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COMMENTARY

Potential Goals, Challenges, and Safety of Focused Ultrasound Application for Central Nervous System Disorders

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1. BACKGROUND

Ultrasound (US) has been used for diagnostic imaging purposes [1] and therapeutic neuromodulation [2]. It has shown promising results for neurology and neurosurgery, but it still faces some challenges regarding efficacy and safety. This commentary discusses those issues to identify the gaps that could be covered in future research studies.

2. POTENTIAL GOALS AND CHALLENGES

Some neuromodulatory techniques are non-invasive (such as transcranial magnetic stimulation (TMS), and focused US (FUS)) [3, 4], while others require electrode implantations [3, 5]. Non-invasive techniques are devoid of conventional surgical risks [6,7], such as bleeding or infection [7-9].

The application of non-invasive methods may show limitations. For example, magnetic fields decay with distance, so TMS is effective at the cerebral cortex level [6, 9] but does not reach subcortical nuclei. Despite this, both low-intensity FUS (LIFUS) and TMS may be applied in a single procedure since they do not interfere with each other [10].

FUS may be an imaging and a therapeutic tool simultaneously [11]; FUS application may be US-guided with a single equipment [12, 13] which may be more accessible and less expensive than its magnetic resonance imaging (MRI)-guided counterpart [12]. However, further innovation is needed to couple those techniques to Doppler ultrasonography so US-guided FUS could be complemented with cerebral blood flow hemodynamic measurements, although some equipment is currently available for this purpose [12].

MRI [6, 14, 15] is used for guiding FUS application to specific brain regions, in both preclinical [16, 17] and clinical studies [7, 18]. However, its use is limited since some FUS targets, such as the globus pallidus internus, are not visible in conventional 3T MRI [19].

MRI-guided FUS is still advantageous over US-guided FUS because of its better contrast resolution and the ability to monitor the US-induced temperature rise by thermometry [12, 20]. This may be relevant for cancer patients, where thermal ablation and delimitation of tumor borders are crucial for therapeutic efficacy [12]. Nevertheless, it should also be considered that thermal ablation may interfere with MRI since some of its parameters are temperature-dependent [21]. Novel technologies such as MRI-based acoustic radiation force imaging may be useful to reduce those artefacts [21].

Also, acoustic intensity attenuation by the skull is 33% in rats [22] and 73% in mice [13]. This attenuation is 30-60 times higher than that in soft tissue [11]. This effect results from several mechanisms, including a loss of energy through friction as acoustic waves propagate across some materials [6].

The human skull is thicker and harder than that of rodents. As a result, bone attenuation of US is 20-fold higher than that in soft tissue [21]. Mathematical models have been developed to simulate wave propagation through the skull [23]. Computational modeling suggests that the human skull yields an attenuation of 56% in peak pressure and 84% in peak intensity [24].

Despite this, some devices may reach the human thalamus [18], making FUS's clinical applications plausible [6]. Also, FUS may be applied to the peripheral nervous system preventing skull interference [15, 25, 26].

Further technical limitations of FUS have been reported [19], including an error in spatial precision of target location

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due to skull and scalp heterogeneities altering US propagation [27, 28]. This may impede achieving enough temperature rise at the target site in 6-27% of the patients [7, 29]. Those heterogeneities include a different density between cortical bone and bone marrow [7, 27] or a relatively large skull volume [7] and may cause US reflection, especially at high frequencies [7, 27]. A frequency of 650 kHz may avoid errors in FUS focusing [21]. Using lower frequencies may reduce this effect, but it might induce tissue damage by cavitation [21, 27]. Some methods [28] and algorithms [7, 27] have been developed to correct those errors [28]. Software improvements help achieve this goal, but hardware developments are also important.

Wearable LIFUS devices (30-150 mW/cm^2) have been developed for several medical applications [30]. Some of them may function as Internet-of-Things' devices allowing remote communication with a physician to control treatment parameters through a mobile phone application [30]. Miniature devices are suitable for chronic implantation within the muscle [31] or the brain [32]. Acoustic retinal prosthetics may project ultrasonic holograms onto the retina [23]. Several devices for LIFUS application have been developed mainly for bone healing and soft tissue regeneration, and as a therapeutic modality for systemic inflammatory disorders affecting joints [33].

3. POTENTIAL SAFETY OF FUS

Regarding HIFUS, its thermal effect is exploited to get tissue ablation, but it may not be convenient when LIFUS is applied.

According to preclinical studies, increased temperature in the skull after a 40-min pulsed LIFUS stimulation (760 mW/cm^2 I_{SPPA}) is lower than 0.2 ºC [34]. This treatment is not associated with hemorrhage or tissue damage [34]. Even a higher intensity LIFUS treatment (7.59 W/cm^2 I_{SPPA}) applied for two weeks is devoid of damaging effects [22]. Additional studies are consistent with those results [17, 35, 36]. Also, LIFUS does not alter blood-brain barrier (BBB) permeability [37].

LIFUS (3.5 W/cm^2 I_{SPPA}) does not increase glial fibrillary acidic protein expression [37]. However, the effects of small temperature changes in brain tissue cannot be ruled out [6].

Regarding HIFUS, no histological damage is observed after a 10-s exposure of the rat sciatic nerve to 300 W/cm^2 [38]. However, at 30-60 s, minor lesions are observed; at 2 min exposure, clear morphological damage is present, including axonal degeneration and demyelination; and with 3-4 min exposure, extensive cell death is produced [38]. For tissue ablation, causing cell death is part of the therapeutic effect of HIFUS, although it should be monitored carefully.

FUS application to the sciatic nerve of a mechanical pressure above 5.7 MPa yields irreversible damage [39]. Pressure levels not exerting damage were incapable of producing neuromodulation [39], but this might depend on the setting of other FUS parameters.

Clinical trials report mild side-effects of LIFUS application (17.1 W/cm^2 I_{SPPA}), including neck pain, sleepiness, muscle twitches, itchiness, and headache [10]. However, it should be considered that these studies delivered TMS and LIFUS simultaneously, so those side-effects may be related to TMS or a TMS-LIFUS interaction.

In clinical trials, HIFUS may produce transient headaches [19]. Other reported side-effects are gait disturbances, sensory deficits, paresthesias, dizziness, nausea [19, 40], fever, and localized skin edema and erythema [20].

Since HIFUS causes tissue ablation, some side-effects may be permanent [19] although most of them are only transient. HIFUS may cause perilesional edema, which may recover after one month [27].

An analysis of 178 HIFUS procedures for different neurological conditions in 136 patients showed that there was no cognitive deficit after treatment [41] except for those patients with a pre-existent deficit which might be worsened after HIFUS [41]. A full description of side-effects of HIFUS thalamic ablation in those patients is already published [41].

HIFUS may also increase BBB permeability [16, 42], allowing potentially toxic substances to enter the central nervous system (CNS) [42]. This mechanism occurs at mechanical pressures above 0.1 MPa [43] and is transient [11] but may last for 24 h [29].

However, this effect may be used therapeutically, since the FUS may disrupt the BBB in a specific brain region to enhance availability of drugs that do not cross the BBB [19,29]. This may increase their effect in the target nuclei avoiding their distribution in the whole CNS [9,16], reducing side-effects in non-targeted brain tissue [29].

With this strategy, drug concentrations in the brain may be 14-fold higher [29]. In the medical setting, the BBB may be globally disrupted using intraventricular osmotic agents, but HIFUS may yield this effect in individual brain regions [44].

This strategy might be complemented using drug-containing US-sensitive nanoparticles, allowing drug delivery in a selected region subjected to a US beam [8, 45]. Those nanoparticles do not cause brain injury or BBB disruption by themselves [45]. Experimental models have shown that subthreshold anesthetic doses administered with this formulation may inhibit visual evoked potentials when the primary visual cortex is sonicated [45], suggesting that low doses may be effective.

HIFUS may be applied to awake patients [27] as it occurs in functional neurosurgery, reducing anesthetic risks. However, some HIFUS protocols still require general anesthetics [12]. In addition, in awake patients, neurological side-effects may be evaluated in-between the several sonication steps required to complete ablation [7,21], allowing detection of some side-effects as soon as they appear. Also, patients may interrupt the procedure using a "stop sonication" button [21].

CONCLUSION

The main goals for FUS application include avoiding some surgical risks, a combined application with TMS, MRI, or US-guidance; and its application for neurosurgical procedures in awake patients. Its challenges include: some brain regions are not suitable targets, temperature-rise should be carefully monitored and might affect some MRI parameters, it is remarkably attenuated by the skull, and requires accurate

mathematical modeling. Regarding safety, preclinical studies suggest that it may cause axonal degeneration, demyelination, cell death, and BBB disruption (although this might be used therapeutically). Clinical studies have reported mostly mild and transient side-effects but, when they are related to tissue ablation, may be permanent. Also, it may worsen a pre-existent cognitive deficit. Further studies are required to combine FUS with Doppler ultrasonography, but wearable devices for neuromodulation are under development, so technological achievements will be crucial for exploiting the potential of FUS' applications.

Further studies are needed to explore how US impacts apoptosis (which may be an alternative method for treating cancer) or the formation of reactive oxygen species (which may be detrimental in some circumstances). Those effects may be mediated by mitochondrial function and gene expression [46]. This makes US a promising alternative for diverse medical conditions.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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