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REVIEW ARTICLE

Brain-focussed ultrasound: what's the "FUS" all about? A review of current and emerging neurological applications

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ABSTRACT

MR-guided focussed ultrasound surgery (MRgFUS) allows for precise non-invasive thermal ablation of target tissues for a wide range of clinical applications. It is an innovative and rapidly expanding technology, which has already established itself as an effective and safe incisionless alternative in the treatment of various soft tissue tumours, with many more research studies underway to extend its therapeutic envelope. The non-invasiveness of the procedure makes FUS particularly attractive in functional neurosurgery, where existing treatment options are not suitable for all patients. Several clinical trials have demonstrated the feasibility and favourable safety profile of MR-guided focused ultrasound surgery in essential tremor, Parkinson's disease and other neurological conditions. This article reviews the existing evidence base for the neurological applications of FUS and the evidence for its emerging roles in the treatment of a range of brain disorders.

INTRODUCTION

Focussed ultrasound (FUS) refers to a relatively new non-invasive therapeutic modality that uses high intensity focussed ultrasound (HIFU) to treat a variety of disorders. It has been a subject of medical fascination for nearly three-quarters of a century, ever since early experiments by Lynn et al in 1942 showed that extracorporeal high intensity focussed sonication could cause tissue destruction.¹ Subsequent pioneering work by the Fry brothers, at the University of Illinois in the 1950's, led to the observation that FUS could produce targeted neural destruction with almost no effects to the surrounding tissues.² Their findings more than 50 years ago inspired a great deal of research in the field of focussed therapeutic ultrasound, but improvement in the technique was extremely slow and hampered by the lack of real-time monitoring of tissue effects. Today, modern FUS equipment uses MRI guidance to deliver effective and safe sonication to very precise targets.

FUS is a rapidly evolving technology, with the potential to revolutionise many areas of normal clinical practice.³ Worldwide, over 50 clinical applications are being researched to treat a variety of medical conditions, including cardiovascular, neurological, oncological, endocrinological, gynaecological, psychiatric, musculoskeletal

and urological diseases.³ The launch of the world's first FUS trial for Alzheimer's disease was the most recent example of the ever growing and exciting applications of FUS.⁴

In the USA, HIFU therapy has already gained approval from the Federal and Drug Administration for the treatment of uterine fibroids, essential tremor (ET), painful bone metastases, prostate cancer and benign prostatic hyperplasia.³

In the UK, FUS has been approved by the National Institute for Health and Care Excellence for the treatment of localised prostate cancer and uterine fibroids.^{5,6} It is also being considered as a therapeutic option for symptomatic breast fibroadenoma.⁷ Other UK research studies exploring its use in the treatment of liver, renal, pancreatic, breast, soft tissue, metastatic bone tumours and multiple myeloma are underway.⁸⁻¹⁰

6 months ago, our institution (Imperial College Healthcare NHS trust) was the first in the UK to start treating patients with ET using MR-guided FUS (MRgFUS) with very promising early results. Being non-invasive, FUS is of particular interest in the field of neurosurgery, where it is becoming an attractive therapeutic alternative in the treatment of a wide range of conditions. This review will focus on these aspects of transcranial FUS.

TRANSCRANIAL MRGFUS ABLATION: MECHANISM OF ACTION

The ability of ultrasound to produce temperature rises was first observed by Wood and Loomis in 1927.¹¹ Similar to a magnifying glass concentrating the sun's rays onto a precise spot capable of burning a hole only at this exact point, HIFU causes significant increase in temperature in a defined focal plane of the ultrasound beam. This HIFU-induced temperature rise causes protein denaturation, DNA breakdown and eventually thermal coagulative necrosis which at high intensity is the most common and desired mechanism of action of FUS. In human tissues, therapeutic thermal ablation is generally achieved at temperatures above 56° for 1 s, without any significant damage to the surrounding structures.¹²

The thermoablative properties of FUS were first used in the 1940's by Lynn et al on *ex vivo* tissue samples and on animal brains, when it was observed that successful production of focal lesions within the central nervous system was dependent on overcoming the skull's strong impedance to ultrasound wave transmission.^{1,13} In the 1950's, the Fry brothers used FUS to treat patients with Parkinson's Disease (PD), observing that FUS produced sharply demarcated lesions, without any significant damage outside the target area.¹⁴ At the time, FUS delivery to the brain was only possible through direct access to the brain via craniotomy.

In the 1970's, Fry and Barger led key research on the acoustic properties of the human skull. It was discovered that the highly reflective and attenuating properties of the skull were due to its highly heterogeneous and complex nature, which presents strong variations in acoustic and absorptive properties. It is these heterogeneities in density, speed of sound and ultrasonic absorption coefficient, which combine to prevent the smooth propagation of sonographic signal through the skull.¹⁵

More recent advances in skull aberration corrective techniques and phased-array transducers have led to the development of fully non-invasive therapeutic transcranial sonication using *a priori* CT data fused to MR images.^{16–25} Combined with MR guidance to provide high resolution visualisation of the therapeutic target, real time monitoring and thermal feedback, FUS energy can be deposited at selected sites of the brain to produce discrete therapeutic results. Figure 1 depicts the multiple transducers trajectories, which can be used to focus onto one small point where the ablation effect is produced.

NEUROLOGICAL APPLICATIONS OF MRGFUS ABLATION

Essential tremor

With an estimated worldwide prevalence of 5%, ET is the most common movement disorder in adults, but is frequently underdiagnosed.²⁶ The disease manifests itself as an uncontrolled rhythmic shaking of the upper limbs, during a voluntary movement.²⁷ The tremor is usually bilateral and symmetrical, and if severe, can spread to other body parts or even occur at rest.^{27,28} The symptoms can be very debilitating, with affected individuals having difficulties performing daily tasks such as writing or holding a cup. ET is traditionally said to have a bimodal age of

Figure 1. Sagittal T_2 weighted image of the brain, showing the depth of brain targets amenable to modern MRgFUS techniques. The lines indicate the multiple possible ultrasound beam trajectories to reach a target in the thalamus. MRgFUS involves incisionless deep brain focal ablation, without the trajectory planning constraints associated with the more traditional neurosurgical alternatives. MRgFUS, MR-guided focussed ultrasound surgery.

onset, in early and late adulthood, and its prevalence increases with age.²⁸ It can either be sporadic or hereditary—a positive family history is usually seen in at least 50% of affected patients.²⁹

The pathophysiology of ET remains to be fully elucidated. For a long time, the disease was believed to be due to neuronal hyperexcitability alone, a theory which was comforted by the observation that alcohol ingestion can sometimes help relieve tremor symptoms.^{30,31} More recent evidence suggests that the development of the disease is in fact linked to structural neurodegenerative changes within the cerebellothalamocortical tract.³² In particular, the ventral intermedial nucleus (Vim) of the thalamus is thought to play a role in ET symptomatology.³³

More recently, areas within the posterior subthalamic area, the cerebellothalamic tract and the zona incerta have also been implicated in the pathogenesis of ET.³⁴

Surgical therapies that target the thalamus have been the mainstay of treatment in patients with drug-resistant disease. Such techniques include thalamotomy (using radiofrequency or gamma knife radiosurgery) and deep brain stimulation (DBS). Radiofrequency and gamma knife thalamotomy are effective treatment options, but their efficacy needs to be balanced with their high rate of postoperative complications (2–46%), as well as the substantial delayed clinical effects and potential long-term radiation-related risks of gamma knife radiosurgery.^{35,36}

Due to its reversible nature, effectiveness and overall safety profile, thalamic DBS has gained most clinical popularity. It can be unilateral or bilateral depending on the nature and severity of the disease. The Vim of the thalamus is the most common

target in DBS. Vim-DBS has been practiced since 1991 and its effectiveness has been confirmed in several studies.^{37–42} DBS, however, has shortcomings, including diminishing effectiveness over time and also the need for general anaesthesia.⁴² Tolerance to thalamic stimulation can occur in approximately 30% of cases, together with other complications such as hardware-related adverse effects (infections, lead and pulse generator problems) in 9–12% of patients and most importantly intracerebral haemorrhage (approximately 2% risk).^{43–46}

The Vim is an amenable and attractive target for FUS due to its central location in the brain, which helps limit ultrasound reflection and distortion by the skull. Several studies took place in the 2010's to confirm the feasibility, safety and efficacy of MRgFUS-thalamotomy (Table 1). Evidence, so far, suggests that this procedure is effective and usually well-tolerated, with a very low rate of permanent side-effects.⁵³ In the USA, HIFU has been an Federal and Drug Administration approved treatment option in patients with refractory ET, since 2016. There are currently approximately 23 treatment sites worldwide.^{54,55}

The first clinical trial using MRgFUS to treat ET was a Phase I study that took place in 2011 at the University of Virginia.⁴⁷ 15 patients with severe medication refractory tremor, who had not had previous brain surgery, were enrolled. Following treatment, the average tremor in the contralateral, dominant hand had significantly reduced from a mean of 20.4 on the Clinical Rating Scale for Tremor (CRST) to 4.3 and 5.2 at 3 and 12 months respectively (79 and 75% tremor reduction respectively). Disability scores on the CRST improved by 85% and patients reported significant improvement in their quality of life on the Quality of Life in ET questionnaire following treatment (37 vs 12%). The only serious adverse event reported during the study was dysaesthesia of a finger in one patient. Transient side effects included paraesthesia, unsteadiness and ataxia. These side effects resolved rapidly and paraesthesia persisted in only three patients after 1 year. MRgFUS was able to target precisely the region of interest, with mean error distances of less than 1 mm in the lateral and anteroposterior dimensions, and of around 2 mm in the dorsoventral dimension.⁴⁷

In 2013, Lipsman et al reported the results of a small trial looking at the short-term outcomes of MRgFUS.⁴⁸ The four treated patients had immediate and obvious improvements in tremor of the contralateral hand after each sonication. These improvements persisted at 1 and 3 months (relative reduction in tremor of 89.4 and 81.3% respectively). Functional impairment (ability to perform fine and motor tasks) improved by 45.5 and 39.6% respectively at 1 and 3 months. The only reported side effect after 3 months was paraesthesia in one patient. One patient developed a deep vein thrombosis, likely related to the immobilisation rather than a direct complication of the procedure itself.

In 2014, Chang et al observed a significant improvement in all the patients who underwent MRgFUS treatment for medication refractory ET.⁴⁹ Out of the 11 patients enrolled, 3 were unable to complete treatment due to subtherapeutic heating at the target

site. Variability in skull volume was thought to be the main contributing factor for treatment failure in these patients.⁴⁹

Results from a more recent, international, sham-controlled study confirmed these promising results in 76 patients and showed a significant 47% improvement in hand tremor score at 3 months, which persisted at the 1-year follow up.⁵⁰ Disability scores also improved significantly (Table 1). Sensory and gait disturbances were the most common reported side effects but the only serious adverse event observed was permanent hypaesthesia of the thumb and index finger in one patient. As in the previous studies, there was no significant improvement in the ipsilateral hand.

Zaarour et al⁵¹ have recently reported the results of a clinical trial of 30 patients with ET, PD, and ET-PD.⁵¹ They observed immediate cessation of tremor in all patients and significant improvement in mean CRST score (77 and 80% respectively at 1 and 6 months). Minor transient motor or sensory disturbances were noted following treatment—none of the side effects persisted at the 3 months follow-up.

All the clinical trials targeting the Vim have assessed unilateral treatment only. One recent trial has shown successful outcome of MRgFUS cerebellothalamic tractotomy (CTT), where the posterior subthalamic area was targeted as an alternative to the Vim, in patients with bilateral, non-head dominant tremor.⁵² Unilateral CTT was performed in 18 patients, and bilateral CTT was performed in 3 patients. Unlike in Vim ablation where only one high-power sonication is needed for therapeutic effect, here high-power sonication was repeated at least four times to achieve sufficient temperature at the focal point (using data from Magara et al⁵⁶). Following MRgFUS-CTT, there was a mean reduction in the ET Rating Scale (ETRS) score of 55% (from 57.6 to 25.8) at 1 year, albeit with significantly different results observed depending on baseline tremor severity—patients with high pre-operative tremor score showed less improvement in their symptoms (Table 1). Patients' estimation of their mean global tremor relief was 92% for the treated hand at 2 days and 77% at 12 months. A trend towards improvement in head tremor was also noted (six patients, improvement from baseline score of 1.2 to 0.25). Of the 17 patients who had postural tremor at baseline, only one still had postural tremor at follow-up. In all patients, improvements were sustained at 1 year. The only side effect reported was worsening gait instability, which persisted at 3 months in one patient only.

The authors suggest that in addition to the promising results, this alternative target, which spares the thalamocortical network thought to contribute to motor and cognitive deficits, may make MRgFUS more amenable to bilateral ablations, as bilateral treatment of the CTT appeared to be well tolerated and not associated with significant side effects.⁵² Patients who underwent bilateral procedure showed significant improvement in hand function subscore (HF16) in their dominant and non-dominant hands (mean improvement of 81.5 and 67% improvement respectively at one year, based on the two patients treated).

Table 1 summarises the FUS trials to date in ET.

Table 1. Summary of MRgFUS trials in ET⁴⁷⁻⁵²

Study	Patients (n)	Target	Results ^a		Side effects ^c	
			Hand tremor (% improvement)	Disability (% improvement)	Most commonly reported transient side effects	Persisting adverse events
Elias et al ⁴⁷	15	Contralateral Vim	<ul style="list-style-type: none"> 78.9% at 3 months^d 74.5% at 12 months^e 	<ul style="list-style-type: none"> 84.6% at 12 months^f 	Facial paraesthesia (60%), finger paraesthesia (33%), unsteady feeling (33%), ataxia (27%) ^g (<3 months duration)	Facial or finger paraesthesia (20%) finger dysaesthesia (6.7%) (at 12 months)
Lipsman et al ⁴⁸	4	Contralateral Vim	<ul style="list-style-type: none"> 89.4% at 1 month 81.3% at 3 months^h 	<ul style="list-style-type: none"> 51.1% at 3 months 	Finger paraesthesia (50%)	Finger paraesthesia (25%) (at 3 months)
Chang et al ⁴⁹	11 ⁱ	Contralateral Vim	<ul style="list-style-type: none"> 68.6% at 1 month^j 70.6% at 3 months^j 72.5% at 6 months^j 	<ul style="list-style-type: none"> 79.3% at 6 months^k 	Transient mild balance problems (9%) ^l	None
Elias et al ⁵⁰	76 ^m	Contralateral Vim	<ul style="list-style-type: none"> 47% at 3 months 40% at 12 months 	<ul style="list-style-type: none"> 62% at 3 months 62% at 12 monthsⁿ 	Paraesthesia (38%), gait disturbance (36%), headache (14%), limb dysmetria (12%), disequilibrium sensation (9%), tinnitus (5%), fatigue (5%), contralateral weakness (4%) ^o	Paraesthesia (14%), gait disturbance (9%), taste disturbance (4%), limb dysmetria (4%), contralateral weakness (2%), disequilibrium sensation (2%) (at 12 months)
Gallay et al ⁵²	21 ^p	Cerebellothalamic tract	<i>Dominant hand</i> ^q <ul style="list-style-type: none"> 74% at 3 months 78% at 12 months <i>Non-dominant hand</i> ^r <ul style="list-style-type: none"> 67% at 12 months^r 	<ul style="list-style-type: none"> 77% at 1 year^s 	Slight worsening of pre-existing gait instability (23.8%) ^t	Slight worsening of pre-existing gait instability (4.8%) ^u
Zaarour et al ⁵¹	18 ^v	Contralateral Vim	<ul style="list-style-type: none"> 77.1% at 1 month 79.9% at 6 months^w 	<ul style="list-style-type: none"> 72.5% at 6 months^x 	Table 2	None

Note, patients with higher baseline tremor scores improved less (41 and 40% at 3 and 12 months) compared to patients with lower baseline tremor scores (90% at 3 and 12 months). Difference was less accentuated for the two patients with severe baseline tremor who received bilateral treatment: 75 and 88% improvement in their dominant hand respectively.

ET, essential tremor; MRgFUS, MR-guided focussed ultrasound surgery; Vim, Ventral intermediate nucleus of the thalamus.

^aAs measured by improvement in relevant subsection of the Clinical Rating Scale for Tremor (CRST) score unless otherwise specified (percentage approximated).

^bRefers to contralateral treated hand. None of the studies showed significant improvement in the ipsilateral hand except the Gallay et al study.

^cFUS thalamotomy-related side effects only are mentioned. Percentages presented have been calculated by authors (LB & WG) from number of patients experiencing each adverse effect in the relevant study.

^dCalculated by authors: reduction from baseline tremor CRST score of the contralateral hand from 20.4 to 4.3.

^eCalculated by authors: reduction from baseline tremor CRST score of the contralateral hand from 20.4 to 5.2.

^fCalculated by authors: reduction from baseline disability CRST score from 18.2 to 2.8. There was also an improvement in Quality of Life in Essential Tremor (QUEST) questionnaire from 37 to 12%.

^gMost common equipment related side effects (MRI, stereotactic frame, sonication) included head pain/headache (13 patients), nausea/emesis (8 patients), light-headedness (6 patients), vertigo-like symptoms (5 patients), scalp numbness (4 patients) and warmth sensation (4 patients).

^hAlso improvement of 45.5 and 39.6% at 1 and 3 months respectively in completion of gross and fine motor tasks (part B of the CRST).

ⁱOnly eight patients completed treatment.

^jCalculated by authors: reduction in mean baseline tremor CRST score from 5.1 to 1.6, 1.5 and 1.4 at 1, 3 and 6 months respectively.

^kCalculated by authors: reduction in mean baseline disability CRST score from 13.5 to 2.8 at 6 months.

^lTransient equipment related side effects included vestibular symptoms in 5 out of 11 patients, which was attributed to high magnetic field exposure.

^m56 patients underwent MRgFUS thalamotomy and 20 patients received sham treatment.

ⁿThere was also a 46% improvement in Quality of Life in Essential Tremor (QUEST) questionnaire at 3 months.

^oPercentages represent total percentages of FUS thalamotomy-related side effects over the 12 month follow-up period. Most common equipment-related events, which only lasted during the procedure, included head discomfort (30%), pin site pain/bruising (30%), vertigo (21%), nausea (20%) and back pain (9%).

^p18 patients received unilateral treatment, 3 patients received bilateral treatment one year apart.

^qMeasured by improvement in treated hand function subscore (HFI6) of the Essential Tremor Rating Scale (ETRS).

^rMean global tremor relief as estimated by the patients.

^sCalculated by authors (five patients).

^tCalculated by authors (one patient).

^uTrial also included 12 patients with PD and ET-PD, Table 2.

^vCalculated by authors from baseline Quality of Life in Essential Tremor (QUEST) score of 44.8–12.3 at 6 months.

^wCalculated by authors from baseline Quality of Life in Essential Tremor (QUEST) score of 44.8–12.3 at 6 months.

^xCalculated by authors from baseline Quality of Life in Essential Tremor (QUEST) score of 44.8–12.3 at 6 months.

In an interesting retrospective study comparing DBS with MRgFUS in patients with ET, Huss et al concluded that although DBS was more effective for the treatment of axial tremor, MRgFUS was equally effective as unilateral or bilateral DBS in the treatment of contralateral hand tremor.⁵⁷ Recently, a cost-effectiveness comparative analysis of DBS, radiosurgery and MRgFUS for ET concluded that MRgFUS was an attractive treatment option not only in terms of effectiveness (mean calculated added utility was highest for MRgFUS compared to the other two procedures) but also in terms of cost, with MRgFUS found to be significantly less expensive than DBS (mean cost \$20,593 and \$27,906 respectively) and of similar cost to SRS (\$20,013).⁵⁸ In the UK, early economic evaluation in the NHS suggests that the cost of brain FUS treatment may be about one third of that of DBS (approximately £13,600 vs £35,500 respectively). These figures are provisional estimates provided internally by our institution's research and development team and a full cost-effectiveness is currently underway to assess this further.

Other neurological applications of MRgFUS ablation

MRgFUS technology has been successfully applied to patients suffering other neurological disorders to ablate other deeply located intracranial targets with great precision.⁵⁹

In a recent study by Moser et al, MRgFUS thalamotomies and tractotomies performed on patients suffering with neurogenic pain, ET or PD achieved mean three-dimensional accuracies of less than 1 mm in over 90% of cases.⁵⁹ In comparison, traditional invasive neurosurgical alternatives such as DBS have precision in the order of 2 mm.⁶⁰

Parkinson's disease

A unique challenge in the treatment of PD is finding the most appropriate intracranial target. Vim-DBS is already a well-established therapy for movement disorders.^{37,43} More recently, the subthalamic nucleus and the globus pallidus internus have emerged as potential alternative targets.⁶¹

Through targeted ablation of the Vim, globus pallidus or the pallidothalamic tract, MRgFUS has shown promising results in the treatment of drug-resistant PD in small clinical trials, with reported improvement of up to 61% in the motor score of Unified PD Rating Scale (UPDRS) at 3 months, minimal side effects and a favourable safety profile (Table 2).^{51,56,62,64,65} One small study reported motor improvement of 73.5% following MRg-FUS globus pallidus internus ablation, however, this study only included one patient.⁶³

In the largest trial so far (27 patients), Bond et al⁶⁴ observed a 50% mean hand tremor reduction 3 months after MRgFUS thalamotomy in patients with tremor dominant PD. These results persisted at 1 year (40.6% tremor reduction), although a high placebo effect (22%) was observed in the patients who received sham treatment.⁶⁴ More recently, Zaarour et al presented the results of MRgFUS Vim ablation in 12 patients with PD and ET-PD with significant improvements in tremor.⁵¹

There are further ongoing clinical trials investigating the use of MRgFUS ablation of either the Vim, the subthalamic nucleus or the globus pallidum, the results of which will provide useful information in the quest for the best target site for PD.⁶⁶⁻⁶⁸

Table 2 summarises the FUS trials to date in PD.

Chronic neuropathic pain

The medial thalamus has been implicated in the aetiology of chronic neuropathic pain for many years and stereotactic central lateral thalamotomy has been used as a treatment option.⁶⁹ Jeanmonod and his team have reported encouraging results using MRgFUS-central lateral thalamotomy in patients suffering with chronic neuropathic pain, with an improvement in mean pain relief of 49 and 57% at 3 and 12 months respectively.⁷⁰ The only reported complication, an intracranial bleed, led to monitoring of cavitation detection and the maintenance of sonication temperatures to below 60° in subsequent MRgFUS clinical trials using Exablate 4000.

Obsessive compulsive disorder (OCD) and depression

The pathophysiology of OCD and depression is thought to involve hyperactivity within the frontostriatal-pallidal-thalamic circuits, specifically the orbitofrontal cortex, anterior cingulate cortex and caudate nucleus of the corticostriatal circuit.⁷¹ Neurosurgical capsulotomy to disrupt the anterior limb of the internal capsule has been used to treat patients with OCD, with variable safety and efficacy.⁷¹ In a small early trial, Jung et al have demonstrated promising results using bilateral MRgFUS anterior capsulotomy to treat patients with obsessive-compulsive disorder (OCD) and depression.⁷²

Brain tumours

Experience with MRgFUS ablation of brain tumours has, so far, been limited to small studies, but further trials are underway to evaluate FUS treatment potential in this field.⁷³⁻⁷⁶ With the current state of technology, MRgFUS is most effective on deep, centrally located brain lesions, which are particularly amenable to therapeutic sonication. Exploring the use of FUS on peripherally located intracranial targets, where the close proximity between skull and brain parenchyma makes FUS delivery more challenging, could open new therapeutic avenues.

Epilepsy

A potentially exciting application of MRgFUS therapy is in the treatment of epilepsy. There is a very early clinical trial currently underway at the University of Virginia to evaluate the safety and efficacy of MRgFUS ablation of selected subcortical epileptic foci.⁷⁷ The potential of this approach to allow non-invasive ablation of epileptogenic foci in the outpatient setting, with minimal side effects, may provide a substantial improvement over the more invasive current treatment options.

MRG FUS: OTHER MECHANISMS OF ACTIONS AND POTENTIAL NEUROLOGICAL APPLICATIONS

Thermal ablation is, thus far the most used and established in practice, but is not the only action of FUS. Potential additional

Table 2. Summary of MRgFUS trials in PD^a 51,56,62–65

Reference	Patients (n)	Protocol	Outcome	Safety
Magara et al ⁵⁶	13	Unilateral MRgFUS PTT ^b	<ul style="list-style-type: none"> Mean UPDRS reduction 7.6%, mean GSR 22.5% when single sonication at peak energy^c Mean UPDRS reduction 60.9%, mean GSR 56.7% when multiple sonications at peak energy^d 3 month follow-up 	No side effects
Schlesinger et al ⁶²	7	MRgFUS Vim ablation	<ul style="list-style-type: none"> Immediate cessation of tremor in all patients Mean UPDRS reduction 49.7%^e PDQ-39 reduction 48.9%^f Sustained effects (mean follow up 7.3 months) 	<ul style="list-style-type: none"> No side effects beyond 3 months No serious side effects reported Transient adverse events^g: minor sensory or motor disturbances (33%)
Na et al ⁶³	1	MRgFUS ablation of the globus pallidus internus	<ul style="list-style-type: none"> UPDRS reduction 69.8, 73.5 and 66% at 1, 3 and 6 months respectively^h 	No adverse events reported
Bond et al ⁶⁴	27	Patients randomly assigned to either sham procedure or MRgFUS thalamotomy	<ul style="list-style-type: none"> Mean hand tremor reduction 50 and 40.6% at 3 and 12 months respectivelyⁱ Mean UPDRS reduction 32% at 12 monthsⁱ Note high placebo response (mean tremor reduction 21.5% at 3 months with sham treatment) 	Not available
Zaarour et al ⁵¹	12 ^j	MRgFUS ViM ablation	<ul style="list-style-type: none"> Immediate cessation of tremor in all patients Mean UPDRS reduction of 34.1 and 46.2% at 1 and 6 months respectively^k PDQ-39 score reduction of 32.4 and 46.2% at 1 and 6 months respectively^l 	<ul style="list-style-type: none"> No side-effects beyond 3 months No serious side effects reported Transient adverse events^m: gait ataxia (16.7%), unsteady feeling (13.3%), taste disturbances (13.3%) asthenia (13.3%), hand ataxia (10%)

GSR, global symptom relief; MRgFUS, MR-guided focussed ultrasound; PD, Parkinson's disease; PDQ, Parkinson's disease Questionnaire; PTT, pallidothalamic tract; UPDRS, Unified Parkinson's Disease Rating Scale; Vim, Ventral intermediate nucleus of the thalamus.

^aRefers to tremor dominant PD except for Magara et al which also includes four akinetic PD with on-dyskinesia.

^bFirst four patients received a single application of the peak energy, subsequent seven patients received 4–5 repeated applications of the peak energy.

^cFour patients.

^dNine patients.

^eCalculated by authors from baseline UPDRS score of 37.4–18.8 post-treatment. Motor UPDRS reduction was 27% at 3 months.

^fCalculated by authors from baseline PDQ-39 of 42.3–21.6 post-treatment.

^gPercentages calculated by authors from number of patients experiencing hypogeusia, subjective unsteady feeling, and disturbance when walking tandem after the procedure. Brief equipment-related side effects included vertigo (57.1%), headache (42.9%), dizziness (28.6%) and lip paraesthesia (14.3%).

^hCalculated by authors, from baseline UPDRS score of 53–16, 14, and 18 at 1, 3 and 6 months follow-up respectively. Motor UPDRS reduction was 50%.

ⁱOnly preliminary results published. Limited data available regarding statistical significance

^jIncludes nine patients with PD and three patients with ET-PD. Trial also included 18 patients with ET, the results for these patients are presented in Table 1.

^kCalculated by authors from baseline UPDRS score of 24.9–16.4 at 1 month and 13.4 at 6 months. Refers to motor part of the UPDRS.

^lCalculated by authors from baseline score of 38.6–26.1 at 1 month and 20.6 at 6 months.

^mPercentage calculated by authors from number of patients experiencing each adverse effect in the study out of the 30 treated patients, including the 18 ET patients. Brief equipment-related adverse events included vertigo (46.7%), headache (36.7%), short lasting dizziness (13.3%), nausea (10%), burning scalp sensation (10%), vomiting (6.7%) and lip paraesthesia (6.7%).

applications include enhanced drug delivery through opening of the blood brain barrier (BBB) and neuromodulation.

Opening of the BBB and enhancement of drug delivery

When ultrasound waves are applied in a pulsed rather than continuous manner, they exert pressure changes onto the propagating

medium, through a series of alternating compressions and rarefactions. At high enough intensities, such mechanical effects lead to the formation of bubbles, which oscillate, expand and exert shear forces onto the nearby cells. This process is known as cavitation.

The higher the pulse duration, pulse number and repetition frequency, the stronger the oscillation and contraction of the

Table 3. Neurological applications of FUS^{90,91}

FUS application	Mechanism of action	Potential clinical applications
High-intensity continuous application	<ul style="list-style-type: none"> Thermal effect: coagulative tissue necrosis 	Ablation
High-intensity pulsed application	<ul style="list-style-type: none"> Thermal effect: regional hyperthermia Mechanical effect: stable cavitation 	Increased vascular permeability, blood brain barrier opening, enhanced drug delivery
Low-intensity pulsed application	<ul style="list-style-type: none"> Activation and inactivation of neurochemical signalling 	Neuromodulation

FUS, focussed ultrasound.

bubbles, such that in its extreme form, cavitation, in this case referred to as “inertional” cavitation, will cause these bubbles to explode and damage the surrounding tissues and blood vessels. For this reason, the formation of gas bubbles is carefully monitored and avoided during MRgFUS brain ablative treatments, since the results may be much less predictable and controllable in an area where precise lesion placement is crucial to the success or failure of a procedure. Monitoring is usually achieved using a passive cavitation mapping system through acoustic feedback of the oscillating microbubbles.

With careful planning and control, however, cavitation can be used advantageously. In 2001, in a key experiment, Hynynen and his team demonstrated that the intravenous administration of exogenous microbubbles reduced the amount of energy required for cavitation to occur.⁷⁸ This low energy controlled cavitation is referred to as stable⁷⁹ and causes gentle stretching of the endothelial wall, increased vascular permeability, and in the brain, results in local opening of the BBB that could be used for enhancing drug delivery to the brain without significant vascular damage.^{79,80}

The ability of FUS to promote transient BBB opening has opened up a large further area of research to try to utilise this finding for targeted intracranial drug delivery, including delivery of chemotherapy drugs,^{81–83} and more recently, to the first MRgFUS clinical

trial on patients with Alzheimer’s disease.⁸⁴ Additional potential neurological applications of FUS-induced cavitation also include sonothrombolysis for stroke.

Neuromodulation

When pulsed FUS is applied at even lower intensities than that applied for its drug-enhancing action, animal studies have shown that neuromodulation can happen.^{85–87}

In contrast to the microbubble-based BBB opening observed with FUS-induced stable cavitation, or the irreversible tissue ablation observed with continuous HIFU application, the application of low intensity pulsed FUS can produce reversible neuronal excitation and inhibition and has been shown to stimulate cortical activity in healthy human volunteers.⁸⁸ The exact mechanism of action is not entirely known and several theories have been suggested.⁸⁹ FUS-mediated neuromodulation has many potential clinical applications. It is currently being investigated at the University of California Los Angeles for the treatment of epilepsy for example.⁹⁰ There is also early evidence suggesting that MRgFUS-subthalamotomy modulates the activity of relevant metabolic brain networks in PD patients, thus potentially opening new horizons for treatment.⁹¹

A summary of the main mechanisms of action of transcranial brain FUS is presented in Table 3.^{91,92}

Table 4. Summary of advantages and current limitations of brain MRgFUS

Advantages of MRgFUS	Current limitations of MRgFUS
Non-invasive	Uncertainty regarding possibility of bilateral treatment
No radiation	Long-term effects unknown
Effective	Not suitable for peripherally-located brain lesions
Safe	Less successful if dense skull
Minimal comorbidity	
No anaesthesia	
No surgery associated complication	
Immediate, sustained effects	
Reduced hospital stay	

MRgFUS, MR-guided focussed ultrasound.

THE UNKNOWNNS AND CHALLENGES OF MRG FUS: NEW HORIZONS

FUS brain surgery has been a subject of fascination to researchers and clinicians alike for many decades. In the field of neurological disorders, it is becoming an established treatment option for ablation of deep and centrally located brain lesions, such as the thalamus. In patients with ET, it is a safe, effective and cost-effective alternative to invasive neurosurgery. Regions of the brain close to the skull are currently less amenable to MRgFUS because of skull heating and ultrasound refraction but promising technology developments using lower frequency transducers are on the way to expand its treatment envelope.

Compared to other surgical options, evidence so far shows that MRgFUS has immediate effects and has not been associated with any of the more severe complications that have occurred following the much more invasive procedure of DBS; in particular, no case of major intracerebral haemorrhage has so far been reported with the use of MRgFUS and the procedure has overall been well-tolerated in clinical trials. Most reported adverse

effects are transient and include sensorimotor disturbances, in a similar proportion to other surgical therapies. The non-invasiveness of MRgFUS is one of its key advantages, meaning it can be performed as a day case and avoid the need for hospital admission and its associated costs and complications. It is also carried out without any anaesthesia, with patients fully awake, and its potential risks are greatly reduced in comparison to DBS, which is of especial relevance in these patients who are usually elderly and relatively medically unfit.

Successful treatment outcome is closely linked to the ability of FUS to penetrate the skull and, therefore, patients should be carefully selected for treatment. In particular, patients with very absorptive skull vaults, or with high skull volume, may not be such good candidates for treatment, and pre-treatment calculation of a skull density ratio may help optimise FUS treatment outcomes.⁹³

There is so far limited data on the long-term outcome of MRgFUS thalamotomy, and whether tolerance to treatment does develop over time. MRgFUS is currently limited to

unilateral thalamotomy as the safety of bilateral procedures has so far not been established.

Its advantages and current limitations are summarised in Table 4.

CONCLUSION

FUS brain surgery has been a subject of immense interest to physicians for many decades, not the least because of the skull's imperviousness to ultrasound.

Hundreds of patients suffering with various neurological disorders have now been treated with MRgFUS worldwide. The technology is innovative, non-invasive and has so far demonstrated a favourable safety and efficacy profile. It is particularly interesting for the treatment of motion disorders where it relies on real-time monitoring of the lesion and patient feedback for precise targeting and treatment optimisation. Further research is needed to expand its therapeutic envelop, for the great benefit of many more patients. With its low-associated morbidity and mortality, brain FUS may represent a cost-efficient alternative to traditional neurosurgery.

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