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INTRODUCTION:

MRI-guided focused ultrasound (MRgFUS) has emerged as a powerful, incision-less technique that permits precise treatment of neurological disorders. Through MRI guidance, focused ultrasound beams are delivered transcranially to create small therapeutic lesions in highly specific locations within the brain. These ablations can be used to effectively treat a variety of conditions by disrupting the neural circuitry that is propagating abnormal signals.

Interest in MRgFUS is rapidly increasing due to the utility of stereotactic intervention in medically refractory movement disorders, particularly where existing surgical options remain unsuitable for patients. Advances in feasibility and safety have led to rapid growth in clinical applications and research investigations, particularly in the field of functional neurosurgery for movement disorders. The treatment is particularly applicable to patients with tremor, and MRgFUS thalamotomy has been shown to be an effective therapy for tremor.

St Vincent's Hospital will become the first hospital in Australia and the southern hemisphere to deliver MRgFUS therapy. The \$6.5 million dollar technology has been installed in St Vincent's Hospital radiology department and MRgFUS treatment for tremor patients is scheduled to commence in late 2018.

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Magnetic Resonance Imaging Guided Focused Ultrasound (MRgFUS): stereotactic neurosurgery without an incision



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HISTORY OF STEREOTACTIC INTERVENTIONS FOR MOVEMENT DISORDERS

Surgical intervention of deep structures of the brain movement disorders and psychiatric disease has a long history since the 1950's. In particular thalamotomy and pallidotomy were effective to suppress movement disorders including tremor and dystonia by interrupting cortical, cerebellar and basal ganglia connections. Stereotactic lesions are usually created using focal heating from a radiofrequency (RF) electrode passed through the brain to the target structure. Electrical stimulation was often used to test the target area before committing to a permanent lesion, and these observations were seminal in later development of deep brain stimulation. With RF lesional surgery some patients experienced significant adverse events due to the inherent risks of passing instruments into the brain including



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stroke or haemorrhage and consequences of lesions encroaching nearby structures resulting in permanent neurological deficit. It was also observed that bilateral thalamotomy or pallidotomy carried a higher risk for deterioration in speech, swallowing and gait, and therefore most procedures were performed unilaterally to minimize side effects.

Thalamotomy and pallidotomy declined dramatically after the advent of levodopa treatment for Parkinson's

disease in the late 1960s. The success of levodopa for Parkinson's motor symptoms was tempered by the later realization of delayed motor complications in levodopa treated Parkinson's patients including severe dyskinesia, which led to renewed interest in pallidotomy in the 1980s and brief renaissance of lesional surgery in the 1990s. Limitations of stereotactic lesions particularly side-effects associated with bilateral lesions drove interest in neurostimulation culminating in the development of modern era of deep brain stimulation (DBS) with thalamic stimulation for tremor by Alim Benabid and the Grenoble group in 1987. Studies of basal ganglia circuit dysfunction in the MPTP monkey model of Parkinson's disease elucidated the overactivity in the subthalamic nucleus (STN) as a critical node in PD pathophysiology and an efficient target for Parkinson's motor symptoms. The first Parkinson's patients were treated with STN DBS in 1993 by the Grenoble group. DBS utilizes pacemaker technology to deliver continuous high-frequency electrical stimulation through implanted electrodes to specific targets within the brain. Advantages of DBS over RF lesions include reversibility, adaptability of therapy via stimulation parameter programming and the ability to safely perform bilateral procedures to control motor symptoms on both sides of the body. Disadvantages of DBS include the need for instruments to be passed into the brain resulting in 1-2 per cent risk of intracerebral haemorrhage and stroke, and ongoing risks of infection and breakage of the implanted devices. Randomized controlled trials have shown DBS to be an effective therapy for medically refractory movement disorders including Parkinson's disease, dystonia and tremor.

BRIEF HISTORY OF MRgFUS TECHNOLOGY

The therapeutic application of focused ultrasound was pioneered in the 1950's by Lindstrom and Leksell in Sweden and the Fry brothers of the University of Illinois USA. Due to the inefficiency of the ultrasound traversing bone, these procedures required an acoustic window to be provided by means of a craniotomy. In 1992 Hynynen proposed using an array of multiple focused ultrasound beams under MRI guidance to treat brain tumors, and was first to use the term MRI guided Focused Ultrasound. In 1998 Insightec an Israeli technology

Figure 1. Insightec Exablate 4000 system. Note hemispherical ultrasound transducer array with specialised table, allowing patient and head assembly to move in and out of the MRI bore for intra-procedural scanning and out for clinical testing of tremor.



company partnered with GE to develop the first clinically effective, commercial MRgFUS system. The first successful clinical trials of MRgFUS were in 2003 for uterine fibroids. In 2006 Insightec achieved a major breakthrough by developing the first version of ultrasound transducer arrays capable of penetrating the skull to treat brain tissue, and being accurately focused using MRI guidance and a skull CT based algorithm. While recent advances in multi-element transducers have largely overcome skull thickness as a barrier to clinical MRgFUS, a small minority of patients have unfavourable low skull-density ratio, as determined by CT algorithm and are unsuitable for MRgFUS.

MRgFUS PROCEDURAL ASPECTS

MRgFUS utilizes multiple transducers to transmit high intensity focused ultrasound energy through the skull to ablate a precise area of brain. The machine employs two technologies: focused ultrasound beam which heats and ablates targeted tissue whilst avoiding damage to adjacent tissue not in the therapeutic target, and real-time MRI thermometry (thermal imaging sequences accurate to 0.5 degree C) to monitor the heating effect and confirm spatial accuracy of lesion placement. The currently available commercial system, Insightec Exablate 4000 uses 650 KHz high intensity ultrasound waves delivered from 1024 sources mounted in a hemispheric array (**Figure 1**) with a natural focus where the beams converge.

The phase of each source can be varied, using an algorithm taking into account the predicted impedance of the overlying skull bone, such that waves summate or cancel to maximize transfer of energy across the skull. Beams traversing air filled sinuses or calcified structures such as choroid plexus are inactivated, usually leaving 80-90% of total beams available for therapy delivery. Convergent ultrasound energy is dissipated at the focal point as heating, creating a "heat spike" which is measured directly using specific MRI thermometry sequences (**Figure 2**).

The procedure begins with the patient's head being shaved and placed in a stereotactic frame under local anaesthesia. An elastic membrane is placed over the frame and seals the head assembly with is filled with circulating chilled, degassed water in order to prevent excessive scalp heating and facilitate acoustic coupling. The natural focus is aligned with MRI localized brain target region using both mechanical adjustment of the patient's head position within the hemispherical array, and by adjusting phase of ultrasound beams to shift the position of the focal point (phase focusing). These adjustments allow the visualised heat spike to be precisely aligned with desired, MRI determined target. The delivery of MRgFUS therapy (sonication) takes place in the MRI bore with simultaneous MRI thermometry. The treatment episode comprises a series of verification sonications at 43-45°C, to determine specific energy requirements for temperature rise and verify spatial accuracy followed by focal heating at temperatures 48-50°C is assessed which

allows determination of clinical effects and side effects without inducing a permanent lesion. Clinical testing of tremor, motor symptoms and side effects is performed repeatedly after each sonication. Once the optimal lesion site is determined both radiologically and clinically the energy delivery is increased to generate focal heating 56-60°C and create a permanent stereotactic lesion. T2 MRI imaging is used to visualise the lesion post sonication and confirm correct placement.

A major advantage of MRgFUS intervention is its minimal invasive nature without requiring skin incision or skull opening. Patients remain awake, and do not require general anaesthesia. The procedure takes place in an MRI suite rather than an operating theatre and sterile fields are unnecessary. The treatment is completed in one session of 2-4 hours duration.

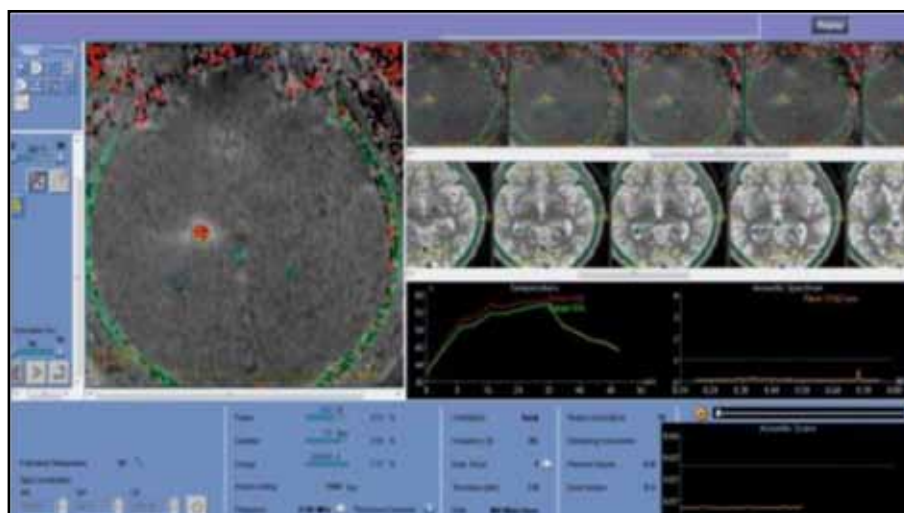
OVERVIEW OF TARGETS AND INDICATIONS:

The most well studied target for MRgFUS is the ventral intermediate (VIM) nucleus of the thalamus for tremor. Other targets within the thalamus including nucleus ventralis oralis anterior/posterior (VOA/VOP) are being investigated for treatment of focal upper limb dystonia. Basal ganglia targets, including the globus pallidus internus (GPi) for Parkinson's disease and dystonia, are being developed within clinical trials. The subthalamic nucleus (STN) has been targeted for the treatment of Parkinson's disease. An emerging development is the use of MRI diffusion tensor imaging (DTI) tractography to visualise white matter tracts connecting the cerebellum, basal ganglia and thalamus, including the dentatorubrothalamic tract and pallidothalamic tract, which are targeted directly using MRgFUS (Chazen et al 2018, Gallay et al 2018).

ESSENTIAL TREMOR

MRgFUS VIM thalamotomy has been shown to be effective in the treatment of essential tremor in a multicenter randomized sham controlled rater blinded study of 76 patients with 1 year follow-up (Elias et al 2016). Compared with the sham procedure MRgFUS thalamotomy resulted in 47% improvement in contralateral upper limb tremor compared with no significant change in tremor in the sham treatment group. Quality of life and disability also

Figure 2. MRI thermometry provides real time MRI thermal brain imaging during MRgFUS sonication. Note thermal image of thalamic target during sonication and real-time heating curve showing temperature.



improved significantly only in the active MRgFUS group. Benefits for tremor were maintained at 12 months. Side effects were most commonly transient parasthesias and gait unsteadiness, with only one patient experiencing a severe adverse event, persistent numbness in one hand. On the basis of this study, MRgFUS was granted FDA approval for treatment of essential tremor in 2016 and Australian TGA approval was granted in 2017. An extension study following the same cohort has shown stable improvement in tremor to two years follow up (Chang et al 2017). A recent study evaluated the safety and side effect profile of MRgFUS thalamotomy in 186 patients from five studies. Procedure-related serious adverse events were very infrequent (1.6 per cent), with no intracerebral hemorrhages or infections. Adverse events were usually transient and were commonly rated as mild (79 per cent) and rarely severe (1 per cent). As previously reported, abnormalities in sensation and balance were the commonest thalamotomy-related adverse events. (Fishman et al 2018)

PARKINSON'S DISEASE

Studies have reported beneficial effects of MRgFUS VIM thalamotomy for treatment of Parkinson's tremor (Bond et al 2017, Zaaroor et al 2018) with improvement in tremor of up to 60 per cent. MRgFUS pallidotomy has also been reported beneficial for cardinal motor symptoms of rigidity and bradykinesia and relief of dyskinesia (Jung et al 2018). Unilateral subthalamic nucleotomy using MRgFUS has been shown to be beneficial in

reducing Parkinson's motor symptoms by approximately 50 per cent in both ON and OFF dopaminergic medication state, with one patient experiencing upper limb dyskinesia (hemichorea/hemiballism) contralateral to the subthalamic lesion, which resolved within three months (Martinez-Fernandez et al 2018).

DYSTONIC TREMOR AND DYSTONIA

Dystonic tremor may closely resemble and be misdiagnosed as essential tremor. It typically produces a jerky tremor of hands and head, worse in certain positions or with particular tasks. A recent study reported beneficial effects of MRgFUS VIM thalamotomy in three patients with dystonic tremor (Fasano et al 2017). MRgFUS thalamotomy targeting VOA/VOP is being studied as a treatment for focal upper limb dystonia in Japan (Horisawa et al 2018), where conventional RF thalamotomy of VOA/VOP is an established treatment for focal upper limb dystonia including writer's cramp and musician's dystonia.

OTHER EMERGING CLINICAL APPLICATIONS FOR MRgFUS

There is burgeoning research into the use of MRgFUS for the ablative treatment of brain tumours, epilepsy, psychiatric disorders such as obsessive compulsive disorder and pain. Neuropathic pain was actually the first brain condition treated successfully using MRgFUS using medial thalamotomy (Martin et al 2009).

MRgFUS can also be used to disrupt the blood-brain barrier (BBB) for targeted medication delivery of chemotherapy, antibiotics, immunological agents or neurotrophic growth factors. Reversible BBB disruption can be facilitated by injection of micro-bubbles into the circulation which oscillate, stretching the vessel wall, and gadolinium enhanced MRI can be used to monitor the area of BBB disruption (Weintraub et al 2017). MRgFUS can also be used to ultrasonically disperse insoluble protein aggregates in the brain such as amyloid and tau, and is being investigated as potential therapy for Alzheimer's disease (Meng et al 2017). Additionally, focused ultrasound offers the possibility of reversible neuromodulation by using the mechanical and non-thermal properties of low-intensity acoustic energy (Fomenko et al 2018). The reversible effect at low temperature allows for therapeutic testing while creating lesions using MRgFUS. The ability to modulate neuronal activity with high spatial resolution may soon be applied clinically and offers great potential in elucidating brain networks.

COMPARISON OF MRgFUS WITH CURRENT THERAPIES AND SAFETY CONSIDERATIONS

MRgFUS ablative therapy aims to provide immediate improvement of symptoms. Real-time feedback and monitoring allows refinement of the target site and focused therapeutic dosing. It also has a high safety profile with minimal complications. There currently remains no randomized head-to-head studies directly comparing DBS and MRgFUS but there are several studies that have compared the therapies using the available data which have concluded that MRgFUS thalamotomy for tremor provides therapy benefits equivalent to conventional RF thalamotomy or thalamic DBS (Kim et al 2017).

From a safety perspective, MRgFUS eliminates the need for skin incision, skull opening or instruments being passed into the brain. This greatly reduces the risk of intracerebral haemorrhage or stroke, which have so far not been reported (Fishman et al 2018, Gallay et al 2018). MRgFUS is associated with a relatively frequent

incidence of mild transient side effects, in particular parasthesiae following MRgFUS thalamotomy. MRgFUS can be considered minimally invasive by virtue of its novel transcranial delivery system however a small permanent brain lesion mediates the therapeutic effects. Precise placement of MRgFUS lesions is critical to the success of MRgFUS therapy and conversely misplaced lesions have potential to result in permanent neurological deficit. Given the criticality of correct lesion placement for safety, it is reassuring that the available evidence suggests the MRgFUS is very accurate. A recent study of 180 MRgFUS treatments found the mean lesion location 3D accuracy was 0.73 ± 0.39 mm to the intended target (Gallay et al 2018). MRgFUS also minimizes infection and bleeding and has a shorter recovery time. The patient does not require general anaesthetic and does not experience hardware complications or require programming of device therapy. Procedural times and expense are less than for DBS and despite high establishment costs, the technology may provide a more affordable option in resource deficient countries.

CONCLUSIONS AND PERSPECTIVES

MRgFUS has emerged as a novel, noninvasive alternative to conventional neurosurgery for treatment of a number of brain disorders. As a feasible method for precision ablation in deep brain structures it provides immediate and sustained improvement in tremor and has great potential to be equally effective in other movement disorders. It does not involve implantation of instruments or devices, does not require laborious postoperative adjustments or replacements, has no risk of infection and is more economical than deep brain stimulation. As stereotactic lesions enjoy a renaissance, MRgFUS is increasingly the preferred methodology. Neither lesions nor neurostimulation guarantees therapeutic control or represent a cure for underlying brain disorders, particularly patients with chronic neurodegenerative conditions who continue to deteriorate. Nevertheless, MRgFUS provides a new way to significantly improve quality of life for patients with movement disorders and potentially other neurological conditions in the future.

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