This article has been accepted for publication in IEEE Open Journal of Engineering in Medicine and Biology. This is the author's version which has not been fully edited and content may change prior to final publication. Citation information: DOI 10.1109/OJEMB.2023.3263690

# Low-intensity focused ultrasound neuromodulation for stroke recovery: A novel deep brain stimulation approach for neurorehabilitation?

Mahmut Martin Yüksel[*1,2], Shiqi Sun [4,5,6], Charles Latchoumane[4,5,6], Jocelyne Boch[4,5,6,7] Gregoire Courtine[5,6,7,8], Estelle Emeline Raffin[1,2, *], Friedhelm Christoph Hummel[1,2,3,*]

[*] authors contributed equally

[1] Defitech Chair of Clinical Neuroengineering, Neuro-X Institute (NIX) and Brain Mind Institute (BMI), École Polytechnique Fédérale de Lausanne (EPFL), Geneva, Switzerland**.**

[2] Defitech Chair of Clinical Neuroengineering, Neuro-X Institute (NIX) and Brain Mind Institute (BMI), EPFL Valais, Clinique Romande de Réadaptation Sion, Switzerland

[3] Clinical Neuroscience, University of Geneva Medical School, Geneva, Switzerland.

[4] Neuro-X Institute (NIX) and Brain Mind Institute (BMI), School of Life Sciences, Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland.

[5] Department of Clinical Neuroscience, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland.

[6] Defitech Center for Interventional Neurotherapies (NeuroRestore), EPFL/CHUV/UNIL, Lausanne, Switzerland.

[7] Department of Neurosurgery, CHUV, Lausanne, Switzerland.

**CORRESPONDENCE TO:**

Friedhelm Hummel
Neuro-X Institute (INX) and Brain Mind Institute (BMI)
Ecole Polytechnique Fédérale de Lausanne (EPFL)
Campus Biotech, Room H4.3.132.084
Chemin des Mines 9, 1202 Geneva, Switzerland
and
EPFL Valais,
Clinique Romande de Réadaptation
Av. Grand-Champsec 90, 1951 Sion
Email: friedhelm.hummel@epfl.ch

This article has been accepted for publication in IEEE Open Journal of Engineering in Medicine and Biology. This is the author's version which has not been fully edited and content may change prior to final publication. Citation information: DOI 10.1109/OJEMB.2023.3263690

**ABSTRACT** Stroke as the leading cause of adult long-term disability and has a significant impact on patients, society and socio-economics. Non-invasive brain stimulation (NIBS) approaches such as transcranial magnetic stimulation (TMS) or transcranial electrical stimulation (tES) are considered as potential therapeutic options to enhance functional reorganization and augment the effects of neurorehabilitation. However, non-invasive electrical and magnetic stimulation paradigms are limited by their depth focality trade-off function that does not allow to target deep key brain structures critically important for recovery processes. Transcranial ultrasound stimulation (TUS) is an emerging approach for non-invasive deep brain neuromodulation. Using non-ionizing, ultrasonic waves with millimeter-accuracy spatial resolution, excellent steering capacity and long penetration depth, TUS has the potential to serve as a novel non-invasive deep brain stimulation method to establish unprecedented neuromodulation and novel neurorehabilitation protocols. The purpose of the present review is to provide an overview on the current knowledge about the neuromodulatory effects of TUS while discussing the potential of TUS in the field of stroke recovery, with respect to existing NIBS methods. We will address and discuss critically crucial open questions and remaining challenges that need to be addressed before establishing TUS as a new clinical neurorehabilitation approach for motor stroke recovery.

**INDEX TERMS** Stroke, Transcranial Ultrasound Stimulation, Non-Invasive Deep Brain Stimulation, Neuromodulation, NIBS

**IMPACT STATEMENT** This review summarizes and discusses current concepts, research, challenges and opportunities of non-invasive deep brain stimulation by means of transcranial ultrasound stimulation (TUS) with the vision of its application in the framework of stroke recovery and neurorehabilitation.

Stroke remains to be the second leading cause of death and the leading cause of long-term neurological disability in adults worldwide.[1] Globally, stroke affects over 13.7 million humans every year causing over 5.7 million deaths per year[2] and leaving over two-third of the survivors with neurological disabilities.[3] With over 101 million prevalent cases worldwide, stroke is one of the major causes for disability-adjusted life years (DALYs).[4] Despite traditional neurorehabilitation approaches, less than 15% of patients will fully recover from a stroke.[5,6] Thus, enhancing the effects of neurorehabilitation through novel neurotechnology-based strategies is crucial to significantly promote stroke recovery.

## 1. Rational for neuromodulation with high spatial resolution, focality and depth penetration to enhance stroke recovery

The majority of strokes are of ischemic nature in which the middle cerebral artery (MCA) is most often affected.[7] This results in hypoxia-induced damages in frontal, temporal and parietal lobes including crucial network compartments such as the primary somatosensory or primary motor cortices, basal ganglia, thalamus, caudate and internal capsule.[8] Moreover, considering the results from large-scale, prospective studies which showed that a majority of stroke lesions are subcortical and that pure cortical lesions are accountable for less than 15% of the total number of strokes[9–11], it becomes clear that further work to establish long-ranging, deep-penetrating neuromodulation techniques is necessary for post-stroke rehabilitation.[12] Furthermore, for infarctions not affecting deep brain regions it is assumed that central, interconnecting structures such as the thalamus nuclei or the basal ganglia are crucial for information flow integration and reorganization between functional cortices. Importantly, subcortical regions such as the thalamus are interconnecting different cortical regions enabling "top-down" and "bottom-up" processing and are involved in large-scale plasticity.[17] They are, therefore, essential in the process of stroke recovery.[18–20] As a matter of fact, recent neuroimaging studies showed that stroke is, indeed, a network disease in which network plasticity determines the outcome following stroke.[21–23] As shown in longitudinal neuroimaging studies, dynamic changes of functional connectivity between cortical and subcortical deep brain regions are predominant and influential for the recovery process following stroke.[24,25]
In sum, as the whole brain is undergoing significant changes following a stroke[24–27], reorganization of functional neural networks including communication pathways with deep brain structures is a pivotal process for motor recovery in post-stroke patients.[25,28,29]

Beside these large-scale reorganization, the classical model used to describe stroke recovery relies on the concept of disbalanced interhemispheric interactions/inhibition (IHI).[30]

However, whether disbalanced IHI is an adaptive or a maladaptive process in post-stroke patients is still a matter of debate in the field.[31–33] It remains controversial whether the ipsilateral (contralesional) respectively contralateral (ipsilesional) hemisphere is dominantly involved in the recovery processes.[34] Several investigations showed that not only the affected hemisphere, but also the non-affected hemisphere showed modified activity levels and plasticity induction in post-stroke patients.[35] Based on the IHI hypothesis, a large number of clinical trials have used non-invasive brain stimulation (NIBS)-based neuromodulation to inhibit the overactive contralesional motor cortex (M1)[33,36–39] and consequently increase the activity of the hypoactive ipsilesional M1[40,41] or vice versa[34] with the aim of improving motor outcomes. Hence, first-generation NIBS such as transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES) are the most prominent stimulation paradigms to modulate neural activity and to induce neuroplasticity to support neurorehabilitation.[42–44] For instance, cortical excitability of the affected and non-affected hemispheres is changing throughout recovery.[45,46] Consequently, traditional high-frequency rTMS or anodal tDCS protocols have been used to increase excitability of the ipsilesional (affected) hemisphere. Alternatively low-frequency rTMS or cathodal tDCS have also been tried to inhibit the contralesional (non-affected) hemisphere to improve motor recovery.[47–50] By re-balancing activity levels and interactions between both hemispheres, these techniques have previously demonstrated improved functional recovery in both subacute[45] and chronic stroke survivors.[51] However, this model as well as its relevance to design NIBS based neurorehabilitation protocols has been recently criticized. As a matter of fact, it has been controversially discussed if and when overexcitability is benefiting or maladaptive for post-stroke motor recovery, probably calling for more sophisticated and personalized recovery phase-dependent NIBS protocols.[33,37,52]

In addition, TMS and tES are critically hampered by their depth-focality trade off, due to their limited spatial resolution[53,54] and short-ranged penetrability.[45-47,58] Non-invasive electromagnetic stimulation of deep brain regions can only be obtained by sacrificing focality whereby a wider electrical field spread is stimulating untargeted brain regions as well.[59] However, as subcortical structures are small and anatomically highly interconnected, high focality is particularly required for deep brain stimulation to avoid stimulation of non-targeted structures[28] leading potentially to relevant unwanted side effects[60]. Hence, given the role of subcortical structures in stroke recovery, both penetrability and focality are crucial factors for transcranial neurostimulation for achieving precise modulation of network activity in post-stroke patients.[61]

Over the course of the last decades, different techniques have been implemented for deep brain stimulation. Invasive approaches, especially deep brain stimulation (DBS), have been discussed for stroke recovery due to promising preclinical results suggesting their potential for neurorehabilitation in patients.[19,61–65] Accordingly, a first preclinical, invasive study showed that neuromodulation of the dentate nucleus via DBS improved stroke recovery.[65] DBS of the cerebellar dentate nucleus (DN)[66–68] has also led to improved motor recovery, probed in a first-in-human trial (NCT02835443). Also of interest, Phillips *et al.* (2000) presented in a case-report support for an improvement of motor control in a post-stroke patient who received DBS into the periventricular gray matter on the left lateral aspect of the third ventricle[69]. Post-stroke pain symptoms have also been successfully treated with DBS of the ventroposterolateral[70,71] (VPL) and ventroposteromedial (VPM)[19,72] nucleus of the thalamus. However, clinical applicability and adoptability of invasive neurostimulation is limited due to surgical complication risk profile[73,74], limited accessibility to all brain regions[73], cumbersome maintenance[75] and by patient compliance[76] which is hindering the possibility to let DBS become a widespread neuromodulation option.

Transcranial ultrasound stimulation (TUS) is a novel and non-invasive alternative technique to reach deep brain regions.[75,77–79] In contrast to conventional NIBS the penetrability and focality of TUS is less limited by the biophysical instances when penetrating deep brain regions.[80–83] Thus, TUS appears to be a superior technique in terms of deep brain stimulation with its excellent focality, penetrability and steering capacities.[75,78,84] Furthermore, increasing studies in smaller animals[85–87], monkeys[88–90], sheep[91] and first-in-humans studies[92] are highlighting the potential safety and feasibility of TUS as a novel NIBS method.[78,93–96] However, as all relatively new techniques, TUS comes with a number of challenges that need to be addressed before being usable in large scale clinical practice for stroke recovery. In the present review we will discuss the discussed mechanisms underlying TUS neuromodulatory effects and highlight several promising applications of TUS for motor stroke recovery.

## 2. The underlying mechanisms of ultrasonic neuromodulation

William Fry and colleagues demonstrated seventy years ago, the reversible inhibitory effects of ultrasound on the central nervous system of frogs, monkeys, and cats without any concomitant brain damage.[97,98] Precisely, in one of his studies, Fry showed that ultrasonic stimulation of the lateral geniculate nucleus could reversibly suppress sensory-evoked potentials in the cat primary visual cortex applied through a cranial window.[99] Since that

pioneering work, ultrasound stimulation has repeatedly been shown to elicit action potentials in hippocampal slices or even evoke motor behaviors in mice without evidence of brain damage, demonstrating the potential relevance of the technique for neuromodulation purposes.[100,101]

Ultrasound in medical contexts utilizes piezoelectric materials which transmit high frequency sound waves when electrically stimulated.[102] These ultrasonic sound waves with high frequencies over 20kHz are above human hearing abilities.[103] Due to the biophysical properties of ultrasound and interaction of acoustic waves with tissue, the waves propagate through biological tissue with vibrational character creating acoustic radiation force (ARF).[96,104] Part of the energy is transmitted into mechanical deformation of the tissue and another part converted into thermal energy.[105] The main parameters used to calibrate ultrasound exposure are fundamental frequency, sonication intensity, pulse width, pulse repetition frequency, sonication duration and duty cycle (Figure 1). [86,88] These parameters in different constellations can lead to variable transitions of underlying mechanisms determining the TUS effects.

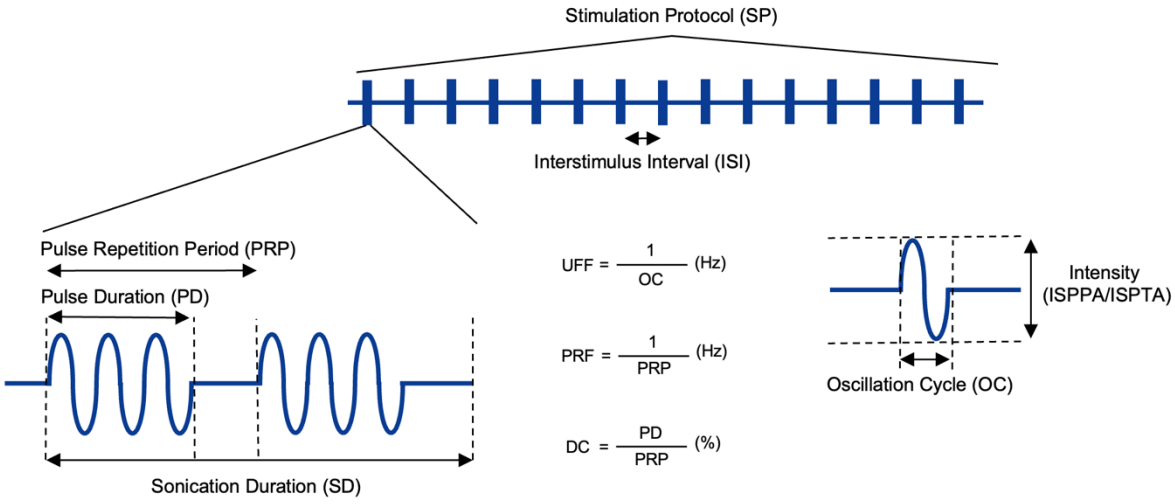


**Figure 1: Parameters defining ultrasonic neuromodulation**.

DC = duration cycle, ISI = interstimulus interval, ISPPA = intensity spatial peak pulse average, ISPTA = intensity spatial peak temporal average, PD = pulse duration, PRF = pulse repetition frequency, SD = sonication duration, SP = stimulation protocol, UFF = ultrasound fundamental frequency

Currently, there are three dominant mechanisms considered to underlie neuromodulatory effects: cavitation, temperature and mechanical deformation[82,83]. While they can operate conjointly, the way they translate into molecular signals to neurons is unclear (Figure 2). Importantly, the contribution of different neuromodulatory mechanisms can vary depending on ultrasonic parameter settings and on interacting neural tissue properties, leading to neuronal excitation or inhibition.[106–108]

Firstly, the intramembrane cavitation or nucleation model postulates that non-ionizing ultrasonic waves are influencing neural activity on the cellular level by creating cavitation or fracture of the cell membrane mechanically, changing capacitance and therefore, inducing ion flows between intracellular and extracellular leading to neural activation or inhibition[104,109–112]. More precisely, acoustic cavitation is induced when pressure goes below the vaporization point of the membrane lipophilic zone. The formation of these bubbles inside the cell membrane is likely to result in a neuromodulation effect. Interestingly, the on-going US-based interventions that precisely target cavitation, are currently using low frequency and high pressure to induce blood–brain barrier opening and litho- and histotripsy.[113–116] In contrast, the usual parameter space used in neuromodulation studies (higher frequencies and lower pressure) reported neural activity changes without any evidence of cavitation.[105,117] Therefore, cavitation is unlikely to contribute to neuromodulatory effects.

The thermal effect of ultrasound is mainly due to a phenomenon called absorption, in which the mechanical energy is converted into heat in the sonicated tissue.[118] Numerous studies have shown reversible suppression of neural activity following ultrasound induced thermal rise.[119] This temperature rise might explain especially the inhibitory effect of TUS, as modulation of neural activity in the mammalian brain is associated with changes in temperature in the order of + 0.1 °C.[120,121] In more details, the inhibitory effects found to be associated with thermal effects of TUS seem to involve increased potassium channels conductance, which in turn, decrease resting membrane potential and neuronal firing.[122,123] Some thermo-sensitive potassium channel subtypes have been identified, i.e., TREK1,2, and K2P or TRAAK. All in all, there is increasing evidence supporting the role of the thermal effects in TUS induced neuronal inhibition, with maximal effects for temperature rise of + 0.5 °C.[124]

Importantly, in most of the experimental work ultrasound stimulation triggers both thermal rise and mechanical factors, which makes the two explanatory mechanisms hard to disentangle. It is proposed that both, the thermal and mechanical energy, through acoustic radiative forces (ARF) alter the membrane capacitance, denaturizes membrane components and gates channels such that depolarization, and therefore, activation modulation of the cell is the result.[104] On its own, there is a large body of evidence showing that mechanical waves induce a flexoelectric effect by twisting dielectric components of the cell membrane through transmitted ARF.[125] This promotes substrate enzymatic reactions and the resulting molecules then alter gating of mechanosensitive ion channels (TREK-1, TREK-2, TRAAK, Piezo1). It is also discussed that non-mechanosensitive channels and receptors leading to modulation of neural activity (i.e., astrocytic TRPA1, neuronal NMDAR, $Na_v1.5$ channel[122,126–128]) are

activated due to further ultrasound-channel resonance and further exhibitory and inhibitory effects on voltage-dependent channels as shown in rats.[104,129]

Interestingly, Weinreb *et al.* (2022) showed within neuronal cultures that sonication via extremely short pulses induced action potentials in disconnected neurons eliminating network-effects and enabling the examination on single-neuron level.[82] The study setup used for UFF 500 kHz, peak pressures of 0.35–1.32 MPa, and durations of 4 μs-40 ms extremely short ultrasound pulses and examined one by one the above introduced mechanisms.[82] Interestingly, the study results precluded proposed mechanisms such as cavitation, heating, presynaptic release or mechano-sensitive receptors. Instead, the results implicate an upstream post-synaptic mechanism involved in the action potential generation following sonication.[82] Concerning recent studies in humans using online protocols (i.e., short pulses of TUS coupled with simultaneous recordings of task behavior, motor evoked potentials or other time-correlated recordable neural potentials), some of them are pointing to potential off-target auditory confounds that can cause or contribute to the online inhibitory effects arising from the physical properties of ultrasound.[130–132] Proper auditory masking and adjusted pulse configurations must be used in future work to disentangle the different sources of neuromodulatory effects.[133]

In conclusion, the exact mechanisms underlying neuromodulation are largely unclear and it can be stated that several individual mechanisms may be present at the same time depending on parameter settings and that variation of ultrasonic parameters will result in shifting of mechanism composition[105] which will lead to differential neuromodulatory effects, such as inhibitory vs. excitatory or local vs. additional effects in connected areas.[111]

This article has been accepted for publication in IEEE Open Journal of Engineering in Medicine and Biology. This is the author's version which has not been fully edited and content may change prior to final publication. Citation information: DOI 10.1109/OJEMB.2023.3263690

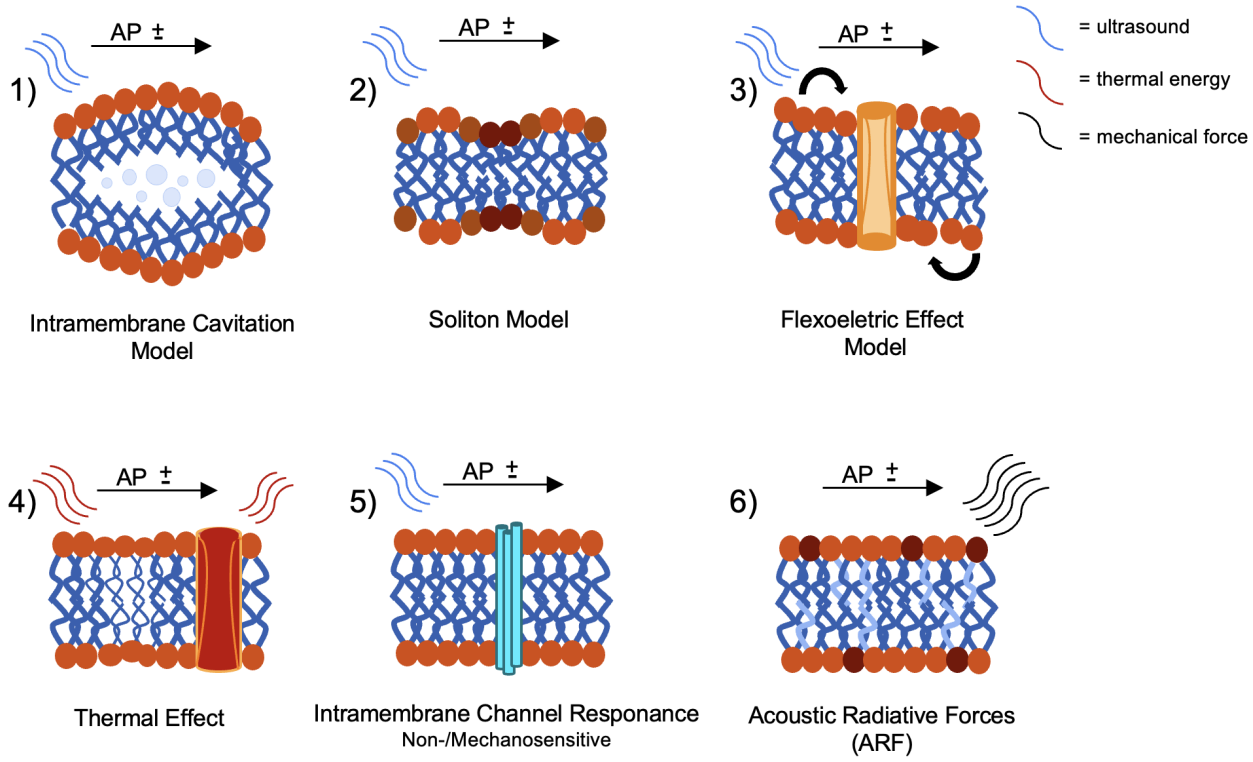


**Figure 2: Underlying mechanism for ultrasonic neuromodulation.**

Legend: Blue waves demonstrating ultrasound as a spectrum of compartments, red and black waves as distinctive compartments of ultrasound medium. 1) High-frequency ultrasound waves propagate through biological tissue and induce microbubbles in liquid or liquid-like medium leading to intramembrane cavitations. Microbubbles deform membrane structure and/or collapse resulting in AP changes and modulating neural activity. 2) Accordingly, to the soliton model it is assumed that membrane diameter of neurons is fluctuating in correlation to the depolarization flow across the membrane. Ultrasonic waves transducing mechanical force have immediate influence on membrane dilation/compression leading to modulation of AP propagation. 3) Mechanical vibration of ultrasound propagation result in rotations and momentum of membrane walls across all dimensional axis leading ion flows through membrane gaps. 4) Ultrasound waves admit energy in form of heat during propagation and when encountering forces or obstacles. Same principle is utilized when using HI-FUS for thermal ablation. Ultrasound transmitted with lower intensities transmits lower thermal energy levels which can result in modulation of membrane channel behavior or mild denaturation of relevant protein structures leading to modulation of neural activity. 5) Mechanical forces can also interact with mechanosensitive and non-mechanosensitive channels within the membrane wall. 6) Acoustic radiative forces (ARF) are created when ultrasonic waves collide with obstacles or forces. Increased momentum and mechanical forces can lead to transient or permanent alterations within membrane components.[103,104,125,127,134]

AP± = action potential induced voltage changes across membrane

## 3. Clinical ultrasound applications and safety aspects

Ultrasound as a clinical tool is used for multiple tasks ranging from diagnostic to therapeutic applications depending on the parameter space.[135] Focused ultrasound can be divided into three main subgroups: high-intensity (HI-FUS), medium-intensity (MI-FUS) and low-intensity FUS (LI-FUS and TUS) (Table 1).[136]

HI-FUS is an established, FDA-approved method for several clinical applications such as ablation of tumors[137–139], for thalamotomy for treatment of essential tremor (ET)[140], for Parkinson's disease (PD)[141] or for neuropathic pain management[142]. In the context of stroke treatment, some studies elaborated HI-FUS as an additional approach for thrombolysis, so called "sonothrombolysis" in acute stroke.[143–145] With less intensity, MI-FUS can be used for transient opening of blood brain barrier (BBB) and therefore for enhancing therapy for neuropsychiatric disorders through stronger uptake of medication[146,147], gene therapy[148–150] or chemotherapy.[146,151,152] HI-FUS and MI-FUS applications are outside the scope of this review, we refer the reader to some excellent reviews on the topic.[170] "Low intensity" TUS refers to the magnitude of ultrasonic intensity similar to or below the one commonly used for diagnostic US, and able to transiently suppress or excite neuronal responses.

There is no formal expert consensus on safety standards for the application of TUS yet. In the absence of specific consensus guidelines at the present time, relevant societies, foundations, and regulatory bodies, including the Focused Ultrasound Foundation (FUSF), the International Society for Therapeutic Ultrasound (ISTU), the IEEE Ultrasonics, ferroelectrics, and frequency control society (IEEE-UFFC), and the US Food and Drug Administration (FDA) have published recommendations. Most of the labs worldwide adhere to the safety standards for diagnostic ultrasound published by the Food and Drug Administration (FDA, 2019 "Marketing Clearance of Diagnostic Ultrasound Systems and Transducers", Section 5.2.7 Table 3 and Section 5.2.7.1.4).[153] These guidelines are validated in the context of diagnostic ultrasound imaging, including human transcranial applications, and can be considered applicable for transcranial ultrasonic stimulation in humans. The Food and Drug Administration (FDA) cephalic acoustic exposure guidelines are defined as spatial-peak pulse-average intensity (ISPTA) of 720 mW/cm2, and either mechanical index (MI) = 1.9 or derated spatial-peak temporal-average intensity ISPPA = 190 W/cm2.[108,154] Safety assurance was also confirmed for obstetrical ultrasound when executed within FDA-approved guidelines regarding intensity setting.[155] These parameters specified by FDA guidelines have been extensively validated in

the context of biomedical ultrasound and are historically used as an informal benchmark for neuromodulation applications of low-intensity ultrasound.

In the aim of promoting good standard practices when conducting TUS experiments, the iTRUSST consortium (https://itrusst.github.io/) publishes on its website an open example of standard operating procedure performed at the Donders Institute (Nijmegen, The Netherlands). An important step is how to make sure that the sonication parameters stay within the safety limits. Based on the FDA regulations, thermal risk is within clinical range of applicability and no further thermal risk assessment is required with protocols using an ISPTA below 720 mW/cm2. In the common scenario that stimulation intensities exceed this threshold, acoustic and thermal modeling accounting for the presence of the skull should be conducted to derive an informed estimate of maximum temperature rise (FDA, 2019). This modeling is achieved with a combination of skull imaging (either MRI or CT), skull segmentation (e.g., with SimNIBS, ©2019, SimNIBS Developers), an acoustic model, and finally a thermal model in k-Wave (i.e., a MATLAB toolbox for acoustic and thermal simulations). A conservative threshold for temperature rise is set at TR < 1 °C for the brain and TR < 2 °C for the skull. Below this threshold, temperature rise is deemed safe for any tissue type, not only in healthy participants, but also in patients with compromised thermoregulation, and without requirement for a medical doctor or a dedicated trained person present to respond instantly to heat-produced physiological stress.[156] When the temperature rise briefly exceeds this limit, thermal damage risk is better assessed in the context of thermal dose (TD), as measured in cumulative equivalent minutes relative to one minute at 43°C (CEM43°C). This measure of thermal effects incorporates both temperature level and exposure length. In healthy participants, without medical or trained response present, the thermal dose should be smaller than 2 CEM43°C [156].

A similar informed stepwise approach should be taken to demonstrate mechanical safety. Specifically, with a peak rarefaction pressure (Pr) below 1 MPa, based on the stimulation parameters, no further mechanical risk assessment is required. In the scenario that stimulation pressures exceed this threshold, a further informed estimate of the peak rarefaction pressure acoustic is derived from measurement or modeling accounting for the presence of the skull. A conservative threshold for acoustic pressure is set at Pr < 2 MPa. Below this threshold, mechanical bioeffects are deemed safe for any tissue type. Of importance, first human safety studies were conducted showing that intensities with up to 5 W/cm$^2$ did no harm to the tissue in histological evaluation, making TUS neuromodulation a valid therapeutic tool[157] provided current safety work in temporal lobe epilepsy patients who underwent sonication prior to resection of anterior-mesial temporal lobe.[94] Their results suggest that TUS at intensities up to

5760 mW/cm$^2$ may be safe for neuromodulation in humans.[94] As for long-term safety and efficacy, a recent study from Munoz *et al.* (2022) shared data regarding TUS towards deep brain regions such as the striatum in primates for a time frame of 2 years, using $I_{sppa}$ between 0.5 and 7.8 W/cm2 and $I_{spta}$ were between 10.1 and 156.7 mW/cm$^2$.[95] The authors showed successful modulations of motivation and decision accuracy, but no behavioral impairment nor neurological trauma with parameters within FDA recommendations.[95]

In summary, modeling tools and specific MR sequences (such as the Acoustic Radiation Force Impulse (ARFI) sequence, able to image temperature rise and ultrasound beam, should be used to ensure safety and strict compliance with international safety guidelines.[158]

| **Ultrasound modality** | **Focal peak intensity** | **Wave form** | **Proposed effect** | **Clinical Applications** |
|---|---|---|---|---|
| Unfocused | <0.1 W/cm$^2$ [159]<br><0.72 W/cm$^2$ [160] | Pulsed waves [140] | Transmitting sound waves and recording echo for imaging construction accordingly to tissue constancy[103] | Diagnostics such as Transcranial Doppler US, abdominal US, musculoskeletal US or echocardiography[161–163] |
| **Focused US (FUS)** | | | | |
| Low-intensity FUS (LI-FUS) / Transcranial ultrasound stimulation (TUS) | 1 – 3 W/cm$^2$ [164]<br>3 – 35 W/cm$^2$ [136]<br>0.5 – 10 W/cm$^2$ [165] | Pulsed waves [140] | Several proposed effects: Heating, Mechanical influence leading to acoustic cavitations within lipid bilayer, flexoelectric effect and activating wall-integrated ion channels or radiation force[136] | Neuromodulation for neuropsychiatric disorders[79,87,88,140,166,167] |
| Medium-intensity FUS (MI-FUS) (including TUS) | 10 W/cm$^2$ [165] | Pulsed waves [140] | Transient opening of blood-brain-barrier (BBB) caused by transcytosis, endothelial fenestration, opening of tight junctions or repairable damage in endothelium[168] | Improved uptake of medication, gene therapeutic agents or chemotherapy in the brain[140,146–148] |

| | | | | |
|---|---|---|---|---|
| High-intensity FUS (HI-FUS) | >1000W/ $cm^2$ [169,170] | Continuous waves [140] | Mechanical and thermal induced coagulation leading to necrosis of tissue[171] | Clinical ablation of biological tissue such as for tumor ablation or for thalamotomy but also for (virtual) lesioning of neural circuit checkpoints for Parkinson's disease (PD), essential tremor (ET) or pain treatment.[136,138,139,159]<br><br>Discussed as potential thrombolysis method ("sonothrombolysis") in stroke[77,143–145] |

**Table 1:** Overview regarding ultrasound in the clinical usage

## 4. Potential targets for TUS in stroke recovery

In this section, we will review some promising applications of TUS for stroke recovery. Capitalizing on the intrinsic TUS features (i.e., good depth-focality trade-off), we will insist on the exciting opportunities TUS could bring to the field (see Figure 3 for a summary of the applications and Supplementary Table 1 for a summary of human TUS studies).

*Peripheral nerve stimulation (PNS)*

The stimulation of peripheral nerves or peripheral nerve endings has been shown to improve outcomes of post-stroke patients.[172–176] In 1996, Glanz *et al.* (1996) published that functional electrical stimulation (FES) to peripheral nerve parties showed significant increasement of muscle strength in post-stroke patients.[177] Following a major body of research regarding FES was conducted in both acute[178–180] and chronic[181–183] stroke patients showing improved neurorehabilitation results of upper limb functions. This could recently also be shown for EMG-based robotic rehabilitation systems for restoration of upper limp functions in stroke survivors.[325,326] Particularly, somatosensory stimulation facilitated enhancement of motor functions in both subacute[173,184,185] and chronic[175,186,187] post-stroke patient populations. This seems to be optimal when FES is used in close synchrony with voluntary movement accordingly to neuroimaging studies utilizing fMRI.[327, 328] The combination of peripheral nerve and central

brain stimulation seem to even lead to larger beneficial effects.[188,189] Due to the excellent focality and steering capacities of FUS-based neuromodulation, US-PNS has been successfully performed in numerous studies in animals and a few human studies showing inhibitory and exhibitory neuromodulation effects.[78,136,190–192] Young and Henneman had already shown in 1961 that US could differentially modulate the activity of Aδ- and C-fibers, depending on the fiber diameter, US intensity, and US exposure time. [193] More recently, additional technical assistance via focal depth controller has been proposed to further improve peripheral nerves targeting for neurorehabilitation[194], making FUS a very selective method for peripheral nerve stimulation. Alternatively, peripheral vagus nerve stimulation (PVNS) demonstrated stabilizing effects on plasticity and enhanced outcome of neurorehabilitation measures for stroke patients.[195–197,] It is also possible to selectively stimulate the peripheral vagus nerve as shown in animal models[198–200] which would later be applied to post-stroke patients to improve the current approaches.

*Spinal cord stimulation (SCS)*

In most cases a stroke affects central brain regions leading to necrosis of components of neural networks controlling motor, sensory or cognitive functions.[201] When central pathways are interrupted the signal transduction to execute motor functions is impaired, however, more distal pathways are still functionally available such as ascending and descending tracts within the spinal cord.[202,203] The role of such tracts, for example the corticospinal tract, in stroke is not well-elaborated yet.[204] However, it was recently shown that injury to the corticospinal tract can be used a predictor to upper extremity recovery in post-stroke patients.[205] Moreover, SCS has been shown to stabilize motor control and to induce neuroplasticity to facilitate recovery in rat modeled following cerebral ischemia [206], providing another promising neuromodulatory targets for stroke recovery. Since early work on ultrasound targeting the spine suggests the possibility to modulate spinal cord activity [134,207] future study should investigate the potential of ultrasound for selective spinal tracts enhancement. Recently, Liao et al (2021) provided recent results showing LI-FUS-based SCS to lumbar 4 (L4) and lumbar 5 (L5) segments that stimulation sparked neural circuit activity visualizable in electromyography (EMG) and modulated somatosensory evoked potentials (SEPs) in rats [208], providing promising perspectives for stroke patients.

*Cortical stimulation*

No research of TUS neuromodulation for stroke in humans has been published yet. However, Wu *et al.* (2020) showed in rats that cortical penumbra-specific stimulation via TUS could show improved outcome of endothelin-1 induced middle cerebral artery occlusion (MCAO) strokes.[209]. In accordance, Kim *et al.* (2021) recently published a concept of wearable TUS approach for rats which suffered a MCAO stroke.[210] The system targeted mainly cortical M1 region and partly subcortical regions such as the striatum with ISPPA of 1.6 W/cm$^2$. The stimulation resulted in improved cerebral hemodynamic changes and enhanced post-stroke rehabilitation.[210]

The interest for cortical neuromodulation via high-resolution TUS is large due to the focality of ultrasonic stimulation in the millimeter resolution space.[105,106,211–217] For instance, Lee *et al.* (2021) published in multiple studies that TUS had excitatory modulation effects on single cortical regions such as S1, secondary somatosensory cortex (S2) or V1.[92,218] In this regard, Legon *et al.* (2014) could show that TUS can not only target spatially discrete brain regions in human subjects within S1 but also increased the sensory detection thresholds for those such that two-point and frequency discrimination were improved in the verum vs sham group.[219] Especially interesting for stroke rehabilitation where phases of hypo- and hyper-excitability are changing over time, both excitatory and inhibitory neuromodulation effects have been published in humans.

Critically, some TUS parameters have been applied in independent labs around the world and the respective results showed consistent offline excitatory effects over M1.[78,81,220,221,222] Notably, Zeng *et al.* (2022) used theta burst patterned TUS to induce long-lasting plasticity change in primary motor cortex region up to 30 min after sonication.[223] In contrast, studies using online TUS parameters (short pulses) such as in Legon et al (2018)[211], Nakajima *et al.* (2022)[224] and Fomenko et al (2020)[107] showed mainly inhibitory effects on motor evoked potentials (MEPs), potentially providing both options for regulating hyper- or hypo-excitability during stroke recovery. Yu et al (2021) recently showed a first publication of TUS with ISPPA of 5.9 W/cm$^2$ over M1 showing modulation of movement-related cortical potential with high spatiotemporal resolution.[214] In light of movement impairment following stroke, the published work provided translational substance for enhancing endogenous motor cortical processes in humans.[214]

*Subcortical, deep brain regions*

Focal lesions induced by stroke are interrupting neural networks and white matter connections between central subcortical regions such as basal ganglia or thalamus nuclei

determining neurological impairment and long-term outcome of post-stroke patients.[28] Particularly, the thalamus as the central and integrative hub of functional brain networks[225] is essential for integration and for reorganization of the post-stroke brain as shown in neuroimaging studies highlighting the thalamocortical network dynamics.[226–229] Hence, deep-penetrating TUS with high resolution qualify as an excellent neuromodulation tool for elaborating the role of subcortical structures in post-stroke recovery and potentially for improvement of the motor recovery process by modulating neural network dynamics.[230]

Several studies have shown both exhibitory effects in animals[231–233] and humans[92,234,235] and inhibitory effects in animals[87,119,236] and humans[107,211,216] for TUS in deeper brain regions. A first human study applying TUS for neuromodulation to thalamus, Legon *et al.* (2018) showed physiological and behavioral effects targeting the unilateral thalamus containing the ventro-posterior lateral (VPL) nucleus using a combined approach with TMS and TUS with a single-element transducer using 500 ms burst, 0.5 MHz center frequency and ISPPA of 7.03 W/cm$^2$. The study reported thalamic neuromodulation via TUS was resulting in P14 SEP and time-locked gamma power inhibition, attenuation of alpha and beta power in EEG analysis during stimulation and significant decrease in discrimination ability in behavioral tests in the stimulation group compared to the sham group.[215] This study as a first of its own, showed safe neuromodulation effects by targeting deep brain structures of the human brain with TUS.

Sonication of the striatum is also of potential interest in stroke because of apparent impaired striatal functioning in patients and the involvement of the striatum especially in motor recovery.[48,237,238] After intensive and safe TUS of the striatum, Munoz and colleagues showed improved decision making in primates together with widespread BOLD signals changes.[95] Recently, Nakajima et al (2017) presented work in which a four-element FUS transducer (NeuroFUS CTX-500, Brainbox Ltd, Cardiff, UK) with fundamental frequency of 0.5 MHz with 30ms burst repeated every 100ms for 40s was used to stimulate basal ganglia, more precisely, the striatum (anterior and posterior putamen) and the subthalamic nucleus and evaluate its role in motor control processes.[239] They first applied their sonication parameters over M1 and demonstrated significant inhibition of MEPs. Later applied to the anterior putamen, they found significant impaired stopping performance at a stop reaction time task. Concurrent fMRI revealed circuit activity between anterior putamen and anterior inferior frontal cortex (IFC).[224] This multimodal approach contributed to the understanding of both the parameter setting of TUS neuromodulation toward cortical and subcortical regions and the interconnections of deep brain structures to cortical regions.[224] Finally, a case-report concerning deep brain stimulation via TUS by Monti et al (2016) showed recovery of a brain injury patient

improving motor functions and task-related results following ultrasonic therapy to the thalamus.[240]

It becomes clear that TUS has excellent properties for targeting deep brain regions, perhaps even combinable and applicable in DBS patients and beyond.[157] Sarica *et al.* (2022) recently published their work in an ex-vivo setting regarding appropriate parameters for TUS to enhance adaptability of such applications and to not produce hazardous temperatures on DBS lead.[157]

Alternatively, non-invasive stimulation[65,241,242] but also invasive[63,65,242] stimulation of the cerebellum has been tried out for post-stroke recovery. Preclinical studies proved DBS stimulation to the cerebellum for post-stroke conditions to be effective in rodents.[63,65] As for DBS approaches, a first-in-human clinical trial is elaborating this effect in human post-stroke subjects (NCT02835443). Regarding NIBS, Wessel *et al.* (2018) provided a comprehensive review of the most common approaches via tDCS/tACS and rTMS to the cerebellum in humans.[241] In a recent study Koch et al (2019) showed that non-invasive, cerebellar intermittent θ-burst stimulation via repetitive TMS (rTMS) induced cerebellar-cortical neuroplasticity benefiting motor-rehabilitation with regard to gait ability and walking balance in post-stroke patients.[243] These subcortical targets are of particular interest for ultrasonic neuromodulation considering the excellent depth penetrability, millimeter-precise focality and superior steering capacities of TUS.[81,136] Cooperrider et al (2022) used TUS to modulate the lateral cerebellar nucleus (LCN) in rodents, homologue of the human dentate nucleus (DN) to enhance sensorimotor recovery.[244] Significant improvement was noted after one day in the rodent TUS group compared to the group without TUS.[245] Still in mice, Baek et al (2020) examined the effect of TUS over the LCN applied on 3 consecutive days following induced middle cerebral artery occlusion (MCAO). Their results showed that TUS suppressed not only pathological delta activity but rebalanced interhemispheric interactions.[246] On a cellular level, it is hypothesized that the increased survival rate of purkinje cells within the cerebellum is responsible for these beneficial effects for neurorecovery.[247] In conclusion, more studies regarding deep brain structure stimulation via TUS are needed as the number of in-human studies are very limited yet. To determine and understand appropriate parameters for clinical feasibility and efficacy, for paving the way of a novel non-invasive deep brain stimulation method, more research must be conducted

*Adaptive TUS neuromodulation for stroke*

Neural oscillations are a key factor to modulate pathological progress and recovery in stroke.[230] Furthermore, non-invasively evoked neural oscillation changes have recently been discussed as potential, promising therapeutic option to restore intrinsic homeostasis to support the neurorecovery process following a stroke.[230]

As the oscillatory behavior of neural populations change over the reorganization course following a stroke, several approaches for phase-dependent neuromodulation have been proposed.[46,61,248–250] To target local brain regions, the principle of closed-loop neuromodulation holds the potential to build fully adaptive neuro-recovery BCI systems for stroke rehabilitation.[251–255] Current adaptive neuromodulation proposals utilize electromagnetic stimulation paradigms combined with electric recording systems.[253,256–258] Due to interference between electromagnetic stimulation signals and the electrical nature of the recorded signals, fully adaptive systems are hindered leading often to non-real-time systems which record and stimulate neural activity alternatingly.[259–262] Ultrasonic neuromodulation can here supplement or complement existing NIBS systems to build novel adaptive brain stimulation approaches. A first attempt presented a wearable TUS system for rats and sheeps.[210,263] Due to the mechanical, thermal and non-ionizing nature of ultrasonic stimulation, electromagnetic artifacts are less likely to occur compared to TMS or tES.[264] In combination with neuroimaging methods such as EEG this can lead to artifact-reduced closed-loop adaptive neuromodulation.[83,212,265] Concussively, TUS hold, as a future perspective, further potential to enable real-time neuromodulation through applied neurostimulation while simultaneously recording of neural activity to open the way of bidirectional brain machine interface (BBMI) or BBCI approaches due to the non-interfering nature of ultrasound stimulation with electromagnetic recording.[266–268]

This article has been accepted for publication in IEEE Open Journal of Engineering in Medicine and Biology. This is the author's version which has not been fully edited and content may change prior to final publication. Citation information: DOI 10.1109/OJEMB.2023.3263690

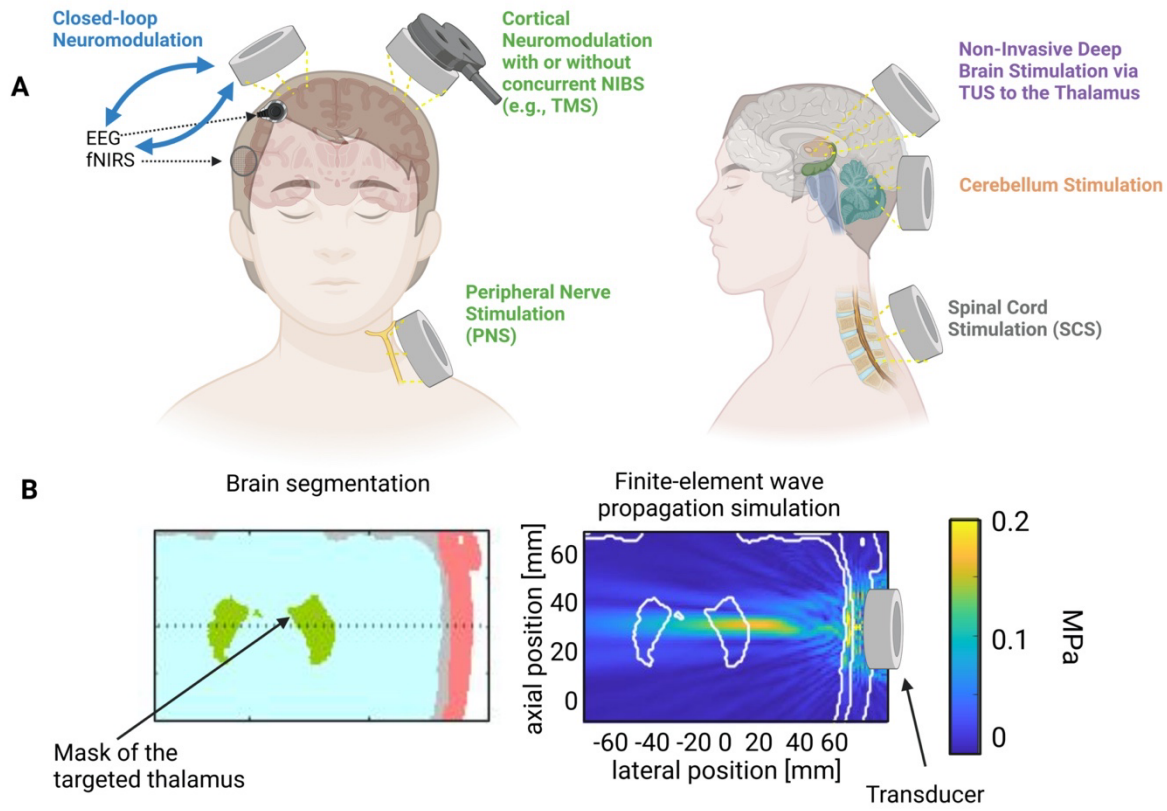


**Figure 3: Overview of potential TUS-based neuromodulation approaches in stroke**

A) Illustration of different TUS targets regarding neuromodulation for the purpose of stroke neurorehabilitation. Left, frontal view illustrates cortical neuromodulation with or without conventional NIBS methods such as TMS, peripheral neurostimulation (PNS) to central cranial nerves i.e. vagus nerve and closed-loop approaches utilizing recording systems such as EEG or fNIRS to adjust TUS application parameters. Right, lateral view illustrates non-invasive deep brain stimulation via TUS to the thalamus, deep brain stimulation to the cerebellum and spinal cord stimulation (SCS) via TUS. B) Finite-element wave propagation simulation using a MATLAB package (k-Wave toolbox: http://www.k-wave.org/) targeting the human posterior thalamus.

## 5. Conclusions

We presented in this review a large array of relevant studies investigating the use of TUS for neuromodulation with a prospective vision for stroke-rehabilitation and post-stroke recovery. TUS holds the potential of becoming a practicable neuromodulation and therapy solution for stroke and beyond. Ultrasonic neuromodulation has several advantageous properties when compared to more conventional non-invasive neurostimulation approaches such as TMS or tES. To name a few of the advantages, deep penetration, high spatiotemporal resolution, and excellent steering capacity are three main factors to differentiate TUS from other non-invasive neurostimulation paradigms.

*TUS as a potential neuromodulation tool in stroke recovery*

Figure 4 summarizes the way ultrasonic neuromodulation may act on brain tissues and at the systems level on brain activity leading to therapeutic solutions for stroke neurorehabilitation. Considering stroke as a network disease in which subcortical-cortical networks are a driving instance for the neurorehabilitation process, it becomes evident that long-ranging ultrasonic stimulation of subcortical regions are of interest. High focality of TUS adds additional value to solve the hitch of non-invasive, deep brain stimulation of highly interconnected subcortical regions with rather limited volumetric target space. Furthermore, the potential of combining TUS with more conventional non-invasive brain stimulation methods as TMS has been probed in several animal and human studies indicating a great possibility of complementary clinical applications. Finally, the presented parameters used in studies meet the requirements of the FDA-approved diagnostic ultrasound settings and, therefore, qualify for clinical adaptability. However, the next important steps will be to determine in upcoming studies the most efficient and safe TUS protocols for neuromodulation to enhance residual functions and stroke recovery ideally in a personalized way, e.g., targeted to specific phases after stroke (subacute vs. chronic), lesion patterns, connectomics/disconnectomics patterns and/or level of functional deficit.

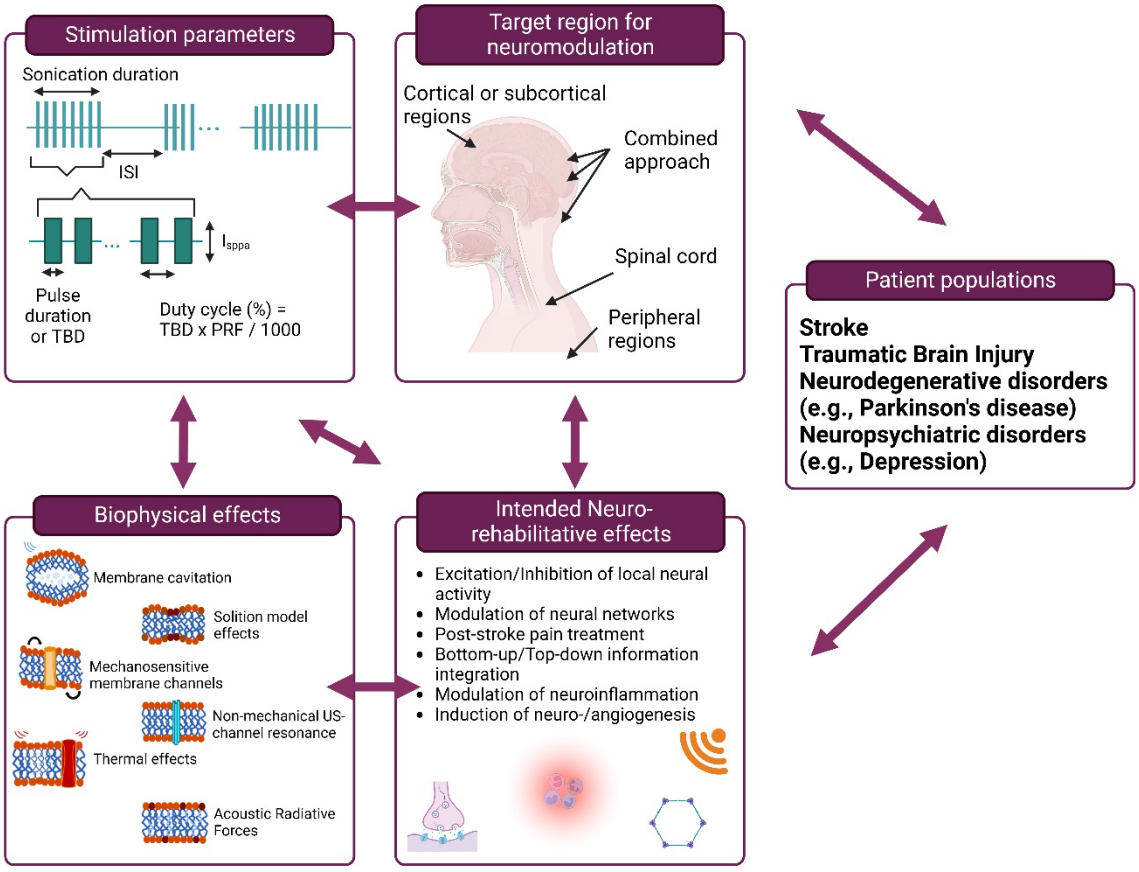


**Figure 4**: Flow diagram schematic for development of ultrasonic neuromodulation protocol leading to therapeutic solutions for neurorehabilitation.

*Open questions and challenges of ultrasonic neuromodulation*

Recent results of studies including TUS are showing great potential for neuromodulation. However, a variety of mechanisms are discussed but not fully elucidated yet. As neuromodulation is defined by a fine-balanced setting of parameters it remains important to evaluate TUS in further in-human studies to establish consistent neuromodulation protocols for precise excitation and inhibition of both cortical and subcortical structures. Additionally, an important open question in the field is whether online acoustic stimulation is inducing indirect neural activity changes via auditory pathways leading to a cluttered conclusion about the actual neuromodulation of ultrasound. Therefore, a better understanding of the relationship between the US parameters' space and the associated biophysical mechanisms is needed to critically translate the beneficial effects of TUS observed in animal models and to translate those for stroke. Thus, it remains crucial to evaluate TUS in further pre-clinical and human studies elaborating the individual mechanism hypotheses.

*Reporting guidelines for TUS parameters*

The absence of no formal expert consensus on safety standards for the application of TUS poses a significant challenge for researchers to compare results and draw meaningful conclusions. Therefore, the purpose of reporting guidelines to proffer a set of recommendations for the systematic reporting of TUS parameters in future studies is needed to establish a norm for this burgeoning field. Importantly, relevant societies, foundations, and regulatory bodies, including the Focused Ultrasound Foundation (FUSF), the International Society for Therapeutic Ultrasound (ISTU), the IEEE Ultrasonics, ferroelectrics, and frequency control society (IEEE-UFFC), and the US Food and Drug Administration (FDA) are supporting an international consortium comprised of dozens of experts to establish consensus on these matters (iTRUSST: https://itrusst.github.io/).

Such reporting guidelines must encompass the critical parameters that are fundamental to comprehending the TUS intervention applied. These parameters include the specifications of the ultrasound device employed, the ultrasound parameters such as frequency, intensity, duration, and mode of application. They should specifically provide guidelines for mechanical and thermal safety as well as guidelines for exclusion/inclusion criteria for healthy volunteers and patients. Additionally, it should contain detailed information about the location of the ultrasound application and the targeted brain region. Furthermore, it is imperative to report any unwanted effects experienced during or after the TUS intervention and any measures taken to mitigate them. Upcoming guidelines must also provide guidance on the evaluation of the TUS effects, including the outcome measures used to assess the intervention's effectiveness, such as behavioral, cognitive, or physiological measures. Furthermore, it must incorporate information on the statistical methods utilized in analyzing the data, the effect size, and the confidence intervals. Optimally, this could be established by a digital infrastructure such as an open-source software tool for researchers to collect different protocols and compare those with each other to eventually determine the “standard” among them. Thus, development of reporting guidelines for TUS neuromodulation parameters are a critical requirement for establishing a benchmark for future studies in this field. The guidelines must present a comprehensive set of recommendations for the systematic reporting of the essential parameters and evaluation of TUS effects to ensure that research findings can be accurately compared and replicated, and the potential clinical applications of TUS can be fully realized. Potential core factors for such guidelines for reporting TUS parameters in research studies could be the following ones:

1. Ultrasound device: Provide a detailed description of the ultrasound device used, including the manufacturer, model, and specifications such as the type of transducer, the number of elements, and the pulse repetition frequency.
2. Ultrasound parameters: Report the ultrasound frequency, intensity, duration, and mode of application, including information on whether the ultrasound was delivered continuously or pulsed and the pulse duration.
3. Targeted brain region: Provide information on the location of the ultrasound application and the targeted brain region, including the stereotactic coordinates if applicable.
4. Adverse effects: Report any adverse effects experienced by participants during or after the tUS intervention, including any measures taken to mitigate these effects.
5. Outcome measures: Specify the outcome measures used to assess the intervention's effectiveness, such as behavioral, cognitive, or physiological measures.
6. Statistical analysis: Describe the statistical methods used to analyze the data, including the effect size, confidence intervals, and any adjustments made for multiple comparisons.

However, implementing such guidelines in future research studies will help to promote transparency and standardization in reporting TUS parameters for establishing a transparent ground for researchers to compare results and draw meaningful conclusions…'

*Critical issues and the limitation of TUS neuromodulation*

TUS has the potential to modulate cortical excitability, enhance neuroplasticity, and promote functional recovery after stroke. However, there are critical issues and limitations that need to be addressed before TUS can be widely used in clinical practice for stroke rehabilitation. One critical issue is the lack of standardization in TUS parameters. As mentioned, there is currently no consensus on the optimal ultrasound frequency, intensity, duration, or mode of application for stroke rehabilitation. Furthermore, the optimal target brain region for TUS intervention in stroke patients is still uncertain, and different studies have used different brain regions as targets. This variability in TUS parameters can lead to inconsistencies and heterogeneity in study outcomes, limiting the comparability and generalizability of results. Another limitation is the variability in individual responses to TUS intervention. The efficacy of TUS may depend on several factors, including stroke severity, lesion location, and time since stroke onset. The complex interplay between these factors and the effects of TUS on cortical

plasticity and functional recovery make it challenging to predict and optimize treatment outcomes for individual patients. Therefore, identifying patient-specific factors that may influence the efficacy of TUS intervention is crucial for selecting appropriate patients and optimizing treatment outcomes. Finally, the feasibility of delivering TUS intervention in stroke rehabilitation is another critical issue. TUS requires specialized equipment and trained personnel, which may limit its availability and accessibility in clinical settings. Moreover, the safety and tolerability of TUS intervention in stroke patients need to be carefully evaluated, as adverse effects such as headache, nausea, and dizziness have been reported in some studies. Additionally, the practicality of integrating TUS intervention into existing stroke rehabilitation protocols and the cost-effectiveness of this approach need to be considered. In conclusion, although TUS holds promise as a non-invasive and potentially effective neuromodulation technique for stroke rehabilitation, there are critical issues and limitations that need to be addressed. Standardization of TUS parameters, identification of patient-specific factors that influence treatment response, and careful evaluation of safety and feasibility are essential for advancing the use of TUS in stroke rehabilitation. Future research should aim to establish a consensus on optimal TUS parameters and target brain regions, identify biomarkers that predict treatment response, and evaluate the long-term effects of TUS intervention on functional outcomes in stroke patients.

*Future outlook for TUS*

Ultrasonic neuromodulation holds massive potential for applicability and adaptability in clinical contexts as the majority of the parameter ranges are within FDA-approved guidelines for diagnostic ultrasound applications. First and foremost, TUS is highly interesting for clinicians when complementing traditional non-invasive stimulation paradigms in reaching deeper brain regions for neuromodulation without the challenge of the depth-focality trade-off or invasiveness. These prosperities qualify TUS as a neurostimulation tool to become widespread adoptable.

Moreover, combining online-application of TUS with existing recording systems such as EEG, MEG or fMRI simultaneously would enable to modulate brain network properties adaptively. Prospectively, this could enable real-time closed-loop neuromodulation or BBCI systems for stroke. Also, the concept of online and offline application of TUS ought to be distinguished in future studies. Most current studies follow the design of offline applications which can show long-lasting effects post-stimulus. However, online application of TUS benefits more when moving forward towards real-time, ultrasonic neuromodulation.

This article has been accepted for publication in IEEE Open Journal of Engineering in Medicine and Biology. This is the author's version which has not been fully edited and content may change prior to final publication. Citation information: DOI 10.1109/OJEMB.2023.3263690

Lastly, the number of in-human TUS applications are not sufficient for large-scale conclusions, yet. Further TUS investigations for humans are needed to establish protocols which can evaluate individual parameters' value for neuromodulatory effects and to elucidate safe patient conditions to enhance widespread adaptability.

Overall, the clinical evidence of ultrasonic neuromodulation leading to neuroprotection, recovery and neurorehabilitation for stroke is still limited. Promising neuromodulatory effects are presented in several studies and, thus, translation to neurorehabilitation protocols is potentially promising and achievable. However, the presented studies in this review indicate further expansion potential for TUS applications in both humans and animals regarding stroke rehabilitation. Especially, protocols and parameter variations to achieve specific neuromodulation effects are still to be defined. Hence, additional fundamental studies are needed to establish clinically adoptable protocols of ultrasonic neuromodulation as a complementary therapy option for stroke.

**Acknowledgements:**

This work was supported by the Bertarelli Foundation (Catalyst Bridging the sensorimotor loop, to FCH, ER, GC), by the Swiss National Science Foundation (PRIMA PR00P3_179867 to ER), and by the Defitech Foundation (Morges, to FCH, GC, JB).

# SUPPLEMENTARY MATERIALS

## **Supplementary Table 1**: Clinical TUS studies

| **Region of interest Targets** | | **Specifics** | **Study title** | **References** | **Subjects** | **Modalities and task** | **Study Design** | **Parameters** | **Modulation effects** | **Main results** |
|---|---|---|---|---|---|---|---|---|---|---|
| Cortical | Prefrontal cortex (PFC) | Right PFC, healthy participants | Transcranial Focused Ultrasound to the Right Prefrontal Cortex Improves Mood and Alters Functional Connectivity in Humans | Sanguinetti *et al.* (2020)[166] | n =48 | fMRI measuring functional connectivity for resting-state and post-stimulation, mood questionnaire | Randomized, placebo-controlled, double-blind study | UFF = 0.5 MHz<br>PD = 65 µs<br>PRF = 40 Hz<br>DC = 26%<br>SD = 30 s<br>ISPTA = 130 mW/cm2 | Unspecific modulation | TUS modulated mood and emotional regulation networks in the prefrontal cortex |
| | | Bilateral medial PFC (mPFC) | Neuromodulation Using Transcranial Focused Ultrasound on the Bilateral Medial Prefrontal Cortex | Kim *et al.* (2022)[269] | n = 7 | EEG, MRI, CT | Randomized, sham-controlled study | UFF = 0.25 MHz<br>SD =20 min<br>AIF = 3 W/cm$^2$<br>MI = 0.6<br><br>excitatory protocol:<br>DC = 70%<br>SI = 5 s<br><br>suppression protocol:<br>DC = 5%<br>SI = none | Excitation and Suppression | Modulation of delta power for both protocols compared to shame in bilateral mPFC |
| | Posterior frontal cortex | Contralateral to maximal pain, chronic pain patients | Transcranial Ultrasound (TUS) Effects on Mental States: A Pilot Study | Hameroff *et al.* (2013)[270] | n= 31 | Heart rate, systolic and diastolic blood pressure, oxygen saturation, visual analog scale for pain (NRS) and mood (VAMS/Global Affect) | Double blind, sham-controlled, crossover study | UFF = 8 MHz, MI = 0.7 max Intensity = 0.15 kW/cm2 | Unspecific modulation | Improved Mood/Global Affect at 10 min ($p$= 0.03) and 40 min ($p$ = 0.04) following stimulation compared with placebo. NRS pain reported slightly enhanced ($p$ = 0.07) at 40 min. |
| | Inferior frontal cortex (IFC) | + Striatum and STN | A causal role of anterior prefrontal-putamen circuit for response inhibition revealed by transcranial ultrasound stimulation in humans | Nakajima *et al.* (2022)[224] | n = 20 (stages 1 and 3), n = 30 (stage 2), n = 20 (stage 5) | fMRI, TMS, finger movement task with stop-signal | 5 stage study protocol, unknown study design | UFF = 0.5 MHz<br>SD = 40s<br>PD = 30ms<br>DC = 30%<br><br>Stage 1:<br>ISPTA = 9 W/cm$^2$<br><br>Stage 3 and 5:<br>ISPTA = 10.7 W/cm$^2$ | Suppression | TUS induced sustainable suppression for longer than 60 min |
| | | Right IFC + S1 + sham | Response inhibition is driven by top- | Fine *et al.* (2019)[271] | n = 63 (total) | Stop-Signal task, EEG, behavioral task, | unknown | UFF = 500 kHz<br>PD = 0.25 ms | unknown | Sonication of rIFC enhanced significantly |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | down network mechanisms and enhanced with focused ultrasound | | Group 1: n = 25 (TUS to rIFC)<br><br>Group 2: n=23 (TUS to S1)<br><br>Group 3: n.= 15 (sham) | | | PRF = 1 kHz<br>DC = 24%<br>SD = 0.5 ms<br>MI = 0.9<br>ISPPA= 22.4 W/cm$^2$ | | inhibition action providing evidence for top-down relevance in stop-signal task |
| | M1 | +SMA and PMd stimulation, healthy participants | Transcranial focused ultrasound for BOLD fMRI signal modulation in humans | Ai *et al.* (2016)[222] | n = 6 | fMRI scan (cortical BOLD at 3T and sub-cortical BOLD at 7T) | Pre-/post-interventional study | SD = 500 ms<br>ISPPA = 6 W/cm$^2$<br><br>3T MRI experiment:<br>UFF = 500 kHz<br>PRF = 1kHz,<br>DC = 36%<br><br>7T MRI experiment:<br>UFF = 860 kHz<br>PRF = 0.5kHz<br>DC = 50% | Increased activation (fMRI) | Sonication to sensorimotor cortex led to BOLD responses in both cortical and subcortical areas in 3T and 7T fMRI |
| | | Healthy participants | Effects of transcranial focused ultrasound on human primary motor cortex using 7T fMRI: a pilot study | Ai *et al.* (2018)[272] | n = 5 | fMRI, finger tapping task | Sham controlled study | UFF = 500 kHz<br>PD = 0.36ms<br>PRF = 1kHz;<br>DC = 36% SD = 500ms<br>ISPPA= 16.95 W/cm$^2$ | Increased activation (fMRI) | Spatially restricted modulation of cortical activity in finger representing area of M1 |
| | | Healthy participants | Increased excitability induced in the primary motor cortex by transcranial ultrasound stimulation | Gibson *et al* (2018)[221] | n = 43 | TMS, EMG (induced MEP) | Single blind, sham-controlled study | UFF = 2.32 MHz<br>SD = 2 min<br>DC < 1%<br><br>ISPPA = 34.96 W/cm$^2$ | Excitation | TUS increased excitability in M1 by 33.7% immediately following stimulation ($p = 0.009$), and 32.4% for 6 min later ($p = 0.047$) |
| | | Healthy participants | Transcranial focused ultrasound neuromodulation of the human primary motor cortex | Legon *et al.* (2018b)[215] | n = 50 | TMS, EMG (MEPs), SICI, ICF, stimulus response reaction time task | Sham controlled study | UFF = 500 kHz<br>PD = 0.36 ms<br>PRF = 1 kHz<br>DC = 36%<br>SD = 500 ms<br>MI = 0.9<br>ISPPA= 17.12 W/cm$^2$<br>ISPTA= 6.16 W/cm$^2$ | Inhibition | TUS induced inhibitory effects leading to behavioral advantage and significantly reduced reaction time |
| | | Healthy participants | Systematic examination of low-intensity ultrasound parameters on human motor | Fomenko *et al.* (2020)[106] | n = 16 | TMS, EMG (MEPs), visuomotor task | Double blinded study | UFF = 500 kHz<br>PRF =1000Hz<br>SD = 0.1–0.5s<br>DC=10/30/50%<br>ISPPA = 0.93/2.78/4.63 W/cm2 | Inhibition | $GABA_A$-mediated short-interval intracortical inhibition was increased and reaction time |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | cortex excitability and behavior. | | | | | | | on visuomotor task was |
| | | Healthy participants | Transcranial Focused Ultrasound Neuromodulation of Voluntary Movement-related Cortical Activity in Humans | Yu *et al.* (2021)[214] | n = 15 | EEG and ESI (MRCP), EMP, voluntary foot tapping task | sham-controlled study | UFF = 0.5 MHz<br>SD = 500ms<br>PRF = 3000 Hz<br>ISPPA = 5.9 W/cm$^2$<br>ISPTA = 702 mW/cm$^2$ | Excitation | TUS significantly increased MRCP source profile amplitude (MSPA) when compared to the sham ultrasound condition. Higher PRF led more increased MSPA than low PRF |
| | | Healthy participants | Time course of the effects of low-intensity transcranial ultrasound on the excitability of ipsilateral and contralateral human primary motor cortex. | Xia *et al.* (2021)[273] | n = 22 | TMS, EMG (MEP) | Sham controlled study | UFF = 0.5 MHz<br>SD = 500 ms<br>PRF = 1000 Hz<br>DC = 30%<br>ISSPA = 2.32 W/cm$^2$ | Suppression | TUS induced online-suppressive effects on ipsilateral M1 cortical excitability but did not produce long-lasting effects nor induced contralateral modulation or IHI |
| | | Left M1, Healthy participants | Transcranial ultrasound stimulation of the human motor cortex | Zhang *et al.* (2021)[274] | n = 24 | TMS, EMG (MEP), stop-signal task | Crossover, sham-controlled study | UFF = 0.5MHz<br>SD = 500ms<br>ISI = 8s<br>TD = 15 min<br>PRF = 100Hz<br>DC = 5%<br>MI = 0.696<br>ISPPA = 8.053 W/cm$^2$ | Excitation | Ultrasound induced neuromodulation lasted for 30 min and reduced reaction time for stop-signal task when TUS is applied to left M1 |
| | | Healthy participants | Ultrasound stimulation of the motor cortex during tonic muscle contraction | Heimbuch *et al.* (2022)[275] | n = 10 (experiment 1)<br>n = 8 (experiment 2) | MRI, TMS, EMG (MEP) | Pre-/post-interventional study | UFF = 0.5MHz<br>DC = 36%<br>PRF = 1000Hz<br>ISPTA = 1.4 W/cm$^2$ | No effect | No significant effect during tonic motor contraction |
| | | Theta burst patterned TUS beam, healthy participants | Induction of Human Motor Cortex Plasticity by Theta Burst Transcranial Ultrasound Stimulation | Zeng *et al.* (2022)[223] | n = 20 | TMS, EMG, | Sham controlled study | UFF = 0.5MHz<br>SD = 80s<br>PRF = 5Hz/1kHz<br>DC = 10/32%<br>ISPPA = 2.26 W/cm$^2$<br>ISPTA = 0.72 W/cm$^2$ | Excitation | Theta burst patterned TUS induced excitation which lasted for 30 min and repetitive TUS and sham showed no significant change in excitability |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | S1 | Healthy participants | Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans | Legon *et al.* (2014)[219] | n = 10 | EEG (C3, CP1, CP5 and P3); SEPs induced through MNS; two-point discrimination tasks | Sham controlled study | UFF = 500 kHz<br>SD = 500 ms<br>PRF = 1 kHz<br>DC = 36%<br>MI = 1.13<br>ISPPA = 23.87 W/cm$^2$ | Inhibition | tLI-FU modulated short-latency and late-onset evoked cortical activity elicited in humans by somatosensory, median nerve stimulation and discrimination ability improved through TUS to S1 |
| | | Healthy participants | Transcranial Focused Ultrasound Modulates Intrinsic and Evoked EEG Dynamics | Mueller *et al.* (2014)[216] | n = 25 | EEG (C3, CP1, CP5, P3) SEPs induced through MNS | Sham controlled study | UFF = 500 kHz<br>PD = 0.36 ms<br>PRF = 1 kHz<br>DC = 36%<br>SD = 500 ms<br>ISPPA = 23.87 W/cm2 | Inhibition | TUS changed the phase distribution of beta frequencies but not gamma brain activity and in-phase rate of all frequencies. Spatial specificity was accurate on cm level. |
| | | Healthy participants | Image-guided transcranial focused ultrasound stimulates human primary somatosensory cortex | Lee *et al.* (2015)[92] | n = 18 | EEG, fMRI, tactile sensations task | Sham controlled study | UFF = 250 kHz<br>PRF = 500 Hz<br>TBD = 1 ms<br>DC = 50%<br>SD = 300 ms<br>ISPPA = 3 W/cm$^2$<br>ISPTA = 1.5 W/cm$^2$ | Excitation | TUS elicited cortical evoked potentials similar to SEP after MNS and led to precise tactile sensations in accordance to the stimulated area (contralateral hand) but also ipsilateral hand |
| | | Healthy participants | Transcranial focused ultrasound enhances sensory discrimination capability through somatosensory cortical excitation | Liu *et al.* (2021)[235] | n = 9 | EEG and ESI, sensory vibration frequency discrimination task | Sham controlled, crossover study | UFF = 500 kHz<br>SD = 500 ms<br>PRF = 300 Hz<br>ISSPA = 1.10 W/cm$^2$<br>ISPTA = 67.13 mW/cm$^2$ | Excitation | Improvement of sensory abilities to differentiate haptic vibrations accordingly to their frequencies and excited magnitude of N300 component indicating modulation towards higher excitability of activated S1 during TUS |
| | S1 +S2 | Healthy participants | Simultaneous stimulation of the human primary | Lee *et al.* (2016)[234] | n = 10 | fMRI, EEG, tactile sensory task | Double blind, sham- | UFF = 210 kHz<br>PRF = 500 Hz<br>TBD = 1ms | Excitation | Simultaneous S1 and S2 stimulation via |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | and secondary somatosensory cortices using transcranial focused ultrasound | | | | controlled study | PD = 1 ms<br>DC = 50%<br>SD = 500 ms<br>ISPPA = 35.0 W/cm$^2$<br>ISPTA = 17.5 W/cm$^2$ | | TUS elicited several, variational tactile sensations in corresponding and non-corresponding hands and fingers areas. |
| | Temporal lobe | Temporal epilepsy patients | Safety of focused ultrasound neuromodulation in humans with temporal lobe epilepsy | Stern *et al.* (2021)[94] | n = 8 | MRI, Histological evaluation, Neuropsychological testing | Pre-/post-interventional study | UFF = 650 kHz<br><br>Activation protocol:<br>DC = 50%<br><br>Suppression protocol:<br>DC = 5%<br>SD = 30s<br><br>ISPTA = 720 – 5760 mW/cm$^2$ | Unknown | MRI-guided TUS with up to 5760 mW/cm$^2$ intensity does not harm temporal lobe tissue in histological evaluations and neuropsychological testings showed no significant difference between pre- and post-stimulation |
| | V1 | Healthy participants | Transcranial focused ultrasound stimulation of human primary visual cortex | Lee *et al.* (2016)[218] | n = 19 | fMRI, EEG, phosphene perception task | Single blind, sham-controlled study | UFF = 270 kHz<br>PRF = 500 Hz<br>PD = 1 ms<br>DC = 50%<br>SD = 300 ms<br>ISPPA = 3 W/cm$^2$<br>ISPTA = 100mW/cm$^2$ | Excitation | Phosphene perception was reported from V1 TUS and excitatory peaks present in EEG recordings. |
| | Broad cortical regions | AD-relevant brain regions, healthy participants and AD patients | Transcranial pulse stimulation with ultrasound in Alzheimer's disease-a new navigated focal brain therapy | Beisteiner *et al.* (2020)[93] | n(healthy)= 10<br>n(AD)= 35 | EEG data recorded at CP3, SEPs, neuropsychological tests, fMRI for functional connectivity (FC) | Multicenter pre-/post interventional study | Transcranial pulse stimulator (TPS) from NEUROLITH:<br>Admitting single ultrashort ultrasound pulses,<br>PRF = 5 Hz<br>TNP = 6000<br>PD = 3 µs<br>0.3 mj/mm$^2$ | Unspecific neuromodulation | Improvement of neuropsychological scores following ultrasonic treatment, oscillational changes N70, N140 and P27 in EEG and upregulated memory network modulation regarding FC in fMRI |
| | | Depression in AD patients | Transcranial pulse stimulation (TPS) improves depression in AD patients on state-of-the-art treatment | Matt *et al.* (2022)[276] | n = 18 | fMRI, Beck Depression Inventory (BDI-II) | Multicenter pre-post interventional study | Transcranial pulse stimulator (TPS) from NEUROLITH:<br>Admitting single ultrashort ultrasound pulses,<br>PRF = 5 Hz<br>TNP = 6000 | Unspecific neuromodulation | Significant improvement of BDI-II after TPS therapy and normalized FC between the salience network (right anterior insula) and the ventromedial network (left |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | PD = 3 µs<br>0.3 mj/mm$^2$ | | frontal orbital cortex) |
| Subcortical | Thalamus | Post-traumatic, unconscious patient (19 days post injury) | Non-invasive ultrasonic thalamic stimulation in disorders of consciousness after severe brain injury: a first-in-man report | Monti *et al.* (2016)[240] | n = 1 | Chart review, response to command, and reliable communication (by yes/no head gesturing) | Case report, part of an ongoing clinical trial | UFF = 650 kHz<br>PD = 0.5 ms<br>DC = 5%<br>PRF = 100 Hz<br>ISPTA = 0.72 W/cm$^2$ | unknown | Improved conscious state of patient after 3 days of sonication. After 5 days of sonication willingness to walk was enhanced. |
| | | Unilateral sensory nuclei of thalamus, healthy participants | Neuromodulation with single-element transcranial focused ultrasound in human thalamus | Legon *et al.* (2018)[215] | n = 40 | EEG, SEPs induced by MN stimulation, two-point discrimination tasks | Sham controlled study | UFF = 500 kHz<br>PD = 0.36 ms<br>PRF = 1 kHz<br>DC = 36%<br>ISPPA: 7.03 W/cm$^2$ | Inhibition | Inhibition of SEP (P14), alpha, beta, and locked gamma power. Increases sensation threshold leading to decreased sensation in discrimination task following sonication |
| | | Right anterior thalamus, healthy participants | Sonication of the anterior thalamus with MRI-Guided transcranial focused ultrasound (tFUS) alters pain thresholds in healthy adults: a double-blind, sham-controlled study | Badran *et al.* (2020)[277] | n = 19 | Sensory threshold, pain tolerance thresholds to a thermal stimulus | Double blind, sham-controlled, crossover study | UFF = 650 kHz<br>PD = 5 ms<br>PRF = 10 Hz<br>DC = 5%<br>SD = 30 s<br>ISPTA = 719 and 995 mW/cm$^2$ | Inhibition | Tolerance thresholds to thermal stimulus were increased following sonication, meaning sensitivity of thermal sensation was decreased |
| | | Central Thalamus region | Ultrasonic Deep Brain Neuromodulation in Acute Disorders of Consciousness: A Proof-of-Concept | Cain *et al.* (2022)[278] | n = 11 (acute disorder of consciousness patients) | Neurobehavioral assessment post-TUS, MRI-guided sonication + BOLD | unknown | UFF = 650 kHz<br>PD = 0.5 ms<br>PRF = 100 Hz<br>DC = 5%<br>SD = 30 s<br>ISI = 30s<br>ISPTA = 719.73 mW/cm$^2$ | Unknown | Sonication of central thalamus region resulted in significant improvement of behavioral scores one week following sonication compared with baseline. Decrease of BOLD signals in frontal and basal ganglia regions during sonication compared to baseline. |
| | Striatum and subthalamic nucleus (STN) | + IFC | A causal role of anterior prefrontal-putamen circuit for response | Nakajima *et al.* (2022)[224] | n = 20 (stages 1 and 3), n = 30 (stage 2), | fMRI, TMS, finger movement task with stop-signal | 5 stage study protocol, unknown study design | UFF = 0.5 MHz<br>SD = 40s<br>PD = 30ms | Inhibition | TUS induced sustainable suppression for longer than 60 min and |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | inhibition revealed by transcranial ultrasound stimulation in humans | | n = 20 (stage 5) | | | DC = 30%<br><br>Stage 1: ISPTA = 9 W/cm$^2$<br><br>Stage 3 and 5: ISPTA = 10.7 W/cm$^2$ | | stimulation of M1 |
| | Left Globus Pallidus (GP) | Healthy volunteers | Real time and delayed effects of subcortical low intensity focused ultrasound | Cain *et al.* (2021)[279] | n = 16 | MRI-guided (BOLD) | unknown | UFF = 650 kHz<br>DC = 5%<br>PRF = 10/100Hz<br>SD = 30s<br>ISI = 30s<br>Sessions=2x2x 10min<br>ISPTA= 720mW/cm$^2$ | unknown | TUS targeting left GP in healthy individuals modulated broad neural network activity accordingly to BOLD MRI signal analysis |
| | Hippocampus | Drug-resistant temporal lobe epilepsy | Focused Ultrasound Platform for Investigating Therapeutic Neuromodulation Across the Human Hippocampus | Brinker *et al.* (2020)[280] | n = 1 | MRI-guided | unknown | UFF = 548 kHz<br>DC = 35-50%<br>PRF = 500 Hz<br>SD = 500ms<br>ISI = 140 s<br>Sessions=20x<br>ISPTA= 2.25-W/cm$^2$ | unknown | A laboratory-built experimental device platform purposed for delivery of repetitive-TUS to the hippocampus was applied and resulted in no adverse effects |
| | Hippocampus and Substancia nigra | AD and PD patients | Focused transcranial ultrasound for treatment of neurodegenerative dementia | Nicodemus *et al.* (2019)[281] | n (AD) = 11<br>n (PD) = 11 | MRI-guided, Cognitive, and motor assessment | Pre-/post-interventional study | UFF = 2MHz | unknown | 62.5% of all patients had one or more improved cognitive scores without data incongruence. 87% had stable/ improved fine motor scores and 87.5% had stable/ improved gross motor scores. No adverse events were reported. |

Table 2: Human TUS studies regarding CNS

AD = Alzheimer's disease, AIF = Acoustic intensity at focus, DC = duration cycle, ESI = electrophysiological source imaging, FC = functional connectivity, ICF = intracortical facilitation, IFC = inferior frontal cortex, IHI = interhemispheric inhibition, ISI = interstimulus interval, ISPPA = intensity spatial peak pulse average, ISPTA = intensity spatial peak temporal average, MI = mechanical index, MNS = median nerve stimulation, MRCP = movement-related cortical potential, PD = Parkinson's disease/pulse duration, PMd = dorsal premotor cortex, PRF = pulse repetition frequency, SD = sonication duration, SICI = short interval intracortical inhibition, SMA =

supplementary motor area, TD = total duration, TNP = Total number of pulses, TBD = tone-burst duration, UFF = ultrasound fundamental frequency

## REFERENCES


1. Katan M, Luft A. Global Burden of Stroke. *Semin. Neurol.* 2018;
2. Kuriakose D, Xiao Z. Pathophysiology and treatment of stroke: Present status and future perspectives. Int. J. Mol. Sci. 2020;21.
3. Visvanathan A, Mead G, Dennis M, Whiteley W, Doubal F, Lawton J. Maintaining hope after a disabling stroke: A longitudinal qualitative study of patients' experiences, views, information needs and approaches towards making treatment decisions. *PLoS One*. 2019;14.
4. Feigin VL, Stark BA, Johnson CO, Roth GA, Bisignano C, Abady GG, Abbasifard M, Abbasi-Kangevari M, Abd-Allah F, Abedi V, et al. Global, regional, and national burden of stroke and its risk factors, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* 2021;20.
5. Grefkes C, Fink GR. Recovery from stroke: current concepts and future perspectives. *Neurol. Res. Pract.* 2020;2.
6. Hendricks HT, Van Limbeek J, Geurts AC, Zwarts MJ. Motor recovery after stroke: A systematic review of the literature. *Arch. Phys. Med. Rehabil.* 2002;83.
7. Nichols L, Bridgewater JC, Wagner NB, Karivelil M, Koelmeyer H, Goings D, Hope TD. Where in the brain do strokes occur? A pilot study and call for data. *Clin. Med. Res.* 2021;19.
8. Gao Y, Liu X, Liu K, Xu Y. Middle Cerebral Artery Strokes. In: Encyclopedia of Gerontology and Population Aging. 2020.
9. Bogousslavsky J, Melle G Van, Regli F. The lausanne stroke registry: Analysis of 1,000 consecutive patients with first stroke. *Stroke*. 1988;19.
10. Kang DW, Chalela JA, Ezzeddine MA, Warach S. Association of Ischemic Lesion Patterns on Early Diffusion-Weighted Imaging with TOAST Stroke Subtypes. *Arch. Neurol.* 2003;60.
11. Wessels T, Wessels C, Ellsiepen A, Reuter I, Trittmacher S, Stolz E, Jauss M. Contribution of diffusion-weighted imaging in determination of stroke etiology. *Am. J. Neuroradiol.* 2006;27.
12. Corbetta M, Ramsey L, Callejas A, Baldassarre A, Hacker CD, Siegel JS, Astafiev S V., Rengachary J, Zinn K, Lang CE, et al. Common behavioral clusters and subcortical anatomy in stroke. *Neuron*. 2015;85.

13. del Mar Sáez de Ocariz M, Nader JA, Santos JA, Bautista M. Thalamic Vascular Lesions. *Stroke*. 1996;27.
14. Chen XY, Wang Q, Wang X, Wong KS. Clinical Features of Thalamic Stroke. Curr. Treat. Options Neurol. 2017;19.
15. Buompadre CM, Arroyo HA, El-Kik S, Pereyra G, Diaz L, Bonduel M, Jaimovich R, Ceciliano A, Villasante F, Cárdenas R, et al. Basal ganglia and internal capsule stroke in childhood - Risk factors, neuroimaging, and outcome in a series of 28 patients: A tertiary hospital experience. *J. Child Neurol.* 2009;24.
16. Weinberger J, Thompson L, Samii M. The significance of basal ganglia infarction. *J. Stroke Cerebrovasc. Dis.* 1995;5.
17. Rauschecker JP. Cortical control of the thalamus: Top-down processing and plasticity. *Nat. Neurosci.* 1998;1.
18. Ohara S, Lenz FA. Reorganization of somatic sensory function in the human thalamus after stroke. *Ann. Neurol.* 2001;50.
19. Elias GJB, Namasivayam AA, Lozano AM. Deep brain stimulation for stroke: Current uses and future directions. Brain Stimul. 2018;11.
20. Staines WR, Black SE, Graham SJ, McIlroy WE. Somatosensory gating and recovery from stroke involving the thalamus. *Stroke*. 2002;33.
21. Schulz R, Park E, Lee J, Chang WH, Lee A, Kim YH, Hummel FC. Interactions between the corticospinal tract and premotor-motor pathways for residual motor output after stroke. *Stroke*. 2017;48.
22. Rehme AK, Grefkes C. Cerebral network disorders after stroke: Evidence from imaging-based connectivity analyses of active and resting brain states in humans. *J. Physiol.* 2013;591.
23. Koch P, Schulz R, Hummel FC. Structural connectivity analyses in motor recovery research after stroke. Ann. Clin. Transl. Neurol. 2016;3.
24. Cheng L, Wu Z, Sun J, Fu Y, Wang X, Yang GY, Miao F, Tong S. Reorganization of Motor Execution Networks During Sub-Acute Phase After Stroke. *IEEE Trans. Neural Syst. Rehabil. Eng.* 2015;23.
25. Wang L, Yu C, Chen H, Qin W, He Y, Fan F, Zhang Y, Wang M, Li K, Zang Y, et al. Dynamic functional reorganization of the motor execution network after stroke. *Brain*. 2010;133.
26. Fregni F, Pascual-Leone A. Technology Insight: Noninvasive brain stimulation in neurology - Perspectives on the therapeutic potential of rTMS and tDCS. Nat. Clin. Pract.

Neurol. 2007;3.

27. Xu J, Wu Z, Nürnberger A, Sabel BA. Reorganization of Brain Functional Connectivity Network and Vision Restoration Following Combined tACS-tDCS Treatment After Occipital Stroke. *Front. Neurol.* 2021;12.
28. Favaretto C, Allegra M, Deco G, Metcalf N V, Griffis JC, Shulman GL, Brovelli A, Corbetta M. Subcortical-cortical dynamical states of the human brain and their breakdown in stroke. *Nat. Commun.* [Internet]. 2022;13:5069. Available from: https://doi.org/10.1038/s41467-022-32304-1
29. Rossini PM, Calautti C, Pauri F, Baron JC. Post-stroke plastic reorganisation in the adult brain. Lancet Neurol. 2003;2.
30. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipović SR, Grefkes C, Hasan A, Hummel FC, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). Clin. Neurophysiol. 2020;131.
31. Takeuchi N, Izumi SI. Maladaptive plasticity for motor recovery after stroke: Mechanisms and approaches. Neural Plast. 2012;2012.
32. Jang SH. Motor function-related maladaptive plasticity in stroke: A review. NeuroRehabilitation. 2013;32.
33. Buetefisch CM. Role of the contralesional hemisphere in post-stroke recovery of upper extremity motor function. Front. Neurol. 2015;6.
34. Dodd KC, Nair VA, Prabhakaran V. Role of the contralesional vs. Ipsilesional hemisphere in stroke recovery. Front. Hum. Neurosci. 2017;11.
35. Prashantha DK, Sriranjini SJ, Sathyaprabha TN, Nagaraja D, Pal PK. Evaluation of the motor cortical excitability changes after ischemic stroke. *Ann. Indian Acad. Neurol.* 2013;16.
36. Luk KY, Ouyang HX, Pang MYC. Low-Frequency rTMS over Contralesional M1 Increases Ipsilesional Cortical Excitability and Motor Function with Decreased Interhemispheric Asymmetry in Subacute Stroke: A Randomized Controlled Study. *Neural Plast.* 2022;2022.
37. Hoyer EH, Celnik PA. Understanding and enhancing motor recovery after stroke using transcranial magnetic stimulation. Restor. Neurol. Neurosci. 2011;29.
38. Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin.

Neurophysiol. 2014;125.

39. Nowak DA, Grefkes C, Dafotakis M, Eickhoff S, Küst J, Karbe H, Fink GR. Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. *Arch. Neurol.* 2008;65.
40. Hummel FC, Celnik P, Pascual-Leone A, Fregni F, Byblow WD, Buetefisch CM, Rothwell J, Cohen LG, Gerloff C. Controversy: Noninvasive and invasive cortical stimulation show efficacy in treating stroke patients. Brain Stimul. 2008;1.
41. Dancause N, Nudo RJ. Shaping plasticity to enhance recovery after injury. In: Progress in Brain Research. 2011.
42. Kubis N. Non-invasive brain stimulation to enhance post-stroke recovery. Front. Neural Circuits. 2016;10.
43. Fisicaro F, Lanza G, Grasso AA, Pennisi G, Bella R, Paulus W, Pennisi M. Repetitive transcranial magnetic stimulation in stroke rehabilitation: review of the current evidence and pitfalls. Ther. Adv. Neurol. Disord. 2019;12.
44. Schlaug G, Renga V, Nair D. Transcranial direct current stimulation in stroke recovery. Arch. Neurol. 2008;65.
45. Seo HY, Kim GW, Won YH, Park SH, Seo JH, Ko MH. Changes in intracortical excitability of affected and unaffected hemispheres after stroke evaluated by paired-pulse transcranial magnetic stimulation. *Ann. Rehabil. Med.* 2018;42.
46. Turner DA, Yang W. Phase-specific manipulation of neuronal activity: a promising stroke therapy approach. Neural Regen. Res. 2021;
47. Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of Interhemispheric Interactions on Motor Function in Chronic Stroke. *Ann. Neurol.* 2004;55.
48. Koch PJ, Hummel FC. Toward precision medicine: Tailoring interventional strategies based on noninvasive brain stimulation for motor recovery after stroke. Curr. Opin. Neurol. 2017;30.
49. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol. 2006;5.
50. Volz LJ, Sarfeld AS, Diekhoff S, Rehme AK, Pool EM, Eickhoff SB, Fink GR, Grefkes C. Motor cortex excitability and connectivity in chronic stroke: a multimodal model of functional reorganization. *Brain Struct. Funct.* 2015;220.
51. Ackerley SJ, Byblow WD, Barber PA, MacDonald H, McIntyre-Robinson A, Stinear CM. Primed physical therapy enhances recovery of upper limb function in chronic stroke

patients. *Neurorehabil. Neural Repair*. 2016;30.

52. Brancaccio A, Tabarelli D, Belardinelli P. A New Framework to Interpret Individual Inter-Hemispheric Compensatory Communication after Stroke. J. Pers. Med. 2022;12.
53. Sollmann N, Hauck T, Tussis L, Ille S, Maurer S, Boeckh-Behrens T, Ringel F, Meyer B, Krieg SM. Results on the spatial resolution of repetitive transcranial magnetic stimulation for cortical language mapping during object naming in healthy subjects. *BMC Neurosci.* 2016;17.
54. Reinhart RMG, Woodman GF. The surprising temporal specificity of direct-current stimulation. Trends Neurosci. 2015;38.
55. Xin Z, Kuwahata A, Liu S, Sekino M. Magnetically Induced Temporal Interference for Focal and Deep-Brain Stimulation. *Front. Hum. Neurosci.* 2021;15.
56. Gomez LJ, Goetz SM, Peterchev A V. Design of transcranial magnetic stimulation coils with optimal trade-off between depth, focality, and energy. *J. Neural Eng.* 2018;15.
57. MacKenbach C, Tian R, Yang Y. Effects of Electrode Configurations and Injected Current Intensity on the Electrical Field of Transcranial Direct Current Stimulation: A Simulation Study. In: Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS. 2020.
58. Datta A, Huang Y, Thomas C, Dayan M, Caparelli-Daquer E. Proceedings #13: Improving penetration depth of transcranial electrical stimulation without compromising surface focality: A modeling analysis. *Brain Stimul.* 2019;12.
59. Deng Z De, Lisanby SH, Peterchev A V. Electric field depth-focality tradeoff in transcranial magnetic stimulation: Simulation comparison of 50 coil designs. *Brain Stimul.* 2013;6.
60. Taljan K, Mcintyre C, Sakaie K. Anatomical Connectivity Between Subcortical Structures. *Brain Connect.* 2011;1.
61. Plow EB, Machado A. Invasive Neurostimulation in Stroke Rehabilitation. Neurotherapeutics. 2014;11.
62. Edwardson MA, Lucas TH, Carey JR, Fetz EE. New modalities of brain stimulation for stroke rehabilitation. *Exp. Brain Res.* 2013;224.
63. Wu Z, Sun F, Li Z, Liu M, Tian X, Guo D, Wei P, Shan Y, Liu T, Guo M, et al. Electrical stimulation of the lateral cerebellar nucleus promotes neurogenesis in rats after motor cortical ischemia. *Sci. Rep.* 2020;10.
64. Gondard E, Teves L, Wang L, McKinnon C, Hamani C, Kalia SK, Carlen PL, Tymianski M, Lozano AM. Deep brain stimulation rescues memory and synaptic activity in a rat

model of global ischemia. *J. Neurosci.* 2019;39.

65. Wathen CA, Frizon LA, Maiti TK, Baker KB, Machado AG. Deep brain stimulation of the cerebellum for poststroke motor rehabilitation: From laboratory to clinical trial. *Neurosurg. Focus*. 2018;45.
66. Machado A, Baker KB. Upside down crossed cerebellar diaschisis: Proposing chronic stimulation of the dentatothalamocortical pathway for post-stroke motor recovery. *Front. Integr. Neurosci.* 2012;
67. Cooperrider J, Furmaga H, Plow E, Park HJ, Chen Z, Kidd G, Kenneth B, Gale JT, Machado AG. Chronic deep cerebellar stimulation promotes long-term potentiation, microstructural plasticity, and reorganization of perilesional cortical representation in a rodent model. *J. Neurosci.* 2014;34.
68. Sui Y, Tian Y, Ko WKD, Wang Z, Jia F, Horn A, De Ridder D, Choi KS, Bari AA, Wang S, et al. Deep Brain Stimulation Initiative: Toward Innovative Technology, New Disease Indications, and Approaches to Current and Future Clinical Challenges in Neuromodulation Therapy. Front. Neurol. 2021;11.
69. Phillips NI, Bhakta BB. Affect of deep brain stimulation on limb paresis after stroke. *Lancet*. 2000;356.
70. Hosobuchi Y. Subcortical electrical stimulation for control of intractable pain in humans. Report of 122 cases (1970-1984). *J. Neurosurg.* 1986;64.
71. Rasche D, Rinaldi PC, Young RF, Tronnier VM. Deep brain stimulation for the treatment of various chronic pain syndromes. Neurosurg. Focus. 2006;21.
72. Boccard SGJ, Pereira EAC, Moir L, Aziz TZ, Green AL. Long-term outcomes of deep brain stimulation for neuropathic pain. *Neurosurgery*. 2013;72.
73. Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, Matthews K, McIntyre CC, Schlaepfer TE, Schulder M, et al. Deep brain stimulation: current challenges and future directions. Nat. Rev. Neurol. 2019;15.
74. Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, Scott R, Ives N, Rick C, Daniels J, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol.* 2010;9.
75. Bystritsky A, Korb AS, Douglas PK, Cohen MS, Melega WP, Mulgaonkar AP, Desalles A, Min BK, Yoo SS. A review of low-intensity focused ultrasound pulsation. Brain Stimul. 2011;4.
76. Rossi M, Bruno V, Arena J, Cammarota Á, Merello M. Challenges in PD Patient

Management After DBS: A Pragmatic Review. Mov. Disord. Clin. Pract. 2018;5.

77. Medel R, Crowley RW, McKisic MS, Dumont AS, Kassell NF. Sonothrombolysis: An emerging modality for the management of stroke. Neurosurgery. 2009;65.
78. Bowary P, Greenberg BD. Noninvasive Focused Ultrasound for Neuromodulation: A Review. Psychiatr. Clin. North Am. 2018;41.
79. Kubanek J. Neuromodulation with transcranial focused ultrasound. *Neurosurg. Focus*. 2018;44.
80. Liu X, Qiu F, Hou L, Wang X. Review of Noninvasive or Minimally Invasive Deep Brain Stimulation. Front. Behav. Neurosci. 2022;15.
81. Zhang T, Pan N, Wang Y, Liu C, Hu S. Transcranial Focused Ultrasound Neuromodulation: A Review of the Excitatory and Inhibitory Effects on Brain Activity in Human and Animals. Front. Hum. Neurosci. 2021;15.
82. Weinreb E, Moses E. Mechanistic insights into ultrasonic neurostimulation of disconnected neurons using single short pulses. *Brain Stimul.* [Internet]. 2022;15:769–779. Available from: https://www.sciencedirect.com/science/article/pii/S1935861X22000833
83. Zhang M, Li B, Lv X, Liu S, Liu Y, Tang R, Lang Y, Huang Q, He J. Low-intensity focused ultrasound-mediated attenuation of acute seizure activity based on EEG brain functional connectivity. *Brain Sci.* 2021;11.
84. Asan AS, Kang Q, Oralkan Ö, Sahin M. Entrainment of cerebellar Purkinje cell spiking activity using pulsed ultrasound stimulation. *Brain Stimul.* 2021;14.
85. Tufail Y, Matyushov A, Baldwin N, Tauchmann ML, Georges J, Yoshihiro A, Tillery SIH, Tyler WJ. Transcranial Pulsed Ultrasound Stimulates Intact Brain Circuits. *Neuron*. 2010;66.
86. King RL, Brown JR, Newsome WT, Pauly KB. Effective parameters for ultrasound-induced in vivo neurostimulation. *Ultrasound Med. Biol.* 2013;39.
87. Dallapiazza RF, Timbie KF, Holmberg S, Gatesman J, Lopes MB, Price RJ, Miller GW, Elias WJ. Noninvasive neuromodulation and thalamic mapping with low-intensity focused ultrasound. *J. Neurosurg.* 2018;128.
88. Wattiez N, Constans C, Deffieux T, Daye PM, Tanter M, Aubry JF, Pouget P. Transcranial ultrasonic stimulation modulates single-neuron discharge in macaques performing an antisaccade task. *Brain Stimul.* 2017;10.
89. Deffieux T, Younan Y, Wattiez N, Tanter M, Pouget P, Aubry JF. Low-intensity focused ultrasound modulates monkey visuomotor behavior. *Curr. Biol.* 2013;23.

90. Folloni D, Verhagen L, Mars RB, Fouragnan E, Constans C, Aubry JF, Rushworth MFS, Sallet J. Manipulation of Subcortical and Deep Cortical Activity in the Primate Brain Using Transcranial Focused Ultrasound Stimulation. *Neuron*. 2019;101.
91. Lee W, Lee SD, Park MY, Foley L, Purcell-Estabrook E, Kim H, Fischer K, Maeng LS, Yoo SS. Image-Guided Focused Ultrasound-Mediated Regional Brain Stimulation in Sheep. *Ultrasound Med. Biol.* 2016;42.
92. Lee W, Kim H, Jung Y, Song IU, Chung YA, Yoo SS. Image-guided transcranial focused ultrasound stimulates human primary somatosensory cortex. *Sci. Rep.* 2015;5.
93. Beisteiner R, Matt E, Fan C, Baldysiak H, Schönfeld M, Philippi Novak T, Amini A, Aslan T, Reinecke R, Lehrner J, et al. Transcranial Pulse Stimulation with Ultrasound in Alzheimer's Disease—A New Navigated Focal Brain Therapy. *Adv. Sci.* 2020;7.
94. Stern JM, Spivak NM, Becerra SA, Kuhn TP, Korb AS, Kronemyer D, Khanlou N, Reyes SD, Monti MM, Schnakers C, et al. Safety of focused ultrasound neuromodulation in humans with temporal lobe epilepsy. *Brain Stimul.* 2021;14.
95. Munoz F, Meaney A, Gross A, Liu K, Pouliopoulos AN, Liu D, Konofagou EE, Ferrera VP. Long term study of motivational and cognitive effects of low-intensity focused ultrasound neuromodulation in the dorsal striatum of nonhuman primates. *Brain Stimul.* 2022;15.
96. Gaur P, Casey KM, Kubanek J, Li N, Mohammadjavadi M, Saenz Y, Glover GH, Bouley DM, Pauly KB. Histologic safety of transcranial focused ultrasound neuromodulation and magnetic resonance acoustic radiation force imaging in rhesus macaques and sheep. *Brain Stimul.* 2020;13.
97. FRY WJ. Intense ultrasound; a new tool for neurological research. *J. Ment. Sci.* 1954;100.
98. Fry WJ, Wulff VJ, Tucker D, Fry FJ. Physical Factors Involved in Ultrasonically Induced Changes in Living Systems: I. Identification of Non-Temperature Effects. *J. Acoust. Soc. Am.* 1950;22.
99. Fry FJ, Ades HW, Fry WJ. Production of reversible changes in the central nervous system by ultrasound. *Science (80-. ).* 1958;127.
100. Kamimura H, Wang S, Chen H, Wang Q, Aurup C, Fan K, Carneiro A, Konofagou E. Ipsi- and contralateral motor response using ultrasound-induced neurostimulation in deeply anesthetized mice. In: Physics Procedia. 2015.
101. Baek H, Yang Y, Pacia CP, Xu L, Yue Y, Bruchas MR, Chen H. Mechanical and mechanothermal effects of focused ultrasound elicited distinct electromyographic

responses in mice. *Phys. Med. Biol.* 2021;66.

102. Zhou Q, Lau S, Wu D, Kirk Shung K. Piezoelectric films for high frequency ultrasonic transducers in biomedical applications. Prog. Mater. Sci. 2011;56.
103. O'Brien WD. Ultrasound-biophysics mechanisms. Prog. Biophys. Mol. Biol. 2007;93.
104. Kamimura HAS, Conti A, Toschi N, Konofagou EE. Ultrasound neuromodulation: Mechanisms and the potential of multimodal stimulation for neuronal function assessment. Front. Phys. 2020;8.
105. Yoo S, Mittelstein DR, Hurt RC, Lacroix J, Shapiro MG. Focused ultrasound excites cortical neurons via mechanosensitive calcium accumulation and ion channel amplification. *Nat. Commun.* 2022;13.
106. Fomenko A, Neudorfer C, Dallapiazza RF, Kalia SK, Lozano AM. Low-intensity ultrasound neuromodulation: An overview of mechanisms and emerging human applications. Brain Stimul. 2018;11.
107. Fomenko A, Chen KHS, Nankoo JF, Saravanamuttu J, Wang Y, El-Baba M, Xia X, Seerala SS, Hynynen K, Lozano AM, et al. Systematic examination of low-intensity ultrasound parameters on human motor cortex excitability and behaviour. *Elife*. 2020;9.
108. Blackmore J, Shrivastava S, Sallet J, Butler CR, Cleveland RO. Ultrasound Neuromodulation: A Review of Results, Mechanisms and Safety. Ultrasound Med. Biol. 2019;45.
109. Tyler WJ. Noninvasive neuromodulation with ultrasound? A continuum mechanics hypothesis. *Neuroscientist*. 2011;17.
110. Plaksin M, Shoham S, Kimmel E. Intramembrane cavitation as a predictive bio-piezoelectric mechanism for ultrasonic brain stimulation. *Phys. Rev. X*. 2014;4.
111. Plaksin M, Kimmel E, Shoham S. Cell-type-selective effects of intramembrane cavitation as a unifying theoretical framework for ultrasonic neuromodulation. *eNeuro*. 2016;3.
112. Plaksin M, Kimmel E, Shoham S. Correspondence: Revisiting the theoretical cell membrane thermal capacitance response. *Nat. Commun.* 2017;8.
113. Tung YS, Marquet F, Teichert T, Ferrera V, Konofagou EE. Feasibility of noninvasive cavitation-guided blood-brain barrier opening using focused ultrasound and microbubbles in nonhuman primates. *Appl. Phys. Lett.* 2011;98.
114. Kim Y, Hall T, Xu Z, Cain C. Transcranial histotripsy therapy: A feasibility study. *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*. 2014;61.
115. Ramaswamy K, Marx V, Laser D, Kenny T, Chi T, Bailey M, Sorensen MD, Grubbs

RH, Stoller ML. Targeted microbubbles: A novel application for the treatment of kidney stones. BJU Int. 2015;116.

116. Todd N, Zhang Y, Arcaro M, Becerra L, Borsook D, Livingstone M, McDannold N. Focused ultrasound induced opening of the blood-brain barrier disrupts inter-hemispheric resting state functional connectivity in the rat brain. *Neuroimage*. 2018;178.
117. Yu K, Niu X, Krook-Magnuson E, He B. Intrinsic functional neuron-type selectivity of transcranial focused ultrasound neuromodulation. *Nat. Commun.* 2021;12.
118. Barnett SB, Rott HD, Ter Haar GR, Ziskin MC, Maeda K. The sensitivity of biological tissue to ultrasound. Ultrasound Med. Biol. 1997;23.
119. Darrow DP, O'Brien P, Richner TJ, Netoff TI, Ebbini ES. Reversible neuroinhibition by focused ultrasound is mediated by a thermal mechanism. *Brain Stimul.* 2019;12.
120. Owen SF, Liu MH, Kreitzer AC. Thermal constraints on in vivo optogenetic manipulations. *Nat. Neurosci.* 2019;22.
121. Yoon K, Lee W, Chen E, Lee JE, Croce P, Cammalleri A, Foley L, Tsao AL, Yoo SS. Localized Blood–Brain Barrier Opening in Ovine Model Using Image-Guided Transcranial Focused Ultrasound. *Ultrasound Med. Biol.* 2019;45.
122. Kubanek J, Shi J, Marsh J, Chen D, Deng C, Cui J. Ultrasound modulates ion channel currents. *Sci. Rep.* 2016;6.
123. Prieto ML, Firouzi K, Khuri-Yakub BT, Madison D V., Maduke M. Spike frequency-dependent inhibition and excitation of neural activity by high-frequency ultrasound. *J. Gen. Physiol.* 2020;152.
124. Darrow DP, O'Brien P, Richner T, Netoff TI, Ebbini ES. A thermal mechanism underlies tFUS neuromodulation. Brain Stimul. 2020;13.
125. Sassaroli E, Vykhodtseva N. Acoustic neuromodulation from a basic science prospective. J. Ther. Ultrasound. 2016;4.
126. Prieto ML, Firouzi K, Khuri-Yakub BT, Maduke M. Activation of Piezo1 but Not NaV1.2 Channels by Ultrasound at 43 MHz. *Ultrasound Med. Biol.* 2018;44.
127. Oh SJ, Lee JM, Kim HB, Lee J, Han S, Bae JY, Hong GS, Koh W, Kwon J, Hwang ES, et al. Ultrasonic Neuromodulation via Astrocytic TRPA1. *Curr. Biol.* 2019;29.
128. Jerusalem A, Al-Rekabi Z, Chen H, Ercole A, Malboubi M, Tamayo-Elizalde M, Verhagen L, Contera S. Electrophysiological-mechanical coupling in the neuronal membrane and its role in ultrasound neuromodulation and general anaesthesia. Acta Biomater. 2019;97.
129. Cui K, Zhang S, Sun J, Zhang X, Ding C, Xu G. Inhibitory effect of ultrasonic

stimulation on the voltage-dependent potassium currents in rat hippocampal CA1 neurons. *BMC Neurosci.* 2019;20.

130. Park JH. Reliability of theta burst stimulation as a neuromodulation tool. *J. Neurophysiol.* [Internet]. 2022;127:1532–1534. Available from: https://doi.org/10.1152/jn.00507.2021
131. Sato T, Shapiro MG, Tsao DY. Ultrasonic Neuromodulation Causes Widespread Cortical Activation via an Indirect Auditory Mechanism. *Neuron*. 2018;98.
132. Guo H, Hamilton M, Offutt SJ, Gloeckner CD, Li T, Kim Y, Legon W, Alford JK, Lim HH. Ultrasound Produces Extensive Brain Activation via a Cochlear Pathway. *Neuron*. 2018;98.
133. Braun V, Blackmore J, Cleveland RO, Butler CR. Transcranial ultrasound stimulation in humans is associated with an auditory confound that can be effectively masked. *Brain Stimul.* 2020;13.
134. Takagi SF, Higashino S, Shibuya T, Osawa N. The Actions of Ultrasound on the Myelinated Nerve, the Spinal Cord and the Brain. *Jpn. J. Physiol.* 1960;10.
135. Klibanov AL, Hossack JA. Ultrasound in radiology: From anatomic, functional, molecular imaging to drug delivery and image-guided therapy. Invest. Radiol. 2015;50.
136. Baek H, Pahk KJ, Kim H. A review of low-intensity focused ultrasound for neuromodulation. Biomed. Eng. Lett. 2017;7.
137. Harris GR. FDA regulation of clinical high intensity focused ultrasound (HIFU) devices. In: Proceedings of the 31st Annual International Conference of the IEEE Engineering in Medicine and Biology Society: Engineering the Future of Biomedicine, EMBC 2009. 2009.
138. Orsi F, Arnone P, Chen W, Zhang L. High intensity focused ultrasound ablation: A new therapeutic option for solid tumors. J. Cancer Res. Ther. 2010;6.
139. MacDonell J, Patel N, Rubino S, Ghoshal G, Fischer G, Clif Burdette E, Hwang R, Pilitsis JG. Magnetic resonance-guided interstitial high-intensity focused ultrasound for brain tumor ablation. *Neurosurg. Focus*. 2018;44.
140. Fishman PS, Frenkel V. Focused Ultrasound: An Emerging Therapeutic Modality for Neurologic Disease. *Neurotherapeutics*. 2017;14.
141. Bond AE, Shah BB, Huss DS, Dallapiazza RF, Warren A, Harrison MB, Sperling SA, Wang XQ, Gwinn R, Witt J, et al. Safety and efficacy of focused ultrasound thalamotomy for patients with medication-refractory, tremor-dominant Parkinson disease a randomized Clinical trial. *JAMA Neurol.* 2017;74.

142. Di Biase L, Falato E, Di Lazzaro V. Transcranial Focused Ultrasound (tFUS) and Transcranial Unfocused Ultrasound (tUS) neuromodulation: From theoretical principles to stimulation practices. *Front. Neurol.* 2019;10.

143. Yang W, Zhou Y. Effect of pulse repetition frequency of high-intensity focused ultrasound on in vitro thrombolysis. *Ultrason. Sonochem.* 2017;35.

144. Ilyas A, Chen CJ, Ding D, Romeo A, Buell TJ, Wang TR, Kalani MYS, Park MS. Magnetic resonance-guided, high-intensity focused ultrasound sonolysis: Potential applications for stroke. *Neurosurg. Focus*. 2018;44.

145. Burgess A, Huang Y, Waspe AC, Ganguly M, Goertz DE, Hynynen K. High-intensity focused ultrasound (HIFU) for dissolution of clots in a rabbit model of embolic stroke. *PLoS One*. 2012;7.

146. Park SH, Kim MJ, Jung HH, Chang WS, Choi HS, Rachmilevitch I, Zadicario E, Chang JW. Safety and feasibility of multiple blood-brain barrier disruptions for the treatment of glioblastoma in patients undergoing standard adjuvant chemotherapy. *J. Neurosurg.* 2021;134.

147. Burgess A, Shah K, Hough O, Hynynen K. Focused ultrasound-mediated drug delivery through the blood-brain barrier. Expert Rev. Neurother. 2015;15.

148. Felix MS, Borloz E, Metwally K, Dauba A, Larrat B, Matagne V, Ehinger Y, Villard L, Novell A, Mensah S, et al. Ultrasound-mediated blood-brain barrier opening improves whole brain gene delivery in mice. *Pharmaceutics*. 2021;13.

149. Lin CY, Hsieh HY, Chen CM, Wu SR, Tsai CH, Huang CY, Hua MY, Wei KC, Yeh CK, Liu HL. Non-invasive, neuron-specific gene therapy by focused ultrasound-induced blood-brain barrier opening in Parkinson's disease mouse model. *J. Control. Release*. 2016;235.

150. Lin CY, Hsieh HY, Pitt WG, Huang CY, Tseng IC, Yeh CK, Wei KC, Liu HL. Focused ultrasound-induced blood-brain barrier opening for non-viral, non-invasive, and targeted gene delivery. *J. Control. Release*. 2015;212.

151. Liu HL, Hua MY, Chen PY, Chu PC, Pan CH, Yang HW, Huang CY, Wang JJ, Yen TC, Wei KC. Blood-brain barrier disruption with focused ultrasound enhances delivery of chemotherapeutic drugs for glioblastoma treatment. *Radiology*. 2010;255.

152. Mainprize T, Lipsman N, Huang Y, Meng Y, Bethune A, Ironside S, Heyn C, Alkins R, Trudeau M, Sahgal A, et al. Blood-Brain Barrier Opening in Primary Brain Tumors with Non-invasive MR-Guided Focused Ultrasound: A Clinical Safety and Feasibility Study. *Sci. Rep.* 2019;9.

153. Services USD of H and H, Administration F and D, Health C for D and R. Marketing Clearance of Diagnostic Ultrasound Systems and Transducers, Guidance for Industry and Food and Drug Administration Staff.
154. Duck FA. Medical and non-medical protection standards for ultrasound and infrasound. Prog. Biophys. Mol. Biol. 2007;93.
155. Miller DL. Safety Assurance in Obstetrical Ultrasound. *Semin. Ultrasound, CT MRI*. 2008;29.
156. Van Rhoon GC, Samaras T, Yarmolenko PS, Dewhirst MW, Neufeld E, Kuster N. CEM43°C thermal dose thresholds: A potential guide for magnetic resonance radiofrequency exposure levels? *Eur. Radiol.* 2013;23.
157. Sarica C, Fomenko A, Nankoo JF, Darmani G, Vetkas A, Yamamoto K, Lozano AM, Chen R. Toward focused ultrasound neuromodulation in deep brain stimulator implanted patients: Ex-vivo thermal, kinetic and targeting feasibility assessment. Brain Stimul. 2022;15.
158. de Bever JT, Odéen H, Hofstetter LW, Parker DL. Simultaneous MR thermometry and acoustic radiation force imaging using interleaved acquisition. *Magn. Reson. Med.* 2018;79.
159. Elhelf IAS, Albahar H, Shah U, Oto A, Cressman E, Almekkawy M. High intensity focused ultrasound: The fundamentals, clinical applications and research trends. Diagn. Interv. Imaging. 2018;99.
160. Barnett SB, Ter Haar GR, Ziskin MC, Rott HD, Duck FA, Maeda K. International recommendations and guidelines for the safe use of diagnostic ultrasound in medicine. *Ultrasound Med. Biol.* 2000;26.
161. Herzberg M, Boy S, Hölscher T, Ertl M, Zimmermann M, Ittner KP, Pemmerl J, Pels H, Bogdahn U, Schlachetzki F. Prehospital stroke diagnostics based on neurological examination and transcranial ultrasound. *Crit. Ultrasound J.* 2014;6.
162. Beaulieu Y. Bedside echocardiography in the assessment of the critically ill. Crit. Care Med. 2007;35.
163. Cosgrove D. Ultrasound contrast agents: An overview. *Eur. J. Radiol.* 2006;60.
164. Xin Z, Lin G, Lei H, Lue TF, Guo Y. Clinical applications of low-intensity pulsed ultrasound and its potential role in urology. Transl. Androl. Urol. 2016;5.
165. Civale J, Rivens I, Shaw A, Ter Haar G. Focused ultrasound transducer spatial peak intensity estimation: A comparison of methods. *Phys. Med. Biol.* 2018;63.
166. Sanguinetti JL, Hameroff S, Smith EE, Sato T, Daft CMW, Tyler WJ, Allen JJB.

Transcranial Focused Ultrasound to the Right Prefrontal Cortex Improves Mood and Alters Functional Connectivity in Humans. *Front. Hum. Neurosci.* 2020;14.

167. Hellman A, Maietta T, Byraju K, Linda Park Y, Shao M, Liss A, Neubauer P, Burdette C, Ghoshal G, Qian J, et al. Low Intensity Focused Ultrasound Modulation of Vincristine Induced Neuropathy. *Neuroscience*. 2020;430.
168. Sheikov N, McDannold N, Vykhodtseva N, Jolesz F, Hynynen K. Cellular mechanisms of the blood-brain barrier opening induced by ultrasound in presence of microbubbles. *Ultrasound Med. Biol.* 2004;30.
169. Huang Y, Wen P, Song B, Li Y. Numerical investigation of the energy distribution of Low-intensity transcranial focused ultrasound neuromodulation for hippocampus. *Ultrasonics*. 2022;124.
170. Izadifar Z, Izadifar Z, Chapman D, Babyn P. An introduction to high intensity focused ultrasound: Systematic review on principles, devices, and clinical applications. J. Clin. Med. 2020;9.
171. Zhou Y, Cunitz BW, Dunmire B, Wang YN, Karl SG, Warren C, Mitchell S, Hwang JH. Characterization and Ex Vivo evaluation of an extracorporeal high-intensity focused ultrasound (HIFU) system. *J. Appl. Clin. Med. Phys.* 2021;22.
172. Tsai SY, Schreiber JA, Adamczyk NS, Wu JY, Ton ST, Hofler RC, Walter JS, O'Brien TE, Kartje GL, Nockels RP. Improved Functional Outcome After Peripheral Nerve Stimulation of the Impaired Forelimb Post-stroke. *Front. Neurol.* 2021;12.
173. Bastos Conforto A, Nocelo Ferreiro K, Tomasi C, Dos Santos RL, Loureiro Moreira V, Nagahashi Marie SK, Baltieri SC, Scaff M, Cohen LG. Effects of somatosensory stimulation on motor function after subacute stroke. *Neurorehabil. Neural Repair*. 2010;24.
174. Li JN, Xie CC, Li CQ, Zhang GF, Tang H, Jin CN, Ma JX, Wen L, Zhang KM, Niu LC. Efficacy and safety of transcutaneous auricular vagus nerve stimulation combined with conventional rehabilitation training in acute stroke patients: A randomized controlled trial conducted for 1 year involving 60 patients. *Neural Regen. Res.* 2022;17.
175. Celnik P, Hummel F, Harris-Love M, Wolk R, Cohen LG. Somatosensory Stimulation Enhances the Effects of Training Functional Hand Tasks in Patients With Chronic Stroke. *Arch. Phys. Med. Rehabil.* 2007;88.
176. Eisner W, Quirbach S, Sohm F, Rehwald R, Kerschbaumer J. A novel - High effective - Methode against neuropathic pain syndromes. *Stereotact. Funct. Neurosurg.* 2017;95.
177. Glanz M, Klawansky S, Stason W, Berkey C, Chalmers TC. Functional

electrostimulation in poststroke rehabilitation: A meta-analysis of the randomized controlled trials. *Arch. Phys. Med. Rehabil.* 1996;77.

178. Popovic MR, Thrasher TA, Zivanovic V, Takaki J, Hajek V. Neuroprosthesis for retraining reaching and grasping functions in severe hemiplegic patients. *Neuromodulation*. 2005;8.
179. Cauraugh JH, Kim S. Two coupled motor recovery protocols are better than one: Electromyogram-triggered neuromuscular stimulation and bilateral movements. *Stroke*. 2002;33.
180. Thrasher TA, Zivanovic V, McIlroy W, Popovic MR. Rehabilitation of reaching and grasping function in severe hemiplegic patients using functional electrical stimulation therapy. *Neurorehabil. Neural Repair*. 2008;22.
181. Handricks HT, LJzerman MJ, deKroon JR, Zilvold G. Functional electrical stimulation by means of the "Ness Handmaster Orthosis" in chronic stroke patients: An exploratory study. *Clin. Rehabil.* 2001;15.
182. Gritsenko V, Prochazka A. A functional electric stimulation - Assisted exercise therapy system for hemiplegic hand function. *Arch. Phys. Med. Rehabil.* 2004;85.
183. Kapadia NM, Nagai MK, Zivanovic V, Bernstein J, Woodhouse J, Rumney P, Popovic MR. Functional electrical stimulation therapy for recovery of reaching and grasping in severe chronic pediatric stroke patients. *J. Child Neurol.* 2014;29.
184. NCT02611375. Conditioning Neural Circuits to Improve Upper Extremity Function. *https://clinicaltrials.gov/show/NCT02611375*. 2015;
185. Conforto AB, Ferreiro KN, Tomasi C, Laurenti R, Loureiro V, Kazue S, Marie N, Baltieri SC, Scaff M, Cohen LG. Neurorehabilitation and Neural Repair Effects of Somatosensory Stimulation on Motor Function After Subacute. *Neurorehabil. Neural Repair*. 2010;24.
186. Alwhaibi RM, Mahmoud NF, Zakaria HM, Ragab WM, Al Awaji NN, Elzanaty MY, Elserougy HR. Therapeutic efficacy of transcutaneous electrical nerve stimulation acupoints on motor and neural recovery of the affected upper extremity in chronic stroke: A sham-controlled randomized clinical trial. *Healthc.* 2021;9.
187. Olsen S, Signal N, Niazi IK, Rashid U, Alder G, Mawston G, Nedergaard RB, Jochumsen M, Taylor D. Peripheral Electrical Stimulation Paired With Movement-Related Cortical Potentials Improves Isometric Muscle Strength and Voluntary Activation Following Stroke. *Front. Hum. Neurosci.* 2020;14.
188. Lindenberg R, Zhu LL, Schlaug G. Combined central and peripheral stimulation to

facilitate motor recovery after stroke: The effect of number of sessions on outcome. *Neurorehabil. Neural Repair*. 2012;26.

189. Celnik P, Paik NJ, Vandermeeren Y, Dimyan M, Cohen LG. Effects of Combined Peripheral Nerve Stimulation and Brain Polarization on Performance of a Motor Sequence Task After Chronic Stroke. *Stroke*. 2009;40.
190. Kim T, Park C, Chhatbar PY, Feld J, Mac Grory B, Nam CS, Wang P, Chen M, Jiang X, Feng W. Effect of Low Intensity Transcranial Ultrasound Stimulation on Neuromodulation in Animals and Humans: An Updated Systematic Review. Front. Neurosci. 2021;15.
191. Guo H, Offutt SJ, Hamilton M, Kim Y, Gloeckner CD, Zachs DP, Alford JK, Lim HH. Ultrasound does not activate but can inhibit in vivo mammalian nerves across a wide range of parameters. *Sci. Rep.* 2022;12.
192. Feng B, Chen L, Ilham SJ. A review on ultrasonic neuromodulation of the peripheral nervous system: Enhanced or suppressed activities? Appl. Sci. 2019;9.
193. Young RR, Henneman E. Functional effects of focused ultrasound on mammalian nerves. *Science (80-. ).* 1961;134.
194. Oh S, Kim DH, Youn I. Low-intensity focused ultrasound stimulator using focal depth controller for improved targeting in neuromuscular rehabilitation. In: Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS. 2017.
195. Kimberley TJ, Prudente CN, Engineer ND, Pierce D, Tarver B, Cramer SC, Dickie DA, Dawson J. Study protocol for a pivotal randomised study assessing vagus nerve stimulation during rehabilitation for improved upper limb motor function after stroke. *Eur. Stroke J.* 2019;4.
196. Dawson J, Liu CY, Francisco GE, Cramer SC, Wolf SL, Dixit A, Alexander J, Ali R, Brown BL, Feng W, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. *Lancet*. 2021;397.
197. Li L, Wang D, Pan H, Huang L, Sun X, He C, Wei Q. Non-invasive Vagus Nerve Stimulation in Cerebral Stroke: Current Status and Future Perspectives. Front. Neurosci. 2022;16.
198. Ji N, Lin WH, Chen F, Xu L, Huang J, Li G. Blood Pressure Modulation With Low-Intensity Focused Ultrasound Stimulation to the Vagus Nerve: A Pilot Animal Study. *Front. Neurosci.* 2020;14.

199. Juan EJ, González R, Albors G, Ward MP, Irazoqui P. Vagus nerve modulation using focused pulsed ultrasound: Potential applications and preliminary observations in a rat. *Int. J. Imaging Syst. Technol.* 2014;24.

200. Wasilczuk KM, Bayer KC, Somann JP, Albors GO, Sturgis J, Lyle LT, Robinson JP, Irazoqui PP. Modulating the Inflammatory Reflex in Rats Using Low-Intensity Focused Ultrasound Stimulation of the Vagus Nerve. *Ultrasound Med. Biol.* 2019;45.

201. Guggisberg AG, Koch PJ, Hummel FC, Buetefisch CM. Brain networks and their relevance for stroke rehabilitation. Clin. Neurophysiol. 2019;130.

202. Maeda M, Mutai H, Toya Y, Maekawa Y, Hitai T, Katai S. Effects of peripheral nerve stimulation on paralysed upper limb functional recovery in chronic stroke patients undergoing low-frequency repetitive transcranial magnetic stimulation and occupational therapy: A pilot study. *Hong Kong J. Occup. Ther.* 2020;33.

203. Marquez-Chin C, Popovic MR. Functional electrical stimulation therapy for restoration of motor function after spinal cord injury and stroke: A review. Biomed. Eng. Online. 2020;19.

204. Jang SH. The role of the corticospinal tract in motor recovery in patients with a stroke: A review. NeuroRehabilitation. 2009;24.

205. Lin DJ, Cloutier AM, Erler KS, Cassidy JM, Snider SB, Ranford J, Parlman K, Giatsidis F, Burke JF, Schwamm LH, et al. Corticospinal tract injury estimated from acute stroke imaging predicts upper extremity motor recovery after stroke. *Stroke*. 2019;50.

206. Choi YH, Lee SU. Enhancement of brain plasticity and recovery of locomotive function after lumbar spinal cord stimulation in combination with gait training with partial weight support in rats with cerebral ischemia. *Brain Res.* 2017;1662.

207. Shealy CN, Henneman E. Reversible Effects of Ultrasound on Spinal Reflexes. *Arch. Neurol.* 1962;6.

208. Liao YH, Chen MX, Chen SC, Luo KX, Wang B, Liu Y, Ao LJ. Effects of Noninvasive Low-Intensity Focus Ultrasound Neuromodulation on Spinal Cord Neurocircuits in Vivo. *Evidence-based Complement. Altern. Med.* 2021;2021.

209. Wu S, Zheng T, Du J, Yuan Y, Shi Q, Wang Z, Liu D, Liu J, Wang X, Liu L. Neuroprotective effect of low-intensity transcranial ultrasound stimulation in endothelin-1-induced middle cerebral artery occlusion in rats. *Brain Res. Bull.* 2020;161.

210. Kim E, Anguluan E, Kum J, Sanchez-Casanova J, Park TY, Kim JG, Kim H. Wearable transcranial ultrasound system for remote stimulation of freely moving animal. *IEEE Trans. Biomed. Eng.* 2021;68.

211. Legon W, Bansal P, Tyshynsky R, Ai L, Mueller JK. Transcranial focused ultrasound neuromodulation of the human primary motor cortex. *Sci. Rep.* 2018;8.

212. Yu K, Sohrabpour A, He B. Electrophysiological Source Imaging of Brain Networks Perturbed by Low-Intensity Transcranial Focused Ultrasound. *IEEE Trans. Biomed. Eng.* 2016;63.

213. Yoon K, Lee W, Lee JE, Xu L, Croce P, Foley L, Yoo SS. Effects of sonication parameters on transcranial focused ultrasound brain stimulation in an ovine model. *PLoS One*. 2019;14.

214. Yu K, Liu C, Niu X, He B. Transcranial Focused Ultrasound Neuromodulation of Voluntary Movement-Related Cortical Activity in Humans. *IEEE Trans. Biomed. Eng.* 2021;68.

215. Legon W, Ai L, Bansal P, Mueller JK. Neuromodulation with single-element transcranial focused ultrasound in human thalamus. *Hum. Brain Mapp.* 2018;39.

216. Mueller J, Legon W, Opitz A, Sato TF, Tyler WJ. Transcranial focused ultrasound modulates intrinsic and evoked EEG dynamics. *Brain Stimul.* 2014;7.

217. Niu X, Yu K, He B. On the neuromodulatory pathways of the in vivo brain by means of transcranial focused ultrasound. Curr. Opin. Biomed. Eng. 2018;8.

218. Lee W, Kim HC, Jung Y, Chung YA, Song IU, Lee JH, Yoo SS. Transcranial focused ultrasound stimulation of human primary visual cortex. *Sci. Rep.* 2016;6.

219. Legon W, Sato TF, Opitz A, Mueller J, Barbour A, Williams A, Tyler WJ. Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. *Nat. Neurosci.* 2014;17.

220. Wang J, Li G, Deng L, Mamtilahun M, Jiang L, Qiu W, Zheng H, Sun J, Xie Q, Yang GY. Transcranial focused ultrasound stimulation improves neurorehabilitation after middle cerebral artery occlusion in mice. *Aging Dis.* 2021;12.

221. Gibson BC, Sanguinetti JL, Badran BW, Yu AB, Klein EP, Abbott CC, Hansberger JT, Clark VP. Increased excitability induced in the primary motor cortex by transcranial ultrasound stimulation. *Front. Neurol.* 2018;9.

222. Ai L, Mueller JK, Grant A, Eryaman Y, Legon W. Transcranial focused ultrasound for BOLD fMRI signal modulation in humans. In: Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS. 2016.

223. Zeng K, Darmani G, Fomenko A, Xia X, Tran S, Nankoo JF, Shamli Oghli Y, Wang Y, Lozano AM, Chen R. Induction of Human Motor Cortex Plasticity by Theta Burst Transcranial Ultrasound Stimulation. *Ann. Neurol.* 2022;91.

224. Koji Nakajima, Takahiro Osada, Akitoshi Ogawa, Masaki Tanaka, Satoshi Oka, Koji Kamagata SA, Yasushi Oshima, Sakae Tanaka and SK. A causal role of anterior prefrontal-putamen circuit for response inhibition revealed by transcranial ultrasound stimulation in humans. *Cell Rep.* [Internet]. 2022;Volume 40. Available from: https://doi.org/10.1016/j.celrep.2022.111197

225. Hwang K, Bertolero MA, Liu WB, D'Esposito M. The human thalamus is an integrative hub for functional brain networks. *J. Neurosci.* 2017;37.

226. Grefkes C, Fink GR. Reorganization of cerebral networks after stroke: New insights from neuroimaging with connectivity approaches. Brain. 2011;134.

227. Matelli M, Luppino G, Fogassi L, Rizzolatti G. Thalamic input to inferior area 6 and area 4 in the macaque monkey. *J. Comp. Neurol.* 1989;280.

228. Nelles G, Spiekermann G, Jueptner M, Leonhardt G, Müller S, Gerhard H, Diener HC. Reorganization of sensory and motor systems in hemiplegic stroke patients: A positron emission tomography study. *Stroke*. 1999;30.

229. van Wijngaarden JBG, Zucca R, Finnigan S, Verschure PFMJ. The Impact of Cortical Lesions on Thalamo-Cortical Network Dynamics after Acute Ischaemic Stroke: A Combined Experimental and Theoretical Study. *PLoS Comput. Biol.* 2016;12.

230. Storch S, Samantzis M, Balbi M. Driving Oscillatory Dynamics: Neuromodulation for Recovery After Stroke. Front. Syst. Neurosci. 2021;15.

231. Yuan Y, Wang Z, Liu M, Shoham S. Cortical hemodynamic responses induced by low-intensity transcranial ultrasound stimulation of mouse cortex. *Neuroimage*. 2020;211.

232. Kim H, Chiu A, Lee SD, Fischer K, Yoo SS. Focused ultrasound-mediated non-invasive brain stimulation: Examination of sonication parameters. *Brain Stimul.* 2014;7.

233. Yoo SS, Kim H, Min BK, Franck E, Park S. Transcranial focused ultrasound to the thalamus alters anesthesia time in rats. *Neuroreport*. 2011;22.

234. Lee W, Chung YA, Jung Y, Song IU, Yoo SS. Simultaneous acoustic stimulation of human primary and secondary somatosensory cortices using transcranial focused ultrasound. *BMC Neurosci.* 2016;17.

235. Liu C, Yu K, Niu X, He B. Transcranial Focused Ultrasound Enhances Sensory Discrimination Capability through Somatosensory Cortical Excitation. *Ultrasound Med. Biol.* 2021;47.

236. Kim H, Park MY, Lee SD, Lee W, Chiu A, Yoo SS. Suppression of EEG visual-evoked potentials in rats through neuromodulatory focused ultrasound. *Neuroreport*. 2015;26.

237. Widmer M, Lutz K, Luft AR. Reduced striatal activation in response to rewarding motor

performance feedback after stroke. *NeuroImage Clin.* 2019;24.

238. Grefkes C, Fink GR. Connectivity-based approaches in stroke and recovery of function. Lancet Neurol. 2014;13.
239. Nakajima A, Shimo Y, Uka T, Hattori N. Subthalamic nucleus and globus pallidus interna influence firing of tonically active neurons in the primate striatum through different mechanisms. *Eur. J. Neurosci.* 2017;46.
240. Monti MM, Schnakers C, Korb AS, Bystritsky A, Vespa PM. Non-Invasive Ultrasonic Thalamic Stimulation in Disorders of Consciousness after Severe Brain Injury: A First-in-Man Report. Brain Stimul. 2016;9.
241. Wessel MJ, Hummel FC. Non-invasive Cerebellar Stimulation: a Promising Approach for Stroke Recovery? Cerebellum. 2018;17.
242. Miterko LN, Baker KB, Beckinghausen J, Bradnam L V., Cheng MY, Cooperrider J, DeLong MR, Gornati S V., Hallett M, Heck DH, et al. Consensus Paper: Experimental Neurostimulation of the Cerebellum. *Cerebellum*. 2019;18.
243. Koch G, Bonnì S, Casula EP, Iosa M, Paolucci S, Pellicciari MC, Cinnera AM, Ponzo V, Maiella M, Picazio S, et al. Effect of Cerebellar Stimulation on Gait and Balance Recovery in Patients with Hemiparetic Stroke: A Randomized Clinical Trial. *JAMA Neurol.* 2019;76.
244. Cooperrider J, Momin A, Baker KB, Machado AG. Cerebellar Neuromodulation for Stroke. Curr. Phys. Med. Rehabil. Reports. 2020;8.
245. Baek H, Pahk KJ, Kim MJ, Youn I, Kim H. Modulation of Cerebellar Cortical Plasticity Using Low-Intensity Focused Ultrasound for Poststroke Sensorimotor Function Recovery. *Neurorehabil. Neural Repair*. 2018;32.
246. Baek H, Sariev A, Lee S, Dong SY, Royer S, Kim H. Deep Cerebellar Low-Intensity Focused Ultrasound Stimulation Restores Interhemispheric Balance after Ischemic Stroke in Mice. *IEEE Trans. Neural Syst. Rehabil. Eng.* 2020;28.
247. Baek H, Sariev A, Kim MJ, Lee H, Kim J, Kim H. A neuroprotective brain stimulation for vulnerable cerebellar Purkinje cell after ischemic stroke: A study with low-intensity focused ultrasound. In: Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS. 2018.
248. Mrachacz-Kersting N, Stevenson AJT, Jørgensen HRM, Severinsen KE, Aliakbaryhosseinabadi S, Jiang N, Farina D. Brain state–dependent stimulation boosts functional recovery following stroke. *Ann. Neurol.* 2019;85.
249. Hussain SJ, Hayward W, Fourcand F, Zrenner C, Ziemann U, Buch ER, Hayward MK,

Cohen LG. Phase-dependent transcranial magnetic stimulation of the lesioned hemisphere is accurate after stroke. Brain Stimul. 2020;13.

250. Raco V, Bauer R, Tharsan S, Gharabaghi A. Combining TMS and tACS for closed-loop phase-dependent modulation of corticospinal excitability: A feasibility study. *Front. Cell. Neurosci.* 2016;10.
251. Ting WKC, Fadul FAR, Fecteau S, Ethier C. Neurostimulation for Stroke Rehabilitation. Front. Neurosci. 2021;15.
252. Hochberg LR. 4 Brain computer interface for paralysis. *J. Neurol. Neurosurg. Psychiatry*. 2021;92.
253. Meng Q. Non-invasive brain monitoring and stimulation. *Diss. Abstr. Int. Sect. B Sci. Eng.* 2019;80.
254. Epperson J, Meyers E, Pruitt D, Wright J, Kilgard M, Hays S. Characterization of an Algorithm for Autonomous, Closed-Loop Neuromodulation During Stroke Rehabilitation. *Arch. Phys. Med. Rehabil.* 2021;102.
255. Sebastián-Romagosa M, Cho W, Ortner R, Murovec N, Von Oertzen T, Kamada K, Allison BZ, Guger C. Brain Computer Interface Treatment for Motor Rehabilitation of Upper Extremity of Stroke Patients—A Feasibility Study. *Front. Neurosci.* 2020;
256. Pellicciari MC, Bonnì S, Ponzo V, Cinnera AM, Mancini M, Casula EP, Sallustio F, Paolucci S, Caltagirone C, Koch G. Dynamic reorganization of TMS-evoked activity in subcortical stroke patients. *Neuroimage*. 2018;175.
257. Keser Z, Buchl SC, Seven NA, Markota M, Clark HM, Jones DT, Lanzino G, Brown RD, Worrell GA, Lundstrom BN. Electroencephalogram (EEG) With or Without Transcranial Magnetic Stimulation (TMS) as Biomarkers for Post-stroke Recovery: A Narrative Review. Front. Neurol. 2022;13.
258. Jiahua X, Bernhard A. S, Andrea A. P252 The hybrid noninvasive brain stimulation modulated the intracortical networks for stroke rehabilitation. *Clin. Neurophysiol.* 2020;131.
259. Holzmann R, Koppehele-Gossel J, Voss U, Klimke A. Investigating Nuisance Effects Induced in EEG During tACS Application. *Front. Hum. Neurosci.* 2021;15.
260. Kohli S, Casson AJ. Removal of gross artifacts of transcranial alternating current stimulation in simultaneous EEG monitoring. *Sensors (Switzerland)*. 2019;19.
261. Gebodh N, Adair D, Chelette K, Esmaeilpour Z, Bikson M, Dmochowski J, Parra LC, Woods AJ, Kappenman E. Modulation of physiologic artifacts during concurrent tDCS and EEG. *Brain Stimul.* 2017;10.

262. Gebodh N, Esmaeilpour Z, Adair D, Chelette K, Dmochowski J, Woods AJ, Kappenman ES, Parra LC, Bikson M. Inherent physiological artifacts in EEG during tDCS. *Neuroimage*. 2019;185.

263. Kim HC, Lee W, Kunes J, Yoon K, Lee JE, Foley L, Kowsari K, Yoo SS. Transcranial focused ultrasound modulates cortical and thalamic motor activity in awake sheep. *Sci. Rep.* 2021;11.

264. Lee W, Kim S, Kim B, Lee C, Chung YA, Kim L, Yoo SS. Non-invasive transmission of sensorimotor information in humans using an EEG/focused ultrasound brain-to-brain interface. *PLoS One*. 2017;12.

265. Nie Y, Guo X, Li X, Geng X, Li Y, Quan Z, Zhu G, Yin Z, Zhang J, Wang S. Real-time removal of stimulation artifacts in closed-loop deep brain stimulation. *J. Neural Eng.* 2021;18.

266. Weiss JM, Flesher SN, Franklin R, Collinger JL, Gaunt RA. Artifact-free recordings in human bidirectional brain-computer interfaces. *J. Neural Eng.* 2019;16.

267. Hughes C, Herrera A, Gaunt R, Collinger J. Bidirectional brain-computer interfaces. In: Handbook of Clinical Neurology. 2020.

268. Yang PF, Phipps MA, Jonathan S, Newton AT, Byun N, Gore JC, Grissom WA, Caskey CF, Chen LM. Bidirectional and state-dependent modulation of brain activity by transcranial focused ultrasound in non-human primates. *Brain Stimul.* 2021;14.

269. Young Goo Kim, Song E. Kim, Jihye Lee, Sungeun Hwang, Seung-Schik Yoo HWL. Neuromodulation Using Transcranial Focused Ultrasound on the Bilateral Medial Prefrontal Cortex. *J. Clin. Med.* [Internet]. 2022;11(13), 38. Available from: https://doi.org/10.3390/jcm11133809

270. Hameroff S, Trakas M, Duffield C, Annabi E, Gerace MB, Boyle P, Lucas A, Amos Q, Buadu A, Badal JJ. Transcranial ultrasound (TUS) effects on mental states: A pilot study. *Brain Stimul.* 2013;6.

271. Fine J, Fini M, Mysore A, Tyler W, Santello M. Response inhibition is driven by top-down network mechanisms and enhanced with focused ultrasound. *bioRxiv*. 2019;

272. Ai L, Bansal P, Mueller JK, Legon W. Effects of transcranial focused ultrasound on human primary motor cortex using 7T fMRI: A pilot study NCT03634631 NCT Shanbao Tong, Junfeng Sun. *BMC Neurosci.* 2018;19.

273. Xia X, Fomenko A, Nankoo JF, Zeng K, Wang Y, Zhang J, Lozano AM, Chen R. Time course of the effects of low-intensity transcranial ultrasound on the excitability of ipsilateral and contralateral human primary motor cortex. *Neuroimage*. 2021;243.

274. Zhang Y, Ren L, Liu K, Tong S, Yuan TF, Sun J. Transcranial ultrasound stimulation of the human motor cortex. *iScience*. 2021;24.

275. Heimbuch IS, Fan TK, Wu AD, Faas GC, Charles AC IM. Ultrasound stimulation of the motor cortex during tonic muscle contraction. *PLoS One* [Internet]. 2022;Available from: https://doi.org/10.1371/journal.pone.0267268

276. Matt E, Dörl G, Beisteiner R. Transcranial pulse stimulation (TPS) improves depression in AD patients on state-of-the-art treatment. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 2022;8.

277. Badran BW, Caulfield KA, Stomberg-Firestein S, Summers PM, Dowdle LT, Savoca M, Li X, Austelle CW, Short EB, Borckardt JJ, et al. Sonication of the anterior thalamus with MRI-Guided transcranial focused ultrasound (tFUS) alters pain thresholds in healthy adults: A double-blind, sham-controlled study. *Brain Stimul.* 2020;13.

278. Cain JA, Spivak NM, Coetzee JP, Crone JS, Johnson MA, Lutkenhoff ES, Real C, Buitrago-Blanco M, Vespa PM, Schnakers C, et al. Ultrasonic Deep Brain Neuromodulation in Acute Disorders of Consciousness: A Proof-of-Concept. *Brain Sci.* 2022;12.

279. Cain JA, Visagan S, Johnson MA, Crone J, Blades R, Spivak NM, Shattuck DW, Monti MM. Real time and delayed effects of subcortical low intensity focused ultrasound. *Sci. Rep.* 2021;11.

280. Brinker ST, Preiswerk F, White PJ, Mariano TY, McDannold NJ, Bubrick EJ. Focused Ultrasound Platform for Investigating Therapeutic Neuromodulation Across the Human Hippocampus. *Ultrasound Med. Biol.* 2020;46.

281. Nicodemus NE, Becerra S, Kuhn TP, Packham HR, Duncan J, Mahdavi K, Iovine J, Kesari S, Pereles S, Whitney M, et al. Focused transcranial ultrasound for treatment of neurodegenerative dementia. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 2019;5.

282. Khan F, Chevidikunnan MF, Shawli LE, Noohu MM. Transcranial low frequency ultrasound (TLFFU) for upper limb rehabilitation on patients with stroke. *Int. J. Physiother.* 2020;7.

283. Verhagen L, Gallea C, Folloni D, Constans C, Jensen DEA, Ahnine H, Roumazeilles L, Santin M, Ahmed B, Lehericy S, et al. Offline impact of transcranial focused ultrasound on cortical activation in primates. *Elife*. 2019;8.

284. Davis S, Donnan GA. Time is penumbra: Imaging, selection and outcome: The Johann Jacob Wepfer Award 2014. Cerebrovasc. Dis. 2014;38.

285. Pires Monteiro S, Voogd E, Muzzi L, De Vecchis G, Mossink B, Levers M, Hassink G,

Van Putten M, Le Feber J, Hofmeijer J, et al. Neuroprotective effect of hypoxic preconditioning and neuronal activation in a in vitro human model of the ischemic penumbra. *J. Neural Eng.* 2021;

286. Yang PS, Kim H, Lee W, Bohlke M, Park S, Maher TJ, Yoo SS. Transcranial focused ultrasound to the thalamus is associated with reduced rxtracellular GABA levels in rats. *Neuropsychobiology*. 2012;65.
287. Chen CM, Wu CT, Yang TH, Liu SH, Yang FY. Preventive Effect of Low Intensity Pulsed Ultrasound against Experimental Cerebral Ischemia/Reperfusion Injury via Apoptosis Reduction and Brain-derived Neurotrophic Factor Induction. *Sci. Rep.* 2018;8.
288. Ji R, Smith M, Niimi Y, Karakatsani ME, Murillo MF, Jackson-Lewis V, Przedborski S, Konofagou EE. Focused ultrasound enhanced intranasal delivery of brain derived neurotrophic factor produces neurorestorative effects in a Parkinson's disease mouse model. *Sci. Rep.* 2019;9.
289. Liu SH, Lai YL, Chen BL, Yang FY. Ultrasound Enhances the Expression of Brain-Derived Neurotrophic Factor in Astrocyte Through Activation of TrkB-Akt and Calcium-CaMK Signaling Pathways. *Cereb. Cortex*. 2017;27.
290. Bobola MS, Chen L, Ezeokeke CK, Olmstead TA, Nguyen C, Sahota A, Williams RG, Mourad PD. Transcranial focused ultrasound, pulsed at 40 Hz, activates microglia acutely and reduces Aβ load chronically, as demonstrated in vivo. *Brain Stimul.* 2020;13.
291. Schregel K, Baufeld C, Palotai M, Meroni R, Fiorina P, Wuerfel J, Sinkus R, Zhang YZ, McDannold N, White PJ, et al. Targeted Blood Brain Barrier Opening With Focused Ultrasound Induces Focal Macrophage/Microglial Activation in Experimental Autoimmune Encephalomyelitis. *Front. Neurosci.* 2021;15.
292. Morse S V., Boltersdorf T, Chan TG, Gavins FNE, Choi JJ, Long NJ. In vivo delivery of a fluorescent FPR2/ALX-targeted probe using focused ultrasound and microbubbles to image activated microglia . *RSC Chem. Biol.* 2020;1.
293. Ichijo S, Shindo T, Eguchi K, Monma Y, Nakata T, Morisue Y, Kanai H, Osumi N, Yasuda S, Shimokawa H. Low-intensity pulsed ultrasound therapy promotes recovery from stroke by enhancing angio-neurogenesis in mice in vivo. *Sci. Rep.* 2021;11.
294. Dubey S, Heinen S, Krantic S, JoAnne McLaurin, Branch DR, Hynynen K, Aubert I. Clinically approved IVIg delivered to the hippocampus with focused ultrasound promotes neurogenesis in a model of Alzheimer's disease. *Proc. Natl. Acad. Sci. U. S. A.* 2020;117.
295. Scarcelli T, Jordão JF, O'reilly MA, Ellens N, Hynynen K, Aubert I. Stimulation of

hippocampal neurogenesis by transcranial focused ultrasound and microbubbles in adult mice. *Brain Stimul.* 2014;7.

296. Mooney SJ, Shah K, Yeung S, Burgess A, Aubert I, Hynynen K. Focused ultrasound-induced neurogenesis requires an increase in blood-brain barrier permeability. *PLoS One*. 2016;11.
297. Deng LD, Qi L, Suo Q, Wu SJ, Mamtilahun M, Shi RB, Liu Z, Sun JF, Tang YH, Zhang ZJ, et al. Transcranial focused ultrasound stimulation reduces vasogenic edema after middle cerebral artery occlusion in mice. *Neural Regen. Res.* 2022;17.
298. Asan AS. Modulation of cerebellar purkinje cell activity with low intensity electric and ultrasound stimulation. Thesis. 2020;
299. Carmichael ST. Cellular and molecular mechanisms of neural repair after stroke: Making waves. Ann. Neurol. 2006;59.
300. Rawlinson C, Jenkins S, Thei L, Dallas ML, Chen R. Post-ischaemic immunological response in the brain: Targeting microglia in ischaemic stroke therapy. Brain Sci. 2020;10.
301. Wang Q, Tang XN, Yenari MA. The inflammatory response in stroke. J. Neuroimmunol. 2007;184.
302. Jickling GC, Liu DZ, Ander BP, Stamova B, Zhan X, Sharp FR. Targeting neutrophils in ischemic stroke: Translational insights from experimental studies. J. Cereb. Blood Flow Metab. 2015;35.
303. Caglayan AB, Beker MC, Caglayan B, Yalcin E, Caglayan A, Yulug B, Hanoglu L, Kutlu S, Doeppner TR, Hermann DM, et al. Acute and post-acute neuromodulation induces stroke recovery by promoting survival signaling, neurogenesis, and pyramidal tract plasticity. *Front. Cell. Neurosci.* 2019;13.
304. Ma Y, Wang J, Wang Y, Yang GY. The biphasic function of microglia in ischemic stroke. Prog. Neurobiol. 2017;157.
305. Li LZ, Huang YY, Yang ZH, Zhang SJ, Han ZP, Luo YM. Potential microglia-based interventions for stroke. CNS Neurosci. Ther. 2020;26.
306. Lian L, Zhang Y, Liu L, Yang L, Cai Y, Zhang J, Xu S. Neuroinflammation in Ischemic Stroke: Focus on MicroRNA-mediated Polarization of Microglia. Front. Mol. Neurosci. 2021;13.
307. Jiang CT, Wu WF, Deng YH, Ge JW. Modulators of microglia activation and polarization in ischemic stroke (Review). Mol. Med. Rep. 2020;21.
308. Anttila JE, Whitaker KW, Wires ES, Harvey BK, Airavaara M. Role of microglia in

ischemic focal stroke and recovery: focus on Toll-like receptors. *Prog. Neuro-Psychopharmacology Biol. Psychiatry*. 2017;79.

309. Fekadu G, Chelkeba L, Melaku T, Tegene E, Kebede A. 30-day and 60-day rates and predictors of mortality among adult stroke patients: Prospective cohort study. *Ann. Med. Surg.* 2020;53.
310. Yang Y, Rosenberg GA. Blood-brain barrier breakdown in acute and chronic cerebrovascular disease. *Stroke*. 2011;42.
311. Kunz WG, Almekhlafi MA, Menon BK, Saver JL, Hunink MG, Dippel DWJ, Majoie CBLM, Liebeskind DS, Jovin TG, Davalos A, et al. Public health and cost benefits of successful reperfusion after thrombectomy for stroke. *Stroke*. 2020;
312. Gauberti M, Lapergue B, De Lizarrondo SM, Vivien D, Richard S, Bracard S, Piotin M, Gory B. Ischemia-reperfusion injury after endovascular thrombectomy for ischemic stroke. *Stroke*. 2018;49.
313. Yang SH, Liu R. Four Decades of Ischemic Penumbra and Its Implication for Ischemic Stroke. Transl. Stroke Res. 2021;12.
314. Manning NW, Campbell BCV, Oxley TJ, Chapot R. Acute ischemic stroke time, penumbra, and reperfusion. Stroke. 2014;45.
315. Ermine CM, Bivard A, Parsons MW, Jean-Claude Baron. The ischemic penumbra: From concept to reality. Int. J. Stroke. 2021;16.
316. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, et al. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. *N. Engl. J. Med.* 2015;372.
317. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, Von Kummer R, Boysen G, Bluhmki E, Höxter G, Mahagne MH, et al. Intravenous Thrombolysis With Recombinant Tissue Plasminogen Activator for Acute Hemispheric Stroke: The European Cooperative Acute Stroke Study (ECASS). *JAMA J. Am. Med. Assoc.* 1995;274.
318. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, et al. Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. *N. Engl. J. Med.* 2008;359.
319. Triccas LT, Burridge JH, Hughes A, Verheyden G, Desikan M, Rothwell J. A double-blinded randomised controlled trial exploring the effect of anodal transcranial direct current stimulation and uni-lateral robot therapy for the impaired upper limb in sub-acute and chronic stroke. *NeuroRehabilitation*. 2015;37.
320. Alexandra M. Kaloss, Lauren N. Arnold, Eman Soliman, Maya Langman, Nathalie

Groot, Eli Vlaisavljevich MHT. Noninvasive Low-Intensity Focused Ultrasound Mediates Tissue Protection following Ischemic Stroke. *BME Front.* 2022; 2022:11.

321. Bolbanabad HM, Anvari E, Rezai MJ, Moayeri A, Kaffashian MR. Amelioration of cerebellar dysfunction in rats following postnatal ethanol exposure using low-intensity pulsed ultrasound. *J. Chem. Neuroanat.* 2017;81.
322. Guo H, Baker G, Hartle K, Fujiwara E, Wang J, Zhang Y, Xing J, Lyu H, Li XM, Chen J. Exploratory study on neurochemical effects of low-intensity pulsed ultrasound in brains of mice. *Med. Biol. Eng. Comput.* 2021;59.
323. Rahman AA, Amruta N, Pinteaux E, Bix GJ. Neurogenesis After Stroke: A Therapeutic Perspective. Transl. Stroke Res. 2021;12.
324. Horn, A., & Blankenburg, F. (2016). Toward a standardized structural-functional group connectome in MNI space. NeuroImage, 124(Pt A), 310–322.
325. Ambrosini, E., Gasperini, G., Zajc, J., Immick, N., Augsten, A., Rossini, M., Ballarati, R., Russold, M., Ferrante, S., Ferrigno, G., Bulgheroni, M., Baccinelli, W., Schauer, T., Wiesener, C., Gfoehler, M., Puchinger, M., Weber, M., Weber, S., Pedrocchi, A., Krakow, K. (2021). A Robotic System with EMG-Triggered Functional Electrical Stimulation for Restoring Arm Functions in Stroke Survivors. Neurorehabilitation and Neural Repair, 35(4).
326. Qian, Q., Hu, X., Lai, Q., Ng, S. C., Zheng, Y., & Poon, W. (2017). Early stroke rehabilitation of the upper limb assisted with an electromyography-driven neuromuscular electrical stimulation-robotic arm. Frontiers in Neurology, 8 (SEP).
327. Iftime-Nielsen, S. D., Christensen, M. S., Vingborg, R. J., Sinkjær, T., Roepstorff, A., & Grey, M. J. (2012). Interaction of electrical stimulation and voluntary hand movement in SII and the cerebellum during simulated therapeutic functional electrical stimulation in healthy adults. Human Brain Mapping, 33 (1).
328. Gandolla, M., Ward, N. S., Molteni, F., Guanziroli, E., Ferrigno, G., & Pedrocchi, A. (2016). The Neural Correlates of Long-Term Carryover following Functional Electrical Stimulation for Stroke. Neural Plasticity, 2016.