Understanding variations in MGB tone responses due to TRN synaptic connectivity

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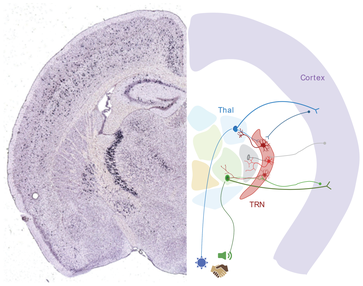
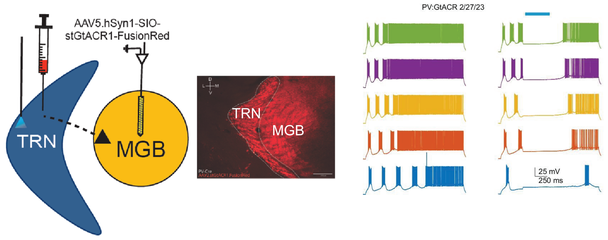
Introduction

Ascending auditory information transmits to the medial geniculate body (MGB) *en route* to the cortex. The thalamic reticular nucleus (TRN) sends feedback inhibition to thalamic nuclei and is thought to provide attentional control over sensory responses through its inhibitory signaling. Recently, molecular and circuit-specific TRN neuronal subtypes within TRN have been described[1,2], though the specific roles these distinct cell types play during sensory relay remains unknown. To explore this circuitry we optogenetically silenced specific TRN cell subtypes while recording tone-evoked responses in vivo from MGB with a silicon microelectrode array. Selective silencing of parvalbumin (PV) or somatostatin (SST) TRN cell subtypes resulted in surprisingly diverse responses: facilitation, suppression, or no change in individual MGB cell tone responses. To investigate the circuitry that may underlie variability in MGB responses, we constructed a model of two thalamic relay columns, consisting of a primary thalamic relay cell reciprocally connected to a PV TRN cell and a higher-order thalamic cell reciprocally connected to a SST TRN cell. Model cells were single-compartment Hodgkin-Huxley models. We then varied the connectivity between these columns. We found that intra-TRN lateral inhibition, or varied reciprocal feedback inhibition between TRN and thalamus, could explain the seemingly opposing effects of TRN silencing on MGB tone responses. Electrical synapses between TRN cells alone did not produce substantial changes in MGB responses, but together with chemical synapses could modulate MGB responses. These results show TRN cell subtypes can exert varying, opposing effects on tone responses of MGB and those differences may result from heterogeneity of connectivity within TRN, or through feedback connectivity across thalamic relay columns.



Methods: injections and electrophysiology

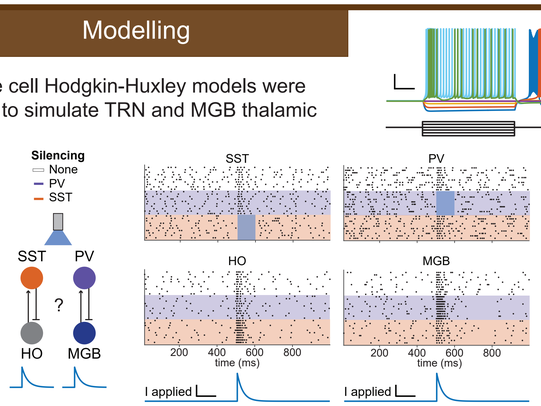


Left: Injection location for tracer and GtACR in auditory TRN. Image shows expression of viral construct in TRN and terminals in MGB.

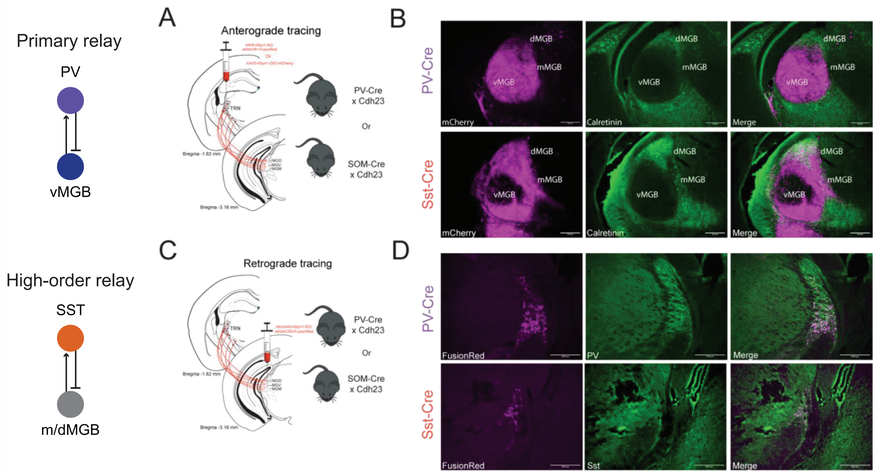
Right: validation of GtACR optogenetic silencing (blue bar) from in vitro recordings of single TRN neurons driven to spike with current injection.

Modelling

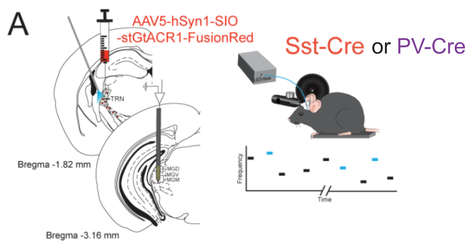
Single cell Hodgkin-Huxley models were used to simulate TRN and MGB thalamic cells.



1. Anatomical tracing of PV and SST subtype projections



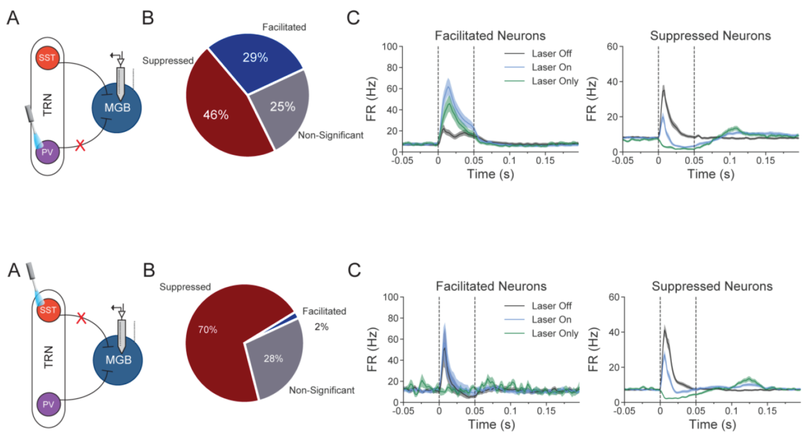
2. Alteration of MGB tone response during PV and SST subtype silencing



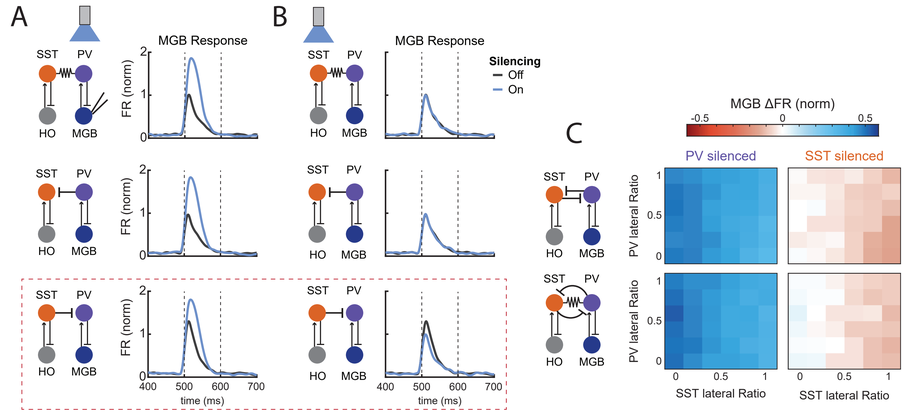
Top: Experimental strategy for in vivo recording of MGB neuron tone responses and optogenetic silencing of TRN neuron subtypes.

B: Percent of MGB neuronal tone responses that were facilitated, suppressed or unchanged by PV-specific (top) and SST-specific (bottom) TRN silencing.

C: Average responses from facilitated and suppressed groups of MGB neurons.

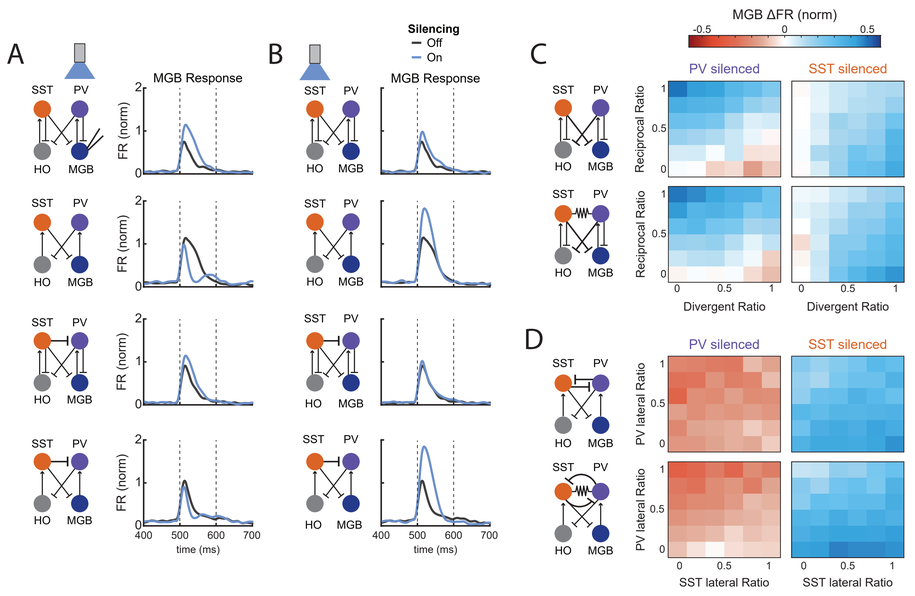


3. Effect of intra-TRN connectivity on MGB response during TRN silencing



A: MGB responses for varied types of lateral connectivity between TRN neurons, with and without PV sub- type silencing, or (B) SST silencing. C. Effect of PV of SST silencing on MGB firing rates for heterogeneous combinations of lateral inhibitory connections, with and without electrical synapses between TRN cells. The ratio of lateral synapses is the percent of trials that included lateral synapses for each TRN cell type.

4. Inhibitory divergence from TRN switches the effect of subtype silencing



A: MGB responses with varying reciprocal (within column) and divergent (across-column) connectivity from TRN to MGB, with and without PV subtype silencing, or (B) SST silencing. C. Effect of TRN cell type-specific silencing on MGB rate with heterogeneous reciprocal and divergent inhibition. Reciprocal ratio is the percent of trials that included a reciprocal TRN-MGB synapse. D. Effect of silencing on MGB rate with heterogeneous lateral inhibitory connections and solely divergent inhibitory synapses from TRN to thalamic cells.

Conclusions and references

Heterogeneity of intra-TRN and TRN-MGB connections can produce the unexpected variety of responses seen in silencing experiments:

- Modeling predicts plausible scenarios, such as SST-PV inhibition or divergent TRN-MGB inhibition, that can facilitate or suppress sensory responses.

- Circuitry from higher-order subnetworks determines sign of sensory responses

- Electrical synapses within the TRN enhance or diminish differences in sensory responses arising from chemical synaptic modulation.

1. Clemente-Perez A... Paz JT (2017) Distinct Thalamic Reticular Cell Types Differentially Modulate Normal and Pathological Cortical Rhythms. Cell Reports 19:2130–2142.
2. Martinez-Garcia RI,... Cruikshank SJ (2020) Two dynamically distinct circuits drive inhibition in the sensory thalamus. Nature 583:813–818.