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Incisionless MR-guided focused ultrasound: Technical considerations and current therapeutic approaches in psychiatric disorders

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Abstract

Introduction: MR-guided focused ultrasound operating at higher intensities have been reported to effectively and precisely ablate deeper brain structures like the basal ganglia or the thalamic nuclei for the treatment of refractory movement disorders, neuropathic pain and most recently neuropsychiatric disorders, while low-intensity focused ultrasound represents an approach promoting mechanical blood-brain-barrier opening and neuromodulation. This narrative review summarizes the

technical development and the therapeutic potential of incisionless MRgFUS in order to treat neuropsychiatric disorders.

Areas covered: A narrative review of clinical trials assessing the safety and efficacy of MRgFUS. A literature review was performed using the following search terms: MR-guided focused ultrasound, psychiatric disorders, noninvasive and invasive brain modulation/stimulation techniques.

Expert opinion: MRgFUS ablation is under clinical investigation (unblinded study design) for obsessive-compulsive disorders (OCDs) [capsulotomy; ALIC] and depression/anxiety disorders [capsulotomy] and has demonstrated an improvement in OCD and depression, although of preliminary character. Low-intensity ultrasound applications have been explored in Alzheimer´s disease (phase 1 study) and healthy subjects.

Currently, limited evidence hinders comparison and selection between MRgFUS and noninvasive/invasive brain modulation therapies. However, comparative, sham-controlled trials are needed to re-examine the preliminary findings for the treatment of psychiatric disorders.

Keywords: Non-invasive MR-guided focused ultrasound; cingulotomy; capsulotomy; deep brain stimulation; depression; obsessive-compulsive disorder; radiosurgery; outcome measures

Article highlights

- Non-invasive ultrsaound ablation (MRgFUS) represents a novel option for lesioning therapy in psychiatric disorders
- Depression and obssessive-compulsive disorder are currently trialed in ongoing studies

- Depending on energy intensity, non-ablative MRgFUS has the potential to modulate multifocal brain circiuts
- Comparative studies including other brain stimulation/modulation approaches are needed in order to determine its therapeutic potential

1. Introduction

Pharmacological and psychotherapeutic interventions represent the first-line treatment for psychiatric disorders.

However, one-third of psychiatric patients achieve a limited response or suffer from drug-associated side effects. Under such circumstances, noninvasive [transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), electroconvulsive therapy (ECT), ablative Gamma Knife radiosurgery (GKRS), MR-guided focused ultrasound (MRgFUS)] and invasive brain modulation procedures [deep brain stimulation (DBS), surface/epidural brain stimulation (EpS), ablative radiofrequency (RFA), extracranial cervical vagus nerve stimulation (VNS)] have resulted in encouraging responsiveness (depending on the applied technique) and are currently under clinical investigation [1-16].

Most recently, a non-invasive approach, namely, stereotactic MRgFUS using high-intensity focused ultrasound lesioning (HIFU; 650-720 kHz) was clinically introduced targeting deeper brain areas, such as the basal ganglia and the thalamic nuclei. So far, HIFU was mainly applied for the treatment of movement disorders, while first studies addressed its potential as an adjunctive treatment strategy in otherwise refractory chronic neuropathic pain and neuropsychiatric disorders [10, 12, 16-24].

The application of therapeutic ultrasound for brain disorders has been under investigation for over 5 decades, but its usefulness has been limited due to the requirement of craniotomy (i.e. bone reflection) and restricted access for the adequate intra-procedural neurological monitoring (MR-thermometry) of hyperthermal ablation [25,26]. Interestingly, the intracranial therapeutic application of ultrasound dates back to the birth of stereotactic neurosurgery with William Fry (1918-1968) and Russels Meyers (1904-1999), who pioneered, among others, the use of ultrasound to treat brain disorders and first treated Parkinson's patients in 1954 [25]. The MRgFUS device [ExAblate 4000 Transcranial System with 1024 elements; INSIGHTEC, Tirat Carmel, Israel] helped overcome these restrictions and allowed precise and accurate MR thermal mapping-controlled ablation of small brain targets within deeper brain structures [27-31].

HIFU (MRgFUS at 650 kHz) has been FDA-approved and received CE marking for lesioning procedures of the thalamic nuclei (nucleus ventralis intermedius, VIM) to treat essential tremor (ET) and tremor-dominant Parkinson's disease (PD). In addition, the use of HIFU has been suggested to treat neuropathic pain (ventralis posterolateralis nucleus of the thalamus, VPL) [18-21, 32]. Currently, the efficacy and safety of HIFU for psychiatric disorders, mainly obsessive-compulsive disorder (OCD) and depression, are being assessed in ongoing in-human studies [11-14,27]. The ability to modulate brain circuits is not a unique result of non-lesioning effects, as in principle, lesions can modulate neural networks in a more permanent fashion, while reversible neuromodulation represents a functional and structural consequence of non-lesioning effects [15, 16, 27, 31].

Herein, we provide a narrative review discussing the technical development and characteristics of high (HIFU, thermal ablation) and low (LIFU, non-thermal) intensity

MRgFUS and current approaches for the treatment of psychiatric disorders. Briefly, possible advantages/disadvantages of MRgFUS (HIFU/LIFU) are compared to non-invasive and invasive (ablative – non-ablative) brain stimulation concepts.

2. Material and methods

Data sources included relevant literature identified through searches of PubMed, MEDLINE/OVID, SCOPUS and manual searches of the bibliographies of known primary and review articles using the search terms stereotactic MR-guided high-intensity focused ultrasound deep brain ablation, capsulotomy, cingulotomy, subcaudate tractotomy, limbic leucotomy, randomized-controlled trials, safety/efficacy, complications, HIFU, psychiatric disorders, depression, Tourette, obsessive-compulsive disorder (OCD) and anxiety disorders to identify primary outcome measures. Due to the limited number of published trials we present the data as a comprehensive (narrative) review.

3. Technical considerations

Therapeutic intracranial use of ultrasound has been under investigation for some decades, but its accessibility has been limited by the necessity of craniotomy and the lack of neuroimaging monitoring (thermal mapping) modalities to precisely control the ablated tissue volume in real time [10, 15]. Technical progress has permitted the accurate application of small brain tissue lesions in a non-invasive manner through the intact cranial vault (incisionless) by using a frame-based (stereotactic) MR-thermal mapping approach. MRgFUS is capable to induce heat-evoked small ablations in deeper brain structures, such as the basal ganglia, the thalamic nuclei and adjunct brain areas. Hyperthermal permanent ablations (HIFU;

high-intensity ultrasound at 650 kHZ) have been performed for a variety of movement disorders and in a fewer studies for neuropathic pain, depression and OCD.

However, an important patient-related factor is the skull density ratio (SDR) that may hamper the MRgFUS transmission rate. General indications and contraindications are characterized by the acoustic properties of the skull as the skull bone (density differences, bone layer thickness) absorbs, reflects and refracts ultrasonic waves. The different acoustic velocities between brain tissue (1500 m/sec) and the skull bone (2700-3000 m/sec) evoke entrapment of the ultrasonic waves with subsequent bone heating and damage [31, 33-34].

The different acoustic velocities of the cranial vault (outer layer = 3000 m/sec; diploie = 2700 m/sec; inner layer = 3000 m/sec) represent another considerable confounder leading to relevant heterogeneity in the ultrasonic wave speed, distribution and absorption rate [31, 35-36]. These technical confounders of the past has been surmounted mainly by applying non-invasive aberration correction techniques, in particular a correcting phase (time-reversal processing; phase conjugation focusing) on the transmit signal of each component of the ultrasound array permitting the therapeutic use of FUS in a non-invasive manner. Thermal ablation (coagulation necrosis) induced by HIFU (MRgFUS at 650 kHz) leads to protein denaturation means of neuronal cell death. It is noteworthy that the ratio between the acoustic intensities of brain tissue (treatment target area) and the skull bone decreases with the intended targets distance to the skull bone/base. Hence, some proposed targets (e.g.for certain neurological indications (e.g. pedunculopontine nucleus (PPN) for Parkinson´s disease), which are located near bone structures (skull base heating), may not be suitable approaches for intracranial ultrasound therapy.

3.1 MRgFUS at lower frequency 220 kHz (low-intensity focused ultrasound; LIFU)

Further progress of MRgFUS exhibited improvements in aberration corrections and cavitation-enhanced heating along with the use of a lower frequency (220 kHz). Given existing technical reports along these lines, these LIFU developments may open the avenue for novel treatment strategies [31]. For instance, low-frequency, low-intensity ultrasound (LIFU) in combination with intravenous injected microbubbles paved the way towards novel clinical treatment approaches using mechanical ablation, blood-brain-barrier opening and non-ablative neuromodulation [30,31,37]. Experimental studies addressing the therapeutic potential of LIFU for third ventriculostomy suggest that oscillations of circulating microbubbles evoke transcranial tissue fraction (cavitation-enhanced ablation) at a lower frequency (220 kHz), while higher frequencies (650 kHz) demonstrated limited effects [38]. Under experimental conditions, LIFU applied with a low-duty cycle was able to create safely sharp lesions adjacent to the optic nerve and white matter fibers. A rising number of experimental studies have demonstrated the potential of LIFU in conjunction with injected microbubbles to open the blood-brain barrier (BBB) transiently and safely. There remain open questions from previously published and ongoing experimental studies that point to the need for further investigations, in particular to address the quantification of vascular permeability and BBB closure dynamics [39, 40].

However, LIFU-induced BBB opening may become valuable in the treatment of Alzheimer´s disease in humans [28, 39-44]. Lastly, LIFU has been applied to promote targeted and precise neural responses in brain structures associated with vision, motor and behavior by neuromodulation means. Although the precise mechanism of action of LIFU remains to be clarified, some working hypotheses have

considered synaptic neurotransmitter release and/or modulation of mechanosensitive channels triggering action potentials as possible pathways by which LIFU exerts its neuromodulatory effects [31]. LIFU (non-ablative, mechanical) has been suggested to evoke effects by inhibiting action potential generation and propagation or by opening the BBB in conjunction with circulating microbubbles. Although not within the scope of our narrative review, it is noteworthy that LIFU exerts its effect on a non-lesioning basis with the capability to serve as a diagnostic (mapping) and therapeutic (neuromodulation) device. LIFU has been investigated in healthy volunteers and is currently being trialed for Alzheimer's disease targeting to mechanically open the BBB [10, 16, 44]. Due to its non-ablative character, LIFU encompass the possibility to perform neuromodulation targeting multiple brain networks. As mentioned, current findings were addressed to investigate healthy subjects and preliminary observations in a small-scale AD phase 1 trial [27, 40].

3.2 MRgFUS at higher frequency 650 kHz (high-intensity focused ultrasound; HIFU)

However, this narrative review will focus on the therapeutic potential of MRgFUS utilizing thermal lesioning (HIFU). Ultrasonic sound waves of 650 kHz (HIFU; ablative) are used to rapidly propagate through intact skull/brain tissue, as interfaces such as bone and skin reflect ultrasonic waves, which may lead to energy loss and decreased precision. With respect to target precision, Moser et al. found a target deviation of 0.5–0.7 (<1 mm) in the mean target accuracy [45]. The HIFU device constitutes of a 1.5 or 3 Tesla MRI systems (GE healthcare and Siemens systems, respectively) and a helmet-like array with 1024 transducer components that frame-based (stereotactic) focus ultrasonic waves precisely onto small structures located deep within the brain (Figure 1a). It is important to note that MRgFUS was approved

(FDA and CE) in combination with MRI scanners from GE Healthcare Inc., and most recently, this approval was extended towards Siemens Healthineers Inc. MRI-based treatment of ET and PD. The device consists of a generator (electrical signal), an amplifier, and a transducer (piezoelectric elements), which can convert the electrical signal into defined sound waves (transmitter) and receive the reflected sound waves to monitor the safety and appropriateness of the transmitted energy. Pre-procedural stereotactic CT scans are mandatory to calculate and integrate individual bone thickness and to correct/adjust the output of each of the separate transducer elements [27, 45]. Focusing the ultrasonic waves produces local brain tissue hyperthermia. Target alignment (reversible) is achieved at a temperature ≤ 45°C (low-power sonication, 150-250 W) with real-time thermal feedback for target verification and adjustment. Real-time clinical evaluation prior to lesioning is achieved with temperature raises in the range of 45-50°C, which in turn is related to the patient´s SDR and permits intraprocedural clinical testing in order to assess an early, reversible response and therefore allowing refinement to verify target accuracy and to avoid ablation-associated side effects. Permanent ablation requires a higher temperature of 52–60°C along with a treatment duration of 10-20 sec (Figure 1b).

This reversible characteristic is of clinical value in movement disorders such as ET and PD (tremor assessment) to predict HIFU treatment response but may be limited in psychiatric disorders (except for safety role) due to the lack of an immediate intraprocedural response in ultrasound treated individuals suffering from psychiatric diseases like OCD or depression (Fig. 1b). In particular for psychiatric disorders applications, the possibility to confirm patient´s feedback represents an unresolved issue of ongoing debate. Future clinical research should seek to include a sham/control group, as this can be done by limiting the temperature below 42°C,

which has been characterized not to evoke permanent lesioning. In addition to its non-invasive nature, MRgFUS (HIFU) offers several advantages: the standardized interventional protocol enables comparative studies (DBS, GKRS, RFA), and the absence of neuro-implants that in part restricted neuroimaging investigations will facilitate pre/post HIFU neuroimaging studies, which may help to elucidate structural and functional changes of neuropsychiatric disorder-associated brain circuits. In general, compared to other noninvasive/invasive (ablative / non-ablative) brain modulation concepts, ultrasound-based intracranial therapies provide a high resolution of both, space and time, operate noninvasively and allow the targeting of deep brain neural structures (basal ganglia, thalamus, cingulate cortex) relevant to a broad variety of neurological and psychiatric disorders [31].

The insufficient number of available in-human studies comparing the impact of MRgFUS [HIFU/LIFU] for the treatment of psychiatric disorders versus other brain stimulation/modulation approaches currently limits a comparative interpretation of the safety, tolerability, ease of application and efficacy of MRgFUS versus noninvasive [GKRS, TMS, tDCS, tACS, ECT] and invasive brain modulation [RFA, surgically implanted brain electrode systems—either surface/epidural, e.g. DBS, MCS) (DBS)] [32, 46-49]. Assessing tremor responsiveness and functional outcomes in ET patients retrospectively, Huss and colleagues found similar results for unilateral motor control and improvement in quality of life when comparing bilateral thalamic DBS (nucleus ventralis intermedius of the thalamus, VIM) versus unilateral thalamic DBS versus unilateral HIFU thalamotomy, with bilateral VIM DBS promoting an overall tremor improvement. Hence, unilateral VIM HIFU may be considered prior to unilateral VIM DBS in ET patients [20, 46]. Further preclinical studies have indicated similar tissue characteristics (diameter and configuration of concentric lesions)

quantified by neuroimaging and immunohistochemical assays of the thalamus after focused ultrasound treatment compared to GKRS. Furthermore, a similar dynamic of the evoked lesions was found for focused ultrasound and GKRS. While the edematous component largely abates (immediate lesions within 48 hours that resolved after 7 days), the areas of coagulative necrosis (zone I and II) persist over a longer time span. It should be noted that radiosurgery-induced lesions appeared with longer latency, were less circumscribed and, most importantly, produced histological changes in white matter areas outside the targeted brain area (e.g. thalamic nuclei), suggesting a less precise and delayed clinical effect of GKRS compared to MRgFUS [47].

It is noteworthy, that frequency represents one of several variables relevant for the delivered amount of energy (e.g. mechanical index, thermal index, spatial-peak-pulse intensity and temporal-peak-pulse intensity). Contrary to HIFU/LIFU using multiple elements, Legon and colleagues investigated the effects of a single-element focused ultrasound approach on the sensory property of the thalamus (ventral posterolateral nucleus; VPL) and observed physiologic and behavioral changes quantified by electrophysiological means (somato-sensory evoked potential) in healthy volunteers [50].

4. Current psychiatric indications using the HIFU approach (thermal lesioning)

4.1 Major depressive disorder (MDD)

The therapeutic potential of MRgFUS is currently being assessed in a phase 1 trial for depressive symptoms in primarily diagnosed OCD patients (NCT 02348411; NCT03421574; anterior limb of the capsula interna (ALIC)) [13, 27, 51]. Despite these preliminary, positive findings in primary diagnosed OCD patients with

depressive symptoms, limited evidence exists so far for the therapeutic potential of HIFU to treat major depressive disorders (MDD), and one has to await the results of ongoing trials (table 1).

In a case report associated with a preliminary study (NCT 02348411), Kim et al. [13] observed significant and sustained (12-month follow-up) improvements in Hamilton Depression Score (HDRS), Beck Depression Inventory (BDI) and Global Assessment of Functioning (GAF) in one refractory female MDD patient (i.e., not responsive to psychotherapeutics or electroconvulsive therapy) bilaterally treated with HIFU targeting the ALIC. However, the tissue volume lesioned was different across hemispheres (right ALIC, 70 mm^3 versus left ALIC, 9 mm^3) [13].

Most recently, Davidson et al. evaluated clinical and neuroimaging effects of MRgFUS capsulotomy (anterior limb of the capsula interna) (ALIC) on limbic circuits in 6 MDD patients and followed up for 12 months (NCT03421574). One third (2 MDD patients) fulfilled the criteria as responder defined as ≥50% reduction in the HAMD-17 along with an improved quality of life. Interestingly, structural pre-/post-sonication neuroimaging revealed fiber circuits within the lesions, which project from the ventromedial / orbitofrontal cortex to the thalamus, the ventral striatum and the medial temporal lobe, structures relevant in the pathophysiology of both, OCD and MDD. Furthermore, metabolic changes were observed predictive to differentiate responders versus non-responders [51].

4.2 Obsessive-compulsive disorder (OCD)

A phase 1 trial in OCD (NCT 01986296/ NCT 03156335; ALIC) is currently ongoing. In contrast, there have been a number of procedures in which HIFU was performed to treat OCD patients. Despite the ongoing phase 1 HIFU-OCD trials (NCT

01986296/ NCT 03156335; ALIC), HIFU-associated responsiveness has been published in four OCD patients treated with ALIC-HIFU thus far (table 1). Assessed by the Yale-Brown Obsessive Scale (Y-BOCS), ALIC-HIFU was found to effectively improve Y-BOCS scores by 33%. Currently, eleven patients have been treated with a mean follow-up of 24 months. HIFU-associated adverse events [nausea, vomiting, dizziness] were transient and mild (NCT 01986296) [11, 12, 14, 27]. ALIC has been targeted in OCD patients based on lessons learned from prior lesioning and DBS studies and, most recently, in MDD. Prefrontal and anterior cingulate cortex brain circuits are connected to the hippocampus, amygdala and thalamus via ALIC fibers (limbic corticothalamic network) that modulate the brain areas crucial for affective and emotional transmission [27]. Similar to ionizing radiation (GKRS), the clinical effects appear to occur over a longer time period in DBS, lesioning interventions such as capsulotomy/cingulotomy and MRgFUS (HIFU) procedures. Although in an early stage, a comparison of the extent of responsiveness (Yale-Brown Obsessive Compulsive Scale YBOCS) suggests that the outcome results with HIFU are below those reported for DBS (Y-BOCS, 41% responder rate), GKRS (Y-BOCS, 51% reduction) and other lesioning approaches such as capsulotomy/cingulotomy (Y-BOCS, 50-55% reduction) depending on the applied technique. Despite the fact, that capsulotomy and cingulotomy exhibited an enhanced outcome compared to DBS and GKRS, DBS seems to be perceived more acceptable, mainly to its reversible characteristics. On the other hand, available OCD literature suggest RFA capsulotomy to be superior to cingulotomy and that RFA is more effective than GKRS [27, 32, 46-49]. Another phase 1 trials observed meaningful improvement (NCT 03156335; ALIC) in mood, anxiety and quality of life in 66% (4/6) of refractory OCD patients. No treatment-associated side-effects were observed, despite transient

headaches, within the observation period of 12 months. Based on these preliminary results, it appears, that capsulotomy responsiveness is higher in OCD compared to MDD, which is in line with previous lesioning studies (RFA). This study group firstly applied PET imaging as potential objective outcome measure and found decreased glucose metabolisms in the middle temporal gyri, central gyri, the right middle frontal gyrus, right posterior cingulate gyrus and connected subcortical structures (amygdala, hippocampus, putamen). [51].

Of note, several targets have been stimulated in DBS trials for OCD (e.g. ALIC, nucleus accumbens, ventral striatum); hence, a comparison of the non-ablative, reversible DBS versus ablative, non-reversible ALIC-MRgFUS effects may be confounded. However, the procedural risk-benefit ratio among the presented techniques (MRgFUS, DBS, GKRS, cingulotomy, capsulotomy) may justify the use of HIFU in view of the low-risk profile. Studies comparing HIFU versus DBS or other brain stimulation strategies have not been conducted thus far.

5. Current neuropsychiatric indications using the LIFU approach (BBB opening)

5.1 Early to moderate Alzheimer´s disease (AD)

Based upon preliminary observations (transient BBB opening, reduced beta-amyloid/tau aggregates) in an experimental setting, Lipsman and co-workers conducted an open-label, observational phase 1 AD safety study applying intravenously injected microbubbles and targeting white matter of the frontal lobe (NCT 02986932

dorsolateral prefrontal cortex) in 5 AD patients. Although of preliminary character, this pilot study found no significant differences when assessing safety, reversibility

and serious clinical and radiographic (^{18}F)-florbetaben-PET adverse events before BBB opening and after 3 months of sonication treatment. Clinical features quantified by AD specific outcome measures (Mini Mental State, Alzheimer´s Disease Assessment Scale, Geriatric Depression Scale, Neuropsychiatric Inventory Questionnaire) remained unchanged before and after MRgFUS (LIFU) [40].

6. Future targeted clinical MRgFUS research

In summary, MR thermal mapping-guided, high-intensity focused ultrasound deep brain lesioning (HIFU) represents an old approach with a novel technology capable of avoiding skin, bone and dural damage, as reported in the initial days of therapeutic ultrasound application and reaching deep brain structures accurately. Published data and preliminary results of ongoing studies have demonstrated the potential usefulness and safety of HIFU as a non-invasive, ablative (thermal lesioning) deep brain modulation device for otherwise refractory psychiatric disorders such as obsessive-compulsive disorder (OCD) and in part depressive symptoms in OCD patients. In particular, lesioning of the anterior limb of the capsula interna (ALIC) by HIFU deserves additional attention for a comparison of the safety and efficacy of HIFU relative to those of cingulotomy / capsulotomy / subcaudate tractotomy / limbic leukotomy, deep brain stimulation (ALIC-DBS) , radiofrequency (RFA) and gamma knife radiosurgery (GKRS) [27].

Kumar and colleagues used a decision analytic model comparing MRgFUS with RFA capsulotomy for OCD and evaluated outcome measures including YBOCS improvement, safety (complication rate, procedural costs) and side effects. Interestingly, MRgFUS was more cost-effective than RFA capsulotomy indicating MRgFUS displayed a lower risk profile along with decreased medical care cost

compared to invasive RFA, [46].

These findings must be interpreted with caution, as it is far too early to compare cost effectiveness among these procedures due to the low number of psychiatric patients treated with MRgFUS. Several ablative approaches have been applied to treat a broad variety of psychiatric and neurological disorders attempting to create precise therapeutic lesions and/or to diminish pathological brain tissue (brain tumors). Given the focus of this narrative review on ablative interventions (HIFU), it may be worth to briefly mention the literature of cingulotomy and capsulotomy, in particular how MRgFUS in psychiatric disorders emerged from previous observations from cingulotomy and capsulotomy [32].

Cingulotomy (dorsal anterior cingulotomy) and capsulotomy, both have been applied in a sufficient numbers of OCD trials. Banks et al retrospectively determined neuroanatomical features in OCD patients treated with cingulotomy in order to explore potential predictive characteristics and to extract phenotype-based inter-individual variability. Using voxel-based morphometry (VBM) and diffusion tensor imaging (probalistic DTI), they found that decreased grey matter in the dorsal anterior cingulate cortex and increased right-sided connectivity (hemispheric asymmetry) significantly correlated with higher responder rate indicating an intra- and inter-individual variability relevant for cingulotomy outcome [52,53]. In addition to invasive lesioning approaches (RFA) of the anterior cingulate cortex, non-invasive GKRS has been used to perform capsulotomy for OCD suffers refractory to pharmacological and behavioral therapies. Similar to invasive ablative procedures and deep brain stimulation, the fronto-striatal circuits (fiber tracts) between the orbito-frontal cortex, the dorsal anterior cingulate cortex and subcortical networks has been largely the intended target. For instance, Rasmussen and co-workers

prospectively evaluated the impact of Gamma Knife ventral capsulotomy and observed significant and sustained improvements (defined as ≥ 35% reduction in YBOCS) in 56% of treated OCD patients observed over a time period of 3 years. Of note, in a meta-analysis comparing capsulotomy with VS/VC-DBS, the responder rate was higher in the lesioning group versus the DBS treated cohort [54]. So far, a broad range of procedures (invasive (RFA) and non-invasive (GKRS) cingulotomy/capsulotomy; VS/VC-DBS) demonstrated clinical improvement in refractory OCD, however, comparative data and a structured framework how to systematically evaluate theses different therapy options has not been established.

Similar procedures have been performed in treatment resistant MDD such as cingulotomy, capsulotomy, subcaudate tractotomy and limbic leukotomy [55, 56]. For example, invasive stereotactic dorsal anterior cingulotomy (microelectrode guided RFA) alone, or in combination with subcaudate tractotomy was found to promote significant to moderate responder rates in MDD patients with a mean follow-up of 30 months. Interestingly, a more pronounced response was observed in the subset of the study cohort, who required one treatment session compared to the subset of MDD patients requiring multiple stereotactic ablative sessions [56]. In one of the largest capsulotomy studies, Christmas and colleagues observed a responder rate of 50% (defined as 50% reduction in HAMD-17/MARDS) and a remitter rate of 40% (defined as 40% reduction in HAMD-17/MARDS) [55]. Contrary to invasive/non-invasive ablations, invasive non-ablative DBS is of reversible character and offers the ability to adjust the stimulation parameters. However, DBS in-human studies for MDD encompass several considerable targets such as the subgenual cingulate cortex (Cg25), the nucleus accumbens (NAC), the ventral striatum/capsula interna (VS/VC), the habenulae, the inferior thalamic pedcuncle (ITT) and the supero-lateral

branch of the medial forebrain bundle (slMFB). Although, all these mentioned DBS targets represent relay spots in affective regulatory brain networks, the target of choice and the optimal stimulation pattern relative to a subset of patients more likely to respond still remains open questions and yet has not been defined [57].

It is noteworthy, that despite MRgFUS, several alternative, incsionless ablative and non-ablative ultrasound techniques are currently under clinical and experimental investigations. Although this review specifically was addressed to MRgFUS, the authors briefly want to describe additional not MR-guided sonication therapeutics. It should be noted that for instance Beisteiner et al. assessed single ultrashort ultrasound pulses (transcranial pulse stimulation; TPS) and provided comprehensive findings including computational modeling data, experimental analysis and in-human TPS studies targeting healthy subjects (10 participants) as well as AD patients (35 patients). TPS (CE marked for AD) was found to be safe, well-tolerated and effective in 35 AD patients quantified by functional neuroimaging and neuropsychological metrics. Using ultrashort pulses instead of periodic waves and extended sonication trains, TPS (single mobile transducer system + infrared camera system) has been assumed to offer several advantages such as increased skull penetration (mechanical confounder), brain heating and decreased stimulation maxima. On a cellular level, it has been hypothesized, that TPS (3 µsec pulses repeated every 200-300 msec) evokes cell membrane associated changes of mechanosensitive ion channels with subsequent distribution changes of several extracellular transmitter circuits (serotonin, dopamine, brain-derived neurotrophic factor BDNF, glia cell-derived neurotrophic factor GDNF) [58]. Another non-thermal ultrasound technique, namely transcranial ultrasound (TUS) was under investigation in a double-blinded cross-over study design (8 MHz TUS versus sham TUS). Applied at the scalp of the

frontotemporal cortex (posterior part) in 14 chronic pain patients, TUS was found to significantly improve mood and in less extent pain severity within 40 minutes after sonication compared to placebo TUS. The precise mechanism of TUS (depth settings 3 cm) remains largely unknown, preliminary TUS is believed to interact with neuronal microtubules relevant for synaptic plasticity and learning/memory brain circuits. Despite transient headache, no TUS-associated severe adverse events were recorded indication the therapeutic safety of TUS [59].

However, based on current available literature, an evidence-derived comparative conclusion in favor or against a particular ultrasound technique [MRgFUS (HIFU/LIFU); TPS, TUS] remains to be established [40, 51, 58, 59].

7. Conclusion

However, based upon its non-invasive and standardized procedural characteristics and the potential therapeutic impact, MRgFUS may be more appropriate than other brain stimulation methods for comparable clinical conditions. While these nascent developments are exciting and MRgFUS constitutes a potential renaissance for ablative and non-ablative brain modulation, the question whether MRgFUS serves as a complementary or competitive procedure compared to NIBS, DBS, RFA and GKRS remains premature to appraise at this stage.

In addition, significant safeguards are highly waranted prior to performing this kind of procedure, as severely ill psychiatric patients deserves ressources that may not be considered ahead of time. Hence, MRgFUS should be performed in research centers set up to carefully study and care for these subjects.

8. Expert opinion

Beyond doubt, the level of evidence differs between the mentioned brain modulation technologies, thus an expert panel-guided procedural recommendation is highly warranted to conceptualize an integrative framework considering the impact of the different brain stimulation therapies (invasive versus non-invasive; ablative versus non-ablative).

Finally, an evidence-derived decision-making and clinical framework in favor of or against a specific brain stimulation therapy is currently hindered due to the insufficient amount of available literature addressed to in-human brain stimulation studies for psychiatric disorders. It is noteworthy, that some brain stimulation therapies may support each other by developing a neural network-based interventional strategy such as TMS prior to DBS. To what extent HIFU may benefit from for example TMS in order to determine suitable network-associated targets remains largely unknown [60, 61, 62]. Decision making for choosing the most suitable lesioning or neuromodulatory methodology is based upon multiple patient and surgeon factors that vary from case to case. Given these facts, decision-making for a particular approach should be guided by pre-existing evidence, if available, and the degree of the invasiveness of the applied brain stimulation therapy. Saying so, the authors propose to consider non-invasive brain stimulation therapies (TMS, tDCS, tACS, ECT) to be applied firstly. In case of failure and/or limited response, invasive treatment options (DBS, RFA) and non-invasive lesioning procedures (GKRS) or even extracranial cervical VNS may represent alternative treatment options. Nevertheless, some patients may prefer a reversible invasive approach (DBS) over a non-reversible non-invasive approach (GKRS). Given the current paucity of evidence for MRgFUS, one has to await long-term results in large-scale

MRgFUS in-human studies in order to estimate the comparative value of MRgFUS. Despite the preliminary character, the reported rate of adverse events appears to be lower for MRgFUS compared to open RFA and GKRS [51].

The dichotomization in responders and non-responders has been increasingly criticized; instead, an objective quantification of outcome measures and the individualized pre-procedural mapping of specific networks is propagated as a suitable methodology to recognize the inter- and intra-individual variability of the underlying network disruption or to integrate it into the selection of the intended brain target and the choice of the applied brain modulation techniques. This holds true for invasive as well as for non-invasive brain modulation approaches. Regardless of the applied technique, intensive clinical research is required until standardized therapy protocols can be established in order to improve proper patient selection. Due to the complexity and dynamic character of neuropsychiatric disorders and the pathophysiology of the underlying brain circuits, multifocal target points may be considered. The implementation of an individualized treatment algorithm in neuropsychiatric disorders represents an elaborate and complex, but forward-looking approach and represents the next step in the clinical and scientific development of validated invasive and non-invasive brain modulation therapy. With this in mind structural and functional neuroimaging, electrophysiological diagnostics [EEG, MEG], digital phenotyping and molecular inflammatory assays may become useful tools to counteract the bias due to the inter- and intra-individual variability. Such acquisition of different quantitative outcome measures (neuroimaging, molecular biology, electrophysiology, digital phenotyping) undoubtedly results in large amounts of data necessitating databank-based, automated and deep-learning pattern recognition systems in order to characterize biotypes of neuropsychiatric patients

more and less likely to respond to a brain modulation therapy [4, 60-62].

First, there was a selection bias in the referenced MRgFUS studies as there was no control of data collection bias such that the investigator who performed MRgFUS did not seem to be blinded to the patients' clinical treatment and conditions. Second, there was no placebo control, which could have been achieved by reversible ultrasound temperature between 40-42°C. Another important issue with MRgFUS that everyone recognizes but has been probably inadequately addressed in the literature represent the different MRgFUS parameters applied in terms of peak temperature, sonication duration, number of sonication, delivered energy and the extent of the created lesion volume. Several factors have been identified, which may impact the effects observed after MRgFUS.

For instances, Chang and co-workers retrospectively evaluated potential issues impacting the clinical effects of MRgFUS such as the relationship between peak temperature and sex, age, skull area of the intended sonication target, number of elements applied, skull volume and SDR. Among those mentioned parameters, skull volume (negatively) and SDR (positively) were found to correlate with the maximum temperature indicating a broad intra- and interindividual variability across the MRgFUS treated patients. Conclusively, a standardized MRgFUS protocol is urgently needed and remains to be established considering these potential confounders [64]

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* = *of importance, describing potential confounders of MRgFUS and how potentially to address these issues*

Table 1. Overview of current psychiatric indications and in-human phase 1 studies (except movement disorders, pain) with MRgFUS (HIFU and LIFU), including the proposed target, study type and ultrasound parameters applied, if available.

Ultrasound Technique	Indication	Target x,y,z in mm AC	Human Studies	Patients	Control	PT	Frequency / Ener
MRgFUS High intensity focused ultrasound Thermal ablation	MD MD OCD OCD	ALIC (7-8, 12, n.a) ALIC (7-8, 12, n.a) ALIC (7-8, 12, n.a) ALIC (7-8, 12, n.a)	[13]NCT 02348411 [51]NCT03421574 [14]NCT 01986296 [51]NCT03156335	1 6 11 6	--- --- --- ---	53°C right / 54 °C left 53°C 51-56°C 53°C	650 kHz / 15348±41 650 kHz 650 kHz 650 kHz
MRgFUS Low intensity focused ultrasound Non-Thermal	AD	BBB DLPFC (frontal lobe)	[40]NCT 02986932	4	---	---	220 kHz / 4.5 W

Abbr. MRgFUS – MR-guided focussed ultrasound; kHz – kilo Hertz; PT – peak temperature in grade Celsius; MD – major depression; OCD – o Alzheimer´s disease; ALIC – anterior part of the capsula interna; DLPFC – dorsolateral prefrontal cortex; BBB – blood brain barrier; x / y / z – vertical; AC - commissura anterior; mm – millimeter; J – Joule; sec – seconds; W – watt; AE – adverse events;

isorders; AD – Alzheimer´s erior; mm – millimeter; J –

Fig.1 a-b. Schematic illustration of the intraprocedural steps of MRgFUS (HIFU) using the following sonication parameters (power 800 W, energy 1040 duration 10-20 sec, duration of cooling 90 sec). The procedural steps include the following: **a.** Anatomic target localization by fusion of stereotactic CT scans wave adjustment) with the acquired MR sequences. **b.** Physiological real-time target verification by MR thermal mapping (≤ 45°C; reversible ablation for testing) and adjustment of sonication algorithms. Treatment step involves permanent ablation (> 45-50°C) leading to permanent coagulation/necrosis [63].

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