Noninvasive Neuromodulation in Essential Tremor Demonstrates Relief in a Sham-Controlled Pilot Trial

Although the precise mechanisms are uncertain, essential tremor (ET) is thought to be caused by tremulous activity within a central tremor neural network, which involves the ventral intermediate nucleus (VIM) of the thalamus.[1,2] Clinical evidence supports targeting the VIM to treat tremor symptoms in ET with various methods.[2] Previous studies have shown that electrical median nerve stimulation evokes activity within the VIM and other regions of the central tremor network.[3] Based on these reports, we hypothesized that median and radial nerve stimulation at the wrist could reduce hand tremor. The objective of this study was to evaluate the efficacy of median and radial nerve stimulation as a noninvasive, nonpharmacological treatment to aid in the symptomatic relief of hand tremor in individuals with ET.

Twenty-three blinded subjects were examined at a single site under an institutional review board-approved protocol (Fig. S1, Table S1). Subjects were randomized to treatment or sham groups. For stimulation, hydrogel electrodes were positioned on the wrist over the median and radial nerves (Fig. 1A; see Supporting Information). Efficacy was measured as the change in the Tremor Research Group's Essential Tremor Rating Assessment Scale (TETRAS) Archimedes spiral drawing task following stimulation compared with prestimulation (Fig. 1B,C).[4] The response in the treatment group was significant compared with both baseline and sham. In the treatment group, blinded rater scores significantly improved following stimulation (1.77 ± 0.21) compared with prestimulation (2.77 ± 0.22; $P = 0.01$; Fig. 1D). This response was achieved without the risks of surgical or pharmacological intervention, such as the risk of hemorrhage or infection with DBS implantation,[5] or side effects of ET medications, including the first-line therapies propranolol and primidone.[6] In the sham group, scores did not change significantly following stimulation (2.37 ± 0.22) compared with prestimulation (2.62 ± 0.14; $P = 0.37$; Fig. 1E). The response to treatment corresponded to an estimated hand tremor amplitude reduction of 60% ± 8.4% and was significantly greater in the treatment than in the sham group ($P = 0.02$; Fig. 1F). Three subjects experienced transient redness and/or itchiness under the hydrogel electrodes that resolved without intervention. No unanticipated device effects occurred during the study.

This was a pilot study with too few subjects for subanalyses of the effects of age, medication status, or medical history. Future studies should expand the subject count, investigate the response rate, repeatability, durability, and effects of chronic use, and add assessments of quality of life. This therapeutic approach was inspired by the idea that peripheral stimulation evokes central activity in brain regions such as the VIM, a thalamic target widely accepted to improve tremor with DBS.[5] Although our data support this idea, other potential mechanisms are possible, including circuitry modulated in previous studies demonstrating tremor reduction by manipulation of peripheral sensory input.[7] Future studies that are able to better characterize the precise mechanism may facilitate improvements to therapy. Nonetheless, this randomized, sham-controlled pilot study suggests that noninvasive neuroperipheral therapy may offer clinically meaningful symptomatic relief from hand tremor in ET with a favorable side effect profile compared with other available therapies. ■

Peter T. Lin, MD,[1] Erika K. Ross, PhD,[2,3] Paula Chidester, MS,[2] Kathryn H. Rosenbluth, PhD,[2] Samuel R. Hamner, PhD,[2] Serena H. Wong, PhD,[2] Terence D. Sanger, MD, PhD,[4] Mark Hallett, MD,[5] Scott L. Delp, PhD[6]*

[1]*Valley Parkinson Clinic, Los Gatos, California, USA*
[2]*Cala Health, Inc., Burlingame, California, USA*
[3]*Department of Neurologic Surgery, Mayo Clinic, Rochester, Minnesota, USA*
[4]*Department of Biomedical Engineering, Biokinesiology, Child Neurology; University of Southern California, Los Angeles, California, USA*
[5]*Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA*
[6]*Department of Bioengineering, Sanford University, Stanford, California, USA*

References

1. Brittain JS, Cagnan H, Mehta AR, Saifee TA, Edwards MJ, Brown P. Distinguishing the central drive to tremor in Parkinson's disease and essential tremor. J Neurosci 2015;35(2):795-806.
2. Louis ED. Essential tremor. Lancet Neurol 2005;4(2):100-110.
3. Hanajima R, Chen R, Ashby P, et al. Very fast oscillations evoked by median nerve stimulation in the human thalamus and subthalamic nucleus. J Neurophysiol 2004;92(6):3171-3182.

*Correspondence to: Scott Delp, PhD, Department of Bioengineering, 443 Via Ortega, Stanford, CA 94305; delp@stanford.edu

Relevant conflicts of interest/financial disclosures: Erika Ross, Paula Chidester, Kathryn Rosenbluth, Samuel Hamner, and Serena Wong are all current or former employees of Cala Health, Inc. Terence Sanger and Scott Delp are consultants and scientific advisers to Cala Health, Inc. Mark Hallett is a scientific adviser to Cala Health, Inc. Peter Lin was a consultant of Cala Health, Inc. while conducting this research.

Funding agencies: Funding for this study was provided by Cala Health, Inc.

Received: 19 December 2017; **Accepted:** 19 January 2018

Published online 17 Apr 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27350

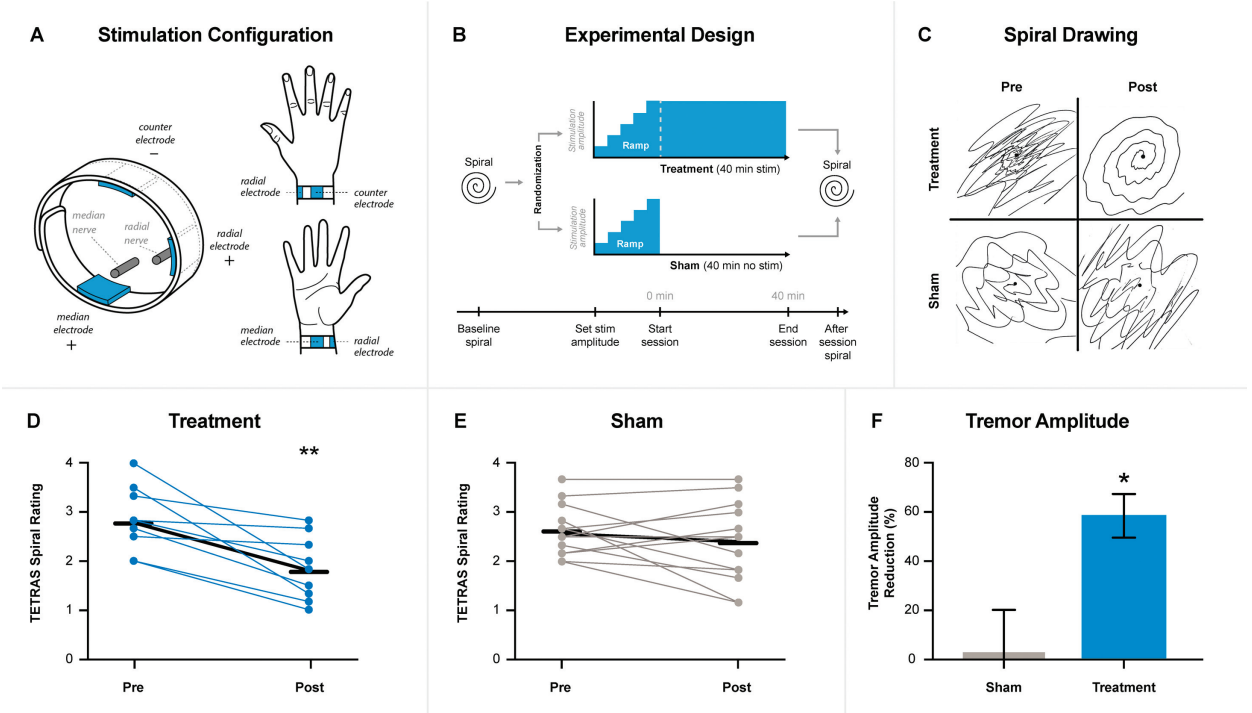

FIG. 1. (A) Electrode placement on subject's wrist to target median and radial nerves, with counterelectrode positioned on posterior surface of the wrist. (B) Spiral drawing assessments were performed before and after treatment or sham stimulation. Both groups underwent the same frequency calibration and stimulation amplitude setting. Treatment consisted of an average of a 1-minute ramp-up of stimulation followed by a 40-minute stimulation, whereas sham included an average of a 1-minute ramp-up followed by a rapid ramp-down of the stimulation. (C) Representative spirals pre- and posttreatment and sham stimulation. (D) Treatment group (n = 10) TETRAS Spiral rating scores with average rating marked with a black line for prestimulation (2.77) and poststimulation (1.77). Two subjects had the same change in rating and had overlapping points. (E) Sham group (n = 13) TETRAS Spiral rating scores with average rating marked with a black line for prestimulation (2.62) and poststimulation (2.37). (F) Tremor amplitude reduction comparison between sham and treatment following stimulation. $^{*}P \leq 0.05$; $^{**}P \leq 0.01$.

4. Elble R, Comella C, Fahn S, et al. Reliability of a new scale for essential tremor. Mov Disord 2012;27(12):1567-1569.
5. Putzke JD, Wharen RE Jr, Obwegeser AA, et al. Thalamic deep brain stimulation for essential tremor: recommendations for long-term outcome analysis. Can J Neurol Sci 2004;31(3):333-342.
6. Koller WC, Vetere-Overfield B. Acute and chronic effects of propranolol and primidone in essential tremor. Neurology 1989; 39(12):1587-1588.
7. Britton TC, Thompson PD, Day BL, Rothwell JC, Findley LJ, Marsden CD. Modulation of postural tremors at the wrist by supramaximal electrical median nerve shocks in essential tremor, Parkinson's disease and normal subjects mimicking tremor. J Neurol Neurosurg Psychiatry 1993;56(10):1085-1089.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's website.

No Evidence of Iatrogenic Human Transmission in Autopsy Confirmed Multiple System Atrophy

Converging evidence suggests that α-synuclein aggregates may share some important properties with prion proteins (including template seeding and pathogenic spreading between cells), and a potential transmission between humans has been speculated leading to intense scientific debate.[1] Despite this experimental evidence, no human-to-human transmission has ever been reported, although epidemiological studies are scarce and limited by potentially prolonged incubation periods.[2,3]

We would like to add more evidence to this controversial topic by reporting data on potential exposure to medical procedures associated with human-to-human prion-related disease transmission in a large group of neuropathology-confirmed MSA patients (n = 192) from the Queen Square Brain Bank. Inoculation of brain homogenates and insertion of surgical devices from patients with MSA, but not from patients with Parkinson's disease (PD), have been demonstrated to induce α-synuclein neurodegeneration in TgM83$^{+/-}$ transgenic mice,[4,5] so we compared the results with a group of consecutive patients with autopsy-confirmed PD (n = 125) and controls (n = 54). Formalin-fixed brain tissue samples were processed using standard protocols, and

*Corresponding author: Dr. Janice L. Holton, Queen Square Brain Bank for Neurological Disorders, UCL Institute of Neurology, 1 Wakefield Street, London, WC1N 1PJ, UK: janice.holton@ucl.ac.uk

Funding agency: This research was supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Relevant conflicts of interests/financial disclosures: Nothing to report.

Received: 2 February 2018; **Accepted:** 6 February 2018

Published online 23 Mar 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27370