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Techniques and Methods

Biophysical effects and neuromodulatory dose of transcranial ultrasonic stimulation

Tulika Nandi [a,b,*], Benjamin R. Kop [a], Kasra Naftchi-Ardebili [c], Charlotte J. Stagg [d,e], Kim Butts Pauly [c,1], Lennart Verhagen [a,1]

[a] Donders Institute for Brain Cognition and Behaviour, Radboud University, Thomas van Aquinostraat 4, 6525 GD, Nijmegen, the Netherlands
[b] Department of Human Movement Sciences, Vrije Universiteit Amsterdam, De Boelelaan 1105, 1081 HV, Amsterdam, the Netherlands
[c] Department of Radiology, Stanford University, 300 Pasteur Drive, Stanford, CA, USA
[d] Wellcome Centre for Integrative Neuroimaging, FMRIB, Nuffield Department of Clinical Neurosciences, University of Oxford, FMRIB Building, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, UK
[e] Medical Research Council Brain Network Dynamics Unit, Nuffield Department of Clinical Neurosciences, University of Oxford, Mansfield Road, Oxford, OX1 3TH, UK

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ABSTRACT

Transcranial ultrasonic stimulation (TUS) has the potential to usher in a new era for human neuroscience by allowing spatially precise and high-resolution non-invasive targeting of both deep and superficial brain regions. Currently, fundamental research on the mechanisms of interaction between ultrasound and neural tissues is progressing in parallel with application-focused research. However, a major hurdle in the wider use of TUS is the selection of optimal parameters to enable safe and effective neuromodulation in humans. In this paper, we will discuss the major factors that determine the efficacy of TUS. We will discuss the thermal and mechanical biophysical effects of ultrasound, which underlie its biological effects, in the context of their relationships with tunable parameters. Based on this knowledge of biophysical effects, and drawing on concepts from radiotherapy, we propose a framework for conceptualising TUS dose.

1. Introduction

Transcranial ultrasonic stimulation (TUS) is a cutting-edge non-invasive brain stimulation technique with much higher spatial resolution and deep brain stimulation capability compared to electromagnetic techniques. Ultrasound has a variety of biophysical effects on tissues, which in turn drive neurobiological mechanisms that lead to neuromodulation. Although the direct links between biophysical effects and neuromodulation are only partly elucidated, fundamental research focused on filling these gaps is progressing in parallel with application-focused research. The major challenge of how to most appropriately set the large number of tunable TUS parameters, recently defined in the ITRUSST standardised reporting consensus [1], remains to be overcome. For fundamental research, manipulating these parameters may allow the development and testing of hypotheses concerning underlying biophysical effects. In application-focused research, establishing a framework for conceptualising 'dose' based on adjustable parameters and knowledge of their associations with biophysical effects is essential for designing studies and ensuring reproducibility. Here, we summarise the relationships between tunable TUS parameters and the thermal and mechanical biophysical effects of ultrasound. Subsequently, we propose a framework for conceptualising dose and a definition based on tunable parameters. The relationships between dose, defined in terms of stimulation parameters, and the neuromodulatory effects are mediated by the biophysical effects of ultrasound. Therefore, we believe that a discussion about biophysical effects is critical to the discussion about dose. For instance, if a user wants to manipulate 'effective dose' (see section about 'Conceptualising dose' for description), a knowledge of the relationships between tunable parameters and biophysical effects is essential. Additionally, we hope that this paper will serve as a summary of the specific aspects of ultrasound physics that are crucial for designing TUS experiments, particularly for an audience whose primary interest and expertise lies in neuromodulation and not in physics. For a full review of empirical papers that have examined the relationships between tunable parameters and neuromodulatory effects, please see Nandi et al. [2], and for a review of parameters relevant to safety, please see the

* Corresponding author. Department of Human Movement Sciences, Vrije Universiteit Amsterdam, De Boelelaan 1105, 1081 HV Amsterdam, the Netherlands.
E-mail addresses: t.nandi@vu.nl (T. Nandi), benjamin.kop@donders.ru.nl (B.R. Kop), knaftchi@stanford.edu (K. Naftchi-Ardebili), charlotte.stagg@ndcn.ox.ac.uk (C.J. Stagg), kimbutts@stanford.edu (K.B. Pauly), lennart.verhagen@donders.ru.nl (L. Verhagen).
[1] Joint last authors.

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ITRUSST consensus on biophysical safety [3].

2. Biophysical effects of ultrasound and their relationships with tunable parameters

Ultrasound can interact with tissues, including neurons and glia, through thermal and mechanical mechanisms outlined in Fig. 1A. It is likely that ultrasound affects the underlying brain tissue via multiple mechanisms simultaneously. The relative contributions of these mechanisms, however, can be influenced by adjusting the stimulation parameters.

The thermal effects, i.e. heat or energy deposition, are proportional to the integral of ultrasound intensity over time. Heat or energy deposition can be increased by increasing the intensity, the pulse duration, or both. If heat deposition were the only mechanism that affected the temperature, then any two sets of pulses with the same energy deposition would have the same temperature rise. However, heat is continuously removed, via conduction to adjacent areas and blood circulation, albeit at a relatively slow rate on the order of seconds. This means that when a pulse or a pulse train is extended to seconds or longer, the temperature rise is lower than for the same energy deposition over a much smaller time period. Heating is known to have neuromodulatory effects [4,5], but for transcranial in vivo applications, in which skull heating is a limiting factor, protocols are specifically designed and chosen to limit heating.

Mechanical effects of TUS can be divided into particle displacement strain, acoustic radiation force (ARF) strain, acoustic streaming, and cavitation. Strain refers to the physical deformation of neurons or parts thereof (e.g., the cell membrane), relative to their original configuration when they experience a pressure or force. Particle displacement strain is caused by the acoustic pressure: tissue is stretched and compressed as the pressure wave passes by. The deformation parallel to the direction of the beam results in normal strain and dominates over shear strain which is caused by unequal deformations at different locations on the axis perpendicular to the beam (Fig. 1C). Particle displacement is directly proportional to the applied acoustic pressure and inversely proportional to the fundamental frequency (f_0). Therefore, particle displacement is larger at lower frequencies (Fig. 1C). However, at lower frequencies, this displacement is also occurring over a larger wavelength. As a result of these opposing relationships, particle displacement strain is constant across frequencies (Fig. 1C).

ARF strain, on the other hand, is caused by the acoustic radiation force which is a force along the ultrasound beam in the direction of propagation, exerted on absorbing or reflecting tissues in the US path [6]. In contrast to particle displacement strain, ARF strain is predominantly shear strain (Fig. 1B). When estimated using some simplifying assumptions [6–8], the ARF strain is directly proportional to the intensity (i.e., pressure squared) at the focus (Fig. 1B). Using the same logic as above, we estimate strain by normalising the displacement to the wavelength and see that while the ARF itself is proportional to f_0, the ARF-induced strain is proportional to f_0 squared (Fig. 1B).

There are two other key points at play: the temporal and spatial response of these two strains. The particle displacement strain varies temporally with each cycle of the ultrasound pulse. In contrast, while the US is on, the ARF is temporally constant at a given point within the medium [9], with the displacement rising exponentially to a maximum over several milliseconds, and decaying exponentially over several milliseconds. Pulsing the US leads to fluctuations in the ARF at the pulse repetition frequency (PRF), a much lower frequency than the fundamental frequency. With respect to the physical location, particle

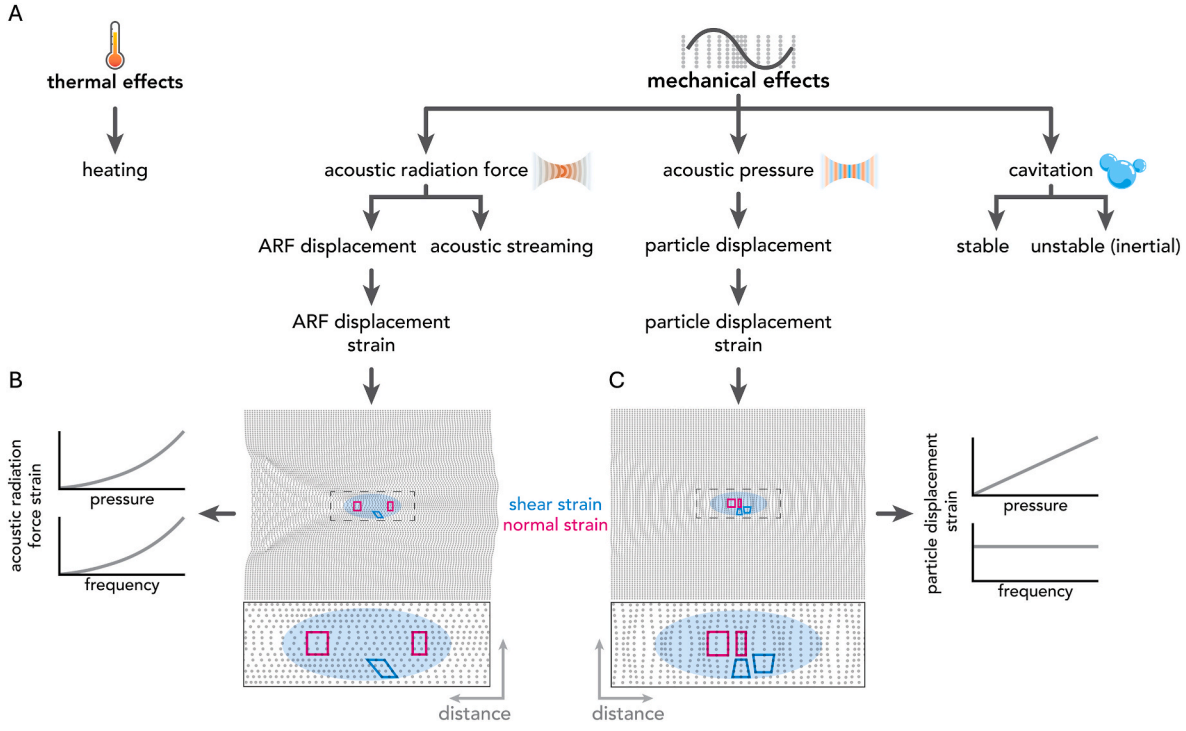

Fig. 1. A. Biophysical effects of ultrasound, including thermal (top left) and mechanical (top right) mechanisms. In the lower panels, the shaded blue area depicts the focal area. B. The bottom-left field depicts ARF displacement, with the transducer on the left and the wave propagation towards the right. ARF strain is denoted denoted between shifted (tip of arrow) and more stationary units. ARF strain increases nonlinearly with both pressure and frequency. C. The bottom-right field conceptually depicts instantaneous particle displacement around the acoustic focus, with the particles in their shifted position at one point in time. Normal strain along the direction of propagation and shear strain with angular distortion are denoted. Particle displacement strain increases with pressure, but remains stable across fundamental frequencies. Both schematic illustrations depicting particle fields and relationships between biophysical effects and frequency/pressure are included to conceptualize the principles and mechanisms discussed in the text. These illustrations are not derived from precise mathematical models or simulations and should be interpreted as qualitative visualizations for explanatory purposes only.

displacement strain is highest at the focus. In contrast, ARF strain is highest where the ARF displacement changes most rapidly, typically in areas adjacent to the focus (Fig. 1B).

In an attenuating medium such as neural tissue, a spatial gradient of ARF is observed as US is absorbed along the beam path. When US passes through a fluid medium, this ARF gradient can cause bulk flow of fluid known as acoustic streaming. The velocity of streaming, and therefore any biological effects caused by it, are highly dependent on the viscosity of the medium, and also the physical boundaries and constraints on the medium.

Cavitation refers to both the pulling of dissolved gas out of sonicated tissues to form gas bubbles, and the oscillation of gas bubbles, including the aforementioned emerging bubbles, existing gas bubbles, or injected microbubbles. Inertial cavitation, a special case of cavitation in which bubbles grow in size and eventually collapse leading to large temperature rises and sudden release of energy, can cause tissue damage and is intentionally avoided during neuromodulation applications. Inertial cavitation is a threshold event i.e., it occurs when a specific threshold, defined by a combination of bubble size, f_0 and peak negative pressure, is exceeded. The pressure threshold for inertial cavitation is lower at lower f_0 [10].

Please note that our discussion about the relationships between stimulation parameters and biophysical effects is limited to linear regimes i.e., ultrasound waves with equal positive and negative pressure amplitudes. Under some conditions, like multiple transducers opposed to each other, or at an angle, there may be complex interactions, including standing waves. A detailed discussion is beyond the scope of this paper [7,11,12], but if standing waves give rise to wave distortion or nonlinear effects, then the relationships and arguments presented in this paper may not hold. The possibility of standing waves is determined by a combination of skull geometry and ultrasound parameters like f_0 and pulse duration [13], and must be carefully simulated for each experimental scenario. In general, as discussed in detail in the ITRUSST standardised reporting paper [1], simulations (or other de-rating procedures) are essential for estimating the true parameters and therefore biophysical effects in situ.

3. Conceptualising dose

We can build on our current knowledge of ultrasound biophysics and parameters to propose hypotheses about the biophysical effects underlying ultrasonic neuromodulation [14], and empirically test their relationships [15]. The development of integrative theoretical frameworks and comprehensive empirical studies is an area of active research, and no consensus has yet been reached. As noted earlier, in practice, efforts to elucidate the underlying mechanisms will proceed in parallel with efforts to optimise TUS effects for basic science and clinical applications. Therefore, we propose a theoretical framework for conceptualising dose, that is agnostic of the underlying biophysical effect.

Knowledge of dose-response relationships is crucial for designing research protocols and for clinical applications. Initial attempts to define acoustic dose have drawn on ideas from radiotherapy [16], and in line with radiotherapy, a distinction must be made between exposure and dose. Shaw et al. [16] describe exposure as the 'energy flux or the acoustic pressure of an ultrasonic wave incident on the region of interest'. Exposure is determined by the source transducer and acoustic properties of the medium. The derated or simulated acoustic pressures/intensities reported in neuromodulation studies are, in essence, measures of exposure. In other words, this is the pressure that the target region of interest is exposed to, after taking into account any attenuation caused by tissues between the transducer and target.

Dose, on the other hand, depends on the interaction of the incident ultrasound wave with the neural tissues of interest. In radiotherapy, there are further distinctions between the absorbed, equivalent, and effective dose. Absorbed dose refers to the amount of energy deposited in the tissues. When a region of interest is exposed to ultrasound, only a fraction of the energy carried by the ultrasound wave is absorbed within this region, while the rest passes through. Absorbed dose is a useful quantity when determining the thermal effects of ultrasound since heating is proportional to the absorbed fraction. An analogue for mechanical effects is that ARF at a given spatial location relates to the energy absorbed at that location.

In radiotherapy, equivalent dose additionally accounts for the differing effects of different types of radiation. The analogue for ultrasound stimulation applications is the biophysical effect underlying any neuromodulatory effects. For instance, for thermal effects, equivalent dose, and therefore temperature rise, simply increases with increasing intensity. However, if neuromodulation is primarily driven by mechanical effects, given a constant exposure, the equivalent dose would increase with increasing f_0 for ARF strain-dependent effects, but be independent of f_0 for particle displacement strain-dependent effects.

Effective dose accounts for the differing sensitivities of various target tissues, in this case, the target neurons or brain region, to the same equivalent dose. In the context of thermal effects, the same temperature rise may have different effects in different brain regions. If mechanical effects are mediated by mechanosensitive ion channels, given the same equivalent dose, the effective dose required to elicit similar responses would differ based on the density of such channels in different target regions [17]. Another example is the variation in stiffness between brain regions [18], and due to ageing and pathology [19–21]. Given the same acoustic pressures and ARFs, the strain and consequent biological effects will vary based on the stiffness of the target tissue. Importantly, the concept of 'effective dose' should consider the multiple levels of organisation at which ultrasound exerts effects, from biophysics to cellular biomechanisms, to circuit-level neurophysiology, to the human brain and behaviour, and to clinical outcomes, while also accounting for the state of the system when stimulation is applied (for review, please see Ref. [2]). Ultrasound can have different, even opposing, effects on individual levels. For example, a specific ultrasound protocol and dose might selectively facilitate inhibitory neurons, leading to neural excitation but circuit-level inhibition [22]. Effective dose is not a property of the stimulation parameters alone but of the interaction with neural systems. Indeed, investigations of effective dose will require an integrative approach bridging across all levels, from biophysics to cellular biomechanisms, to circuit-level neurophysiology, to the human brain and behaviour, and to clinical outcomes.

Finally, when ultrasound leads to neuroplastic effects, the effect of ultrasound will depend on the history of exposure or dosing, and therefore, it is important to record cumulative dose. For TUS, we therefore propose a framework that includes absorbed, equivalent, effective, and cumulative dose (Fig. 2). While this framework is useful to clarify and further our understanding of ultrasonic neuromodulation, there is currently, limited consensus about the biophysical mechanisms and neuronal or regional sensitivities of ultrasound. As our knowledge of TUS expands, we expect the definitions of dose to evolve. For instance, equivalent dose might be weighted by fundamental frequency while effective dose might be weighted by intrinsic mechanosensitive ion channel density.

Our aim in this paper is to introduce a theoretical framework that researchers can use to evaluate and interpret observed dose-response relationships. For instance, we can compare the same dose applied at several different fundamental frequencies (f_0). If the neuromodulatory effect becomes stronger as f_0 increases, we could infer that the effect is likely driven by ARF strain. If on the other hand, instead f_0 does not influence the neuromodulatory effects, it is more likely that the effects are driven by particle displacement strain. Furthermore, the flexibility to define different equivalent and effective doses at different levels will allow researchers to tailor the weightings to their specific outcome of interest. For instance, theoretical models [23] and accumulating evidence [24–26] suggest that different subtypes of neurons can be preferentially targeted by varying the PRF. This suggests a PRF based mechanism of action at the cellular level and therefore, equivalent dose

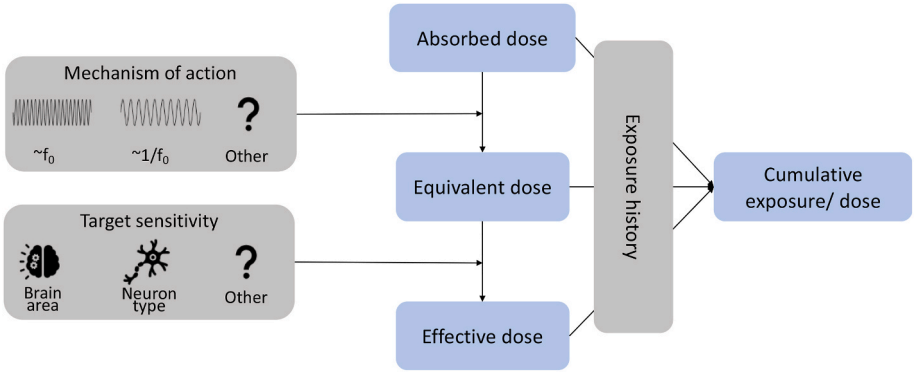

Fig. 2. Theoretical framework for conceptualising transcranial ultrasonic stimulation dose. Absorbed dose depends on the interaction of the incident ultrasound wave with the neural tissues of interest. Equivalent dose additionally accounts for the biophysical effects of ultrasound which drive neuromodulation. Effective dose accounts for the differing sensitivities of target neurons or brain region.

at the cellular level could be weighted by PRF. In other words, given the same absorbed dose, the effects on a chosen neuronal subtype will depend on the PRF. If a particular neuronal subtype responds to a very narrow bandwidth of PRFs, a relatively lower dose would be required to stimulate these neurons at PRFs within their preferred range. In practice, we may denote the PRF-weighted equivalent dose as 'dose at PRF x'. More generally, the effect may be non-linearly related to PRF and the equivalent dose could be estimated by multiplying the absorbed dose with a non-linear function. At the level of a brain region, the net outcome will depend on the relative proportions of different neuronal subtypes and therefore, effective dose could be weighted by the neuronal subtype distribution in the chosen brain region. In other words, given the same PRF weighted equivalent dose, the effects on a chosen brain region will depend on the neuronal subtype distribution in that region. In this example, the flexibility of the dose definitions is exploited to account for the relevant factors that influence dose-response relationships at each level of organization.

We propose the integral of intensity over time as a definition for exposure and therefore as a starting point for defining dose. Dose might be exposure weighted by a moderating factor like PRF, as described in the example above. Until we have reached an informed consensus on the mechanisms underlying ultrasonic neuromodulation, we cannot distinguish between exposure and dose and thus we can use them interchangeably here. Dose will become differentiated from exposure when the key weighting factors are clarified. For example, for thermal effects, absorbed dose may be estimated by weighting the exposure by the absorption coefficient.

All other parameters being constant, increasing pressure increases heating, ARF, particle displacement, and the probability of cavitation. Intensity is proportional to the pressure squared, therefore, any relationship between neuromodulatory effects and intensity, would also hold for pressure squared. The choice between pressure and intensity may depend on the key biophysical effect. Pressure is linearly associated with particle displacement and cavitation, while intensity is linearly associated with ARF. Therefore, the pressure or intensity over time is likely to be an important factor in dose, irrespective of the underlying biophysical effects. Time is included in the definition because prolonged exposure could either lead to cumulative effects on a single neuron, for instance by allowing greater time for ion movement and changes in membrane potential [27], or increase the probability of recruiting additional neurons.

The following equation can be used to estimate exposure (or dose) i.e., integral of intensity over time:

$$\text{Exposure (or Dose)} = \int_0^t I dt, \text{ where}$$

'I' is instantaneous intensity.

't' is the time over which dose is calculated. This could be the pulse, pulse train or pulse train repeat duration, but may also be calculated over longer time periods (like sessions across multiple days) based on the experiment or application.

If the Isppa accounts for the ramping at the pulse level and there is no ramping at other temporal levels, this reduces to:

Exposure (or Dose) = Isppa * PD [* 1/ PRI * PTD * 1/ PTRI * PTRD], where

'Isppa' is the spatial peak pulse average intensity.

PD is the pulse duration.

PRI is the pulse repetition interval.

PTD is the pulse train duration.

PTRI is the pulse train repetition interval.

PTRD is the pulse train repetition duration.

The variables within the square brackets are required only when estimating dose for protocols with pulsing or repetition at one or more timescales. The flexibility to define the dose on multiple timescales is valuable because it allows researchers to choose the timescale that is relevant to their outcomes. For instance, a study measuring action potentials in response to TUS may focus on shorter time scales compared to a clinical study examining the effects of TUS on the incidence of epileptic seizures. When Isppa is expressed in W/cm^2 and durations are expressed in s, the estimated dose is in J/cm^2. Table 1 shows an estimation of dose using Murphy et al. [24] and Mohammadjavadi et al. [28] as examples.

Existing empirical data support our proposed definition. However, several aspects of dose have yet to be comprehensively explored. While both in vitro and in vivo data suggest a scaling of response with intensity and duration, the exact nature of the dose-response relationship is currently unclear. Specifically, dose-response relationships may not always be linear, not even monotonic [29]. Further, the identification of thresholds and ceilings is crucial to avoid underdosing and minimise side effects. Lastly, it is important to consider the potential impact of dose-rate, over and above total dose [30]. Note, for example, that the same integral of intensity over time can be achieved by applying either a low-pressure wave for a prolonged duration or a high-pressure wave for a short time-period. However, for thermal effects in timescales on the order of seconds, greater temperature increases are achieved when energy is delivered over a short time period (a high dose-rate), compared to a low dose-rate where more time is available for the heat to dissipate. In terms of mechanical effects, the dose-rate might interact with the viscoelastic [31] properties of neurons. Indeed, the impact of dose-rate should be a key focus area for future empirical research. Given the complexities of the above factors, we advise against conflating dose with pulsing regimes, such as intending to change dose, by changing the pulse duty cycle. For example, given a constant amplitude, a change from 20 % to 40 % duty cycle could be considered a doubling of dose, while a change from 20 % to 100 % duty cycle would fundamentally alter the

Table 1
Example parameters and estimated exposed dose from Murphy et al., 2024 [24] and Mohammadjavadi et al., 2022 [28].

	Duration (s)	Ramp duration	Ramp shape	Pulse repetition interval/ Frequency	Isppa (W/cm^2)	Dose Pulse Train (J/cm^2)	Observed dose effect
Murphy et al., 2024							
Pulse	0.08	0	rectangular	0.4s/2.5Hz	0.3/1.2/ 2.3/3.7/ 5.4/7.4	0.3/1.2/ 2.3/3.7/ 5.4/7.4	In thalamic excitatory neurons, the initial excitatory response magnitude increases with increasing dose up to 5.4 J/cm^2 and plateaus after that. The subsequent depression is observed only at 3.7 J/cm^2, but not at higher or lower doses.
Pulse Train	5	0	rectangular				

	Duration (s)	Ramp duration	Ramp shape	Repetition interval/ Frequency	(simulated in situ) Isppa (W/cm^2)	Dose Pulse Train Repeat (J/cm^2)	Observed dose effect
Mohammadjavadi et al. 2022 [28]							
Pulse	0.001	0	rectangular	0.002 s/500 Hz	17.26/18.99/ 32.20/50.96/ 83.05/118.44	77.67/85.46/ 144.90/229.32/ 373.73/532.98	No dose effect was examined in this study. The different Isppas were a result of differences in skull attenuation across subjects. Isppa was not systematically varied within subjects. However, a correlation was found between the suppression of visual evoked potentials and tissue displacement estimated using magnetic resonance acoustic radiation force imaging.
Pulse train	0.3	0	rectangular	1 s/1 Hz			
Pulse train repeat	30	0	rectangular				

pulsing regime to a continuous wave which may even be less effective [2,29]. Accounting for these considerations, our proposed definition of dose is a pragmatic and neutral starting point, while our understanding of ultrasonic neuromodulatory mechanisms continues to improve.

4. Conclusions

In this paper, we summarise how the bioeffects of ultrasound can be tuned by adjusting the parameters of the application. We provide a theoretical framework for conceptualising dose and propose a preliminary definition for US dose that is agnostic to the underlying biophysical effect.

CRediT authorship contribution statement

Tulika Nandi: Writing – review & editing, Writing – original draft, Visualization, Project administration, Conceptualization. **Benjamin R. Kop:** Writing – review & editing, Visualization. **Kasra Naftchi-Ardebili:** Writing – review & editing, Visualization. **Charlotte J. Stagg:** Writing – review & editing, Conceptualization. **Kim Butts Pauly:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Lennart Verhagen:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kim Butts Pauly reports a relationship with Attune Neurosciences that includes: consulting or advisory and equity or stocks. Kim Butts Pauly reports a relationship with MR Instruments that includes: non-financial support. Lennart Verhagen reports a relationship with Nudge LLC that includes: consulting or advisory. Lennart Verhagen reports a relationship with Sonic Concepts Ltd that includes: non-financial support. Lennart Verhagen reports a relationship with Image Guided Therapy that includes: non-financial support. Lennart Verhagen has a relationship with Brainbox Initiative as a member of the scientific committee. Charlotte J. Stagg is a Deputy Editor at Brain Stimulation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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