Clinical Recommendations for Non-Invasive Ultrasound Neuromodulation

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Abstract

Non-invasive ultrasound neuromodulation has experienced exponential growth in the neuroscientific literature, recently also including clinical studies and applications. However, clinical recommendations for the secure and effective application of ultrasound neuromodulation in pathological brains are currently lacking. Here, clinical experts with neuroscientific expertise in clinical brain stimulation and ultrasound neuromodulation present initial clinical recommendations for ultrasound neuromodulation with relevance for all ultrasound neuromodulation techniques. The recommendations start with methodological

safety issues focusing on technical issues to avoid harm to the brain. This is followed by clinical issues focusing on important factors concerning pathological situations.

Introduction

Non-invasive ultrasound neuromodulation has experienced exponential growth in the neuroscientific literature, recently also including clinical studies and applications. In contrast to ablative ultrasound with high energy intensities (High Intensity Focused Ultrasound, HIFUS), non-destructive ultrasound neuromodulation applies much lower energy intensities and has been referred to as TUS (Transcranial Ultrasonic Stimulation), LIFUS (Low Intensity Focused Ultrasound), LIPUS (Low Intensity Focused Ultrasound Pulsation), tFUS (transcranial Focused Ultrasound), and TPS (Transcranial Pulse Stimulation). Neuromodulation can be induced by focused or unfocused ultrasound with continuous or pulsed stimulation (Beisteiner et al. 2023). Cellular and animal studies demonstrate a wide range of biological effects evoked by ultrasound neuromodulation (Darmani et al. 2022; Folloni 2022; Collins & Mesce 2022). Although there is an increasing body of evidence regarding ultrasound neuromodulation safety (Aubry et al. 2023, Sarica et al. 2022, Radjenovic et al. 2022; Lee et al. 2021) and potential clinical applications of deep brain stimulation (Di Biase et al. 2021; Badran et al. 2020) a discussion of safety issues from a clinical perspective is yet missing. Despite the field's infancy, therapeutic applications of approximately ten different ultrasound systems have already been described. One of the systems is already approved for clinical therapy (EU) and clinical research (US) (Beisteiner et al. 2023). Published clinical studies have investigated Alzheimer's disease, Parkinson's disease, disorders of consciousness, depression, autism spectrum disorder, epilepsy, post-stroke rehabilitation and chronic pain syndromes. Since ultrasound neuromodulation transfers mechanical energy, it is important to be aware of the high complexity and possible clinical risks of ultrasound neuromodulation. Brain pathology often leads to considerable changes of brain morphology, tissue vulnerability, and functional networks. These aspects exhibit substantial interindividual variations, even in patients with identical diagnoses. Accordingly, the individual clinical features and neuronal network must be thoroughly clarified for every patient involved in a TUS clinical study or therapy. However, clinical recommendations for the secure and effective application of ultrasound neuromodulation in pathological brains are currently lacking. Here, clinical experts with neuroscientific expertise in clinical brain

stimulation and ultrasound neuromodulation present initial clinical recommendations for ultrasound neuromodulation with relevance for all ultrasound neuromodulation techniques. The recommendations start with section I on methodological safety issues focusing on technical issues to avoid harm to the brain. This is followed by section II on clinical issues focusing on important factors concerning pathological situations. When I is observed, II still needs to be considered for clinical ultrasound neuromodulation.

I. Safety Issues

I.a. Biophysical Safety of Ultrasound Neuromodulation

Clinically most important safety issues for ultrasound neuromodulation concern mechanical bioeffects, thermal bioeffects, and target safety.

Mechanical Bioeffects

Critical mechanical effects concern cavitation (formation or collapse of pressure related tissue bubbles) and mechanical stretching (Lee et al. 2021). Both may result in clinically relevant bleeding and cell damage or damage to the blood brain barrier. Mechanical bioeffects depend on the amount of energy focally transferred to brain tissue and the energy deposited as a function of time. Both depend on the ultrasound technique used and are influenced by various factors like ultrasound frequency, amplitude, composition of a single ultrasound pulse (a "pulse" being a sine wave with a single frequency or a mixture of various frequencies applied without pausing), local tissue pressure generated by a single pulse, number of consecutive ultrasound pulses applied, total pulse energy, pause length between pulses, total sonication duration, and use of ultrasound contrast agents (UCA). Defocusing effects of the skull may also be an influential factor. The Mechanical Index (MI) – developed for diagnostic ultrasound and calculated by dividing the peak negative pressure (peak rarefactional pressure after derating (in MPa)) by the square root of the fundamental frequency (in MHz) is often suggested as the primary indicator for potentially harmful effects at the ultrasound focus, particularly for the likelihood of cavitation. In diagnostic cephalic ultrasound an MI<1.9 is considered a safe limit by FDA. However, the MI only considers pressure and frequency of the ultrasound applied. Most of the factors listed above, which may influence focal energy transfer, are not incorporated in the MI calculation. For ultrashort ultrasound pulses (e.g., 3 µs pulses of the Transcranial Pulse Stimulation (TPS) technique) there are even indications that the MI is not applicable. This is based on the fact that inertia of the liquid, its viscosity, and

the initially large Laplace pressure delay the start-up of bubble growth (Holland & Apfel 1989). In a discussion of ultrashort ultrasound pulses from the shockwave field - similar to the TPS pulses - authors conclude that these pulses "lie outside the regime where the MI is expected to be valid". That is, the time scale of the expansion phase of a bubble forced by a TPS pulse is much longer than the pulse length of the TPS pulse (Iloreta et al. 2007). Therefore, for healthy and particularly pathological tissue (which may include non-biological structures), the MI may be helpful but clinical experts should be aware of other factors influencing focal energy absorption and potentially contributing to harmful effects. For every patient the factors listed require consideration for individual prediction of bioeffects (Radjenovic et al. 2022). In general, the evidence level for reliable energy limits for mechanical tissue damage with ultrasound neuromodulation is still poor, and it is very likely that there are several conditions where MI values >1.9 are safe. Currently, no single comprehensive indicator for judging mechanical tissue damage exists. For real-time cavitation detection, hydrophone measurements (which may indicate cavitation sounds) might be used, although not every cavitation will generate clinically relevant tissue damage.

Thermal Bioeffects

Focal energy deposit by ultrasound may increase local temperature and result in thermal tissue damage. Based on existing international regulations for Magnetic Resonance (IEC 60601-2-33; 2008) and implantable devices (EN 45502-1, 1997), damaging thermal effects may occur with focal temperature increases >2° C or absolute temperature >39° C. Much higher temperature rises can be without damage if they are short. Again, the relevant factors for mechanical bioeffects listed above may also influence thermal bioeffects. In addition, local temperature increase depends on tissue characteristics such as heat capacity, absorption coefficient, and local perfusion, which may be abnormal in pathological tissues. For estimation of a possible ultrasound mediated temperature rise, several physical parameters have been suggested. The Thermal Index (TI) can be defined as the ratio of the attenuated acoustic power to the acoustic power needed to raise the temperature by 1° C at a specified tissue focus (Kollmann et al. 2013; Radjenovic et al. 2022). It depends on the tissue model and considers only acoustic output power of the transducer and its aperture diameter. The British Medical Ultrasound Society does not recommend cranial TI (TIC) > 3, while the American Institute of Ultrasound does not recommend TIC>6. As with the MI, the TI may be helpful, but clinical experts should be aware that besides the parameters integrated in the TI calculation also other factors influence thermal bioeffects. A further standard parameter is

Spatial-Peak Temporal-Average Intensity (ISPTA in W/cm^2). For diagnostic applications with transcranial Doppler ultrasound, the FDA set a regulatory limit of ISPTA < 0.72 W/cm2. Since the ISPTA does not take into account the frequency, the same ISPTA will have a lower temperature rise at low frequency compared to high frequency. Animal brain applications up to 25.8 W/cm^2 (Gaur et al. 2020) did not result in tissue damage. As with mechanical bioeffects, the large number of influential factors and large variability in pathological tissue conditions are not considered in the parameters given above. Again, the evidence level for establishing reliable energy limits for thermal tissue damage with ultrasound neuromodulation remains poor, and the recommendations vary considerably. Currently, no single comprehensive indicator for judging thermal tissue damage exists. For real-time temperature monitoring, MR thermometry might be used (Ishihara et al. 1995).

Recommendation 1: Clinical applications require awareness of factors potentially contributing to harmful effects. Methodological safety issues need to be judged by clinical experts. Ultrasound neuromodulation systems should provide safety data regarding local energy absorption as a function of time, local temperature increase and evaluation of the defocusing effect of the skull. Data should include measurements on skull / brain specimens and animal studies with respect to possible tissue damage.

I.b. Targeting Safety of the Ultrasound System

A specific clinical safety issue concerns targeting safety of an ultrasound neuromodulation system. Clinical MRI can clarify intracerebral pathologies and provide the basis for individual targeting. Absorption of mechanical energy in areas with vascular pathologies or tissue abnormalities may increase bleeding risks with possibly harmful outcomes for the sonicated subject. Therefore, it is important to target the ultrasound focus outside brain areas at risk for damage. It is also important to realize that some of these pathologies may be minor and asymptomatic, i.e., they may exist in “healthy subjects”. Ultrasound systems with high focality and neuronavigation provide more secure targeting.

Recommendation 2:

State-of-the-art ultrasound neuromodulation should employ specifically developed and comprehensively tested ultrasound systems allowing focusing in the mm range. It should include neuronavigation based on current individual MRIs to allow precise targeting and avoid brain areas at risk for damage (compare recommendation 1).

II. Clinical Issues

Application of ultrasound neuromodulation in patients requires a thorough clinical evaluation concerning clinical state as well as structural brain changes and functional brain state. This will inform ultrasound targeting. Since asymptomatic pathologies exist, both morphological and functional brain states should also be considered for ultrasound neuromodulation in asymptomatic subjects (e.g., healthy controls).

II.a. Clinical State

Various aspects of a patient's general clinical condition may influence the applicability and clinical indication of ultrasound neuromodulation. Important issues concern individual disease stage, type and number of diagnoses, possible interaction between different clinical manifestations (e.g., depression might have deleterious effects on cognition), the existence of contraindications and patient collaboration. For every patient, all clinical issues need to be clarified, and a risk-benefit evaluation should be conducted. Risk-benefit evaluations should also consider interactions with concomitant medical and non-medical treatments (e.g., physiotherapy or cognitive training). This also holds true for normal subjects participating in research studies.

II.b. Structural Brain Changes

For reasons of safety and adequate targeting, knowledge of the current morphological brain state is essential before application of mechanical energy. Typically, this requires analysis of MR images acquired soon before ultrasound application. Important considerations concern preexisting bleeding (e.g., subdural hematomas in elderly patients), cavernomas (spontaneous annual hemorrhage rate around 7%, Li et al. 2020), other vascular diseases or malformations, dysplasias, tumors, damaged tissue resulting from stroke or trauma, local inflammations, and local infections. Analysis should also include displacements of functional tissue due to mass effects, signs of increased intracranial pressure and possible consequences of the location of pathological tissue (e.g., close to a primary target area). Non-biological structures (brain implants, aneurysm clips, gaseous bubbles) and intracerebral calcifications may also present problems. Solid material can produce sound field distortions and sound scattering with a possible risk of unpredictable secondary energy maxima and thermal effects. Gaseous bubbles increase the risk for cavitation related damage (Lee et al. 2021). Human studies on focused

ultrasound safety in pathological tissues are yet scarce, and a recent review of clinical studies did not report serious adverse events (Beisteiner et al 2023). However, previous data from low intensity focused ultrasound indicate that the risk of hemorrhage may be increased in cases of coagulation disorders / anticoagulation treatment. A study combining tissue plasminogen activator and low-frequency ultrasound was prematurely stopped because 13 of 14 patients showed signs of bleeding in MRI (Daffertshofer et al. 2005). It is also important to realize that pathological morphology directly relates to pathological function. Local atrophy needs to be evaluated, since that affects the functional state of the brain, often in a complex manner. Local atrophy may represent a treatment target, particularly when corresponding to lesion derived brain maps of the same disease (Tetreault et al. 2020). Further, with atrophy the absolute amount of energy transferred to brain tissue is reduced. Increasing evidence from both lesion and stimulation studies indicates that the malfunctioning neural circuits generating specific symptomatology are potential targets for ultrasound neuromodulation (Siddiqi et al. 2021).

II.c. Functional Brain State

Depending on the underlying pathology, the functional network architecture of a patient may be grossly changed. The functional changes depend much on the type of pathology (for review Karahasanovic et al. 2022). Acute lesions (e.g., stroke) typically result in large and transient network reorganizations with activation shifts, recruitment of additional brain areas, and novel hypo- and hyperactivations. This pattern may rapidly change over time and, after several months, may stabilize into a chronic state (Motolese et al. 2023). In contrast, chronic lesions (tumors, inflammatory disease) show a much slower functional reorganization, which may be ongoing over many years. An important issue concerns maladaptive brain activities – these are brain activations which worsen the clinical state. They are well described for language disturbances after stroke (Hartwigsen & Saur 2019), but also exist in motor disturbances (Karahasanovic et al. 2022). Such maladaptive brain activity should be recognized, and further neuromodulatory activation of such areas should likely be avoided. In contrast, clinical benefit may occur with the inhibition of these maladaptive networks. Independent from brain activation changes, suboptimal or incorrect stimulation may worsen symptoms based on their specific functional and structural network connectivity (Siddiqi et al. 2022). For example, stimulation of subthalamic brain areas functionally connected to the subiculum may induce cognitive decline in Parkinson's disease patients (Reich et al. 2022). Stimulation of subthalamic brain areas structurally connected to left prefrontal areas may worsen depressive symptoms (Irmen et al. 2020). There are also brain areas that may improve

symptoms based on their connectivity (Cash et al. 2021). Clinical effects based on local impact at the stimulation site need to be differentiated from clinical effects based on network connectivity (Horn & Fox, 2020). For comprehensive evaluation of possible stimulation effects, functional and structural imaging data are important. Individual diffusion tensor imaging (DTI) is meanwhile increasingly employed in *electrical* deep brain stimulation (DBS). However, with state-of-the-art focused and navigated techniques, non-invasive deep brain stimulation with *ultrasound* may become a future option.

Another important consideration involves determining which functional network drives which symptoms within the same disease. For example, in depression, symptom clusters have been defined that respond to stimulation of different functional circuits (TMS data, Siddiqi et al. 2020). This further underlines the need for individual optimization of clinical ultrasound neuromodulation - even for patients with the same disease.

II.d. Clinical Target Definition

From the previous sections, it is obvious that defining neuromodulation targets in pathological brains is much more complex than in healthy brains. Data generated from brain lesions (including Lesion-Network-Mapping, Boes et al. 2015), functional and structural brain imaging, and clinical brain stimulation have generated important evidence whether target activations result in beneficial or detrimental effects for a specific disease. However, current knowledge on clinical stimulation targets is still limited (Siddiqi et al. 2022). Given that every brain and every patient is different, before application of ultrasound neuromodulation, all individual clinical, morphological and in some cases, functional issues mentioned above (particularly asymptomatic lesions) need to be evaluated. All information should be current (ideally acquired within few days before neuromodulation), since even minor changes may influence target definition. Transmission of focal mechanical energy to vulnerable tissue or areas with increased risk for hemorrhage should be avoided. Detrimental activation of maladaptive brain areas or areas with unfavourable connectivity should not be done. Individual targeting should be informed by the current state of the art in clinical neuroscience, which may include lateralized approaches. Targeted ultrasound should be hypothesis driven with clearly stated and expected functional network changes and then also expected clinical results. Network changes may occur without clear clinical changes.

Recommendation 3:

Every subject should have a thorough clinical evaluation and individual target definition before application of ultrasound neuromodulation. This should include morphological and ideally functional brain evaluations based on high resolution MR imaging. Images should be checked for asymptomatic pathologies. Since applications may involve sonication of pathological tissue with increased vulnerability or base temperature, focal energy should be reduced in such situations (e.g., a patient with fever). Targeting should be based on the state of the art in clinical neuroscience. Individual evaluation should consider possibly maladaptive brain areas and areas with possibly unfavorable connectivity.

III. Expertise Issues

The sections „Safety Issues“ and „Clinical Issues“ inform about the inherent complexity of the secure application of ultrasound neuromodulation in both pathological and healthy brains. Much clinical research is still to be done; however, a considerable body of scientific knowledge already exists and requires consideration. Even if a neuromodulation system is deemed „biophysically safe“, specific expertise is necessary to judge atypical tissue vulnerability, morphological brain distortions, and pathological functional networks. Since every clinical situation is different, responsible clinical operators should possess adequate expertise in diagnosis and treatment of brain diseases and comprehensive neuroscientific knowledge. They need to relate diagnoses and symptoms to possible brain pathologies and judge clinical applicability. Possible effects of variations of ultrasound parameters need to be known. Clinical targeting requires expertise on maladaptive brain activities, brain area connectivity (including beneficial and detrimental ones), possible target area interactions, and expected clinical responses. Establishing indications for additional information (e.g., fMRI, DTI data) requires brain imaging expertise. Responsible operators should be aware that patients often present with complex neuropathological situations. Therefore, defining an optimized neuromodulation setting is a demanding task and requires specific training. This is essential for the responsible physician who is also in charge of adequate training, knowledge and supervision of assisting technologists.

Recommendation 4:

Clinical ultrasound neuromodulation requires expertise in diagnosis and treatment of brain diseases and comprehensive neuroscientific knowledge. The responsible scientist or clinician should have a precise understanding of the safety issues and clinical issues listed in section I

and II. This concerns the biophysical limits of the ultrasound system and the clinical expertise for assessing possible brain risks.

Conclusion

Non-invasive ultrasound neuromodulation with highly focal and navigable state-of-the-art systems allows unprecedented approaches for non-invasive and deep brain stimulation in both healthy and diseased brains. Clinical applications are rapidly spreading. The fact that mechanical energies are applied requires clinical and clinical neuroscientific expertise and a thorough understanding of safety issues relating to the ultrasound system and to the brain. For therapeutic applications, qualified operators should have a background in the diagnosis and treatment of brain diseases.

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