Dysgeusia induced and resolved by focused ultrasound thalamotomy: case report

Philippe De Vloo, MD, PhD,1,2 Alexandre Boutet, MD, PhD,1,2 Gavin J. B. Elias, BA,1,4 Robert M. Gramer, BSc,1,4 Suresh E. Joel, PhD,5 Maheleth Llinas, BSc,1,4 Walter Kucharczyk, MD,3 Alfonso Fasano, MD, PhD,4,6,7 Clement Hamani, MD, PhD,8 and Andres M. Lozano, MD, PhD1,4

1Division of Neurosurgery, Department of Surgery, Toronto Western Hospital—University Health Network, 2Joint Department of Medical Imaging, and 3Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada; 4Department of Neurosurgery, University Hospitals Leuven, KU Leuven, Vlaams-Brabant, Belgium; 5Krembil Research Institute, Toronto, Ontario, Canada; 6General Electric Global Research Center, Bangalore, India; 7Edmond J. Safra Program in Parkinson’s Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, and Division of Neurology, University of Toronto, Ontario, Canada; and 8Center for Advancing Neurotechnological Innovation to Application (CRANIA), Toronto, Ontario, Canada

Dysgeusia, or distorted taste, has recently been acknowledged as a complication of thalamic ablation or thalamic deep brain stimulation as a treatment of tremor. In a unique patient, left-sided MR-guided focused ultrasound thalamotomy improved right-sided essential tremor but also induced severe dysgeusia. Although dysgeusia persisted and caused substantial weight loss, tremor slowly relapsed. Therefore, 19 months after the first procedure, the patient underwent a second focused ultrasound thalamotomy procedure, which again improved tremor but also completely resolved the dysgeusia.

On the basis of normative and patient-specific whole-brain tractography, the authors determined the relationship between the thalamotomy lesions and the medial border of the medial lemniscus—a surrogate for the solitariothalamic gustatory fibers—after the first and second focused ultrasound thalamotomy procedures. Both tractography methods suggested partial and complete disruption of the solitariothalamic gustatory fibers after the first and second thalamotomy procedures, respectively.

The tractography findings in this unique patient demonstrate that incomplete and complete disruption of a neural pathway can induce and resolve symptoms, respectively, and serve as the rationale for ablative procedures for neurological and psychiatric disorders.

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Unconscious taste perception in humans is not entirely understood, and the structures that underlie taste perception are not well mapped.1,2 However, experimental lesioning in animals, clinical observations, and functional imaging studies continue to unveil more details.3 Taste signals originate from taste receptors that are mainly clustered in taste buds on the tongue, palate, and pharynx. Primary taste perception is then transmitted through the fibers of cranial nerves VII, IX, and X, which terminate primarily in the ipsilateral pontine nucleus tractus solitarius (NTS). In primates, and presumably in humans, the NTS projects bilaterally to the ventroposteromedial nucleus pars parvicellularis (VPMpc), the thalamic taste sensory relay.2 Anatomically, the VPMpc is located inferomedially in the ventroposteromedial complex.2 Electrophysiological recordings in anesthetized and awake animals have shown that neurons in the VPMpc can reliably encode the chemical identity and temperature of gustatory stimuli, as well as tactile information from the mouth.5 The chemical and physical characteristics of gustatory stimuli are then projected from the VPMpc to the insula and parietal operculum, where there is bilateral representation of taste.3 Feedback loops from the insular...
The insula projects taste information to the orbitofrontal cortex, which is the presumed basis for limbic responses to taste (Fig. 1). Dysgeusia refers to distortion of the sense of taste, whereas hypogeusia and ageusia allude to decreased and absent taste sensation, respectively. The etiology of dysgeusia is mostly idiopathic but can also result from infectious, toxic/pharmacological, postoperative, degenerative, ischemic, or traumatic damage along the course of the gustatory pathway. Interestingly, dysgeusia has been reported as an adverse effect after both ablative procedures and deep brain stimulation (DBS) targeting the nucleus ventrointermedius of the thalamus (Vim) as a treatment of tremor. In these patients, it has been hypothesized and radiographically suggested that the volume of tissue activation or ablated tissue extends into either the VPMpc or the projections from the NTS to the VPMpc, which are thought to correspond to the medial margin of the medial lemniscus (ML).

Case Report

We present the case of a 75-year-old man who had essential tremor (ET) since his teens that affected his hands symmetrically. He was receiving propranolol, 280 mg/day, with some benefit, whereas primidone, clonazepam, and mirtazapine were ineffective. Taking into account disease severity, effect on his quality of life, his right-handedness, and his advanced age, we performed left-sided MR-guided focused ultrasound (MRgFUS) thalamotomy (x = 15.2; y = 6.4 anterior to posterior commissure [PC]; anterior commissure [AC]–PC = 26.2; z = 0; 9 sonications with peak sonication energy, power, and temperature of 7878 J, 657 W, and 60°C, respectively) (Fig. 2A). This procedure substantially reduced right-arm tremor in the first
3 months (from 5 to 0 of 12 points on right-arm Clinical Rating Scale for Tremor [CRST]–A, from 7 to 4 of 20 points on right-hand CRST-B, and from 13 to 1 of 32 points on CRST-C) (Fig. 2B and C).

However, immediately postoperatively, the patient experienced severe dysgeusia for many types of food, including meat, fish, sweets, and coffee. This dysgeusia, which he described as a “foul taste,” was present irrespective of the location of food in his mouth. It differed from tongue and lip paresthesia, which he only noticed during the first postoperative days, as well as from dysosmia-cacosmia because he reported a normal sense of smell. Over the next 18 months, taste-aversion behavior resulted in substantial weight loss (from 86 to 66 kg), despite efforts to maintain caloric intake.

Unfortunately, right-hand tremor started to recur slowly after 3 months and the patient experienced almost complete relapse by 18 months postoperatively (Fig. 2B and C). We offered the patient re-treatment on the basis of successful re-treatment of other patients with tremor recurrence after MRgFUS thalamotomy, which we and others reported at that time,7–10 with tremor recurrence being the only indication to do this.

Therefore, 19 months after the initial MRgFUS thalamotomy procedure, we performed a second left-sided MRgFUS thalamotomy procedure centered on the previous cavity and based on the imaging analysis of our MRgFUS thalamotomy series7 (x = 14.7; y = 6.6 anterior to PC; AC–PC = 26.3; z = 0; 6 sonications with peak sonication energy, power, and temperature of 11,118 J, 654 W, and 60°C) (Fig. 2A). Again, clear improvement in right-hand tremor was obtained (Fig. 2B and C), but this time the patient also had right hemibody ataxia, reduced proprioception and sense of vibration, and imbalance necessitating a wheelchair for transfers. After 4 weeks of intensive rehabilitation and 8 weeks of ambulant physical therapy, he regained the ability to walk unaided. Strikingly, he also reported that dysgeusia entirely disappeared immediately after the second MRgFUS thalamotomy pro-

![FIG. 2. Anatomical images and results of tremor assessments before and after both MRgFUS thalamotomy procedures. A: T2-weighted (top), T1-weighted (bottom left), and diffusion-weighted (bottom right) axial brain MR images after the first (9 sonications with peak sonication energy, power, and temperature of 7878 J, 657 W, and 60°C, respectively) and second (6 sonications with peak sonication energy, power, and temperature of 11,118 J, 654 W, and 60°C) MRgFUS thalamotomy procedures. B: Right-arm CRST-A (maximum 12 points), right-hand CRST-B (maximum 20), and CRST-C (maximum 32) scores. C: Spiral drawings and handwriting samples made with the right hand.](unauthenticated)
procedure. As soon as the evening after surgery, he enjoyed food that previously appalled him. At the last follow-up, 6 months after the second procedure, ET remained well controlled, and he had regained approximately 10 kg of body weight in the absence of dysgeusia.

To investigate the relationship between the thalamotomy lesions and taste disturbance, we assessed the relationships between the lesion locations and the ipsilateral ML tract. First, the thalamotomy volumes identified on immediately postoperative structural MR images were transformed into standard space (MNI-ICBM-2009c), as previously described.7 To generate the ML tract, high-resolution normative data of a large, diffusion-weighted imaging (DWI) data set were used (Human Connectome Project, www.humanconnectomeproject.org). Although native patient imaging may better reflect the underlying patient-specific connectivity, normative data offer superior spatial resolution and signal-to-noise ratio and have been shown to predict the clinical outcome in patients undergoing DBS.11 Similar to the study by Horn et al.,11 we used a normative whole-brain tractography template, computed with multishell generalized q-sampling imaging (DSI Studio, http://dsi-studio.labserver.org) and data from 985 participants in the Human Connectome Project and compromising a total of approximately 12,000,000 fiber streamlines, to visualize the ML tract (minimum fiber length = 10 mm; fractional anisotropy [FA] threshold = 0.029; step size = 0.47; turning angle = 60°). To track the ipsilateral ML, we used seeds at the level of the brainstem, within the dorsal column, and the ipsilateral thalamus.3 The seed in the dorsal column of the brainstem was manually segmented in Montreal Neurological Institute (MNI) space, while the seed in the postcentral gyrus was derived from the Harvard-Oxford cortical atlas.12 We detected 773 individual ML fibers. Then, the numbers of ML fibers impinged on by lesions from the first (34 [4%]) and second (308 [39%]) thalamotomy procedures were determined with MI-Brain (Imeka).

To validate this normative connectivity analysis, we performed a secondary analysis by using available patient-specific DWI data (3-T Sigma HDx scanner, GE Healthcare) (b = 0 images; 30 directions at b = 1000 sec/mm²; TR 11,700 msec; TE 108 msec; isotropic voxel = 2 mm). As previously described,7,11 DWI acquisition was corrected for motion, eddy currents, and b-vector rotations with FSL (FMRI; http://www.fmrib.ox.ac.uk/fsl/). The ipsilateral ML was tracked in native DWI space by using a deterministic tractography approach implemented in Mrtrix3 (http://www.brain.org.au/software/) (step size = 1 mm; minimum radius of curvature = 1 mm; FA cutoff threshold = 0.2; tracking angle = 45°). A seed was placed in the dorsal column at the level of the brainstem, and only streamlines connecting this area to the ipsilateral postcentral gyrus were included. The spatial relationship between the thalamotomy lesions and the patient-specific ML tract within native DWI space was then examined (Fig. 3E and F). Inspection of the overlap between the two MRgFUS lesions and the patient-specific bundle in DWI space yielded the same basic spatial pattern as the normative analysis. The proportion of impinged fibers and visualization of the ipsilateral ML tract suggest that the medial ML fibers (and thus the hypothesized solitariothalamic gustatory fibers) were presumably intact preoperatively, partially disrupted by the first thalamotomy procedure, and completely disrupted by the second thalamotomy procedure (Fig. 3). Furthermore, we applied computerized thalamic nuclei labels derived from the Hirai and Jones atlas in standard (MNI) space. These labels show that both the first and second lesions were localized to the border region between the ventral lateral and ventral posterior nuclei, with the second lesion extending further inferiorly into the subthalamic white matter.

The patient provided informed consent for the collection and publication of these data.

Discussion

We recently published findings on the first patient who underwent repeat MRgFUS thalamotomy procedures for tremor recurrence.14 Similarly, a second ipsilateral MRgFUS thalamotomy procedure improved tremor at the cost of transient ataxia and imbalance. Other reported surgical options for tremor recurrence after MRgFUS thalamotomy include radiofrequency thalamotomy and DBS of the same target,9 and the latter might be safer than repeated ablation.

Dysgeusia has been reported by 15%–50% of patients who underwent Vim-DBS. Risk factors include bilateral DBS and posteriorly located electrodes bordering or in the sensory thalamus.6 Although half of patients report dysgeusia when specifically asked about it, the first case of dysgeusia was reported 20 years after the introduction of Vim-DBS.13 Dysgeusia may be completely absent in large series,16 suggesting underreporting. The low reported prevalence of dysgeusia after MRgFUS thalamotomy (4%–13%) may also result from underreporting.17

Given the function of taste in recognizing decayed and toxic food, its pleasurable component, and the social role of eating, dysgeusia should be regarded as a major complication of thalamic procedures that may dramatically affect quality of life,1 despite tremor improvement, as illustrated in our patient. Although both thalamotomy procedures were performed on the left side, our patient reported bilateral taste changes. This has previously been reported after unilateral thalamic stroke,18 and again illustrates the complexity of the taste system.

Management options for dysgeusia after Vim-DBS include reprogramming, which appears to be similar to reprogramming in patients with permanent paresthesias15,19 and those who require lead repositioning.19 Based on this single patient, an experimental therapeutic option for dysgeusia after thalamotomy would be to expand thalamotomy with re-treatment, although this may cause serious adverse effects, as observed in our patient.

Because of its small volume and curved course, the gustatory pathway is not directly traceable with tractography. However, the findings of both patients treated with ablation and patients treated with DBS strongly suggest a subthalamic course adjacent to the medial margin of the ML. The subthalamic white matter.

Hence, we used the position of the medial margin of the ML as a substitute for the position of the gustatory tract in this region.6 By using this method, with its inherent limita-
FIG. 3. Diffusion tensor tractography images and projections of the MRgFUS thalamotomy lesions. Projections of the ML (blue shading), as a substitute for the subthalamic course of the solitariothalamic gustatory fibers, and the first (red shading) and second (green shading) MRgFUS thalamotomy lesions on axial (A and B) and coronal (C and D) T1-weighted MR images (MNI-ICBM-2009c template). Labels derived from the Hirai and Jones atlas in MNI space show that both the first and second lesions were localized to the border region between the ventral lateral (pink) and ventral posterior (yellow) nuclei. Intact ML fibers (blue) are progressively impinged and thinned out medially by the first (C) and second (D) thalamotomy lesions, as shown with their respective colors. Individual diffusion-weighted tractography images with consistent color coding, displayed in the coronal (E) and sagittal (F) planes, confirm the results obtained with normative tractography. Figure is available in color online only.
tions, we determined that, at least in our single patient, dysgeusia was associated with a partially disrupted medial ML, and normal taste was associated with either a normal or further disrupted medial ML, presumably resulting in complete disruption or dysfunction of the taste fibers. Although the underlying mechanism remains speculative, we hypothesize that the contralosional gustatory system can only symptomatically compensate for completely muted signal transmission on the pathological side. There are analogous examples, such as central poststroke pain, 20 and conversion transmission on the pathological side. There are analogous examples, such as central poststroke pain, 

Lastly, the use of the medial border of the ML as a tractographic substitute for the solitariothalamic fibers and our inability to map the VPMpc represent important limitations. Although normative data offer superior spatial resolution and signal-to-noise ratio, this approach disregards possible individual anatomical differences. Nevertheless, individual tractography yielded similar results.

Dysgeusia appears to be a relatively prevalent adverse effect of thalamotomy, and increased anatomical knowledge of the taste pathways may reduce its prevalence and even advance surgical rescue options.

References


Disclosures

Dr. Joel is employed by General Electric, which produces imaging devices used for focused ultrasound. Dr. Lozano is the scientific director of Functional Neuromodulation; is a consultant for Medtronic, Abbott, Boston Scientific, Insightec, and the Focused Ultrasound Foundation, which promotes research into focused ultrasound; and has previously received research support from Insightec, which manufactures focused ultrasound devices. Dr. De Vloo has received funding from Research Fund-Flanders (FWO G0A513N), the European Society for Stereotactic Functional Neurosurgery (2016 research grant), and the Healers Foundation, as well as grants for education and travel from EANS, FWO, KU Leuven, Medtronic, Boston Scientific, and St. Jude–Abbott.

Author Contributions

Conception and design: De Vloo, Elias, Gramer, Lozano. Acquisition of data: De Vloo, Boutet, Elias, Gramer, Joel, Llinas, Kucharczyk. Analysis and interpretation of data: De Vloo, Boutet, Elias, Gramer, Joel, Fasano, Hamani. Drafting the article: De Vloo, Elias. Critically revising the article: Boutet, Joel, Llinas, Kucharczyk, Fasano, Hamani, Lozano. Reviewed submitted version of manuscript: Boutet, Elias, Gramer, Kucharczyk, Lozano. Approved the final version of the manuscript on behalf of all authors: De Vloo. Statistical analysis: Boutet, Elias, Joel. Administrative/technical/material support: Gramer, Joel, Llinas. Study supervision: Lozano.

Correspondence

Philippe De Vloo: KU Leuven, Vlaams-Brabant, Belgium. philippe.devlooo@kuleuven.be.

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