NEUROFUS LT™

FOCUSED ULTRASOUND FOR NON-INVASIVE NEUROMODULATION

POWERED BY

SONIC CONCEPTS

INTRODUCING NEUROFUS LT™

NEUROFUS LT™

The NeuroFUS LT™ and PRO™ are turnkey systems that deliver low-intensity (nonthermal) focused ultrasound (FUS) for transcranial brain or transdermal nerve modulation to support neuroscience research studies as well as medical device research and development.

Available in PRO and LT versions, NeuroFUS represents a state-of-the-art, noninvasive neuromodulation method. NeuroFUS hardware is electromagnetically and mechanically compatible with other modern neuroscience methods and neurotechnologies. These compatible neurotechnologies include: human behavior, optical imaging (including fNIRS), EEG, AR/VR immersion or stimulation, peripheral nerve stimulation including VNS, and other neuromodulation methods such as tES, tDCS, tACS, and TMS.

Both NeuroFUS versions are powered by Sonic Concepts, Inc.'s Transducer Power Output™ (TPO™) drive electronics, commander USB interface and focused annular array transducer technology. Both versions of the turnkey system provide ultrasound pulse capability for both cortical and peripheral stimulations with dynamic focal depth adjustment with treatment precision. Each unit is calibrated and comes with a Certificate of Conformance.

The NeuroFUS PRO™ takes the NeuroFUS LT™ version to the next level and comes equipped with the Software Development Kit (SDK) and safety peripherals, and includes a workshop, training and consulting package and access to integration packages including TMS and neuro navigation systems.

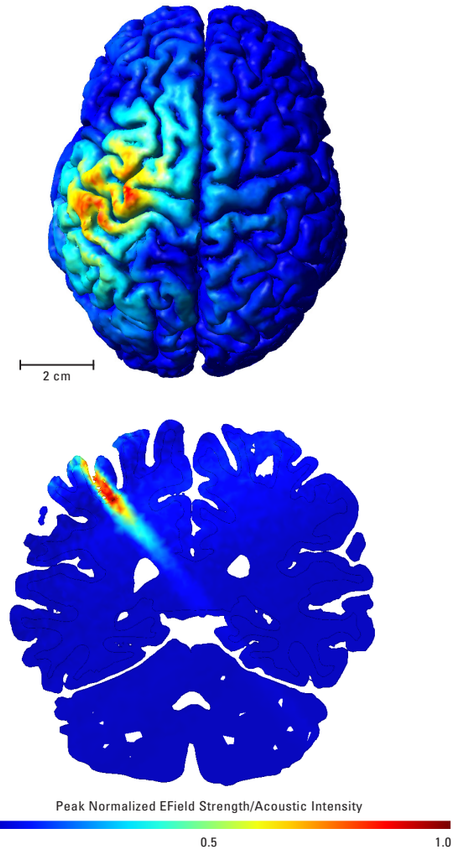
The NeuroFUS system is not an FDA-evaluated medical device. The system is for research purposes only and is not intended for the treatment of any medical disorder or condition. More information is available on the last page.

WHY NEUROMODULATION BY FOCUSED ULTRASOUND?

Transcranial NeuroFUS provides spatial resolutions that are higher than other noninvasive neuromodulation methods.

The top image to the right illustrates the spatial distributions of a typical electric field produced by TMS. The spatial distribution (resolution) of peak electric field strengths produced by TMS extend up to several centimeters in some directions.

The image at bottom-right illustrates transcranial NeuroFUS can significantly modulate physiological EEG activity in the cortex of healthy humans with precise spatial resolution (Legon et al, Nature Neuroscience, 2014). As shown, the shape of the 0.5 MHz transcranial ultrasound focus is an ellipsoid, equivalent to the CTX-500 (see table ahead). This method has been reproduced by others showing focused neuromodulation is safe, confers high spatial resolutions, and is readily compatible with electrophysiology and imaging methods such as EEG and fMRI.



HOW DOES NEUROFUS LT WORK?

The NeuroFUS LT system uses the TPO drive electronics system comprised of four discrete RF signals with independent transmit agility. The TPO uses high-fidelity amplifier technology to produce spectrally pure sinusoidal signals. Each channel supports transmit modes ranging from a single cycle pulse to large bursts.

The NeuroFUS transducer is comprised of four sub-apertures built within the monolithic transducer, low-loss cabling and matching circuitry. The amplified sinusoidal voltage waveform passes through the matching network, cable and into the respective sub-aperture of the transducer, which converts voltage to pressure.

The integrated system uses time delay to electronically steer the acoustic focus along the axis with micrometer resolution. Acoustic intensity and beamforming calibration are performed within a free field environment. The user may implement aberration and attenuation corrections as determined by their internal review board.

To properly couple the transducer's spherical radiating surface to the patient, a solid water coupling material fills the concavity of the spherical bowl until the exit plane of the transducer is flat. With the solid water coupling material in intimate contact with the patient, the acoustic pressure is able to propagate to the subject's treatment sight. The FUS transducer is equipped with a handle for manual positioning about the subject's surface.

WHAT TRANSDUCER TO USE WITH NEUROFUS?

NeuroFUS LT offers three Cortical Focus Transducer (CTX) configurations and one micro-Focused Transducer (uTX). Each NeuroFUS LT uses one TPO to drive all four transducer configurations. Any number of purchased transducer configurations (1 to 4) may be calibrated to the same TPO.

The CTX transducers are offered at 250 kHz, 500 kHz and 1,000 kHz using a 60 mm diameter x 64 mm radius of curvature. Selecting the appropriate CTX transducer depends on the attenuation along the propagation path, focal size and effective frequency in neurostimulation. The uTX-2500 operates at 2.5 MHz and is intended for small animal CTX and/or peripheral neurostimulation.

The table below compares the NeuroFUS transducer configurations focal size with their estimated derated focal intensity*.

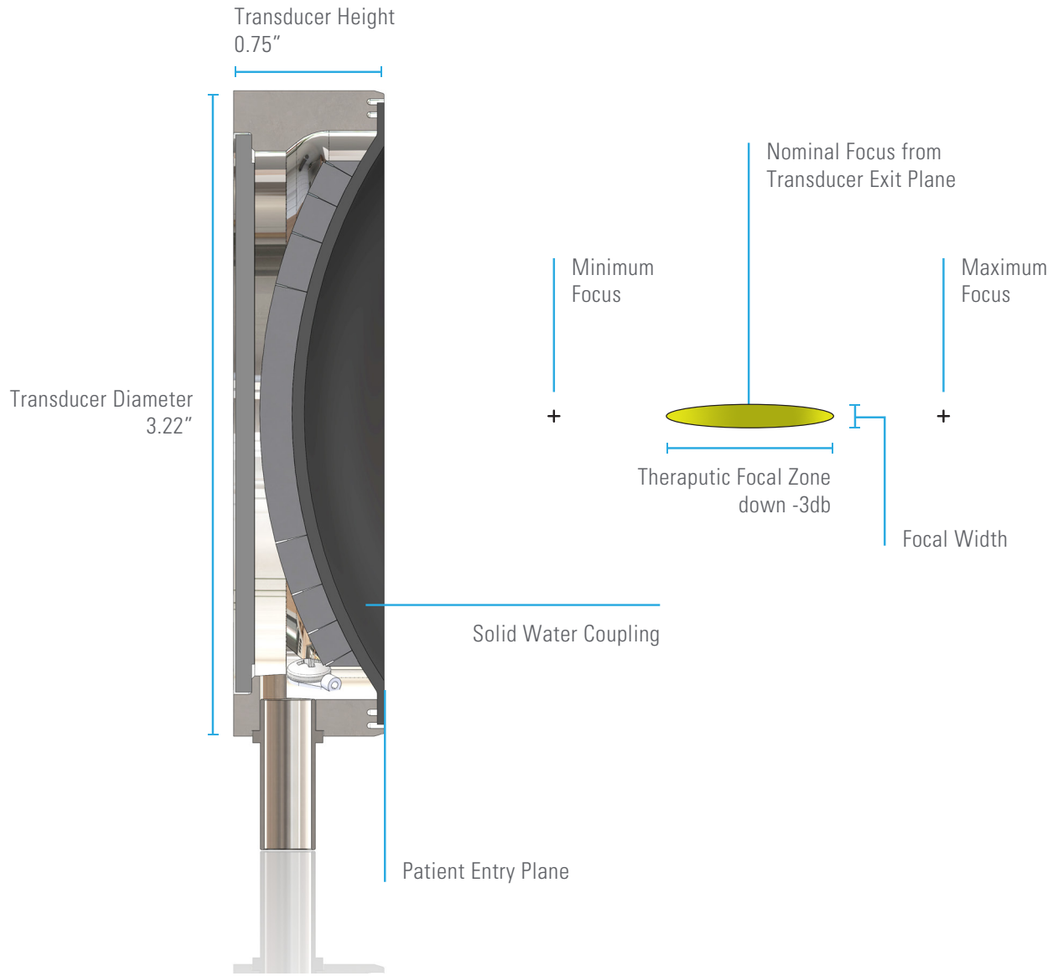
	Center Frequency MHz	Peak Power Watts	Total Acoustic Power Watts	Distance to Focus mm	Focal Intensity (free field) W/cm^2	Focal Intensity (2.7 dB/cm derated) W/cm^2	Focal Lateral Width (dia) mm	Focal Axial Length mm
CTX-250	0.25	16.85	14.3	40	30.0	16.1	6.45	43.99
CTX-500	0.50	4.00	3.4	52	30.0	5.9	3.14	23.04
CTX-1000	1.00	0.95	0.8	52	30.0	1.2	1.53	11.53
uTX-2500	2.50	0.08	0.1	13	30.0	4.0	0.46	2.64

*Human skull average: ncbi.nlm.nih.gov/pubmed/22225300

See NeuroFUS LT versions ahead.

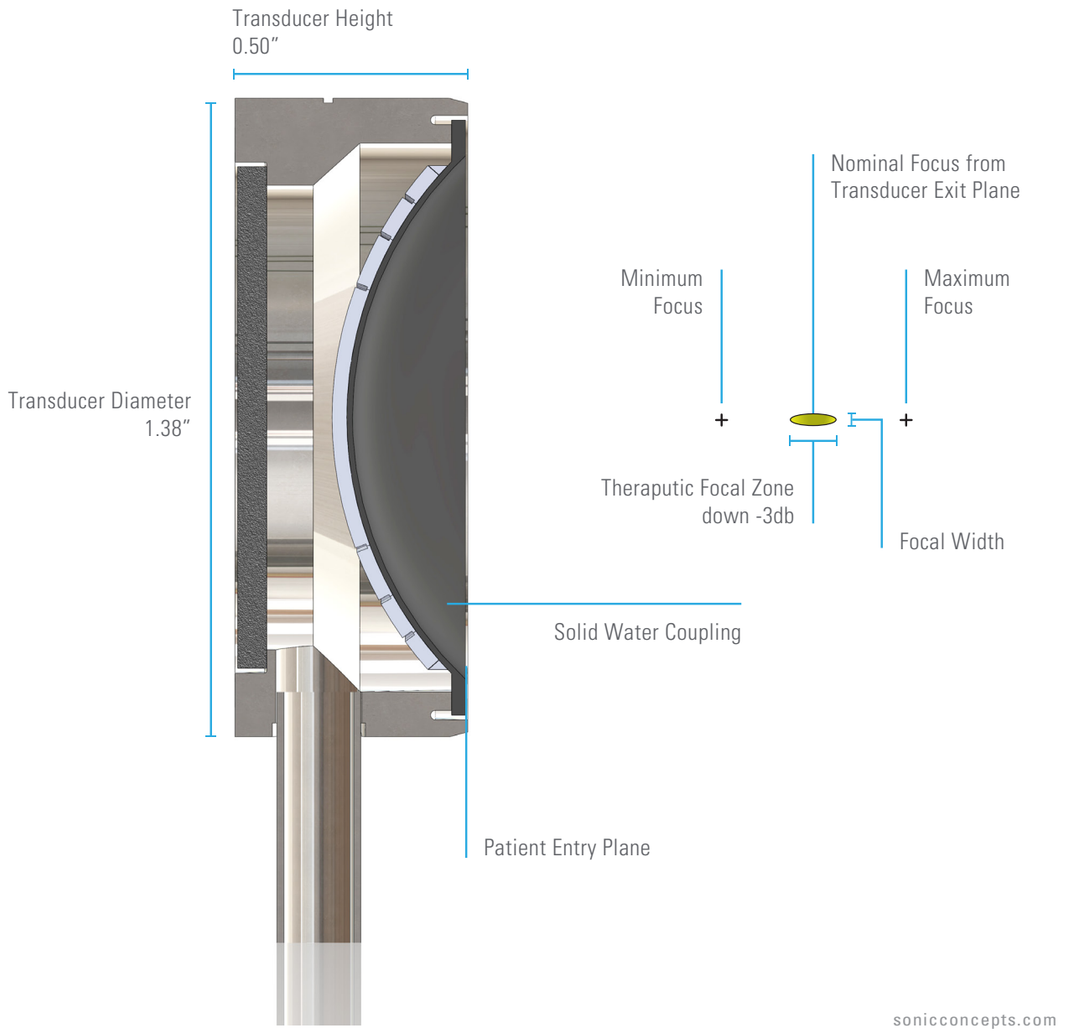
CTX DRAWING

*Not to scale



uTX DRAWING

*Not to scale



NEUROFUS LT TRANSDUCER VERSIONS

	Product Description	Itemized Breakout
CTX-250	**Cortical Focused Transducer ('CTX') - 250** *Intended for use with large subjects* NeuroFUS LT CTX 250 provides a center frequency at 250 kHz and uses 2 discrete elements for axial focal steering. More details include: - 64 mm spherical radius x 64 mm aperture diameter - 6 mm diameter x 39 mm long elipsodial focus down -3dB - Operationg frequency range from 200 to 300 kHz - Axial focal steering from 30 to 70 mm from the patient's entry plane* *Other 40 mm axial steering ranges available upon request	- H-115-2AA HIFU tranducer - TPO-201 2-channel drive electrionics system and parser commander - BCS-103 coupling system - Visual thermochromatic target verification - TPO to acoustic focus calibration & focal steering calibration (assuming a linear free field)
CTX-500	**Cortical Focused Transducer ('CTX') - 500** *Intended for use with large subjects* NeuroFUS LT CTX 500 provides a center frequency at 500 kHz and uses 4 discrete elements for axial focal steering. More details include: - 64 mm spherical radius x 64 mm aperture diameter (f/1) - 3 mm diameter x 22 mm long elipsodial focus down -3dB - Operating frequency range from 400 to 600 kHz - Axial focal steering from 30 to 70 mm from the patient's entry plane* *Other 40 mm axial steering ranges available upon request	- H-104-4AA HIFU transducer - TPO-203 4-channel drive electronics system and parser commander - BCS-102 coupling system - Visual thermochromatic target verification - TPO to acoustic focus calibration & focal steering calibration (assuming a linear free field)

NEUROFUS LT TRANSDUCER VERSIONS

	Product Description	Itemized Breakout
CTX-1000	**Cortical Focused Transducer ('CTX') - 1000** *Intended for use with large subjects* NeuroFUS LT CTX 1000 provides a center frequency at 1,100 kHz and uses 4 discrete elements for axial focal steering. More details include: - 64 mm spherical radius x 64 mm aperture diameter (f/1) - 1.5 mm diameter x 10 mm long elipsodial focus down -3dB - Operationg frequency range from 900 to 1,300 kHz - Axial focal steering from 30 to 70 mm from the patient's entry plane* *Other 40 mm axial steering ranges available upon request	- H-101-4AA HIFU tranducer - TPO-203 4-channel drive electrionics system and parser commander - BCS-102 coupling system - Visual thermochromatic target verification - TPO to acoustic focus calibration & focal steering calibration (assuming a linear free field)
uTX-500	**Micro-Focused Transducer ('uTX') - 2.5** *Intended for peripheral use and/or with small subjects* NeuroFUS LT micro-TX 2.5 provides a center frequency at 2.5 MHz and uses 4 discrete elements for axial focal steering. More details include: - 20 mm spherical radius x 25 mm aperture diameter (f/0.8) - 0.5 mm diameter x 3.0 mm long elipsodial focus down -3dB - Operating frequency range from 2.0 to 3.0 MHz - Axial focal steering from 0 to 10 mm from the patient's entry plane* *Other 40 mm axial steering ranges available upon request	- SU-132-4AA HIFU transducer - TPO-203 4-channel drive electrionics system and parser commander - BCS-132 coupling system - Visual thermochromatic target verification - TPO to acoustic focus calibration & focal steering calibration (assuming a linear free field)

FOCAL INTENSITY

All NeuroFUS LT transducers convert 85 percent of electrical power into acoustic power. The total acoustic power (TAP) remains the same at each transverse plane along the propagation axis, assuming a linear free field. At the spherical surface of the transducer the TAP can be interpreted as intensity (TAP / aperture area), and as pressure, where $I = p^2/(D \times c)$ in Watt/m². The transducer's frequency, spherical size and f-number are used to determine focal gain. This focal gain is then multiplied with the intensity to predict free field estimates of the spatial-peak pulsed average intensity (ISPPA).

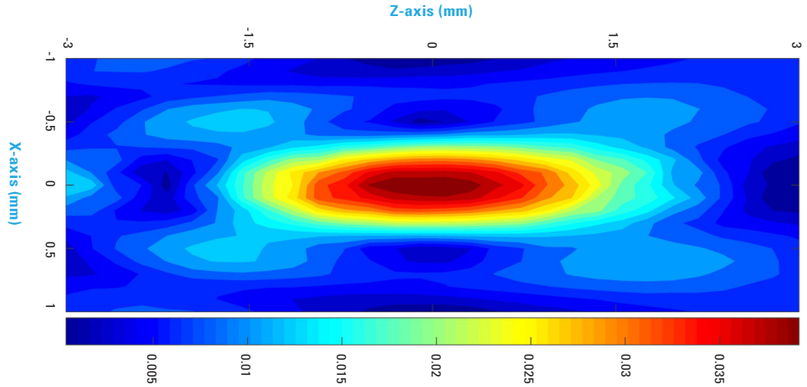
ATTENUATION

Transcranial applied ultrasound will be attenuated along the propagation path. Several studies have shown on average 2.7 dB/cm* is lost through the human skull between the transducer and focus. Of this attenuation, most of the loss is attributed to scattering and reflections within the skull. NeuroFUS hard limits the predicted non-derated (free field) ISPPA. Each NeuroFUS unit's drive electronics are calibrated to the measured non-derated acoustic focus at Sonic Concepts using a needle hydrophone tracible to the National Physical Laboratoy (NPL).

*Human skull average: ncbi.nlm.nih.gov/pubmed/22225300

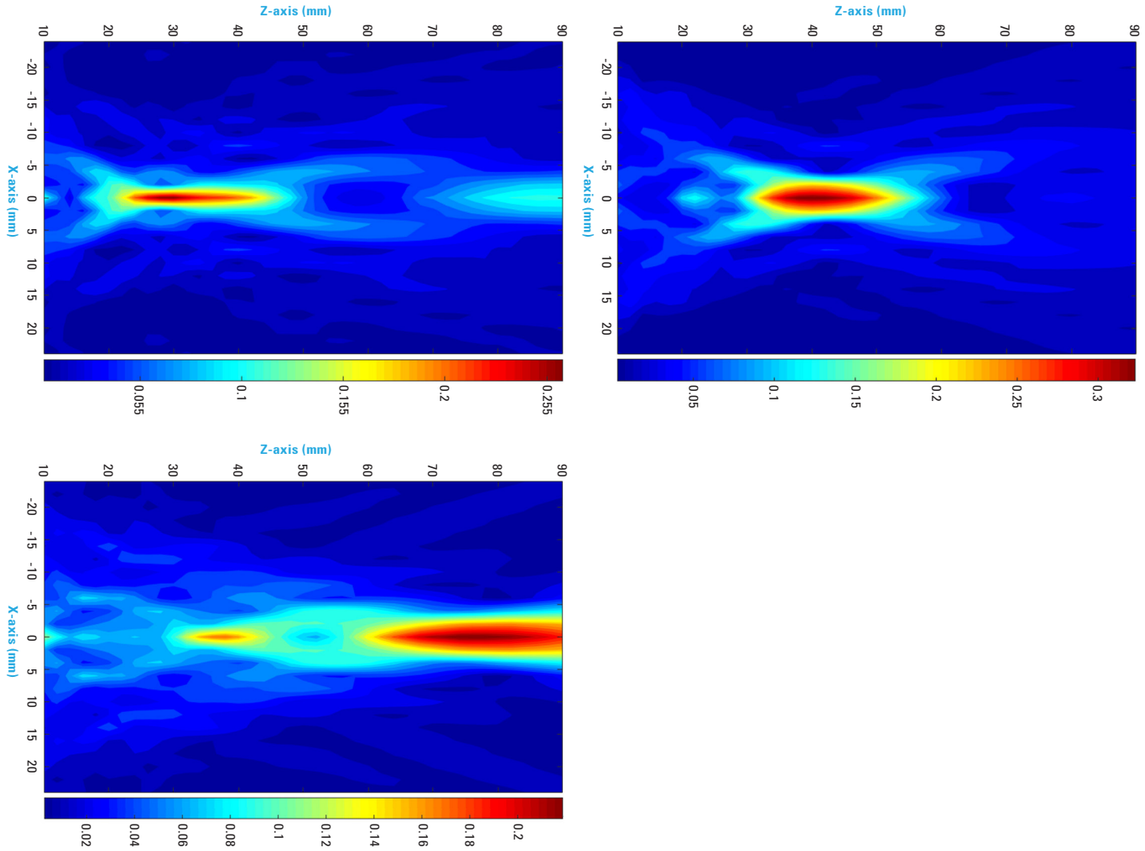
SPATIAL RESOLUTION

The acoustic pressure field below illustrates the uTX-2500 transducer's focus along the transverse plane. The coherent focus measures 0.5 mm lateral width x 2.6 mm axial length down -3 dB from its acoustic maximum. Units are in millimeters and the relative acoustic pressure data is then diplayed using a red (maximum) to blue (minimum) color spectrum.



DYNAMIC FOCAL DEPTH STEERING

The acoustic pressure field maps below illustrate software-controlled spatial modulation of the NeuroFUS CTX-500 along the transverse plane. The NeuroFUS focus is shown at 30 mm (top left), 40 mm (top right), and 75 mm (bottom) depths.



The table below presents the steering range and penetration distance for each NeuroFUS transducer. *Grating Lobe Range* refers to the steering range tested where all grating lobes appear more than 10 dB from the intended main focus. The *Penetration Distance* refers to the distance between the transducer face and the focus, considering the grating lobe range.

	Center Frequency MHz	Distance to Focus mm	Grating Lobe Range mm	Penetration Distance Minimum mm	Penetration Distance Maximum mm
CTX-250	0.25	40	40	20	60
CTX-500	0.50	52	40	32	72
CTX-1000	1.00	52	40	32	72
uTX-2500	2.50	13	7	9.5	16.5

POWER ESTIMATES & COMPARISONS

The table below calculates the effective electrical power required to compensate for the -3 dB steering loss. For example, when steering the CTX-500 to the mininum penetration distance of 32 mm, the power output doubles to correct for the -3 dB loss to maintian the 30 W/cm^2.

	Center Frequency MHz	Peak Power Watts	Total Acoustic Power Watts	Distance to Focus mm	-3 dB of Max Focal Intensity (free field) W/cm^2
CTX-250	0.25	33.73	28.7	40	30.0
CTX-500	0.50	8.00	6.8	52	30.0
CTX-1000	1.00	1.90	1.6	52	30.0
uTX-2500	2.50	0.16	0.1	13	30.0

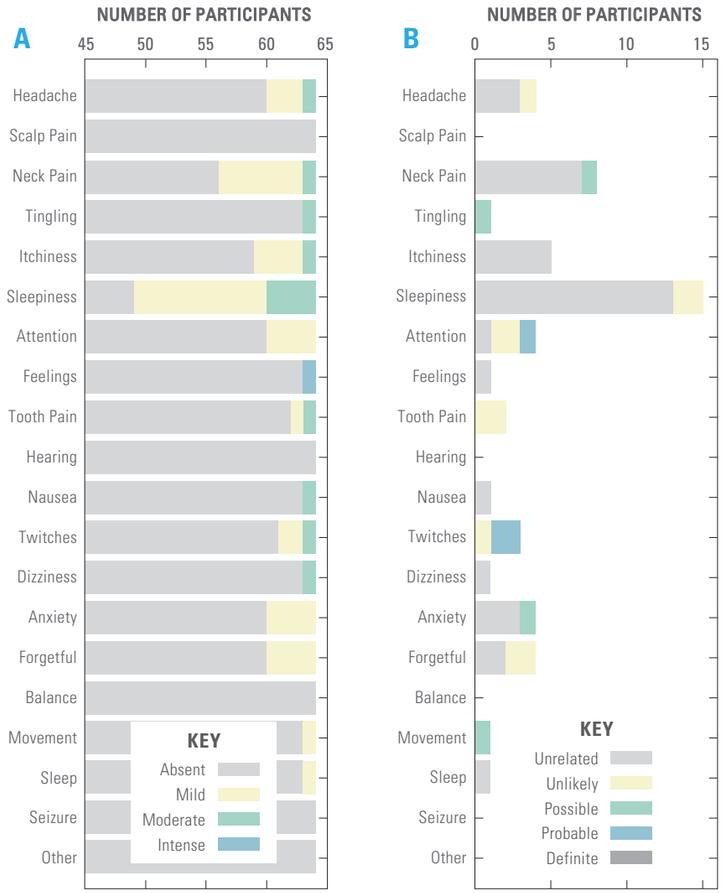
SAFETY

NeuroFUS has been shown to be safe for acute use in numerous animal models including humans. A recent study examined acute safety in 120 human subjects across a series of seven different tFUS neuromodulation studies (adapted from Legon et al etc.). Data from this safety study are illustrated in the figure below.

Histogram (A) illustrates the severity of side effect outcomes while the right histogram (B) shows the outcomes scored by the subjective relation to the pulsed ultrasound treatment.

Here are two power-limiting options to consider:

- I_sppa 30 Watts, no deration correction, with steering amplitude correction. I_spta 720 mW/cm^2.
- I_sppa 30 Watts, no deration correction, with steering amplitude correction. I_spta 15.0 W/cm^2 (or I_sppa *50% duty cycle)



NEUROFUS PRO

NEUROFUS PRO™

NeuroFUS is not agency compliant. NeuroFUS PRO includes enhanced safety features compared to NeuroFUS LT.

NeuroFUS PRO is available upon request *(NeuroFUS LT is upgradable, not including transducer)*

- Software Development Kit (SDK) including several neuromodulation pulse sequences
- Safety peripherals including:
  - RFWattmeter™ monitoring with automatic shutdown
  - Floating ground transducer casing hi-pot tested to pass 2MOPP
  - Peak and average power limiting
- Ergonomic handheld handle and solid coupling bolus (water free)
- Inclusive workshop, training and neuromodulation consultation
- Access to integration packages including TMS and neuro navigation systems

LIMITATIONS & UPGRADES

- The NeuroFUS LT system is not CE marked and is not agency compliant.
- The NeuroFUS LT system does not offer a floating ground transducer with a fully insulated shell that will be tested up to 2 MOPP.
- The NeuroFUS LT system does not include real-time power monitoring using Sonic Concepts' RFWattmeter.
- The NeuroFUS LT system shall pass the customers internal review board or equivalent before use on humans.
- All NeuroFUS LT transducers are upgradable to be MR-compatible.

SONIC CONCEPTS

The launch of NeuroFUS hardware represents a decade-long, science, technology, and engineering development effort. NeuroFUS Products for Research & Development applications are provided by Sonic Concepts.

Sonic Concepts, Inc. founded in 1986 of Bothell, Washington delivers premium ultrasonic systems to biomedical, industrial, marine, and research markets. They specialize in designing and manufacturing High Intensity Focused Ultrasound (HIFU) transducers, electronics, and software. Their systems are installed in leading corporate and academic research labs around the globe.

BRAINBOX

Sonic Concepts is working with Brainbox, Ltd., as their international distributor. Brainbox brings several decades of experience in developing, integrating, and distributing cutting-edge neurotechnologies for neuromodulation and brain mapping to end user scientists, engineers, and physicians conducting neuroscience R&D.

INTELLECTUAL PROPERTY

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