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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 safety issues focusing on important factors concerning pathological situations.

1. 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). TPS differs from other ultrasound neuromodulation techniques in application of ultrashort ultrasound pulses composed of multiple frequencies instead of longer lasting single sine waves. Spatial-peak-temporal-average intensities (ISPTA) are typically lower and peak pressures are typically higher with TPS [1,2]. In general, neuromodulation can be induced by focused or unfocused ultrasound with continuous or pulsed stimulation [3]. Cellular and animal studies demonstrate a wide range of biological effects evoked by ultrasound neuromodulation [4–6]. Although there is an increasing body of evidence regarding ultrasound neuromodulation safety [7–12] and literature about the novel potential for clinical deep brain stimulation [13,14] a discussion of safety issues from a clinical perspective is yet missing. Despite the field's infancy, focused ultrasound systems from various manufacturers have already been published in context with clinical research (for review [7]): Brainsonix Corporation, Insightec Incorporation, Navifus Corporation, Neurosona Corporation, Neurotrek Incorporation, Shengxiang Technology, Sonic Concepts Incorporation, Storz Medical AG. One of the systems (TPS, Storz Medical AG) is already approved for clinical therapy (EU). Published patient studies have investigated Alzheimer's disease, mild neurocognitive disorders, Parkinson's disease, essential tremor, disorders of consciousness, depression, anxiety disorders, schizophrenia, autism spectrum disorder, substance use disorder, epilepsy, post-stroke rehabilitation and chronic pain syndromes [1,3,7–9,15]. 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

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features and neuronal networks must be thoroughly clarified for every patient involved in a TUS clinical study or therapy. However, in contrast to electromagnetic techniques [16,17], 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.

To avoid ambiguities with novel therapies, important issues need to be defined early and awareness raised for a broad readership. 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 safety issues focusing on important factors concerning pathological situations. When methodological safety (I) is observed, clinical safety (II) still needs to be considered for clinical ultrasound neuromodulation. In contrast to other non-invasive neuromodulation techniques (e.g. electromagnetic neuromodulation), ultrasound applies mechanical energy with highly focal spatial restriction. Therefore, recommendations focus on these specific aspects (particularly section I) though a comprehensive clinical discussion of all relevant issues is intended. Some of them may be relevant for all non-invasive neuromodulation techniques.

2. Methodological safety issues

Clinically most important safety issues for ultrasound neuromodulation concern mechanical bioeffects, thermal bioeffects, and target safety. Clinical safety issues extend safety considerations already published for healthy brains [1,7–12]. Since characteristics of different ultrasound neuromodulation systems may vary considerably (e.g., energy output, aperture size, single/multi-channel construction), for every system safety data regarding local energy absorption as a function of time, local temperature increase, and evaluation of the defocusing effect of the skull should be available and regarded by the experimenter/clinician. Ideally, system specific safety data should include measurements on skull/brain specimens, animal studies, and numerical simulations with respect to possible tissue damage.

2.1. Biophysical safety of ultrasound neuromodulation

2.1.1. Mechanical bioeffects

Critical mechanical effects concern cavitation (formation or collapse of pressure related tissue gas bubbles) and possibly mechanical stretching [11]. Both may result in clinically relevant bleeding and cell damage or damage to/opening of the blood brain barrier - particularly in areas with tissue pathologies (e.g., including areas with gaseous bubbles). 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 a well-established safety index. It may correlate with cavitation probability - particularly in the presence of injected microbubbles and is often suggested as the primary indicator for potentially harmful effects at the ultrasound focus.

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 and their possible influence on mechanical safety still needs to be comprehensively researched. For example, it is expected that applying ultrasound in series of shorter pulses or a pulse train reduces the chance of cavitation compared to a longer pulse (e.g. a 1 s pulse as applied in [18]). For pathological tissue containing gaseous bubbles evidence exists that bleeding may occur below 1.9 MI [19]. The blood brain barrier in Alzheimer patients may even open at 0.4 MI in the presence of intravenously injected microbubbles. ([20], medRxiv https://doi.org/10.1101/2023.12.21.23300222). In clinical practice gaseous brain inclusions are a rare but well known patient problem. Since evidence exists that brain inclusions may occur spontaneously [21] and inclusions may be in the range of microbubbles [22], clinicians cannot exclude occurrence of such situations.

For ultrashort ultrasound pulses (e.g., 3 μs pulses of the Transcranial Pulse Stimulation (TPS) technique) there are 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 [23]. 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 [24]. However, there is also evidence, that at large peak pressures a single ultrasound cycle with duration <1 μs can produce cavitation in fat [25]. Therefore, for healthy and particularly pathological tissue (which may include non-biological structures like brain implants, aneurysm clips, gaseous bubbles), 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 various factors influencing focal energy deposition (see listing above) require consideration for individual prediction of bioeffects [10]. 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 might be used. Stable or inertial cavitation is characterized by unique acoustic responses which can be detected by hydrophones which are regularly used in cavitation studies. Note however, that not every cavitation will generate clinically relevant tissue damage.

2.1.2. 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 [26] and implantable devices [27], 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 example, pathological brain areas with reduced perfusion are prone to higher temperature increases than normal tissue. 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 [10,28]. 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 ISPTA [29] did not result in tissue damage. As with mechanical bioeffects, the various factors influencing focal energy deposition (see listing above) 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 [30].

Recommendation 1: Clinical applications require awareness of factors potentially contributing to harmful effects. Since characteristics of different ultrasound neuromodulation systems may vary considerably (e.g., energy output, aperture size, single/multi-channel construction), for every system safety data regarding local energy absorption as a function of time, local temperature increase, and evaluation of the defocusing effect of the skull should be available. Ideally, system specific safety data should include measurements on skull/brain specimens, animal studies, and numerical simulations with respect to possible tissue damage.

2.2. 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. In contrast to electromagnetic fields [31], ultrasound is not distorted by liquid or soft tissue pathologies. Due to already increased risks for spontaneous bleeding, absorption of mechanical energy in areas with vascular pathologies or tissue abnormalities may further increase bleeding risks with possibly harmful outcomes for the sonicated subject. For clinical applications prevalence of small and possibly risky pathologies is a standard problem (compare section IIb). They may well reside very close to intended targets (e.g., in brain stem). The better the focality, the lower the risk for transferring a relevant amount of energy outside the target. Therefore, focusing capabilities in the mm range are 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 which are intended for transcranial stimulation applications provide more secure targeting.

2.2.1. 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, particularly in pathological brains.

3. Clinical safety 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).

3.1. 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. Since complex interindividual variations are a key issue in clinical medicine, a specific factor (e.g., local energy absorption) might well represent a "clinical safety issue" for patient 1, but not for patient 2, despite both having the same primary diagnosis. Consequences for individual patients require individual evaluation and awareness of factors potentially contributing to harmful effects. 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.

3.2. 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 clinical situations with already increased risks for spontaneous bleeding (without ultrasound application). This includes preexisting bleeding (e.g., subdural hematomas in elderly patients), cavernomas (spontaneous annual hemorrhage rate around 7 %), other vascular diseases or malformations, dysplasias, tumors, damaged tissue resulting from stroke or trauma, local inflammations, and local infections (compare [32–34]). 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. It cannot be excluded, that the solid material produces 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 [10]. 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 [3]. Over all human ultrasound neuromodulation studies published, the following mild to moderate events have been reported: localized pain at head or neck, general headache, painless pressure sensations at the stimulation site, muscle twitches, heating sensations, itchiness, anxiety, uncomfortable feelings, mood deterioration, difficulty paying attention, confusion, tenseness, disorientation, noise sensitivity, tingling, nausea, sleepiness, tiredness, dizziness, unsteady gait, tremor worsening, and sweating. It is important to realize that adverse events are also reported when sham (placebo) stimulations are applied. Adverse reactions or side effects of patients need to be recorded with evaluation tools and a follow-up can be conducted [3,9]. 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 [35]. 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 in diseases where atrophied regions are functionally connected to a network which is important for the symptomatology of the disease (e.g., atrophied regions connect to networks for impaired memory in Alzheimer's disease [36]). 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 [37].

3.3. 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 [38]). 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 [39]. In contrast, chronic lesions (tumors, inflammatory disease) show a much slower functional reorganization, which may be ongoing over many years. Although knowledge is yet limited, an important issue concerns maladaptive brain activities – these are brain activations which worsen the clinical state. They are described for language disturbances after stroke (e.g., right frontal cortex activity in post stroke aphasia [40]), but also exist in motor disturbances (e.g., sensorimotor cortex activation in phantom limb pain, [38]). Such maladaptive brain activity should be recognized, and further neuromodulatory activation of associated areas should 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 [41]. For example, stimulation of subthalamic brain areas functionally connected to the subiculum may induce cognitive decline in Parkinson's disease patients [42]. Stimulation of subthalamic brain areas structurally connected to left prefrontal areas may worsen depressive symptoms [43]. There are also brain areas that may improve symptoms based on their connectivity [44]. Therefore, clinical effects based on local impact at the stimulation site need to be differentiated from clinical effects based on network connectivity [45]. 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). 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 [46]). This further underlines the need for individual optimization of clinical ultrasound neuromodulation - even for patients with the same disease.

Though these considerations are relevant for all neuromodulation techniques, the capability for precise targeting and non-invasive deep brain stimulation is unique for ultrasound. For ultrasound neuromodulation consideration of functional brain states therefore is of particular importance.

3.4. 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 (compare review from the DBS field [47]). Data generated from brain lesions (including Lesion-Network-Mapping [48]), 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 [41]. 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 need to be evaluated (particularly asymptomatic lesions). All information should be current (ideally acquired once within few days before neuromodulation), since even minor changes may influence target definition and feasibility (e.g., asymptomatic bleeding). Transmission of focal mechanical energy to vulnerable tissue or areas with increased risk for hemorrhage should be avoided. Detrimental activation of brain areas associated with maladaptive activity or areas with unfavorable connectivity should not be done. In such situations, any type of neuromodulation (not only with ultrasound) could potentially lead to deleterious effects or worsening of symptoms, although for non-invasive neuromodulation this mostly should be transient. 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. It is important to be aware that positive network changes may occur without clear clinical changes.

3.4.1. 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. As far as possible, individual evaluation should consider possible maladaptivity and brain areas with possibly unfavorable connectivity. Their neuromodulation could potentially lead to deleterious effects or worsening of symptoms. Adverse reactions or side effects of patients need to be recorded with evaluation tools and a follow-up can be conducted.

4. Expertise issues

The sections „Methodological Safety Issues" and „Clinical Safety 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. For being able to judge possible risks for a patient, system specific safety data must be known. The relevance of a safety issue for the individual patient needs to be judged (e.g., increased risk for a patient with intracerebral bleeding even when mechanical safety limits are observed). 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.

4.1. 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.

5. 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.

CRediT authorship contribution statement

Roland Beisteiner: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Andres Lozano:** Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Data curation. **Vincenzo Di Lazzaro:** Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Data curation. **Mark S. George:** Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Data curation. **Mark Hallett:** Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

R.B. received research and laboratory support from Medical University (SO10300020), FWF KLIF455, STORZ Medical AG, and Herzfelder Stiftung. A.M.L. is a consultant to Medtronic, Boston Scientific, Abbott, Insightec, and Functional Neuromodulation. V.L. none M.S.G. is a paid consultant for Abbott (DBS), Livanova (VNS), and Sooma (tDCS, Neuralief (vns, trigeminal). He is a patent co-holder for Babystrong (infant taVNS) and Journal Editor for Brain Stimulation (Elsevier Press). M.H. is an inventor of a patent held by NIH for the H-coil for magnetic stimulation; in relation to the patent, he has received license fee payments from the NIH (from Brainsway). He is on the Medical Advisory Boards of Brainsway, QuantalX, and VoxNeuro. He has consulted for Janssen Pharmaceutical and Neurocrine.

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