

Mechanism of Action: Essential Tremor Relief with Peripheral Non-invasive Neuromodulation

Essential Tremor is caused by pathologic oscillatory firing patterns in the thalamus. Essential tremor is one of the most common neurological movement disorders in adults and is characterized by upper limb action tremor typically in the 4-12 Hz range.¹ These tremors occur with voluntary movement and may progressively worsen over time. Although the biomolecular disease etiology remains unknown, there is general consensus that essential tremor results from pathological oscillatory activity within the **Cortico-ponto-cerebello-thalamo-cortical network** (Figure 1).²⁻⁴ Studies⁵⁻⁶ have identified the **ventral intermediate nucleus of the thalamus (VIM)**, which plays a critical role in controlling the flow of information from the cerebellum to

the motor and sensory cortices, a key target within this network for controlling tremor. Researchers posit that loss of cerebellar input to the VIM leads to pathological oscillations in the cortico-thalamic regions, which underlies the tremor.

The two neuromodulation approaches cleared by the Food and Drug Administration (FDA) for the treatment of essential tremor both target the VIM. Deep Brain Stimulation and Transcutaneous Afferent Patterned Stimulation are designed to override or disrupt the pathologic oscillations at the VIM, restoring the normal flow of information through the VIM to the cortices and thereby reducing tremor.

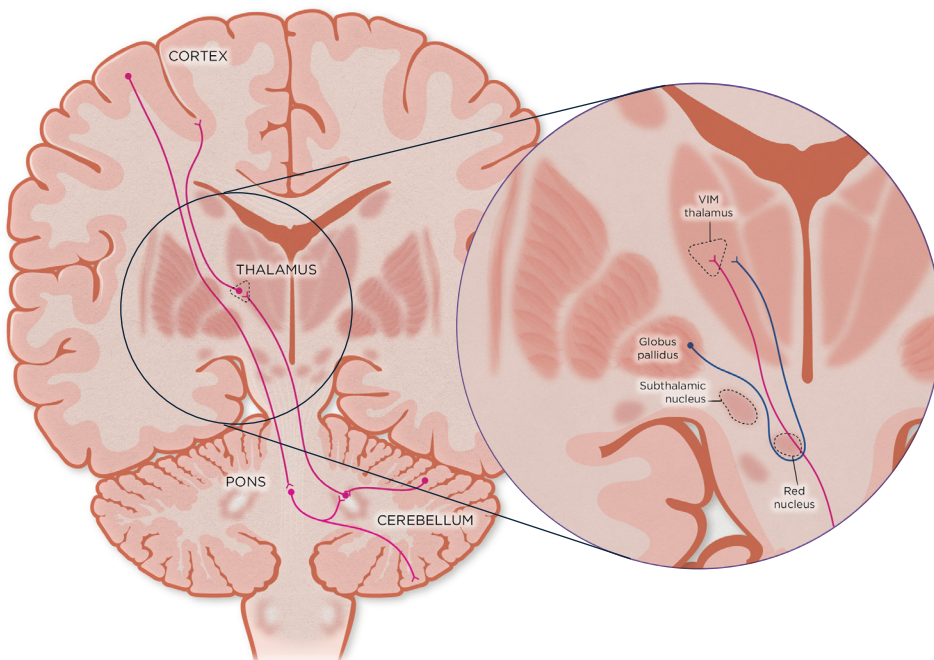


Figure 1. Presumed Pathways Involved in the Pathophysiology of Essential Tremor. The cortico-ponto-cerebello-thalamo-cortical loop (central tremor network) and the Guillain-Mollaret triangle, dentate nucleus to red nucleus to the inferior olivary nucleus to dentate nucleus (via the cerebellar cortex). **The main target for surgical treatment is the ventral intermediate (VIM) nucleus of the thalamus.** The zona incerta is the ventral continuation of the reticular nucleus of the thalamus. It gets input from the prelemniscal radiation and the thalamic fasciculus (composed of the ansa lenticularis fibers and the lenticular fasciculus fibers).

Deep Brain Stimulation (DBS) is an invasive neuromodulation therapy consisting of surgically implanted wires and electrodes that deliver high-frequency stimulation (HFS, >100 Hz) from stimulation electronics implanted in the chest wall to VIM (Figure 2). DBS is thought to provide relief from essential tremor by overriding the pathological oscillatory activity at VIM.^{5,6} VIM was the first site approved by the Food and Drug Administration for DBS (1997 and more recently was likewise the first site approved for thalamotomy by MR-guided focused ultrasound (2016). While DBS with conventional parameters is used continuously as the tremor returns immediately after turning off DBS, recent emerging research in other target areas suggests that bursting firing patterns designed to dephase the oscillations may offer extended relief after stimulation^{7,8}.

Transcutaneous afferent patterned stimulation (TAPS) is a non-invasive neuromodulation therapy consisting of a wrist-worn device with stimulation electronics for calibrating and delivering

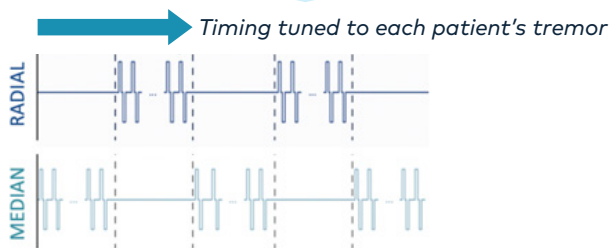
stimulation and electrodes for peripheral nerve stimulation. For essential tremor, the waveform is calibrated with patient-specific stimulation pattern designed to dephase the pathologic oscillatory activity at VIM. The frequency of oscillations at VIM is estimated by using the frequency of tremor detected on board the device, which is correlated to the frequency of bursting at VIM¹. TAPS excites the median and radial nerves which act like wires whose action potentials propagate the signal to the VIM.^{9,10} (Figure 2) TAPS was first cleared by the Food and Drug Administration for use in essential tremor in 2018.

Recent Evidence on TAPS Mechanism of Action

Lin et al.¹¹ and Pahwa et al.¹² were acute Randomized Clinical Trials on the safety and efficacy of TAPS. Mechanistically, these studies support the hypothesis that hand tremors from essential tremor can be relieved by demonstrating a significant reduction in tremor in response to TAPS that

Brain recordings have shown the frequency of hand tremor detected at the wrist is well correlated to frequency of thalamic bursting in the brain¹

Thalamic bursting can be interrupted by stimulating the median and radial nerves out-of-phase at that frequency



Tremor measurement, calibration & stimulation are all done on a wrist-worn device

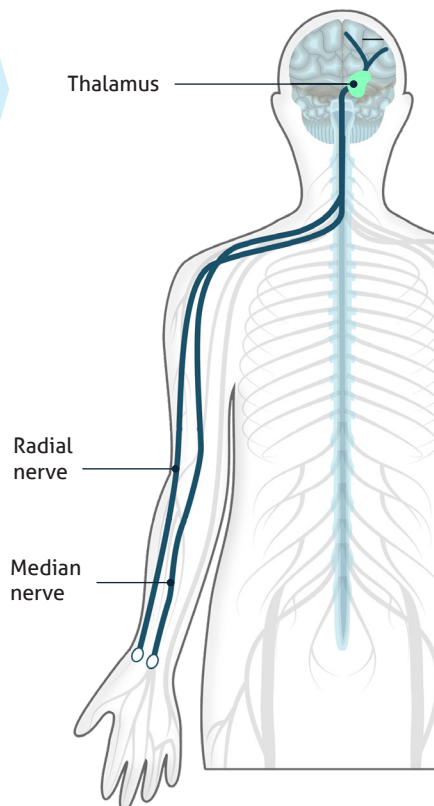


Figure 2. Deep Brain Stimulation (DBS, left) and Transcutaneous Afferent Patterned Stimulation (TAPS, right) target Ventral Inter Mediate nucleus of the thalamus (VIM).

was significantly greater than a sham.

Isaacson et al. was a 3-month study assessing the safety and efficacy of twice-daily TAPS. It was the largest study ever run in essential tremor, with 263 participants completing three months of twice-daily home use. Mechanistically, this study:¹³

- Demonstrated that TAPS is durable over repeated use on endpoints including clinical-ratings, patient-ratings, and also the 21,806 sessions of objective motion capture before and after home use sessions.
- Confirmed that tremor relief endured following therapy (94 mins on average in the 64% reporting response [standard deviation =138, median=60]), unlike traditional DBS, supporting the mechanistic hypothesis that we are modulating circuit dynamics. The duration of relief following therapy was further supported by Yu et al.¹⁴
- Demonstrated a cumulative reduction in baseline that the investigators attribute to possible neurophysiological remodeling/plasticity resulting from repeated delivery of TAPS therapy.

Barath et al. was a Positron Emission Tomography (PET) study investigating the baseline (i.e., off-stimulation) metabolic changes from 3 months of twice-daily TAPS observed in Isaacson et al. This study:¹⁵

- Demonstrated metabolic changes in the tremor network and showed encouraging correlation ($r = 0.7$) between PET and TETRAS baseline, suggesting the baseline improvement observed in PROSPECT comes from changes in neural firing patterns that are now being explored for chronic preventative dosing.

Summary & Importance to Patients

This document describes the mechanism of action and supporting evidence behind Transcutaneous Afferent Patterned Stimulation (TAPS) for essential tremor. Historically, essential tremor patients have had insufficient therapy options between the side effects from oral medications and the risks of brain surgery. —

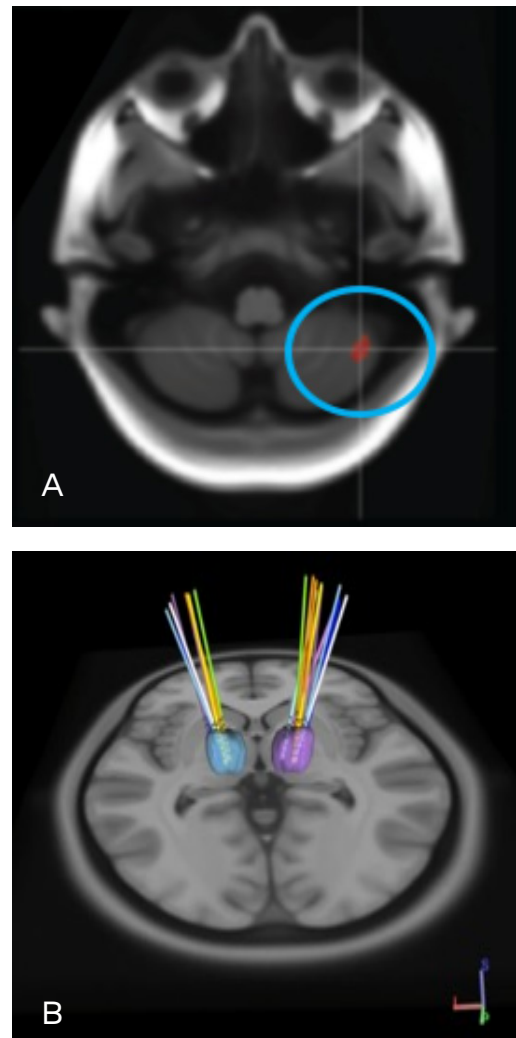


Figure 3. (A) PET imaging data from Barath et al.¹⁵; (B) Targeting for thalamic recording in Sanger et al.¹⁰

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Cala Health, Inc.
875 Mahler Road, Suite 168
Burlingame, CA 94010
888-699-1009

www.CalaHealth.com

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