Targeted Neuroplasticity Training (TNT)

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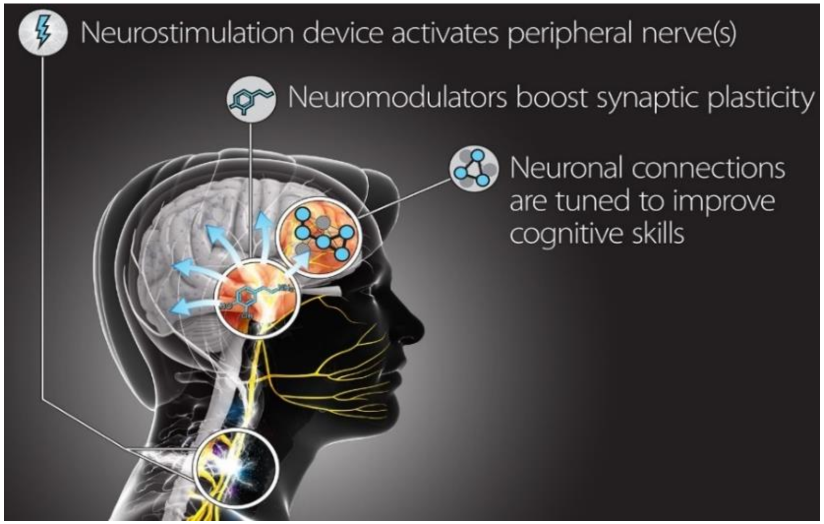
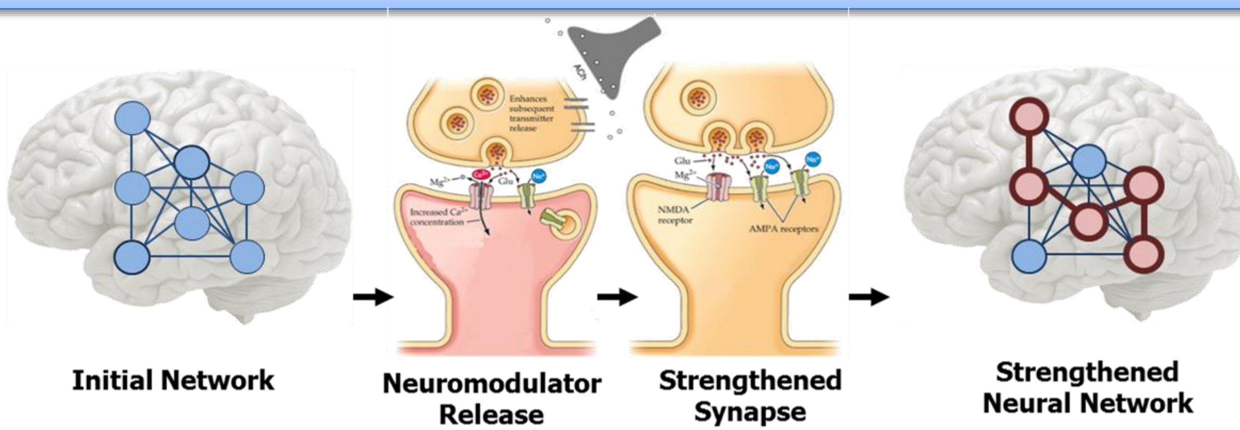
TNT uses peripheral nerve stimulation to improve cognitive skill training and performance

Peripheral Nerve Stimulation Engages Neuromodulatory Circuitry



Cognitive Training Protocols Engage Task-specific Brain Regions

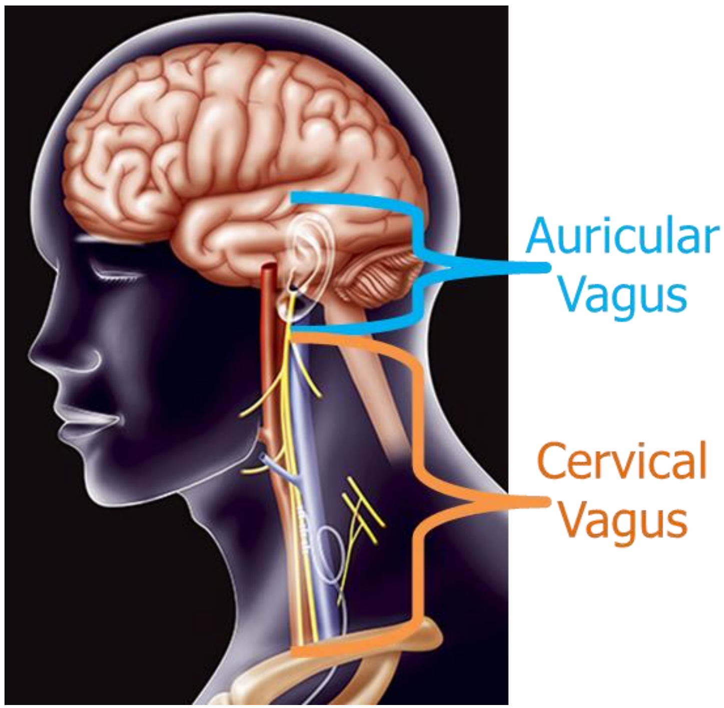
Result: Train personnel faster and improve performance

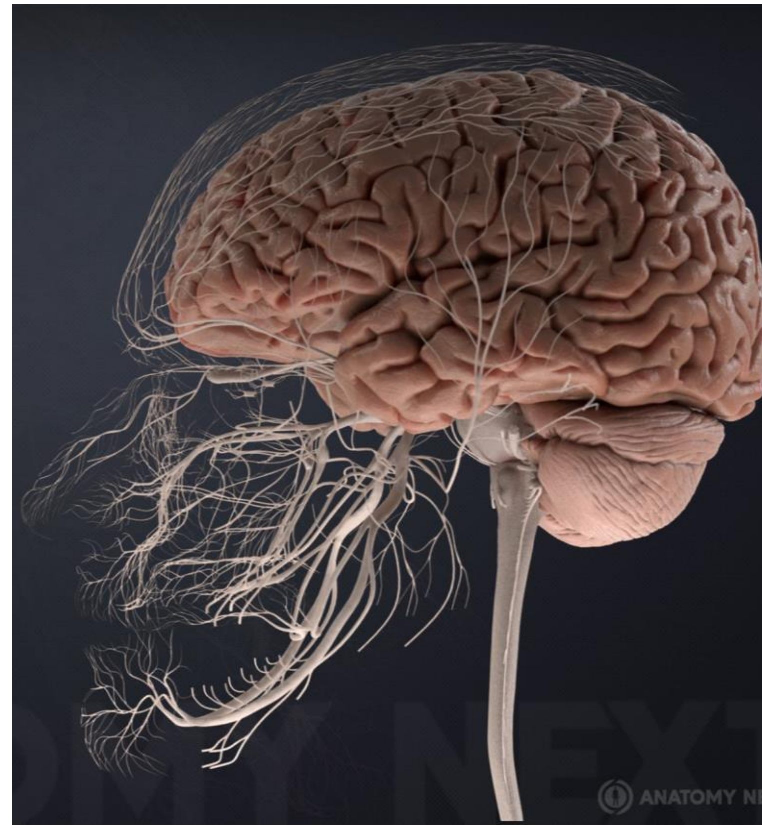


Primary Nerve Targets

Vagus

Trigeminal





Auricular vagus, cervical vagus, and trigeminal nerves are easily accessible in humans through non-invasive means

TNT Program Rationale

Biological Foundations
(Animal studies)

Parameter space
- Intensity
- Duration
- Frequency
- Timing relative to cue

Which nerve/location
- Cervical vagus
- Auricular vagus
- Trigeminal

Human Implementation
(What, where, when, and how to do it)

Non-invasive stimulation
- Cervical vagus
- Auricular vagus
- Trigeminal

Application
- Marksmanship
- Target Identification/Image analysis
- Language learning

Mechanisms
(How and why it works)

Network mapping
Nerve→Brainstem→Cortex

Fiber type: A,B, and/or C

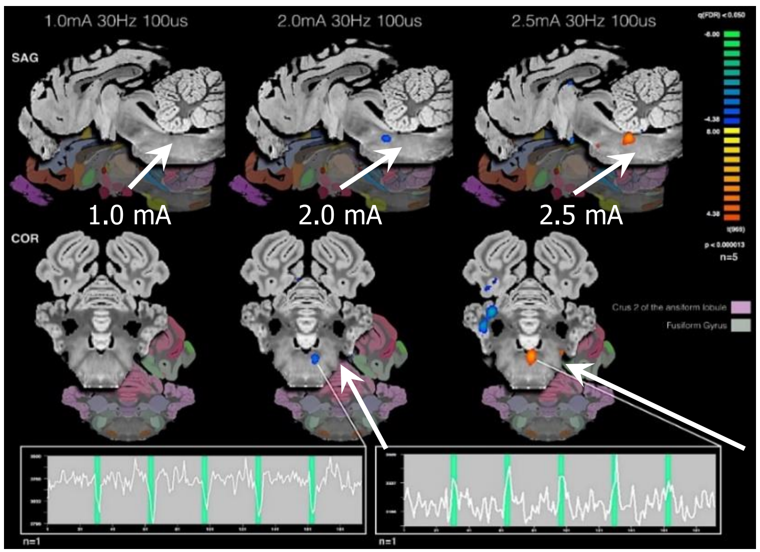
Neuromodulator classification
- ACh, NE, DA, Etc…

Risk Mitigation
- Positive allosteric modulators
- Minimally invasive injectrodes

Program accomplishments to date

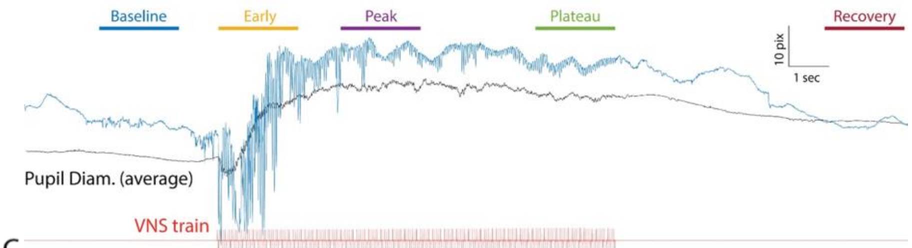
Observable responses to vagal nerve stimulation (VNS) enables noninvasive confirmation of stimulation effects and target engagement

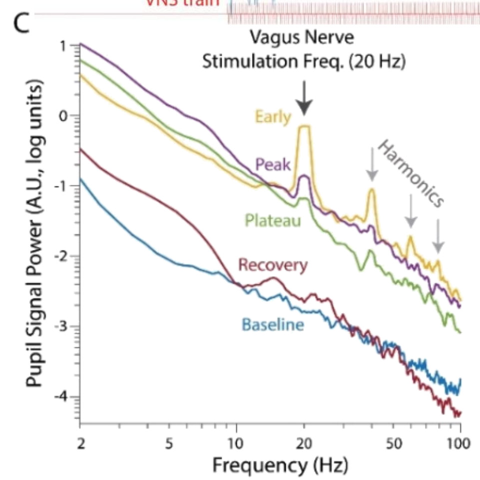
VNS activates brainstem nuclei in a stimulus dependent manner

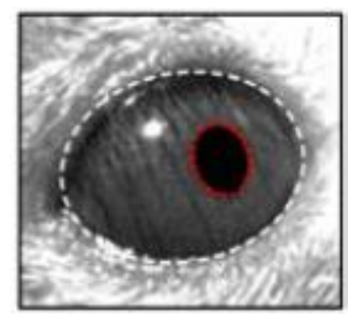


- Differential effects on brainstem activation as a function of stimulus amplitude suggests nerve fiber engagement differences

Phase-locked pupillary dilation as a positive biomarker for VNS efficacy





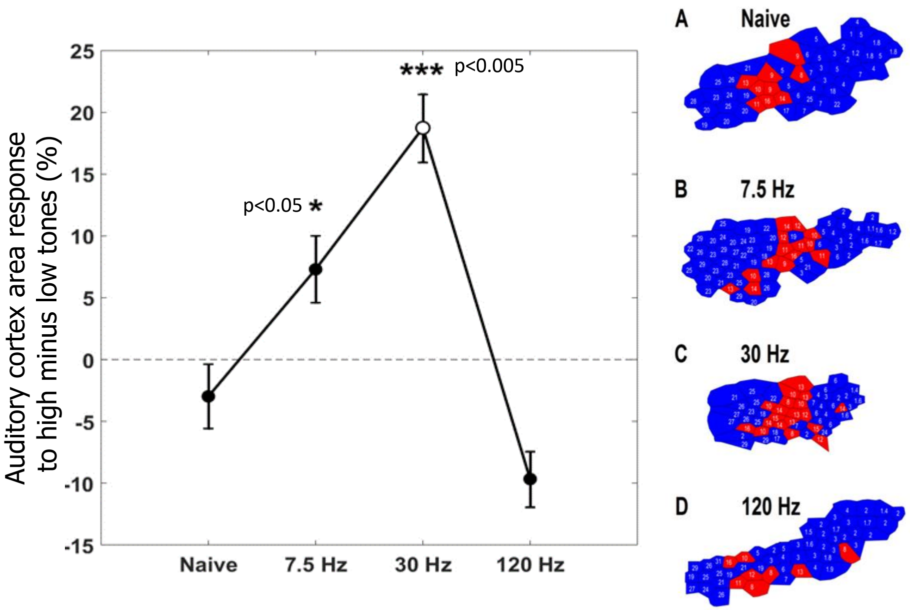


- Track pupil diameter to determine brain state and attentiveness in animal and human studies

Data indicate a dose response profile

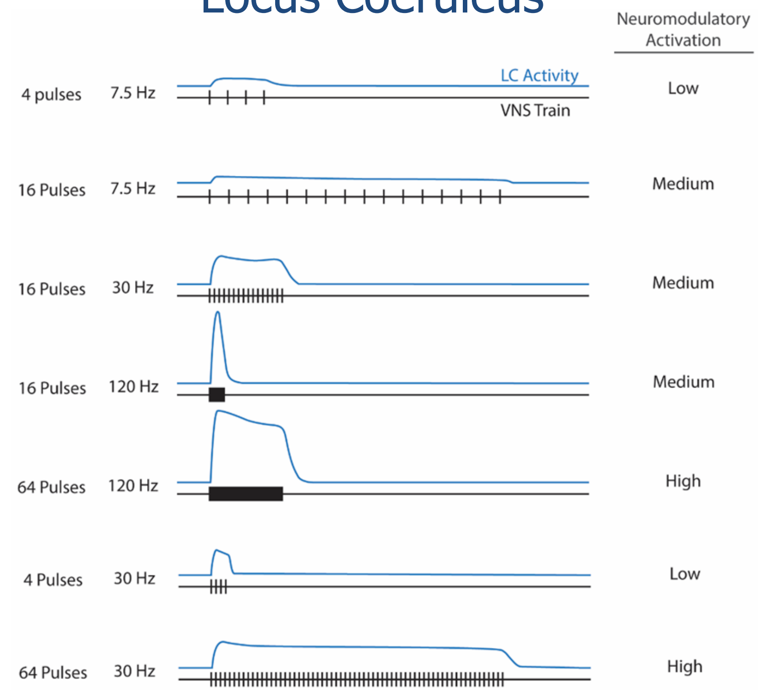
Stimulation Refinement: Determine optimal parameters for maximum effect

Map Plasticity in Auditory Cortex as a Function of Stimulation Parameters



- Frequency of vagus nerve stimulation (VNS) determines whether VNS-tone pairing drives plasticity
  - Maximum auditory cortex plasticity occurs with 30 Hz VNS
  - Maladaptive plasticity occurs with 120 Hz

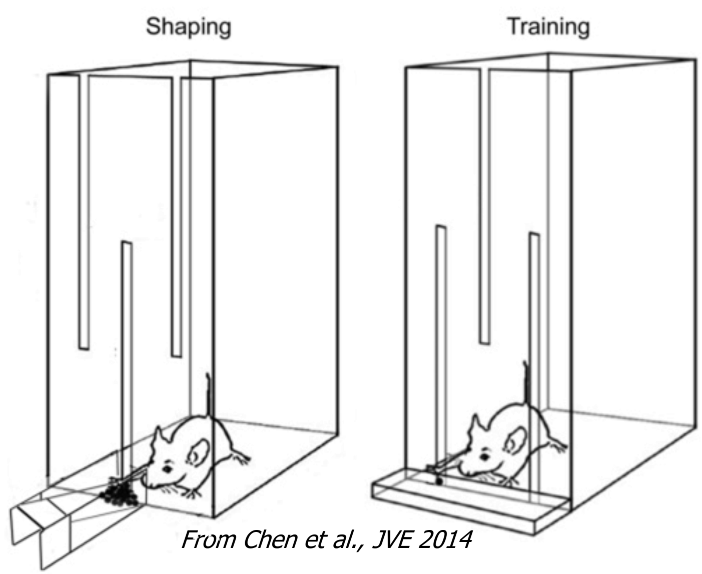
Schematic of VNS-Evoked Activity in the Locus Coeruleus



- The amount and timing of locus coeruleus spiking activity appears critical for plasticity.
  - Interaction between stimulus frequency and stimulus number influences neuromodulatory efficacy

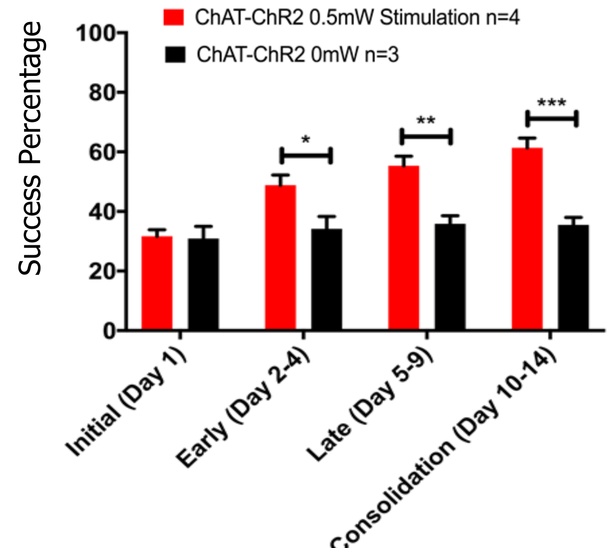
Modulation of motor skill learning via direct stimulation of basal forebrain cholinergic pathway

Basal forebrain stimulation following successful trials enhances learning of skilled forelimb reach and improves performance of established learners



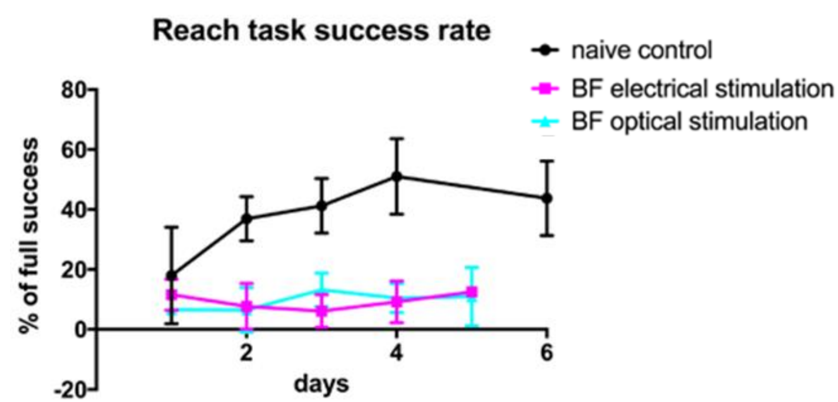
From Chen et al., JVE 2014

Analogous to human coordinated motions, such as archery or basketball, where the reach and position of the hand and arm in space are guided by multisensory integration



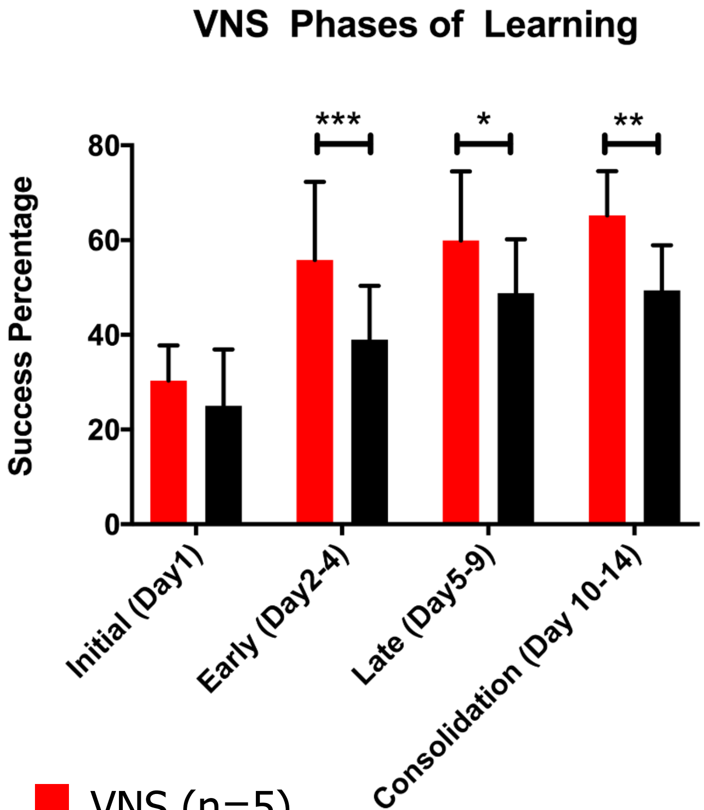
*** $p<0.0001$, ** $p< 0.001$, * $p<0.05$

- Stimulating during unsuccessful trials can impair learning!
- Suggests importance of stimulating only successful trials



VNS improves learning of new skills, as well as performance of previously learned skills

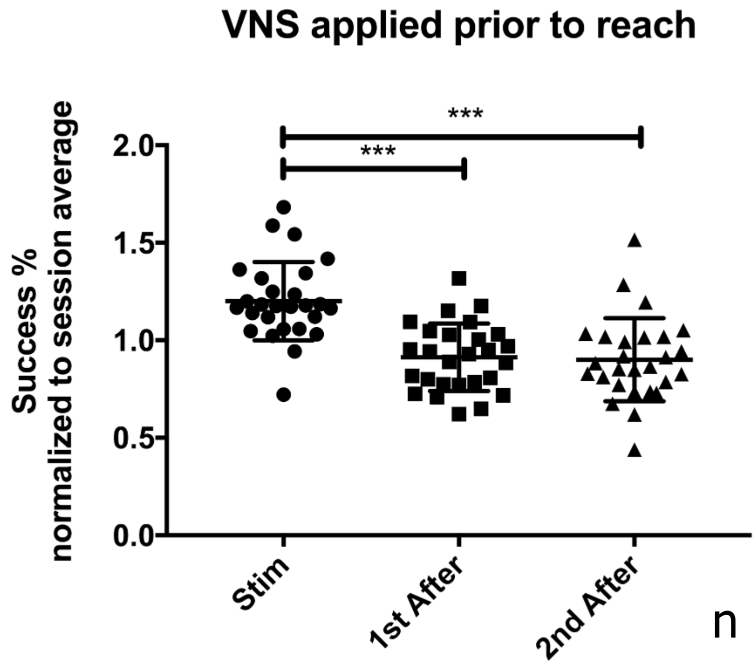
VNS improves motor skill learning



VNS (n=5)
Unimplanted Control (n=13)

*** p<0.0001, ** p< 0.001, * p<0.05

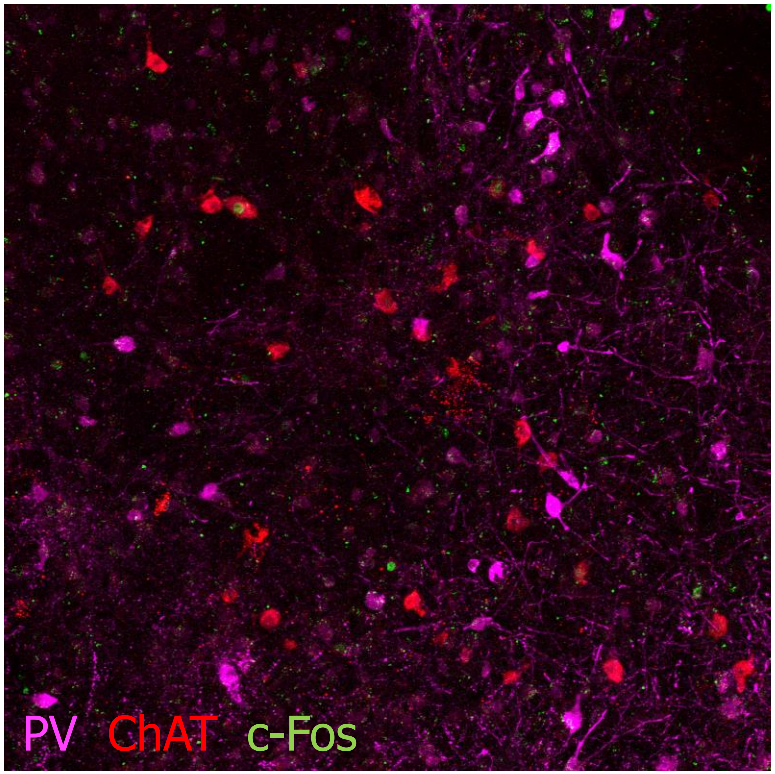
VNS improves real-time motor skill performance



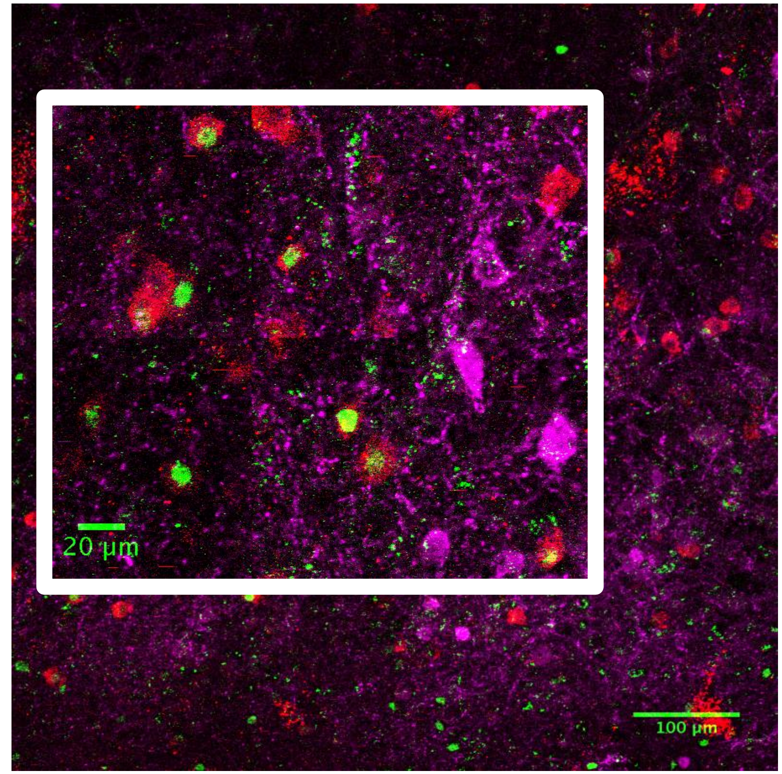
- VNS (2 sec.) on reach initiation improves performance of stimulated vs. unstimulated trials of previously learned motor skill
- Alternating stimulation trial design (stim on 1 trial, stim off 2 trials, etc.)

How does VNS affect activity of basal forebrain (BF) neuronal subtypes?

BF Surgical Sham

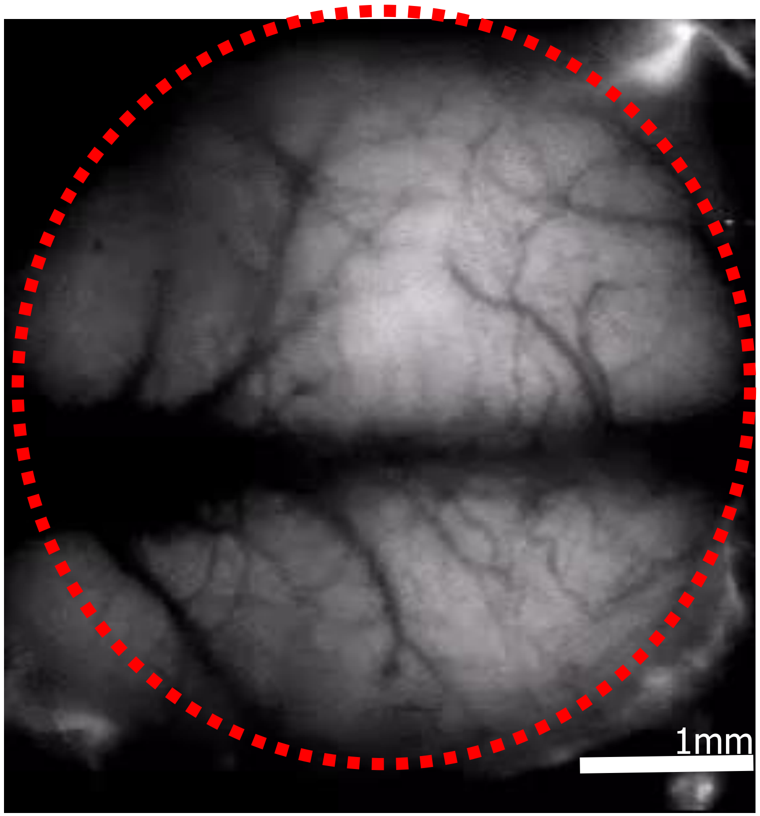


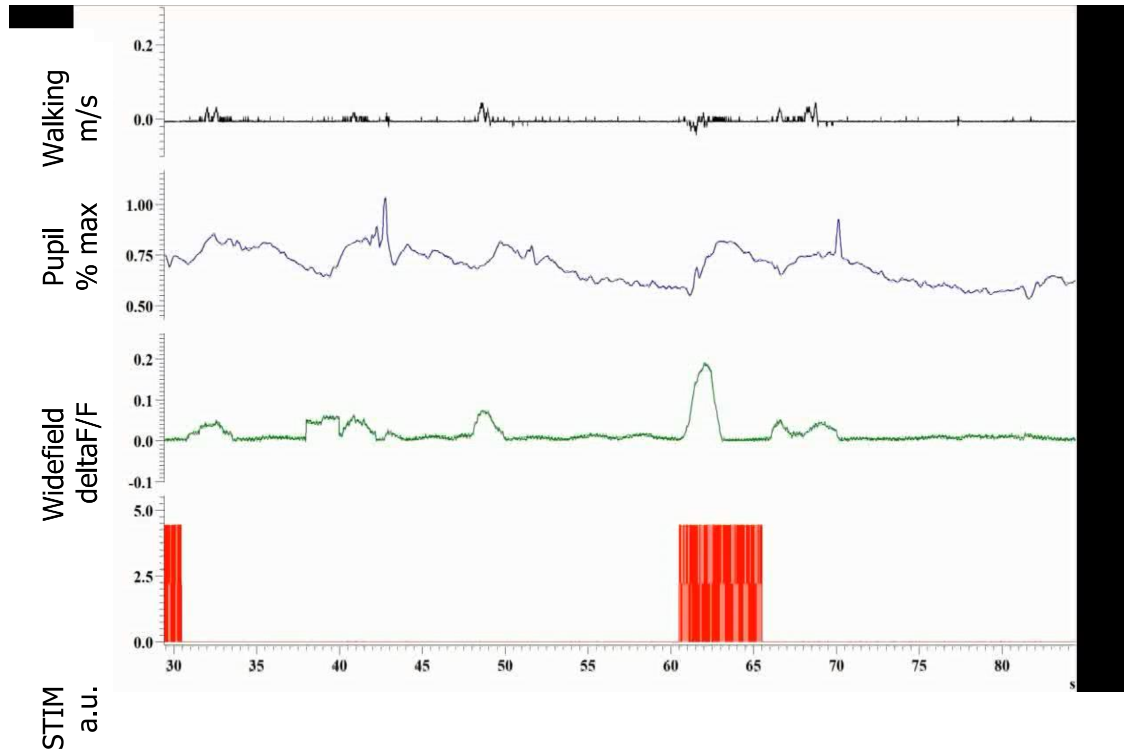
BF Acute VNS



- Acute stimulation of vagus increases neuronal activity (as indicated by c-Fos)
- Cholinergic neurons show greater VNS-activated neuronal activity, compared to Parvalbumin+ (PV) GABAergic interneurons
- Quantification of results and investigation of additional neuronal subtypes TBD

VNS Causes Pupil Dilation and Activation of Neocortex



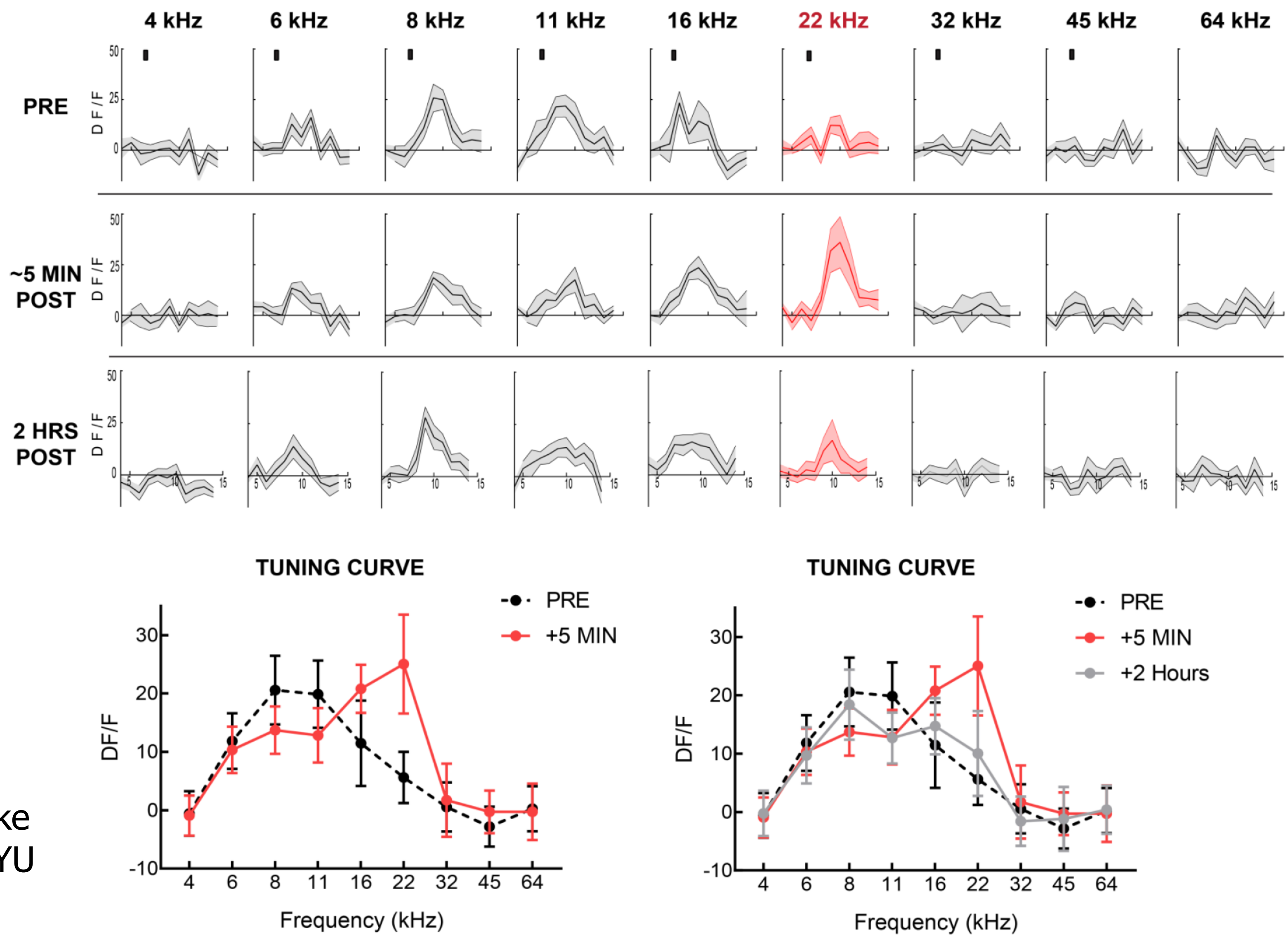


3.5x speed

Stimulation Parameters:
5 seconds, 20 Hz, 125 µA,
25 ms pulse width

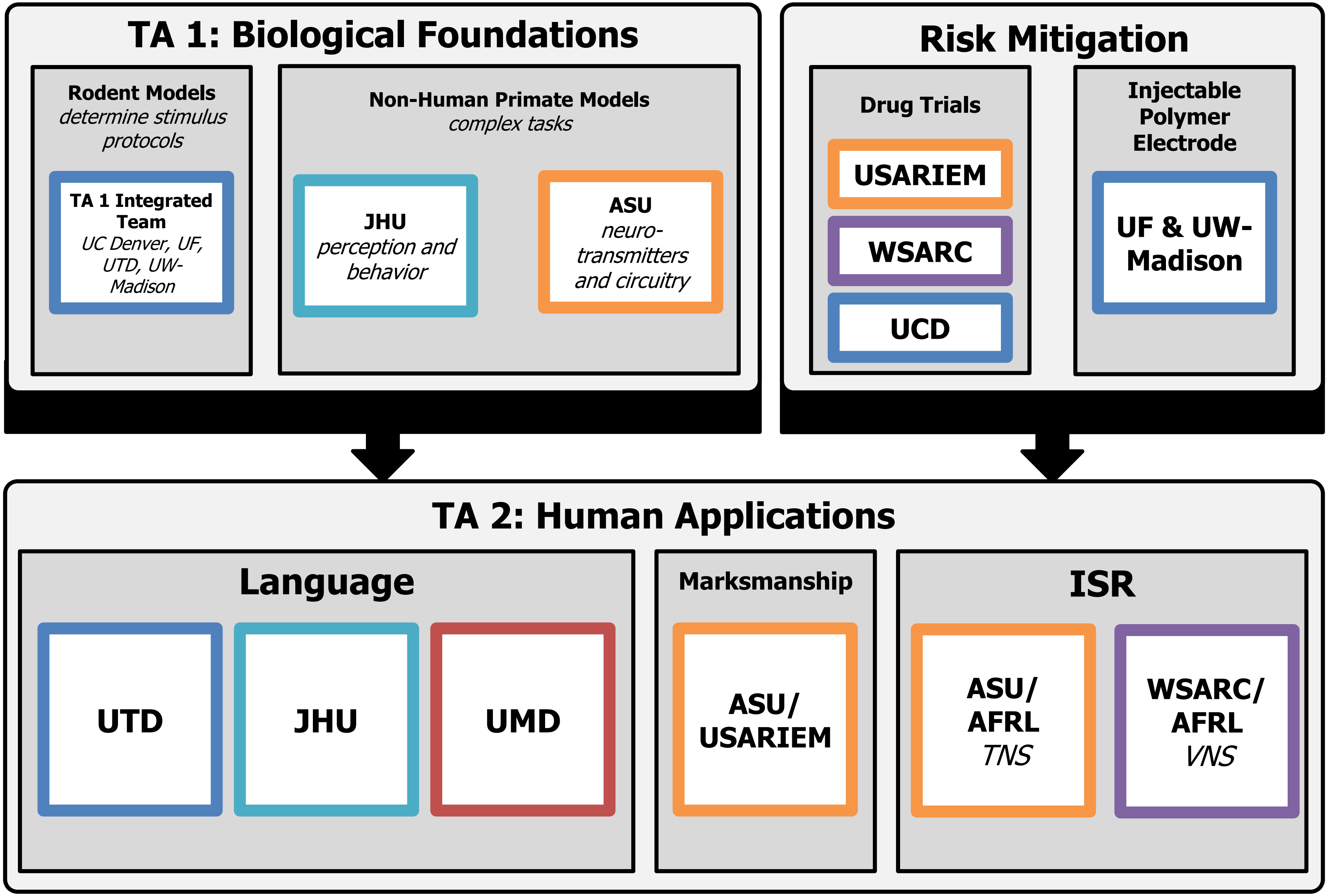
- Performed widefield imaging of cortical neuronal activity in awake mouse before, during, and after VNS. Note strong activation of restricted region of neocortex.

2-Photon Imaging of Acute Cortical Responses to VNS



Froemke Lab, NYU

TNT TA 1-2 Performers



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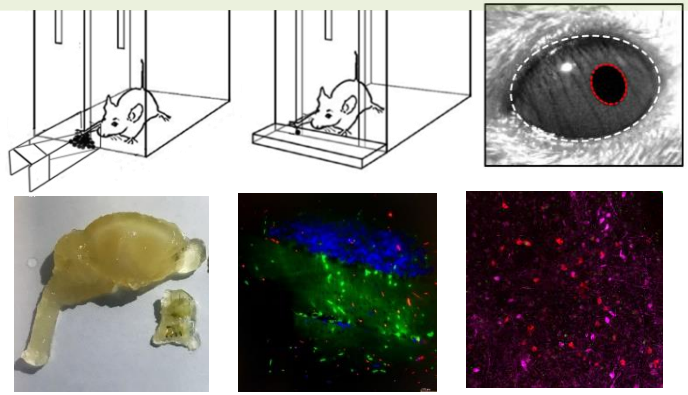
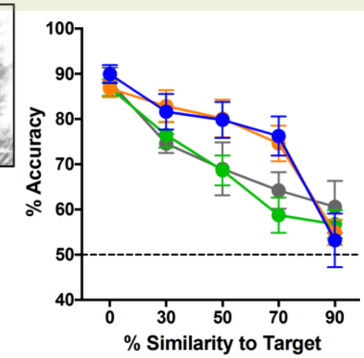
TNT Technical Areas and Schedule

TA1: Biological Foundations

Objective: Perform hypothesis-driven research to measure and demonstrate effects of peripheral neurostimulation in promoting plasticity, and assess quantitative changes in neurophysiology and behavior





TA 2: Human Applications

Objective: Develop, demonstrate, and validate cognitive-skill training applications for humans that leverage peripheral neurostimulation to promote synaptic plasticity

Risk Mitigation: Minimally-invasive electrodes and drug trials