depends on mode of stimulation, so recording minicolumns while awake would be best.
- ➢ All L5 cells that contributed to the bundle were restricted to L5b and had a large tuft in L1 and didn't project to contralateral cortex, even though some were IB and some were RS. But did they check bundling in L1, or maybe short cells also bundle and just end earlier or are part of the same functional minicolumn?
- ➢ Provides sources on minicolumns.
- ➢ Dendrites within a bundle could be electrically coupled so bAPs influence the whole bundle.

Somatodendritic minicolumns of output neurons in the rat visual cortex (Alessandro E. Vercelli, Diego Garbossa, Roberta Curtetti, and Giorgio M. Innoc, 2004)

- ➢ Apical bundling by projection target.
- ➢ Corticocortical cells in L3 and L5 bundle, along with corticostriatal cells.
- ➢ Cells projecting to superior colliculus and a thalamic nucleus bundle, along with corticostriatal cells.

Some thoughts on cortical minicolumns (Kathleen S. Rockland and Noritaka Ichinohe, 2004)

- ➢ Review about minicolumns. Keep in mind all of these facts are probably from different regions/species and there seems to be a lot of variation.
- ➢ How well somata are arranged into vertical columns varies by region and other things e.g. left/right hemisphere. Development involves radial glial guides, which might produce non-functional minicolumn-like structures and age-based differences.

- In regions with stronger columnar organization, 15-20 somata aligned over a thickness 300-500 um. But later in the article, it cites 80-100 but isn't completely sure how that estimate was found.
- Bundles (meaning cells with bundled apical dendrites) include L5 cells, which bundle starting in L4 or maybe earlier. The bundles are joined by superficial cells.
- Bundles consist of more cells than vertically aligned somata. E.g. 5-20 versus 20 to many tens to a few hundred.
- Bundles aren't necessarily formed by vertically aligned cells, and the cells which contribute aren't necessarily part of any vertically aligned cell groups.
- Info about methods used to establish minicolumns/modules.
- L4 small py cells and L6 cells don't contribute to bundles, at least not the same ones as L5/superficial cells.
- There might be two tiers of bundles, one terminating in L1 and one terminating in L4 or the L3/4 border. There might only be one tier in some regions, and there might be a 3rd L2 tier in some regions.
- In monkey V2, most L5 apical dendrites terminated in L4 or deep L3. They intermingled with L6 dendrites. The upper bundle tier is mostly only from L2/3 cells.
- Only ~⅔ of L5 cells contribute to bundles.
- Not sure if this is about L5, but some bundles contain thicker apical dendrites and some do not.
- When dendrites bifurcate, they can still continue in bundles separate for each branch but e.g. with a common bifurcation point so it leads to e.g. two bundles.
- In barrel cortex, thick apical dendrites occur preferentially in barrel walls. Check the citations, because that might be important for L5 TT cells.
- In some areas of mouse cortex, bundles are composed of 6-14 dendrites and separated by 50 to 100 um. In other areas of mouse cortex (frontal cortex so might be different), L5 cell apical bundles are slabs in L4/5 up to 875 um by 50 um and separated by ~25 um.
- Based on the size of apical bundles versus bitufted cell vertically oriented axon arbours, I don't think apical bundles are always the same as minicolumns.
- In rat GRS (granular retrosplenial cortex), there are bundles which originate from L2 cells. 20 to 200 cells contribute. The bundles are targeted selectively by the anteroventral nucleus, whereas distal tufts from L3/5 cells, which are in the inter-bundle space, are targeted by corticocortical input and possibly laterodorsal thalamus.
- In rat V1, zinc-enriched corticocortical terminations intermingle with PV-rich neuropil to form thin walls surrounding patches of thalamocortical terminations labelled by cytochrome oxidase. So I guess TC terminations are what label barrels, too. Thicker dendrites of deeper cells are located preferentially in the hollows. Thinner dendrites (which are from L2 cells) preferentially in the walls. These results suggest thicker dendrites are preferentially targeted by thalamus whereas thinner are preferentially

targeted by CC input and PV cells. The upper layer Zn+ (zinc positive) periodicity doesn't exist in rat barrel cortex but the PV+ honeycomb periodicity exists there.

- ➢ VLGLUT2 labels TC terminations in rats but not monkeys.
- ➢ Thalamic and CC (might be more specific than CC) arbours are typically too large to be minicolumn-specific.
- ➢ Some input axon arbours are small enough and have the right shape to possibly be bundle-specific. Feedback inputs which ascend from white matter to pia vertically, although few synapses on this vertical part of the main axon. Inhibitory double bouquet cells have a vertically oriented axon, although they primarily terminate on oblique dendrites rather than other parts of the apical dendrite.
- ➢ Some studies found that seven or eight bundles are grouped into a 75-100 um wide hexagonal array.

The organization of pyramidal cells in area 18 of the rhesus monkey (Peters A, Cifuentes JM, and Sethares C, 1997)

- ➢ V2.
- ➢ L6a cell apical dendrites aggregate with those of L5, forming "swathes" that reach L4 and are joined by apical dendrites of L4 cells. Most of these apical dendrites form terminal tufts in L3. Tufts which reach L1 are mostly from L2/3 cells.
- ➢ Whereas in V1, L5 apical dendrites form clusters with centers of clusters 23 um apart. L2/3 apical dendrites join these clusters, and all dendrites in these clusters have tufts in L1.

Control of somatosensory cortical processing by thalamic posterior medial nucleus: A new role of thalamus in cortical function (Carlos Castejon, Natali Barros-Zulaica, and Angel Nuñez, 2016)

- Deep layer cells were mostly L5. L5a and L5b were modulated by POm similarly.
- Keep in mind POm probably responds to the sensory input.
- About Methods:
  - L1-applied blockers might spread into L2/3.
  - Extracellular L1 activation can activate axons in L1.
- Divided sensory response into two components. The second component usually starts roughly 20 ms after sensory and might be more connected to NMDA spikes.
- Brief POm stimulation alone evoked spiking lasting up to 150 ms in deep layers and up to 50 ms in superficial layers.
- Inactivating POm enhanced sensory responses both deep/superficial. In contrast to the other results, the first component wasn't influenced for both superficial and deep. There was more spontaneous activity.
- POm stimulation followed by sensory stimulation:
  - Tested delays of 50, 200, 500, 700, and 1000 ms.

    - Deep layers: no interval changes the early component, whereas all intervals reduce the second component spike count/duration.
    - Superficial layers: first component is decreased less for longer intervals so it isn't significant for 1000 ms but follows the trend, whereas the second component is reduced similarly for all durations except much less for 1000 ms than 700 ms.
- Role of L1:
    - Blocking inhibition from L1 increased baseline FRs and cannot untangle the contribution of baseline FRs/membrane potentials from the sensory response.
    - L1 GABAA block or L1 P/Q VG Ca2+ channel block (impacting PV cells) removed or strongly reduced the influence of POm on the sensory response 500 ms later.
    - L1 electrical stimulation 150 ms before sensory stimulation decreased the response. Only impacted the second component for deep whereas impacted both components for superficial.
- S2:
    - S1 L5 alone evoked strong S2 responses, but stimulating S1 L5 150 ms before sensory decreased the S2 response. Both of these influences were blocked by silencing POm.
- In a study on another region, matrix thalamus activates L1 interneurons directly and activates them more than they activate L2/3 py cells. The activated interneurons could then truncate responses in other layers. Window of opportunity for sensory responses.
- Maybe the window for integrating POm/sensory to generate the mGluR response is the same window as before inhibition. In that study, the stimuli might've only been separated 20 ms between start/end of the two stimuli, so might be consistent.

Monosynaptic Connections between Pairs of L5A Pyramidal Neurons in Columns of Juvenile Rat Somatosensory Cortex (Andreas Frick, Dirk Feldmeyer, Moritz Helmstaedter, and Bert Sakmann, 2008)

- P18-P20.
- Connections between L5a cells. By comparing this with Schwindt et al., 1997, input resistance doesn't seem a reliable definition of SH cells across regions.
- L5a-L5a Synaptic Properties:
    - Completely blocked by AMPAR and NMDAR blockers.
    - Low failure rate/amplitude variation. Amplitudes vary widely between synapses.
    - The study claims EPSPs depress strongly, but that is for the amplitude rises relative to just before the EPSP, to reduce the impact of temporal summation.
    - Absolute amplitude does not depress so strongly except at lower frequencies where temporal summation is less impactful.
    - In the example connection, EPSPs last ~40 ms. At 50 and 100 hz, depression begins after the second or third EPSP and occurs somewhat slowly. At 10 and 20

hz, depression mostly occurs between the first two or three EPSPs. Only 5 AP trains were tested.

- L5a-L5a Connectivity:
    - Used a slice which included a few columns.
    - ~15% of connections participate in bidirectional connections. The rest of this section is only 6 connected pairs.
    - Some pairs were septal and some were in a barrel column.
    - For 5/6 pairs, the presynaptic cell is closer to L4 than the postsynaptic cell.
    - For all pairs, the pair is basically vertically aligned, with a range of vertical separations up to near the width of L5a.
- Other:
    - Based on the 6 connected pairs.
    - 70% of dendrite in home column and 90% in home + neighboring septa.
    - Basal dendrite mostly confined to L5 and lower L4.
    - The axon projects into same/neighboring columns in L2/3/4/5.
    - Same-column input from L2/3, L5b, and especially L5a.
    - L5a projects to L5a, L5b.
    - Like L5a -> L5a, L4 -> L5a cell pairs tend towards vertical clustering and more of the pairs are near or in septa. L4 -> L5a is ⅔ on apical. This data is from another study.

Three Types of Cortical Layer 5 Neurons That Differ in Brain-wide Connectivity and Function (Euiseok J. Kim, Ashley L. Juavinett, Espoir M. Kyubwa, Matthew W. Jacobs, and Edward M. Callaway, 2015)

- Adult mouse V1.
- NS (non-striatal) is a third L5 cell type.
- ST -> V2, contralateral V1, other sensory cortices, frontal cortices, and striatum.
- TT does not project to V2 nor contralateral V1.
- TT -> SC, pons, ipsilateral striatum, and the secondary visual thalami LP and LD.
- NS does not project subcortical.
- NS -> V2.
- NS and ST have similar apical thickness.
- Near threshold, all ST and most NS cells were RS. All TT cells were IB.
- 1st ISI/3rd ISI ratios: ST .57, and TT .2 because of initial burst. NS .44 but varies a lot (e.g. .1 and .9). FRs for this were 10-20 hz.
- TT and ST have similar input resistances. NS has much higher input resistance but with a lot of variation and including some cells with much lower input resistance.
- TT and NS had similar % sags (related to Ih) and much larger than ST cells.

- TT cells receive much more dLGN input than ST cells and probably NS cells. This is based on rabies tracing.
- NS receives little or no secondary thalamic input (LD/LP) whereas the other two receive some.
- The cortical inputs from other regions are primarily from L5, a bit over 50%. The next strongest cortical input (not including from V1 itself) is L2/3, but always <30%. The laminar input to all three types were quite similar. These results are ambiguous for NS cells since L6 cells were also labelled.
- According to other studies, TT cells are involved in movement-associated sensory gating.

Anatomy, Physiology, and Synaptic Responses of Rat Layer V Auditory Cortical Cells and Effects of Intracellular GABAA Blockade (Brenda J. Hefti and Philip H. Smith, 2000)

- Rat A1 slice. P21-P42. 5 KCl (standard is 3).
- MGB includes both primary and secondary thalamus.
- Activated MGB TC input, in many cases at the same time as CC fibers.
- Types:
    - RS: during a current pulse, singlets. Adaptation occurs, at least during the first 50 ms. Adaptation might only occur during sufficiently rapid spiking, and the initial adaptation might allow for an initial response at burst frequency.
    - About a third of RS were RS1. No adaptation after the initial adaptation.
    - The other RS cells were RS2. Adaptation never stops during the current pulse. RS1 and RS2 might exist on the same continuum because RS2 cells have a range of degrees of adaptation.
    - IB cells: during current pulse, ~200 hz burst of 3-5 APs. At lower currents, repetitive bursting each riding a slow depolarization. At higher currents, an initial burst followed by a long hyperpolarization, then non-adapting singlets. Burst frequency was the same for a given cell at different injection strengths, and all cells had burst frequencies of ~200 hz.
- Morphology:
    - IB cells had thicker apical dendrites.
    - RS cells have fewer apical branches, especially in L1, and have on average .8 primary branch points in L3 and .1 in L2 (although IB has .8 in L2).
    - IB apical always reaches L1 where it branches a lot.
    - Some RS cells had dual primary apical shafts (meaning branches at some point into two), but these are still slender.
    - There doesn't seem to be a consistent sublaminar distribution of IB/RS.

    - Most RS had a local axon concentrated in the more superficial layers, whereas 2/10 instead concentrated in L5 and L6.
    - IB axon has fewer local collaterals and is concentrated in L5 and L6.
    - Both RS and IB axons always extend into white matter.
- Unless otherwise stated, they activated both TC and CC.
- RS Synaptic Responses to TC + CC:
    - EPSP with consistent latencies ranging 1.5-4 ms.
    - 50/56 RS cells had a GABAA IPSP immediately following the EPSP. The reversal potential is greater than resting potential.
    - Inhibition is strong.
    - GABAA is always accompanied by GABAB (a long lasting hyperpolarization of up to 7 mV.)
    - Single-cell GABAA block made the EPSPs often suprathreshold.
    - The EPSP can be interrupted by the IPSP and then continue.
- IB Synaptic Responses to TC + CC:
    - EPSP with 1.5-3 ms latency. 18/36 of these EPSPs had multiple components likely reflecting input from a bursting IB cell.
    - Only 16/36 was accompanied by GABAA inhibition. Only 1/36 had GABAB inhibition.
    - Spiking is more prominent than for RS.
- IB Synaptic Responses to TC Alone:
    - 3/10 responded with short latency, .5-1 ms, suggesting it is monosynaptic unlike the other responses. Always a single EPSP followed closely by inhibition.
    - Some had the longer latency response, but not all short latency responders have both.
    - I wonder if RS cells actually receive thalamic input because it is associated with IPSPs like for IB cells, and the difference is higher order/lower order conduction velocities.
- Another study found two auditory cortex L5/6 response types. A phasic response type (respond and start of tone and then inhibited) has similar intrinsic physiology to RS cells. Tonic responders (respond throughout the tone) have similar intrinsic physiology to IB cells, and rarely showed inhibition/had broader frequency tuning.
- The study concludes that RS cells do not receive monosynaptic input from thalamus because it has longer latency than IB cell monosynaptic responses. Since MGB includes secondary thalamus, either secondary thalamus axons/synapses have longer latencies (at least 1 ms more than primary thalamus) or secondary thalamus does not canonically synapse proximally on RS cells. Since the inhibition comes soon after the delay, I doubt the EPSPs are generated by lateral connectivity, although proximal lateral connectivity could still exist because there was little spiking with GABA intact.

- The interpretation of stronger RS cell selectivity is surround inhibition by thalamic input to inhibitory cells. But wouldn't it just respond broadly before that, because the inhibition is delayed? Maybe it's because the relative timing of IPSPs/EPSPs is important, but they didn't report IPSPs followed by EPSPs. Maybe RS cells are more selective because their thalamic input is from secondary thalamus.
- IB cells project to MGB. So they probably activated both primary and secondary thalamus.
- IB cells also project to inferior colliculus, to enhance tuning (increased responses to tuning curve peak and less to lower parts of the tuning curve), possibly with modulatory synapses.

Laminar Structure of Spontaneous and Sensory-Evoked Population Activity in Auditory Cortex (Shuzo Sakata and Kenneth D. Harris, 2009)

- Not taking full notes.
- Lateral excitatory connections are typically strong at fairly long distances, whereas they drop off a lot over ~150 um for L2/3. This might explain why L2/3 responses are more selective, because, for a tonotopic map, they are more clustered. So maybe L5 TT cells have broad RFs partially because of lateral connectivity. Or maybe the actual difference is intercolumnar connectivity, not spatial clustering around a specific tone.
- Input from ventral MGB (which is the portion which receives inferior colliculus) synapse most densely on L3b/4 and the L5/6 border. Likewise, the earliest sensory responses are in L4 and part of the subgranular layers.

Spiking in primary somatosensory cortex during natural whisking in awake head-restrained rats is cell-type specific (Christiaan P. J. de Kock and Bert Sakmann, 2009)

- Not taking full notes.
- During non-whisking, ST average 1.6 hz and TT 4 hz. During whisking, ST 5 hz and TT 4.5 hz, although both with large SDs because n=3 and 5 respectively (large sample sizes for non-whisking).
- During whisking, 7/20 L5a cells increased FR significantly. 3 significantly decreased, and the other 10 didn't change significantly.
- L2/3 membrane potential correlates with whisker position. Maybe this is because of its map of scanned space. So maybe the mechanism of modulation by L5a is responsible for this coordinate transform.
- Individual neurons didn't show strong selectivity for whisking position for spiking. So if there is a map of scanned space, it might be primarily in subthreshold modulations.
- Modulation by whisking position is weak.

- Maybe the weak correlation is because the map of scanned space might warp to fit the whisking amplitude, which varies a lot each cycle. Maybe that explains why some studies have found correlations with phase.
- Maybe membrane potential but not spiking correlates with whisker position because the input is modulatory, e.g. predictive or selecting object context for a feature. Whisker position probably isn't represented alone.

Deep Cortical Layers are Activated Directly by Thalamus (Christine M. Constantinople and Randy M. Bruno, 2014)

- Barrel cortex and VPM.
- Many L5/6 cells had sensory responses with the same latency as L4.
- Inactivating L4 did not change the sensory-evoked synaptic input (including oligosynaptic? That would probably inactivate L2/3.)
- Following whisker deflection, L4 response latency 8 ms and L2/3 11 ms. L5 9.5 ms and L6 10.5 ms. Although the average is different, many L5 cells had latencies similar to L4.
- The longer latency L5 EPSPs occured simultaneously with the L2/3 EPSPs.
- The L5 EPSP response latency distribution has two peaks.
- VPM cells were not found to synapse on L5/6 cells with apical extending thru the L4 septal region, and only on topographically aligned pairs (i.e. barrelette/barrel).
- Individual synapses onto L5/6 cells are weak but similar amplitude to TC synapses on L4 cells.
- 4/9 VPM-TT pairs were connected, and 3/18 VPM-ST pairs. This means each receives a large number of inputs because a barrelete contains ~200 cells.
- Under the experimental conditions (sedative rather than anesthesia), both ST and TT were primarily IB. Maybe because of feedback onto the apical tuft.
- The method to determine connectivity is based on correlation.
- Silenced L4 and the TC axons that go into L3, as well as the axon from L2/3 which passes through L4. L2/3 spiking was eliminated.
- Lidocaine did not affect the L5/6 sensory response, although some increased and some decreased.
- Actually, it just didn't change significantly ($p = .64$) but reduced from .16 spikes/stimulus to .12/stimulus, for L5/6.
- When VPM was inactivated, the responses were reduced but not eliminated, like through POm. This would have to be through the synapses in L5 because of the lidocaine. Lidocaine to L1 did not have an impact on the sensory response for L5.
- I assume sensory response always refers to the lowest latency portion.

Cell Type–Specific Thalamic Innervation in a Column of Rat Vibrissal Cortex (Hanno S. Meyer, Verena C. Wimmer, Mike Hemberger, Randy M. Bruno, Christiaan P.J. de Kock, Andreas Frick, Bert Sakmann, and Moritz Helmstaedter, 2010)

- L5 TT cells receive ~300 boutons from VPM and also ~300 for POm.
- A subtype of L5 TT has an additional VPM innervation domain in L4.
- The millisecond latencies between layers for sensory response suggests near simultaneous initial representation in all layers.
- This is based on axodendritic overlap.
- The L5 TT subtype extends a lot of oblique into L4, which most lack.
- Makes some arguments for POm -> L5 TT tuft.
- A study estimated that the L5 TT tuft requires 100 synaptic inputs to evoke the calcium response. This study estimates a similar number of synapses from POm.
- Based on the L5 ST latency, this study suggests that the early input is weak or attenuated by inhibition. That relates to the study which found most L5 RS cells have inhibition, which can interrupt the EPSP but end before the EPSP ends (although it might instead by two separate EPSPs). In that study, when this occured, APs typically only happened before the interruption, but maybe that's because they depolarized them. Maybe the same depolarization occurs, but with slight delay so firing occurs after the interrupting IPSP. This is an alternative explanation to POm latency, if they are actually driven by e.g. VPM or other layers. Maybe the proximal POm synapses are metabotropic.

Cortical Dependence of Whisker Responses in Posterior Medial Thalamus In Vivo (Rebecca A. Mease, Anton Sumser, Bert Sakmann, and Alexander Groh, 2016)

- Used sedative rather than anaesthesia to better mimic awakeness. Deflected multiple whiskers using air puff. At least some of the data/methods are also used in "Corticothalamic spike transfer via the L5B-POm pathway in vivo" and perhaps other studies.
- Only recorded L5b cells which responded within 100 ms (EPSP or spike depending on the recording type). I'm not sure whether the stimulated whiskers were the same used during recording.
- For spike recordings but not Vm recordings, only recorded POm cells which responded with low latency to vS1 activation.
- The anterior third is the POm convergence zone, where both L5b and SpVi inputs arrive. The rest is the nonconvergence zone, driven only by L5b. This isn't entirely proven.
- Throughout the recordings, there were two types of responses. Early responses had latencies typically <50 ms, whereas late responses have longer latency.
- POm Spike Recordings:
    - Early responses are within 50 ms, and are abolished by vS1 silencing. These recordings are therefore in the nonconvergence zone.

    - 5/13 have an early and late response. 8/13 only have the late response.
    - Didn't test the impact of vS1 silencing on the late response.
    - The late response appears to be a general increase in spiking per bin over hundreds of ms, with similar time course to the mGluR POm study.
    - The late response might be caused by the sensory-evoked cortical upstate. 73% of trials have an upstate evoked within 400 ms.
- L5b Spike Recordings:
    - 19/31 have an early response and a late response. The other 12 only have the late response.
- For late spike response examples (both POm and L5b), it is a general increase in spiking over hundreds of ms, with a similar time course to the study on POm mGluR. The time course might result from averaging, but perhaps for both studies.
- In Vm recordings, early/late responses had latencies comparable to those for early/late spiking.
- POm Vm Recordings:
    - Another study on POm cells with ZI and SpVi input found continuous IPSPs on POm cells, but this study did not find that, suggesting only the convergence zone receives ZI and suggesting they recorded the nonconvergence zone. However, brain state might be the cause.
    - 18/30 had an early response, 5 of which sometimes spike during that (all 5 are of the early large type described below). The early response is followed by a late response.
    - The other 12/30 have a late response, time locked to the sensory-evoked upstate. The details and causal direction of the time locking cannot be determined because the LFP travels across columns. But could determine causal direction based on the timescale of LFP propagation.
    - 10/18 early responders had large EPSPs, and 8/18 had small EPSPs. The small EPSPs have slightly faster onset so might be caused by sensory input.
    - Early large and late responses (but not early small responders) had T-type calcium Vm spikes, but late responses had more. Individual cells were variable in whether or not they had a T-type calcium spike.
    - The 5 early large cells with spikes had on average .25/stimulus. The failures to spike are because of hyperpolarization accompanying the large EPSP.
    - They suggest early small responders are simply because of inhibition. I wonder if the early small responses are just cells which are always inhibited enough to prevent T-type Vm spikes, since they have a huge bias on the EPSP amplitude and the non-T-type spike examples are similar amplitude for each early response type. Maybe the early small responders are simply those active to early and therefore

inhibited. Or maybe they fail the T-type spike because they were depolarized beforehand.
    - Another possible cause of the small responses is synaptic depression in L5b -> POm by spontaneous activity (i.e. a recent or ongoing up state).
    - Inhibition by ZI or L6 -> TRN are also possible causes, since some cells had whisker-evoked IPSPs. These IPSPs were abolished by silencing vS1.
- Late responses might be caused by the cortical upstate, which propagates to other columns and therefore has a delay. I wonder if whether or not the stimulated whiskers are in the RF determine whether or not they only have the late response. Wouldn't there be early-only responses, if the upstate begins immediately at the L5b cells with early responses? Maybe that's because they stimulated multiple whiskers, causing propagation from other sources. In studies with single-whisker deflection, do L5b cells in the corresponding column only have the early response?
- A study found that POm only sends signals to cortex when alert.

Convergence of Cortical and Sensory Driver Inputs on Single Thalamocortical Cells (Alexander Groh, Hajnalka Bokor, Rebecca A. Mease, Viktor M. Plattner, Balázs Hangya, Albrecht Stroh, Martin Deschenes, and László Acsády, 2014)

- Sensory input and L5b converge on POm cells, both with driver properties.
- Terminals of the two types can converge on the same dendrite.
- Activating L5 and whisker stimulation summated supralinear. 2.7x the sum of each alone.
- Selectivity of summation of the two sources for latency/order varies by POm neuron. Supralinear summation spans at least -100 to 100 ms, i.e. different integration windows for different POm cells covered that range. However, most had asymmetrical windows, preferring whisker stimulus before L5b stimulation. Note that these results are based on spiking probabilities, so the setup isn't a good mimic of directly activating single cells of each input. Also, wouldn't spiking probability naturally be supralinear?
- Also, although it ranges -100 to 100 ms, most windows are for whisker stimulus first and latencies of up to ~40 ms. A lot have good supralinear summation at 0 latency.
- I'm not sure whether they used laser or L5b stimulation. Air puff lasts 40 ms, which if laser stimulation is brief might explain the bias towards whisker then L5b or maybe laser.
- I think they might've used laser stimulation of L5 CT terminals. The CT pathway strength depended on laser intensity. The CT pathway produced spikes more reliable than sensory input, which is an issue.
- Next, tested POm Vm.
- EPSP summation was not supralinear, actually sublinear. The supralinear spike probability is because of supralinear chance of reaching threshold. That doesn't seem different from supralinear summation of two different inputs from the same source, although one difference is that each axon in a single source has similar chance of

activating, whereas with two sources, there are different conditions e.g. sensory input required versus late response from L5b. Also, there might not be enough sensory inputs to a cell (which can co-activate at least) to reach threshold without L5b.
- 10/20 POm cells had integration peaks between 0 and 10 ms. This means sensory information doesn't have time to influence L5b by the time it reaches POm.
- I'm guessing the prefered delay is just because of sensory latency, since they activated L5 CT terminals directly.
- The EPSP summation at longer delays might involve T-type calcium channel spikes, because they cause long plateau-like depolarizations (is that fact based on e.g. iontophoresis?)
- Provides a source about other zones of convergence.

A Morphological Analysis of Thalamocortical Axon Fibers of Rat Posterior Thalamic Nuclei: A Single Neuron Tracing Study with Viral Vectors (Sachi Ohno, Eriko Kuramoto, Takahiro Furuta, Hiroyuki Hioki, Yasuhiro Tanaka, Fumino Fujiyama, Takahiro Sonomura, Masanori Uemura, Kazuna Sugiyama, and Takeshi Kaneko, 2012)

- Complex axon/dendrite reconstructions.
- Divided POm into posterior and anterior by calbindin (posterior has more calbindin immunoreactivity, without a sharp border). Posterior cells had wider but less numerous dendrites.
- Anterior preferentially had axons in S1 L5, whereas posterior mainly in L1 with wider/sparser arborizations.
- One source which divided POm into rostral and caudal used POm for rostral and POc for caudal. This study uses POm for rostral. POC is smaller and possibly intralaminar nucleus so this makes sense.
- N = 5 for each part anterior/posterior.
- Only the dendrite spread in the mediolateral direction differed significantly. More spread for posterior POm.
- Anterior POm had more numerous dendrites, statistically significant at 20-100 um from soma.
- 2 anterior and all 5 posterior projected to striatum.
- S1, not restricted to vS1. All reconstructed cells projected to S1. At cortex, axon spread was over 1 mm so not restricted to one column.
- All 10 also projected to another region (M1, M2, insular, auditory, or ectorhinal.)
- There is a topographical organization in POm projections to S1, at least on the scale of HL/FL. Specifically, 4 neurons in dorsal POm projected to HL, 2 ventral cells projected to head region, and a neuron between them projected to FL. However, three neurons in the more posterior part of POm sent more widely distributed axons without clear topography.

- The anterior 5 form denser axonal bushes which are in narrower areas. Posterior cells sent more fibers to L1 than anterior cells. Although not significant, anterior sent more fibers to S1 L5 than posterior. These were concentrated in L5a.
- POm terminates in L4 S1 septa according to another study. This study found that a sizeable chunk (average ~⅓, 0-60%) of S1 L4 fibers are in septal and dysgranular regions. Not significantly but still a 5x difference, anterior sent more to L4 than posterior (I'm guessing for barrel cortex).
- Three posterior cells strongly projected to the head region, but sparsely innervated L4 without clear bias towards septal. Only 1 anterior neuron projected mainly to the head region. Axons in some serial sections (guessing not reconstructions) were biased towards septal L4 compared to barrel L4. However, including the anterior cell, they project primarily to L5.
- One anterior neuron had differences from the others. Primarily targeted M1 L2/3 and HL L2/3/4. This neuron is in a POm subregion with many intensely VGluT2-immunoreactive varicosities, unlike the surrounding areas of the other cells.
- POm is mostly less VGluT2 immunoreactive than surrounding nuclei including VPM, but has small islands of immunoreactivity. VGluT2 is mainly used by subcortical excitatory cell fibers, suggesting the islands have different subcortical input from the rest.
- Not including the island neuron, anterior axon length in S1 L5 is ~twice that of posterior.
- Next, tested these results at population level.
- The rostralmost part projects weakly to S1 and more strongly to visual, M2, and cingulate cortices. Besides that part, projects to S1 are moderate to intense.
- Keep in mind having axon in a layer doesn't = forming synapses.
- Anterior projects to L2-L5, especially L5a, in FL and S1 head region. For L4, many fibers were in dysgranular/septal.
- Posterior axon fibers are concentrated in S1 L1.
- At the border between posterior/anterior, many fibers were in both L1 and L5 (the same fibers? Check figure 9.)
- Next, estimated number of varicosities.
- 4 anterior cells and 4 posterior cells have the most varicosities in S1.
- This note is on S1. For 4 anterior cells (non-island), 6-40% (average 20%) of varicosities in S1 were in L1, versus for 5 posterior 40-90% (average 65%) in L1. Those 4 anterior cells sent 40-55% of their varicosities in L5, whereas for the posterior cells 4-40% (average 25%).
- "Axon bush" seems to mean axonal arborization in a region.
- For anterior cells which projected to M1, auditory, or insular cortex, main target was L1.
- For posterior cells which projected to M1, M2, S2, insular, or ectorhinal cortex, main target differed by cell. For 2 neurons, L1, and for 3, L2-5.
- Probably should write about each neuron separately then group them.

- According to another study, POc's main target is S2 instead of S1.
- Only 2/10 cells projected to S2 along with main arborization in S1.
- Still, all 10 cells projected to at least one other region besides S1.
- VPM does not project to striatum.
- 7/10 POm cells projected to striatum, more projecting or more densely (which?) by posterior.
- It has been claimed that POm projections to L4 are preferentially septal/dysgranular, but a study found that the barreloid heads project to septal, which was likely mistaken for POm previously.
- Anterior POm might target L5a cells basally and posterior might target L5a cells apically. L5a cells receive POm apically and basally, according to another study. L2/3 also receives POm apically, and L5a projects to L2, suggesting converging pathways.

Reducing the Uncertainty: Gating of Peripheral Inputs by Zona Incerta (Jason C. Trageser and Asaf Keller, 2004)

- POm whisker responses were low amplitude and median latency 27 ms. This is interpreted as a cortical source, but maybe instead it's because the first part of the response is suppressed by shorter duration IPSPs than the EPSPs. Do the IPSPs and EPSP shapes match this?
- Another study found mean latency of 19 ms compared to 7 ms for VPM. That study found that these POm responses are removed by cortical silencing.
- When suppressed inhibitory input from ZI, shorter latency and larger amplitude. Latencies consistent with trigeminal source.
- ZI is part of the subthalamic nucleus. Maybe L5 CT cells project to ZI at the same time, producing weak responses.
- The results suggest a convergence population and a nonconvergence population.
- ZI gates sensory input to POm.
- ZI targets all higher order nuclei so might be a canonical circuit.
- Electrically stimulating the trigeminal ganglia produces responses with similar latency in POm and VPM.
- Removing ZI inhibition reveals robust short latency EPSPs. So maybe this explains the results of other studies which found IPSPs hiding EPSPs.
- Maybe with ZI active, it requires L5 CT input coincident with sensory, whereas normally it just responds to sensory because of inhibition of the slightly delayed inputs from L5 CT by the earlier spikes.
- Multiwhisker stimulation in the cell's prefered direction.
- Required large amplitude multiwhisker deflections to evoke spikes, reflecting the weak responsivity of POm. Responses were variable in several parameters, and latencies ranged 6 to 66 ms (average 27 ms).

- POm has few or no GABAergic cells in rat.
- Unlike the other sources of inhibitory input, ZI responds with short latency (4 ms) to whisker stimuli. Also, whereas TRN cells terminate on distal dendrites, they terminate perisomatically.
- With ZI whisker region lesions, average latency 21 ms. That doesn't seem like a big effect.
- Spikes per stimulus, response duration, and spontaneous firing increased with ZI lesion.
- There was spontaneous firing before lesion, but not much.
- For control (as well as postlesion) neurons sensory response (i.e. peristimulus time histogram), bimodal distribution suggesting two populations. (Monomodal for single neurons.) So there might be a population with shorter latencies.
- The postlesion latency population distribution reduced compared to control for <30 ms latencies but was very similar for >30 ms. This suggests either some neurons have long latencies even postlesion or ZI input wasn't abolished.
- Compared the cells with >30 ms for control and postlesion groups. Lesion didn't significantly impact onset latency, response magnitude, or duration. Still, spontaneous FRs were higher for postlesion (2.5 vs. .6 hz). So these cells were probably tonically inhibited by ZI. This shows that the similarity in latency between control/postlesion wasn't because of still being inhibited. Instead, they might be cells without direct sensory input.
- For the populations of <30 ms for control and postlesion, more differences were significant. I worry that this is because these had ~3x sample sizes, but that's probably not an issue because there basically aren't any outliers here. Lesion reduced latency (12 ms vs. 21 ms). Spontaneous activity increased from .7 to 2.6 hz. Response magnitude changes from .85 to 1.9 spikes/stimulus. Response duration increased from 30 ms to 42 ms.
- At least 90% of ZI synapses in thalamus are GABAergic, and findings of glutamatergic synapses might be an issue with methods.
- ZI cells fire spontaneously.
- Before lesion, 12% of POm cells responded <8 ms, whereas 33% postlesion.
- Maybe the ZI input to the nonconvergence zone is important for suppressing activity early in the sensory response. Even though the response is long latency either way, this still inhibits slightly earlier activity from earlier L5 CT input, which might be important during ongoing sensory stimulation, especially the longer duration components of sensory responses.
- The results probably show that in the convergence zone, coincident L5 CT and sensory input are not required for firing. The results also suggest that L5 CT input (at least from other whiskers, since most input is from L5 CT cells not in the stimulated columns which probably have lower latency despite their wide RFs) arrives after ~30 ms.

- I wonder if the convergence zone reduction in latency shows that ZI -> thalamus stimulus-induced inhibition is briefer than the excitation from sensory. Or perhaps the sensory doesn't last long but excitation lasts longer because of input from L5. I wonder if the convergence zone POm cells have ~monowhisker RFs and therefore those that responded are for stimulated whiskers, so if L5 projects to POm cells with the same principal whisker, the L5 CT input is lower latency, which would explain how it would lengthen the duration of excitation even in the <30 ms period. Are L5 projections to both parts of POm fairly topological, and the multiwhisker POm RFs instead reflect lateral propagation in L5? Are the short latency POm responses also topological, which would impact the rules for short latency responses?
- ZI projects to all higher order nuclei but does not project to primary thalamus. Should read the cited sources.
- Retinal axons innervate ZI, and ZI projects to pulvinar. Retinal axons also innervate pulvinar. Read the source.
- The sensory responses seem long latency for monosynaptic sensory input, even the putative convergence zone cells.

Motor Cortex Gates Vibrissal Responses in a Thalamocortical Projection Pathway (Nadia Urbain and Martin Deschênes, 2007)

- Follow up to studies on thalamus gating by ZI.
- Ventral division of ZI (ZIv) is the relevant part.
- vM1 suppresses ZI whisker responses.
- Most higher order nuclei receive sensory input.
- Higher order nuclei seem inhibited normally, at least under anesthesia. No citation.
- ZIv receives SpVi.
- One study hypothesized inhibition of ZIv by cholinergic sources which increase FR during arousal. This was found to be the case, and besides reduced ZIv excitability, there was increased Po sensory responses.
- This study found that activating vM1 inhibits ZIv vibrissal responses, and it does so by activating GABAergic cells in ZIv.
- Under anesthesia, whisker-responsive ZIv cells had spontaneous FRs of 10 hz average. They were time related to EEG waves in barrel cortex, which were .5-3 hz.
- All ZIv cells had multiwhisker RFs, 3-19 average 10.
- Whisker deflection evoked short latency ZIv firing 1-3 APs. Overall average 5.5 ms and for shortest latency response for dominant whiskers, 4.2 ms. (Spike times). Then, often followed 6-15 ms later by a single spike or 2-5 AP burst.
- After silencing vS1, ZIv spontaneous activity strongly decreased, the short latency response was unaffected, and the second response was removed for some and diminished

average number of spikes for others. That second peak in spikes/bin slowly regrew as silencing diminished.

- I wonder if the remaining reduced second response is from inputs from elsewhere, since they only silenced barrel cortex, or perhaps because of incomplete silencing.
- Further surround whiskers evoked smaller amplitude (spikes/bin PSTH) /longer latency responses. This is a minor effect for latency, increasing ~linearly from 5 to 6 ms for PW to 4th order SW. Magnitude drops off a lot from PW to 1st order then a bit more from 1st to 2nd, then is basically the same from 2nd to 4th.
- SpVi have a lot of selectivity for deflection direction. ZIv was found in this study to have much lower selectivity, although some. Each whisker in the RF had similar prefered direction. This suggests converging input.
- ZI receives SpVi and PrV according to another study, but PrV lesion didn't have an impact on ZIv and some other details support PrV not being an input. SpVi lesion eliminated whisker responses but other responses on the head e.g. to nose remained. SpVi likely has multiwhisker responses, I think, based on VPMvl losing multiwhisker RFs.
- ZIv and Po receive rostal SpVi whereas VPMvl receives caudal SpVi.
- Cingulate cortex projects to ZId. Somatosensory and motor cortices project to both ZId and ZIv.
- ZI is next to the subthalamic nucleus but not part of it.
- Injected tracer in somatosensory and motor cortex, and found that projections to ZI are always from L5b. Denser in motor cortex. In S1 and S2, most but not all cells were in septal S1 columns.
- vM1 projection overlaps with both the distribution of whisker-responsive ZIv cells and the distribution of ZIv cells which project to Po.
- Somatosensory cortex projects to SpVi, which is sensory. Maybe the assumption that somatosensory corticotrigeminal projections are motor is wrong. If sensory cortical regions produce no motor outputs (instead e.g. helping tuning), maybe motor cortical outputs actually do the same, enhancing responses for behavior e.g. better tuning curves for spinal cord cells to behavioral signals, and the real motor output is corticostriatal.
- S1 + S2 lesion (maybe along with other parietal areas included) reduced ZIv spontaneous activity. <1 hz vs 10 hz. But still had robust vibrissal responses.
- Motor cortex activation evoked excitation with different magnitude/consistency based on location in ZIv. The strongest responses were in the vibrissal-insensitive motor subsector of ZIv. 55% responded with latency 5 ms a barrage of 4-7 APs. The barrage duration lasted up to 25 ms. So that's high burst frequency.
- Whereas in vibrissal-sensitive units, either no spike response or most often a single AP. When those were caused to fire by injection, firing was suppressed by three shocks to motor cortex. Same applied when whisker was stimulated rather than current applied.

- The magnitude of suppression by motor cortex of a given ZIv cell depended a lot of stimulus parameters, i.e. the magnitude and site of motor cortex shock, as well as which whisker was stimulated, in what direction, what amplitude, and what velocity. Usually only achieved complete suppression with low amplitude deflection.
- High velocity deflection (which they used) evokes a burst in SpVi cells. SpVi cells form multiple strong somatic/proximal synapses on ZIv cells. So it would require stronger inhibition than seems possible by motor cortex to eliminate the response to high velocity deflection.
- When used low velocity deflection (or more specifically, vibration), motor cortex shock produced a complete silencing of the response.
- Two possible sources of the inhibition of ZIv by receiving from motor cortex are within ZI itself or anterior pretectal nucleus (APT).
- APT complete lesion left the inhibition by motor cortex intact for 21/24 cells.
- Reconstructed ZId and ZIv cell axons (sample sizes 28 and 17 respectively.)
- Every ZI cell projected to thalamus, APT, SC, and/or other brain regions, and all projected to at least two.
- All labeled cells were targeted by other cells in ZI itself.
- Most collaterals from ZId cells were restricted to ZId, and the innervations in ZIv had few boutons. Whereas all ZIv cells had boutons in both ZIv and ZId.
- In the reconstructed ZIv cell example, it projects to a large area of PO or around it, 1 mm long and not thin.
- No reconstructed cells limited their projections to ZI.
- Since most or all ZI cells are GABAergic, the results suggest lateral inhibition.
- GABA antagonist applied to ZI caused spontaneous firing 52 hz. Cortical stimulation also no longer was able to inhibit ZI spontaneous activity. Instead, motor cortical stimulation evoked large long lasting excitation (on the scale of 50 ms). The duration and PSTH (but different directions of change) is similar to the duration of normal inhibition, almost exactly the same.
- ZIv has a motor, somatosensory, auditory, and visual sector.
- The reconstructed cells had large dendritic arbours (~800 um wide), which supports the idea of wide/dense lateral inhibition.
- During object palpitation, like humans with fingertips, strategy of minimum impact. Whereas instead whisk to navigate and locate objects. I wonder if motor cortex can't completely suppress ZIv for large deflections because those are for localizing things, and motor cortex is in the where pathway. Maybe during object palpitation, lower amplitude -> less motor cortex cell activity -> POm is more inhibited, cutting off the where pathway.
- Hypothetically for motor-based disinhibition of POm, because low amplitude deflections are blocked which is an issue for object palpitation, the signals to ZIv should be time

locked to sensory input caused by whisker movement motor commands that control fine movements.
- Maybe in the exploratory mode (whisking), the inhibition of low amplitude deflections cuts off the what pathway.
- Maybe when a whisker movement command occurs, it activates ZIv cells which e.g. correspond topographically (or in a different coordinate frame) to cut off POm for the broad results of that movement, and the smaller variations from contact are thereby emphasized.
- Because of multiple outputs from activating cortex, the results are not complete proof of the disinhibitory pathway from MC to ZIv to Po.
- Since other regions project to ZI, I'm not convinced this circuit is specifically for sensorimotor integration. If the mechanism of disinhibition is entirely lateral inhibition, the other sources of input would have the same influence. For example, since the dendritic/axonal arbors of ZI cells are so large, maybe it controls the level of activity of thalamus for a particular modality, by sensory input and cortical activity level, like lateral competition between modalities.

Rapid Arrival and Integration of Ascending Sensory Information in Layer 1 Nonpyramidal Neurons and Tuft Dendrites of Layer 5 Pyramidal Neurons of the Neocortex (Yinghua Zhu and J. Julius Zhu, 2004)

- Recorded nonpyramidal L1 cells and the apical dendrites on L5 cells in L1/2.
- Deflection seems to be single whisker.
- Neurons in L1 and apical dendrites + somata of L5 cells respond to 6-15 whiskers robustly. For principal whisker, latency can be 5 ms in both L1 cells and L5 apical.
- The L5 cell apical response is ~1 ms less than the somatic response, for primary (principal?) whiskers.
- Broadly, L2-6 RFs have a principal whisker, and 50% of that response to primary surround whiskers and 25% for secondary. Altho probably different for L5 TT.
- The L1 cells are divided into local circuit and deeper layer projecting. (LCNs and DLPNs).
- For L1 cells and L5 apical, response latency is longer for surround whiskers.
- DLPNs have smaller RFs than LCNs and shorter latency for principal whisker.
- Rat rectal body temperature is 37 degrees.
- Deflections were small. Based on some math <1 degree, maybe much less.
- Studies suggest CNS cell development intrinsic membrane properties takes between P28 and P42.
- Not going to take notes on L1 cells mostly.

- The L1 cells responded to a primary whisker (should use that term incase not topographically aligned) with shortest latency and largest EPSP. So maybe the latency difference is EPSP magnitude.
- Other studies found an L4 EPSP latency of 5-8 ms, so the L1 latencies are too short to be from L4. But if translaminar signalling (of EPSP initiation =/= spiking) doesn't take much time, I'm not convinced, although there might be added latency for L4 spiking.
- L1 cell latency for 1st order surround is ~9 ms and ~13 ms for 2nd order.
- N = 7 for L5 soma and same for apical.
- The tuft was more depolarized than the soma. -55 mV versus -66 mV. That seems like way too large a difference. At trend level (but also useful for analyzing the sample), tuft input resistance 22 and soma 28.
- Deflection evokes a short latency EPSP then a fast IPSP then several delayed PSPs, in soma/tuft of L5. Large enough EPSPs triggered APs and slow or complex calcium-dependent tuft events. The complex tuft "APs" rise from the decay phase of the initial EPSP, suggesting they are initiated by interactions between somatic APs and tuft.
- Soma and tuft had same RFs, 9-14 whiskers. They also have EPSP amplitudes falling off for 1st/2nd order surround whiskers in similar ways. Nearly example same normalized EPSP amplitudes (normalized to PW).
- Latency for soma is 7 ms vs 6 ms for tuft, for principal whisker. For 1st order surround, both ~9 ms but tuft slightly later, and for 2nd order soma ~10 ms and tuft ~12 ms, altho these surround results aren't significant at all.
- Tuft EPSP peak amplitude latency 12 ms vs 16 ms for soma.
- The slow APs in tuft have shorter latency than the fast somatic APs. So I guess they don't result from bAPs. I'm not sure if the same applies to complex Ca2+ APs. Maybe slow Ca2+ APs are bursts, and instead maybe they just reflect tuft input.
- The complex tuft APs had the longest latency. This seems to be based on shortest latencies (so sample sizes of 4-7), which were for PW, somatic APs 14 ms, 11 ms for slow tuft APs, and 16 ms for complex tuft APs. However, the histograms support this, at least based on the times with the largest number which occurred there.
- I'm not sure how or if they determines that the apical dendrites are from L5 cells.
- Are the RFs for APs the same as for EPSPs?
- Maybe the short latency tuft responses are from VPM matrix cells.
- Maybe the higher body temperature used is why, since the tuft events are Ca2+ sensitive.
- How did they determine the slow events were Ca2+ sensitive? They could be NMDA spikes.

https://en.wikipedia.org/wiki/Medial_geniculate_nucleus

- Divided into ventral/medial/dorsal (VMGB, VMGM, VMGD)

- VMGB is auditory-only, whereas the others also receive input from non-auditory pathways.
- I will look up some abbreviations.
- Anesthetics can impact MGN cells.

https://en.wikipedia.org/wiki/Inferior_colliculus

- Some things e.g. abbreviations are from elsewhere.
- Inferior cortex is divided into 3 parts: central nucleus, dorsal cortex, and lateral cortex. ICC: IC central nucleus or CNIC: central nucleus of IC. ICD: IC dorsal cortex.
- The central nucleus is surrounded by dorsal cortex, and the 3rd part is external cortex located laterally.
- Bimodal IC cells are involved in somatosensory-auditory interaction, and receive from the somatosensory nuclei. They are involved in filtering out sounds from e.g. chewing or breathing, possibly.
- Sound location data becomes fully integrated in IC.
- IC receives from medial MGB.
- Inputs from brainstem nuclei are to ICC.
- Based on its wiki article, cochlear nuclei receive input from auditory cortex.

Drivers and modulators in the central auditory pathways (Charles C. Lee and S. Murray Sherman, 2010)

- Review focusing on drivers/modulators in audition.
- ICc is the main input to MGBv
- The IC is divided into ICc (central nucleus), ICl (lateral cortex), ICd (dorsal cortex), and ICca (caudal cortex). ICs means the shell regions, i.e. ICl/ICd/ICca.
- ICs is primarily non-tonotopic, unlike ICc.
- ICs projects to MGBd and MGBm, and the roles of these projections aren't clear.
- Some argued that the ICc -> MGBv and ICs -> MGBd/m are parallel circuits. However, studies suggest that the ICc -> MGBv synapses are driver whereas the ICs -> MGBd/m are modulator. Are they modulators in the sense of distal synapses or just because cortical input is also required? If so, is that finding because of ZI being activated by sensory input?
- MGBd/m are driven by A1 L5.
- Reasons for the claimed modulator/driver pathways:
    - ICc -> MGBv with large EPSPs, depressing synapses, iontotropic glutamatergic synapses (iGluR), dense terminals, thick axons (these are all the driver properties in the table)
    - MGBv -> A1 with all the driver properties
    - MGBd -> A2 with all the driver properties

    - L5 -> MGBd with dense terminal arbours and thick axons
    - ICl -> MGBd with all the modulator properties (small EPSPs, facilitating, iGluRs + mGluRs, sparse terminal arbors, and thin axons).
    - L6 -> MGBv with all the modulator properties.
    - L6 -> L4 with all the modulator properties
    - My goal is to find evidence that IC projects to higher order thalamus with driver properties which then projects to A1 L1/5 with a convergence zone/nonconvergence zone with different sublaminar projections, like POm.
    - What about ICca -> MGBd/m and ICl -> MGBm? Did any of the cited studies break MGB into dorsal/ventral, without a medial section, ruling out some of those possible IC -> MGB drivers?
    - Do some of the modulator pathways also have driver synapses?
- Whereas MGBv is tonotopic, MGBd/m are not tonotopic and project broadly to non-tonotopic, multimodal, and limbic areas.
- MGBd/m have been considered to serve non-information roles e.g. attention. However, both MGBv and MGBd synapse in cortical L4 with driver properties. So even tho MGBd is a high order subnucleus, it still is a driver.
- It argues that modulators in thalamus are worse at information transfer because of lower release probability/distal synapses/prolonged (and so less sensitive to frequency) metabotropic responses, and instead are for modulating excitability and controlling time/voltage-gated channels. That would sort of argue against my idea/understanding that drivers and modulators both have information bearing influences (rather than attention or even modulation based on the information e.g. involved in the temporal steps of a sensory response). As a counterargument, L6 CT cells probably don't use a rate code because of their low firing rates. Furthermore, the responses are extremely sparse but project fairly broadly (but not to every distal dendrite of a given cell), so they might send a lot of information by being highly selective.

Exploring functions for the non-lemniscal auditory thalamus (Charles C. Lee, 2015)

- Review.
- Divides MGB into MGBv/m/d.
- Further subdivisions of MGBd have been proposed.
- MGBv receives tonotopic info from ICC and projects to the tonotopic A1.
- MGBd is not tonotopic and more connected to the non-tonotopic ICd and the non-tonotopic A2.
- MGBm receives polymodal input from IC and projects to many tonotopic, non-tonotopic, association, and limbic cortices. Terminates in L1 and L6.
- A1 L5 -> MGBd -> A2. At least in cat, MGBd has subdivisions.

- MGBm is not a major L5 CT target. Projects to nearly all auditory regions, terminating primarily in L1. Whereas the other two terminate in one or just a few regions.
- So MGBm is part of the m-type. MGBd also is part, at least some of it.

Auditory thalamocortical transformation: structure and function (Jeffery A. Winer, Lee M. Miller, Charles C. Lee, and Christoph E. Schreiner, 2005)

- MGBv synapses on L5. Primarily L3/4.
- MGBd synapses on L1/2/5/6.
- MGBm primarily targets L1/6.
- Deepest ⅓ of L5 has CT cells, and smaller discontinuous patches in superficial L5. Middle L5 projects to IC. Check the sources.