

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

Mahmut Martin Yüksel<sup>\*1,2</sup>, Shiqi Sun<sup>4,5,6</sup>, Charles Latchoumane<sup>4,5,6</sup>, Jocelyne Boch<sup>4,5,6,7</sup>  
Gregoire Courtine<sup>4,5,6,7</sup>, Estelle Emeline Raffin<sup>1,2,\*</sup>, Friedhelm Christoph Hummel<sup>1,2,3,\*</sup>

\* authors contributed equally

<sup>1</sup> Defitech Chair of Clinical Neuroengineering, Neuro-X Institute (NIX) and Brain Mind Institute (BMI), École Polytechnique Fédérale de Lausanne (EPFL), Geneva, Switzerland.

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

<sup>3</sup> Clinical Neuroscience, University of Geneva Medical School, Geneva, Switzerland.

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

<sup>5</sup> Department of Clinical Neuroscience, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland.

<sup>6</sup> Defitech Center for Interventional Neurotherapies (NeuroRestore), EPFL/CHUV/UNIL, Lausanne, Switzerland.

<sup>7</sup> 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](mailto:friedhelm.hummel@epfl.ch)

**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.<sup>1</sup> Globally, stroke affects over 13.7 million humans every year causing over 5.7 million deaths per year<sup>2</sup> and leaving over two-third of the survivors with neurological disabilities.<sup>3</sup> With over 101 million prevalent cases worldwide, stroke is one of the major causes for disability-adjusted life years (DALYs).<sup>4</sup> Despite traditional neurorehabilitation approaches, less than 15% of patients will fully recover from a stroke.<sup>5,6</sup> 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.<sup>7</sup> 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.<sup>8</sup> 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<sup>9-11</sup>, it becomes clear that further work to establish long-ranging, deep-penetrating neuromodulation techniques is necessary for post-stroke rehabilitation.<sup>12</sup> 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.<sup>17</sup> They are, therefore, essential in the process of stroke recovery.<sup>18-20</sup> 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.<sup>21-23</sup> 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.<sup>24,25</sup> In sum, as the whole brain is undergoing significant changes following a stroke<sup>24-27</sup>, reorganization of functional neural networks including communication pathways with deep brain structures is a pivotal process for motor recovery in post-stroke patients.<sup>25,28,29</sup>

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

However, whether disbalanced IHI is an adaptive or a maladaptive process in post-stroke patients is still a matter of debate in the field.<sup>31–33</sup> It remains controversial whether the ipsilateral (contralesional) respectively contralateral (ipsilesional) hemisphere is dominantly involved in the recovery processes.<sup>34</sup> 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.<sup>35</sup> 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)<sup>33,36–39</sup> and consequently increase the activity of the hypoactive ipsilesional M1<sup>40,41</sup> or vice versa<sup>34</sup> 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.<sup>42–44</sup> For instance, cortical excitability of the affected and non-affected hemispheres is changing throughout recovery.<sup>45,46</sup> 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.<sup>47–50</sup> By re-balancing activity levels and interactions between both hemispheres, these techniques have previously demonstrated improved functional recovery in both subacute<sup>45</sup> and chronic stroke survivors.<sup>51</sup> 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.<sup>33,37,52</sup>

In addition, TMS and tES are critically hampered by their depth-focality trade off, due to their limited spatial resolution<sup>53,54</sup> and short-ranged penetrability.<sup>45–47,58</sup> 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.<sup>59</sup> 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<sup>28</sup> leading potentially to relevant unwanted side effects<sup>60</sup>. 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.<sup>61</sup>

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.<sup>19,61–65</sup> Accordingly, a first preclinical, invasive study showed that neuromodulation of the dentate nucleus via DBS improved stroke recovery.<sup>65</sup> DBS of the cerebellar dentate nucleus (DN)<sup>66–68</sup> 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<sup>69</sup>. Post-stroke pain symptoms have also been successfully treated with DBS of the ventroposterolateral<sup>70,71</sup> (VPL) and ventroposteromedial (VPM)<sup>19,72</sup> nucleus of the thalamus. However, clinical applicability and adoptability of invasive neurostimulation is limited due to surgical complication risk profile<sup>73,74</sup>, limited accessibility to all brain regions<sup>73</sup>, cumbersome maintenance<sup>75</sup> and by patient compliance<sup>76</sup> which is hindering the possibility to let DBS become a widespread neuromodulation option.

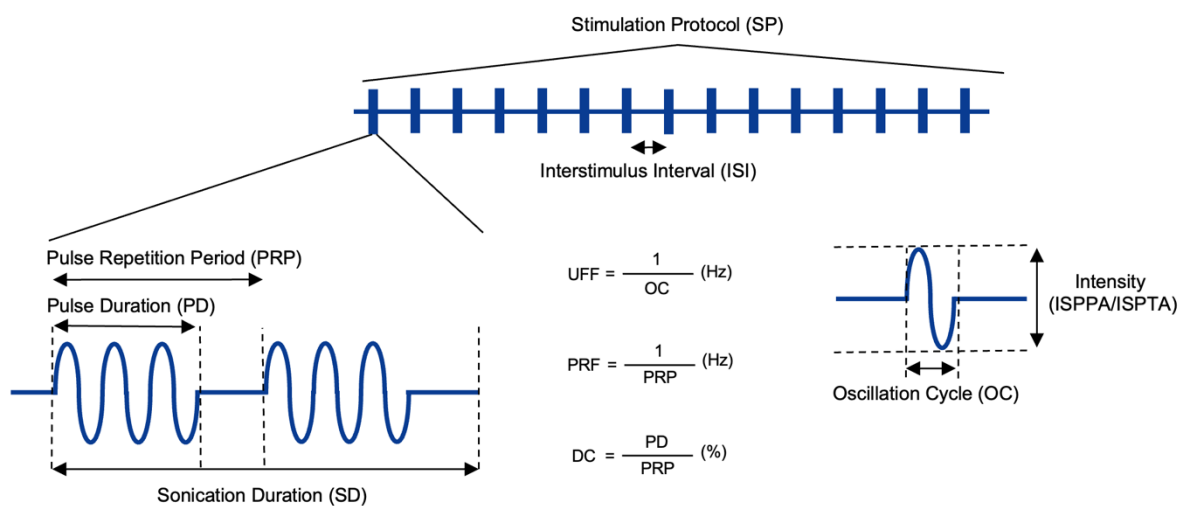
Transcranial ultrasound stimulation (TUS) is a novel and non-invasive alternative technique to reach deep brain regions.<sup>75,77–79</sup> In contrast to conventional NIBS the penetrability and focality of TUS is less limited by the biophysical instances when penetrating deep brain regions.<sup>80–83</sup> Thus, TUS appears to be a superior technique in terms of deep brain stimulation with its excellent focality, penetrability and steering capacities.<sup>75,78,84</sup> Furthermore, increasing studies in smaller animals<sup>85–87</sup>, monkeys<sup>88–90</sup>, sheep<sup>91</sup> and first-in-humans studies<sup>92</sup> are highlighting the potential safety and feasibility of TUS as a novel NIBS method.<sup>78,93–96</sup> 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.<sup>97,98</sup> 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.<sup>99</sup> 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.<sup>100,101</sup>

Ultrasound in medical contexts utilizes piezoelectric materials which transmit high frequency sound waves when electrically stimulated.<sup>102</sup> These ultrasonic sound waves with high frequencies over 20kHz are above human hearing abilities.<sup>103</sup> 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).<sup>96,104</sup> Part of the energy is transmitted into mechanical deformation of the tissue and another part converted into thermal energy.<sup>105</sup> 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).<sup>86,88</sup> 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<sup>82,83</sup>. 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.<sup>106–108</sup>

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<sup>104,109–112</sup>. 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.<sup>113–116</sup> In contrast, the usual parameter space used in neuromodulation studies (higher frequencies and lower pressure) reported neural activity changes without any evidence of cavitation.<sup>105,117</sup> 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.<sup>118</sup> Numerous studies have shown reversible suppression of neural activity following ultrasound induced thermal rise.<sup>119</sup> 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.<sup>120,121</sup> 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.<sup>122,123</sup> 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.<sup>124</sup>

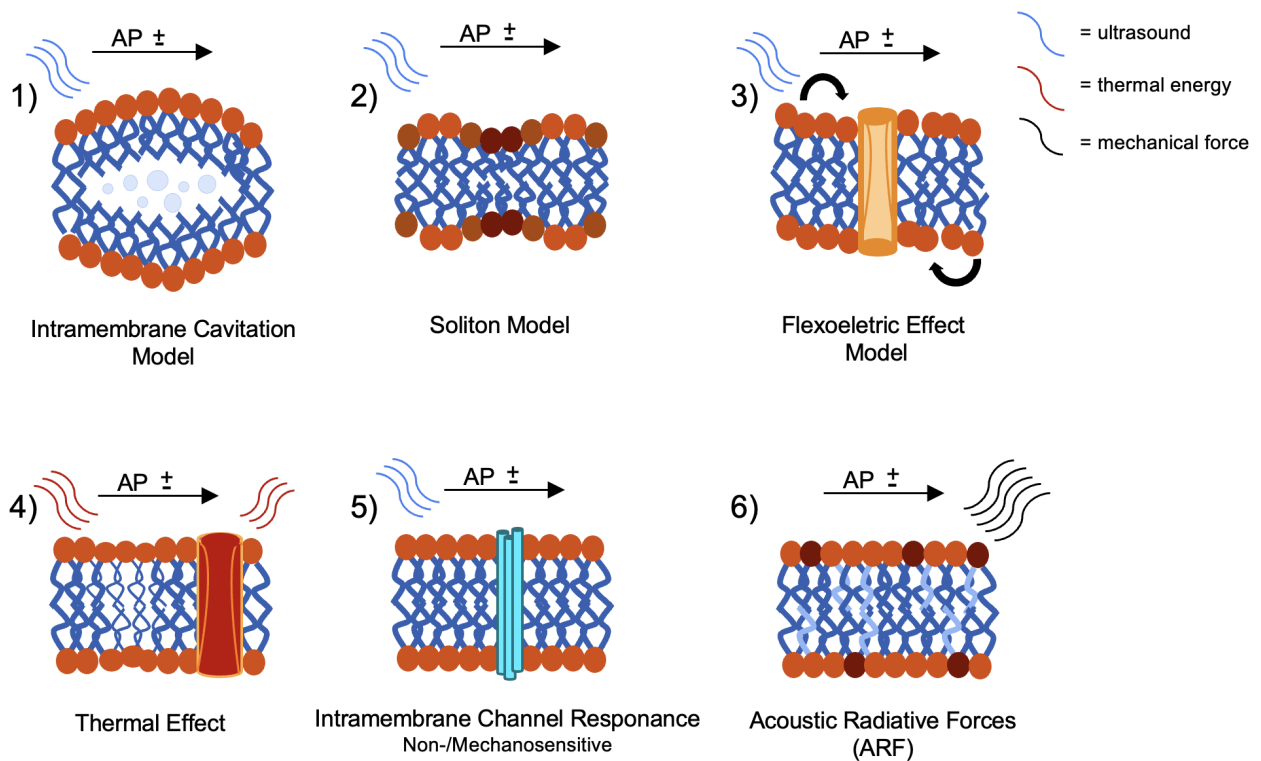
Importantly, in most of the experimental work ultrasound stimulation triggers both thermal rise and mechanical factors, which makes the two explanatory mechanisms hard to disentangle. It is proposed that both, the thermal and mechanical energy, through acoustic radiative forces (ARF) alter the membrane capacitance, denaturizes membrane components and gates channels such that depolarization, and therefore, activation modulation of the cell is the result.<sup>104</sup> 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.<sup>125</sup> 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<sub>v</sub>1.5 channel<sup>122,126–128</sup>) are

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

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.<sup>82</sup> The study setup used for UFF 500 kHz, peak pressures of 0.35–1.32 MPa, and durations of 4  $\mu$ s-40 ms extremely short ultrasound pulses and examined one by one the above introduced mechanisms.<sup>82</sup> 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.<sup>82</sup> 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.<sup>130–132</sup> Proper auditory masking and adjusted pulse configurations must be used in future work to disentangle the different sources of neuromodulatory effects.<sup>133</sup>

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<sup>105</sup> which will lead to differential neuromodulatory effects, such as inhibitory vs. excitatory or local vs. additional effects in connected areas.<sup>111</sup>





**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.<sup>103,104,125,127,134</sup>

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.<sup>135</sup> 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).<sup>136</sup>

HI-FUS is an established, FDA-approved method for several clinical applications such as ablation of tumors<sup>137–139</sup>, for thalamotomy for treatment of essential tremor (ET)<sup>140</sup>, for Parkinson's disease (PD)<sup>141</sup> or for neuropathic pain management<sup>142</sup>. In the context of stroke treatment, some studies elaborated HI-FUS as an additional approach for thrombolysis, so called “sonothrombolysis” in acute stroke.<sup>143–145</sup> 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<sup>146,147</sup>, gene therapy<sup>148–150</sup> or chemotherapy.<sup>146,151,152</sup> HI-FUS and MI-FUS applications are outside the scope of this review, we refer the reader to some excellent reviews on the topic.<sup>170</sup> “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).<sup>153</sup> 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/cm<sup>2</sup>, and either mechanical index (MI) = 1.9 or derated spatial-peak temporal-average intensity ISPPA = 190 W/cm<sup>2</sup>.<sup>108,154</sup> Safety assurance was also confirmed for obstetrical ultrasound when executed within FDA-approved guidelines regarding intensity setting.<sup>155</sup> 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/cm<sup>2</sup>. 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  $TR < 1\text{ }^{\circ}\text{C}$  for the brain and  $TR < 2\text{ }^{\circ}\text{C}$  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.<sup>156</sup> 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<sup>156</sup>.

A similar informed stepwise approach should be taken to demonstrate mechanical safety. Specifically, with a peak rarefaction pressure ( $P_r$ ) 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  $P_r < 2\text{ MPa}$ . 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<sup>2</sup> did no harm to the tissue in histological evaluation, making TUS neuromodulation a valid therapeutic tool<sup>157</sup> provided current safety work in temporal lobe epilepsy patients who underwent sonication prior to resection of anterior-mesial temporal lobe.<sup>94</sup> Their results suggest that TUS at intensities up to

5760 mW/cm<sup>2</sup> may be safe for neuromodulation in humans.<sup>94</sup> 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  $I_{\text{Sppa}}$  between 0.5 and 7.8 W/cm<sup>2</sup> and  $I_{\text{Spta}}$  were between 10.1 and 156.7 mW/cm<sup>2</sup>.<sup>95</sup> The authors showed successful modulations of motivation and decision accuracy, but no behavioral impairment nor neurological trauma with parameters within FDA recommendations.<sup>95</sup>

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.<sup>158</sup>

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

High-intensity FUS (HI-FUS)	>1000W/ cm <sup>2</sup> 169,170	Continuous waves 140	Mechanical and thermal induced coagulation leading to necrosis of tissue <sup>171</sup>	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. <sup>136,138,139,159</sup>  Discussed as potential thrombolysis method ("sonothrombolysis") in stroke <sup>77,143-145</sup>
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**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.<sup>172-176</sup> 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.<sup>177</sup> Following a major body of research regarding FES was conducted in both acute<sup>178-180</sup> and chronic<sup>181-183</sup> 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.<sup>325,326</sup> Particularly, somatosensory stimulation facilitated enhancement of motor functions in both subacute<sup>173,184,185</sup> and chronic<sup>175,186,187</sup> 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.<sup>327, 328</sup> The combination of peripheral nerve and central

brain stimulation seem to even lead to larger beneficial effects.<sup>188,189</sup> 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 excitatory neuromodulation effects.<sup>78,136,190–192</sup> Young and Henneman had already shown in 1961 that US could differentially modulate the activity of A $\delta$ - and C-fibers, depending on the fiber diameter, US intensity, and US exposure time.<sup>193</sup> More recently, additional technical assistance via focal depth controller has been proposed to further improve peripheral nerves targeting for neurorehabilitation<sup>194</sup>, 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.<sup>195–197</sup> It is also possible to selectively stimulate the peripheral vagus nerve as shown in animal models<sup>198–200</sup> 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.<sup>201</sup> 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.<sup>202,203</sup> The role of such tracts, for example the corticospinal tract, in stroke is not well-elaborated yet.<sup>204</sup> However, it was recently shown that injury to the corticospinal tract can be used a predictor to upper extremity recovery in post-stroke patients.<sup>205</sup> Moreover, SCS has been shown to stabilize motor control and to induce neuroplasticity to facilitate recovery in rat modeled following cerebral ischemia<sup>206</sup>, providing another promising neuromodulatory targets for stroke recovery. Since early work on ultrasound targeting the spine suggests the possibility to modulate spinal cord activity<sup>134,207</sup> 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<sup>208</sup>, 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.<sup>209</sup> In accordance, Kim *et al.* (2021) recently published a concept of wearable TUS approach for rats which suffered a MCAO stroke.<sup>210</sup> The system targeted mainly cortical M1 region and partly subcortical regions such as the striatum with ISPPA of 1.6 W/cm<sup>2</sup>. The stimulation resulted in improved cerebral hemodynamic changes and enhanced post-stroke rehabilitation.<sup>210</sup>

The interest for cortical neuromodulation via high-resolution TUS is large due to the focality of ultrasonic stimulation in the millimeter resolution space.<sup>105,106,211–217</sup> 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.<sup>92,218</sup> 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.<sup>219</sup> 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.<sup>78,81,220,221,222</sup> 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.<sup>223</sup> In contrast, studies using online TUS parameters (short pulses) such as in Legon *et al.* (2018)<sup>211</sup>, Nakajima *et al.* (2022)<sup>224</sup> and Fomenko *et al.* (2020)<sup>107</sup> 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<sup>2</sup> over M1 showing modulation of movement-related cortical potential with high spatiotemporal resolution.<sup>214</sup> In light of movement impairment following stroke, the published work provided translational substance for enhancing endogenous motor cortical processes in humans.<sup>214</sup>

### *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.<sup>28</sup> Particularly, the thalamus as the central and integrative hub of functional brain networks<sup>225</sup> is essential for integration and for reorganization of the post-stroke brain as shown in neuroimaging studies highlighting the thalamocortical network dynamics.<sup>226–229</sup> 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.<sup>230</sup> Several studies have shown both excitatory effects in animals<sup>231–233</sup> and humans<sup>92,234,235</sup> and inhibitory effects in animals<sup>87,119,236</sup> and humans<sup>107,211,216</sup> 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<sup>2</sup>. 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.<sup>215</sup> 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.<sup>48,237,238</sup> After intensive and safe TUS of the striatum, Munoz and colleagues showed improved decision making in primates together with widespread BOLD signals changes.<sup>95</sup> 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.<sup>239</sup> 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).<sup>224</sup> 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.<sup>224</sup> 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.<sup>240</sup>

It becomes clear that TUS has excellent properties for targeting deep brain regions, perhaps even combinable and applicable in DBS patients and beyond.<sup>157</sup> 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.<sup>157</sup>

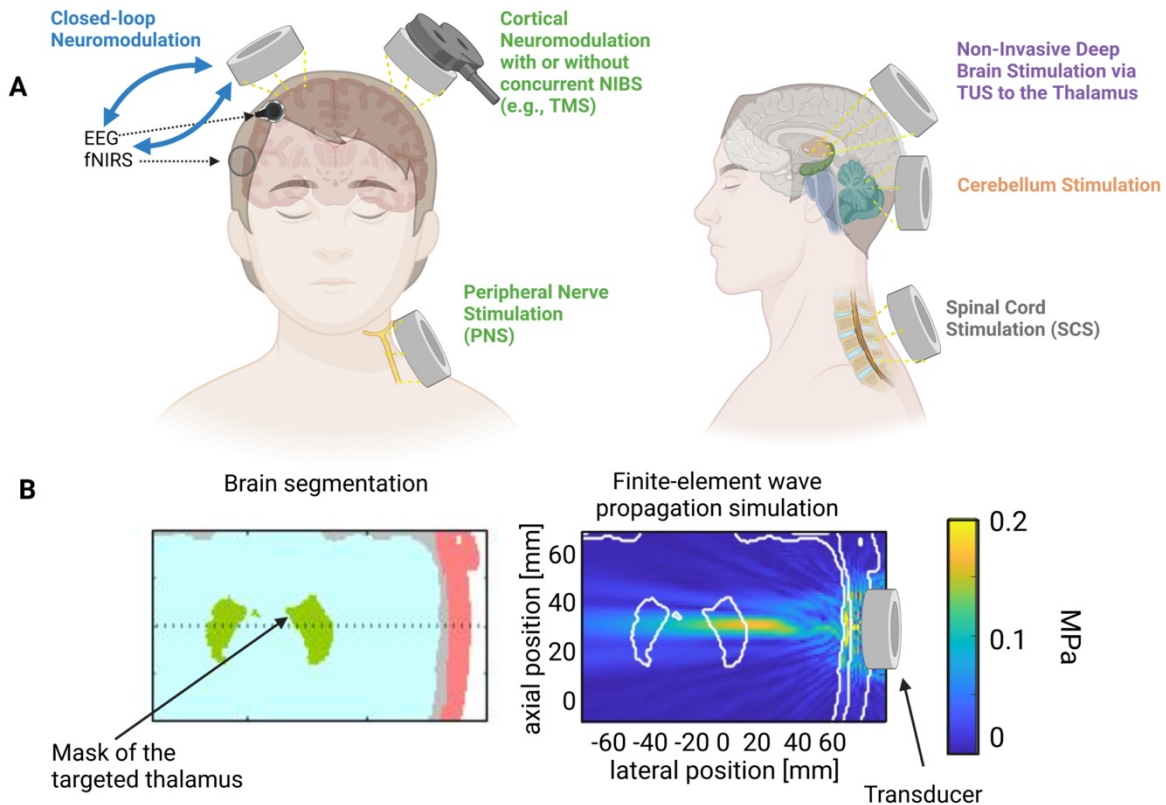
Alternatively, non-invasive stimulation<sup>65,241,242</sup> but also invasive<sup>63,65,242</sup> stimulation of the cerebellum has been tried out for post-stroke recovery. Preclinical studies proved DBS stimulation to the cerebellum for post-stroke conditions to be effective in rodents.<sup>63,65</sup> 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.<sup>241</sup> In a recent study Koch *et al.* (2019) showed that non-invasive, cerebellar intermittent  $\theta$ -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.<sup>243</sup> These subcortical targets are of particular interest for ultrasonic neuromodulation considering the excellent depth penetrability, millimeter-precise focality and superior steering capacities of TUS.<sup>81,136</sup> 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.<sup>244</sup> Significant improvement was noted after one day in the rodent TUS group compared to the group without TUS.<sup>245</sup> 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.<sup>246</sup> 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.<sup>247</sup> 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.<sup>230</sup> 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.<sup>230</sup>

As the oscillatory behavior of neural populations change over the reorganization course following a stroke, several approaches for phase-dependent neuromodulation have been proposed.<sup>46,61,248–250</sup> 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.<sup>251–255</sup> Current adaptive neuromodulation proposals utilize electromagnetic stimulation paradigms combined with electric recording systems.<sup>253,256–258</sup> 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.<sup>259–262</sup> 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.<sup>210,263</sup> Due to the mechanical, thermal and non-ionizing nature of ultrasonic stimulation, electromagnetic artifacts are less likely to occur compared to TMS or tES.<sup>264</sup> In combination with neuroimaging methods such as EEG this can lead to artifact-reduced closed-loop adaptive neuromodulation.<sup>83,212,265</sup> 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.<sup>266–</sup>

268



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

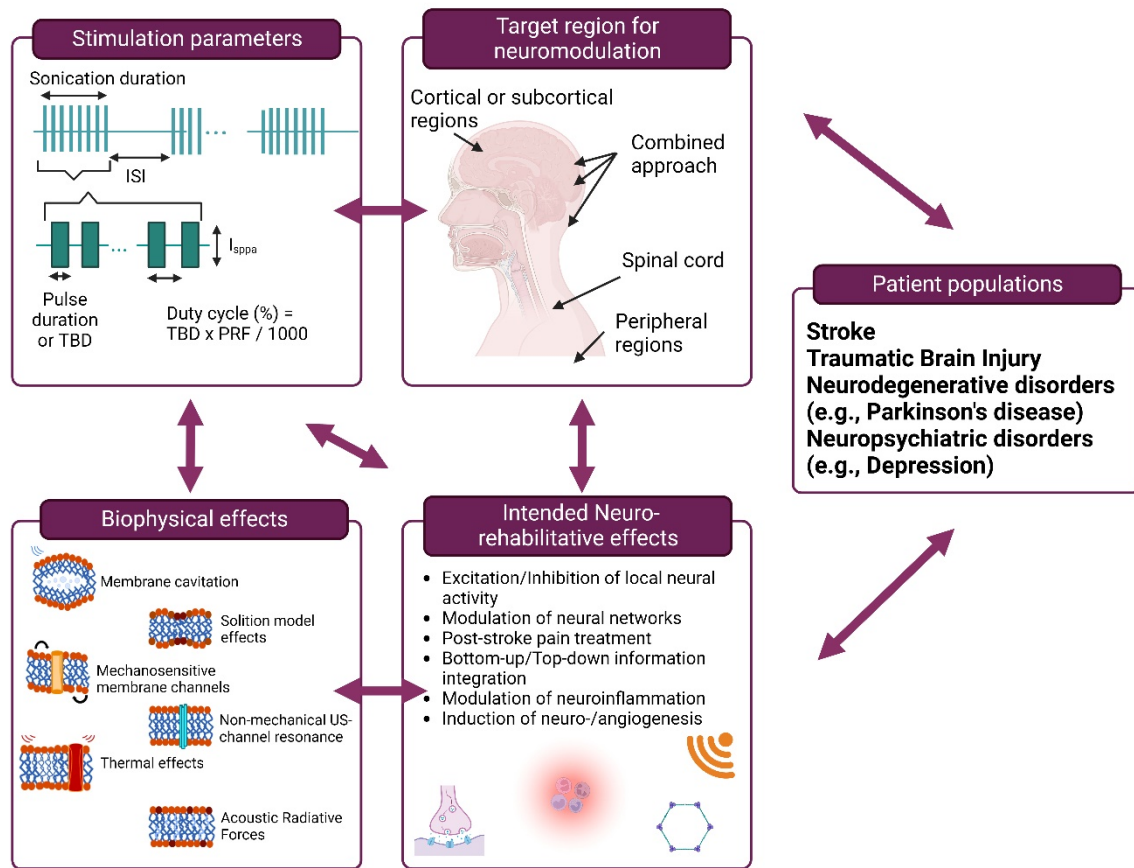
A) Illustration of different TUS targets regarding neuromodulation for the purpose of stroke neurorehabilitation. Left, frontal view illustrates cortical neuromodulation with or without conventional NIBS methods such as TMS, peripheral neurostimulation (PNS) to central cranial nerves i.e. vagus nerve 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.



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.

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## SUPPLEMENTARY MATERIALS

**Supplementary Table 1: Clinical TUS studies**

Region of interest		Specifics	Study title	References	Subjects	Modalities and task	Study Design	Parameters	Modulation effects	Main results
Targets										
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 <i>et al.</i> (2020) <sup>166</sup>	n = 48	fMRI measuring functional connectivity for resting-state and post-stimulation, mood questionnaire	Randomized, placebo-controlled, double-blind study	UFF = 0.5 MHz PD = 65 $\mu$ s PRF = 40 Hz DC = 26% SD = 30 s ISPTA = 130 mW/cm <sup>2</sup>	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 <i>et al.</i> (2022) <sup>269</sup>	n = 7	EEG, MRI, CT	Randomized, sham-controlled study	UFF = 0.25 MHz SD = 20 min AIF = 3 W/cm <sup>2</sup> MI = 0.6  excitatory protocol: DC = 70% SI = 5 s  suppression protocol: DC = 5% 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 <i>et al.</i> (2013) <sup>270</sup>	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/cm <sup>2</sup>	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 <i>et al.</i> (2022) <sup>224</sup>	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 SD = 40s PD = 30ms DC = 30%  Stage 1: ISPTA = 9 W/cm <sup>2</sup>  Stage 3 and 5: ISPTA = 10.7 W/cm <sup>2</sup>	Suppression	TUS induced sustainable suppression for longer than 60 min
		Right IFC + S1 + sham	Response inhibition is driven by top-	Fine <i>et al.</i> (2019) <sup>271</sup>	n = 63 (total)	Stop-Signal task, EEG, behavioral task,	unknown	UFF = 500 kHz 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)  Group 2: n=23 (TUS to S1)  Group 3: n.= 15 (sham)			PRF = 1 kHz DC = 24% SD = 0.5 ms MI = 0.9 ISPPA= 22.4 W/cm <sup>2</sup>		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 <i>et al.</i> (2016) <sup>222</sup>	n = 6	fMRI scan (cortical BOLD at 3T and sub-cortical BOLD at 7T)	Pre-/post-interventional study	SD = 500 ms ISPPA = 6 W/cm <sup>2</sup>  3T MRI experiment: UFF = 500 kHz PRF = 1kHz, DC = 36%  7T MRI experiment: UFF = 860 kHz PRF = 0.5kHz 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 <i>et al.</i> (2018) <sup>272</sup>	n = 5	fMRI, finger tapping task	Sham controlled study	UFF = 500 kHz PD = 0.36ms PRF = 1kHz; DC = 36% SD = 500ms ISPPA= 16.95 W/cm <sup>2</sup>	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 <i>et al.</i> (2018) <sup>221</sup>	n = 43	TMS, EMG (induced MEP)	Single blind, sham-controlled study	UFF = 2.32 MHz SD = 2 min DC < 1%  ISPPA = 34.96 W/cm <sup>2</sup>	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 <i>et al.</i> (2018b) <sup>215</sup>	n = 50	TMS, EMG (MEPs), SICI, ICF, stimulus response reaction time task	Sham controlled study	UFF = 500 kHz PD = 0.36 ms PRF = 1 kHz DC = 36% SD = 500 ms MI = 0.9 ISPPA= 17.12 W/cm <sup>2</sup> ISPTA= 6.16 W/cm <sup>2</sup>	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 <i>et al.</i> (2020) <sup>106</sup>	n = 16	TMS, EMG (MEPs), visuomotor task	Double blinded study	UFF = 500 kHz PRF =1000Hz SD = 0.1–0.5s DC=10/30/50% ISPPA = 0.93/2.78/4.63 W/cm <sup>2</sup>	Inhibition	GABA <sub>A</sub> -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 <i>et al.</i> (2021) <sup>214</sup>	n = 15	EEG and ESI (MRCP), EMP, voluntary foot tapping task	sham-controlled study	UFF = 0.5 MHz SD = 500ms PRF = 3000 Hz ISPPA = 5.9 W/cm <sup>2</sup> ISPTA = 702 mW/cm <sup>2</sup>	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 <i>et al.</i> (2021) <sup>273</sup>	n = 22	TMS, EMG (MEP)	Sham controlled study	UFF = 0.5 MHz SD = 500 ms PRF = 1000 Hz DC = 30% ISSPA = 2.32 W/cm <sup>2</sup>	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 <i>et al.</i> (2021) <sup>274</sup>	n = 24	TMS, EMG (MEP), stop-signal task	Crossover, sham-controlled study	UFF = 0.5MHz SD = 500ms ISI = 8s TD = 15 min PRF = 100Hz DC = 5% MI = 0.696 ISPPA = 8.053 W/cm <sup>2</sup>	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 <i>et al.</i> (2022) <sup>275</sup>	n = 10 (experiment 1) n = 8 (experiment 2)	MRI, TMS, EMG (MEP)	Pre-/post-interventional study	UFF = 0.5MHz DC = 36% PRF = 1000Hz ISPTA = 1.4 W/cm <sup>2</sup>	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 <i>et al.</i> (2022) <sup>223</sup>	n = 20	TMS, EMG,	Sham controlled study	UFF = 0.5MHz SD = 80s PRF = 5Hz/1kHz DC = 10/32% ISPPA = 2.26 W/cm <sup>2</sup> ISPTA = 0.72 W/cm <sup>2</sup>	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 <i>et al.</i> (2014) <sup>219</sup>	n = 10	EEG (C3, CP1, CP5 and P3); SEPs induced through MNS; two-point discrimination tasks	Sham controlled study	UFF = 500 kHz SD = 500 ms PRF = 1 kHz DC = 36% MI = 1.13 ISPPA = 23.87 W/cm <sup>2</sup>	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 <i>et al.</i> (2014) <sup>216</sup>	n = 25	EEG (C3, CP1, CP5, P3) SEPs induced through MNS	Sham controlled study	UFF = 500 kHz PD = 0.36 ms PRF = 1 kHz DC = 36% SD = 500 ms ISPPA = 23.87 W/cm <sup>2</sup>	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 <i>et al.</i> (2015) <sup>92</sup>	n = 18	EEG, fMRI, tactile sensations task	Sham controlled study	UFF = 250 kHz PRF = 500 Hz TBD = 1 ms DC = 50% SD = 300 ms ISPPA = 3 W/cm <sup>2</sup> ISPTA = 1.5 W/cm <sup>2</sup>	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 <i>et al.</i> (2021) <sup>235</sup>	n = 9	EEG and ESI, sensory vibration frequency discrimination task	Sham controlled, crossover study	UFF = 500 kHz SD = 500 ms PRF = 300 Hz ISSPA = 1.10 W/cm <sup>2</sup> ISPTA = 67.13 mW/cm <sup>2</sup>	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 <i>et al.</i> (2016) <sup>234</sup>	n = 10	fMRI, EEG, tactile sensory task	Double blind, sham-	UFF = 210 kHz PRF = 500 Hz TBD = 1ms	Excitation	Simultaneous S1 and S2 stimulation via

			and secondary somatosensory cortices using transcranial focused ultrasound				controlled study	PD = 1 ms DC = 50% SD = 500 ms ISPPA = 35.0 W/cm <sup>2</sup> ISPTA = 17.5 W/cm <sup>2</sup>		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 <i>et al.</i> (2021) <sup>94</sup>	n = 8	MRI, Histological evaluation, Neuropsychological testing	Pre-/post-interventional study	UFF = 650 kHz  Activation protocol: DC = 50%  Suppression protocol: DC = 5% SD = 30s  ISPTA = 720 – 5760 mW/cm <sup>2</sup>	Unknown	MRI-guided TUS with up to 5760 mW/cm <sup>2</sup> 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 <i>et al.</i> (2016) <sup>218</sup>	n = 19	fMRI, EEG, phosphene perception task	Single blind, sham-controlled study	UFF = 270 kHz PRF = 500 Hz PD = 1 ms DC = 50% SD = 300 ms ISPPA = 3 W/cm <sup>2</sup> ISPTA = 100mW/cm <sup>2</sup>	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 <i>et al.</i> (2020) <sup>93</sup>	n(healthy)= 10 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: Admitting single ultrashort ultrasound pulses, PRF = 5 Hz TNP = 6000 PD = 3 μs 0.3 mj/mm <sup>2</sup>	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 <i>et al.</i> (2022) <sup>276</sup>	n = 18	fMRI, Beck Depression Inventory (BDI-II)	Multicenter pre-post interventional study	Transcranial pulse stimulator (TPS) from NEUROLITH: Admitting single ultrashort ultrasound pulses, PRF = 5 Hz 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 $\mu$ s 0.3 mJ/mm <sup>2</sup>		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 <i>et al.</i> (2016) <sup>240</sup>	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 PD = 0.5 ms DC = 5% PRF = 100 Hz ISPTA = 0.72 W/cm <sup>2</sup>	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 <i>et al.</i> (2018) <sup>215</sup>	n = 40	EEG, SEPs induced by MN stimulation, two-point discrimination tasks	Sham controlled study	UFF = 500 kHz PD = 0.36 ms PRF = 1 kHz DC = 36% ISPPA: 7.03 W/cm <sup>2</sup>	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 <i>et al.</i> (2020) <sup>277</sup>	n = 19	Sensory threshold, pain tolerance thresholds to a thermal stimulus	Double blind, sham-controlled, crossover study	UFF = 650 kHz PD = 5 ms PRF = 10 Hz DC = 5% SD = 30 s ISPTA = 719 and 995 mW/cm <sup>2</sup>	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 <i>et al.</i> (2022) <sup>278</sup>	n = 11 (acute disorder of consciousness patients)	Neurobehavioral assessment post-TUS, MRI-guided sonication + BOLD	unknown	UFF = 650 kHz PD = 0.5 ms PRF = 100 Hz DC = 5% SD = 30 s ISI = 30s ISPTA = 719.73 mW/cm <sup>2</sup>	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 <i>et al.</i> (2022) <sup>224</sup>	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 SD = 40s 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%  Stage 1: ISPTA = 9 W/cm <sup>2</sup>  Stage 3 and 5: ISPTA = 10.7 W/cm <sup>2</sup>		stimulation of M1
Left Globus Pallidus (GP)	Healthy volunteers	Real time and delayed effects of subcortical low intensity focused ultrasound	Cain <i>et al.</i> (2021) <sup>279</sup>	n = 16	MRI-guided (BOLD)	unknown	UFF = 650 kHz DC = 5% PRF = 10/100Hz SD = 30s ISI = 30s Sessions=2x2x 10min ISPTA= 720mW/cm <sup>2</sup>	unknown	TUS targeting left GP in healthy individuals modulated broad neural network activity according to BOLD MRI signal analysis	
Hippocampus	Drug-resistant temporal lobe epilepsy	Focused Ultrasound Platform for Investigating Therapeutic Neuromodulation Across the Human Hippocampus	Brinker <i>et al.</i> (2020) <sup>280</sup>	n = 1	MRI-guided	unknown	UFF = 548 kHz DC = 35-50% PRF = 500 Hz SD = 500ms ISI = 140 s Sessions=20x ISPTA= 2.25- W/cm <sup>2</sup>	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 Substantia nigra	AD and PD patients	Focused transcranial ultrasound for treatment of neurodegenerative dementia	Nicodemus <i>et al.</i> (2019) <sup>281</sup>	n (AD) = 11 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

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