Limitations

We acknowledge the limitations of this study, with its open-label treatment and retrospective analysis. However, the sustained self-reported improvements, together with partial waning of treatment at around 3 or 4 months in many patients, as well as the long-term treatment and follow-up in the majority of patients argue against placebo response being the only explanation for benefit.

Conclusions

Our data support the efficacy of BTX in the treatment of proximal tremor. Functionally meaningful improvements were observed in the majority of patients, and these results should be verified with a randomized, double-blind, placebo-controlled trial.

Legends to the Videos

Video Segment 1. This video demonstrates the position-dependent upper limb proximal tremor with internal-external rotatory component. Note that the tremor is maximal with the hands held in the nose-targeting position. The muscles injected were teres major (20 units), teres minor (20 units), pectoralis major (20 units), supraspinatus (10 units), infraspinatus (10 units), biceps (5 units). and triceps (5 units; total dose, 90 units).

Video Segment 2. This is a video clip of the same patient in video segment 1, 5 weeks after botulinum toxin injections.

References

1. Elble RJ. Tremor: clinical features, pathophysiology, and treatment. Neurol Clin 2009;27:679-695.
2. Wissel J, Masuhr F, Schelosky L, Ebersbach G, Poewe W. Quantitative assessment of botulinum toxin treatment in 43 patients with head tremor. Mov Disord 1997;12:722-726.
3. Novak I, Campbell L, Boyce M, Fung V. Botulinum toxin assessment, intervention and aftercare for cervical dystonia and other causes of hypertonia of the neck: international consensus statement. Eur J Neurol 2010;17:94-108.
4. Simpson D, Gracies J, Graham H, et al. Assessment: botulinum neurotoxin for the treatment of spasticity (an evidence-based review). Neurology 2008;70:1691-1698.
5. Brin M, Lyons K, Doucette J, et al. A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. Neurology 2001;56:1523-1528.
6. Trosch R, Pullman S. Botulinum toxin A injections for the treatment of hand tremors. Mov Disord 1994;9:601-609.
7. Jankovic J, Schwartz K, Clemence W, Aswad A, Mordaunt J. A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. Mov Disord 1996;11:250-256.
8. Van Der Walt A, Sung S, Spelman T, et al. A double-blind, randomized, controlled study of botulinum toxin type A in MS-related tremor. Neurology 2012;79:92-99.
9. Alusi SH, Worthington J, Glickman S, Bain PG. A study of tremor in multiple sclerosis. Brain 2001;124(pt 4):720-730.
10. Kitagawa M, Murata J, Kikuchi S, et al. Deep brain stimulation of subthalamic area for severe proximal tremor. Neurology 2000;55: 114-116.
11. Kim MC, Son BC, Miyagi Y, Kang JK. Vim thalamotomy for Holmes' tremor secondary to midbrain tumour. J Neurol Neurosurg Psychiatry 2002;73:453-455.
12. Krauss JK, Jankovic J. Head injury and posttraumatic movement disorders. Neurosurgery 2002;50:927-939; discussion 939–940.
13. Murata J, Kitagawa M, Uesugi H, et al. Electrical stimulation of the posterior subthalamic area for the treatment of intractable proximal tremor. J Neurosurg 2003;99:708-715.
14. Sławek J, Szymkiewicz-Rogowska A, Friedman A. Rubral tremor of Holmes, rare case of pathological tremor: case report [article in Polish]. Neurol Neurochir Pol 2000;34:775-782.
15. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. Lancet Neurol 2011;10:148-161.
16. Trompetto C, Curra A, Buccolieri A, Suppa A, Abbruzzese G, Berardelli A. Botulinum toxin changes intrafusal feedback in dystonia: a study with the tonic vibration reflex. Mov Disord 2006;21:777-782.
17. Kaji R, Rothwell JC, Katayama M, et al. Tonic vibration reflex and muscle afferent block in writer's cramp. Ann Neurol 1995;38:155-162.
18. Lapatki BG, van Dijk JP, van de Warrenburg BP, Zwarts MJ. Botulinum toxin has an increased effect when targeted toward the muscle's endplate zone: a high-density surface EMG guided study. Clin Neurophysiol 2011;122:1611-1616.

A Noninvasive Handheld Assistive Device to Accommodate Essential Tremor: A Pilot Study

Anupam Pathak, PhD,[1] John A. Redmond, PhD,[1] Michael Allen,[1] and Kelvin L. Chou, MD[2*]

[1]*Lift Labs Design, San Francisco, California, USA* [2]*Departments of Neurology and Neurosurgery, University of Michigan, Ann Arbor, Michigan, USA*

online video

ABSTRACT

Background: We explored whether a noninvasive handheld device using Active Cancellation of Tremor (ACT) technology could stabilize tremor-induced motion of a spoon in individuals with essential tremor (ET).

Methods: Fifteen ET subjects (9 men, 6 women) performed 3 tasks with the ACT device turned on and off. Tremor severity was rated with the Fahn-Tolosa-Marin Tremor Rating Scale (TRS). Subjective improvement was rated by subjects with the Clinical Global Impression Scale (CGI-S). Tremor amplitude was measured using device-embedded accelerometers in 11 subjects.

Results: TRS scores improved with ACT on (versus off) in all 3 tasks: holding (1.00 ± 0.76 vs. 0.27 ± 0.70; $P = 0.016$), eating (1.47 ± 1.06 vs. 0.13 ± 0.64; $P = 0.001$), and transferring (1.33 ± 0.82 vs. 0.27 ± 0.59; $P = 0.001$). CGI-S improved with eating and transferring, but not the holding task. Accelerometer measurements demonstrated 71% to 76% reduction in tremor with the ACT device on.

Conclusions: This noninvasive handheld ACT device can reduce tremor amplitude and severity for eating and transferring tasks in individuals with ET.

Key Words: essential tremor, treatment, noninvasive device

Essential tremor (ET) causes upper limb action tremors that may interfere with daily tasks such as eating.[1] Medications for ET are variably effective and sometimes limited by side effects.[2] Surgical treatments are effective but typically reserved for more severe tremor.[2,3] Improved therapies are needed for individuals who do not respond to medications but do not want to consider surgery.

We have developed a noninvasive handheld device using Active Cancellation of Tremor (ACT) technology to stabilize an eating utensil such as a spoon. The ACT system senses tremor direction and moves the spoon in the opposite direction to stabilize it (Supporting Fig. 1a). The device weighs about 100 g, with dimensions similar to an electric toothbrush (40 × 50 × 175 mm). Its rechargeable battery lasts for more than 90 minutes of continuous use.

In this pilot study, we explored whether the ACT device could stabilize a spoon held by ET subjects. We hypothesized that the device would steady the spoon during holding, eating, and transferring tasks.

Patients and Methods

Subjects

Consecutive subjects meeting diagnostic criteria for ET[4] with at least a "2" on the feeding or drinking item of the Fahn-Tolosa-Marin Tremor Rating Scale (TRS)[5] were recruited from the University of Michigan Movement Disorders Clinic. Subjects could have undergone deep brain stimulation (DBS) surgery, but had to meet inclusion criteria with the stimulation turned off and have their stimulation turned off for testing. The study was approved by the Institutional Review Board for Human Research at the University of Michigan.

ACT Prototype

The ACT device comprises 4 key subsystems: the spoon, the motion-generating platform, the controller/sensor, and the power supply. The spoon attaches to the motion-generating platform and can be removed, cleaned, or replaced. The motion-generating platform uses 2 DC motors connected with mechanical yokes that couple the vertical and horizontal motion of the spoon. The sensor/controller subsystem uses a triaxial accelerometer embedded in the spoon base to sense the direction of tremor in the x (horizontal) and y (vertical) directions (Supporting Fig. 1a) and directs the motors to move the spoon in the opposite direction. Power is supplied by a rechargeable battery in the handle. For this trial, the prototype was connected to data acquisition hardware (100-Hz sampling rate, 12-bit accuracy) and a laptop computer running a data acquisition program (written in LabView, version 2010; National Instruments Corporation, Austin, TX; see Supporting Fig. 1b).

Clinical Testing

Overall tremor severity was evaluated in each subject using the TRS[5] while off medication. The study involved 3 tasks (holding, eating, and transferring objects) with the ACT device using the dominant hand, except in 2 subjects whose dominant hand tremor was so severe with DBS turned off that the ACT device was ineffective. The nondominant hand was used for these 2 subjects.

For the *holding* task, subjects held the device midway between the table and their mouth. We rated tremor severity for the spoon tip, adapted from the TRS upper limb tremor item. For the *eating* task, subjects filled the spoon with foam blocks and lifted the spoon to their lips. Tremor severity rating for this task was adapted from the TRS feeding item. For the *transferring* task, subjects transferred a spoonful of foam blocks into an empty cup 75 cm away. Tremor severity rating for this task was adapted from the TRS pouring item.

Subjects performed each task at baseline with the ACT device turned off while data and ratings were recorded for 15-second durations. Subjects then performed each task with the device turned on and off, although the order was randomized. In these trials, both subject and neurologist were blinded and not told whether the device was turned on or off. After each task, subjects rated the amount of improvement using the Clinical Global Impression Scale (CGI-S). This is a 7-point scale quantifying the subject's impression of whether his or her ability to perform the task changed. Scoring was as follows: 1 = very

Additional Supporting Information may be found in the online version of this article.

*Correspondence to: Dr. Kelvin L. Chou, University of Michigan Medical School, 2301 Commonwealth Blvd., Ann Arbor, MI 48105-2945, USA; klchou@med.umich.edu

Funding agencies: This study was supported by NIH grant 5R44NS070438.

Relevant conflicts of interest/financial disclosures: Anupam Pathak is the CEO and founder of Lift Labs Design (his company is commercializing ACT technology for this device that will be released in 2013 and is funded by NIH grant 5R44NS070438) and is an inventor on two patents for Active Cancellation of Tremor Technology. John A.Redmond is a consultant for Lift Labs Design. Michael Allen is an employee of Lift Labs Design.
Full financial disclosures and author roles may be found in the online version of this article.

Received: 19 June 2013; **Revised:** 14 November 2013; **Accepted:** 26 November 2013

Published online 27 December 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.25796

TABLE 1. Baseline characteristics of the cohort

Subject	Age	Sex	Dominant hand	DBS patient	Disease duration (y)	Positive family history	Medications at time of testing	TRS feeding score	TRS drinking score	TRS total score
1	59	F	R	N	40	Y	Primidone	2	3	37
2	73	M	R	Y	32	Y	Propranolol	3	3	47
3	69	M	R	Y	10	Y	Propranolol, primidone	3	4	62
4	80	M	R	Y	65	Y	Gabapentin	3	4	69
5	61	M	R	N	50	Y	Atenolol	4	4	67
6	75	M	R	Y	17	Y	Nadolol	3	3	38
7	78	F	L	N	5	N	Primidone	3	2	36
8	66	M	L	N	15	N	Propranolol, primidone	2	3	40
9	68	F	L	N	30	N	Propranolol, topiramate	2	4	53
10	68	F	R	N	35	Y	Propranolol, primidone	3	3	55
11	68	F	R	N	45	Y	Propranolol, primidone	2	2	43
12	64	M	L	N	11	Y	Primidone	1	3	22
13	72	M	R	Y	57	Y	None	4	3	71
14	67	F	R	N	15	N	Topiramate	2	3	41
15	79	M	L	N	8	Y	Primidone, gabapentin	2	3	38
Mean (SD)	69.8 (6.3)	9 M/6 F	10 R/5 L	5 DBS	29 (19)	11 Y/4 N		2.6 (0.9)	3.1 (0.6)	47.9 (14.3)

much improved, minimal symptoms; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse, severe exacerbation of symptoms.

Signal Processing

Accelerometer data in both directions of motion cancellation (horizontal x and vertical y) were used to determine tremor motion. Acceleration data as a function of time (Supporting Fig. 2a) were postprocessed with a band-pass filter, resolving the signal into the frequency domain using Fourier transformation. The band-pass filter (first order, cutoff frequencies of 2 and 25 Hz) removed high-frequency noise. The filter also attenuated low-frequency gravitational effects, assuming that the patients' intentional motion occurred well below the 2-Hz cutoff frequency. Gravitational artifacts for more pronounced hand rotations may have contributed to error on the horizontal axes. Although this error is assumed to be small because the hand is mostly horizontal, the acceleration signals serve as estimates for the true segmental motion. The fast Fourier transform (FFT) allows the dominant frequency of vibration and magnitude of acceleration to be identified (Supporting Fig. 2b). Through double integration of the acceleration at the dominant frequency with respect to time, the amplitude of the tremor was determined. Overall magnitude of tremor motion was determined by taking the Euclidean norm of the accelerometer readings in the 2 directions of motion cancellation. The resulting accelerometer data are depicted as a waveform by plotting acceleration against time (Supporting Fig. 2a). This methodology was validated in the vertical plane of motion using a high-speed camera (120 fps) that recorded the vertical motion of the spoon. Image processing (MATLAB, version R2010a; MathWorks, Inc., Nattick, MA) yielded the vertical absolute position over time, confirming the vertical tremor amplitude determined from the accelerometer.

Using the described signal extraction method, the peak amplitude of the spoon's displacement was then recorded for each test. Although tremor frequencies can vary across a range between 2 and 15 Hz, higher tremor amplitudes correlate with lower frequencies.[6] In the example shown in Supporting Figure 2b, the peak amplitude of tremor occurred at 5 Hz.

Statistical Analysis

Changes in TRS score and CGI-S ratings for each task with the ACT device turned on and off were compared using the Mann-Whitney test. A $P < 0.05$ was considered significant. The change in TRS item for each task was calculated by taking the difference of the TRS item from the blinded tests (device turned on or off) and the baseline. For each of the 3 tasks, the percentage of tremor reduction was extracted from the postprocessed accelerometer data.

Results

Table 1 shows the baseline characteristics of the 15 subjects. Change in TRS scores significantly improved on all 3 tasks with the device turned on (Table 2). CGI-S scores improved significantly with eating and transferring, but not holding (see Supporting Video).

Eleven subjects (9 men, 2 women; mean age, 70.5 ± 5.7 years; mean disease duration, 30 ± 19 years) had accelerometer and video motion data that could be analyzed; 4 subjects had excessive signal noise discovered during postprocessing that prevented their use. Accelerometer recordings of these 11 subjects showed improvement in tremor amplitude for all tasks (Table 3; Supporting Fig. 2a), including the

TABLE 2. Clinical results with the Active Cancellation of Tremor (ACT) device turned off and on.

	ACT off		ACT on		
n = 15	Mean	SD	Mean	SD	P
Change (ΔTRS) in holding	0.27	0.70	1.00	0.76	0.016[a]
Change (ΔTRS) in eating	0.13	0.64	1.47	1.06	0.001[a]
Change (ΔTRS) in transferring	0.27	0.59	1.33	0.82	0.001[a]
Holding CGI-S	3.40	0.91	3.00	1.20	0.14
Eating CGI-S	4.00	0.66	2.13	1.41	0.000[a]
Transfer CGI-S	3.67	1.45	2.27	1.28	0.013[a]

TRS, Fahn-Tolosa-Marin Tremor Rating Scale. A positive change in TRS indicates improvement in tremor.
[a]Indicates a $P < 0.05$.

holding task. With the ACT device turned off, a strong acceleration peak at the subject's dominant tremor frequency was noticed, which was greatly reduced with the ACT device turned on (Supporting Fig. 2b).

Discussion

This small pilot study tested a noninvasive handheld device using ACT technology to stabilize a spoon held by ET subjects. The device significantly reduced spoon tremor with the eating and transferring tasks based on clinical ratings as well accelerometer data. Furthermore, subjects reported improved tremor with the eating and transferring tasks with the ACT device turned on, using the CGI-S.

Subjects and the evaluating neurologist were not told whether the device was on or off. The device prototype also does not emit a sound or cause a palpable sensation that can be detected by the user when turned on. Despite this, true blinding may have been difficult to achieve in a study like this. The potential to unblind was greatest during the eating and transferring tasks because they used foam blocks to represent food, which provided evidence of stabilization. However, with the device turned on, subjects did not notice improvement in the holding task (based on CGI-S) despite that both TRS and accelerometer measurements showed considerable improvement. This suggests that at least during this task, subjects were blinded about whether the device was on or off.

There is a clear need for this type of noninvasive device in managing tremor. Weighting the limb is a commonly recommended noninvasive way to manage limb tremor,[7] but has little evidence to support it.[8,9] Also investigated have been tremor suppression orthoses,[10-12] which function by physically forcing a person's tremor to cease.[13] Because our device stabilizes tremor while allowing the hand to shake, it has the added benefits of being comfortable and easily adopted by users.

There are other limitations to this small pilot study. Two subjects had severe tremor amplitude with DBS turned off, preventing use of our device, suggesting that the device is most suitable for mild-moderate tremors. We plan another trial to study the tremor amplitude limit at which the ACT device is no longer effective. In addition, only tremor while using a spoon was evaluated. Improvement with eating was not demonstrated, and the acceptability for long-term use remains unknown.

Our results demonstrate the effectiveness of a noninvasive handheld device using ACT technology to stabilize a spoon. The device is lightweight and compact and could potentially be outfitted with other tools, such as a fork or mascara applicators. It has great potential to help individuals accomplish tasks that would otherwise be frustrating because of tremor.

TABLE 3. Tremor amplitude reduction based on accelerometer measurements

			Tremor reduction (%)							
Subject	Tremor amplitude ACT off (cm)[a]	Tremor amplitude ACT off (cm)[a]	Combined	Holding	Eating	Transferring	Primary peak frequency ACT off (Hz)	Primary peak frequency ACT on (Hz)	Secondary peak frequency ACT off (Hz)	Secondary peak frequency ACT on (Hz)
2	1.2	0.3	70%	77%	67%	66%	5.40	5.20	—	—
3	1.6	0.2	82%	75%	90%	82%	5.90	5.30	—	—
4	2	0.6	65%	63%	65%	67%	5.60	5.50	11.45	—
5	1	0.2	78%	84%	74%	77%	5.04	5.12	10.00	—
6	1.7	0.5	70%	56%	85%	69%	5.00	5.10	—	—
8	1.9	0.4	77%	75%	79%	78%	5.87	5.60	—	—
9	0.8	0.2	80%	77%	82%	82%	5.60	5.45	—	—
10	1.7	0.6	72%	80%	74%	61%	5.40	4.80	—	—
12	1.6	0.3	77%	81%	75%	76%	5.60	5.30	—	—
13	0.5	0.2	41%	30%	50%	42%	4.20	4.40	—	—
15	1.4	0.1	89%	90%	93%	85%	5.90	5.60	12.00	—
Mean	1.4	0.35	73%	72%	76%	71%	5.41	5.22	11.15	—
Standard deviation	0.47	0.16	13%	17%	12%	12%	0.51	0.36	1.03	—

[a]Tremor amplitude is the average amplitude of the subject during the 3 tasks. Frequency data are reported for the eating task.

Legend to the Video

This video demonstrates subjects using the device during 3 tasks: holding, eating, and transferring, with the device turned off and then on.

Acknowledgments: We thank Elizabeth Sullivan for her help in coordinating the study visits.

References

1. Louis ED. Essential tremor. Handb Clin Neurol. 2011;100:433-448.
2. Deuschl G, Raethjen J, Hellriegel H, Elble R. Treatment of patients with essential tremor. Lancet Neurol. 2011;10:148-161.
3. Umemura A, Jaggi JL, Hurtig HI, et al. Deep brain stimulation for movement disorders: morbidity and mortality in 109 patients. J Neurosurg. 2003;98:779-784.
4. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord. 1998;13(Suppl 3):2-23.
5. Fahn S, Tolosa E, Marin C. Clinical Rating Scale for Tremor. In: Jankovic J, Tolosa E, eds. Parkinson's Disease and Movement Disorders. 2nd ed. Baltimore, MD: Williams & Wilkins; 1993:271-280.
6. Calzetti S, Baratti M, Gresty M, Findley L. Frequency/amplitude characteristics of postural tremor of the hands in a population of patients with bilateral essential tremor: implications for the classification and mechanism of essential tremor. J Neurol Neurosurg Psychiatry. 1987;50:561-567.
7. O'Connor RJ, Kini MU. Non-pharmacological and non-surgical interventions for tremor: a systematic review. Parkinsonism Relat Disord. 2011;17:509-515.
8. Hewer RL, Cooper R, Morgan MH. An investigation into the value of treating intention tremor by weighting the affected limb. Brain. 1972;95:579-590.
9. Morgan MH, Hewer RL, Cooper R. Application of an objective method of assessing intention tremor—a further study on the use of weights to reduce intention tremor. J Neurol Neurosurg Psychiatry. 1975;38:259-264.
10. Rocon E, Belda-Lois JM, Ruiz AF, Manto M, Moreno JC, Pons JL. Design and validation of a rehabilitation robotic exoskeleton for tremor assessment and suppression. IEEE Trans Neural Syst Rehabil Eng. 2007;15:367-378.
11. Rocon E, Manto M, Pons J, Camut S, Belda JM. Mechanical suppression of essential tremor. Cerebellum. 2007;6:73-78.
12. Rocon E, Ruiz AF, Pons JL, Belda-Lois JM, Sánchez-Lacuesta JJ. Rehabilitation robotics: a wearable exo-skeleton for tremor assessment and suppression. In: 2005 IEEE International Conference on Robotics and Automation. Barcelona, Spain; 2005:2271-2276.
13. Rocon E, Bueno L, Ceres R, Calderon L, Pons JL. Theoretical control discussion on tremor supression via biomechanical loading. In: Craddock GM, McCormack LP, Reilly RB, Knops HTP, eds. Assistive Technology—Shaping the Future. Amsterdam, The Netherlands: IOS Press; 2003:827-831.