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Neuromodulation with Ultrasound: Hypotheses on the Directionality of Effects and a Community Resource

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ABSTRACT

Low-intensity Transcranial Ultrasound Stimulation (TUS) is a promising non-invasive technique for deep-brain stimulation and focal neuromodulation. Research with animal models and computational modelling has raised the possibility that TUS can be biased towards enhancing or suppressing neural function. Here, we first conduct a systematic review of human TUS studies for perturbing neural function and alleviating brain disorders. We then collate a set of hypotheses on the directionality of TUS effects and conduct an initial meta-analysis on the human TUS study reported outcomes to date (n = 32 studies, 37 experiments). We find that parameters such as the duty cycle show some predictability regarding whether the targeted area's function is likely to be enhanced or suppressed. Given that human TUS sample sizes are exponentially increasing, we recognize that results can stabilize or change as further studies are reported. Therefore, we conclude by establishing an Iowa-Newcastle (inTUS) resource for the systematic reporting of TUS parameters and outcomes to support further hypothesis testing for greater precision in brain stimulation and neuromodulation with TUS.

Keywords: Non-invasive brain stimulation, focal ultrasound stimulation, low intensity, neuromodulation, excitation, inhibition, suppression, clinical application

Highlights:

- Systematic review of human TUS studies for enhancing or suppressing neural function
- Collated set of hypotheses on using TUS to bias towards enhancement or suppression
- Meta-analysis results identify parameters that may bias the directionality of effects
- TUS resource established for systematic reporting of TUS parameters and outcomes

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INTRODUCTION

In the last decade, low-intensity focused Transcranial Ultrasound Stimulation (TUS) has emerged as a promising non-invasive brain stimulation technique for neuromodulation in research and clinical settings. TUS uses sound waves—in the 100 to 1,000 kHz range—that pass through the skull to deliver focal acoustic energy onto a targeted brain area. Compared to other more established non-invasive brain stimulation techniques, such as Transcranial Magnetic Stimulation (TMS), transcranial Direct Current Stimulation (tDCS) or transcranial Alternating Current Stimulation (tACS), TUS offers several advantages: i) focal deep brain targeting (Fig. 1); ii) multi-target, including bi-hemispheric, stimulation capabilities; and, iii) neuromodulatory effects that can last tens of milliseconds to hours after the sonication period has ended (Blackmore et al., 2023; Deffieux et al., 2015; Deffieux et al., 2013; Legon et al., 2014; Mueller et al., 2014). The neural effects of TUS depend on factors including the intensity and duration of the acoustic wave. In this review, we primarily focus on *low-intensity* TUS as used for neuromodulation (typically <50 W/cm^2) (Food & Drug Administration, 2019; Lee et al., 2021), with some consideration of *moderate-intensity applications* (>190 W/cm^2) used for perturbing the blood-brain barrier (Kim et al., 2021; Spivak et al., 2022; T. Zhang et al., 2021) and *high-intensity focused ultrasound* (up to 10,000 W/cm^2) used for clinical thermal ablation in neurosurgery patients (Zhou, 2011). The duration of TUS effects is another factor, with immediate effects during TUS stimulation referred to as "online" effects and those that can last after TUS stimulation referred to as "offline" effects.

Ultrasound for clinical imaging or thermal ablation has a long history. However, low-intensity ultrasound for neuromodulation remains a relatively nascent approach for non-invasive brain stimulation. Therefore, much remains to be understood about the mechanisms of TUS neuromodulation. Yet, considerable research progress has been made with TUS in humans, nonhuman animal models and with computational modeling, narrowing the range of possible mechanistic hypotheses.

Candidate mechanisms for TUS neuromodulation. Low intensity TUS in animal models has been shown to interact with neural tissue via mechanical effects. The sonication wave either directly changes the permeability of ion channels within neuronal membranes, such as voltage-gated sodium, calcium and potassium channels (e.g., K2P, TRP and Piezo1), or it temporary mechanically alters the cell membrane properties. Several mechanisms have been proposed including changes in membrane turgidity, in the dynamics of lipid microdomains or in the formation of microbubbles within the lipid bilayer (Anishkin et al., 2014; Babakhanian et al., 2018; Petersen et al., 2016; Suki et al., 2020; Tyler, 2011). TUS also impacts on the coupling between neurons and glial cells (Oh et al., 2019). The combination of TUS mechanical effects leads to an increase in action potentials by excitatory and inhibitory neurons (Tyler, 2011; Yoo et al., 2022). TUS has been shown to be capable of inducing muscle contraction and limb or tail flicking when rodent motor cortex is stimulated with low to moderate intensities (Kim et al., 2020; Lee et al., 2018; Tufail et al., 2010). However similar motor responses have yet to be observed and reported in human and non-human primates (Darmani et al., 2022).

At the lower intensities for neuromodulation, TUS can influence neural tissue without causing substantial damage, heating or adverse effects, as reported in human and non-human primates (Gaur et al., 2020; Spivak et al., 2021; Verhagen et al., 2019). However, care should be taken with more continuous stimulation protocols where the continuity of stimulation (duty cycle; see Box 1) is high (Roumazeilles et al., 2021; Verhagen et al., 2019). Overall, TUS does not appear to cause significant heating or cavitation to brain tissue when the time averaged intensity (ISPTA, see Box 1) remains below 14 W/cm2. Temperature changes for low-intensity TUS are commonly <1°C (Baek et al., 2017; Yoo et al., 2011), and thermal effects can alter cell membrane capacitance during "online" TUS. However, thermal effects are unlikely to play a considerable role for longer-lasting "offline" TUS effects (Ozenne et al., 2020; Verhagen et al., 2019). The mechanism of action for the longer-lasting offline effects is not yet well understood. Because these effects

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last tens of minutes, or in some case hours, after the sonication period (Bault et al., 2023; Pasquinelli et al., 2019), they likely engage neuroplasticity mechanisms, such as modulation of AMPA and NMDA glutamatergic receptors and/or post-synaptic Ca^{2+} mediated changes to receptor properties. Interestingly, TUS effects on neuronal NMDA receptors appears to be indirect via, for instance, TUS modulation of astrocytes that can then influence neuronal plasticity (Blackmore et al., 2023). TUS pulsed at a theta (4-8 Hz) rhythm (theta-burst TUS; tb-TUS) is being studied for its capability to induce LTP-like plasticity (Oghli et al 2023, Samuel et al. 2022, Samuel et al. 2023, Zeng et al. 2022), which we consider as part of 'offline' stimulation protocols in section II or this review paper. Of importance for future clinical applications, the repeated use of TUS sessions does not appear to negatively impact on the integrity of brain tissue as assessed by MRI (Munoz et al., 2022).

Directionality of TUS neuromodulation. There is substantial interest in understanding the conditions under which TUS could be used to bias the directionality of neuromodulatory effects on the targeted brain area and its network or on behavior (Blackmore et al., 2023; Mihran et al., 1990; Tsui et al., 2005; Zhang et al., 2023). To describe the directionality of effects we use the terms enhancement versus suppression throughout, reserving the terms excitation and inhibition for reports where it was possible to directly record from identified excitatory and inhibitory neurons with animal models.

Recordings from identified excitatory and inhibitory neurons during TUS with animal models provide clearer mechanistic insights because the neuronal recordings can also be combined with causal manipulation, such as blocking specific ion channels. For instance, recent studies with murine models have reported that short sonication durations (<1 sec) can lead to net excitation (attributed to more action potentials for excitatory neurons during TUS), whereas longer sonication durations (> 1 sec) can lead to net suppression (i.e., more strongly driving inhibitory neurons) (Mihran et al., 1990; Tsui et al., 2005). Other TUS studies have suggested that higher sonication Pulse Repetition Frequencies (PRF >100 Hz) can lead to net excitation (Manuel et al., 2020; Zhang et al., 2023).

The caveat is that many nonhuman animal studies are conducted under anesthesia, which can alter the balance of excitatory-inhibitory neuronal activity. By comparison, although human TUS studies are often conducted without anesthesia, access to single units (neurons) is only possible with specialist FDA or ethical board approved electrodes for clinical monitoring in neurosurgery patients. There is currently a paucity of direct neuronal recording studies in humans during TUS.

Nonetheless, similar challenges in identifying the directionality of effects on neurons and neuronal networks have been a focus of research using other non-invasive brain stimulation approaches, including TMS (Fitzgerald et al., 2006). TMS researchers now regularly apply higher duty cycles to tip the directionality of TMS neuromodulatory effects on cortical areas towards net excitation (i.e., potentiation). By contrast, low-duty cycle TMS pulses are associated with net inhibition (i.e., de-potentiation or suppression) of muscle potentials or motor cortical responses (Solomon et al., 2024). Therefore, although the effects of TMS and TUS on neurons and neural systems differ, there appears to be some correspondence in the stimulation parameter space that may result in net excitation or suppression of function.

Research into TUS mechanisms and effects is both informing and being guided by computational modeling, which allows the more thorough systematic exploration of TUS stimulation parameters in ways difficult to achieve with empirical study alone. In a computational *Neuronal Intramembrane Cavitation Excitation* (NICE) model developed to study activation and suppression effects on modeled excitatory and inhibitory neuronal populations, TUS effects were simulated as intramembrane cavitation causing changes in ion channel conductivity (Plaksin et al., 2016). The NICE model explored a broad set of TUS parameters, including TUS intensity and the continuity of stimulation (duty cycle). Box 1 summarizes the common TUS parameters and their measuring units. Key parameters are the average acoustic intensity (intensity spatial

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peak pulse average, ISPPA), temporally averaged intensity (ISPTA), sonication duration (SD), duty cycle (DC), pulse repetition frequency (PRF), thermal index (TI) and mechanical index (MI). Box 2 shows guidelines on the ultrasound parameter limits that human low-intensity TUS studies typically follow. The NICE model was initially evaluated with a more limited set of the then available data from human and nonhuman animal studies, and the model showed a high level of predictability. For instance, increases in intensity (ISPPA, Box 1) and duty cycle can tip the balance from suppression to activation in the modelled populations of excitatory and inhibitory neurons (Plaksin et al., 2016). Several reviews have now conducted similar case-by-case or ad-hoc comparisons of TUS parameters with the NICE model predictions, with mixed support for or against the NICE model (Ai et al., 2018; Dell'Italia et al., 2022; Forster et al., 2023b; Zhang et al., 2023). In Box 3, we collate a set of net enhancement versus suppression hypotheses linked to TUS parameters that may be able to bias the directionality of effects.

The uncertainty about the extent to which TUS can be used to enhance or suppress neurobiological function limits its research potential (Chen et al., 1997; Fitzgerald et al., 2006). Rather than exploring the TUS parameter space, many researchers opt to emulate the TUS parameters of prior studies reporting specific positive findings, limiting the necessary exploration of the entire parameter space for a nascent field. We recognize the complexity of neural circuits and systems and the limitations in aiming to evaluate predictions with a relative paucity of data in humans. However, we also recognize that stepwise progress and evaluation are needed as sign-posts in this research endeavor, not unique to TUS or other brain perturbation approaches with longer histories of use (e.g., invasive deep-brain electrical stimulation, TMS, tACS, tDCS; Fig. 1) (Derosiere et al., 2020; Klink et al., 2021). Therefore, since there are now over 30 human TUS studies (by January 1st, 2024; Figure 3), to us the time seems ripe for a research sign-post and an open resource that can accommodate growth in the field. For instance, there are now a range of reported behavioral and neurobiological outcomes with human TUS, ranging from eliciting somatosensory sensations with TUS applied to the somatosensory cortex, the enhancement or suppression of the threshold for motor-evoked potentials (MEPs) with TUS applied to motor cortex (including in combination with TMS), the perception of visual phosphenes or modulation of visual motion perception from TUS applied to the visual cortex, and mood improvement induced by TUS to the prefrontal cortex (these and others are summarized in Tables 1-3). With these human low-intensity TUS data accumulating, a more extensive review and meta-analysis than previously possible can now be conducted, which will be a step towards the next evaluation period when the samples sizes further grow.

Our key objectives with this review are twofold. In the first part, we summarize the current state of the literature on human TUS applications for perturbing the brain and as a possible treatment of neurological and psychiatric disorders. This literature review identifies epistemic gaps in our understanding of how TUS could be better applied to patients and whether TUS can be better used to enhance or suppress function. In the second part, we evaluate the collated set of net enhancement versus suppression hypotheses (Box 3) and conduct an initial meta-analysis of the available human low-intensity TUS reports. We conclude by establishing an Iowa-Newcastle (inTUS) resource and tools for using TUS, to encourage TUS researchers to more systematically explore and report on the broader TUS parameter space and outcomes. These are in line with the International Transcranial Ultrasonic Stimulation Safety and Standards (ITRUSST) consortium that has proposed standards to enable comparison and reproducibility across studies (Martin et al., 2024).

Part I. TUS applications review

Compared to pharmaceutical drugs that can affect many parts of the brain and body, TUS allows the stimulation of specific targets within the brain with relatively high spatial precision. Here, we review potential applications for low-intensity TUS that are currently investigational or could be based on related developments using other approaches (e.g., TMS). We also, albeit more selectively, consider moderate-

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intensity applications for Blood Brain Barrier (BBB) perturbation and high-intensity TUS for clinical thermal ablation. While the primary goal of BBB opening is to regionally increase the permeability of BBB to enhance the efficacy of brain drug delivery, BBB opening alone could induce neuromodulatory effects (Chu et al., 2015).

Ia. Low-intensity TUS applications

Motor and somatosensory system mapping. Intraoperative clinical motor and somatosensory cortical mapping is important for planning neurosurgical treatment. TMS over the motor cortex is regularly used to induce muscle contractions and limb movements. The effect of TMS on the amplitude of muscle-evoked potentials is an accepted measure of motor cortical enhancement (increased motor-cortical evoked EEG potentials) or suppression (decreased MEPs) (Fitzgerald et al., 2006). In preclinical research, low-intensity (or moderate-intensity) TUS focused on motor cortex in rodents can induce muscle contractions (King et al., 2014; Tufail et al., 2010; Yoo et al., 2011; Younan et al., 2013), including limb, tail, whisker or eye muscle contraction (King et al., 2014). TUS in humans targeting the motor cortex has been reported to either enhance or suppress MEPs (Table 1) (Gibson et al., 2018; Lee et al., 2016a; Legon, Bansal, et al., 2018; Samuel et al., 2022; Xia et al., 2021; Zeng et al., 2022; Y. Zhang et al., 2021). Stimulation of the primary motor cortex with TUS has been found to decrease reaction times in a stimulus-response task, interpreted as enhanced motor performance (Fomenko et al., 2020; Legon, Bansal, et al., 2018; Zhang et al., 2022; Y. Zhang et al., 2021).

For mapping of human somatosensory cortex, TUS has been reported to either enhance or suppress somatosensory evoked potentials (SEPs) recorded with EEG, and TUS can elicit a range of somatosensory perceptions, such as tactile sensations in the hand contralateral to the stimulated somatosensory cortex (Lee et al., 2015; Legon et al., 2014). Legon *et al.* demonstrated impaired performance in a tactile spatial discrimination task from TUS stimulation of the ventro-posterior lateral nucleus of the thalamus (Legon, Ai, et al., 2018). This was reflected in the disruption of the corresponding SEP component (Legon, Ai, et al., 2018). Dallapiazza *et al.* (Dallapiazza et al., 2017) targeting the swine sensory thalamus. These pre-clinical studies with animal models and humans demonstrate the feasibility of using TUS to modulate the somatosensory system safely and to map superficial and deep brain structures noninvasively in patients using TUS. For clinical motor or somatosensory cortical mapping, TUS would need to be used to induce motor behavior or somatosensory percepts by stimulating motor/somatosensory sites, or to suppress ongoing motor functions (hand squeeze, arm drop).

Speech and language mapping. Intra-operative brain mapping using electrical stimulation is used by neurosurgeons to identify brain areas crucial for speech and language (Benzagmout et al., 2007; Chang et al., 2015; Duffau, 2010; Mandonnet et al., 2017; Mathias et al., 2016). The gold-standard approach identifies speech and language areas using electrical stimulation to elicit speech arrest, naming or other language difficulties (Duffau, 2010; Mathias et al., 2016). However, because of the limited time in the operating room for patient brain mapping, there is considerable interest in developing pre-operative non-invasive brain stimulation (NIBS) approaches for speech and language brain mapping. For instance, TMS, when used with MRI-based neuro-navigation to target neocortical speech and language regions, can lead to speech arrest or anomia, which generally corresponds to the locale of intra-operative mapping using electrical stimulation (Tarapore et al., 2013). Furthermore, TMS is often integrated with adjunctive methodologies such as electroencephalography (EEG), functional magnetic resonance imaging (fMRI), or diffusion tensor imaging (DTI) to bolster the precision and specificity of brain-behavioral mapping. To date there do not appear to be TUS studies focused on speech and language mapping, defining a clear research need. For this clinical application, TUS would need to temporarily suppress brain areas important for speech production and language function, analogous to the current use of electrical stimulation for intra-operative mapping of neocortical areas involved in these processes.

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Mood disorders. TUS has been explored as a possible treatment for psychiatric mood disorders. In a study from 2013, in humans with chronic pain, TUS administered to the posterior frontal cortex contralateral to the source of pain elicited a significant mood enhancement after 40 minutes (Hameroff et al., 2013). Sanguinetti *et al.* reported that TUS targeting the right ventrolateral prefrontal cortex led to reports of improved mood in healthy individuals after TUS (Sanguinetti et al., 2020). In a double-blind pilot study, Reznik and colleagues applied TUS to the right fronto-temporal cortex of depressed patients, resulting in mood improvement (Reznik et al., 2020; Shimokawa et al., 2022). Forster *et al.* used TUS to indirectly manipulate cingulate cortex activity in a learned helplessness task, demonstrating the potential to affect the response to acute stressors that can induce symptoms of depression (Forster et al., 2023). Further pre-clinical and clinical trial studies would be necessary to evaluate TUS efficacy in alleviating or even alleviating mood disorder symptoms. With such applications, TUS could be used to target highly-interconnected brain network hubs associated with depression risk or resilience to modulate function (Trapp et al., 2023). The 'dose' and longevity of TUS effects would need to be systematically explored.

Schizophrenia. Early pilot results for patients suffering from psychosis are now available. In a double-blind, randomized, sham-controlled study, 15 sessions of TUS over the left dorsolateral prefrontal cortex (DLPFC) could alleviate negative symptoms in schizophrenia patients and enhance cognitive performance in a continuous performance test (Zhai et al., 2023). TUS was well tolerated with patients in the active group not reporting more adverse effects than patients in the sham group. The use of TUS seems particularly promising due to the involvement of deep-brain structures, such as the thalamus in this condition (Mukherjee & Halassa, 2024). For TUS application to schizophrenia, TUS could be used to suppress the function of areas reducing the positive or negative symptoms associated with schizophrenia.

Disorders of Consciousness. Low-intensity TUS has shown the capability to hasten the recovery of behavioral responsiveness in patients with disorders of consciousness (Lee et al., 2016a). Monti and colleagues documented a case where low-intensity TUS aimed at the thalamus was associated with the emergence from a minimally conscious state in patients experiencing disorders of consciousness following severe brain injury (Monti et al., 2016). For this clinical application, TUS would need to enhance the function of thalamic nuclei and interconnectivity with other brain areas, such as the centro-median-perifascicular nuclei of the thalamus and the mesencephalic reticular formation (Chudy et al., 2023). However, a more permanent approach, such as electrical deep brain stimulation (DBS), may be required in some patients or a combination of TUS 'mapping' followed by DBS.

Alzheimer's disease. Cognitive decline associated with dementia would benefit from approaches that can enhance cognitive function. In a study with 11 Alzheimer's disease (AD) patients using transcranial pulse stimulation (TPS; typically shorter pulses of low-intensity ultrasound stimulation over a longer period of time) targeting the hippocampus, the authors reported that 63% of patients improved on one or more cognitive assessments (Nicodemus et al., 2019). In another study involving 35 AD patients, shock waves were applied to the dorsolateral prefrontal cortex (Beisteiner et al., 2020). The patients' neuropsychological scores significantly improved after TPS, and these improvements were reported to have persisted for up to three months. Overall, these results demonstrate not only the capability of TUS for pre-operative cognitive mapping but also the potential of TPS to be further researched to enhance cognitive function.

Parkinson's disease. In a study by Nicodemus *et al.* involving 11 patients undergoing TUS application for Parkinson's Disease (PD) targeting the substantia nigra, it was reported that 87% of the patients had either stable or improved fine motor scores and 88% had stable or improved gross motor scores (Nicodemus et al., 2019). Samuel *et al.* used a technique called accelerated theta-burst TUS targeting the primary motor cortex in 10 PD patients, studying its impact on neurophysiological and clinical outcomes (Samuel et al., 2023). Their patients received both active and sham TUS conditions, and the authors measured TMS-elicited motor-evoked potentials (MEPs) before and after treatment. The study found a significant increase

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in TMS induced MEP amplitudes following TUS but not sham treatment. For non-invasive brain stimulation clinical applications related to PD, TUS of the subthalamic nucleus would need to suppress its function in a lasting way and with the precision to target the motor segment of the nucleus, rather than its limbic or sensory segments.

Epilepsy. TUS application to an epileptogenic site has the potential to modulate seizure frequency. To evaluate these possibilities, Lee et al. applied low-intensity TUS to individuals dealing with drug-refractory epilepsy undergoing intracranial electrode monitoring with stereo-electroencephalography (SEEG) (Lee et al., 2022). Two of the six patients studied showed a decrease in seizure occurrences, while one experienced an increase. The TUS effects reported were close to electrode contacts positioned close to the subsequent neurosurgical treatment site for epilepsy. Across all frequency bands in the local-field potential recorded from the SEEG electrodes, there was a notable decrease in spectral power for all six patients following TUS. However, there was no clear relationship between these immediate effects on interictal epileptiform discharges and alterations in seizure frequency (Lee et al., 2022). Another study introduced a device for delivering pulsed low-intensity TUS to the hippocampus in humans, with no reported adverse events after multiple sessions (Brinker et al., 2020). A recently published pilot study by Bubrick et al. described the application of serial TUS in patients with mesial temporal lobe epilepsy. TUS was delivered in 6 sessions over 3 weeks. No adverse events or side effects were reported. Early results were promising with significant seizure reduction in 5 out of 6 patients, observed up to 6 months after TUS application (Bubrick et al., 2024). For epilepsy treatment TUS should aim to reduce the probability of seizures, but for clinical mapping of epileptogenic sites TUS eliciting epileptiform activity could be a useful clinical mapping tool during epilepsy monitoring procedures.

Sudden unexpected death in epilepsy. Sudden unexpected death in epilepsy (SUDEP) refers to the sudden unexpected death of a person with epilepsy that cannot be explained by trauma, drowning, or status epilepticus. On post-mortem examination, no structural or toxicological cause of death can be ascertained. SUDEP is one of the leading causes of premature deaths in epilepsy, accounting for more than a 20-fold increase in the risk of sudden death in epileptic patients compared with the general population (Ficker et al., 1998; Kløvgaard et al., 2022). Among all neurological conditions, it ranks second after stroke in terms of years of potential life lost (Thurman et al., 2014). Rare cases of SUDEP of patients in epilepsy monitory units have shown that cessation of breathing (apnea) following seizures precedes terminal asystole and death (Bateman et al., 2008; Nashef & Brown, 1996; Ryvlin et al., 2013). Animal models (Johnston et al., 1995) confirm a primary role of respiratory dysfunction in SUDEP. In the human patient work by Dlouhy and colleagues (Dlouhy et al., 2015; Harmata et al., 2023; Rhone et al., 2020), it was shown that when a circumscribed site in the amygdala, referred to as the Amygdala Inhibition of Respiration (AIR) site, is affected either by the spread of seizure or by electrical stimulation, apnea occurs without the patient feeling any air hunger or alarm (Lacuey et al., 2017; Nobis et al., 2019). In a subsequent study by Harmata et al., 2023, electrical stimulation or stimulation evoked seizure within a focal region of the AIR site evoked apnea that persisted well beyond the end of stimulation or seizure. Because this site in the amygdala caused persistent inhibition of respiration, the authors referred to this site as the pAIR site. The AIR site, therefore, is posited as a brain region that mediates seizure-induced inhibition of breathing which can persist for minutes and may lead to SUDEP.

Localization and characterization of the AIR site and pAIR site have so far been done using electrical stimulation in patients who have electrodes implanted for potential surgical remediation of epilepsy. This puts a severe constraint in that only a limited population of individuals with epilepsy who are candidates for electrode implantation have contributed to the characterization of the sites. Extension to a larger population of epileptic patients without amygdala implantation and non-epileptic patient controls require the use of non-invasive methods. Given the deep subcortical location of the AIR and pAIR sites, approaches such as TMS are less suitable for this purpose. Because TUS has the capability to target deep

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areas with higher spatial resolution, it can be used to target not only the AIR sites in the amygdala and the respiratory network underlying SUDEP. TUS would likely need to suppress amygdala function to prevent apnea. Although there is a pressing research need, we could not find studies, in epilepsy patients or other cohorts, reporting TUS effects either that evoked apnea or stimulated breathing. Rather than controlling SUDEP risk during epileptic seizures, if TUS cannot be implemented continuously, its utility may be better suited to identify people at very high risk based on seizure-associated apnea, following by using TUS to attempt to modulate the AIR site to confirm its location for subsequent neurosurgical ablation to reduce epilepsy patient SUDEP risk.

Stroke and neuroprotection in brain injury. Low-intensity TUS has been studied for its potential neuroprotective benefits following brain injury (Bretsztajn & Gedroyc, 2018; Schellinger et al., 2015). Brief application of TUS appears to boost the density of brain-derived neurotrophic factor (BDNF) in the hippocampus, suggesting that TUS may enhance neuroplasticity (Tufail et al., 2010). Furthermore, TUS has the ability to elevate BDNF and vascular endothelial growth factor (VEGF) expression in astrocytes while also appearing to prevent cell apoptosis (Su et al., 2017; Yang et al., 2015). Chen *et al.* treated mice with TUS before inducing cerebral ischemia and reported increased BDNF expression, improved neurological function and decreased neuronal cell apoptosis (Chen et al., 2018).

In a randomized controlled trial, Wang *et al.* investigated the effects of TUS combined with cognitive rehabilitation on post-stroke cognitive impairment (Wang et al., 2022). The research involved 60 patients randomly divided into observation and control groups, with the observation group receiving both TUS intervention and conventional cognitive rehabilitation. The observation group exhibited improvement in a range of cognitive measures compared to the control group, which only received conventional cognitive rehabilitation. Other authors have studied how low-intensity TUS can affect outcomes from recurrent stroke in mice. Wu *et al.* reported that continuous TUS treatment before secondary stroke lessened neuronal damage and increased BDNF expression (Wu et al., 2019). This type of work suggests that TUS could be a potential preventive therapy for recurrent stroke, presuming it can be delivered continuously as needed. In another study, TUS was reported to enhance neurological recovery post-stroke in mice by promoting angio-neurogenesis (Ichijo et al., 2021). In related studies of TUS applied to the body rather than the brain, TUS was reported to be capable of boosting vasculogenesis by facilitating the formation of vascular networks in human umbilical vein endothelial-cell cultures (Imashiro et al., 2021). Hanawa *et al.* introduced TUS as a potential non-invasive therapy for ischemic heart disease. They found that TUS treatment significantly improved left ventricular function and increased capillary density in a porcine model of chronic myocardial ischemia (Hanawa et al., 2014), highlighting the research need to evaluate whether similar effects can be replicated in the brain.

TUS has also been explored as a non-invasive thrombectomy tool to enhance thrombolysis with tissue plasminogen activator in acute stroke (Schellinger et al., 2015). For stroke thrombectomy, TUS would act to break up thrombocytes with or without a tissue plasminogen activator. An earlier study, by Liu *et al.*, indicated that administering TUS soon after a stroke could yield neuroprotective effects (Liu et al., 2019). Thus, there has been interest in evaluating whether initiating TUS promptly post-stroke could effectively enhance cerebral blood flow, revive local circulation, save the ischemic penumbra, and minimize brain tissue harm. A Phase II clinical trial showed low-intensity TUS could enhance the thrombolytic efficacy of tissue plasminogen activator. However, TUS appears to have also led to a higher incidence of a cerebral hemorrhage in patients concurrently treated with intravenous tPA (Daffertshofer et al., 2005). Another Phase II clinical trial conducted across four centers, reported that in individuals with acute ischemic stroke, TUS amplified tPA-induced arterial recanalization, showing only a non-significant trend toward an elevated rate of stroke rehabilitation when compared to the control group. The occurrence of symptomatic

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intracerebral hemorrhage was comparable between the active and control groups (Katsanos et al., 2020; Schellinger et al., 2015).

Hypertension and cardiovascular system effects. As a promising noninvasive therapy for drug-refractory hypertensive patients, Li and colleagues demonstrated the antihypertensive effects and protective impact on organ damage by using low-intensity TUS stimulation in spontaneously hypertensive rats (Li et al., 2023). The experiment involved daily 20-minute TUS stimulation sessions targeting the ventrolateral periaqueductal gray in the rats for two months. Their results showed a significant reduction in systolic blood pressure, reversal of left ventricular hypertrophy, and improved heart and kidney function. The sustained antihypertensive effect may be attributed to the activation of antihypertensive neural pathways and the inhibition of the renin-angiotensin system. Ji and colleagues explored the feasibility of using low-intensity TUS to modulate blood pressure in rabbits (Ji et al., 2020). The study used a TUS system to stimulate the left vagus nerve in rabbits while recording blood pressure in the right common carotid artery. Different TUS intensities were tested, showing a decrease in systolic and diastolic blood pressure, mean arterial pressure and heart rate (Ji et al., 2020). The higher the TUS intensity, the more significant the blood pressure reduction. These pre-clinical studies in animal models highlight the possibility of non-invasive, non-drug management of hypertension using TUS, opening avenues for treating clinical hypertension non-invasively. For this clinical application, TUS would need to suppress sympathetic nodes (e.g., rostral ventro-lateral medulla) or enhance parasympathetic nodes (e.g., medial prefrontal cortex) in the central autonomic network (Macefield & Henderson, 2020; Shoemaker, 2022).

Ib. Moderate intensity TUS applications

Enhancing pharmacological- and immuno-therapy through the blood-brain barrier. A significant challenge in drug- or immune-therapy is the limited effectiveness of drugs and vectors that do not easily traverse the blood-brain barrier (BBB) (Hynynen et al., 2006; Mehta et al., 2021), an issue that has been explored in the context of using antibodies to amyloid β to treat Alzheimer's disease. TUS has the ability to temporarily open the BBB, facilitating the entry of such vectors into the brain from the blood stream. Systemic injection of microbubbles when combined with TUS temporarily opens the BBB, with BBB integrity restored within 4–6 hours (Hynynen et al., 2006; Mehta et al., 2021). Lipsman and colleagues conducted a phase I safety trial, using TUS to safely and reversibly open the BBB in five patients diagnosed with early to moderate Alzheimer's disease (Lipsman et al., 2018). They achieved predictable BBB opening at approximately 50% of the power at which cavitation was observed during a test using the NeuroBlate system. Right after the ultrasound treatment, a distinct rectangular-shaped enhancement was visible in the targeted brain region on T1-weighted gadolinium MR images. This enhancement was resolved within 24 hours after the procedure, suggestive of successful closure of the BBB. The moderate intensity TUS did not lead to any significant clinical or radiographic adverse events, nor a noticeable decline in cognitive scores at the three-month follow-up when compared to baseline. Importantly, no serious adverse events, such as hemorrhages, swelling, or neurological deficits were reported either on the day of the procedure or during the follow-up study period. Rezai *et al.* employed TUS to breach the BBB in a study involving six AD patients (Rezai et al., 2020). Post-treatment contrast-enhanced MRI scans displayed rapid and significant enhancement in the hippocampus, which subsequently resolved. Throughout the several TUS treatments, no adverse effects were observed, and there was no cognitive or neurological function decline. In a study by Jeong *et al.* involving four AD patients, moderate-intensity TUS of the hippocampus did not exhibit evidence of actively opening the BBB, as observed in T1 dynamic contrast-enhanced MRI (Jeong et al., 2021; Jeong et al., 2022). However, the authors found that the regional cerebral metabolic rate of glucose (rCMRglu) in the superior frontal gyrus and middle cingulate gyrus significantly increased following TUS treatment. The patients also demonstrated mild improvement in measures of cognitive function, including memory, after TUS. Although BBB opening could lead to neuromodulatory effects, its effects at the network level are distinct from those achieved with TUS (Liu et al., 2023).

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Ic. High-intensity ultrasound for thermal ablation

Parkinson's disease. Moser et al. introduced high-intensity MR-guided TUS for thermal ablation as a potential treatment option for Parkinson's disease, employing it to target and ablate the connections between the thalamus and globus pallidus (Moser et al., 2013). Their approach improved the patients' Unified Parkinson's Disease Rating Scale (UPDRS) score by 57%. This therapeutic impact of high-intensity ultrasound was replicated by Magara *et al.* in 2014, who used MR-guided TUS to thermally ablate the unilateral pallidothalamic tract in PD patients, resulting in significant improvement in the UPDRS score three months post-surgery (Magara et al., 2014).

Essential tremor. TUS at higher intensities that cause tissue ablation has FDA-approved application for essential tremor following large, randomized clinical trials (Choi & Kim, 2019; Krishna et al., 2018). Precision TUS thermal ablation of subthalamic nuclei is increasingly considered as an alternative to deep brain stimulation for select patients (Rohani & Fasano, 2017). MR-guided focused ultrasound is being employed in treating essential tremor (ET) with the thalamic ViM nucleus as the primary target (Abe et al., 2020; W. S. Chang et al., 2015; Elias et al., 2013; Elias et al., 2016; Lipsman et al., 2013; Meng et al., 2018). This non-invasive thalamotomy technique has demonstrated therapeutic benefits for essential tremor patients and received FDA approval for unilateral treatment (Elias et al., 2016). The reported side effects of thermal ablation with high-intensity TUS include early symptoms of dizziness, nausea/vomiting, headache, skull overheating, flushing, and late symptoms such as ataxia and paresthesias (Abe et al., 2020; W. S. Chang et al., 2015; Elias et al., 2013; Elias et al., 2016; Lipsman et al., 2013; Meng et al., 2018). Further research is necessary to better establish TUS approaches for thermal ablation in ET patient therapy.

Epilepsy. In a recent case report, MR-guided high-intensity TUS was found to be effective in a patient with medically intractable epilepsy, resulting in 12 months of seizure freedom (Abe et al., 2020). For a more extensive review of TUS for thermal ablation in epilepsy patients, see (Cornelssen et al., 2023).

Part II. Net enhancement and suppression hypotheses and meta-analysis

In this section, we consider the rationale for the hypotheses regarding the directionality of TUS effects (Box 3), overview the approach for the meta-analysis and discuss the initial results obtained. We conclude by establishing an Iowa-Newcastle (inTUS) community resource for TUS parameter and outcome reporting to encourage further hypothesis development and testing.

Net enhancement and suppression hypotheses. The hypotheses summarized in Box 3 are based on TUS parameters that have been highlighted by the TUS literature may be able to bias effects towards enhancement or suppression. These hypotheses were generated from the NICE model (Plaksin et al., 2016; Plaksin et al., 2014) and preclinical studies with animal model of TUS effects reported to result in greater excitation or inhibition using direct recordings of excitatory and inhibitory neurons. The NICE model hypothesized that key parameters associated with net activation or suppression (using the authors' terminology) are sonication intensity in the target brain area (ISSPA in brain) and the continuity of stimulation (duty cycle, DC). The NICE model predictions are shown in Figure 4 with a light blue line defining the border between enhancement (higher DC and intensity) and suppression (lower DC and intensity) resulting from the NICE modeling. In this regard ISPTA, which mathematically integrates ISSPA by the sonication DC, can be considered the TUS "dose". Other parameters of interest are the length of the

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sonication pulse (Sonication Duration, SD) with shorter SDs (<500 ms) tending to elicit more action potentials from excitatory neurons, and longer SDs (>500 ms) tending to bias towards suppression via greater excitation of *inhibitory* neurons (Mihran et al., 1990; Tsui et al., 2005). Other studies have suggested that pulse-repetition frequency (PRF), the frequency with which the ultrasound pulse is turned on/off can bias towards greater net excitation or suppression (Kim et al., 2023; Yu et al., 2020).

Segregating online versus longer lasting 'offline' effects. Studies of online or offline effects tend to use different TUS parameters (compare Tables 1 and 2). Offline effects of TUS stimulation are induced for longer time periods of time (seconds or minutes) by keeping the intensity of stimulation within FDA guidelines. Therefore, for offline studies, DC and ISPTA values are often kept low (Box 2). For this reason, we summarize the online and offline studies in separate tables (Tables 1-2) and include this distinction as a factor in the meta-analyses.

Meta-analysis inclusion criteria and analysis approach.

This review follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We searched PubMed/MEDLINE (www.ncbi.nlm.nih. gov/pubmed), Web of Science (https://www.webofscience.com), and Scopus (https://www.scopus.com) databases.

We searched these databases for studies published through 1st January 2024 by employing the combination of the following keywords and terms: 'human', 'ultrasound', 'focused', 'low-intensity', 'stimulation', 'transcranial', 'neuromodulation', 'TUS', 'FUN', 'LIFUS' 'clinical', 'treatment'. We searched only for articles published in English. The included studies encompassing both healthy individuals and patients with various medical conditions. Four authors (HC, NS, CP and MZ) searched for and curated the included studies to ensure that the survey was as comprehensive as possible. The PRISMA recommended search process is shown in Fig. 3. Eligibility criteria for the meta-analysis focused on human studies involving low-intensity TUS for brain stimulation or neuromodulation applied. Of this total, only 32 were included in the meta-analysis. For the meta-analysis we only included studies that either reported a basic set of TUS stimulation parameters or those sufficient for estimating the required parameters necessary for the meta-analysis. For this reason, we had to exclude 4 diagnostic ultrasound studies (Gibson et al., 2018; Guerra et al., 2021; Hameroff et al., 2013; Schimek et al., 2020), which did not report the parameters we needed for the meta-analysis. These studies used an ultrasound imaging system, and therefore could not carefully control the continuity or intensity of the ultrasound system. We excluded studies with moderate-intensity or high-intensity ultrasound used for, respectively, BBB perturbation or thermal ablation.

The reported studies' TUS parameters and reported effects were used to populate the data tables (Table 1 for online studies and Table 2 for offline studies). Most parameters required for the analysis could be found in the reported studies, or could be calculated from the parameters given. If a given study conducted multiple complete experiments, the sample sizes reflect the overall number of experiments rather than the number of studies/papers, and if separate experiments tested different values of a given parameter with the same result or reported directionality, the experiment eliciting the strongest effect was input into the meta-analysis. A number of experiments (n = 14 out of 37), although reporting ISPPA values in water, did not report ISSPA values in the brain required for our analyses, a recognized problem for this field (Martin et al., 2024). For these studies, we applied an accepted approximation of ISPPA values as the sonic wave passes through and loses much of its energy at the skull, whereby typically 70-75% of the intensity is lost (Lee et al., 2015; Oghli et al., 2023). We compared these approximations to simulations using k-plan software (Jaros et al., 2020; Treeby & Cox, 2010), targeting the same regions as in the reported experiments

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with the reported ISPPA in water. Comparing the two values (k-plan simulations versus the approximated derated values) showed a low margin of error of 5% between the two sets of values in the comparisons, therefore we used the approximated values for studies not reporting ISPA in the brain.

Probable net enhancement versus suppression was characterized as follows. Although many studies have reported behavioral influences, these alone are often not sufficient to determine neurobiological effects, for the following reason. Although many studies may use sham control (e.g., no TUS), it is difficult to rule out other sources for placebo effects in the behavioral reports. We thereby focused on the studies reporting neurobiological effects and characterized these effects as probable net enhancement versus suppression, using the following approach. For net enhancement, we followed the prior approach from the TMS field whereby EEG-evoked responses that are magnified in the target area as a function of TUS application can be characterized as probable enhancement (see Tables 1-2). We included positive fMRI BOLD effects resulting from TUS as a probable enhancement. For suppression, we also followed the prior approach from the TMS field whereby EEG evoked responses that were reduced indicate likely suppression. Wherever possible, we relied on independently characterized directionality of effects, and cite the original sources that conducted the characterization in Tables 1 and 2. As an example of a study categorized as 'suppression' of function, Legon et al. (2014) examined TUS combined with EEG to modulate the primary somatosensory cortex (S1) in healthy human subjects. The authors reported that TUS significantly attenuated somatosensory evoked potentials. The effects were specific to the targeted region, because the changes were abolished when the acoustic beam was focused away from S1. As another example, another group that applied TUS to S1 of participants performing a sensory discrimination task reported augmented somatosensory spatiotemporal EEG responses, interpreted as increased local excitability or 'enhancement' by our terminology (Liu et al., 2021).

The resulting data tables were submitted to a logistic regression model for testing with R Studio. The R script used to generate the results from the data tables is shared as part of the resource developed in the paper, see below. The first statistical model tested the NICE model predictions regarding ISPPA, Duty Cycle and their interaction (logit ~ OfflineOnline + DC + Isspa + DC * Isppa). The sample sizes were 37 experimental observations, 35 error degrees of freedom. We also tested models including only ISPTA (as the TUS 'dose' integrating the two parameters: ISPPA and DC), PRF or SD from the hypotheses. A single model with all factors and all interactions would have been preferred but with these sample sizes does not have sufficient degrees of freedom for evaluating so many factors and multi-level interactions in the same model. This can be revisited in the future when sample sizes increase through the inTUS resource.

Human TUS meta-analysis results. The meta-analysis used the data in Tables 1 and 2. The tables summarize the range of TUS parameters of interest for the studies reporting probable enhancement or suppression of TUS effects, with the rationale for characterization of the directionality of TUS effects, independently evaluated wherever possible as cited in Tables 1-2 rightmost column. These are further separated by studies aiming to elicit online (Table 1) or offline effects (Table 2).

We first tested the NICE model predictions of TUS intensity (ISPPA in the brain) and DC. The logistic regression with ISPPA in the brain, DC, and online/offline studies as factors were significantly different from a constant model ($X^2 = 11.7$, $p = 0.020$). The statistical model showed a significant effect for DC ($p = 0.046$), no significant effect for ISSPA ($p = 0.256$) and a statistical trend for a difference in the Online and Offline study parameters used ($p = 0.061$)—as might be expected given the different parameters that are often used for online and offline studies. The interaction of DC and ISPPA in the brain was not significant ($p = 0.504$). The DC effect can be seen in Figure 4 as a greater than 0.6 likelihood for higher

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DCs to be associated with enhancement. Lower duty cycles are more mixed and intensity does not seem to be a strong explanatory factor or in interaction with DC. Lower DCs are more equally likely to lead to enhancement or suppression. The other parameters of interest were not significant predictors with these datasets for pulse repetition frequency (PRF: $p = 0.324$) or ISPTA ($p = 0.787$). However, sonication duration was a significant predictor in the hypothesized direction (SD: $p = 0.04$), see Fig. 5.

Given the still limited sample size of human TUS studies to date, we interpret these meta-analysis results with caution. A key observation is that the NICE model is not as strongly predictive as initially evaluated (Dell'Italia et al., 2022; Zhang et al., 2023). Nonetheless, DC, in particular, may indeed be able to tip the balance towards greater net enhancement for DC > 20% (Fig. 4A-C) or suppression for DC < 20%. The area of suppression (low duty cycles across the range of intensities) can, by these results, equally often result in enhancement as suppression. Other parameters of interest are sonication duration (Thurman et al., 2014), which has been highlighted in animal model recordings from excitatory and inhibitory neurons to result in greater excitatory neuron activity at lower SDs (< 500 ms) or suppression with higher sonication durations (> 500 ms) (Mihran et al., 1990; Tsui et al., 2005). The other takeaway point from the meta-analysis is that many researchers are opting for lower DCs, presumably to ensure ISPTA values are not far off the FDA threshold, associated in our results with suppression, highlighting a clear need for more systematic exploration and computational modeling of the entire TUS parameter space.

Theta Burst TUS for lasting neuromodulation: Theta-burst TUS (tb-TUS) is being studied for its capability to induce cortical LTP-like plasticity (Oghli et al 2023, Samuel et al. 2022, Samuel et al. 2023, Zeng et al. 2022), which are identified in Table 2. For instance, tb-TUS consists of more continuous (than typical online) stimulation, such as 80-second trains of 20-millisecond sonication pulses spaced over 200 milliseconds pulsed at a 4-8 Hz theta rhythm. These studies were too few to consider separately and were included in the 'offline' studies for the meta-analysis (Table 2). As the number of tb-TUS studies grows, it may be important to evaluate tb-TUS outcomes separately to other stimulation protocols.

Meta-analysis limitations. A key limitation of this meta-analysis is the relatively small sample size. Non-categorical, data-driven or multi-variate analyses of these data are not currently possible, which would be possible with greater sample sizes. Another limitation is the inherent selection bias of retrospective studies, whereby researchers may limit their exploration of the TUS parameter space based on studies with positive findings and/or those targeting similar behaviors and brain areas. Also, we and others have noted that few TUS researchers, as a rule, share the full set of key parameters necessary for meta-analysis and secondary hypothesis testing, even though the ITRUSST community has devised a list of parameters that all TUS studies should aim to report (Martin et al., 2024). Thus, we had to simulate the derated ISPTA values in the brain, warranting caution when interpreting these results. Therefore, these results need to be considered as tentative and possible to stabilize or change with larger sample sizes. We report them here primarily to encourage more systematic exploration and reporting of the TUS parameter space, complemented with computational modeling to fill in the gaps in the empirical research. The meta-analysis, thus, is intended to be re-evaluated in combination with a TUS parameters and outcome reporting resource, as follows.

Establishing the inTUS resource. To help to address these limitations, we establish the inTUS resource. We have openly shared the data and tools on the Open Science Framework https://osf.io/arqp8/. This open repository contains the data tables and the R script to regenerate the statistical tests and results, which can be repeated as the data tables expand with input from future studies. The resource has a form that researchers can complete to submit parameters and outcomes as part of their published work to be incorporated. We encourage TUS researchers to contribute more accurate values, if these are missing, from their prior studies and to more systematically report the more complete set of values in future. This will allow the data to be mined more systematically, which may further support or refute these hypotheses, help to develop new ones

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and better show the crucial interactions between parameters in relation to effects characterized in greater depth than was possible here. We anticipate that this effort will dovetail with a need for further NICE and other computational modeling. TUS effects could also be modeled across the cortical depth, in interaction with other brain areas (Thorpe et al., 2024) or with the cellular properties of subcortical regions. We also welcome input via the online form on improving the criteria for assessing neurobiological or behavioral effects, which will benefit the entire TUS community and is a key objective of the ITRUSST consortium https://itrusst.com/.

Summary. Given the sample size limitations, these retrospective meta-analysis results are tentative, with the possibility that the results may stabilize or change. The combination of the meta-analysis and resource are made openly available to further support and encourage the TUS research community to more systematically report TUS parameters and study outcomes using the current or a more extended (e.g., data driven, multi-variate) approach. Furthermore, we encourage the TUS research community to explore the full parameter space whenever possible.

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599 **BOXES**

PARAMETERS	DESCRIPTION	DEFINITION	UNITS
ISPPA	Intensity - Spatial Peak Pulse Average	Refers to the Average acoustic intensity	W/cm^2
ISPTA	Intensity - Spatial Peak Temporal Average	Temporally averaged intensity over the sonication duration (ISPPA * Duty Cycle)	W/cm^2
SD	Sonication Duration	Period during which TUS is applied to the brain target	Seconds
DC	Duty Cycle	Ratio of sonication on and off time	%
PRF	Pulse Repetition Frequency	The number of pulses per second delivered to the target	Hz
MI	Mechanical Index	Characterizes the likelihood of mechanical cavitation caused by TUS	
TI	Thermal Index	Estimate of temperature rise in tissue due to TUS exposure.	°C

600

601 **Box 1. Transcranial focused ultrasound stimulation (TUS) key parameters.** Shown are the
602 abbreviations and measurement value definitions for the key TUS parameters.

603

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FDA LIMITS FOR DIAGNOSTIC ULTRASOUND

ISPPA	≤ 190 W/cm2
ISPTA	≤ 720 mW/cm2
MI	≤ 1.9
TI	< 6

Box 2. Recommendations for TUS parameters. Currently, there are no established and universally recognized guidelines for the safe application of TUS. Nevertheless, FDA guidelines exist for diagnostic ultrasound, and as such much of the TUS literature has taken these limits into consideration. These are summarized in the table above, see Box 1 for a description of these parameters. The International Transcranial Ultrasonic Stimulation Safety and Standards (iTRUSST) consortium has recently established recommendations based on existing guidelines for diagnostic ultrasound from regulatory bodies such as the Food and Drug Administration (FDA), the British Medical Ultrasound Society (BMUS) and the American Institute of Ultrasound in Medicine (AIUM). In brief the MI should be below 1.9 and temperature rise in soft tissue below 2 degrees Celsius (https://arxiv.org/abs/2311.05359). Importantly, those recommendations should be considered in parallel to individualized simulations to further reduce the risk of adverse bioeffects.

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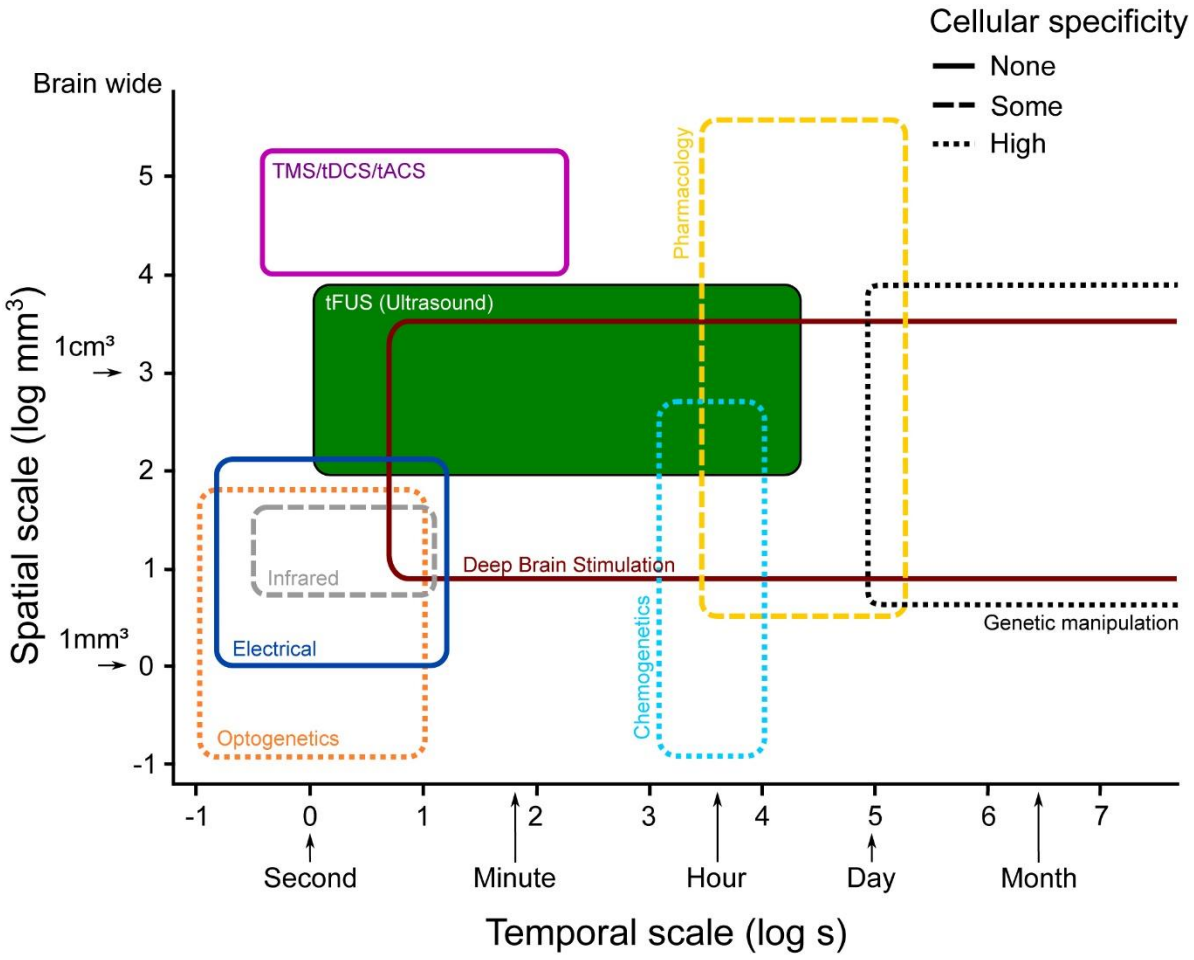
Directionality of TUS Hypotheses

	Intensity (Isspa brain)	Sonication duration (SD)	Duty Cycle (DC)	Pulse Repetition Frequency (PRF)
Enhancement weighted	Higher intensity	<500 ms	> 30%	> 300 Hz
Suppression weighted	Lower intensity	>500 ms	< 30%	< 300 Hz

Box 3. Net enhancement versus suppression hypotheses. Summarized hypotheses on how net enhancement or suppression could be biased with TUS parameters.

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621 **FIGURES**

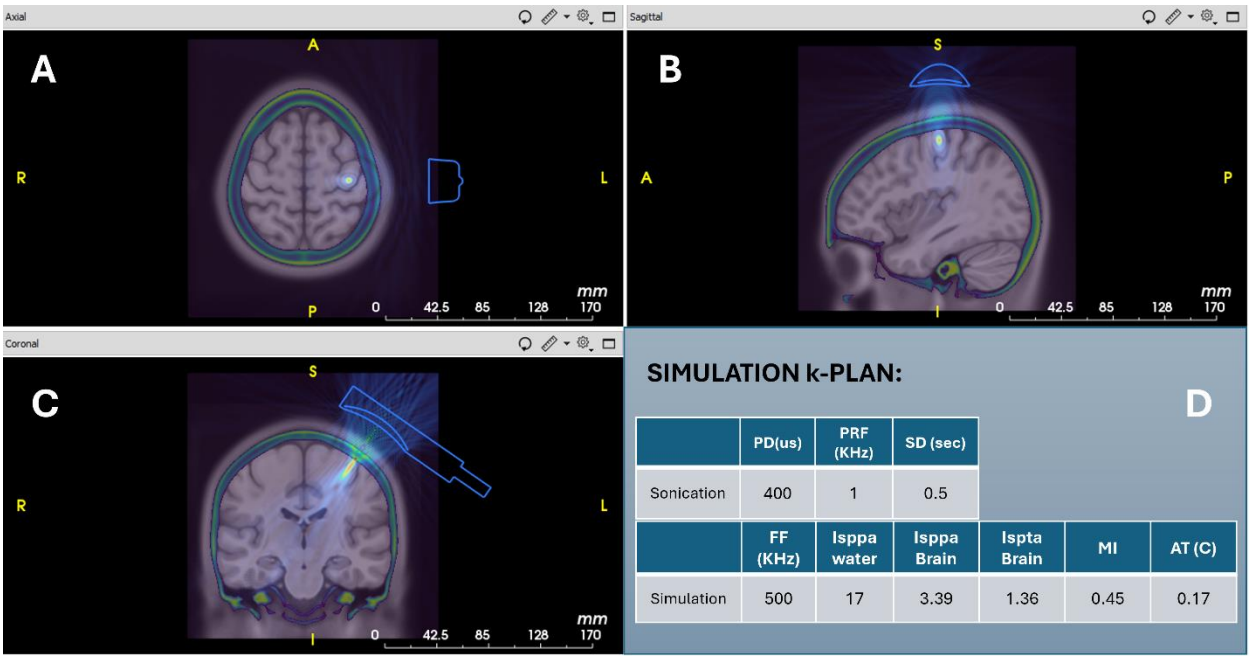


622

623 **Figure 1. Schematic overview of the specificity of brain perturbation techniques.** Brain perturbation
624 techniques vary in the precision of the spatial and temporal effects that can be elicited, on logarithmic
625 (log10) scales. This includes transcranial Focused Ultrasound Stimulation (TUS), in green. Some
626 approaches with cellular specificity are shown that are currently primarily in use with nonhuman animals
627 as models (optogenetics, infrared neuromodulation, chemogenetics and genetic manipulation). Figure
628 modified with permission from P.C. Klink, from (Klink et al., 2021).

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	PD(us)	PRF (KHz)	SD (sec)
Sonication	400	1	0.5

	FF (KHz)	Isppa water	Isppa Brain	Ispta Brain	MI	AT (C)
Simulation	500	17	3.39	1.36	0.45	0.17

Figure 2. Low-intensity Transcranial Ultrasound Stimulation for Neuromodulation in Humans. (A, B, C) Example focal TUS targeting of a human motor cortex using k-plan software (BrainBox, Inc.) (D) TUS simulation software uses an input set of parameters (e.g., pulse duration, PD, sonication duration, pulse repetition frequency, PRF, transducer properties and fundamental frequency (FF), intensity in water (ISSPA), to simulate and calculate the approximate TUS intensity in the target brain region using the participant's MRI and CT scans if available, or template human brain and CT scans. Simulation software will also generate the complete set of minimal parameters for reporting.

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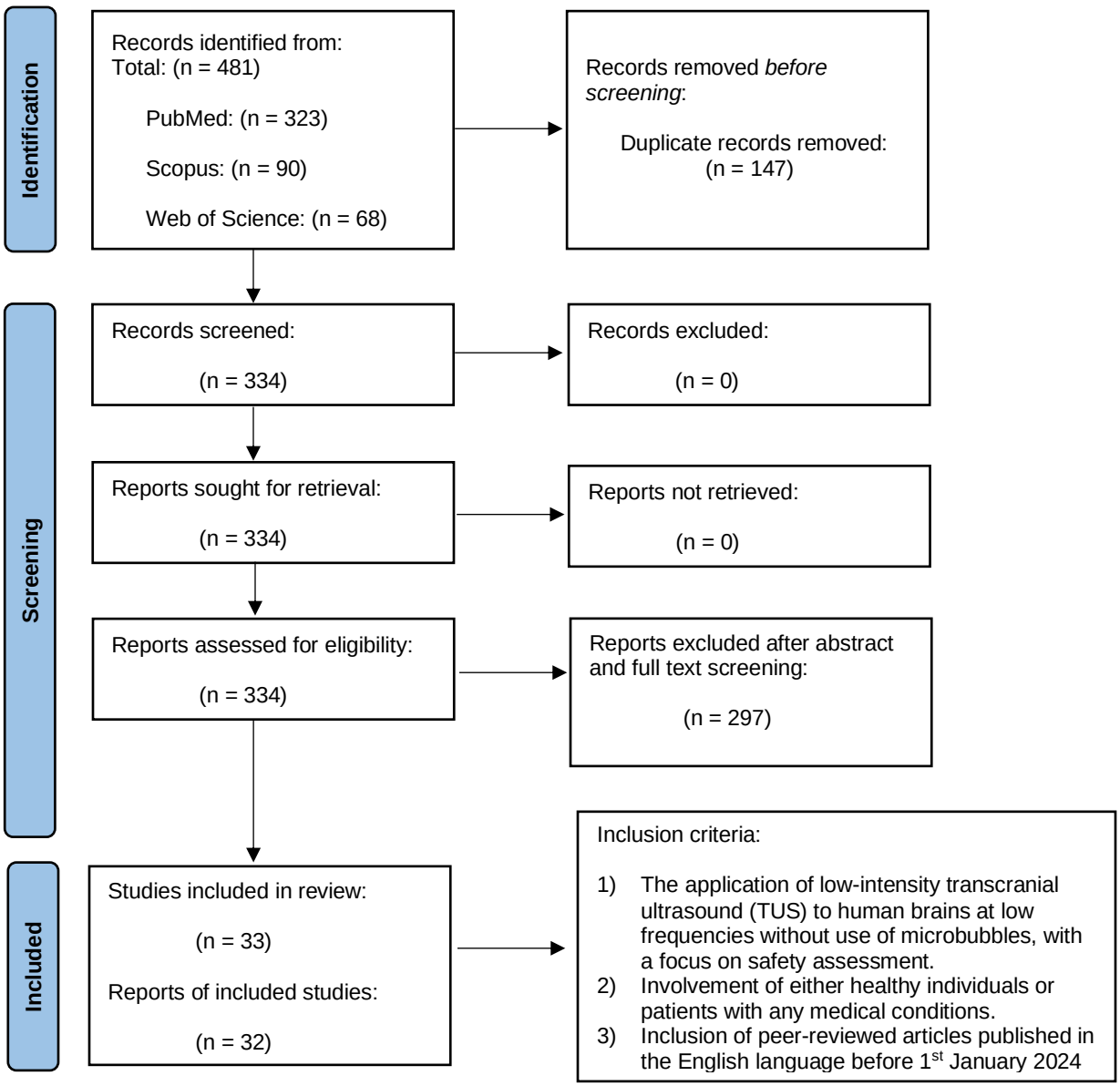


Figure 3. Meta-analysis selection and inclusion criteria using the PRISMA recommended approach. Selection and inclusion criteria for the meta-analysis, with resulting sample sizes for the meta-analysis.

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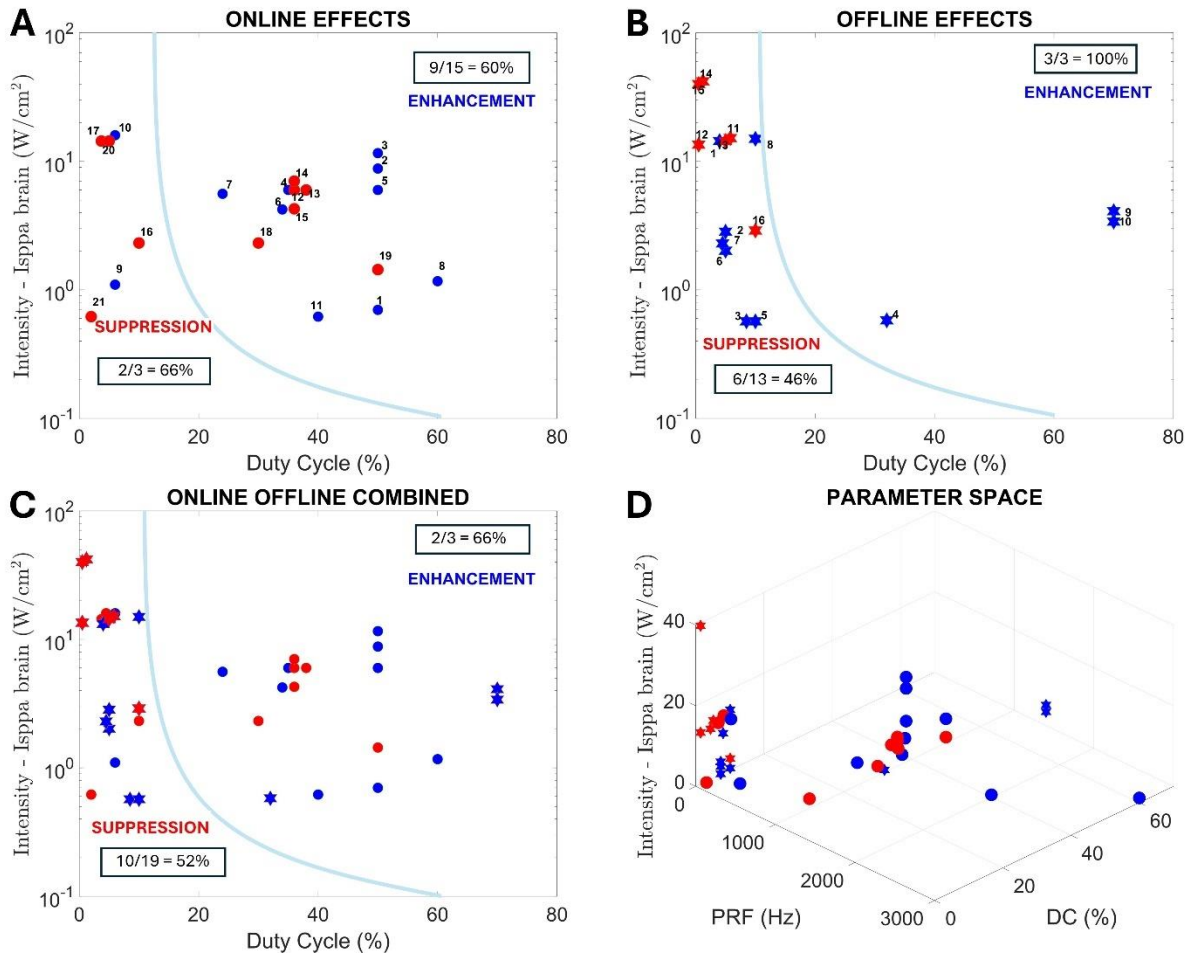


Figure 4. Meta-analysis effects relative to NICE model predictions. (A) Online effects meta-analysis based on the studies in Table 1, segregated by probable enhancement versus suppression. Light blue line shows the NICE model boundary between suppression and enhancement (potential net excitation). Blue circles are human studies reporting probable enhancement, red circles probable suppression. Index numbers correspond to studies numbered in Table 1. (B) Same format and analysis approach showing the "offline" effects studies in Table 2 with stars. Index numbers correspond to studies numbered in Table 2. (C) Combined figure with online (Table 1) and offline (Table 2) studies. Same symbol and color use as in A-B. (D) Additional hypothesized parameters like pulse repetition frequency (PRF) can be plotted in multi-dimensional spaces as shown.

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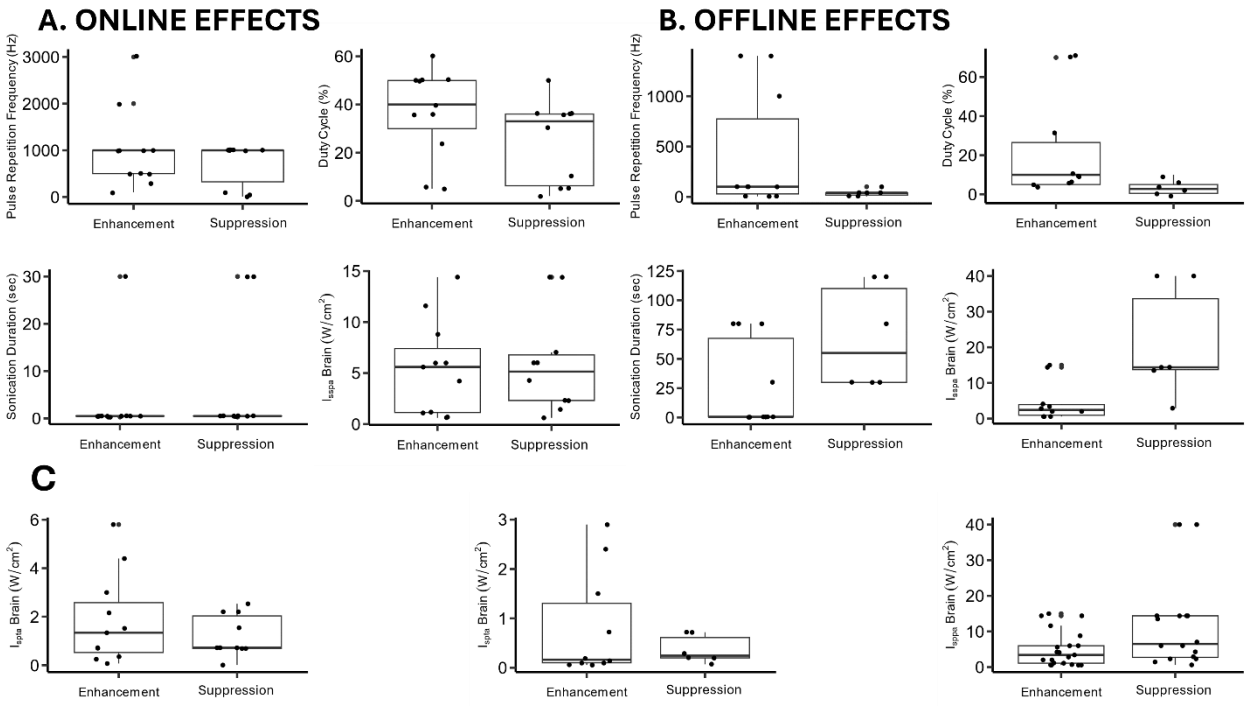


Figure 5. Box plots of meta-analysis results for the key TUS parameters. Shown are boxplots for each of the TUS parameters of interest segregated by probable enhancement or suppression (data from Tables 1 and 2). Plots show TUS parameters: Pulse Repetition Frequency (PRF), Duty Cycle, Sonication Duration, ISPPA. These are shown separately for Online effects (A) and Offline effects (B). The logistic regression only showed a significant effect for Duty Cycle, but we recognize that the results are underpowered at this stage. (C) Shows results for ISPTA, the potential ultrasound 'dose' parameter that integrates ISPPA and DC. This is shown for online (left panel), offline (middle panel) effects, and for ISPPA in the brain for both offline and online effects combined (right panel)

ONLINE EFFECTS	PROBABLE ENHANCEMENT OF FUNCTIONS									
STUDY	**TARGET**	**FF (KHz)**	**PRF (Hz)**	**DC (%)**	**SD (sec)**	**PD (ms)**	**Isppa Water (W/cm2)**	**Ispta Brain (W/cm2)**	**Isppa Brain (W/cm2)**	**Reported Effect** [independently characterized]
1. (Lee et al., 2015)	Hand Region S1	250	500	50	0.30	1	3	0.35	0.70	TUS enhanced somatosensory evoked potentials. [Wang et al. 2019]
2. (Lee et al., 2016a)	S2 and S2+S1	210	500	50	0.50	1	35	4.40	8.80	TUS elicited tactile sensations and enhanced somatosensory evoked potentials. [Wang et al. 2019; G. Darmani et al. 2022]
3. (Lee et al., 2016b)	V1	270	500	50	0.30	1	16.60	5.80	11.60	Simultaneous TUS and 3T fMRI resulted in increased BOLD signal in V1. With EEG: increased potentials (e.g., P100 and P200). Produced phosphene perception in some subjects. [Zhang et al. 2021]
4. (Ai et al., 2016) Exp 1 (3T)	Sensorimotor	500	1000	36	0.50	0.36	24	2.16	6	TUS in sensorimotor cortex led to focal BOLD activation. [Yüksel et al.(2023)]
5. (Ai et al., 2016) Exp 2 (7T)	Caudate	860	1000	50	0.50	0.5	24	3	6	TUS in caudate led to focal BOLD activation in subcortical areas. [Yüksel et al. (2023)]
6. (Ai et al., 2018)	M1 (thumb)	500	1000	36	0.50	0.36	16.95	1.52	4.23	Increased fMRI BOLD signal in motor cortex (M1) thumb representation during a cued tapping task. [Wang et al. 2019; Biase et al. 2019]
7. (Fine et al., 2020)	VLPFC	500	1000	24	0.50	0.24	22.40	1.34	5.60	TUS of right ventro-lateral PFC (VLPFC), enhanced frontal EEG potential (P300) for stop-trials in a stop signal task. (Enhanced inhibition action.) [Yüksel et al. (2023)]
8. (Yu et al., 2020a)	M1 (leg area)	500	3000	60	0.50	0.2	5.90	0.70	1.17	Increased movement-related cortical activity when compared to sham, with the highest PRF used. [Yüksel et al. (2023)]
9. (Liu et al., 2021)	S1	500	300	6	0.50	0.2	5.64	0.07	1.10	TUS increased local excitability of S1 area EEG responses during sensory discrimination tasks. Early and late phase EEG potentials were enhanced. N300 potential amplitude was also enhanced.
10. (Kuhn et al., 2023)	Entorhinal Cortex	650	100	5	30	0.5	57.60	0.72	14.40	Increased fMRI activity in entorhinal cortex and functional connectivity.
11. (Zhang et al., 2023)--> Exc	M1 (hand area)	500	2000	40	0.50	0.2	2.46	0.25	0.62	Excitatory protocol, combining TUS + TMS of motor cortex increased M1 excitability and decreased intracortical inhibition.
AVERAGE		**476**	**991**	**37**	**3.2**	**0.5**	**19.4**	**1.9**	**5.5**	

718

719

720

ONLINE EFFECTS	PROBABLE SUPPRESSION OF FUNCTION									
STUDY	**TARGET**	**FF (KHz)**	**PRF (Hz)**	**DC (%)**	**SD (sec)**	**PD (ms)**	**Isppa Water (W/cm2)**	**Ispta Brain (W/cm2)**	**Isppa Brain (W/cm2)**	**Reported Effect** [independently characterized]
12. (Legon et al., 2014)	S1	500	1000	36	0.50	0.36	23.9	2.2	6	TUS to S1 attenuates somatosensory evoked potentials. Improved tactile discrimination task performance.
13. (Mueller et al., 2014)	S1	500	1000	36	0.50	0.36	23.9	2.2	6	Disrupted intrinsic brain activity and phases for beta, not for gamma. [Zhang et al. 2021]
14. (Legon et al., 2018a)	Thalamus VPL	500	1000	36	0.50	0.36	14.5	2.53	7.03	Attenuation of somatosensory evoked component. Attenuation of alpha and beta power. [Zhang et al. 2021]
15. (Legon et al., 2018b)	M1	500	1000	36	0.50	0.36	17.12	1.54	4.28	Attenuation of motor evoked potential during single-pulse TMS. Attenuation of intracortical facilitation (ICF), unaffected SICI.
16. (Fomenko et al., 2020)	M1	500	1000	10	0.50	0.1	9.28	0.69	2.32	TMS motor evoked potential suppression in a dose-dependent manner and increase in short interval intracortical inhibition. [Zhang et al. 2021; Yüksel et al. (2023)]
17. (Cain et al., 2021b)--> Mode 1	Globus Pallidus	650	100	5	30	0.5	57.6	0.72	14.40	TUS decreased fMRI BOLD signal and within the brain network observed.
18. (Xia et al., 2021)	M1	500	1000	30	0.50	0.3	9.26	0.69	2.32	Inhibition of ipsilateral M1 potential after TUS.
19. (Butler et al., 2022)	Visual Cortex (area MT)	500	1000	50	0.30	0.5	5.76	0.72	1.44	TUS to visual area hMT+ produced attenuation of visual motion EEG evoked potentials.
20. (Kuhn et al., 2023)	Amygdala	650	10	5	30	5	57.6	0.72	14.40	Decreased functional inter-connectivity with amygdala.
21. (Zhang et al., 2023) --> Inhibitory TUS	M1 (hand area)	500	50	2	0.50	0.4	2.46	0.01	0.62	Inhibitory protocol: TUS + TMS --> Increased short and long interval intracortical inhibition with reduced intracortical fascilitation.
AVERAGE		**530**	**716**	**24.6**	**6.4**	**0.8**	**22.1**	**1.2**	**5.9**	

Table 1. Human 'online' effect TUS studies categorized by probable enhancement or suppression. Summarized are the TUS parameters reported in human studies focusing on inducing online effects and their reported neurobiological effects summarized by likely excitatory or inhibitory effects. Independently confirmed effects cite the independent assessment source.

OFFLINE EFFECTS		PROBABLE ENHANCEMENT OF FUNCTION								
STUDY	**TARGET**	**FF (KHz)**	**PRF (Hz)**	**DC (%)**	**SD (sec)**	**PD (ms)**	**Isppa Water (W/cm2)**	**Ispta Brain (W/cm2)**	**Isppa Brain (W/cm2)**	**Reported Effect** [independently characterized]
1. (Monti et al., 2016)	Thalamus	650	100	5	30	0.50	57.60	0.72	14.40	One patient case study. Emergence from minimally conscious state three days after sonication. Recovery of motor and oromotor functions and full language comprehension.
2. (Y. Zhang et al., 2021)	Motor Cortex	500	100	5	0.5	0.50	8.05	0.14	2.84	TUS induced modulation of TMS motor evoked potentials, lasted 30 min. Improved stop signal task performance. [Yüksel et al. (2023)]
3. (Zeng et al., 2022) **tbTUS protocol**	left M1	500	5	10	80	20.00	2.26	0.057	0.57	Their Theta-burs TUS protocol: TUS + TMS increased corticospinal excitability, increased intracortical facilitation and decreased short interval intracortical inhibition. LTP-like effects lasted 30 to 60 min. [C. Sarica et al. 2022]
4.(Zeng et al., 2022) **rTUS protocol**	M1	500	1000	32	0.5	0.32	2.30	0.184	0.58	Their rTUS protocol: Increased TMS motor evoked potentials. [C. Sarica et al. 2022]
5. (Samuel et al., 2022) **tbTUS protocol**	M1	500	5	10	80	20.00	2.26	0.057	0.57	TUS + TMS tbTUS protocol, increased motor evoked potentials, decreased short interval intracortical inhibition, and no changes in intracortical facilitation.
6. (Ren et al., 2023)	M1	500	100	5	0.5	0.50	8.09	0.10	2.02	TUS induced LTP-like plasticity in ipsilateral M1. Interhemispheric balance of M1 excitability modulated by TUS.
7. (Zhai et al., 2023) **rTUS protocol**	lDLPFC	500	100	5	0.5	0.50	8.09	0.10	2.02	TMS motor evoked potentials increased significantly after rTUS protocol to DLPFC, inducing LTP-like plasticity. Alleviated negative symptoms and improved cognitive performance in schizophrenic patients.
8. (Bault et al., 2023)	dACC & PCC	500	5	10	80	20.00	33.80	1.50	15	Reduction in GABA levels in the posterior cingulate cortex (PCC) lasted 30 min. Increase rsfMRI connectivity in dorsal anterior cingulate cortex (dACC) & PCC lasted 50 min. TUS on PCC increased functional connectivity with the dACC.
9. (Kim et al., 2023)	S1	250	1400	70	0.2	0.50	14.70	2.90	4.10	This study produced evoked EEG TUS responses like somatosensory evoked potentials as well as resting-state functional connectivity changes that outlasted the sonication for 1 hour.
10. (Kim et al., 2023)	VPL	250	1400	70	0.2	0.50	9.10	2.40	3.40	
AVERAGE		**465**	**422**	**22.2**	**27.2**	**6.3**	**14.6**	**0.8**	**4.6**	

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OFFLINE EFFECTS	PROBABLE SUPPRESSION OF FUNCTION									
STUDY	**TARGET**	**FF (KHz)**	**PRF (Hz)**	**DC (%)**	**SD (sec)**	**PD (ms)**	**Isppa Water (W/cm2)**	**Ispta Brain (W/cm2)**	**Isppa Brain (W/cm2)**	**Reported Effect** [independently characterized]
11. (Badran et al., 2020)	Anterior Thalamus	650	10	5	30	5	57.52	0.72	14.38	Significant reduction of thermal pain sensitivity. TUS-induced antinociceptive effects. [Yüksel et al. (2023)]
12. (Sanguinetti et al., 2020)	Fronto-Temporal Cortex	500	40	0.5	30	0.13	54	0.07	13.5	Decrease in functional connectivity (rsFMRI) in resting state network between right Inferior Frontal Gyrus and left limbic areas. Increased FC between rIFG and rMFG.
13. (Cain et al., 2022)	Central Thalamus	650	100	5	30	0.5	57.60	0.72	14.4	BOLD signal decreased in Frontal Cortex and Basal Ganglia. [Yüksel et al. (2023)]
14. (Forster et al., 2023a)	l(PFG)	500	40	0.5	120	0.13	160	0.20	40	Decrease in EEG mid-frontal theta which lasted up to 90 min post-TUS.
15. (Forster et al., 2023b)	IFG	500	40	0.5	120	0.13	160	0.20	40	Inhibition of rIFG
16. (Oghli et al., 2023) **tbTUS protocol**	M1 (hand area)	500	5	10	80	20	11.73	0.29	2.90	tbTUS plasticity effects reduced by channel blockers.
AVERAGE		**550**	**39.2**	**3.6**	**68.3**	**4.3**	**83.5**	**0.4**	**20.9**	

Table 2. Human 'offline' effect TUS studies categorized by probable enhancement or suppression. Summarized are the TUS parameters used in human studies focusing on inducing longer lasting or 'offline' effects.

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Introduction to the inTUS Resource:
Iowa Newcastle
focused Transcranial Ultrasound Stimulation Resource

The Iowa Newcastle human low-intensity TUS Resource consists of the following resource items, linked to Caffaratti et al. ***Neuromodulation with Ultrasound: Hypotheses on the Directionality of Effecs and a Community Resource.***

The resource documents can be found on the Laboratory of Comparative Neuropsychology data share on Open Science Framework: https://osf.io/arqp8/ under Cafferatti_et_al_inTUS_Resource.

Resource documents:

- **Data Tables for Offline and Online Effects** – Tables_Online_Offline_Effects.xlsx, these will continue to be updated by the corresponding authors, please email us the parameters needed to populate the table for your experiment or use the Google Forms link below to submit your values.
- **R-Script** to generate the figures and statistical tests using R Studio
  - Rmd_Output_06_24.pdf is an example output file generated 6-24
  - Rmd_TUS_Effects_06_24.Rmd is an executable R script
  - Table_R_version_06_24.csv is the R readable data spreadsheet
- **Matlab GUI:** created by Ryan Calmus for controlling the NeuroFUS system.
- **Qualtrics Form** to submit your own data to be added by the corresponding authors. Please find link to the form below:
  - https://uiowa.qualtrics.com/jfe/form/SV_4VOvb0fdwvACDkO

Using the resource:

To regenerate the manuscript figures with the latest tables, Download the *R data table* and *R_script*. Run it in RStudio, making sure it can access the latest data table.

Contributing to the resource:

Please use the Qualtrics Link and Form to submit your preprint or published paper values. These will be checked in relation to your paper and once verified will be input into the data tables. The link is also available here: https://uiowa.qualtrics.com/jfe/form/SV_4VOvb0fdwvACDkO

Only humans?

This resource was established with human low-intensity tFUS studies. We will be working on the resource being extended to nonhuman animals of different species. Please use the Qualtrics Form if you're interested or have suggestions about non-human animal data contributing to the resource.

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Competing interests statement

The authors declare no competing or financial interests.

Data availability

The datasets and R script generated in this study have been deposited in the Open Science Framework https://osf.io/arqp8/ in the Caffaratti_et_al_inTUS_Resource folder.

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