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Tremor and Other Hyperkinetic Movements

Reviews

Focused Ultrasound for Essential Tremor: Review of the Evidence and Discussion of Current Hurdles

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Abstract

Background: While there is no breakthrough progress in the medical treatment of essential tremor (ET), in the past decades several remarkable achievements happened in the surgical field, such as radiofrequency thalamotomy, thalamic deep brain stimulation, and gamma knife thalamotomy. The most recent advance in this area is magnetic resonance-guided focused ultrasound (MRgFUS).

Methods: The purpose of this review is to discuss the new developments and trials of MRgFUS in the treatment of ET and other tremor disorders.

Results: MRgFUS is an incisionless surgery performed without anesthesia and ionizing radiation (no risk of cumulative dose and delayed side effects). Studies have shown the safety and effectiveness of unilateral MRgFUS-thalamotomy in the treatment of ET. It has been successfully used in a few patients with Parkinson's disease-related tremor, and in fewer patients with fragile X-associated tremor/ataxia syndrome. The safety and long-term effects of the procedure are still unclear, as temporary and permanent adverse events have been reported as well as recurrence of tremor.

Discussion: MRgFUS is a promising new surgical approach with a number of unknowns and unsolved issues. It represents a valuable option particularly for patients who refused or could not be candidates for other procedures, deep brain stimulation in particular.

Keywords: Essential tremor, MRI-guided focused ultrasound, Parkinson's disease, thalamotomy, treatment, tremor

Citation: Rohani M, Fasano A. Focused ultrasound for essential tremor: review of the evidence and discussion of current hurdles. Tremor Other Hyperkinet Mov. 2017; 7. doi: 10.7916/D8Z89JN1

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Editor: Elan D. Louis, Yale University, USA

Received: March 9, 2017 **Accepted:** April 17, 2017 **Published:** May 5, 2017

Funding: A.F. has received grant support from the University of Toronto, the McLaughlin Centre, and the Michael J. Fox Foundation, none of which has been used for this work.

Financial Disclosures: A.F. has received speaking honoraria from UCB pharma, Medtronic, Boston Scientific, Abbvie, Novartis, Chiesi pharmaceutical, Ipsen, and TEVA; he is on an advisory board for Abbvie and Ipsen and provided consultancies for UCB Pharma, Medtronic, Boston Scientific, and Abbvie.

Conflict of Interest: The authors report no conflict of interest.

Ethics Statement: Not applicable for this category of article.

Introduction

Essential tremor (ET) is a common movement disorder, the most common one in the adult population. According to some studies its prevalence reaches up to 9% in people older than 60 years.[1] It usually presents as a bilateral postural 8–12 Hz tremor of the hands, followed by a kinetic and resting component too; the upper limbs are usually symmetrically involved but with disease progression the head and voice (less commonly legs, jaw, face, and trunk) may be involved too.[2]

The etiology of ET is not clearly understood probably as a result of the heterogeneity of the underlying pathological process; in fact, ET possibly represents a syndrome rather than a defined disease.[3] Accordingly, although a strong family history has been reported in many families with an autosomal dominant pattern of inheritance, no major causal gene has been identified so far.

A significant percentage of ET patients never visit a physician since the symptoms are mild and non-disturbing; but in some patients the symptoms (kinetic tremor in particular) are severe enough to interfere with daily activities and cause social embarrassment.[4] In these cases treatment is recommended.[1,5] Figure 1 depicts a possible treatment flowchart of ET: the first-line agents are propranolol, primidone, and topiramante, each of these agent should be used alone up to the

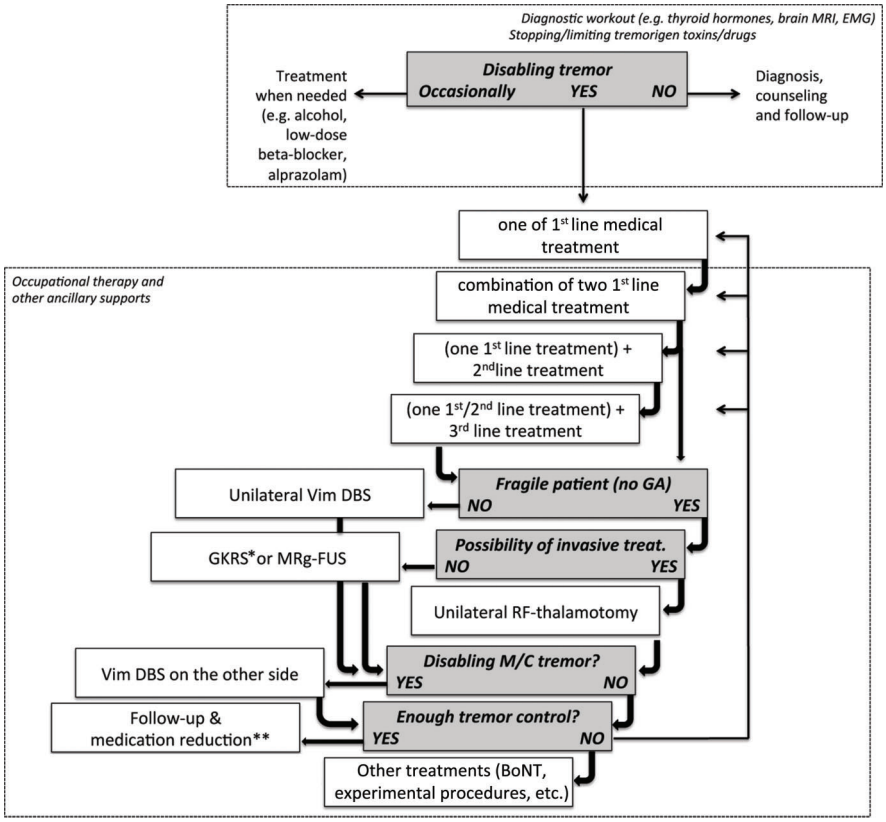

Figure 1. **A Decision Tree for the Treatment of Tremor.** In patients with a limb tremor, unilateral procedure (either DBS or ablation) may sometimes be sufficient to reduce the disability. In the case of disabling bilateral limb, head, voice, or trunk tremors, a bilateral procedure is necessary. As bilateral thalamotomies carry a high risk of dysarthria, dysphagia or balance problems, mostly Vim-DBS is applied. Other less studied targets are the Zi, especially in its caudal part (Raprl), Vop and Voa nuclei of the thalamus (modified from ref. 75). BoNT, Botulinum Neurotoxin; DBS, Deep Brain Stimulation; EMG, Electromyogram; GA, General Anesthesia; GKRS, Gamma Knife Radiosurgery; M/C, Midline and/or Contralateral Tremor; MCS, Motor Cortex Stimulation; MRgFUS, MRI-guided Focused Ultrasound (of Vim); QoL, Quality of Life; Raprl, Prelemniscal Radiation; RF, Radiofrequency; rTMS, Repetitive Transcranial Magnetic Stimulation; Vim, Ventrointermedius Nucleus of the Thalamus; Voa, Ventral Oral Anterior of the Thalamus; Vop, Ventral Oral Posterior Nucleus of the Thalamus. *To be considered in patients with a severe bleeding risk (e.g., ongoing anticoagulation). **Medication reduction can contribute to the worsening of midline/contralateral tremor.

highest tolerated dose and when ineffective they can be used in combination; many other second- and third-line agents can be added (e.g., gabapentin, clonazepam, botulinum neurotoxin injections) but these rarely suffice. In this scenario (i.e., tremor affects the quality of life and it is drug resistant), surgery should be considered. It has been estimated that medical treatments are not effective or not tolerated in about 50% of ET patients.[1,6]

While there is no significant progress in the medical field of ET, the surgical field has been very active and there are advances in this area.[7] The surgical modalities used for ET include three major categories: 1) ablation (i.e., thalamotomy), 2) deep brain stimulation (DBS) of the ventrointermedius nucleus (Vim) of the thalamus, and 3) non-invasive (e.g., transcranial magnetic stimulation) and superficial brain stimulation (e.g., extradural or subdural motor cortex stimulation), which are still experimental and will not be discussed further.[8] There are different types of ablative therapies: a thalamotomy can be performed by using radiofrequency (RF), the gamma knife (GK), and the recently introduced magnetic resonance-guided focused ultrasound (MRgFUS).[7,9] These ablative (i.e., destructive) techniques can be further divided into invasive (RF) or non-invasive (GK and MRgFUS) techniques. Table 1 highlights the principal features of the non-experimental surgical options available thus far.

In this review we will critically review the role of MRgFUS-thalamotomy in the treatment of ET, explaining the technique, mechanism of action, benefits, and side effects.

Review methods

We performed a review by searching MEDLINE and using the key words "focused ultrasound," "magnetic resonance guided focused ultrasound," "focused ultrasound thalamotomy" or "magnetic resonance guided focused ultrasound thalamotomy." A targeted search of the bibliographies of relevant articles was also performed to identify additional studies. Only original articles published in English until January 2017 were included in this review. In case of a partly overlapping patient population reported by the same group, the study with the largest population was chosen and in case of a dual publication,

Table 1. The Features of the Neurosurgical Procedures Currently Used for Movement Disorders (listed chronologically).[31,49,59]

	Radiofrequency Lesioning	Deep Brain Stimulation	Gamma Knife Radio Surgery	MR-guided Focused Ultrasound
Technique	A probe inserted into the brain is used to burn neurons in a selected area to create a focal lesion	One or more electrodes are inserted into the brain and are then connected to a implantable pulse generator providing constant electrical stimulation to modulate neuronal activity in the targeted brain region	Ionizing radiations are transmitted through the intact skull to generate a permanent lesion in a specific brain region	Ultrasound waves are transmitted through the intact skull to generate a permanent lesion in a specific brain region
Targeting	Neuroimaging, neuronal recording, intra-operative stimulation, intraoperative test lesions	Neuroimaging, neuronal recording, intra-operative stimulation, (real-time MRI guidance in selected centers)	Neuroimaging	Neuroimaging, thermic maps, real-time MRI guidance, intraoperative test lesions
Worldwide experience	Over 50 years	Over 30 years	Over 15 years	4 years
Ablation (irreversible effects)	Yes	No	Yes	Yes
Use of general anesthesia	No	Yes	No	No
Invasive/incisions	Yes	Yes	No	No
Possibility of bilateral procedure	No	Yes	No	No
Device implantation	No	Yes	No	No
Benefit onset	Immediate	Delayed (when programming is completed, up to 6 months)	Delayed (up to 1 year)	Immediate

Abbreviation: MRI, Magnetic Resonance Imaging.

the study was considered once. In total we included 30 articles on MRgFUS in humans. Other included papers were reviews or original articles on technical aspects and experimental uses (e.g., animal studies) of FUS.

History

For years ultrasound has been used as an effective diagnostic tool in almost all fields of medicine and also as a therapeutic instrument in some areas. Examples of the latter are renal stones (lithotripsy) and cataract surgery (phacoemulsification).[10] The use of high-intensity focused ultrasound (HIFU) for ablation of living tissues goes back to the 1940s when Lynn[11] ablated fresh liver tissue without destruction of surrounding areas and then moved to the brain of living animals. The Fry brothers further explored HIFU to ablate brain tissues.[12,13] In 1959 their experience led to its first-time application in the treatment of tremor in patients with Parkinson's disease (PD) in whom the globus pallidus was ablated after part of the skull bone was removed.[14] Later on, with the discovery of levodopa and afterward DBS, the role of ultrasound in treating movement disorders faded out. In the 1990s the combination of magnetic resonance imaging (MRI) with HIFU brought renewed interest in its use for the treatment of neurologic disorders.[10]

Technical aspects of MRgFUS

MRgFUS is a relatively new modality of treatment based on two technologies, the aforementioned HIFU and MRI to plan targeting and monitor the treatment real time, also using temperature maps. Preclinical animal models demonstrated the safety, validity, and efficacy of this technology in generating brain lesions and disrupting the blood–brain barrier (BBB).[15] Subsequently, HIFU entered clinical practice, being widely used for a number of approved applications, including accelerating fracture repair[16] and non-invasive ablation of a

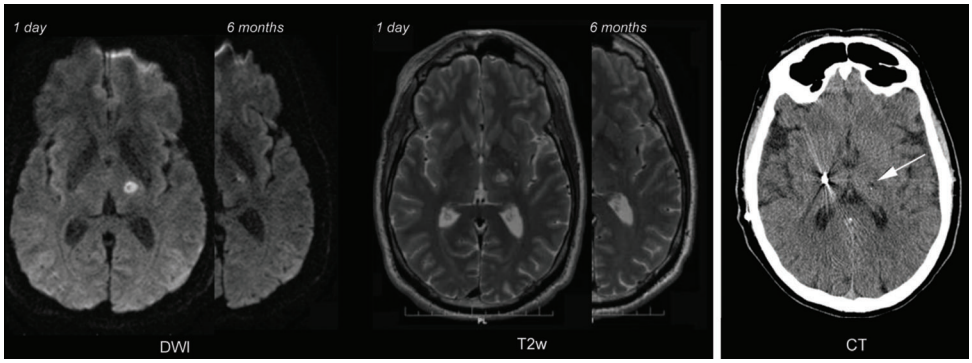

Figure 2. **Neuroimaging of Neurosurgical Procedures for Tremor.** Brain MRI of a tremor patient 1 day and 6 months after MRgFUS-thalamotomy of the left hemisphere (right). CT scan of another tremor patient who underwent left RF-thalamotomy (arrow) followed by right Vim-DBS (left). DBS, Deep Brain Stimulation; DWI, Diffusion-weighted Imaging; MRgFUS, MRI-guided Focused Ultrasound (of Vim); RF, Radiofrequency; T2w, T2-weighted Imaging; Vim, Ventrointermedius Nucleus of the Thalamus.

variety of benign and malignant tumors, such as uterine fibroids, breast cancer, bone metastasis, and prostate tumors.[17–21]

The lesional power of ultrasound is based on two major mechanisms: thermal and non-thermal.[10] As for the former, the therapeutic goals of MRgFUS can be defined according to the level of ultrasound energy provided: low-intensity FUS (LIFU) can reversibly affect neural function, thus representing another way to perform neuromodulation; moderate energy levels can be employed to safely open the BBB for different aims (e.g., localized delivery of therapeutics); HIFU is sufficient to create a coagulation lesion in the brain with the goal of developing a minimally invasive way to create focal brain lesions. In fact, at a temperature of over 44℃ for some seconds, irreversible cell death by coagulative necrosis will occur.[22] To reach these temperatures, usually an equal amount of ultrasound energy is applied continuously. As the energy absorption in the ultrasound beam path is lower, the surrounding tissue is spared.[22] Ultrasound's non-thermal effects are due to alternating pressure and subsequently formation of air bubbles, a process termed acoustic cavitation. It has been hypothesized that adverse effects are due to non-thermal effects, so that the production of bubbles should be avoided during the procedure.[23,24]

Poor penetration of ultrasound in the skull was a barrier to using ultrasound for intracranial and brain diseases. This problem was solved by a system preventing the heating of the cranium bones. It consists of a spherical, phased array, multi-element transducer helmet operating at a frequency of 0.5–1.5 MHz that allows focusing of ultrasound energy coupled with software that compensates for skull-induced wavefront distortions.[25,26]

The typical patient treatment protocol includes a preoperative computed tomography scan of the entire cranium to measure skull thickness. On the treatment day, a frame is fixed to the shaved head of the patient under local anesthesia; at the same time the scalp is inspected for scars and other lesions that could compromise the passage of ultrasound. Then an elastic diaphragm filled with cool water is attached to the scalp and connected to the ultrasound transducer (Exablate Neuro, Insightec, Tirat Carmel, Israel). The procedure is done in an MRI unit without general anesthesia and sedatives.

During the procedure a series of low-power "sonications" (40–45℃) confirmed the accurate targeting and focusing, as these "test lesions" do not induce permanent changes but are enough to induce a transient effect, either positive or negative. Next, by gradual increment of the duration of sonication the lesion is progressively created and enlarged until a satisfactory clinical effect is reached.[27,28] The temperature at the target is monitored by proton resonance frequency through MR thermometry. The location and size of the lesion, the clinical effects, and the side effects are monitored continuously by assessing the alert patient during the surgery. Pain and burning sensations, and the discomfort caused by prolonged lying are managed accordingly, usually by an anesthesiologist who is present during the procedure. Overall, the treatment lasts 3–4 hours and ends once the clinical and radiologic effects are deemed satisfactory. Following the procedure, the patient undergoes a neurological examination in the recovery room, and post-treatment MR images are obtained to assess the lesion location and size (Figure 2).

MRgFUS in neurological diseases

Virtually any brain structure can be targeted with MRgFUS using a stereotactic atlas and neuroimaging. Refractory neuropathic pain was the first application of this technology in a study on nine patients with different types of pain in whom the centrolateral thalamus was targeted: all of them reported immediate improvement and 57% pain relief at the 1-year follow-up.[29] More recently, MRgFUS targeting the anterior limb of the internal capsule (capsulotomy) was performed in four patients with obsessive compulsive disorder (OCD), resulting in a 33% reduction of the Yale–Brown OCD scale and a significant improvement of anxiety and depression.[30]

Among the neurological indications, tremor is the most explored disorder and also the first to receive Food and Drug Administration (FDA) approval, in July 2016. This has been possible for several reasons: 1) RF thalamotomy and Vim-DBS have a long tradition in patients with medically refractory ET;[9,31] 2) the Vim is centrally

located within the brain, which reduces the distortional effects of the skull on focusing the ultrasound energy; 3) tremor can be easily assessed during the procedure; 4) tremor reduction can substantially reduce disability with unilateral treatment just treating the dominant hand.

MRgFUS for tremor is the focus of this review and it will be discussed in depth in the following paragraphs.

MRgFUS-thalamotomy in ET

There are multiple small-sample studies on the efficacy of MRgFUS-thalamotomy in the treatment of ET. Lipsman and colleagues[27] reported the very short-term results in four patients with refractory ET: there was a remarkable reduction of tremor score of the operated hand, by 89.4% and 81.3% at the 1- and 3-month follow-up visits, respectively. One of their patients had persistent paresthesia and another one developed deep vein thrombosis, probably related to the long immobilization associated with the procedure.[27] Elias et al.[28] reported their results in 15 ET patients followed up for 1 year, showing a significant improvement of hand tremor scores (reduced by 74.5%) as well as quality of life and disability scores. Chang and colleagues[24] performed unilateral MRgFUS-thalamotomy in 11 ET patients, but the skull thickness did not allow the required therapeutic temperature in the thalamus to be reached in three of them; analyzing the data of eight patients up to 6 months after the procedure, the authors found a significant improvement of tremor.[24]

The largest study published so far is a multicenter randomized controlled clinical trial study that enrolled 76 ET patients and allocated them to unilateral MRgFUS-thalamotomy or sham surgery with a 3:1 ratio.[32] Hand tremor scores improved by 47% at the 3-month assessment (primary endpoint), a significant difference from patients who received a sham procedure (improved by only 1%); the benefit decreased at the 12-month assessment (40% improvement compared with baseline). Adverse events were commonly reported, including paresthesia and balance disturbances, respectively seen in 14% and 9% of patients at the end of the observation period.[32]

Other targets of MRgFUS in ET

Gallay et al.[33] used MRgFUS to perform cerebellothalamic tractotomy (CTT) in 21 ET patients. Three of the patients successively underwent a bilateral procedure 1 year later. All the patients showed significant and sustained improvement of tremor scores at the 1-year evaluation. However, pre-existing gait imbalance worsened in five patients, only temporarily in four of them.[33] Overall, the study showed acceptable tolerance of bilateral CTT, which can be a potential advantage of this target compared to Vim, where bilateral ablations can cause serious side effects such as imbalance, gait problems, and cognitive and speech disturbances.[31]

Vim-MRgFUS in non-ET tremors

Vim-MRgFUS has been used for tremor associated with PD. Tremor ceased after treatment in all subjects in a case series of seven patients but recurred in a mild form in three of them 6 months later; the procedure was associated with a significant improvement in quality of life.[34] A blinded sham-controlled study for PD tremor is currently ongoing and preliminary results are only available in abstract form.[35,36] In this study, 27 patients with tremor-dominant PD received either a unilateral MRgFUS-thalamotomy or sham surgery with a 2:1 ratio. The sham group received surgery after 3 months. The 1-year tremor scores for all 19 patients completing the follow-up period showed a significant reduction of tremor scores by 41% and of the Unified PD rating scale (UPDRS) on medication by 32%. However, the 3 months results were not significantly different between the two groups because of a significant placebo effect in patients receiving sham surgery (22% tremor reduction).[36]

Reports on two patients with fragile X-associated tremor/ataxia syndrome effectively and safely treated with unilateral MRgFUS-thalamotomy have been recently published.[37,38] We have seen the same promising results in a small series of patients with dystonic tremor and ET-like tremors seen in dystonia patients (tremor associated with dystonia and tremor associated with dystonia gene) (personal unpublished experience).

Other targets of MRgFUS in non-ET tremors

Magara and colleagues[39] for the first time performed unilateral pallidothalamic tract (the confluence of the ansa lenticularis and lenticular fasciculus) ablation using MRgFUS in 13 patients with tremor-dominant PD. Their first four patients underwent the same protocol used for thalamic procedures but they experienced recurrent symptoms 3 months later. Therefore, the remaining nine patients were treated with four or five repetitions of the same protocol. At the 3-month follow-up, an average reduction of 61% of the total score UPDRS and 57% of the Global Symptom Relief was reported. The use of multiple sonications was likely attributed to the different tissue reactions of white matter tracts compared with grey matter, as also observed in a patient receiving MRgFUS-anterior limb capsulotomy for OCD.[30,39]

Na and coworkers[40] reported the first unilateral MRgFUS-pallidotomy in a PD patient with levodopa-induced dyskinesias who achieved a reduction of UPDRS on and off medication by 60% and 55%, respectively.

MRgFUS-thalamotomy compared to other surgical modalities

Classic thalamotomy is done by inserting an electrode through a craniotomy, generating thermal energy by means of RF. With intraoperative microelectrode recording and macrostimulation, it is possible to precisely assess the target for benefits and adverse effects before a permanent ablation is made. No general anesthesia is needed. On the other hand, the invasiveness of the technique increases the risk of infection and hemorrhage.[31] Unilateral or bilateral Vim-DBS share similar features (particularly the invasiveness and targeting with microelectrode recording and macrostimulation) and similar potential risks of hemorrhage and infection, the latter being even higher as hardware is implanted in the body and also because the battery has to be changed every 3–6 years. In addition to hardware implantation, DBS has two main differences: it requires general anesthesia (in order

to insert the battery in the chest) and it can be adjusted to optimize control of symptoms and side effects over the years. The international randomized controlled trial comparing standard RF-thalamotomy and Vim-DBS concluded that although both treatments yield similar tremor control in the short-term, DBS is safer and guarantees better tremor control in the longer term at the price of possible hardware-related complications.[41] Furthermore, the reversibility of DBS allows the insertion of the electrode in the hemisphere contralateral to the first operated side (regardless of the first procedure type).[42] In fact, DBS is the only non-ablative surgical procedure used for tremor treatment, and it is well known that the risk of gait and balance disturbance, and cognitive and speech difficulties is intolerably high with bilateral ablative procedures.[31] Targeting both hemispheres has the advantage of improving the tremor of both body sides and also axial symptoms, such as head, face, and voice tremor.[43]

Bilateral DBS (or DBS contralateral to another ablative treatment previously done) is not risk-free with respect to ataxia symptoms; however, these are usually reversible with further adjustments of stimulating parameters.[44] Recently, prolonged bilateral Vim-DBS has been linked to a delayed pseudo-progressive ataxia syndrome that can be reverted by turning stimulation off for several days.[45]

GK thalamotomy is a non-invasive and incisionless procedure without risk of hemorrhage and infection.[46,47] Targeting is based on anatomy without microelectrode recording and stimulation of the target before permanent ablation. Since its results are delayed for weeks to months, assessment of the positive and side effects during the procedure is not possible. These delayed effects can also cause further progression of the lesion, thus causing unpredictable progressive side effects.[48,49]

Tables 1 and 2 summarize the features of the current neurosurgical approaches to tremor. No head to head randomized trial comparing the newer surgical treatments has been performed so far and therefore any comparison is speculative. Nevertheless, a comparison can be certainly driven by clinical experience and previous comparative studies. Huss and colleagues[43] performed a retrospective study comparing the results of unilateral MRgFUS-thalamotomy (15 patients) with bilateral or unilateral thalamic DBS (57 and 13 patients, respectively). They showed similar positive results regarding tremor reduction and quality of life improvement across the three groups. Not surprisingly, this study found better midline and bilateral tremor control with DBS targeting both hemispheres; interestingly, unilateral Vim-DBS was superior to unilateral MRgFUS-thalamotomy in the control of midline tremors.[43]

Table 2. The Features of the Current Neurosurgical Approaches to Movement Disorders (listed chronologically).[31,49,59]

		Radiofrequency Lesioning	Deep Brain Stimulation	Gamma Knife Radio Surgery	MR-guided Focused Ultrasound
Possible target(s)	Vim	Yes	Yes	Yes	Yes
	Vop	Yes	Yes	No	No
	GPi	Yes	Yes	(Yes)[a]	Yes
	STN	(Yes)[a]	Yes	No	No
	Zi	(Yes)[a]	Yes	No	No
Effect on	Tremor	Effective	Effective (Vim>STN>GPi)	Effective but delayed	Effective but variable (Vim>GPi)
	Bilateral/midline signs	No	Yes	No	No
Other outcome attributes	Benefit onset	Immediate	Delayed (when programming is completed, up to 6 months)	Delayed (up to 1 year)	Immediate
	Recurrence of symptoms/tolerance	Yes (disease progression)	Yes (disease progression)	Yes (disease progression)	Yes (disease progression and healing process)
	Log-term data	Yes	Yes	Yes[a]	Unknown
	Quality of the evidence	fair	good	poor	fair

Table 2. Continued

		Radiofrequency Lesioning	Deep Brain Stimulation	Gamma Knife Radio Surgery	MR-guided Focused Ultrasound
Risks	Brain bleeding[c]	Yes	Yes	No	No?
	Infection	Yes	Yes	No	No
	Hardware malfunction	No	Yes	No	No
	Temporary side effects[d]	Yes	Yes	No	Yes
	Permanent side effects[d]	Yes	No	Yes	Yes
	Hyper-response of brain tissue[e]	No	No	Yes	Yes
	Radiation-related (delayed effects)	No	No	Yes	No
Other features	Need of being monitored/multiple visits	No	Yes	No	No
	Need of battery changes	No	Yes	No	No
	Adjustable over time	No	Yes	No	No
	Reversible	No	Yes[b]	No	No
	Possible in patients with MRI contraindications	Yes	Yes[f]	Yes	No
	"Ideal" candidate profile	Patients not able to be regularly seen (e.g., with psychiatric diseases), fragile subjects (old patients in whom general anesthesia is not possible)	Young patients needing long-term adjustments. Only possible option for patients requiring bilateral or midline tremor control	Patients with bleeding risk (e.g., on anticoagulant treatment), high infection risk or not able to be regularly seen (e.g., with psychiatric diseases)	Patients with high infection risk or not able to be regularly seen (e.g., with psychiatric diseases) Not possible in patients with high skull thickness, not possible in patients with previous brain surgery

Abbreviations: DBS, Deep Brain Stimulation; GPi, Globus Pallidus Pars Interna; MRI, Magnetic Resonance Imaging; STN, Subthalamic Nucleus; Vim, Ventrointermedius Nucleus of the Thalamus; Vop, Ventro-oralis Posterior Nucleus of the Thalamus; Zi, Zona incerta.
[a]Limited experience.
[b]Not in case of intraoperative complications (e.g., stroke).
[c]Causing no symptoms, stroke-like symptoms, death.
[d]Paresthesia, sensory loss, weakness, ataxia, visual field defects, speech and swallowing difficulties NOT caused by an intraoperative complication (e.g., stroke).
[e]Unpredictable brain tissue reaction characterized by edema and non-radial spreading of the lesioning effects.
[f]But no further MRI after the procedure (selected manufacturers).

Table 3. The Problems, Unknowns, and Possible Future Indications (based on experimental evidence) of FUS.

Problems
Variable effects on symptoms control
Decay of tremor control in the short term
Relatively high number of persistent side effects
Unpredictable hyper-response of brain tissue
Not suitable to target both hemispheres
Not possible in patients with MRI contraindications
Not possible in patients with high skull thickness
Not possible in patients with previous brain surgery
Limited experience
Patients' misperception of being non-surgical
Unknowns
Long-term effects
Re-operation of the same brain area (e.g., in case of tremor recurrence)
Efficacy of lesioning less centered brain targets (e.g., GPi)
Safety of bilateral procedures
Efficacy of DTI MRI to better target brain nuclei/fibers
Safety of STN lesioning (risk of hemiballismus)
Bleeding risk in selected populations (e.g., patients on anticoagulants)
Impact of placebo effect in previous and future RCTs
Possible future applications
Opening the BBB using moderate-intensity pFUS to improve the delivery of therapeutic agents (growth factors and genes)[60–68]
Improving the spread of nanoparticles combined with CED for the delivery of protein and gene therapy to the brain[69]
Neuromodulation with a high degree of spatial resolution (either activation[60,70] or suppression of neuronal activity[71]) using low-intensity pFUS
"Enhanced sonication" through inertial cavitation by microbubbles compressed and expanded by FUS[72]
Sonothrombolysis of clotted blood in ICH, thereby facilitating minimally invasive evacuation of the clot via craniostomy and aspiration tube[73]

Abbreviations: BBB, Blood–Brain Barrier; CED, Convection Enhanced Delivery; DTI, Diffusion Tensor Imaging; FUS, Focused Ultrasound; GPi: Globus Pallidus Pars Interna; ICH, Intracerebral Hemorrhage; pFUS, Pulsed-mode Focused Ultrasound; RTC, Randomized Controlled Trial; STN, Subthalamic Nucleus.

Although limited, the aforementioned considerations should guide clinicians in the selection of the best surgical option for movement disorders, tremor in particular. In our opinion, DBS has significant advantages and should be favored when possible. Figure 1 depicts a possible decision tree for the selection of tremor patients needing surgery.

The current hurdles of MRgFUS

During a relatively short period of time, MRgFUS has become extremely popular and clinical experience is rapidly growing. This process has already identified a number of problems, detailed in Table 3.

MRgFUS procedures have been associated with a variable outcome: for example, tremor reduction ranged from –20% to +88% in the largest RCT performed so far.[32] The same trial has also found that tremor control degraded by 23% over the first year, thus pointing to the possibility that the combination of brain healing and tremor progression will not guarantee enough symptomatic relief in the medium and long term.[32]

MRgFUS is perceived as a safe procedure but it has been associated with a relatively high number of persistent side effects: 9% of gait disturbance and 14% of paresthesia 1 year after surgery in the recent aforementioned large trial.[32] MRgFUS-thalamotomy is created without electrophysiological localization techniques that were developed for RF thalamotomy (intraoperative recording and stimulation). Given the fact that the main danger posed by RF-thalamotomy is not the incision, burr hole, or electrode pass but the ablation itself, it has been recently commented that "MRgFUS thalamotomy may actually be riskier than classic RF-thalamotomy, which, in turn, is riskier than DBS."[50] On the other hand, during the MRgFUS procedure real-time brain MRI is used to monitor target localization and the size of the ablation area. Another still not fully elucidated problem is the unpredictable brain tissue reaction seen in some patients, a phenomenon already reported in GK procedures.[47] It consists of a large amount of edema and non-radial spreading of lesioning effects. The former is typically associated with transient adverse effects; the latter is more dangerous and its

phenomenology probably relies on the anatomy of the targeted area (fiber directions and ratio between neuronal bodies and axons).

Another problem of MRgFUS for movement disorders is related to the fact that many patients need bilateral procedures and this limits in particular the usefulness of this technique in pallidotomies performed to treat diseases such as dystonia or PD. In addition, it is not emphasized enough that many patients cannot undergo MRgFUS; examples include patients with pacemakers or other contraindications to MRI or patients with high skull thickness. In fact, a study on 25 patients (one with PD, 15 with ET, and nine with OCD) found that skull volume and density significantly affect the maximum temperature achieved in the deep brain.[51] For example, patients with high skull density may undergo skin lesions and local pain in order to receive enough lesioning energy in the deep brain. Another contraindication of MRgFUS is a history of previous brain surgery, because some of these patients' brain areas may receive more energy than predicted by software, assuming that the entire skull is intact.

Probably the most important hurdle of MRgFUS is related to the many unknowns of a relatively new treatment that gained popularity rather fast. In this respect, although public opinion and patients perceive it as a "non-surgical" intervention, MRgFUS is not risk-free. This virtually puts many people at risk, as ET is the most prevalent movement disorder and up to 50% of patients become refractory or intolerant to medication.[6]

Table 3 also lists the unknowns of MRgFUS: we already touched on the possible long-term decay of benefit and it is currently unknown whether reoperation of the same target is feasible and safe. The lesioning power of MRgFUS is very strong in the central brain target (such as the thalamus) but full impact on more lateral structures such as the GPi is currently unknown. As mentioned earlier, MRgFUS is only performed unilaterally in patients with movement disorders because of safety concerns. However, it has been used to induce bilateral lesions in other indications and it is therefore possible that the further development of targeting procedures will make bilateral lesions possible with a staged fashion. For example, diffusion tensor imaging (DTI) MRI might be particularly suitable for tremor patients since Vim is a functional rather than anatomical target, representing the entry zone of the cerebello-dento-thalamic tract. We have successfully proved that DTI MRI might be useful in targeting Vim with MRgFUS.[37] DTI MRI might be used to safely target smaller and riskier structures, such as the subthalamus. In fact, although subthalamotomy is rarely performed because of the risk of hemiballism, we are aware of a few centers trying to perform MRgFUS-subthalamotomies in PD patients.

MRgFUS is an incisionless procedure with no risk of infection, cerebrospinal fluid leakage, and possibly bleeding. As for the last one, the real risk is still unexplored, particularly in patients at risk such as in the case of coagulopathy or anticoagulant use.

Finally, many patients are now requesting MRgFUS because they like the non-invasive fashion of the procedure. Not surprisingly, studies are now dealing with impressive placebo effects. For instance, a case report of a PD patient has reported an impressive reduction of UPDRS off medication but no changes in L-dopa equivalent daily dosage;[40] more importantly, a still ongoing sham-controlled study has found a non-significant effect of MRgFUS-thalamotomy at the 3-month visit (primary endpoint) because of a 22% improvement in the sham group (vs. 50% in the active treatment group).[36]

The (possible) future of MRgFUS in tremor conditions

Some of the possible future applications of MRgFUS listed in Table 3 are very close to an experimental application in humans. Among them, "enhanced sonication" might represent a future modality of performing lesions in tremor patients, particularly for patients with high skull density and/or a too lateral target. The most promising application is the possibility of neuromodulate brain circuits with high spatial resolution. In fact, MRgFUS can be used to change neuronal function without causing lesion and ablation. The role of HIFU using temperatures not able to induce permanent ablations is well known since it is used for thalamic mapping during MRgFUS-thalamotomy. In some of these cases, a sustained improvement of tremor even without ablating the Vim has been reported.[27] A similar approach has been successfully used in the animal model of epilepsy.[52]

In addition to HIFU, another promising way to neuromodulate brain targets is using LIFU, particularly with the so-called pulsed-mode FUS.[9,10]

The neuromodulating property of FUS is probably related to changes of voltage-gated ion channels and neuronal membrane permeability resulting in modulation of action potentials.[53,54]

Animal experiments employed LIFU to stimulate the hippocampal, motor cortex, and frontal eye field.[53,55,56]

In human volunteers stimulation of the primary sensory cortex caused electroencephalography changes and tactile perception.[57,58]

Conclusion

Stereotactic brain lesioning has been used for decades and it is a well-established effective treatment for medically refractory patients with ET and certain patients with PD (asymmetric tremor-dominant or dyskinetic patients).[31] The scientific community shifted attention from lesioning to DBS when the latter became the standard of care. With the very recent FDA approval (July 2016) of MRgFUS-thalamotomy for refractory unilateral ET, both preclinical and clinical research on this technique are rapidly expanding for several indications. We are therefore witnessing a revival of ablative procedures.

In this article, we reviewed recent clinical trials and some of the preclinical experimental works using MRgFUS for the treatment of tremor.

MRgFUS seems to be an outstanding achievement in interventional neurology and functional neurosurgery. This technology is the result of developments in HIFU and modern MRI techniques. It is a non-invasive and incisionless procedure able to ablate deep brain tissue, its therapeutic effects are immediate, and patients can return quickly to normal life. In contrast to RF ablative surgeries and DBS, MRgFUS has no risk of infection and (possibly) bleeding and it does not use ionizing irradiation. There are promising results of its effectiveness in ET and other tremor syndromes. Other studies in other movement

disorders and neurologic diseases are underway. There are also promising results of MRgFUS in neuromodulation and focal disruption of the BBB for therapeutic goals.

Our review has also emphasized the many problems and unknowns related to this novel procedure. It is too early to draw definite conclusions on the value and unsolved issues of MRgFUS, but the good news is that one more option is now available for tremor patients. We believe that a deep understanding of the efficacy and safety of these procedures is needed for the appropriate selection of the surgical patients. Future studies comparing the different treatment modalities are certainly needed.

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