Mechanism of Action Concept: Tremor Suppression with Peripheral Nerve Stimulation

ET is one of the most common movement disorders, and though the mechanisms are not fully understood, it is known that activity changes in the cerebello-thalamo-cortical loop (central tremor network) underly the disorder (Figure 1).\textsuperscript{1,2} The most effective treatment option to date is deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus (VIM), which is a key relay point within this circuit. DBS in the VIM (Figure 2) is thought to decrease tremor by functioning in effect as a thalamic filter, interrupting thalamic neuronal oscillations within the circuit with electrical stimulation and reducing hand tremor.\textsuperscript{3}

This same central tremor network is accessible via peripheral nerves that project to the VIM, including the median and radial nerves in the wrist (Figure 2). Electrical stimulation of these nerves is able to change activity in the VIM in a manner that is a representation of the bursting paradigm at the median and radial nerves in the wrist.\textsuperscript{4} It has been demonstrated that median nerve stimulation-induced changes in sensory and motor excitability are contingent upon activity in the VIM and cerebellum, suggesting that the relay through the VIM is key in this network.\textsuperscript{5} Additionally, median and radial nerve stimulation at specific stimulation frequencies has been shown to evoke very fast oscillations in the VIM, which is known to induce thalamic neuronal inhibition and interrupt pathological tremor oscillations, as related to DBS.\textsuperscript{6,7}
Previous studies have demonstrated the effective use of electrical stimulation of the median and radial nerves for the control of hand tremor. Based on the above described physiology, it is thought that this effect is caused by engagement and activation of sensory nerves that project through the median and radial nerves (Figure 2). Based on these observations, the wrist-worn Cala Therapy is designed to stimulate the median and radial nerve system that non-invasively targets the central tremor network and interrupting the tremulous signal via the VIM. This device has demonstrated that frequency-dependent stimulation of the median and radial nerves can temporarily yet significantly reduce symptomatic hand tremor in patients with ET.

**Figure 2** Schematic of Deep Brain Stimulation implanted pulse generator and stimulation lead (left) and Cala bioelectronic circuit therapy via ventral intermediate nucleus of the thalamus (VIM).
References