

Low-intensity Transcranial Ultrasound Stimulation



Estelle Raffin,
CNRS researcher,
Grenoble, France



Outline

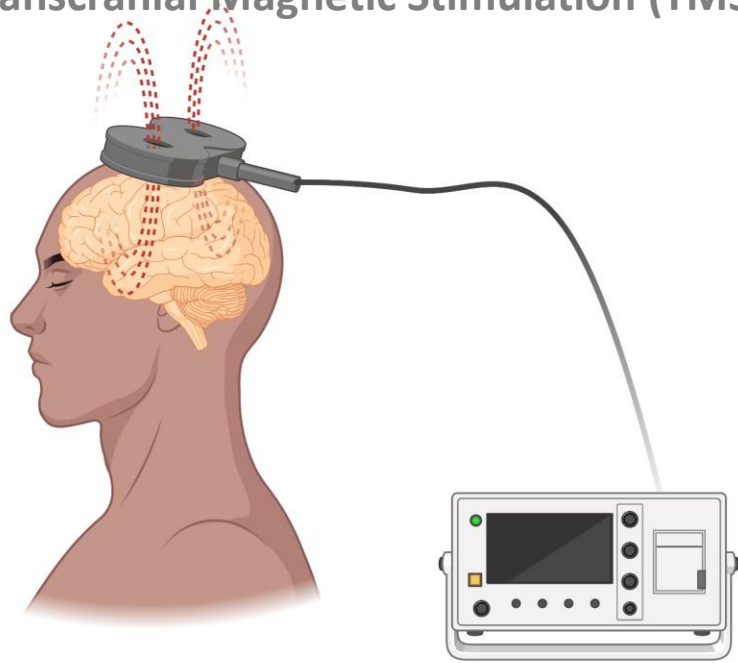
- The conventional NIBS techniques & their limitations
- Other opportunities to remotely transfer energy?
- Historical developments of TUS
- Mechanisms of TUS
- TUS for Neuromodulation (online & offline applications)
 - Animal work
 - Human work
- Clinical applications
- Designing experiments

Brain stimulation wish-list:

- Non-invasive
- Focal
- Surface & deep

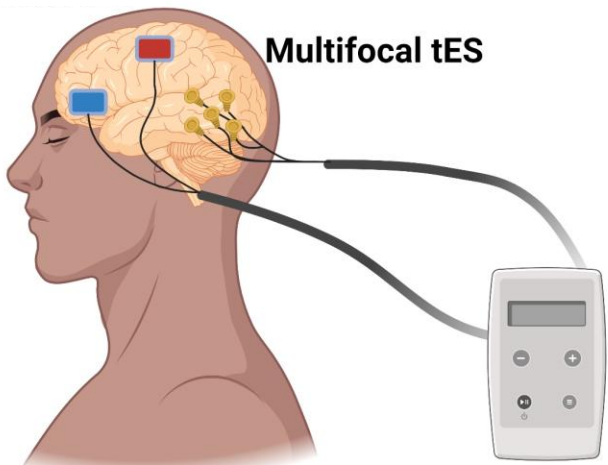
The conventional NIBS techniques and their limitations

Transcranial Magnetic Stimulation (TMS)



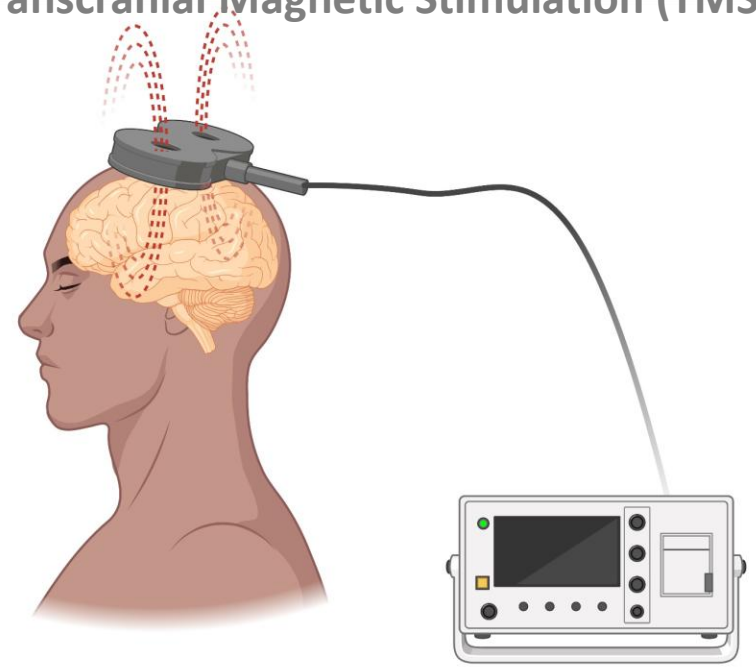
Transcranial Electric stimulation (tES)

Bifocal tES



Conventional non-invasive brain stimulation techniques

Transcranial Magnetic Stimulation (TMS)



Single pulse ⚡

Probe corticospinal excitability

Double pulse ⚡⚡

Probe cortical excitation/inhibition

DIAGNOSTIC TOOL

Repeated ⚡⚡⚡⚡

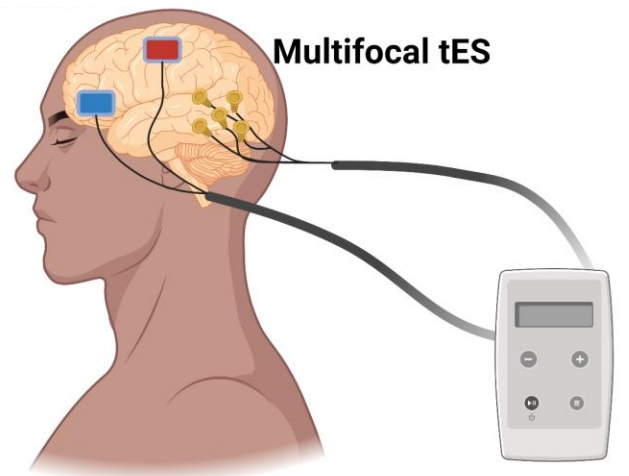
Modulate brain activity

Low frequency: Inhibitory - LTD-like
High frequency: Excitatory - LTP-like

THERAPEUTIC TOOL

Transcranial Electric stimulation (tES)

Bifocal tES



Multifocal tES

tDCS

Continuous current
Anodal: Excitatory
Cathodal: Inhibitory

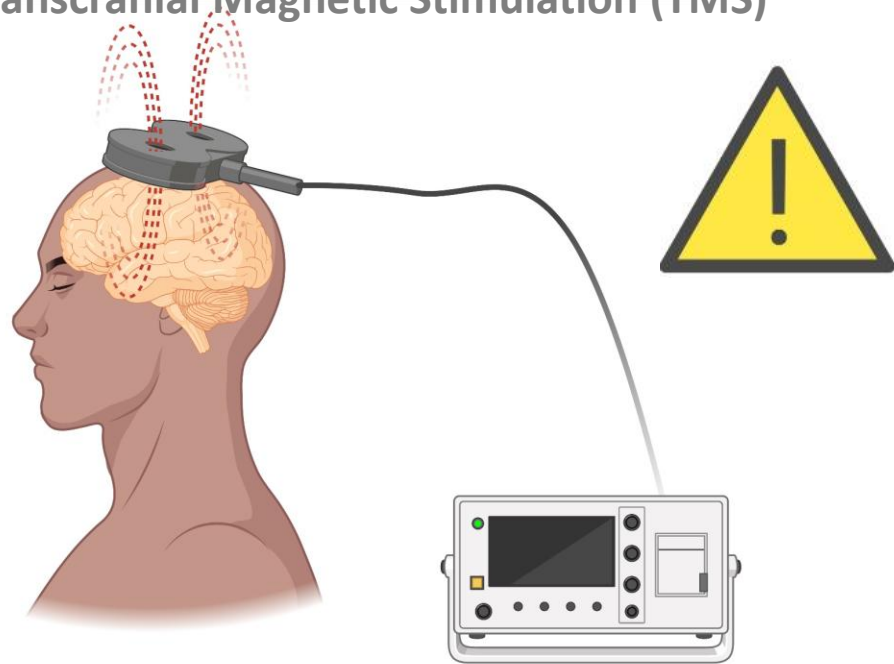
tACS

Alternative current
Frequency-dependent effects (Hz)

tRNS

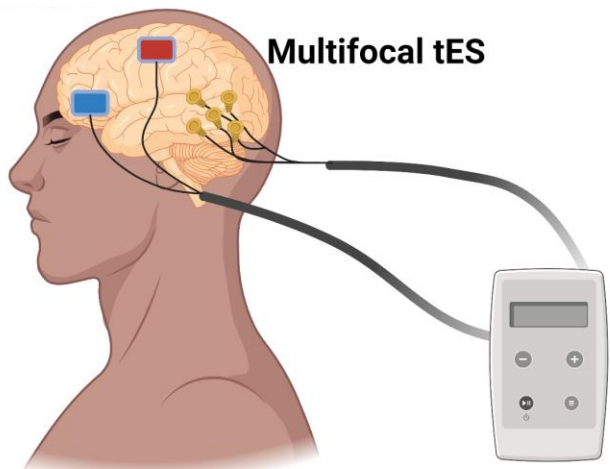
Alternative current
Random frequencies (1-640Hz)

Transcranial Magnetic Stimulation (TMS)

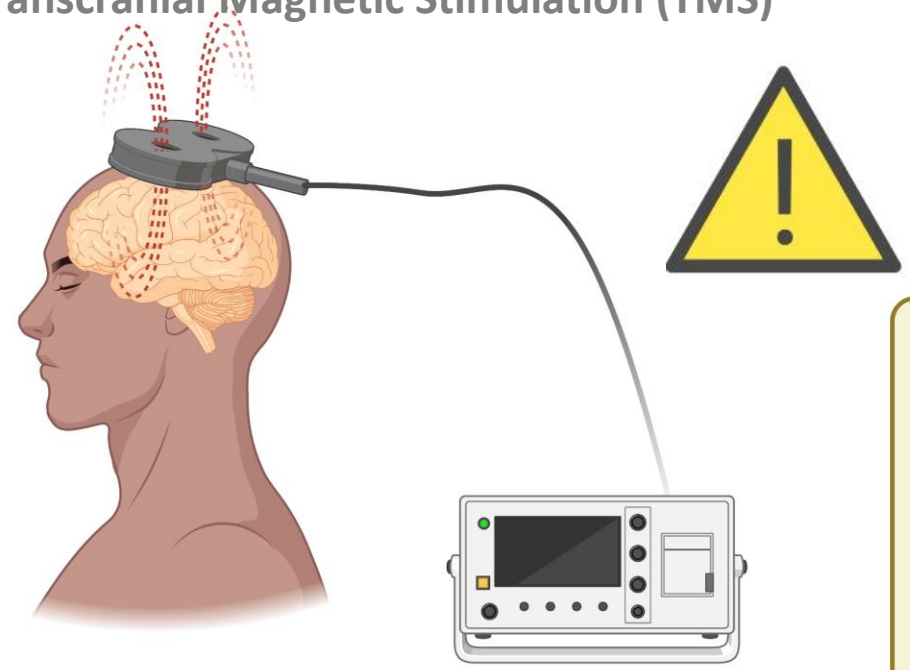


Transcranial Electric stimulation (tES)

Bifocal tES

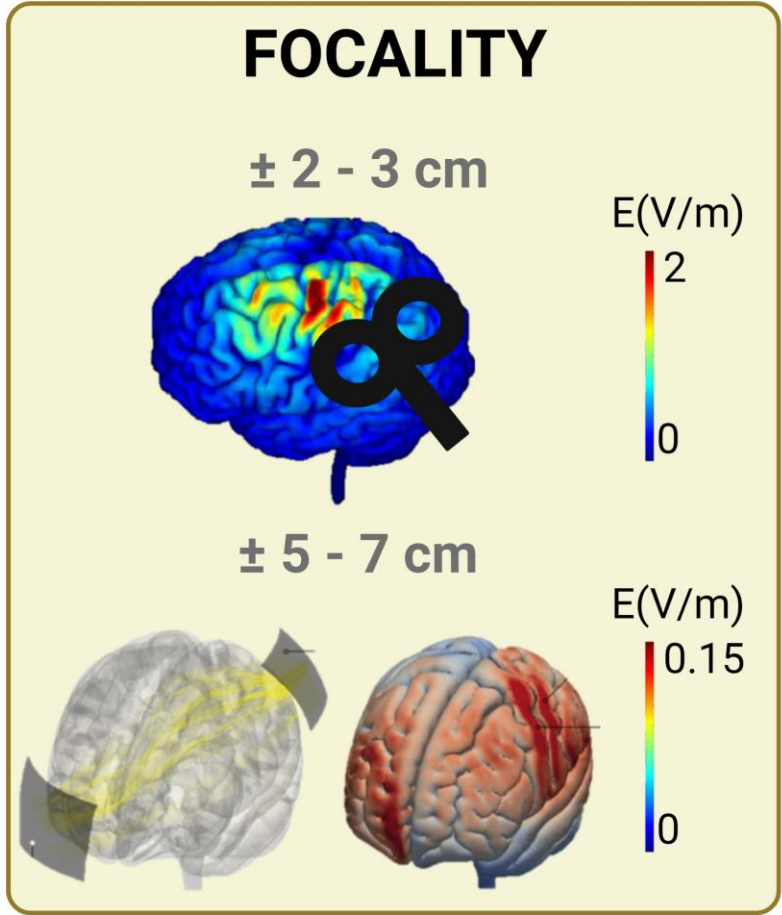
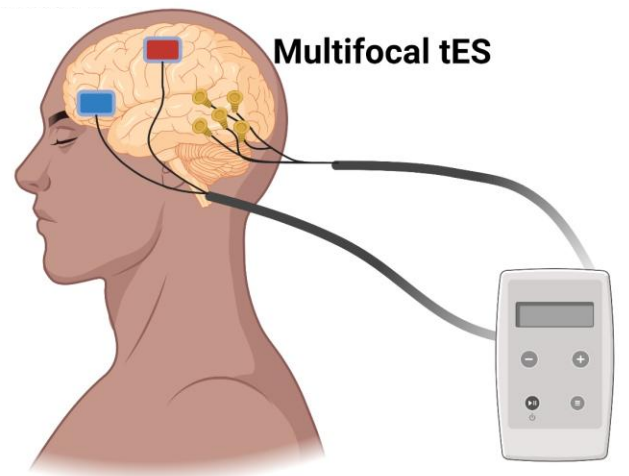


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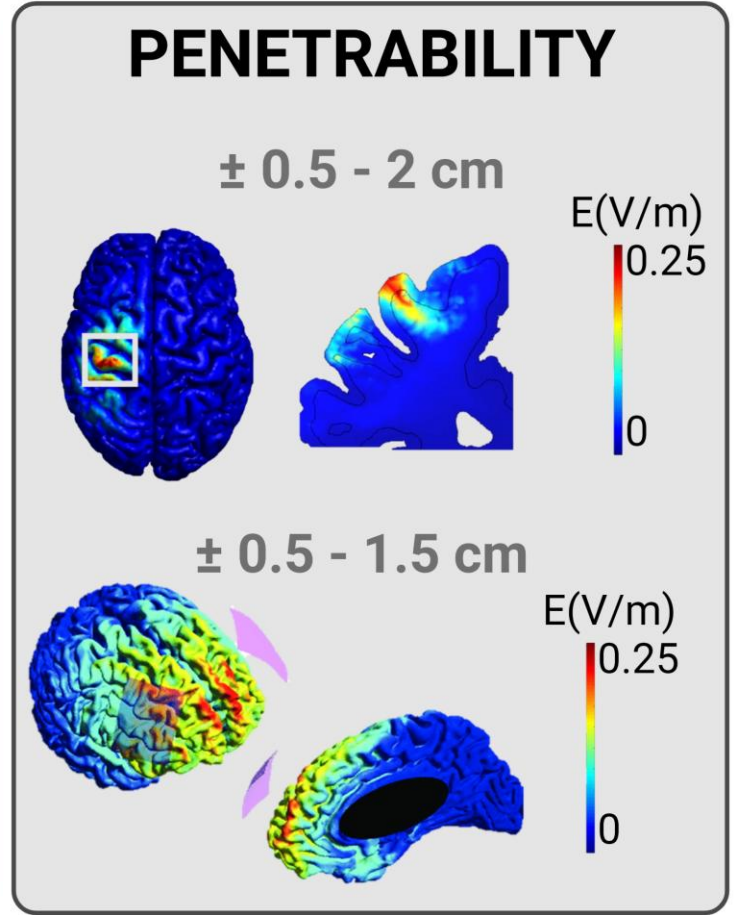
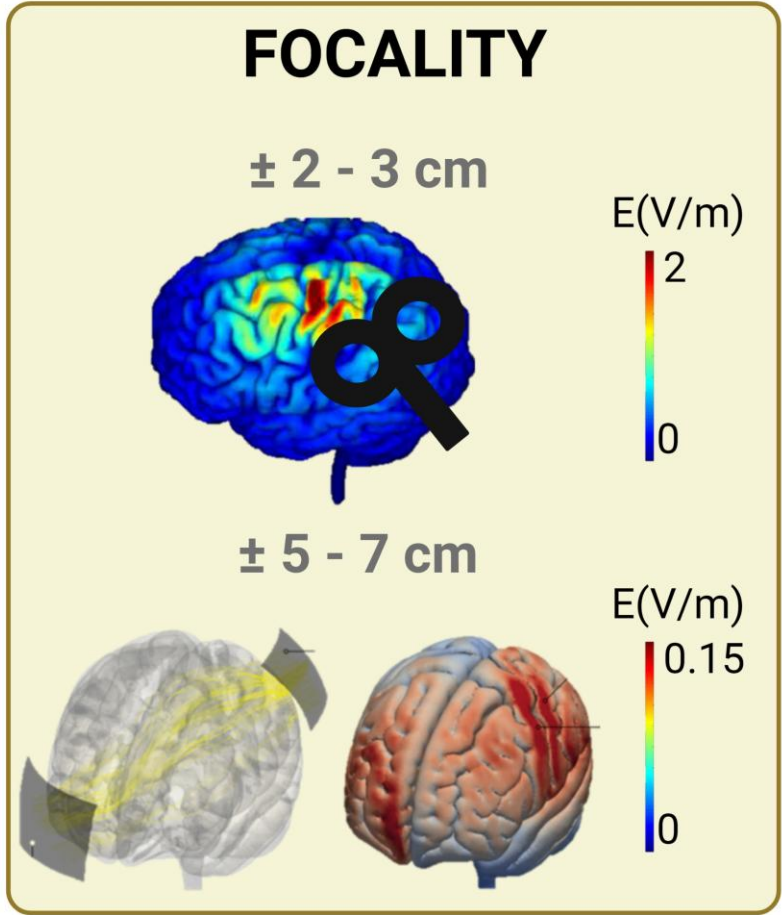
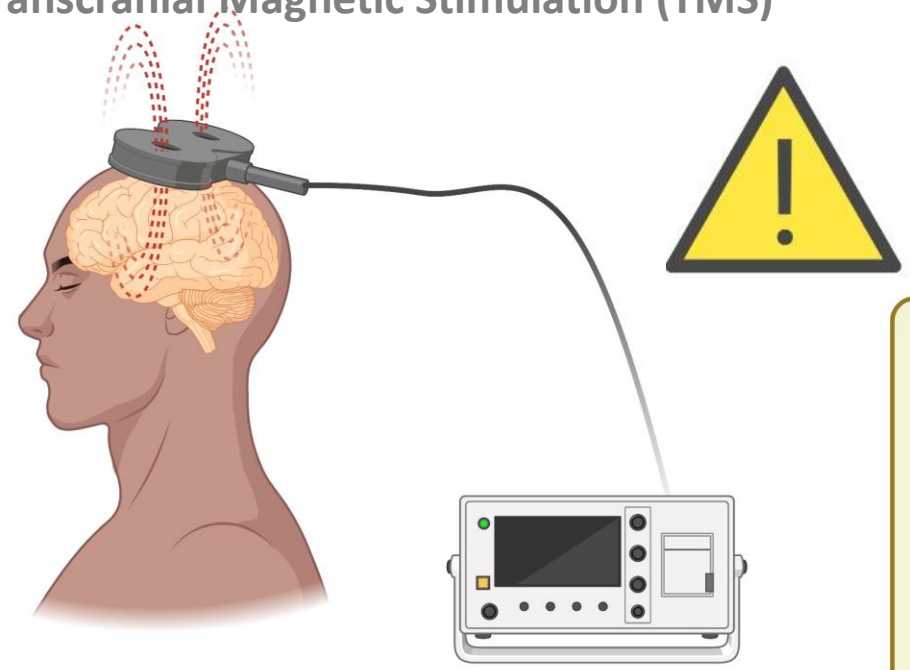


Transcranial Electric stimulation (tES)

Bifocal tES

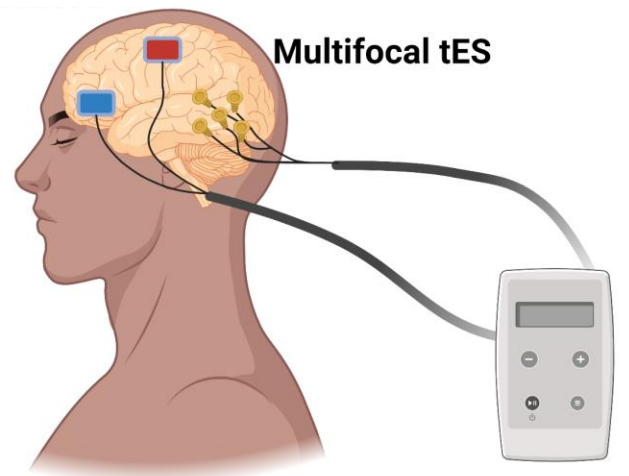


Transcranial Magnetic Stimulation (TMS)

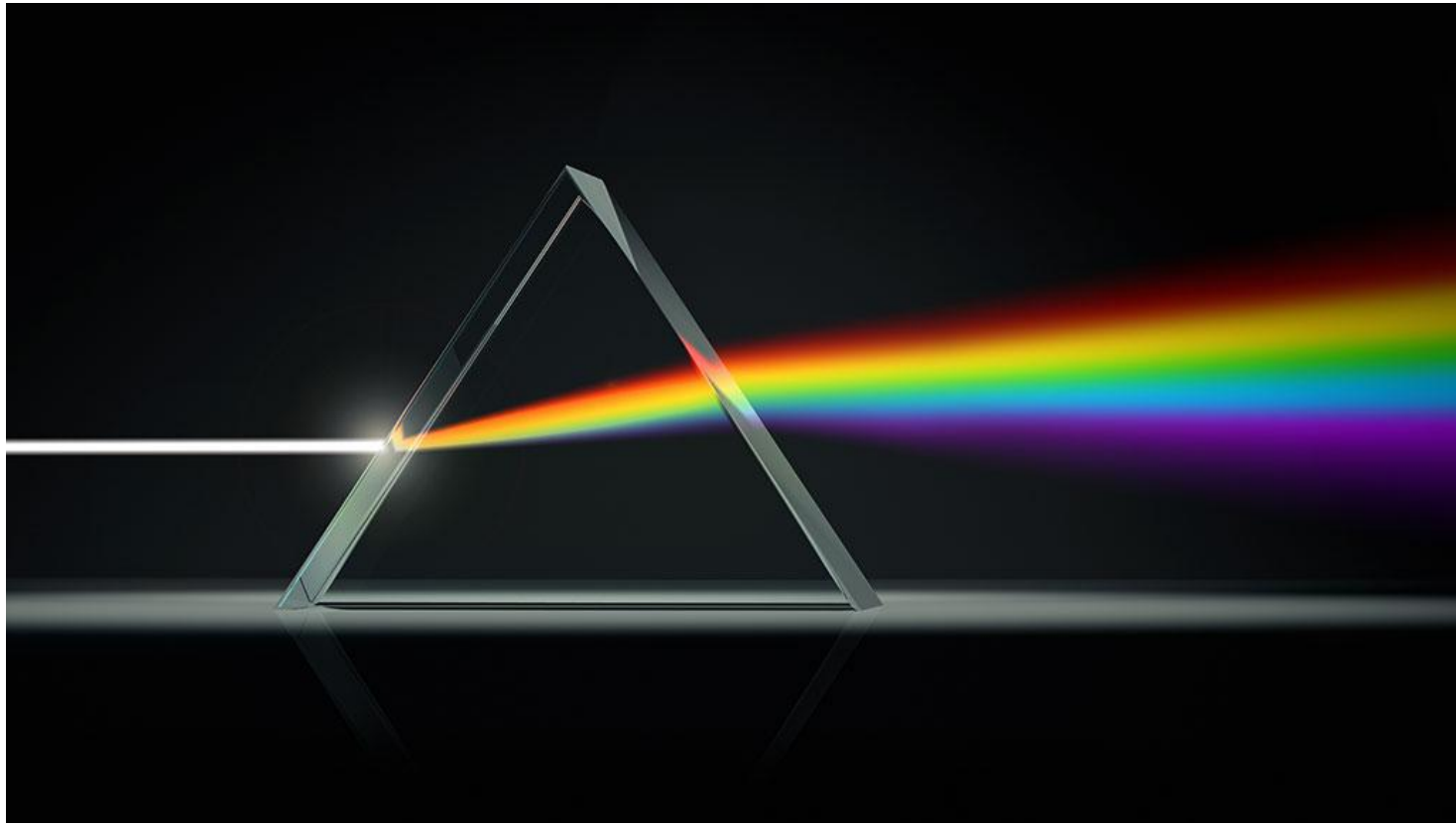


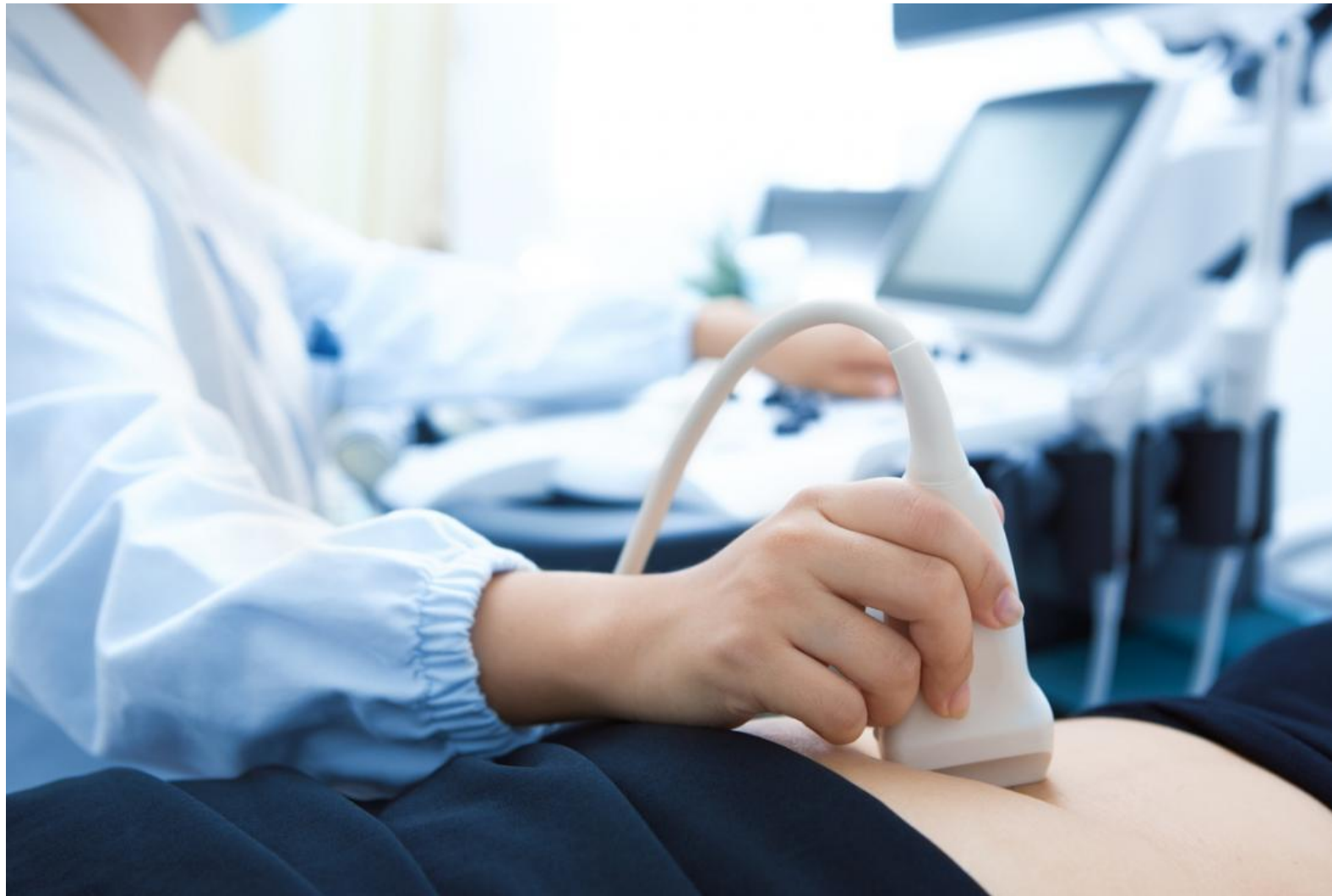
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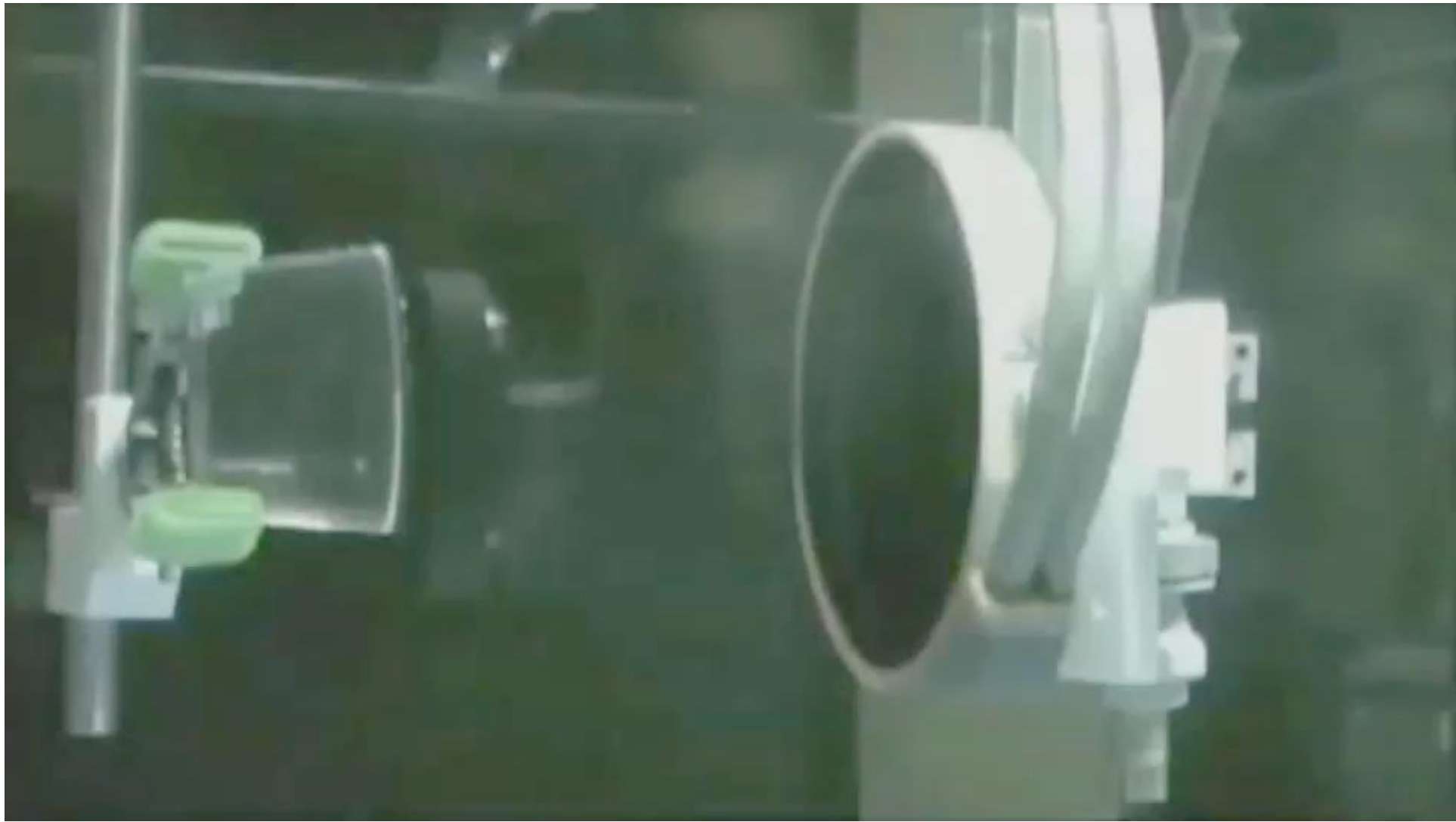
Bifocal tES

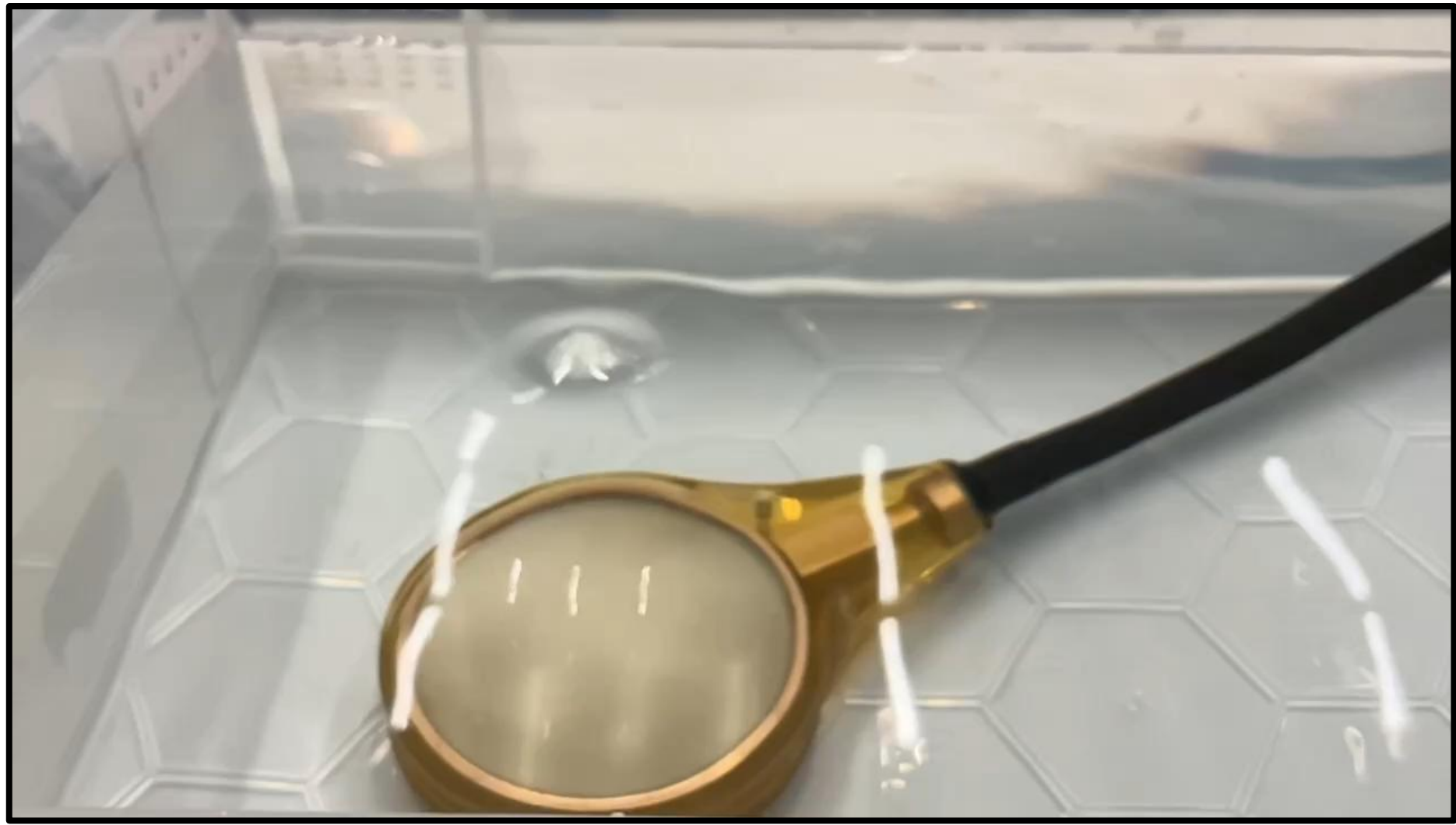


Other opportunities to remotely transfer energy

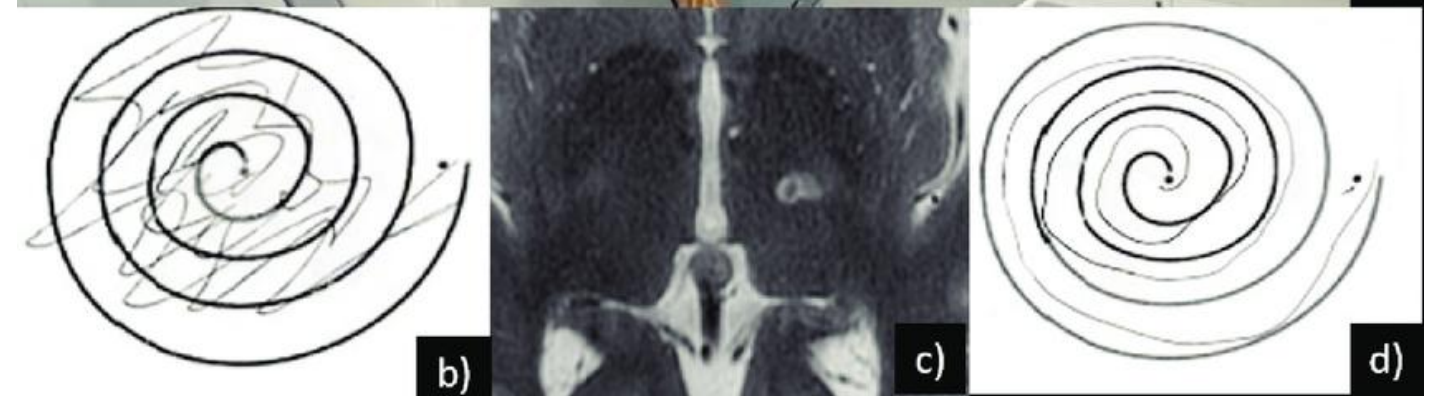








High-intensity TUS for thalamotomy



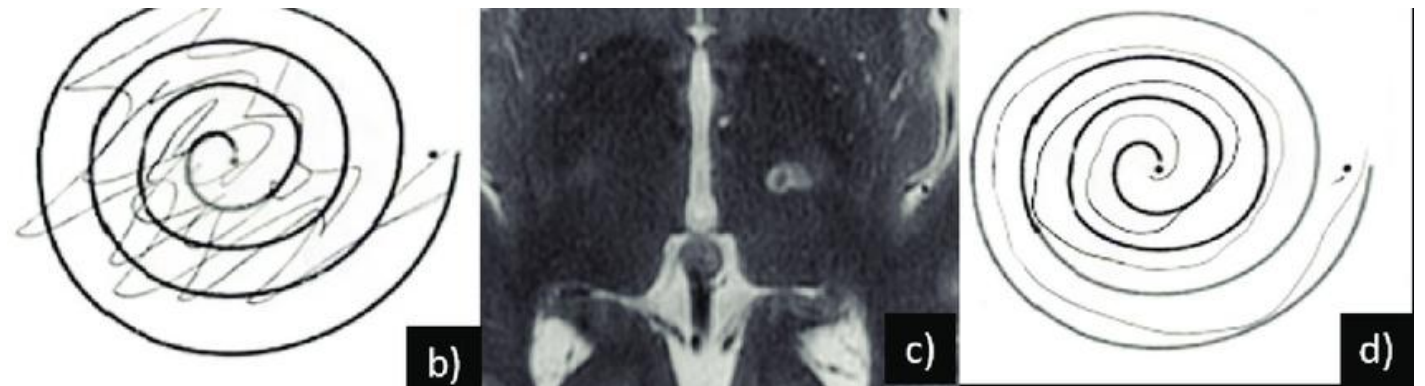
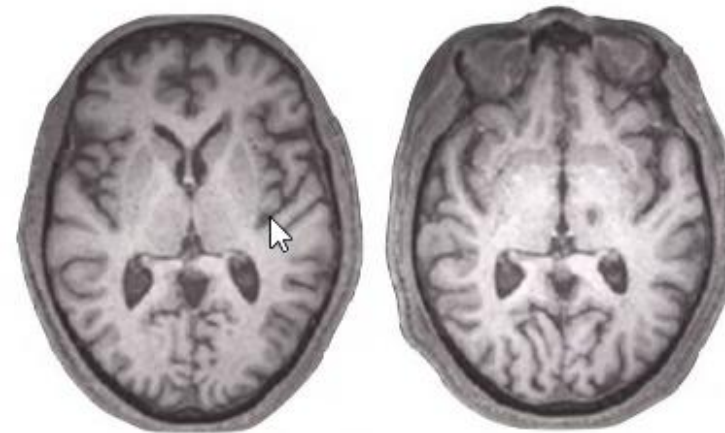
Palombo et al., 2021,

High-intensity TUS for thalamotomy



Palombo et al., 2021

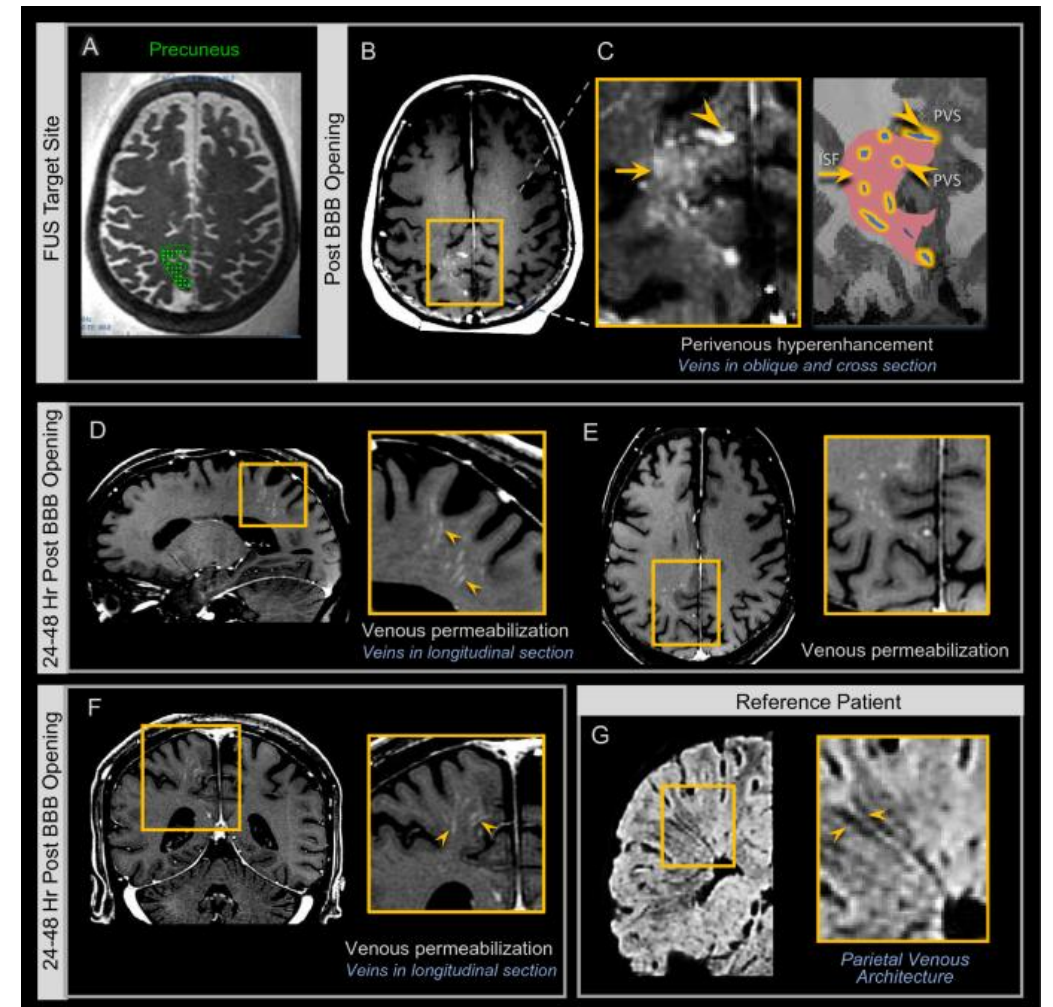
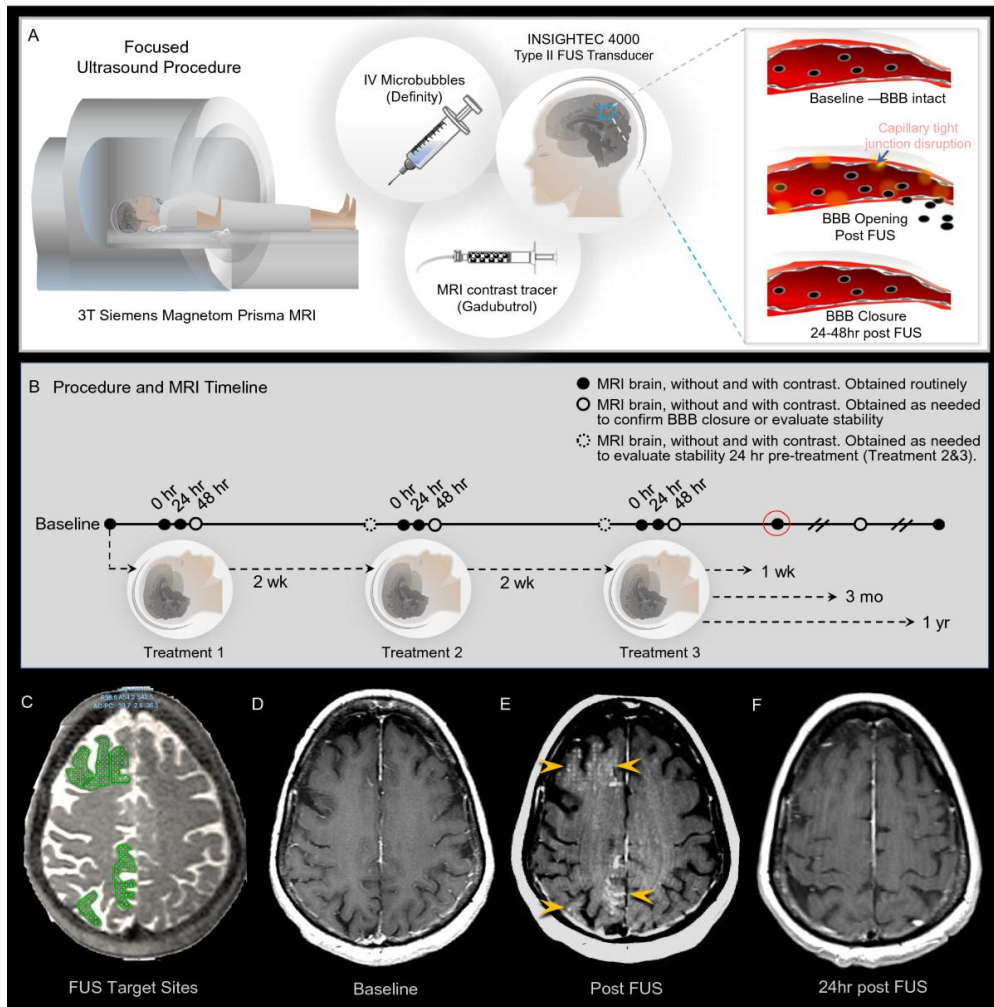
high intensity focused ultrasound
thalamotomy

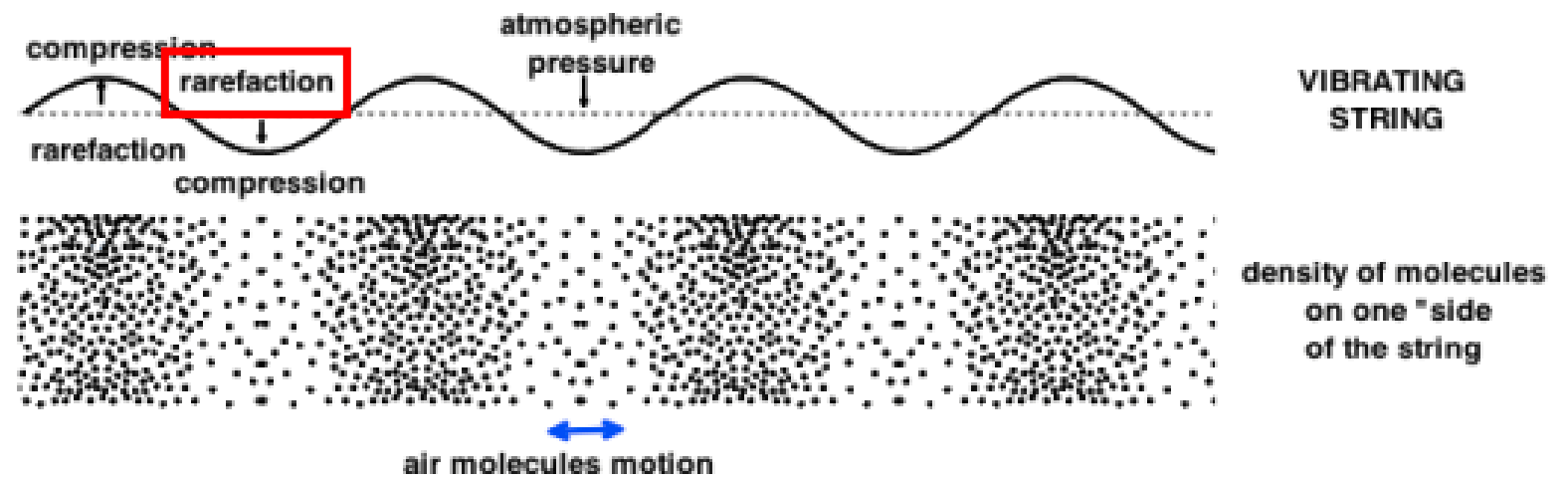
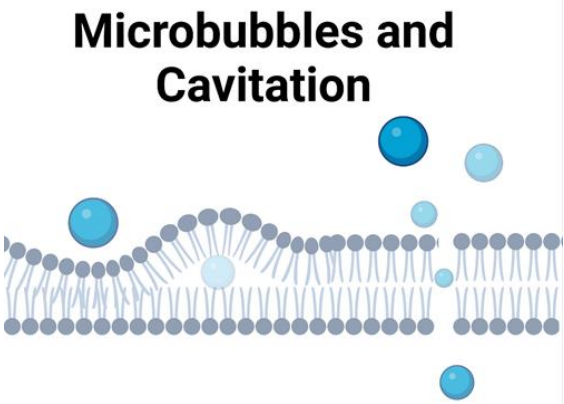


High-intensity TUS for thalamotomy



Opening blood-brain barrier with high precision





➔ Caused by the ultrasonic **negative pressure** during the rarefaction phase of an acoustic wave propagation

The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES ▼ TOPICS ▼ MULTIMEDIA ▼ CURRENT ISSUE ▼ LEARNING/CME ▼ AUTHOR CENTER PUBLICATIONS ▼

ORIGINAL ARTICLE | BRIEF REPORT f X in E

Ultrasound Blood–Brain Barrier Opening and Aducanumab in Alzheimer’s Disease

Authors: Ali R. Rezaei, M.D., Pierre-Francois D’Haese, Ph.D., Victor Finomore, Ph.D., Jeffrey Carpenter, M.D., Manish Ranjan, M.B., B.S., Kirk Wilhelmsen, M.D., Rashi I. Mehta, M.D., and Marc W. Haut, Ph.D. [Author Info & Affiliations](#)

Published January 3, 2024 | N Engl J Med 2024;390:55-62 | DOI: 10.1056/NEJMoa2308719 | VOL. 390 NO. 1

Applications of ultrasound

Applications	US parameters
Neurosurgery	High-intensity
Opening Blood-Brain Barrier (BBL)	Low-intensity + micro-bubbles
Drug delivery	Lipid/Nano containers
Sonogenetics	Viral expression of ion-channels
Functional imaging	High-speed, computational, bubbles
Neuromodulation	Low-intensity

Different names for pretty much the same thing...

FUS

fUS

tFUS

LIPUS

LIFUP

LILFU

TPS

FUN

TUS

...

Historical developments of TUS

Late 50's

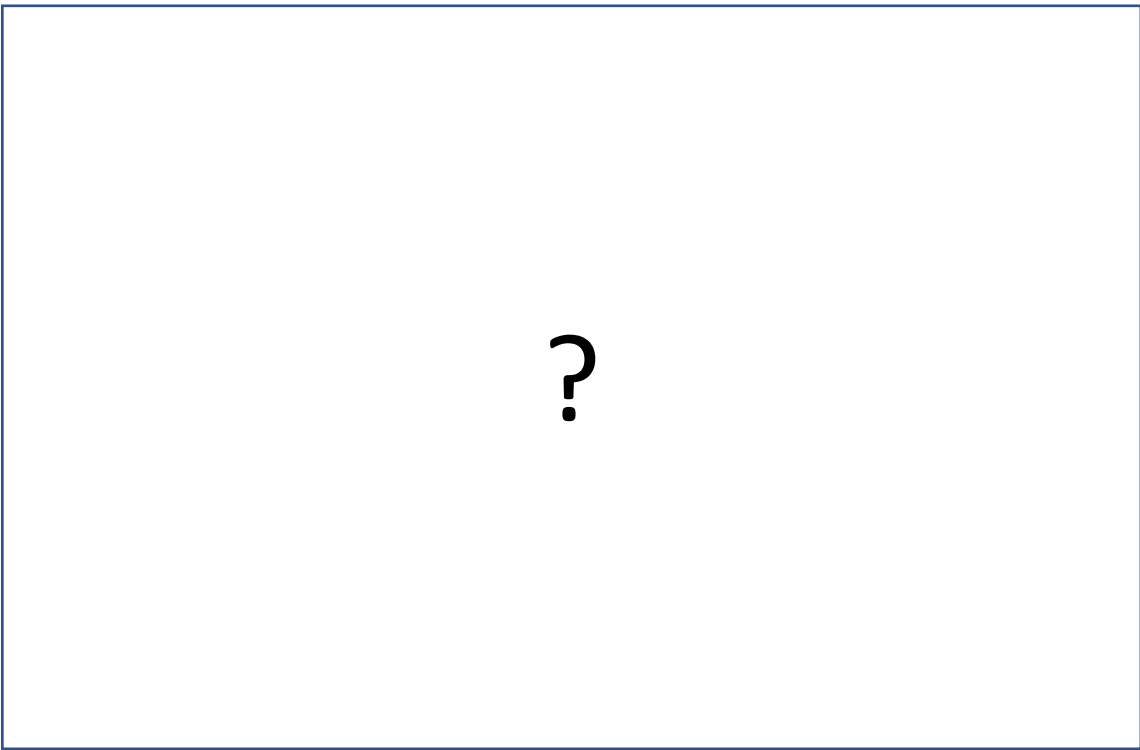


Surgery

Low intensity

High intensity

Intensity



Late 50's



Neuromodulation

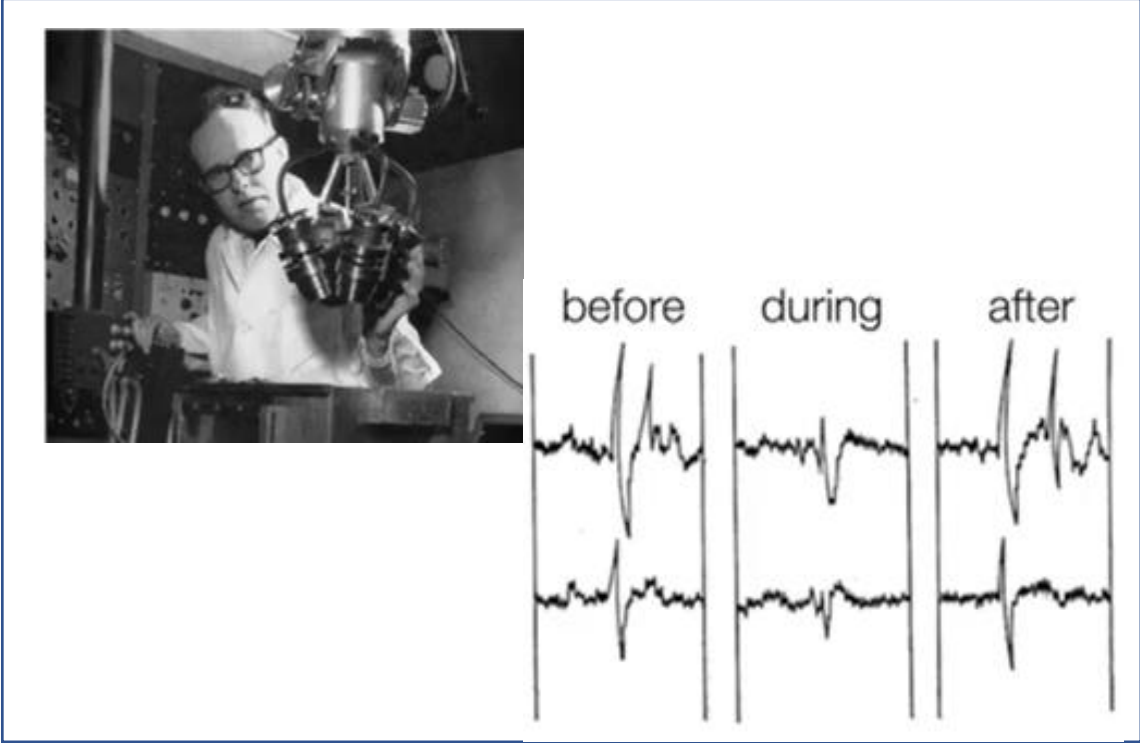
Surgery



Low intensity

High intensity

Intensity



Late 50's



Surgery

Neuromodulation

Low intensity

High intensity

Intensity

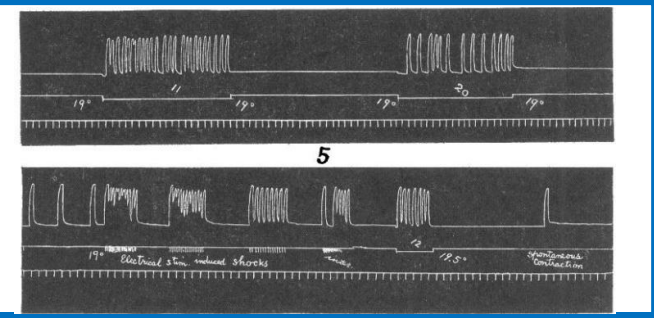


THE EFFECT OF HIGH FREQUENCY SOUND WAVES ON HEART MUSCLE AND OTHER IRRITABLE TISSUES

E. NEWTON HARVEY

From the Loomis Laboratory, Tuxedo Park, N. Y. and the Physiological Laboratory, Princeton University

Received for publication July 19, 1929



1929

1950

1960-90s

2010

2014

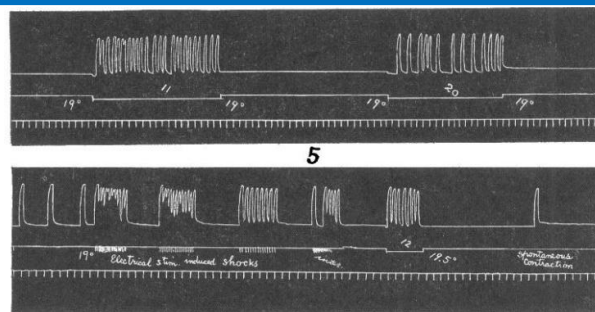
US can excite nerve fibers in isolated turtle and frog muscle

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Science • Volume 127, Issue 3289, Pages 83 - 84 • 1958

Production of reversible changes in the central nervous system by ultrasound

Fry E.J.^a, Ades H.W.^b, Fry W.J.^a

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^a Bioacoustics Laboratory, University of Illinois, Urbana, IL

^b Division of Neurophysiology and Acoustics, U.S. Naval School of Medicine, Pensacola, FL

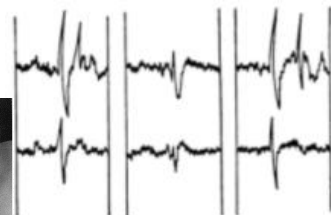


Fig. 1. Cortical potentials evoked by a flash of light (left) before irradiation, (middle) at the termination of irradiation, (right) 30 minutes after irradiation.

1929

US can excite nerve fibers in isolated turtle and frog muscle

1950

US transiently suppresses amplitude of VEP in cats

1960-90s

2010

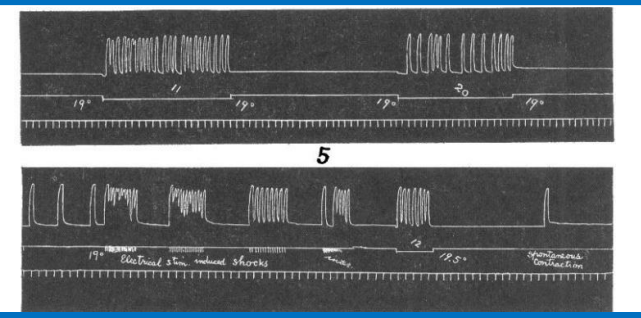
2014

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US transiently suppresses amplitude of VEP in cats

1960-90s
Stimulation of inner ear structures and auditory nerve

2010

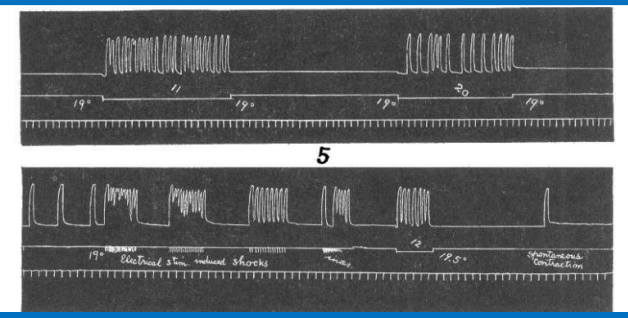
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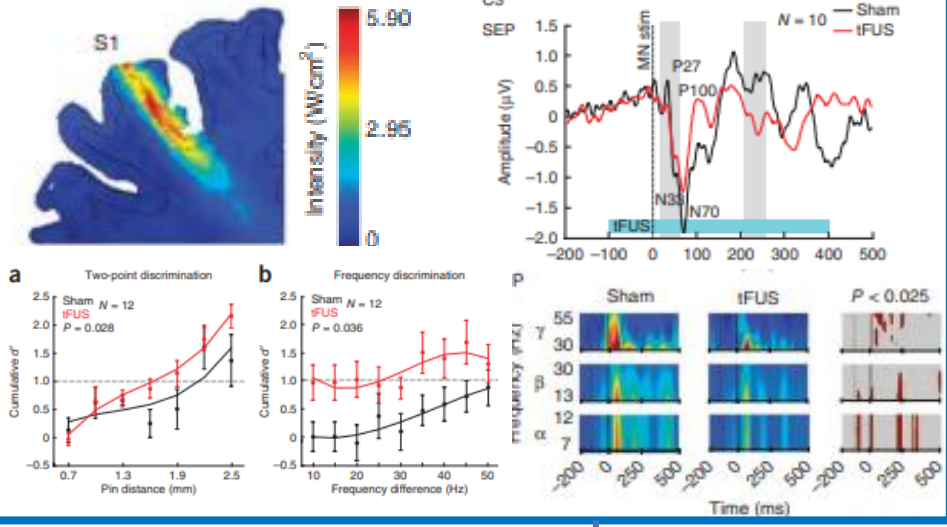
Fig. 1. Cortical potentials evoked by a flash of light (left) before irradiation, (middle) at the termination of irradiation, (right) 30 minutes after irradiation.

TECHNICAL REPORTS

nature neuroscience

Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans

Wynn Legon¹, Tomokazu F Sato¹, Alexander Opitz^{1,2}, Jerel Mueller³, Aaron Barbour¹, Amanda Williams¹ & William J Tyler^{1,3,4}



1929 1950 1960-90s 2010 2014

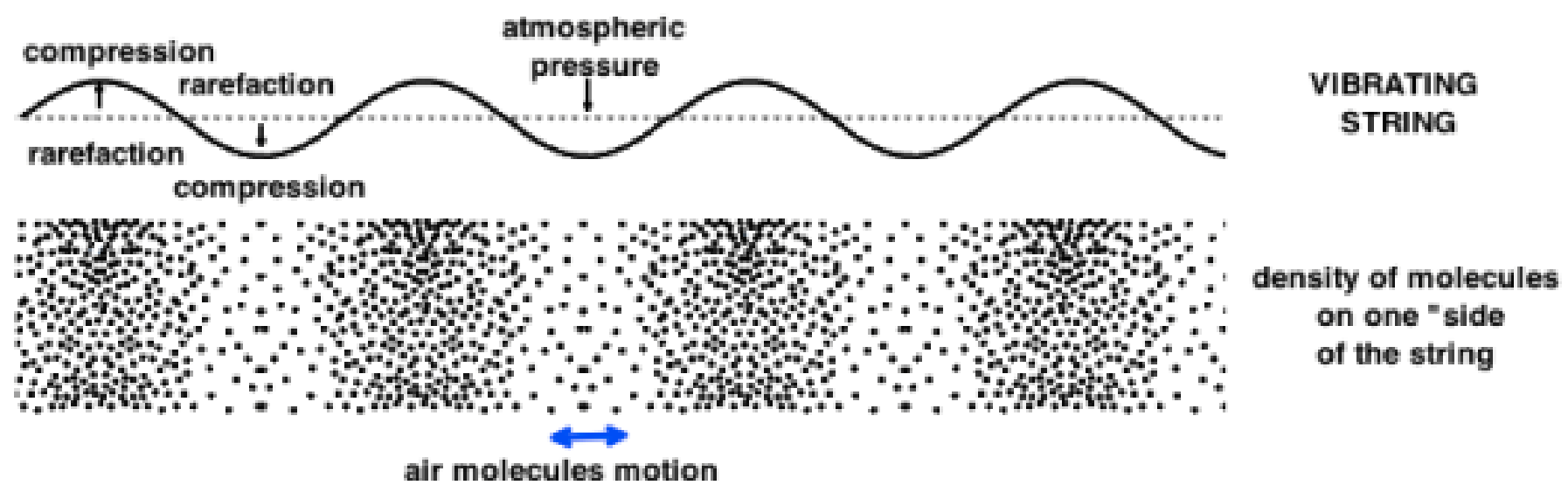
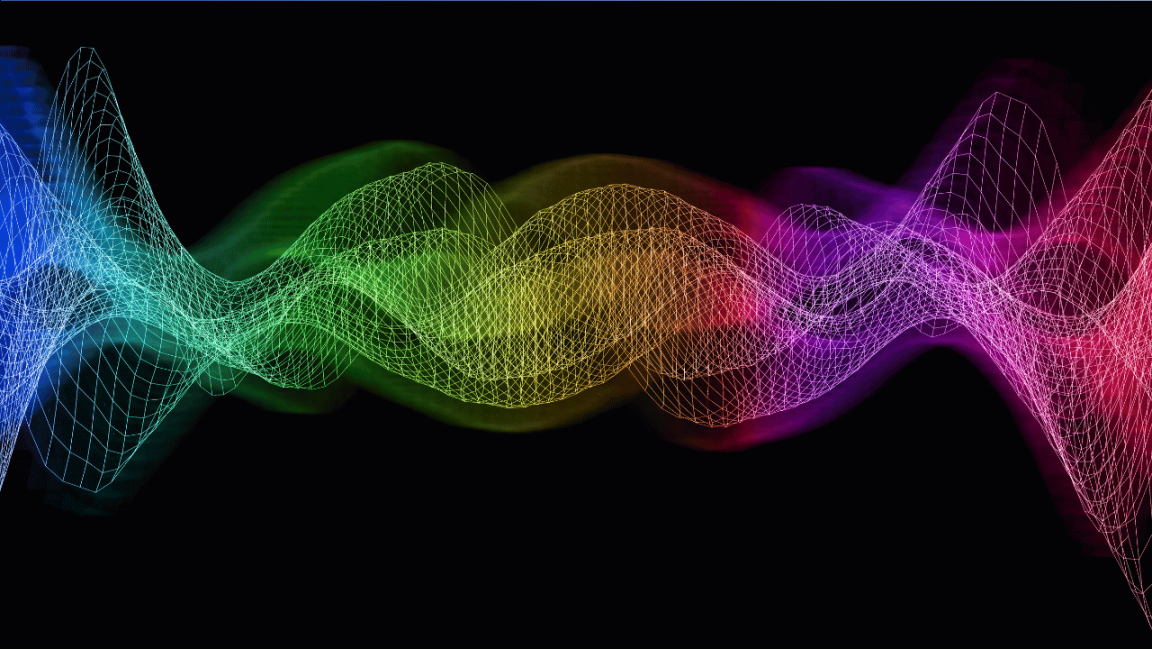
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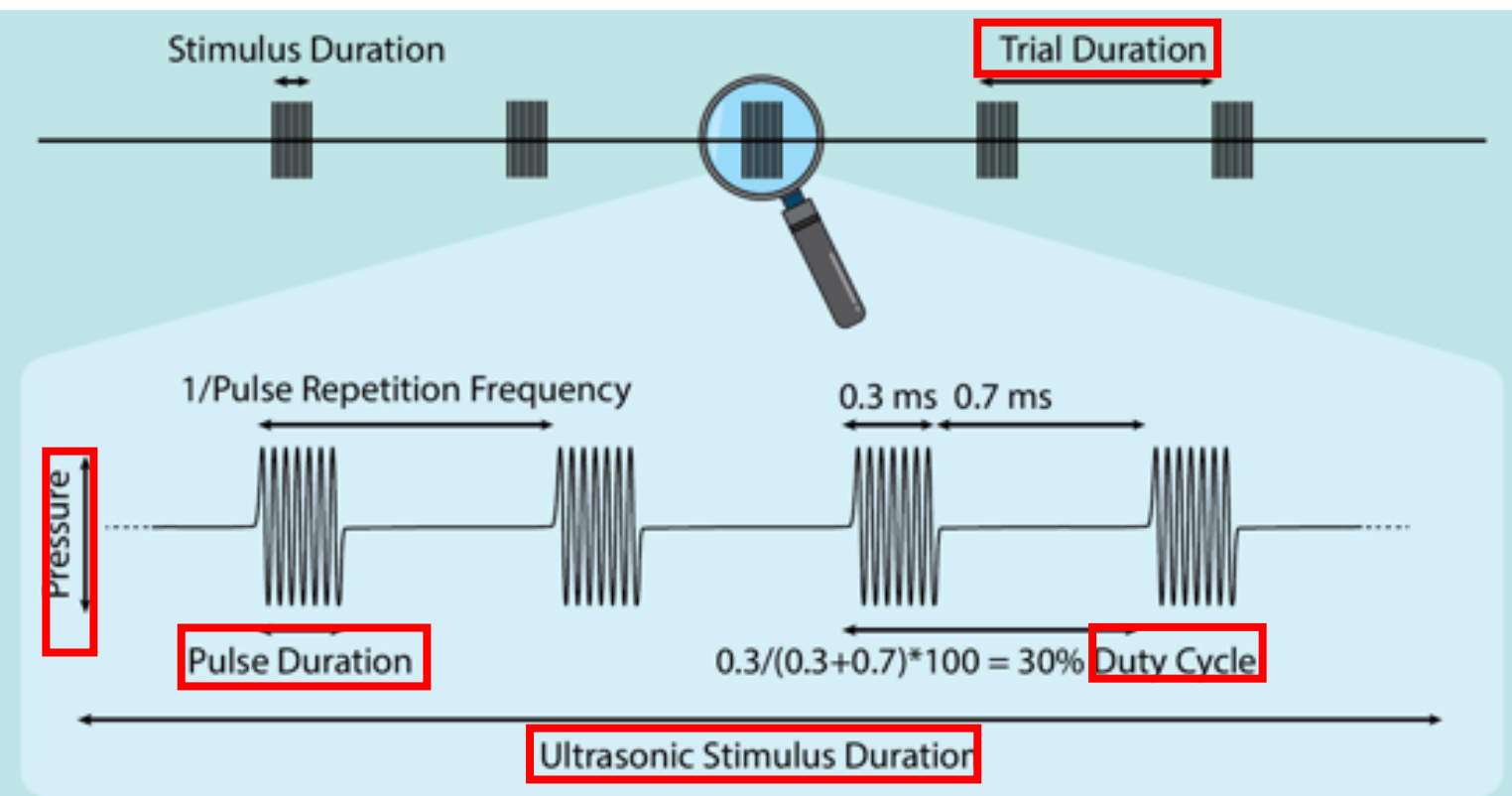
US excited neural activity of hippocampus and motor cortex in rat

US modulates the activity in human S1

Mechanisms of TUS

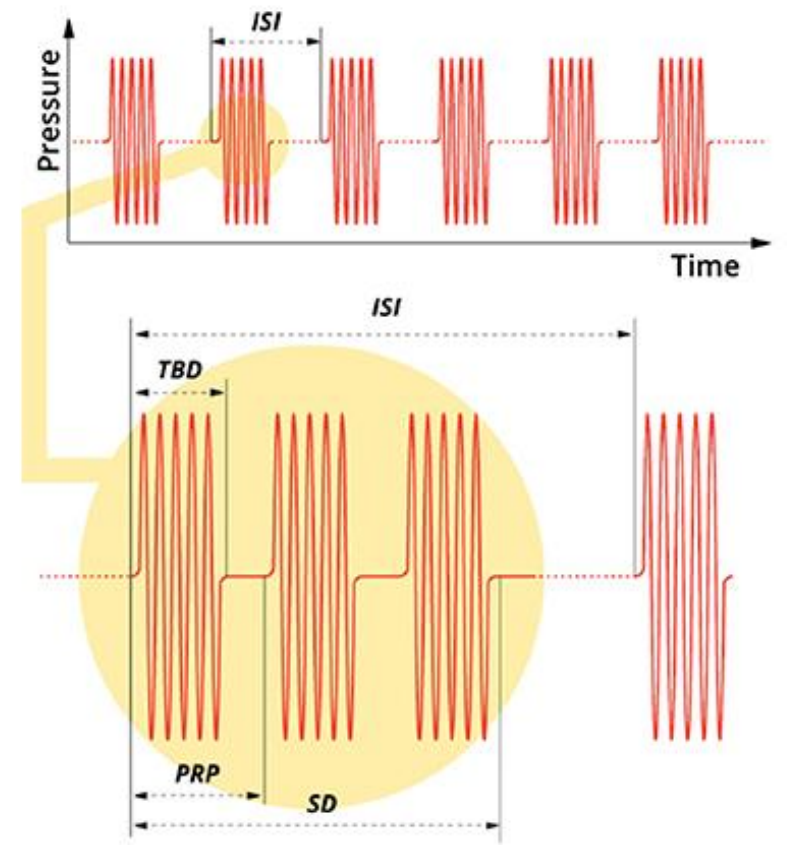


US mechanisms



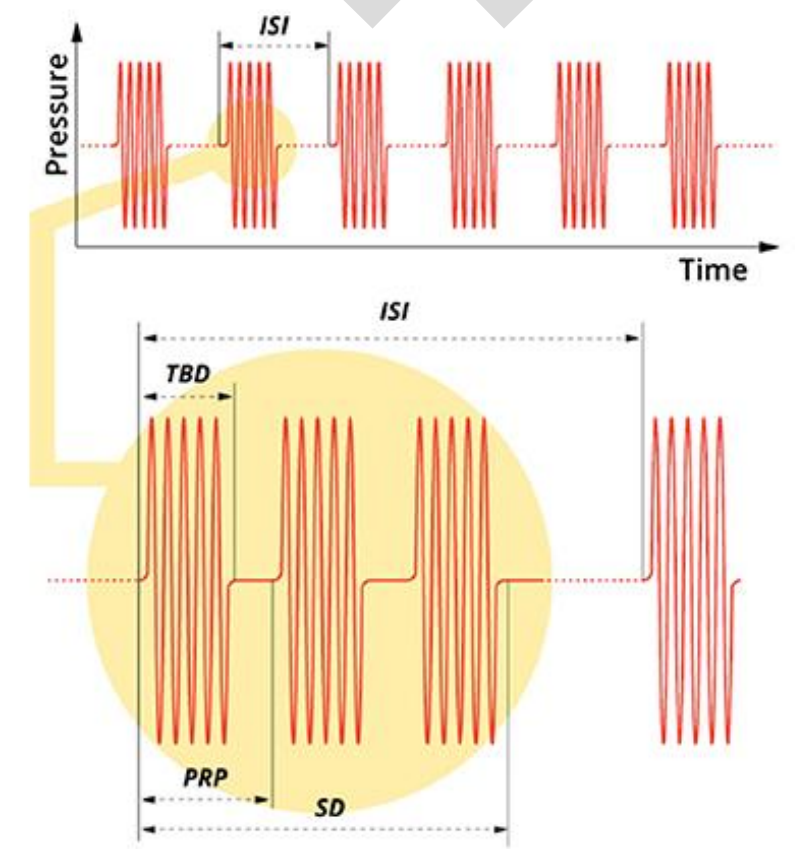
Parameter (Abbreviation)	Unit	Synonym
Fundamental frequency (FF)	kHz, MHz	Center frequency (f_c)
Pulse duration (PD)	ms	Tone burst duration (TBD), Pulse length (PL)
Pulse repetition interval (PRI)	ms	Pulse repetition period (PRP)
Pulse repetition frequency (PRF)	Hz, kHz	-
Duty cycle (DC)	%	Duty factor (DF), as a ratio between 0 and 1
Sonication duration (SD)	ms, s	Burst duration (BD)
Inter-stimulation interval (ISI)	s, min	Burst interval (BI) - Sonication duration (SD)
Peak rarefactional pressure (P_r)	kPa, MPa	Peak negative pressure (PNP)
Spatial-peak pulse-average intensity (I_{SPPA})	W/cm ²	-
Spatial-peak temporal-average intensity (I_{SPTA})	mW/cm ²	-
Mechanical index (MI)	(unitless)	-

Fundamental frequency



Amplitude envelope

Fundamental frequency



Acoustic Radiation Force (ARF) ← Amplitude envelope Fundamental frequency



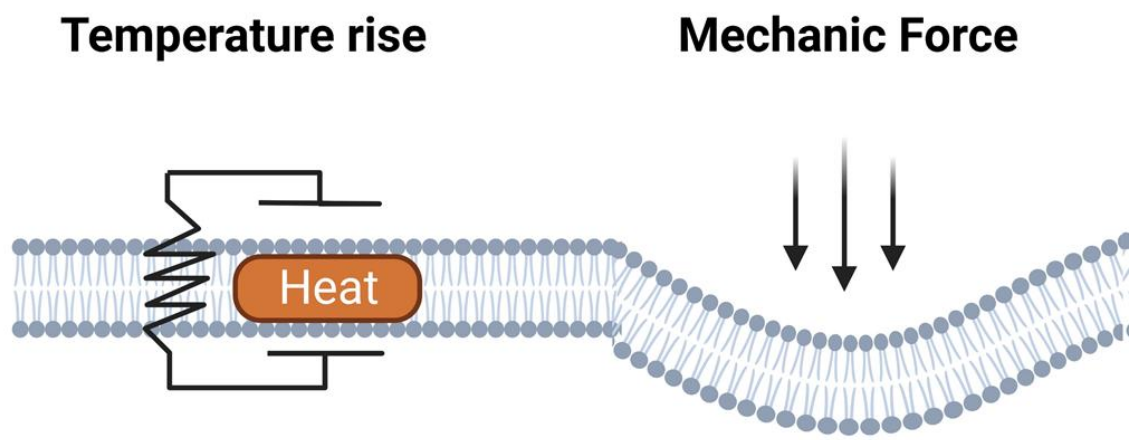
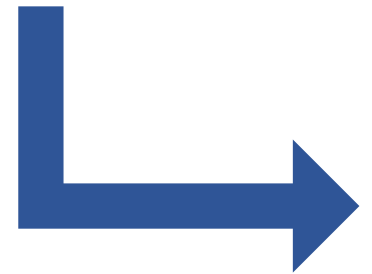
→ Physical phenomenon resulting from the **interaction of an acoustic wave with an obstacle** placed along its path

Acoustic Radiation Force (ARF)

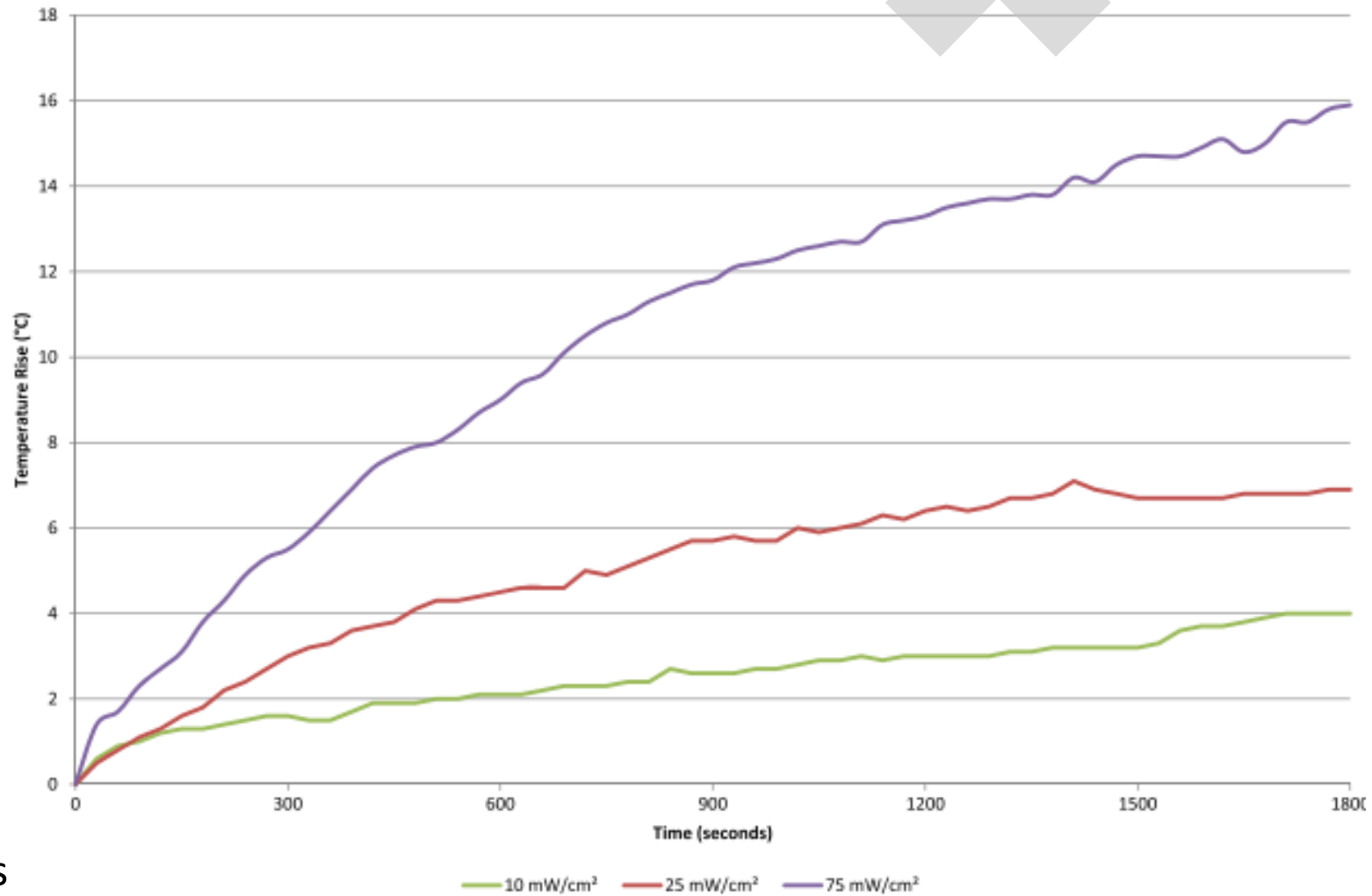
← Amplitude envelope

Fundamental frequency 

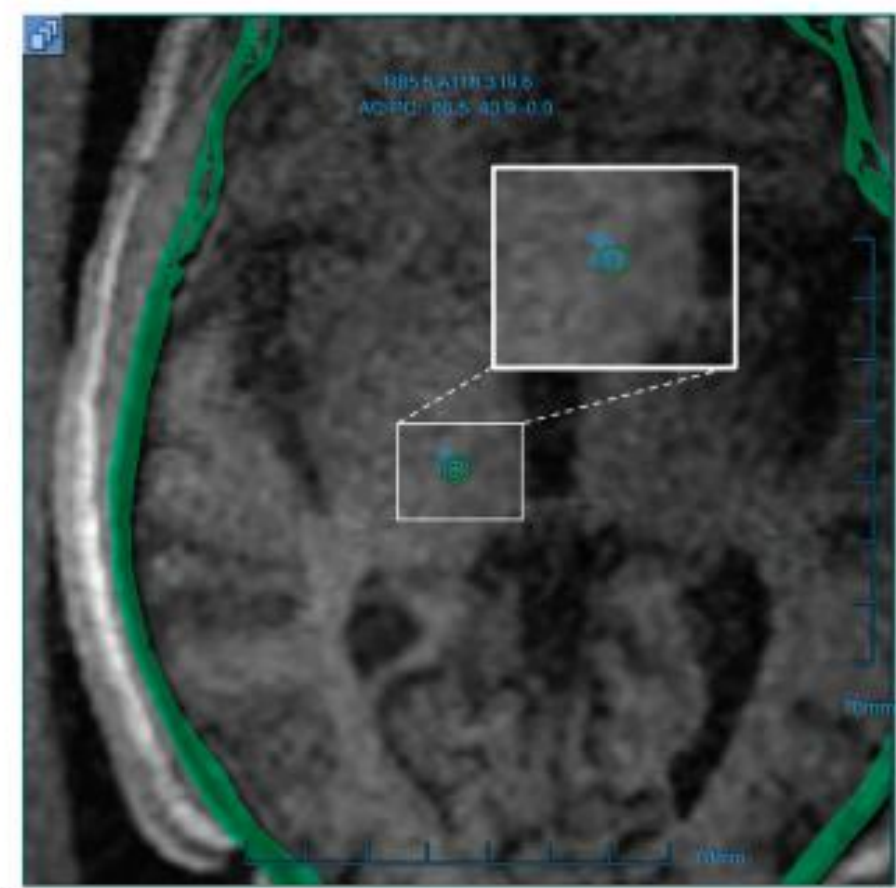
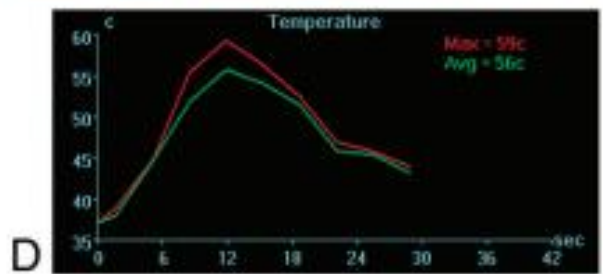
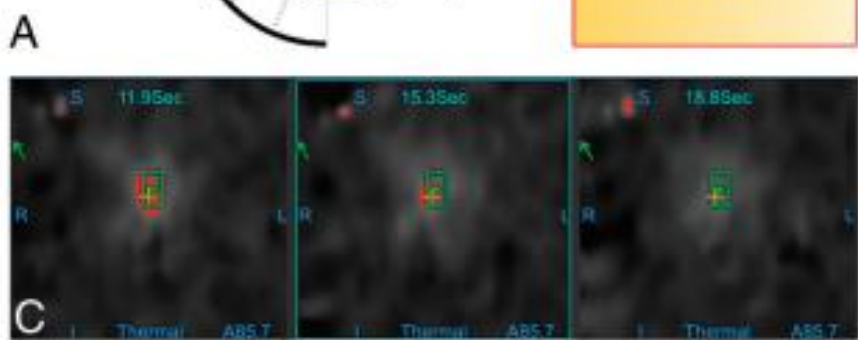
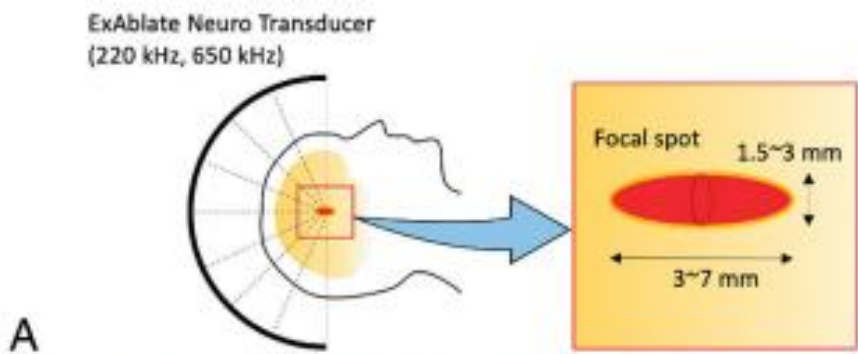
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Acoustic Radiation Force (ARF) ← Amplitude envelope Fundamental frequency



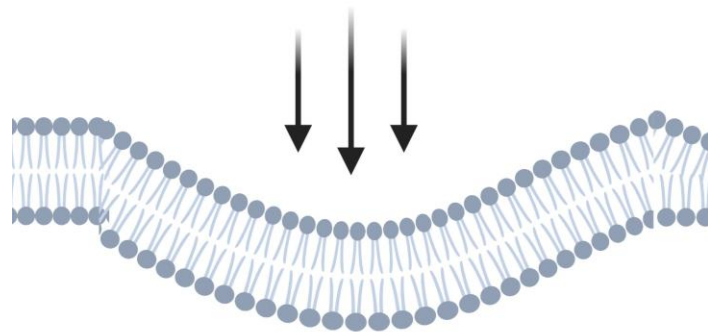
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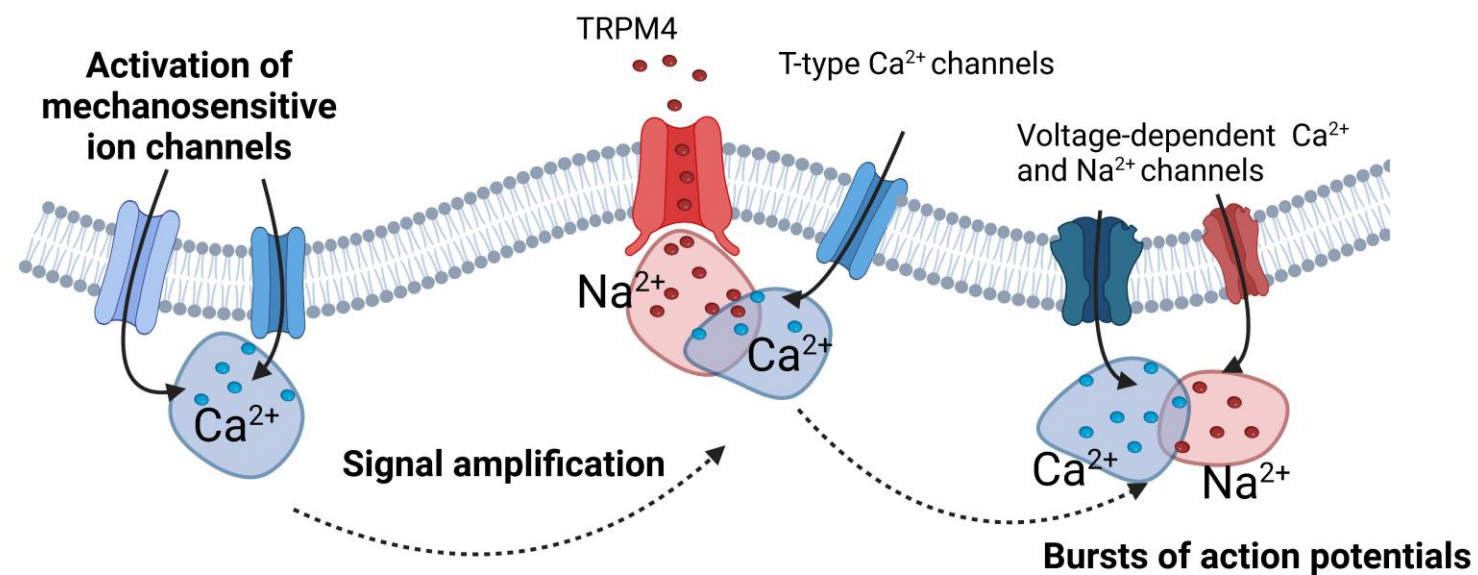
Acoustic Radiation Force (ARF) ← Amplitude envelope Fundamental frequency



Mechanic Force



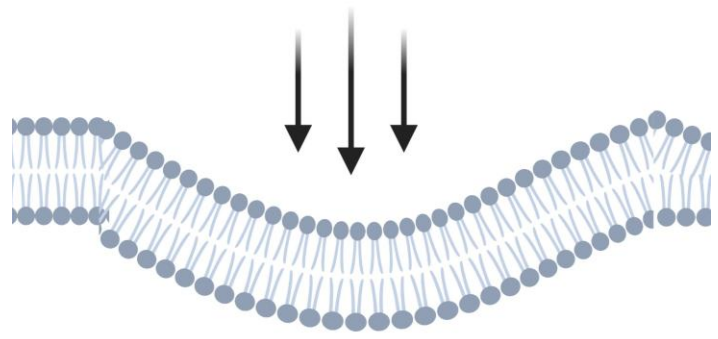
Hypothesis 1: Membrane permeability
US indirectly manipulates mechanosensitive calcium channels in the membrane



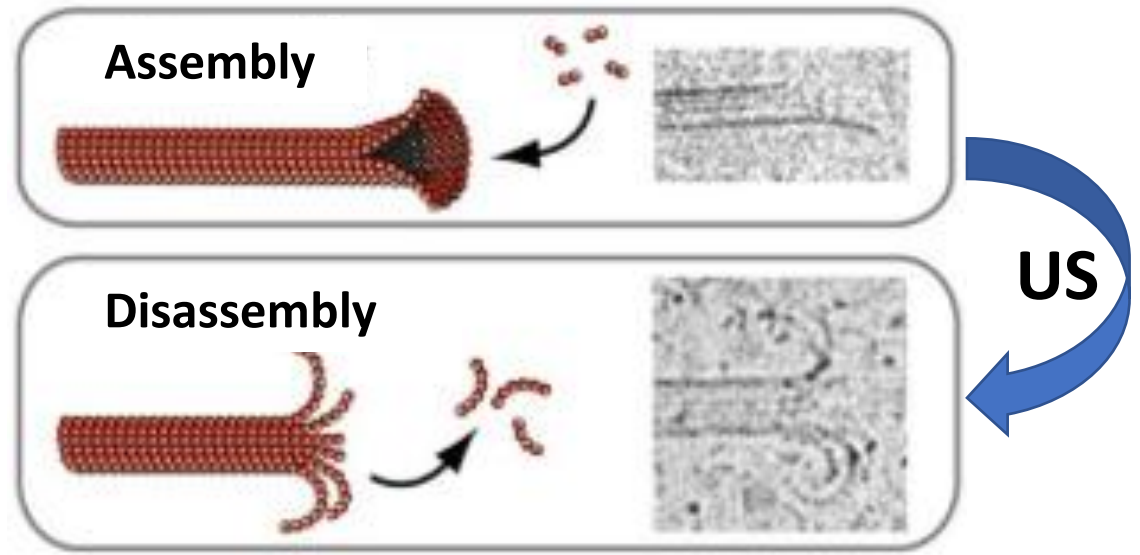
Acoustic Radiation Force (ARF) ← Amplitude envelope Fundamental frequency



Mechanic Force



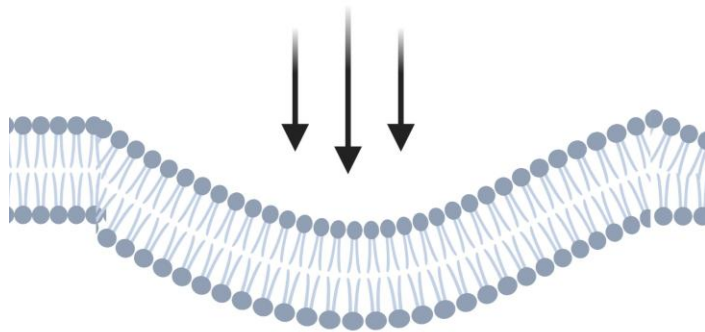
Hypothesis 2: Effect on the cytoskeleton
Change of membrane conformational state



Acoustic Radiation Force (ARF) ← Amplitude envelope Fundamental frequency

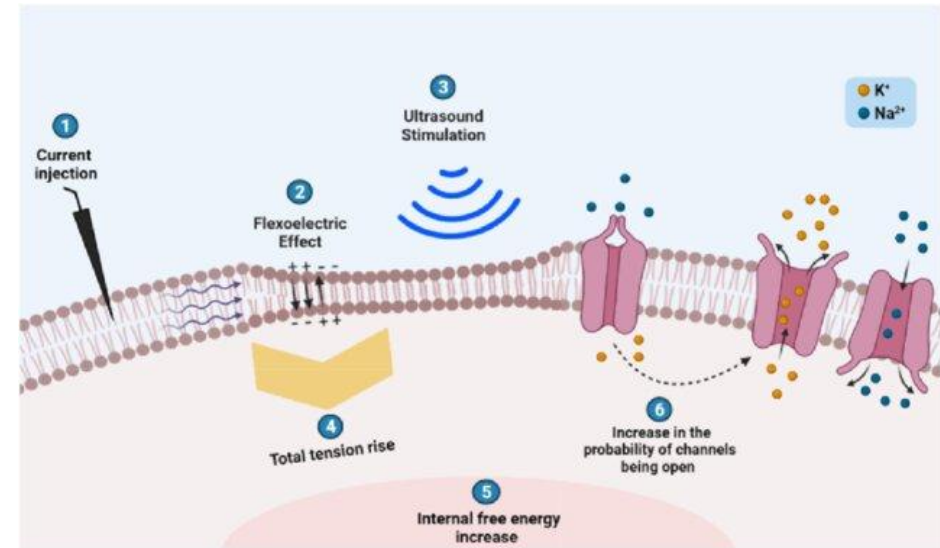


Mechanic Force



→ Flexoelectricity: curvature-induced membrane polarization

Hypothesis 3: Membrane capacitance
US compresses the neural membrane bilayers and leads to a capacitive current which activates neurons

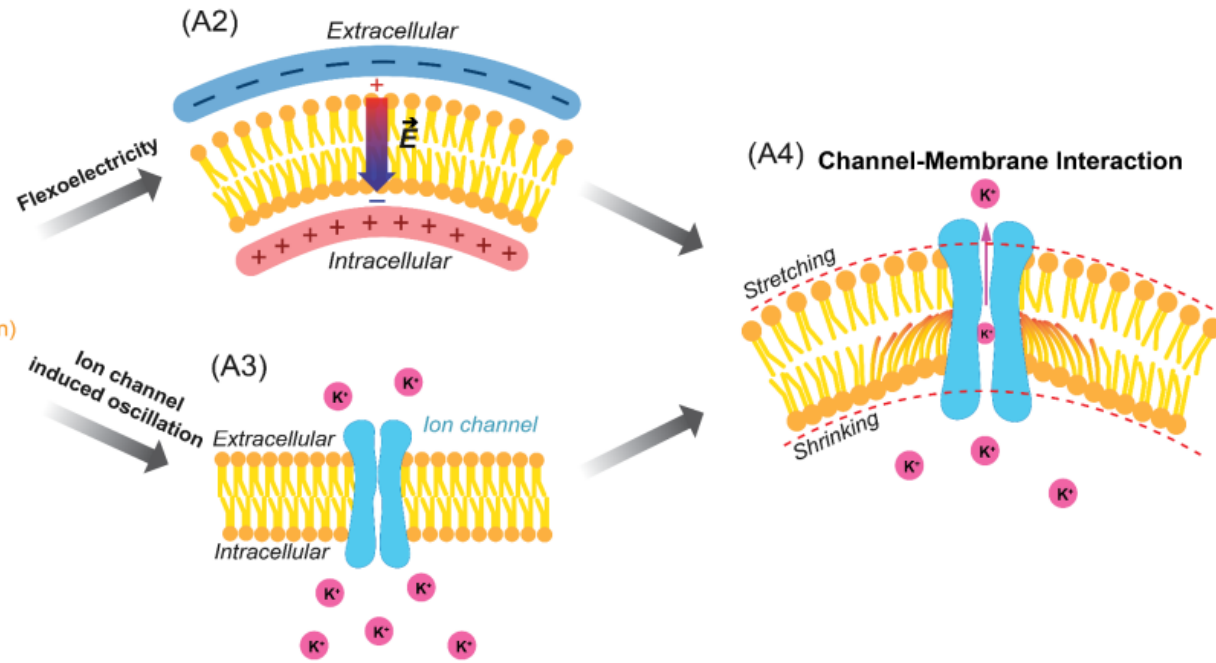
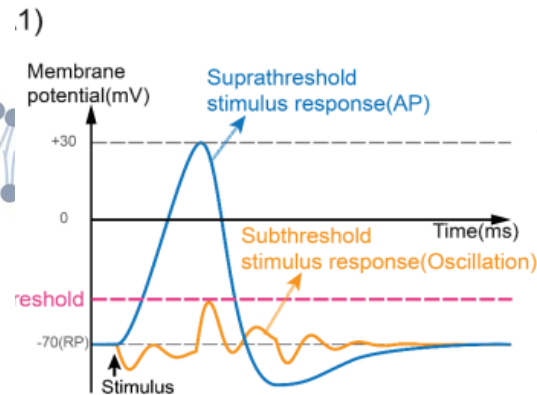
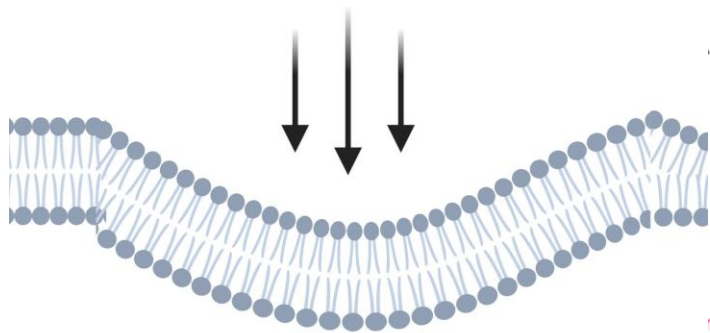


Acoustic Radiation Force (ARF) ← Amplitude envelope Fundamental frequency



The Channel-membrane interaction (CMI) hypothesis

Mechanic Force



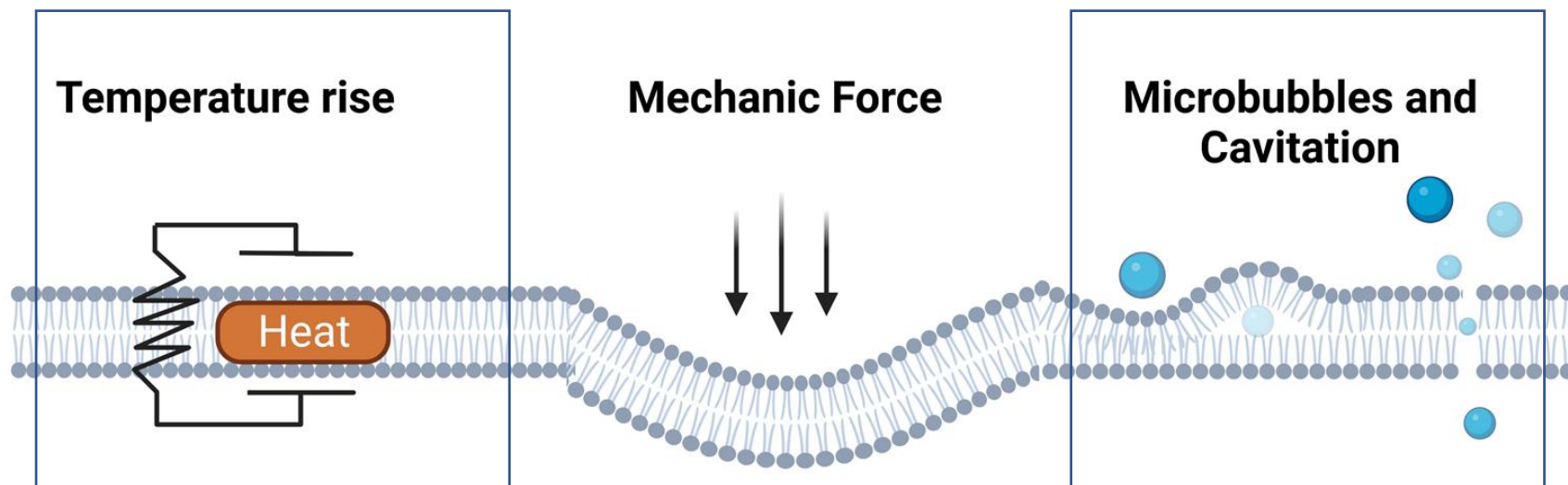
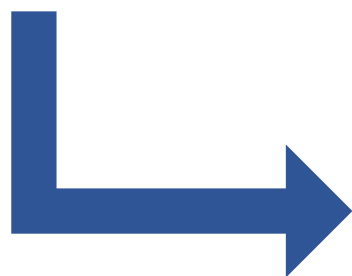
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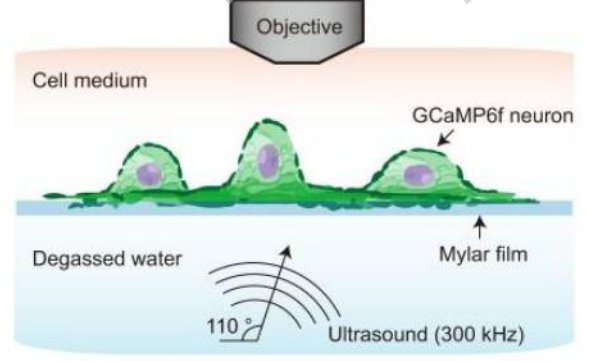
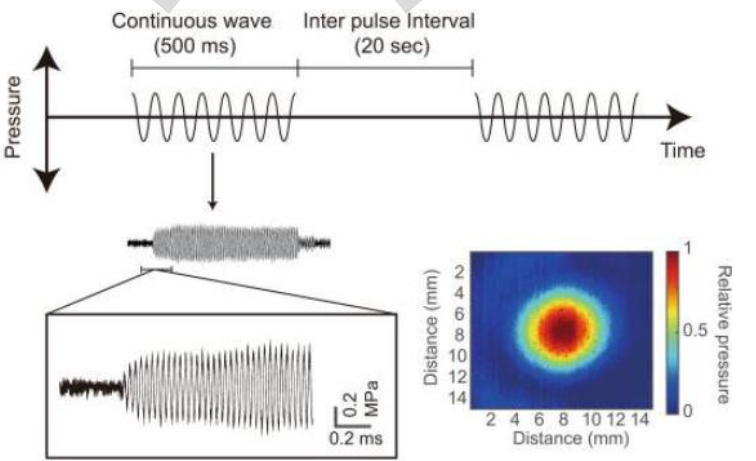
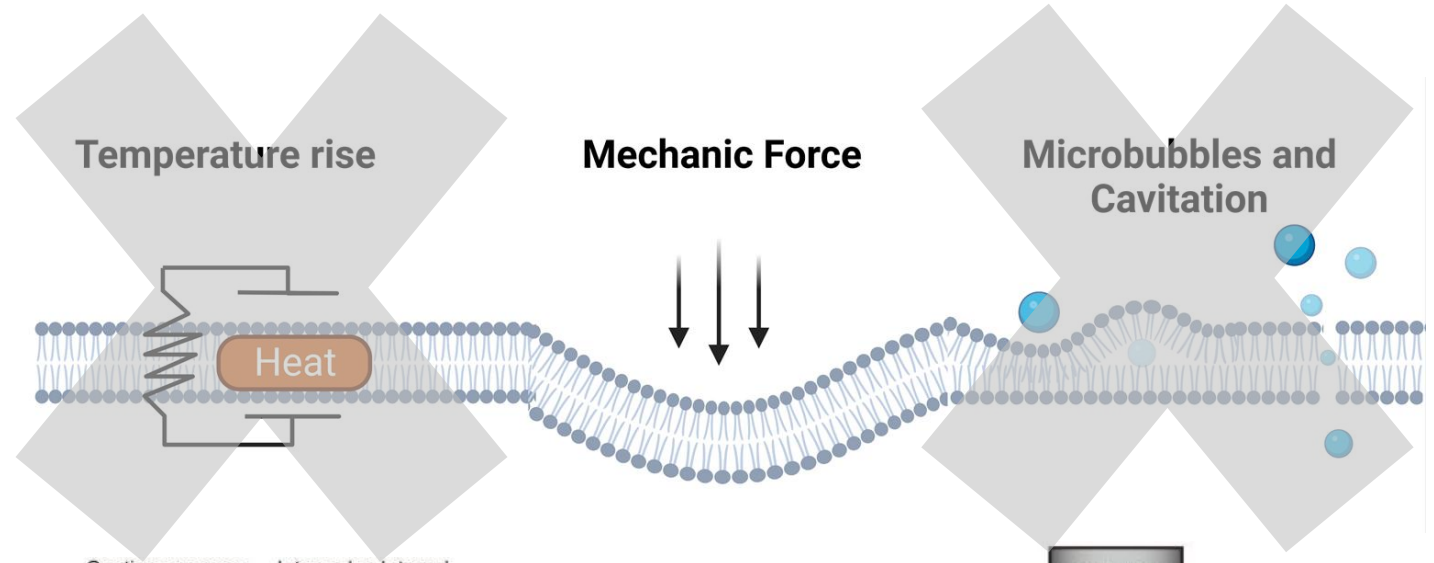
← Amplitude envelope

Fundamental frequency

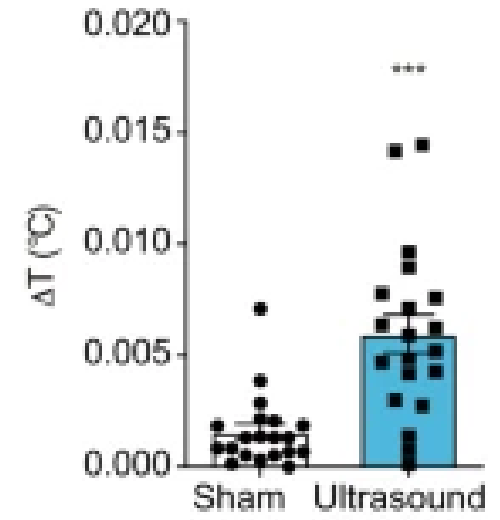


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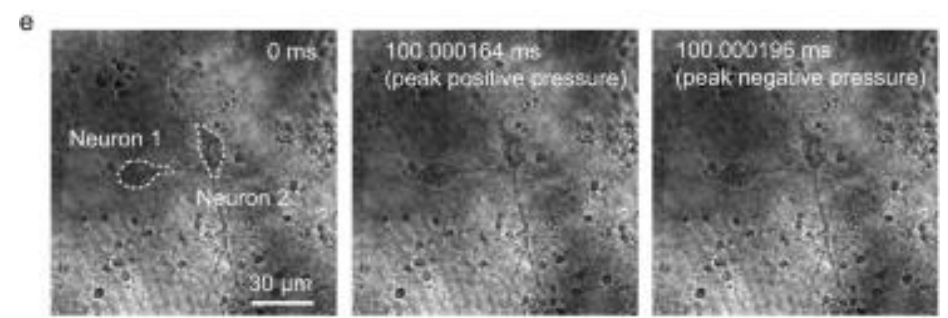




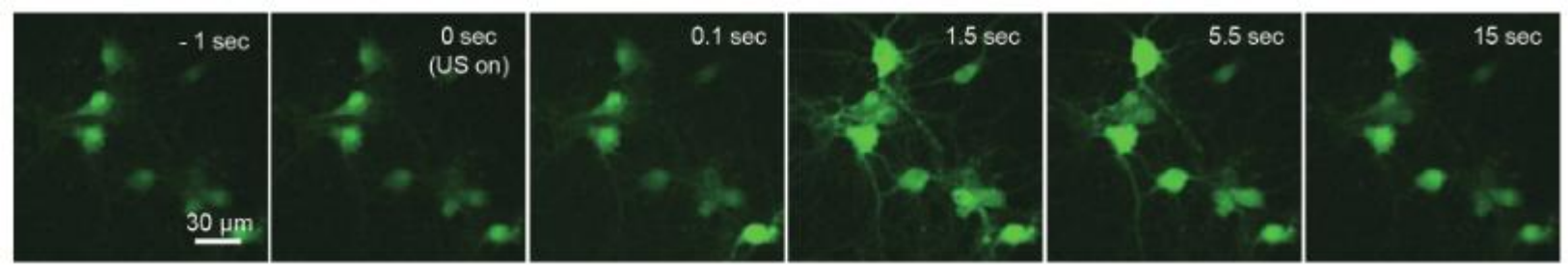
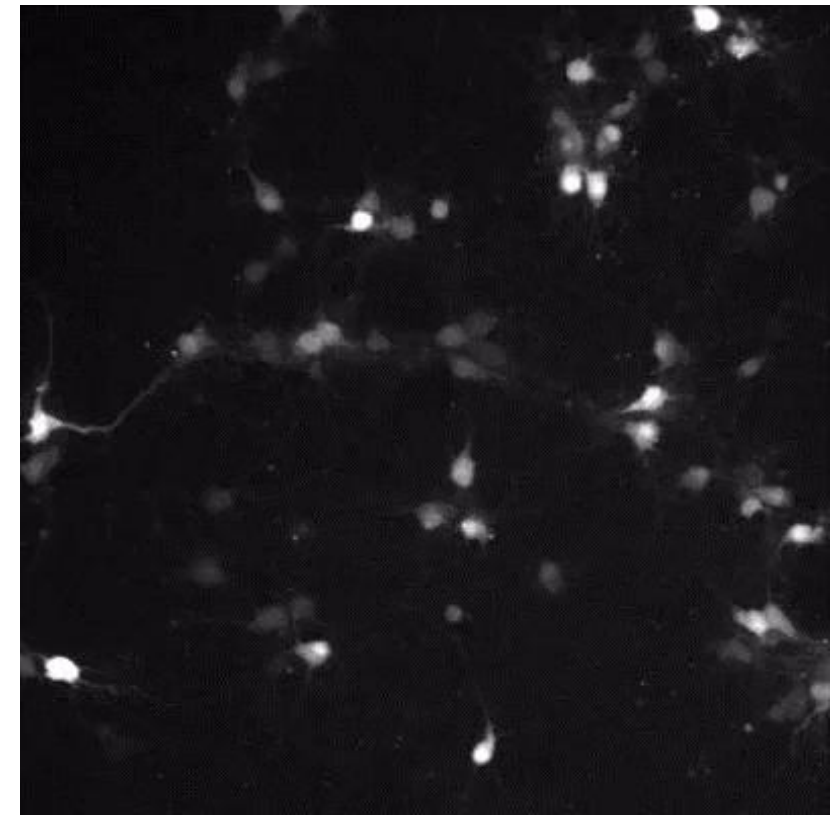
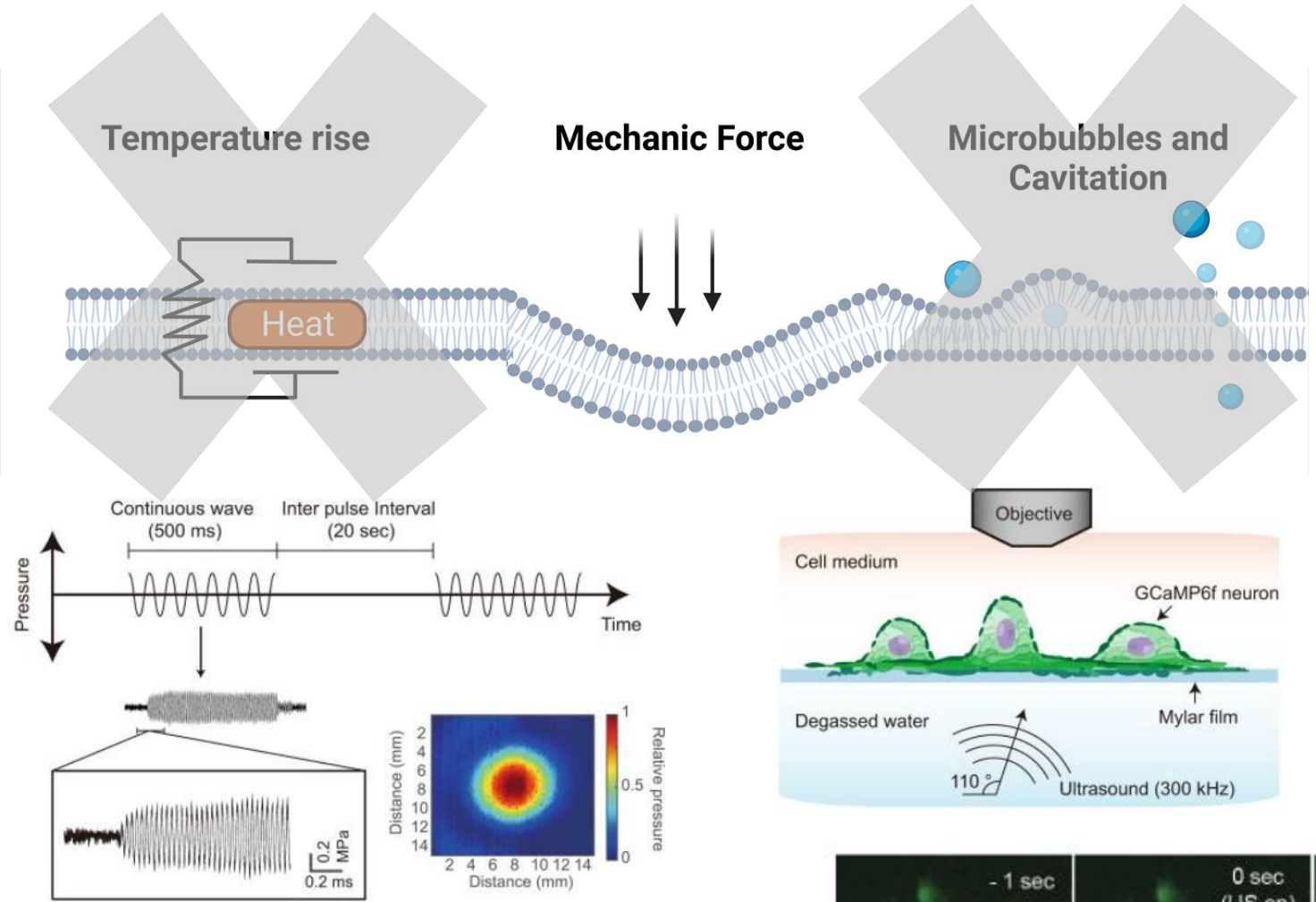
Fiber optic thermometer



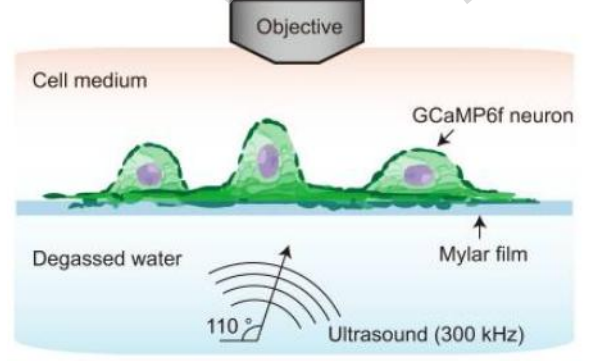
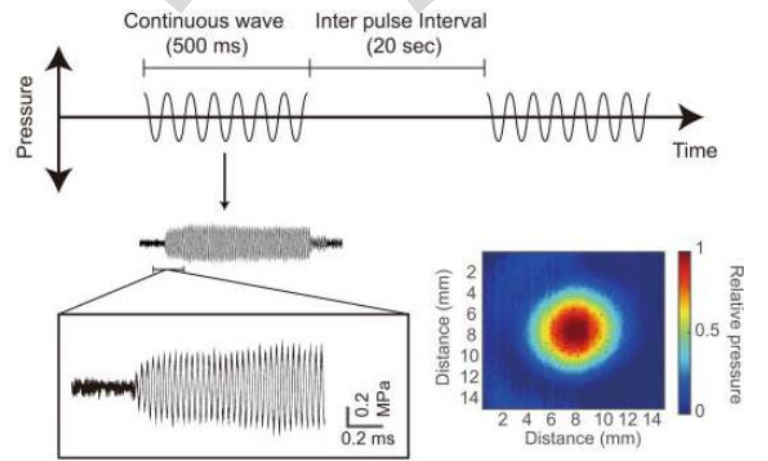
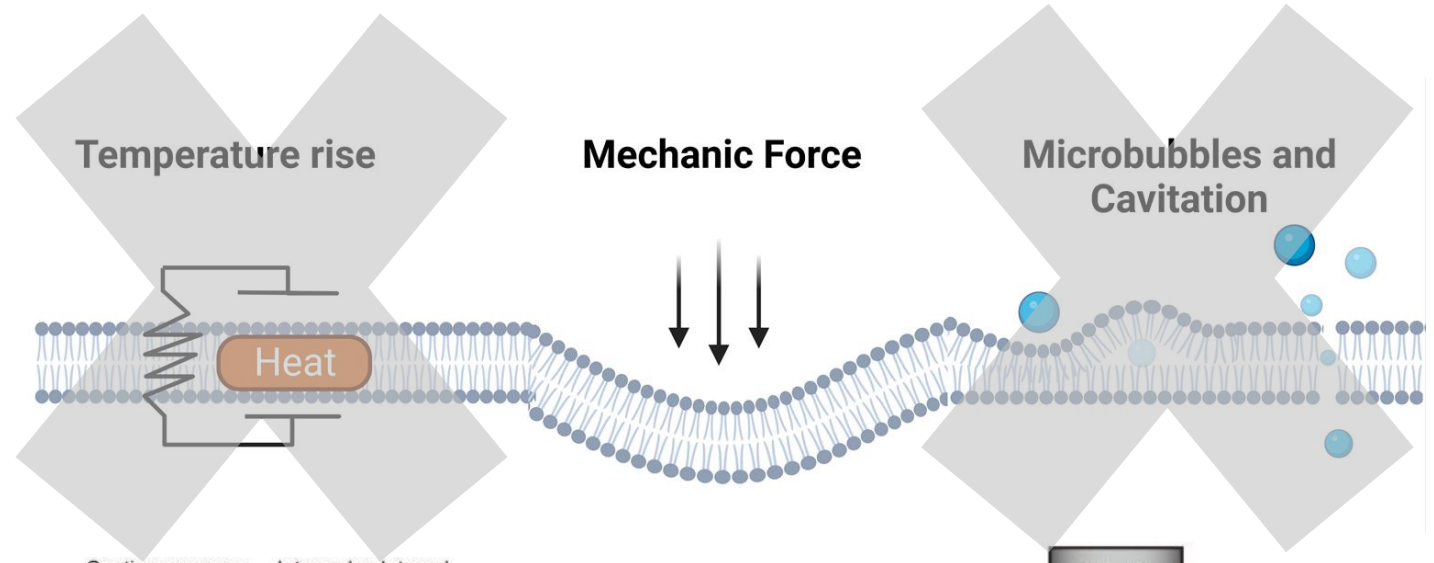
Fiber optic thermometer & Ultra-high speed camera



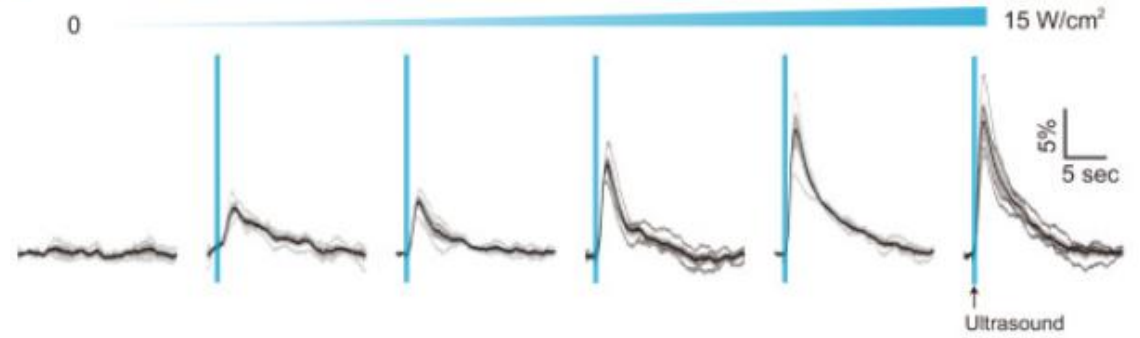
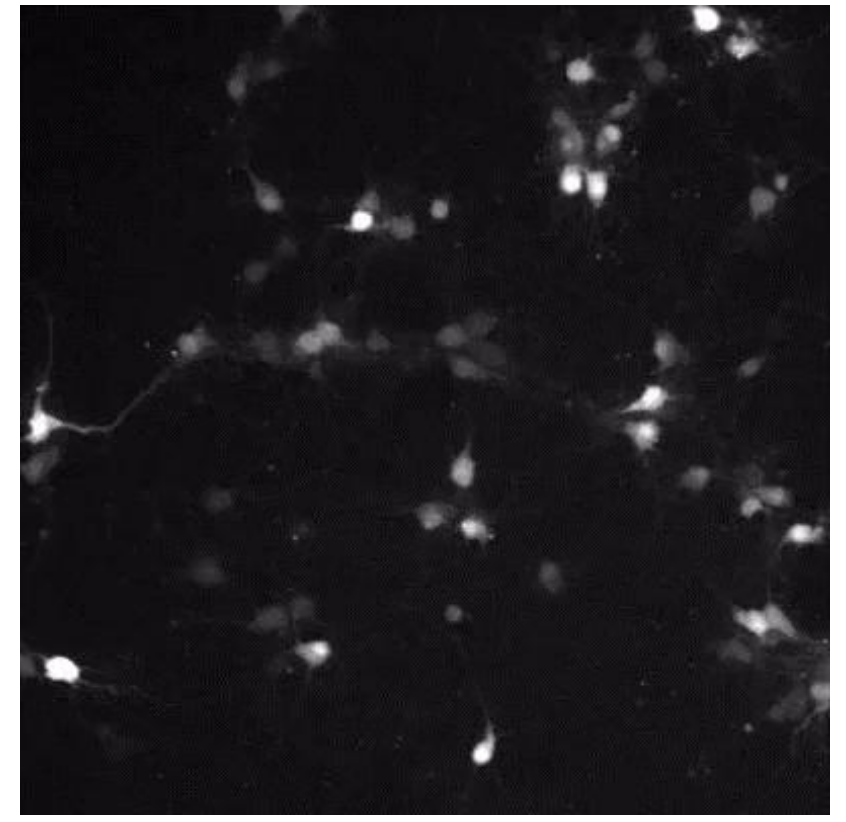
Neural calcium response, recorded by epifluorescence imaging



US mechanisms

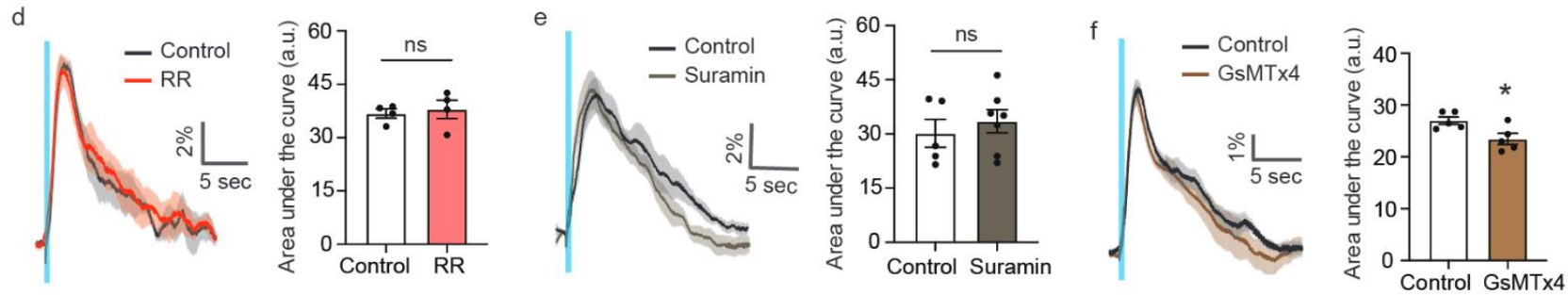
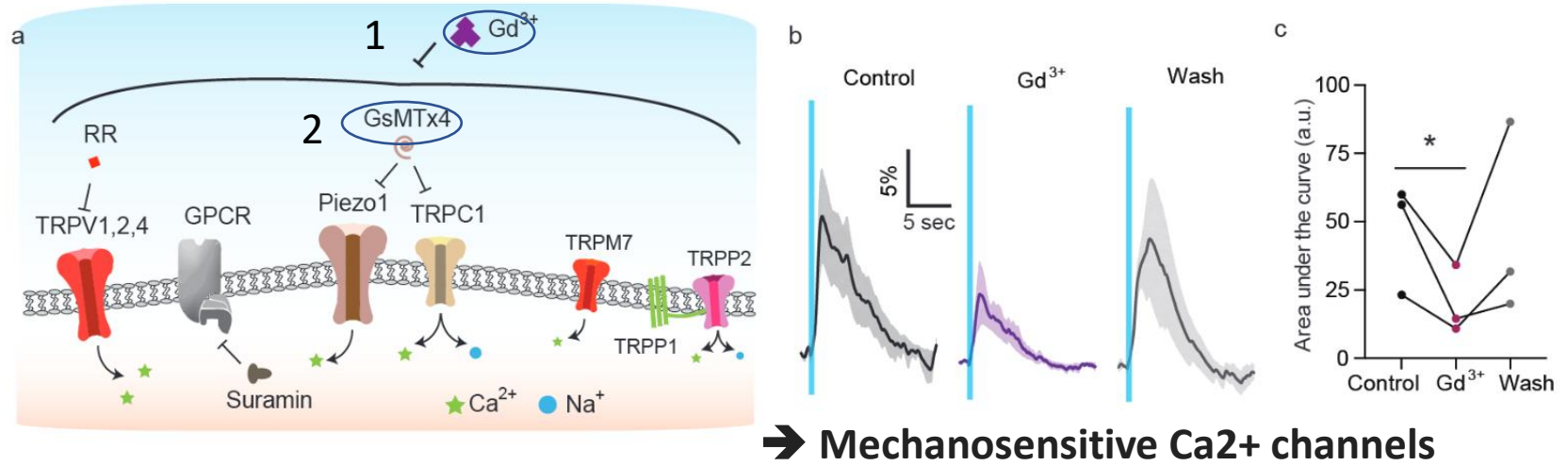


Neural calcium response, recorded by epifluorescence imaging

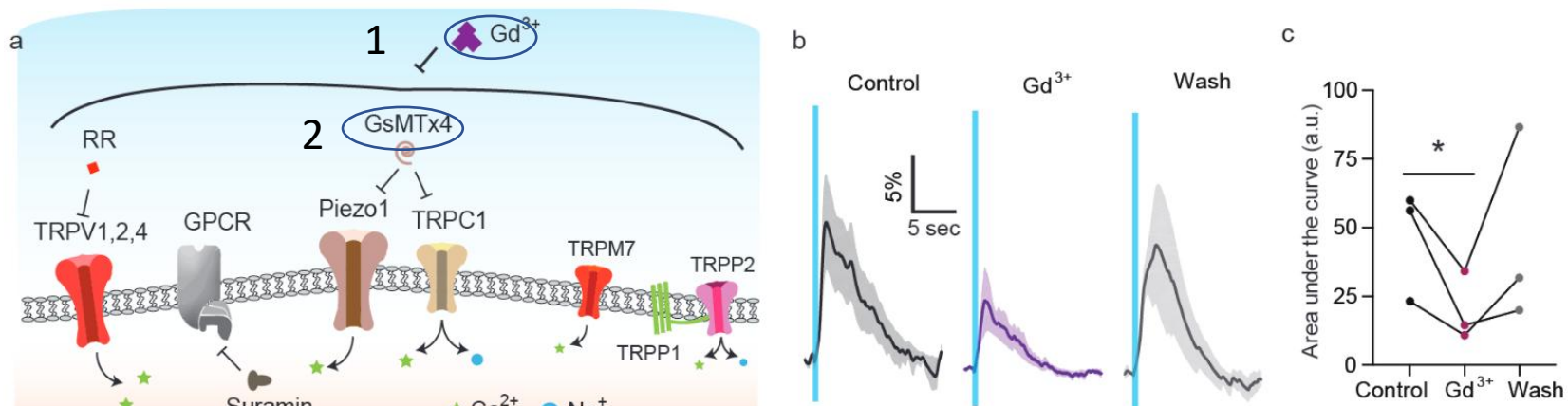


Quantification of calcium responses as function of ultrasound intensity

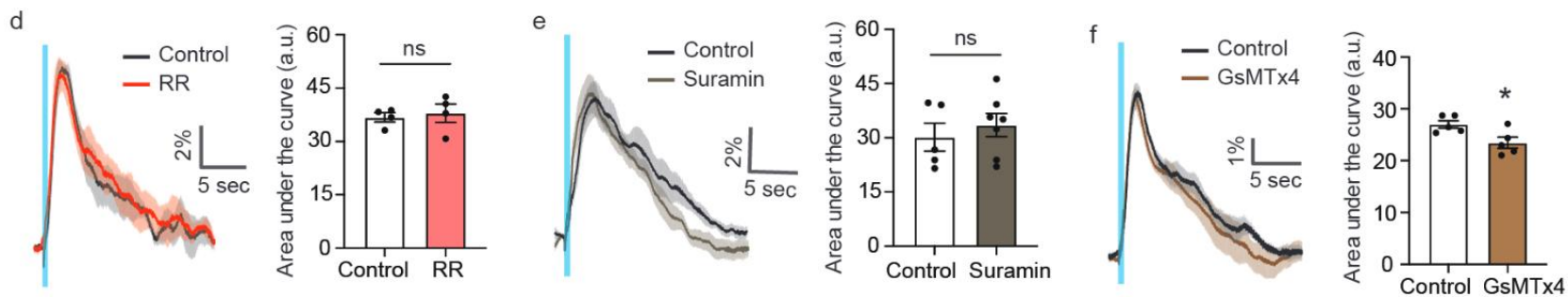
Pharmacological inhibition of mechanosensitive receptors



Pharmacological inhibition of mechanosensitive receptors

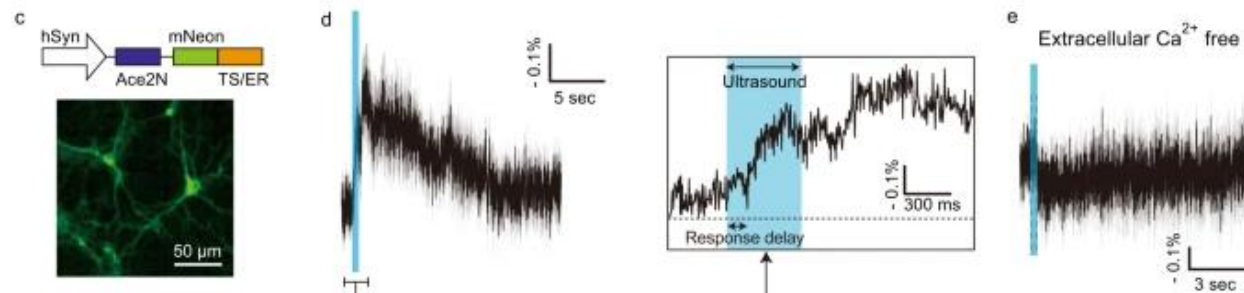


➔ Mechanosensitive Ca²⁺ channels

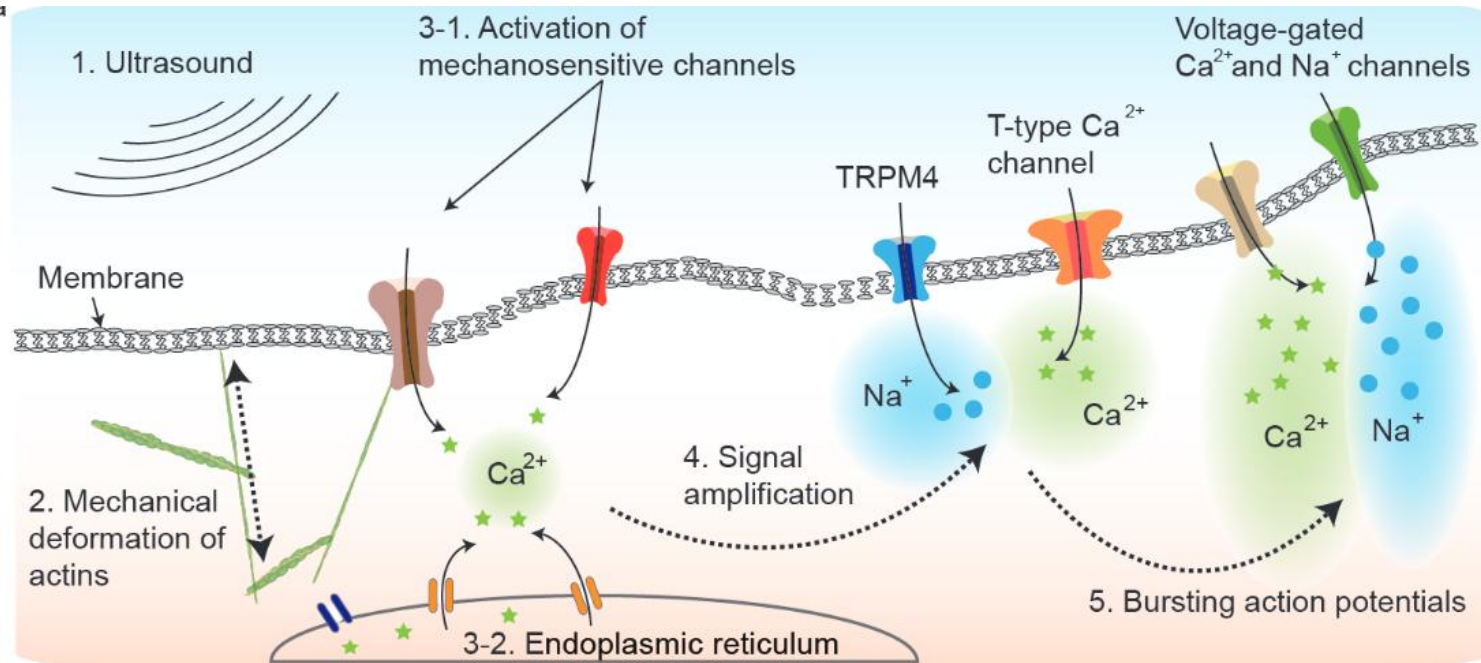


Transmembrane voltage imaging using the genetically encoded voltage indicator Ace2N

Yoo et al., 2022

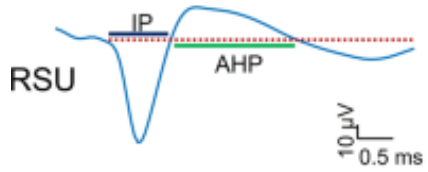


→ Role of mechanosensitive Ca^{2+} channels, amplified by Voltage-dependent Ca^{2+} and Na^{2+} channels

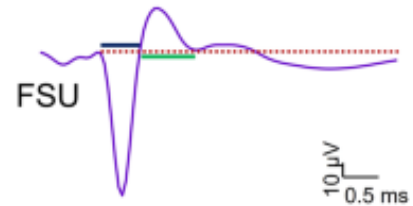


- Opening of specific **calcium-permeable mechanosensitive ion channels.**
- Calcium ions accumulate until they trigger the opening of **calcium-sensitive sodium channels.**
- This leads to depolarization of the cell membrane and the opening of **voltage-gated calcium channels,**
- Leading to the large responses observable by GCaMP6f imaging

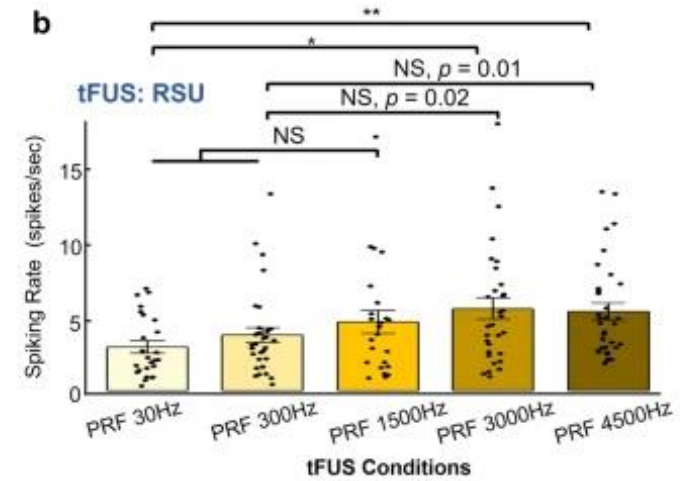
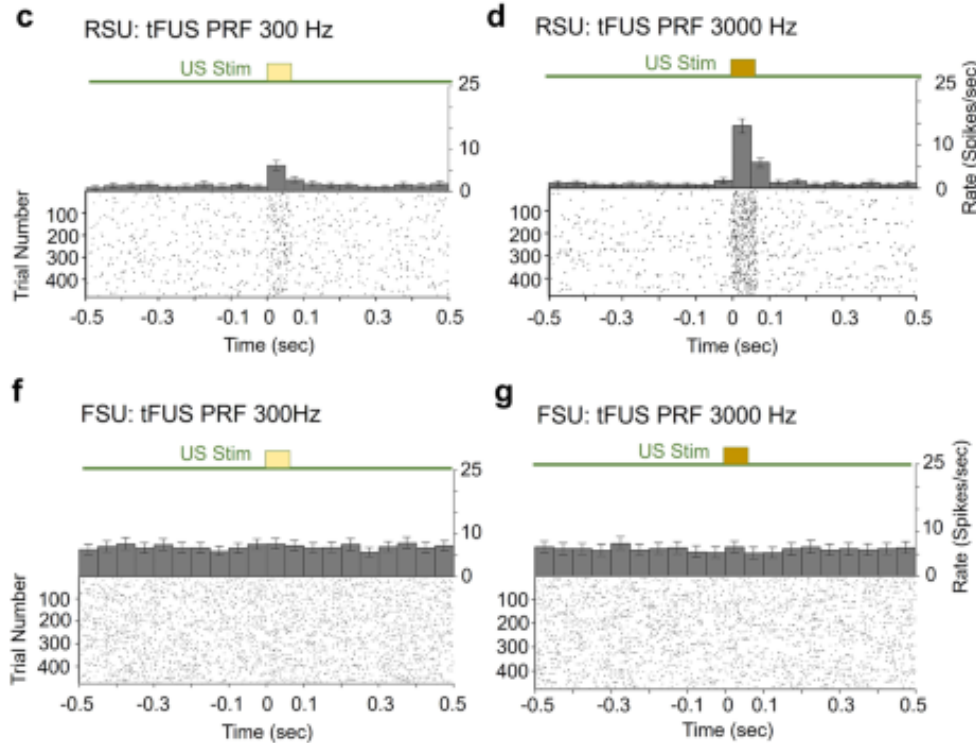
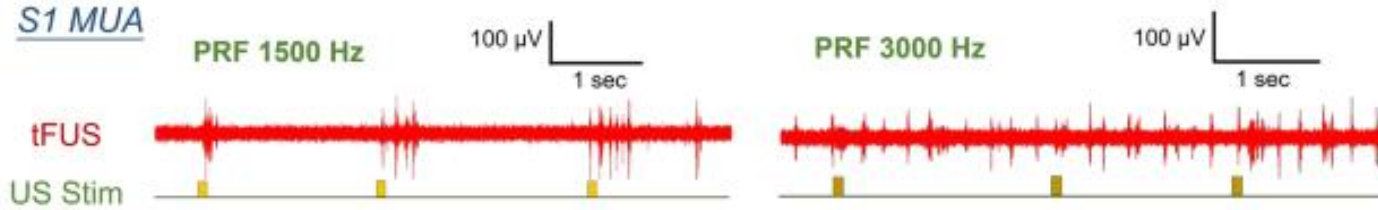
→ At the neuron's level



→ Excitatory



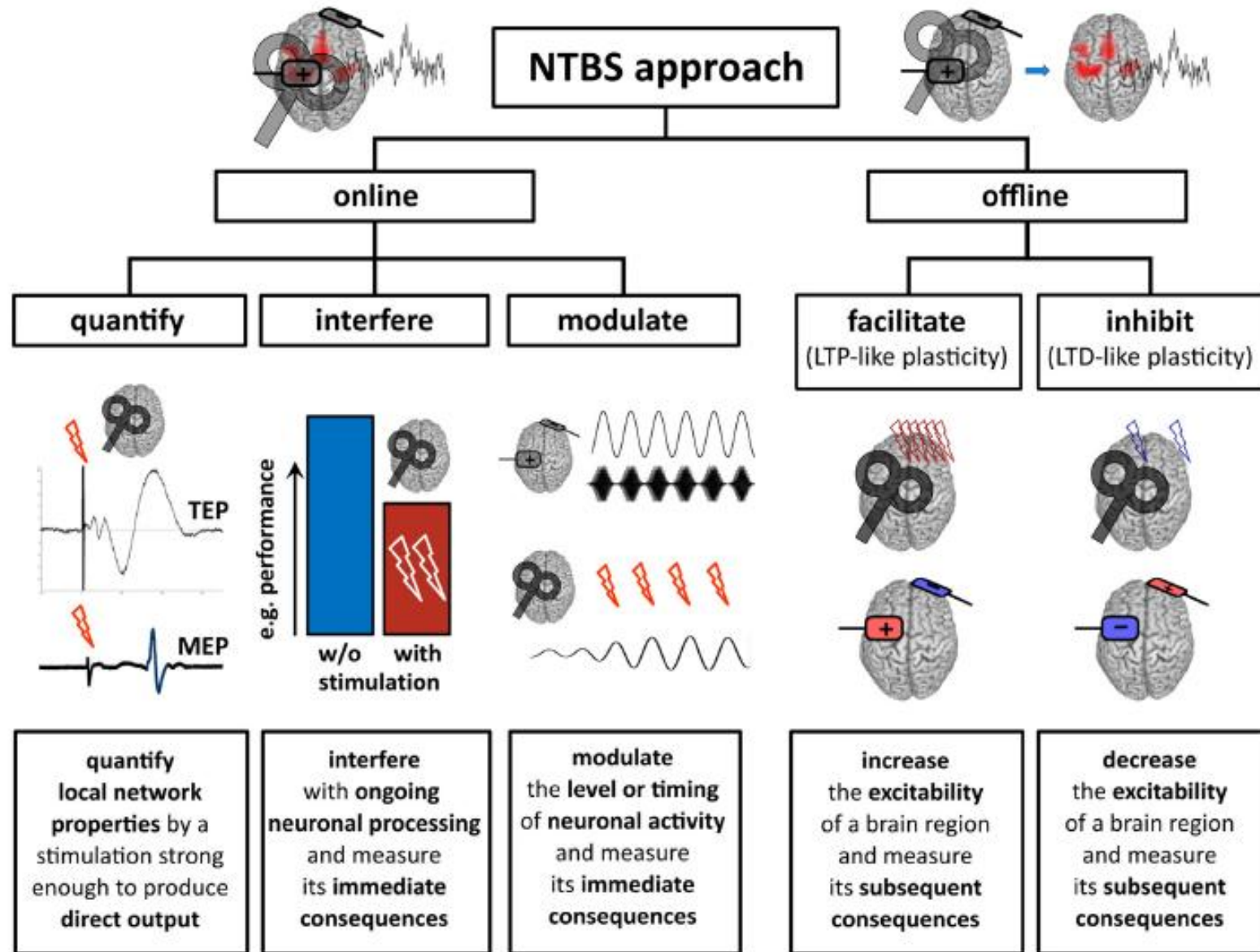
→ Inhibitory



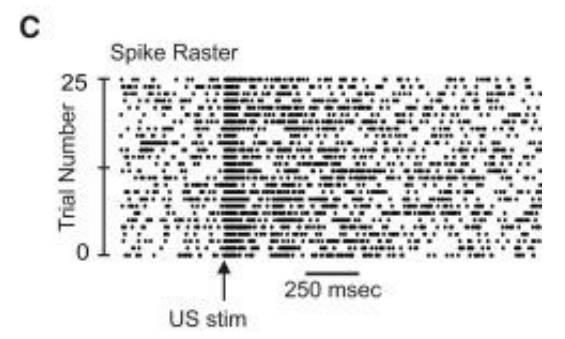
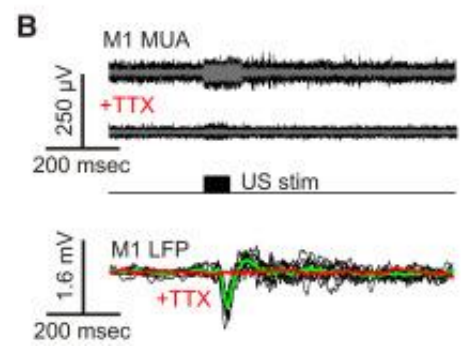
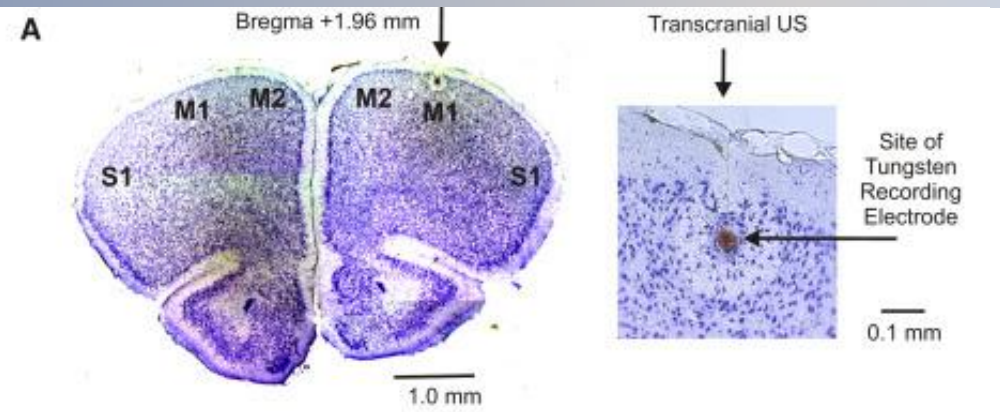
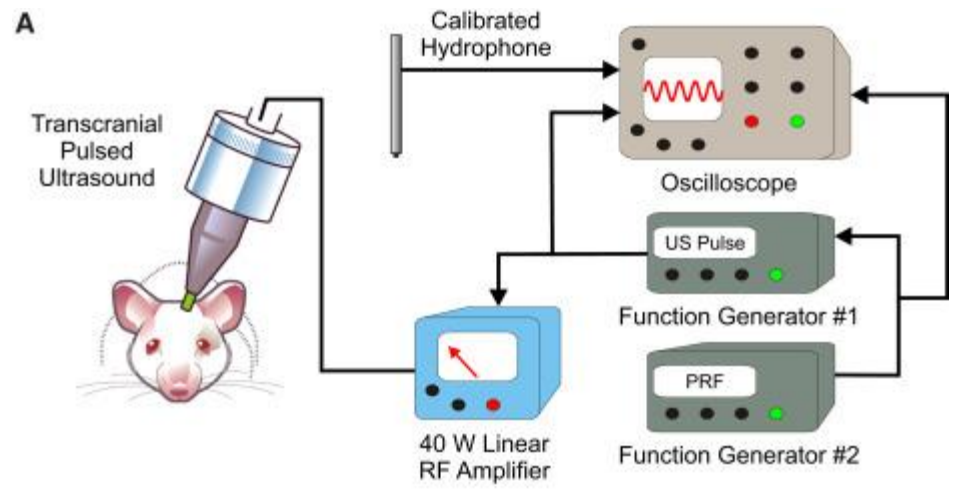
- RSU responses are time locked to TUS, FSU are delayed
- RSU spiking rates increase with increasing PRF

TUS for Neuromodulation

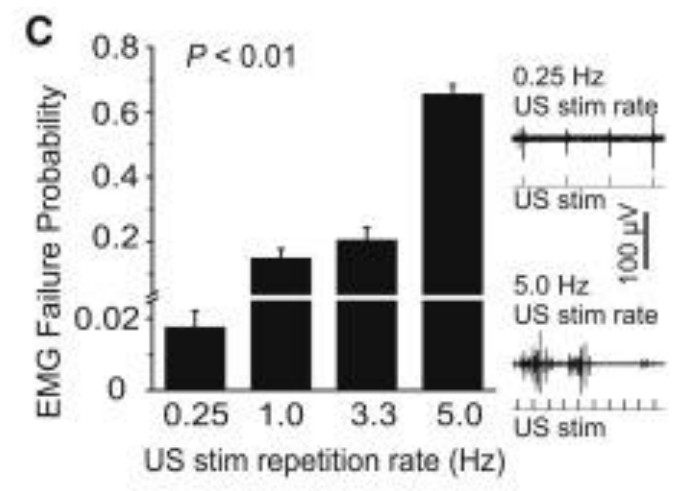
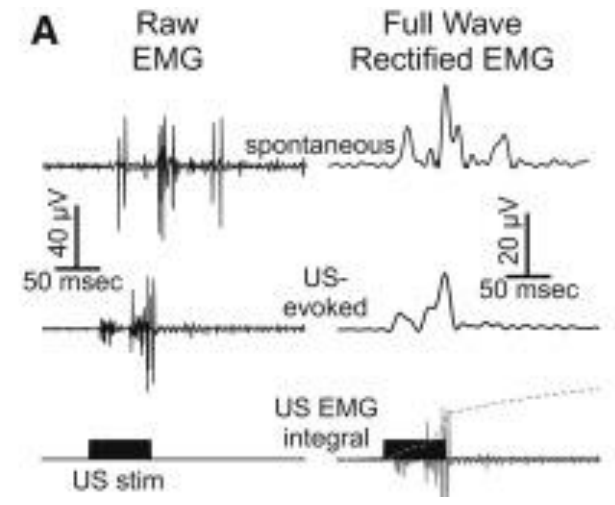
In vitro & Animal work



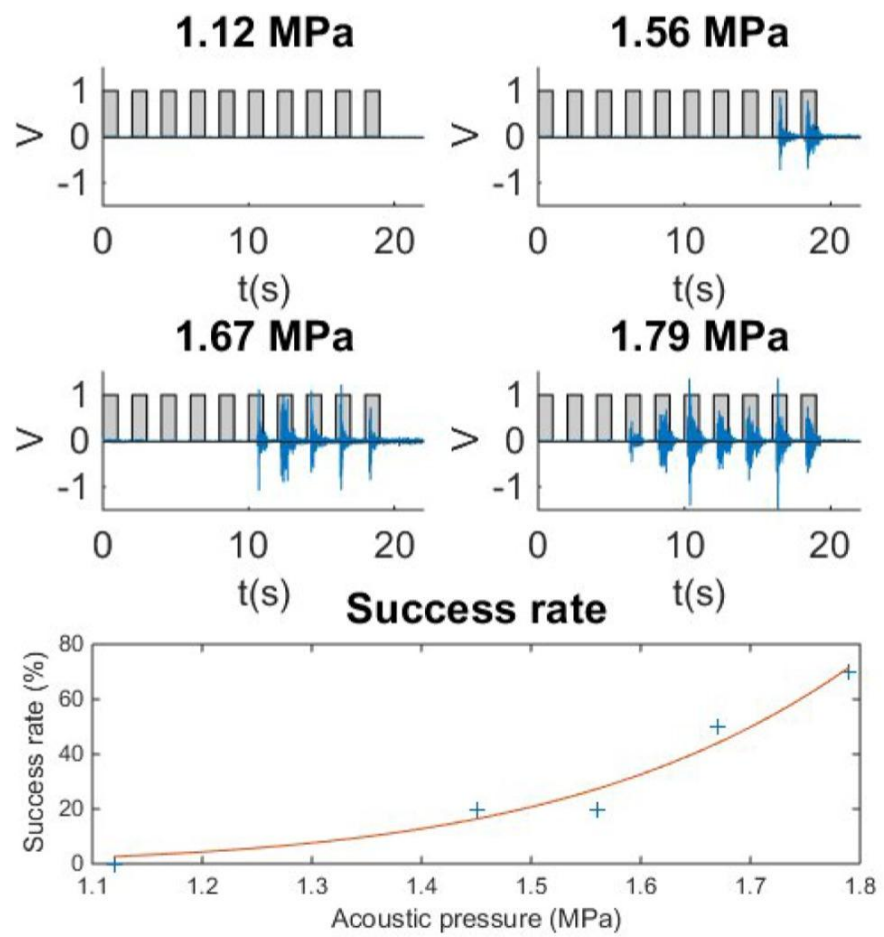
Online protocols



➔ Pulsed US triggers cortical action potentials to drive peripheral muscle contractions

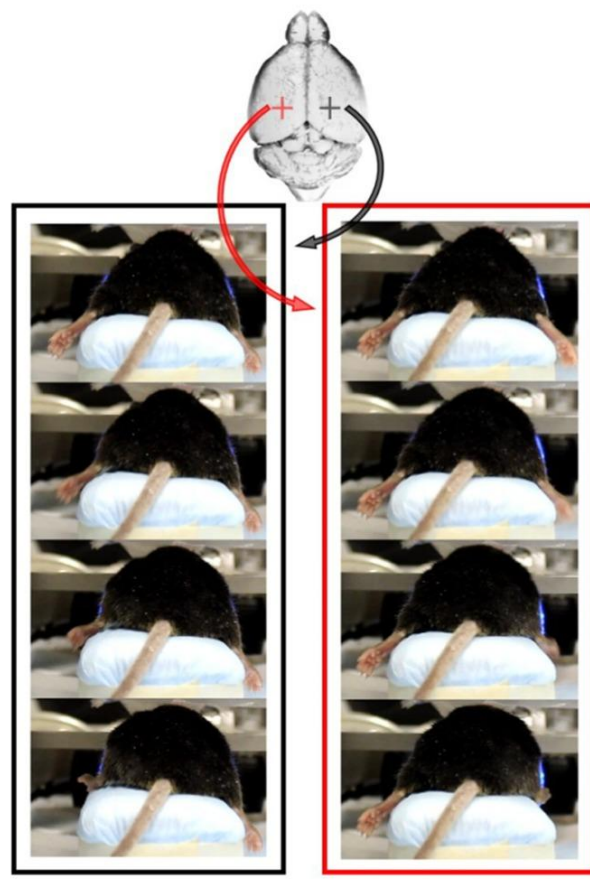


Online protocols



(a)

US MEP?

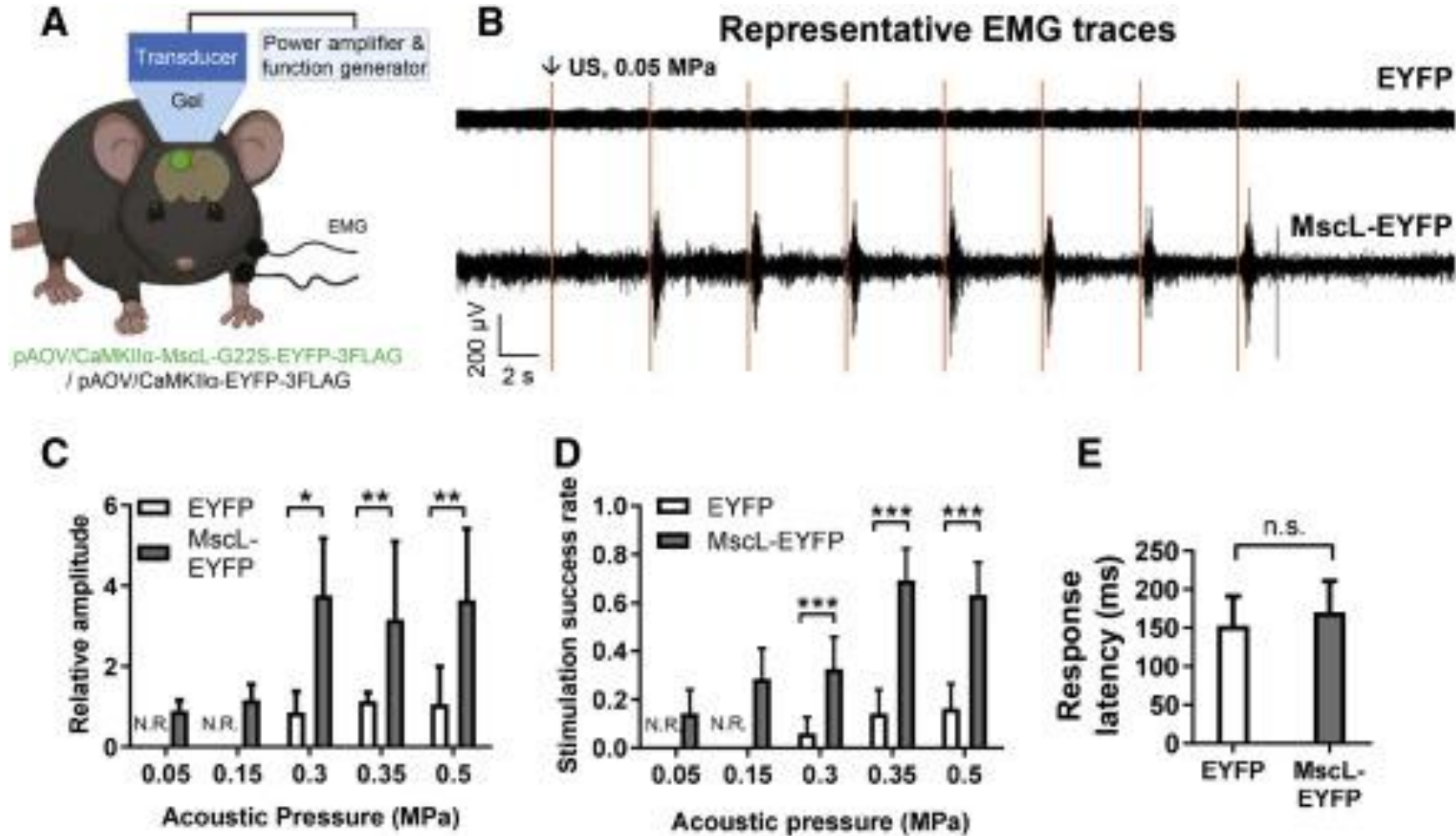


(b)



FUS sonications were carried out at 1.9 MHz with 50% duty cycle, pulse repetition frequency of 1 kHz, and duration of 1 s

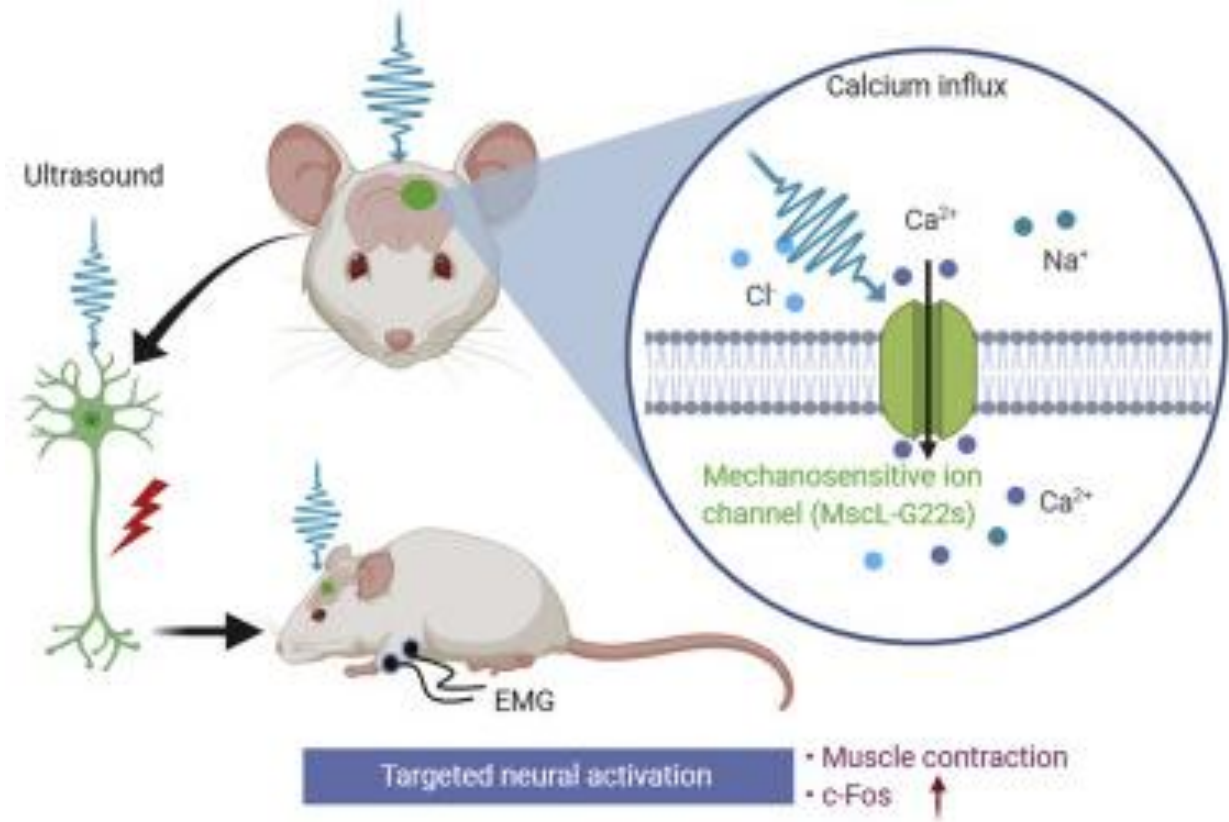
Online protocols



Can ultrasound EMG response be associated with a motor evoked potential?

- EMG onset is at 40-200ms
- Studies looked at EMG success rate or threshold rather than amplitude

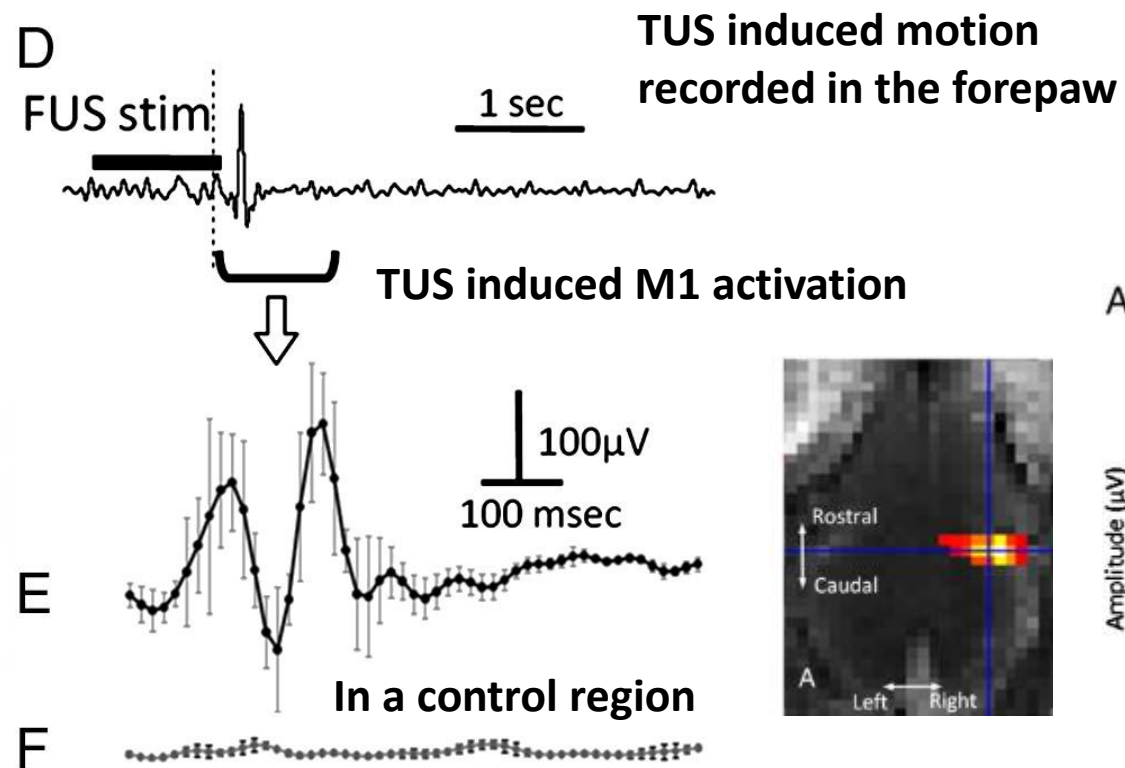
- EMG success rate varies with
 - Intensity
 - Duty cycle
 - Tone burst duration



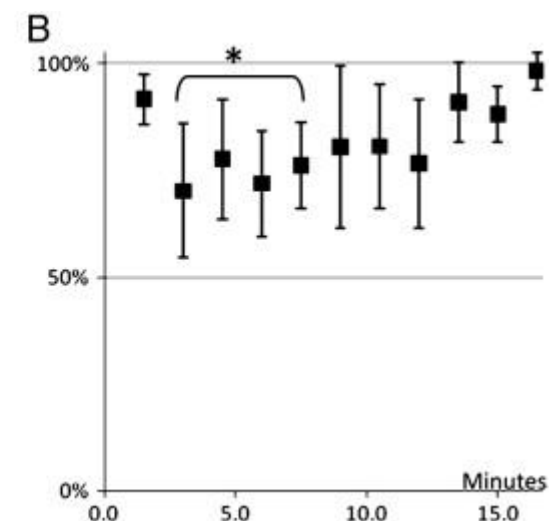
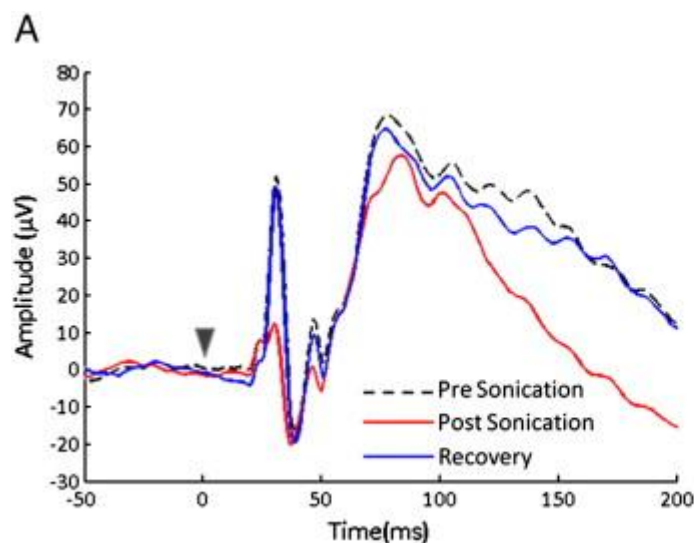
Brain stimulation wish-list:

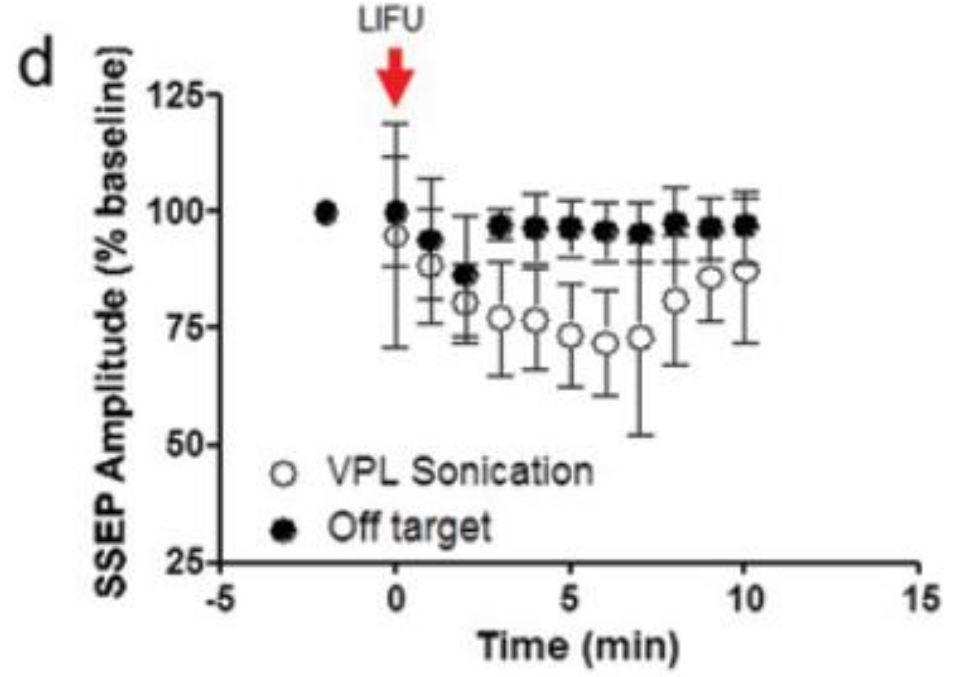
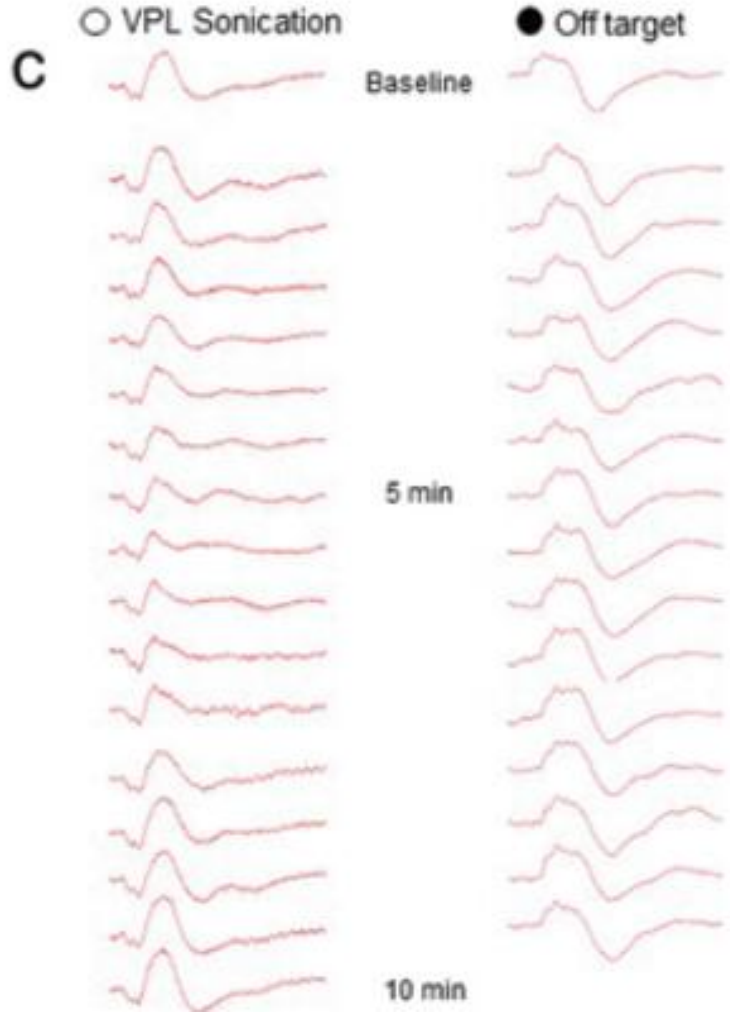
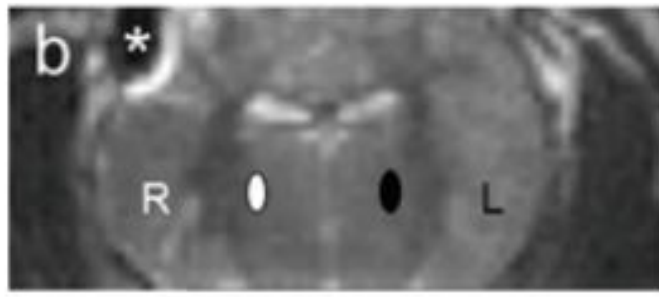
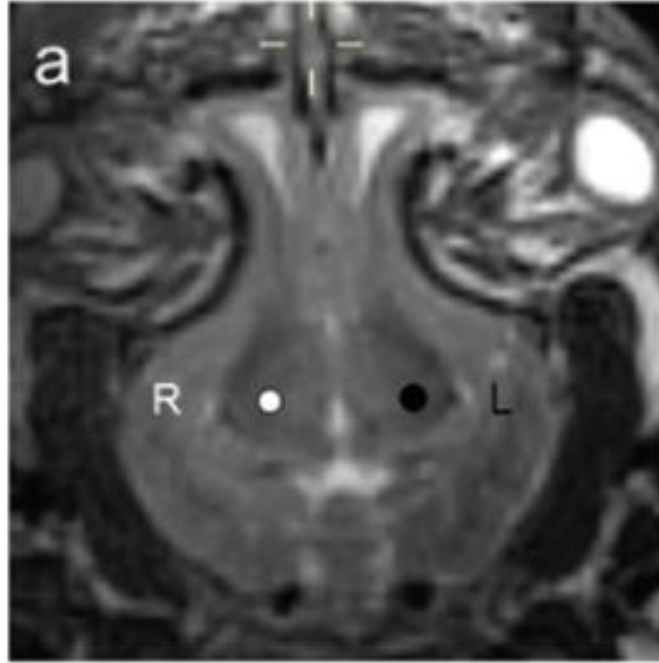
- Non-invasive ✓
- Focal ✓
- Surface & deep ✓
- Long-lasting
- Robust & effective
- Measurable
- Relevant for behaviour

Long-lasting effects of TUS?



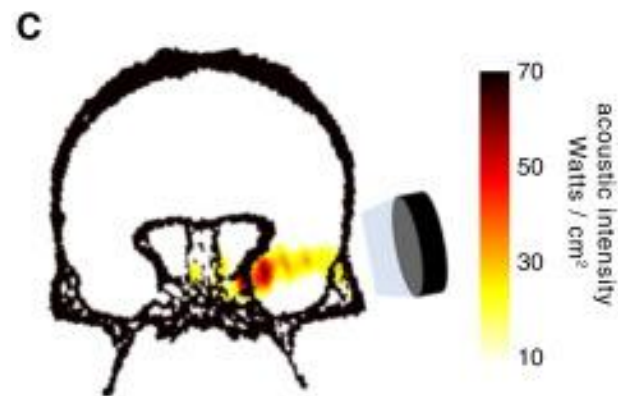
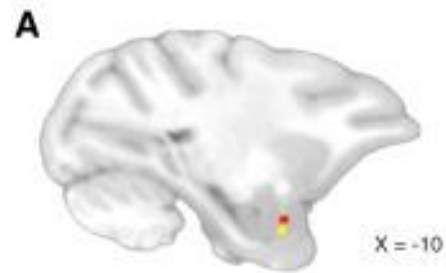
VEP recordings



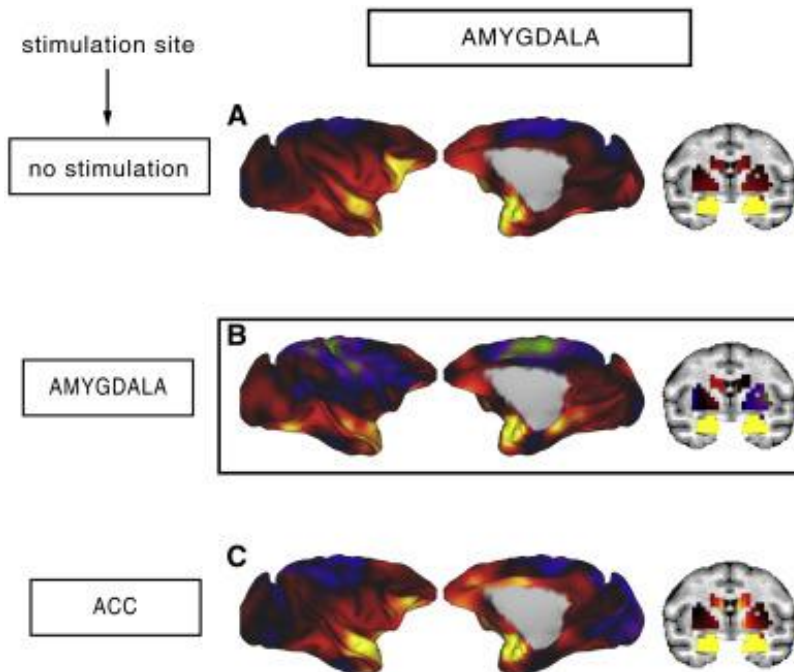
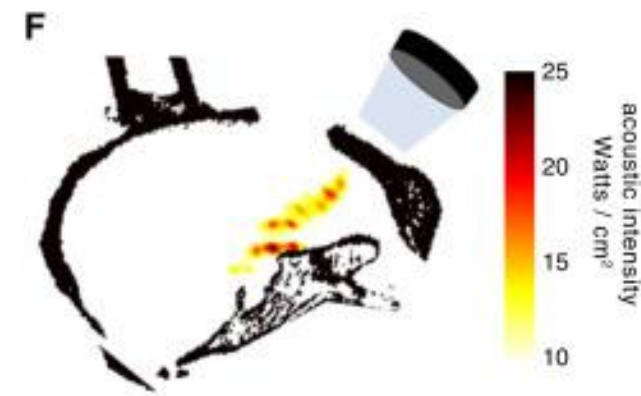


Towards offline neuromodulation in animals

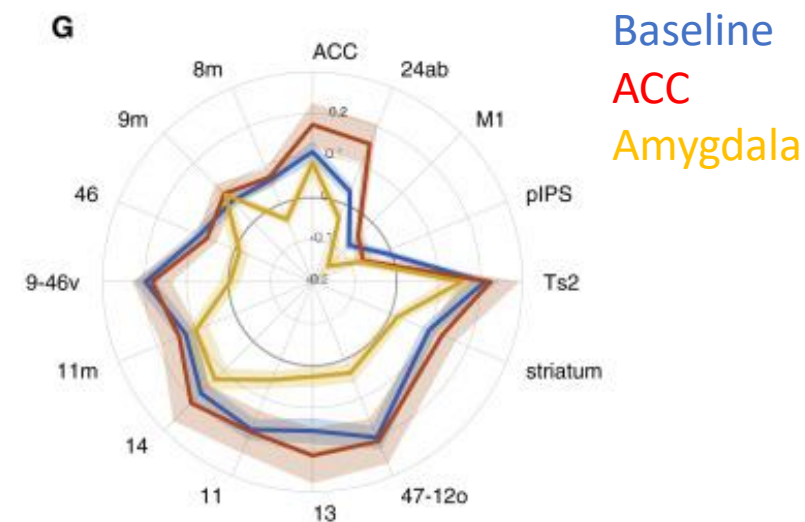
AMYGDALA



ACC



Connectional fingerprint



TUS for Neuromodulation

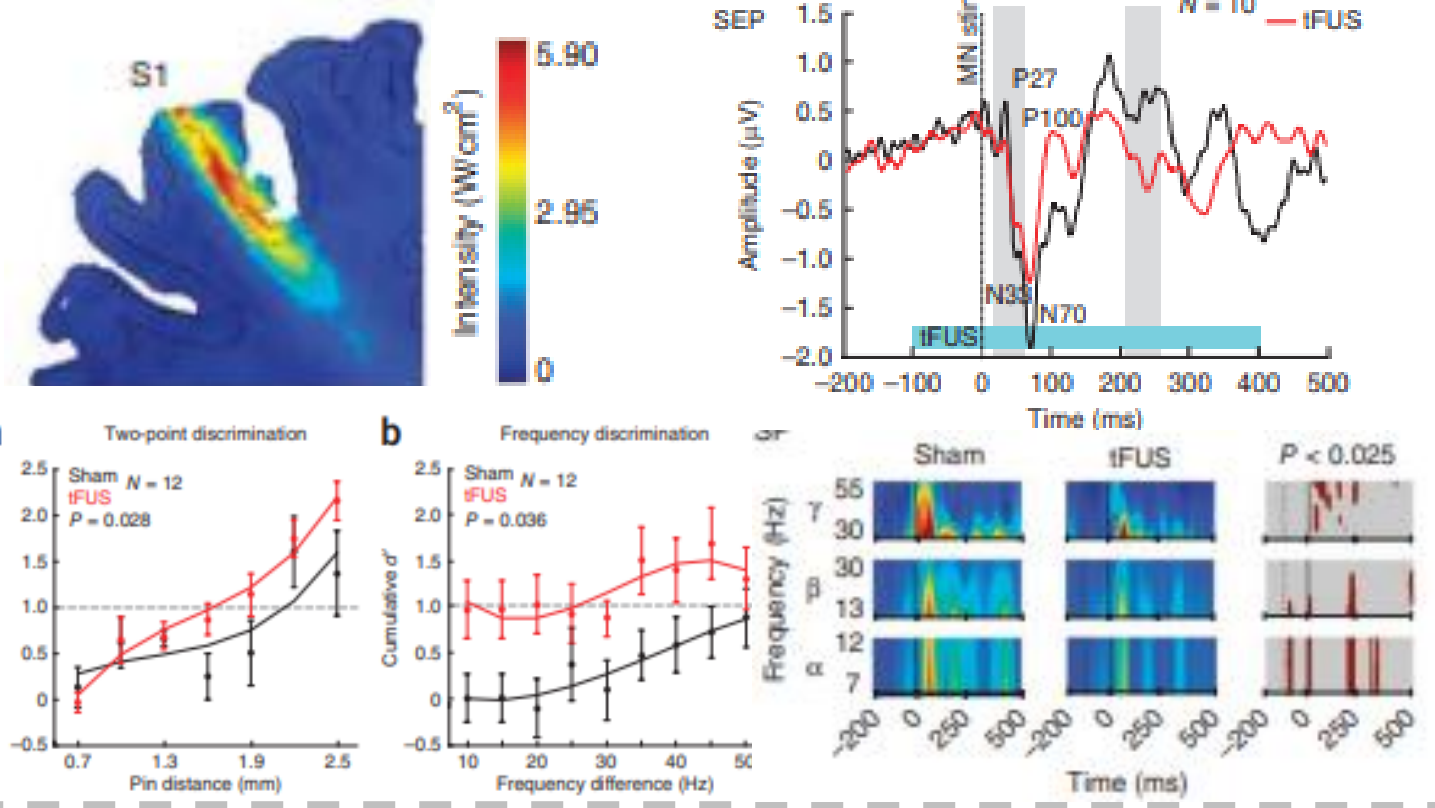
Human work

TECHNICAL REPORTS



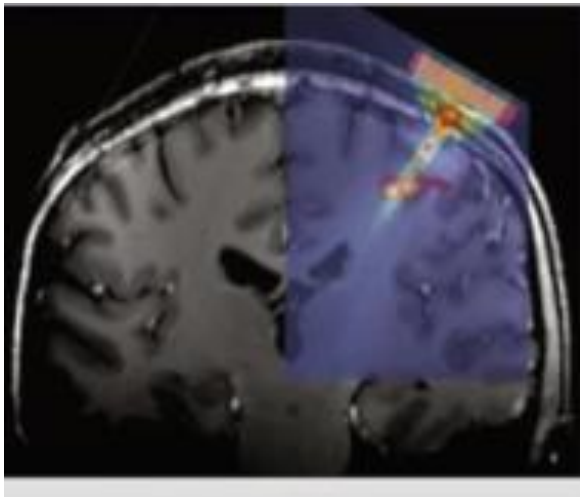
Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans

Wynn Legon¹, Tomokazu F Sato¹, Alexander Opitz^{1,2}, Jerel Mueller³, Aaron Barbour¹, Amanda Williams¹ & William J Tyler^{1,3,4}

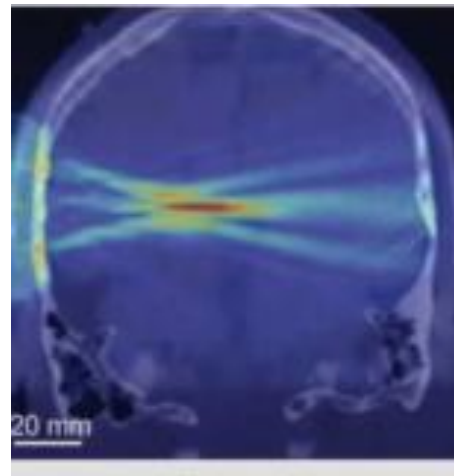


Legon et al., 2014, Nature Neurosc.

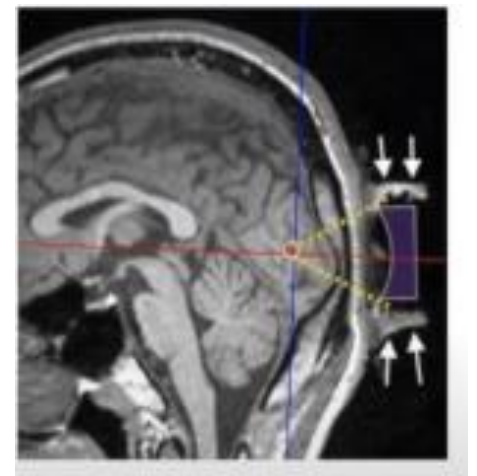
Primary motor cortex



Thalamus



Primary visual cortex



Primary motor cortex

- 20 Legon W 2018b
- 31 Ai L 2018
- 23 Gibson BC 2018
- 19 Fomenko A 2020
- 32 Yu K 2021
- 21 Xia X 2021
- 24 Zhang Y 2021
- 26 Zeng K 2022
- 30 Heimbuch IS 2022
- 22 Nakajima K 2022
- 28 Zhang M-F 2022

- 27 Samuel N 2022
- 25 Ren L 2023
- 29 Zhang T 2023
- 33 Shamli Oghli Y 2023

Primary somatosensory cortex

- 34 Legon W 2014
- 35 Mueller J 2014
- 36 Lee W 2015
- 37 Lee W 2016a
- 38 Lee W 2017
- 39 Liu C 2021
- 40 Kim H-C 2023

Frontal cortex

- 46 Sanguinetti JL 2020
- 51 Kim YG 2022
- 22 Nakajima K 2022
- 52 Park TY 2022
- 48 Forster A 2023a
- 47 Forster A 2023b
- 49 Ziebell P 2023
- 50 Fine JM 2023

Secondary somatosensory cortex

- 37 Lee W 2016a

Visual cortex

- 41 Lee W 2016b
- 42 Schimek N 2020
- 44 Braun V 2020
- 43 Butler CR 2022
- 45 Nandi T 2023

Anterior cingulate cortex

- 53 Yaakub SN 2023

Posterior cingulate cortex

- 53 Yaakub SN 2023

Basal ganglia

- 54 Cain JA 2021b
- 22 Nakajima K 2022

Amygdala

- 55 Kuhn T 2023

Entorhinal cortex

- 56 Schafer ME 2021
- 55 Kuhn T 2023

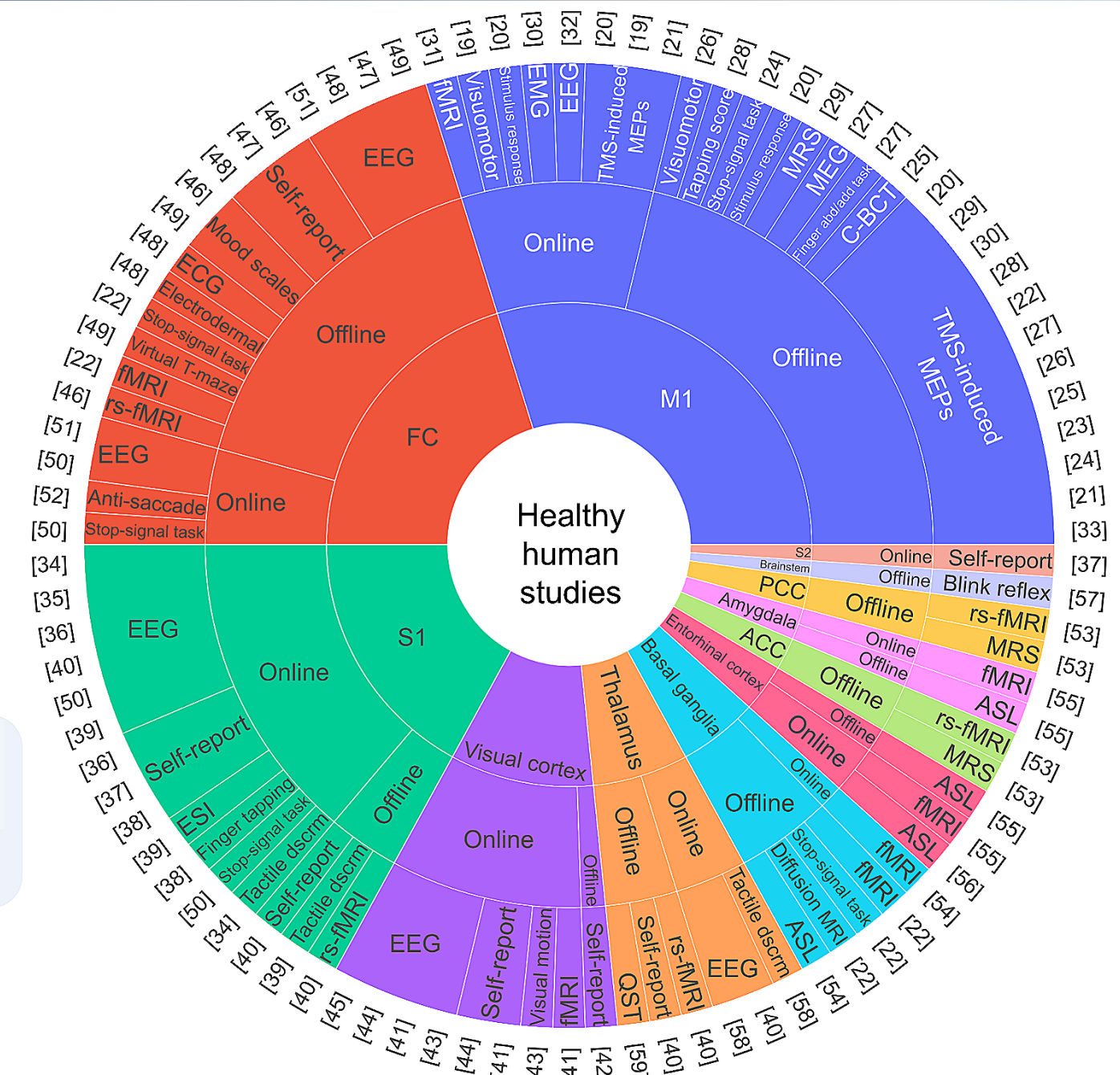
Thalamus

- 58 Legon W 2018a
- 59 Badran BW 2020
- 40 Kim H-C 2023

Brainstem

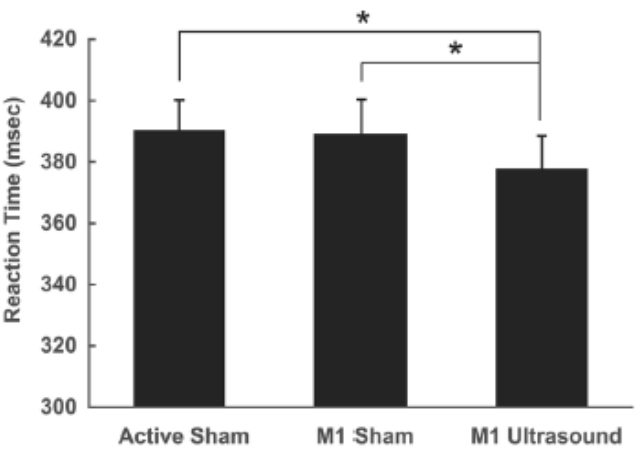
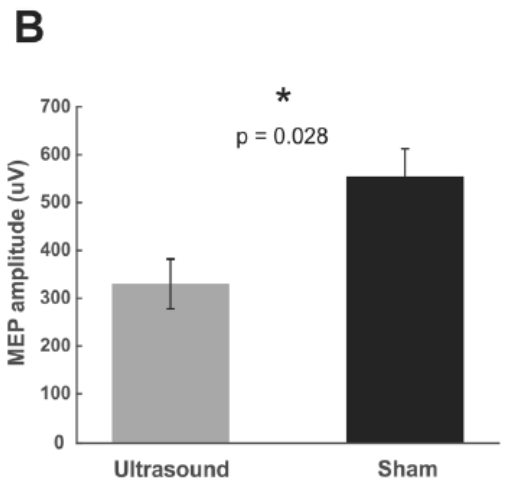
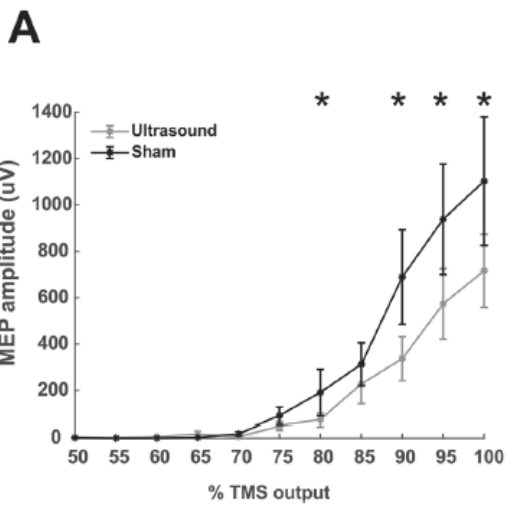
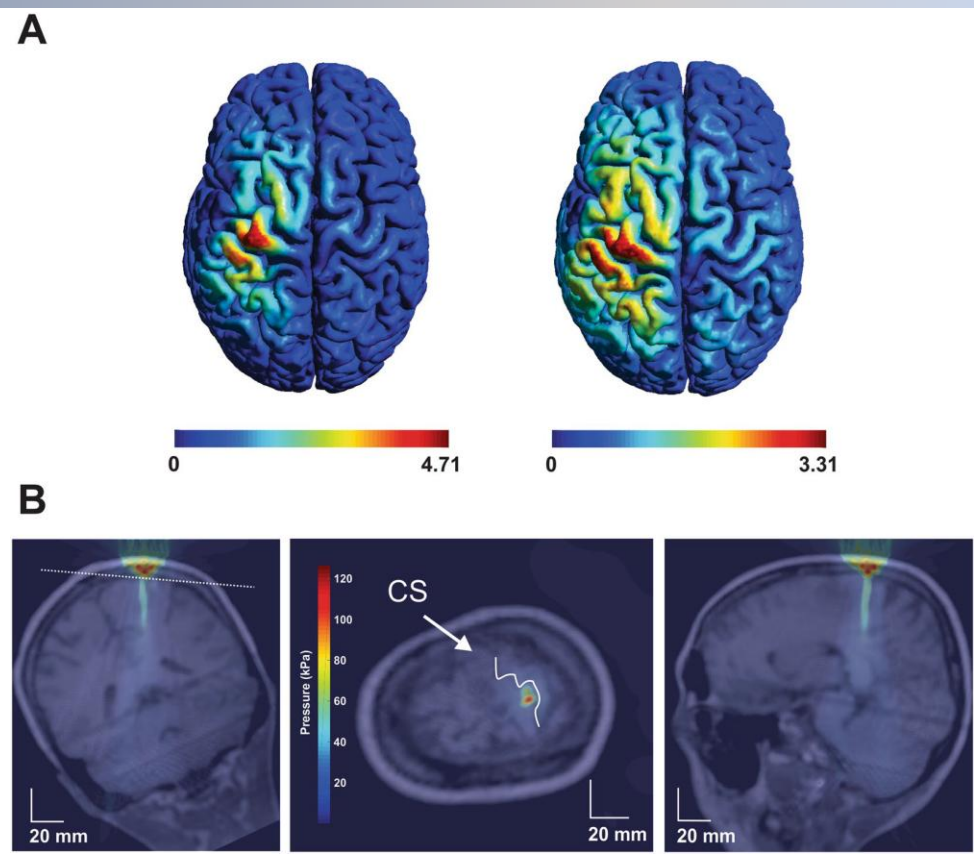
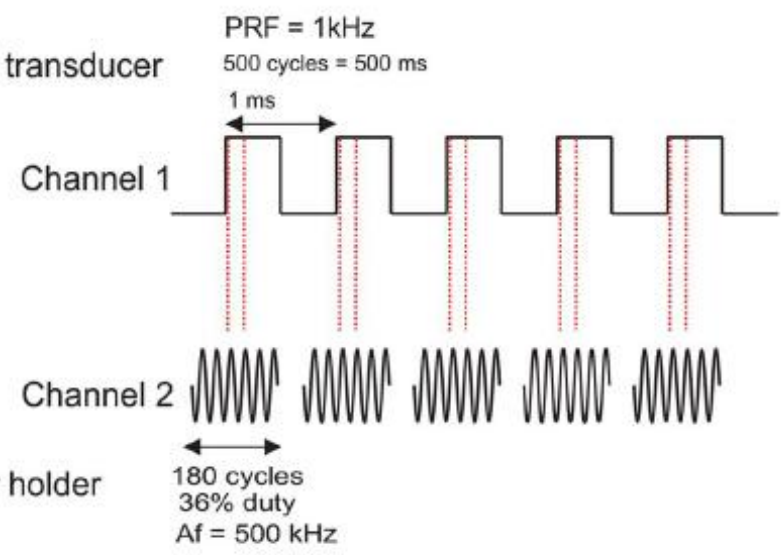
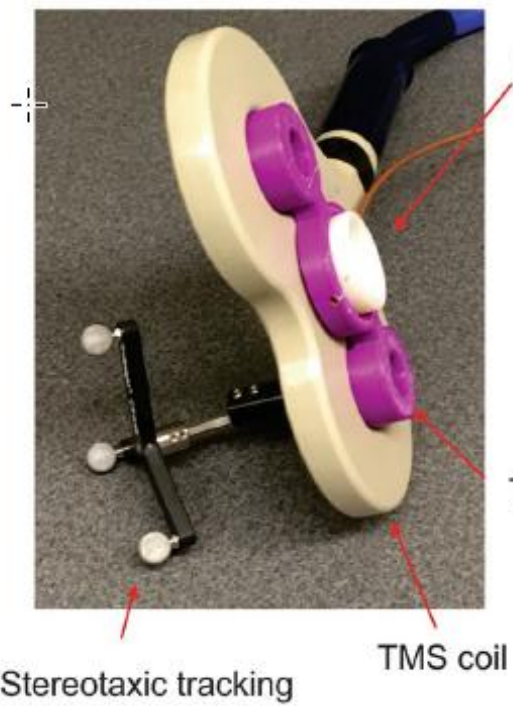
- 57 Guerra A 2021



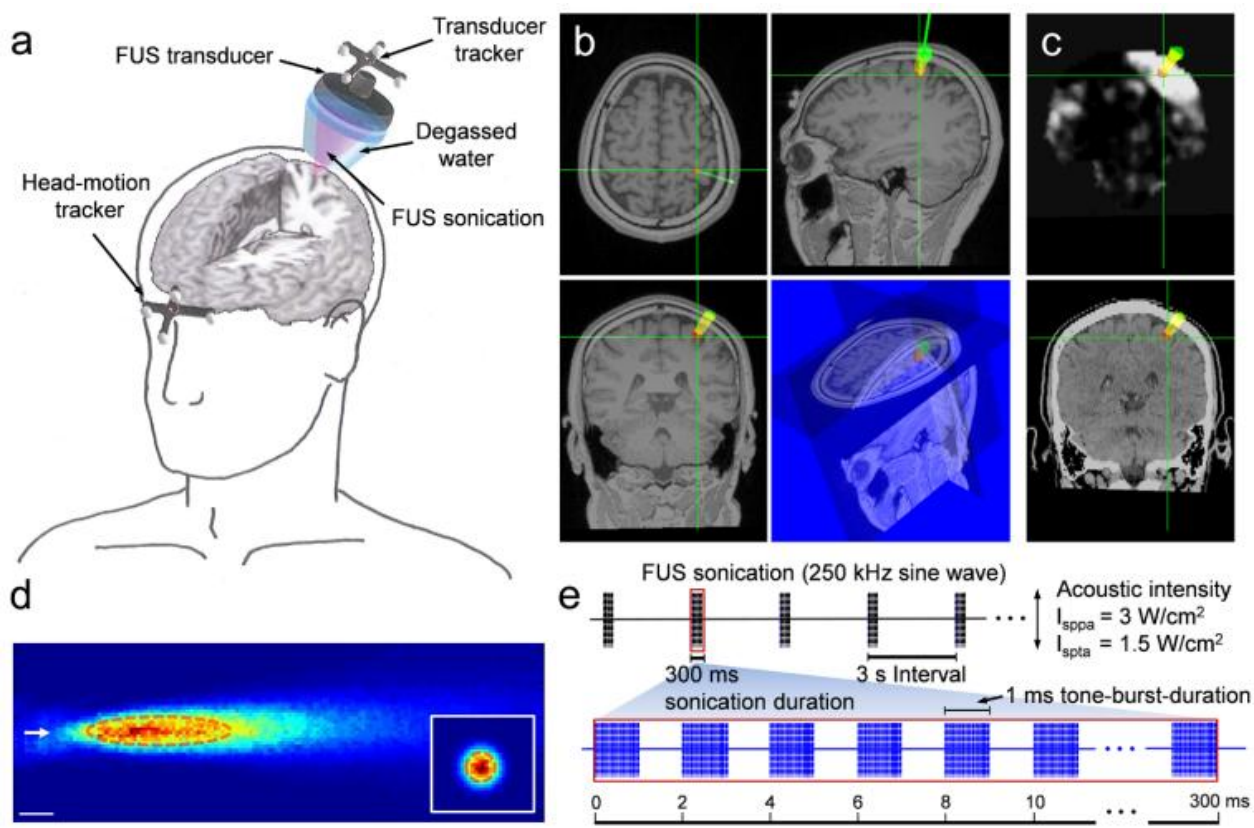


34 Legon W 2014	23 Gibson BC 2018	57 Guerra A 2021	28 Zhang M-F 2022	40 Kim H-C 2023
35 Mueller J 2014	46 Sanguinetti 2020	32 Yu K 2021	52 Park TY 2022	33 Shamli Oghli 2023
36 Lee W 2015	42 Schimek 2020	21 Xia X 2021	27 Samuel N 2022	49 Ziebell P 2023
37 Lee W 2016a	44 Braun V 2020	24 Zhang Y 2021	25 Ren L 2023	53 Yaakub SN 2023
41 Lee W 2016b	59 Badran 2020	26 Zeng K 2022	45 Nandi T 2023	50 Fine JM 2023
38 Lee W 2017	19 Fomenko 2020	30 Heimbuch 2022	48 Forster A 2023a	
58 Legon W 2018a	56 Schafer 2021	51 Kim YG 2022	55 Kuhn T 2023	
20 Legon W 2018b	39 Liu C 2021	22 Nakajima 2022	47 Forster A 2023b	
31 Ai L 2018	54 Cain JA 2021b	43 Butler CR 2022	29 Zhang T 2023	

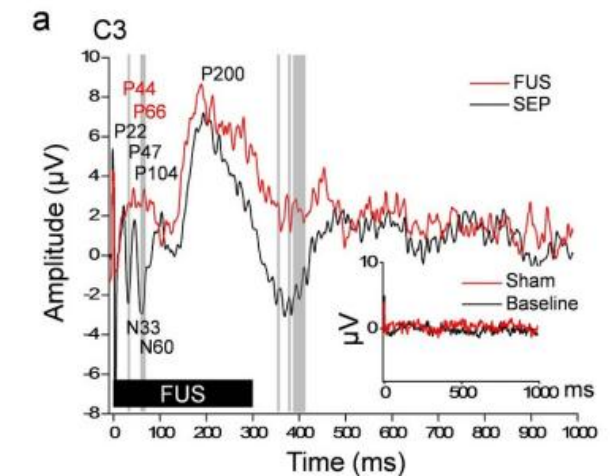
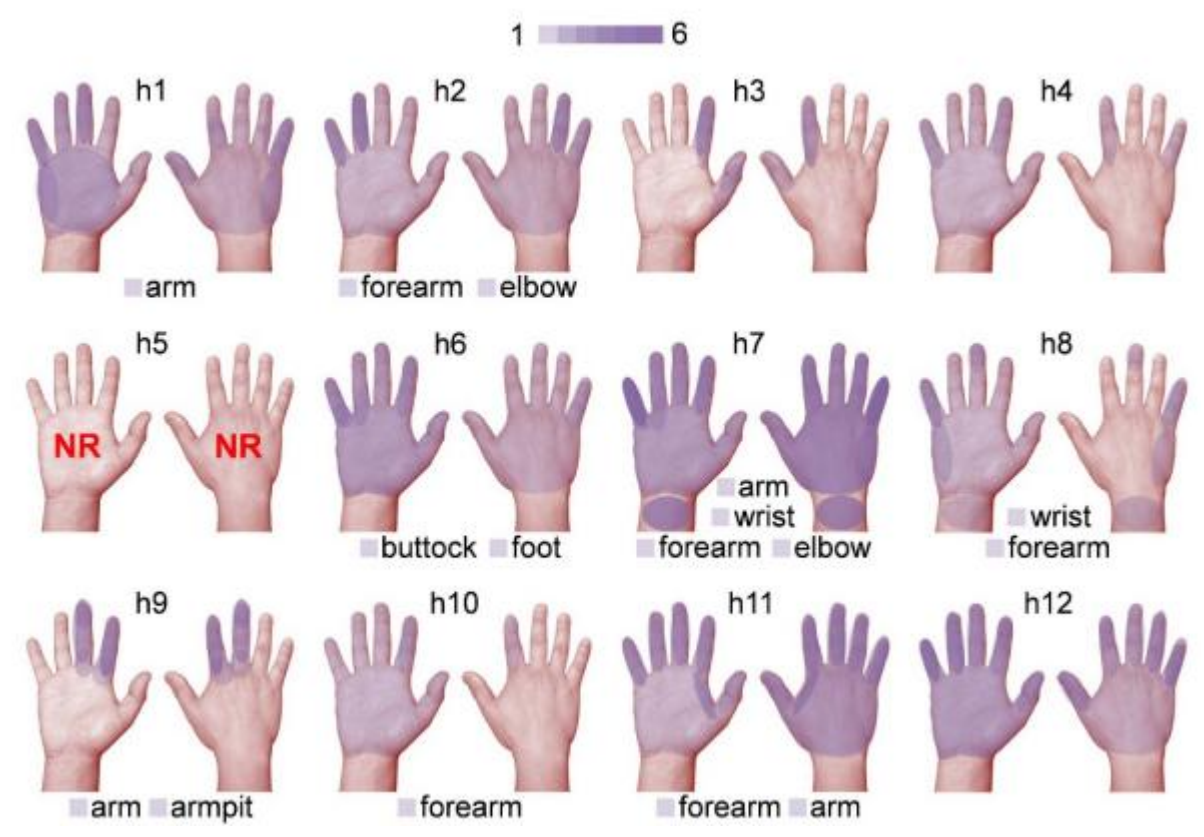
US in humans – Online neuromodulation



US in humans – Online neuromodulation



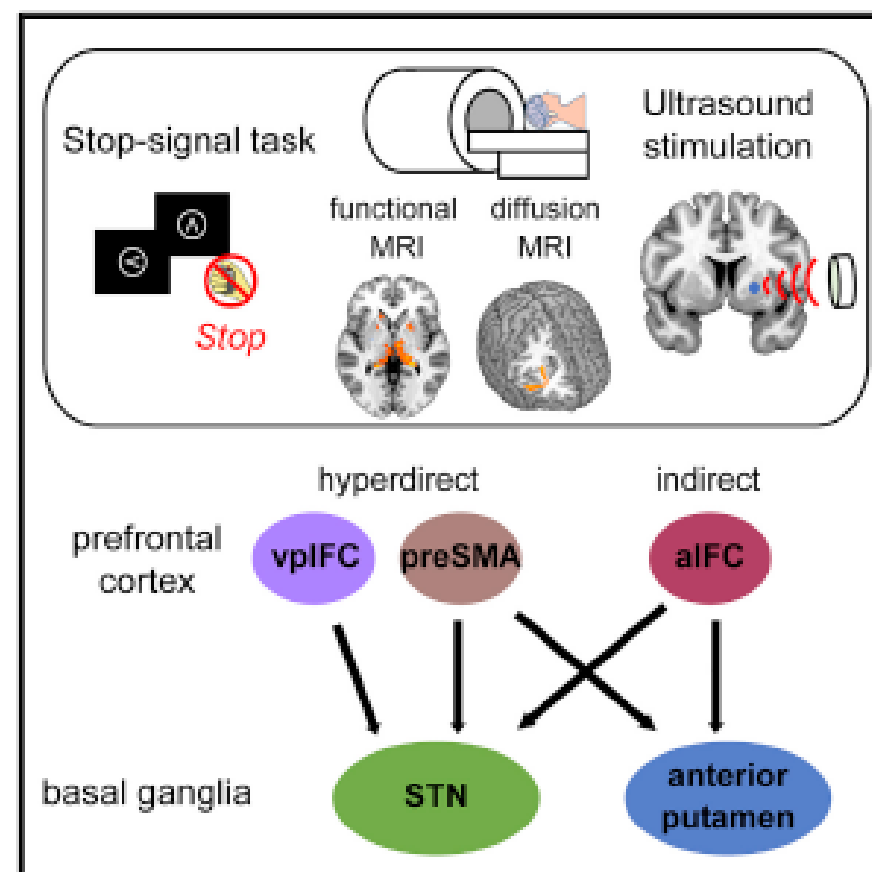
Types of sensations	Ratio of subjects reported	
Tingling	11/11	100.0%
SOM	11/11	100.0%
Heaviness	6/11	54.5%
Numbness	2/11	18.2%
Feeling of weak electrical current flow	3/11	27.3%
Itching	2/11	18.2%
Brushing	1/11	9.1%
Cooling	1/11	9.1%



Cell Reports

A causal role of anterior prefrontal-putamen circuit for response inhibition revealed by transcranial ultrasound stimulation in humans

Graphical abstract



Authors

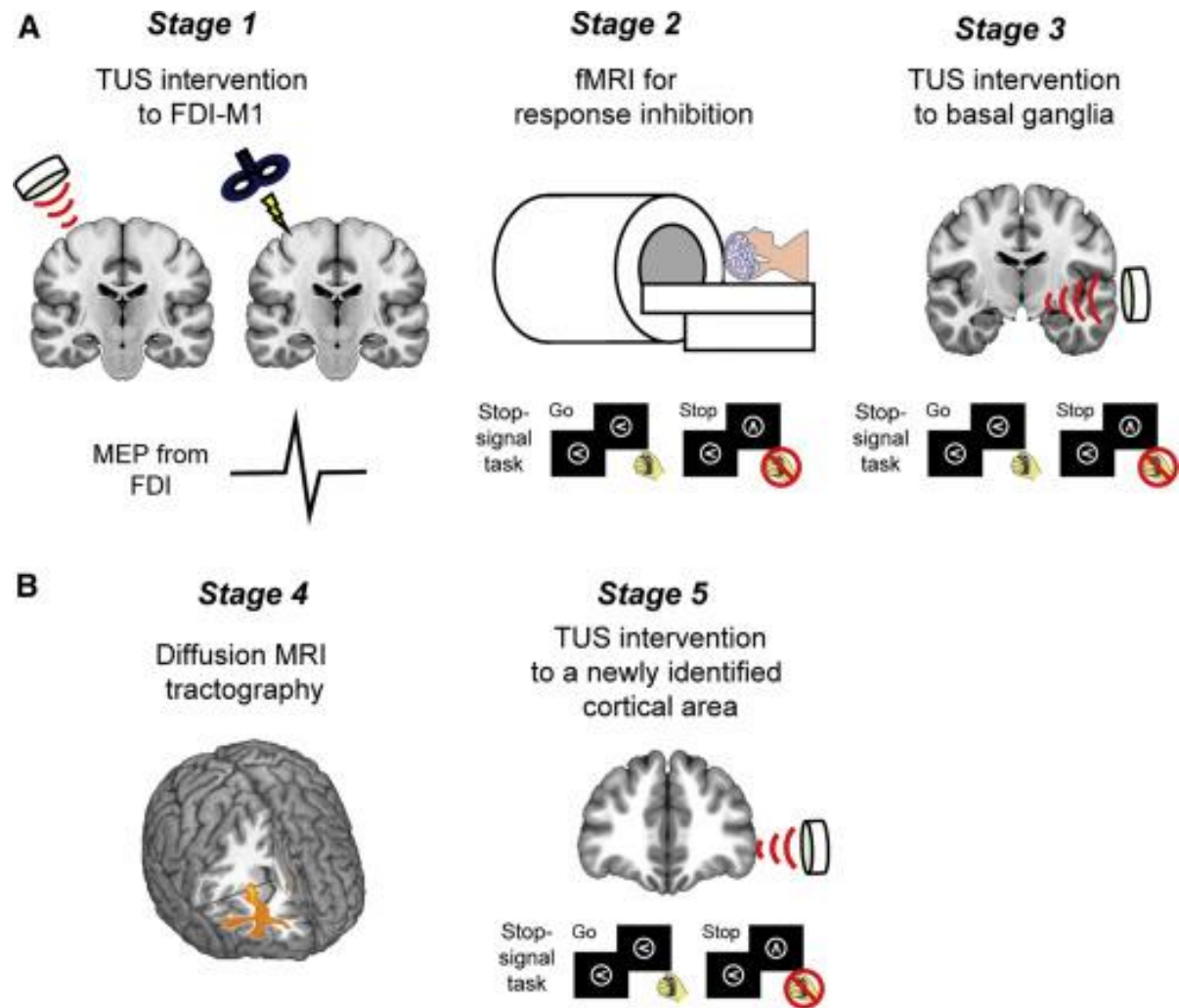
Koji Nakajima, Takahiro Osada, Akitoshi Ogawa, ..., Yasushi Oshima, Sakae Tanaka, Seiki Konishi

Correspondence

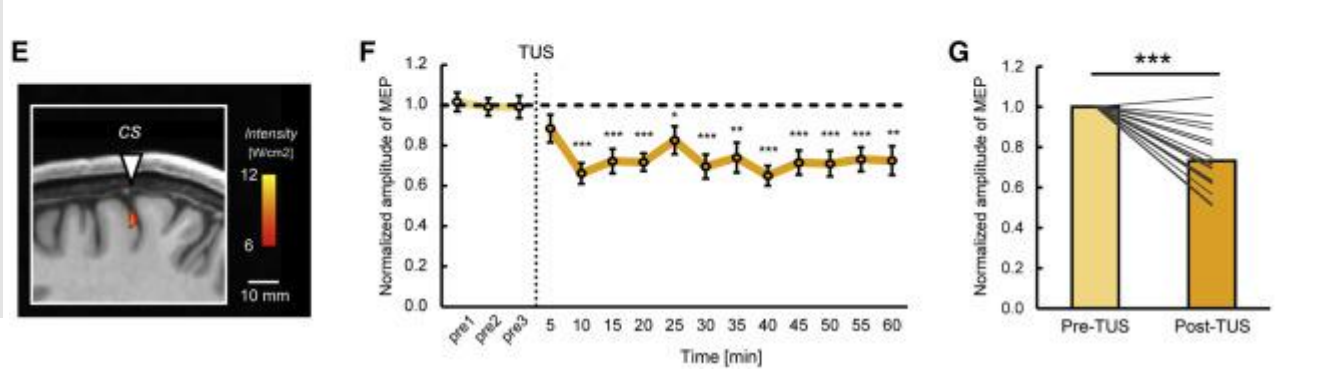
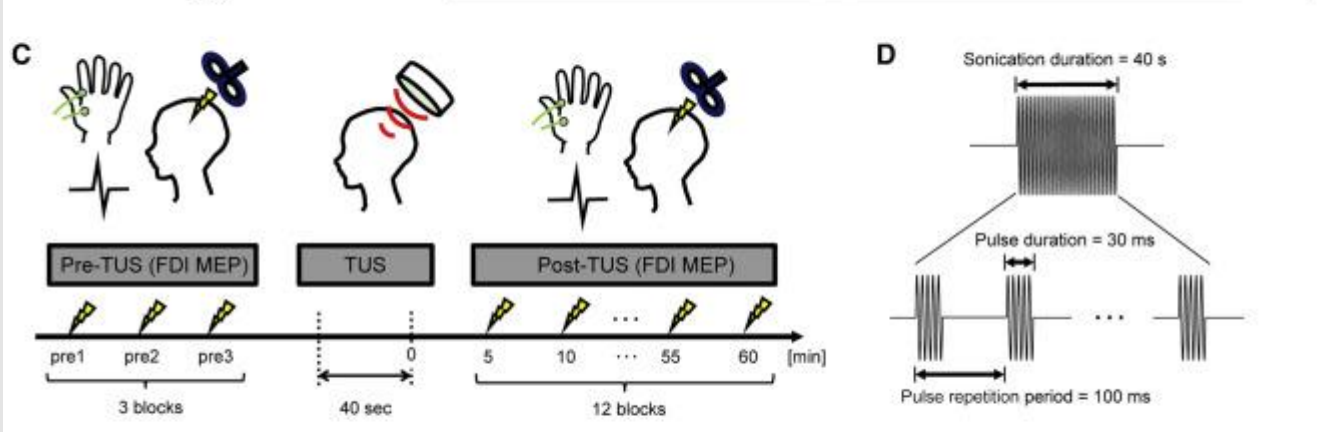
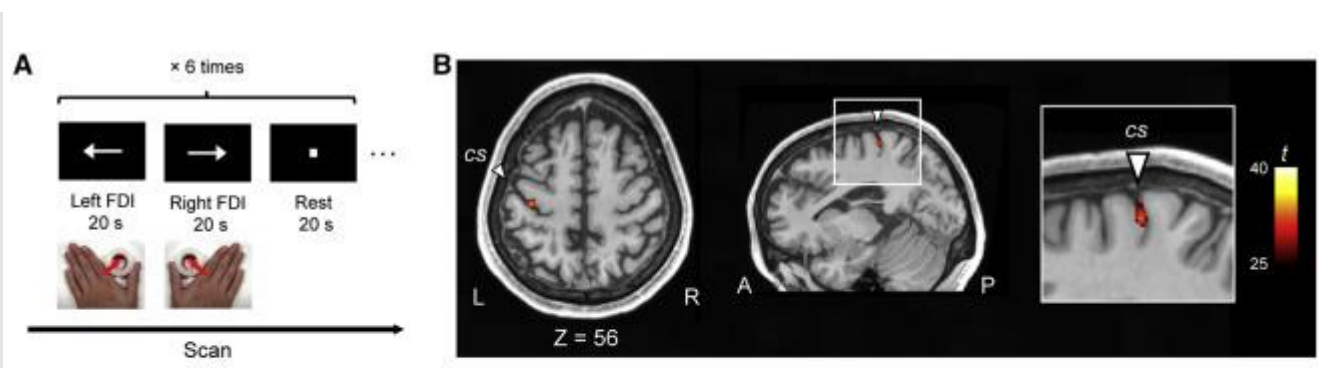
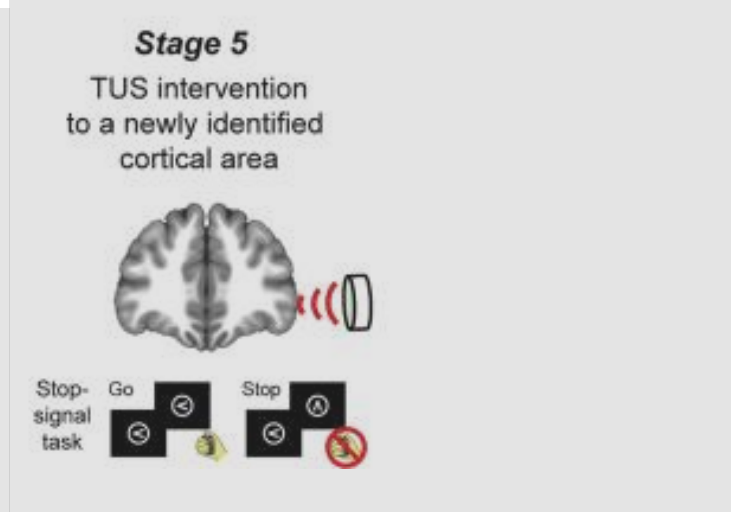
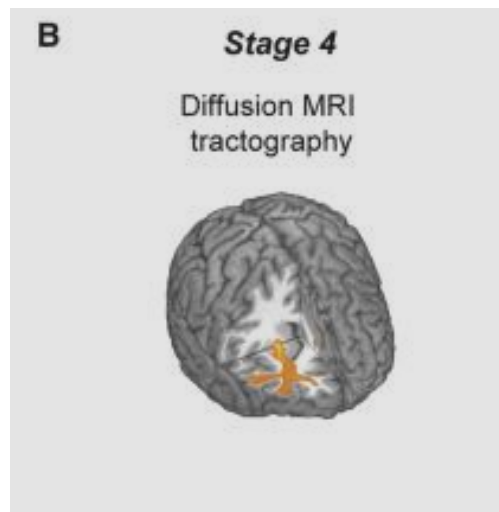
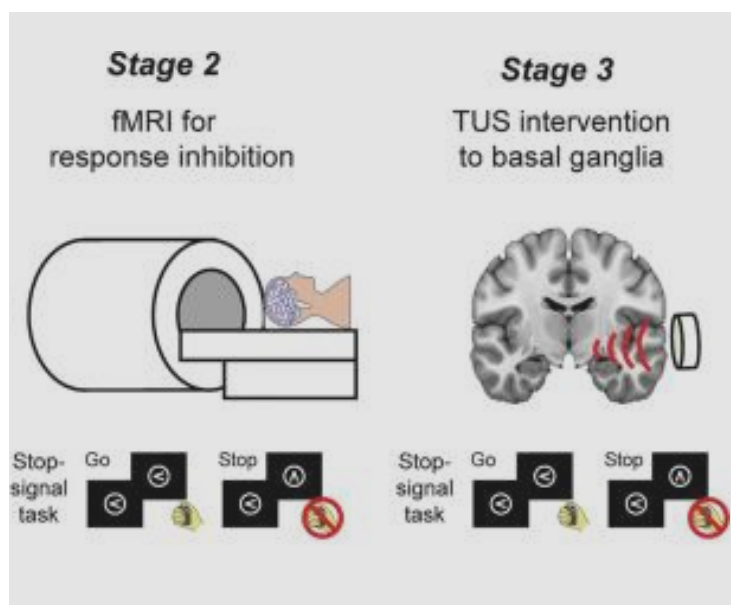
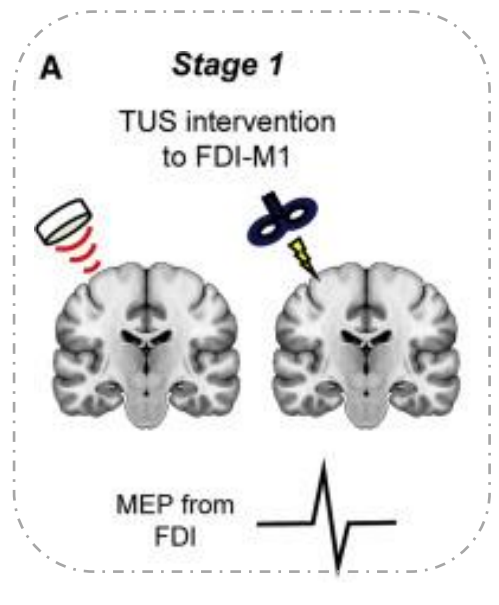
tosada@juntendo.ac.jp (T.O.), skonishi@juntendo.ac.jp (S.K.)

In brief

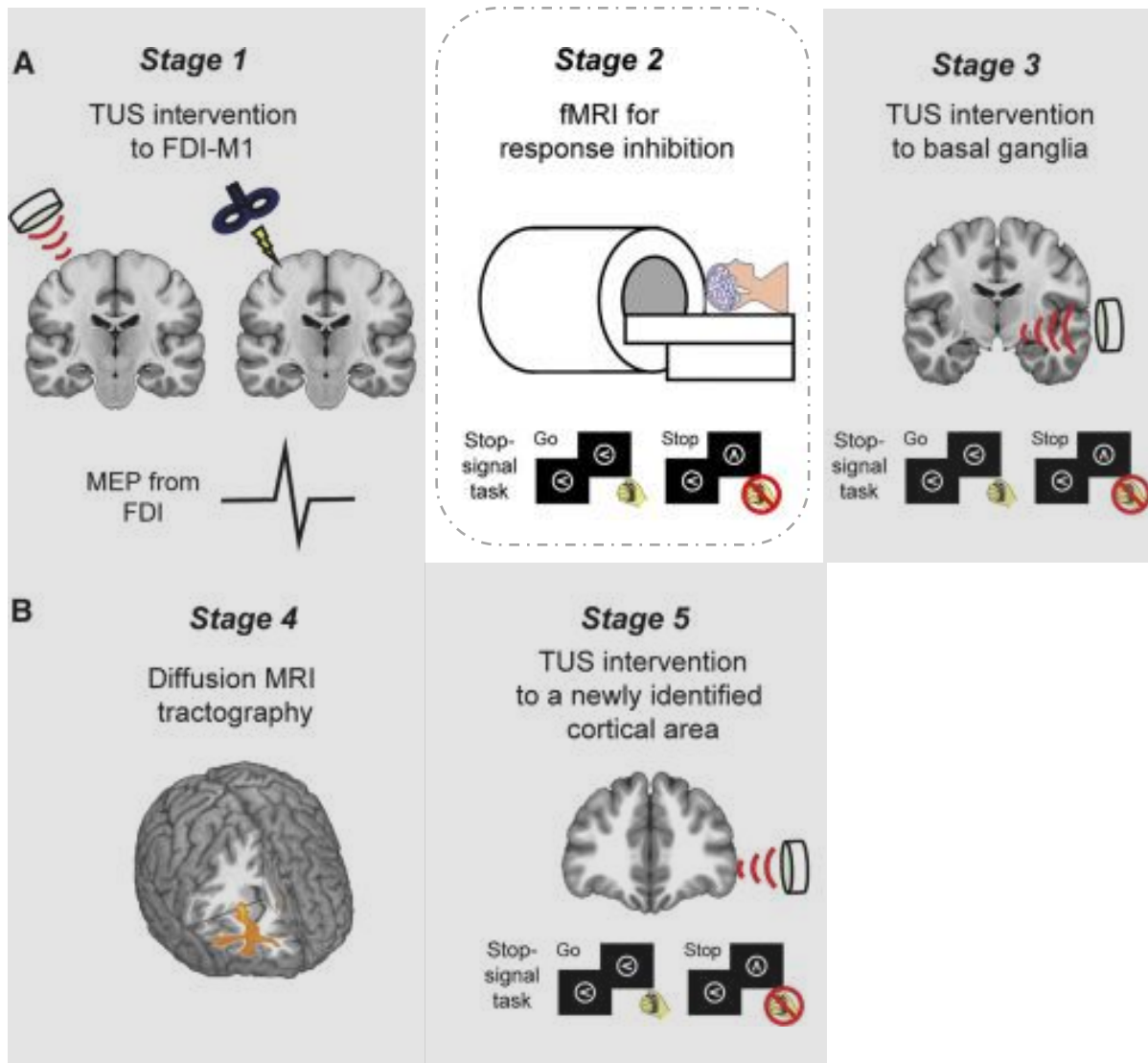
Nakajima et al. find that ultrasound stimulation to the right anterior putamen and the right anterior inferior frontal cortex (aIFC), a cortical counterpart of the anterior putamen, elicits impaired stopping performance. The aIFC-anterior putamen circuit in the indirect pathway serves as an essential route for stopping.



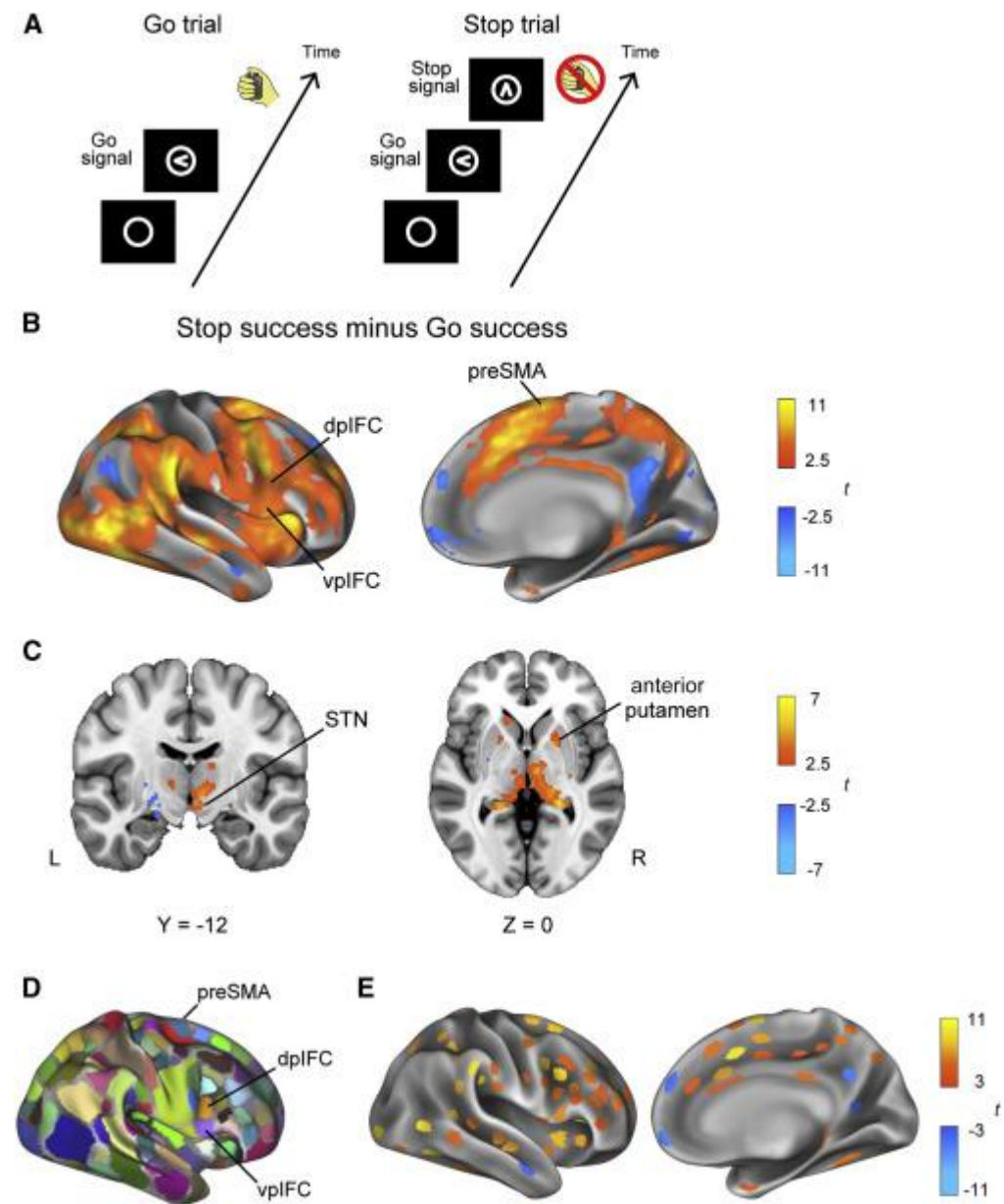
Towards offline neuromodulation

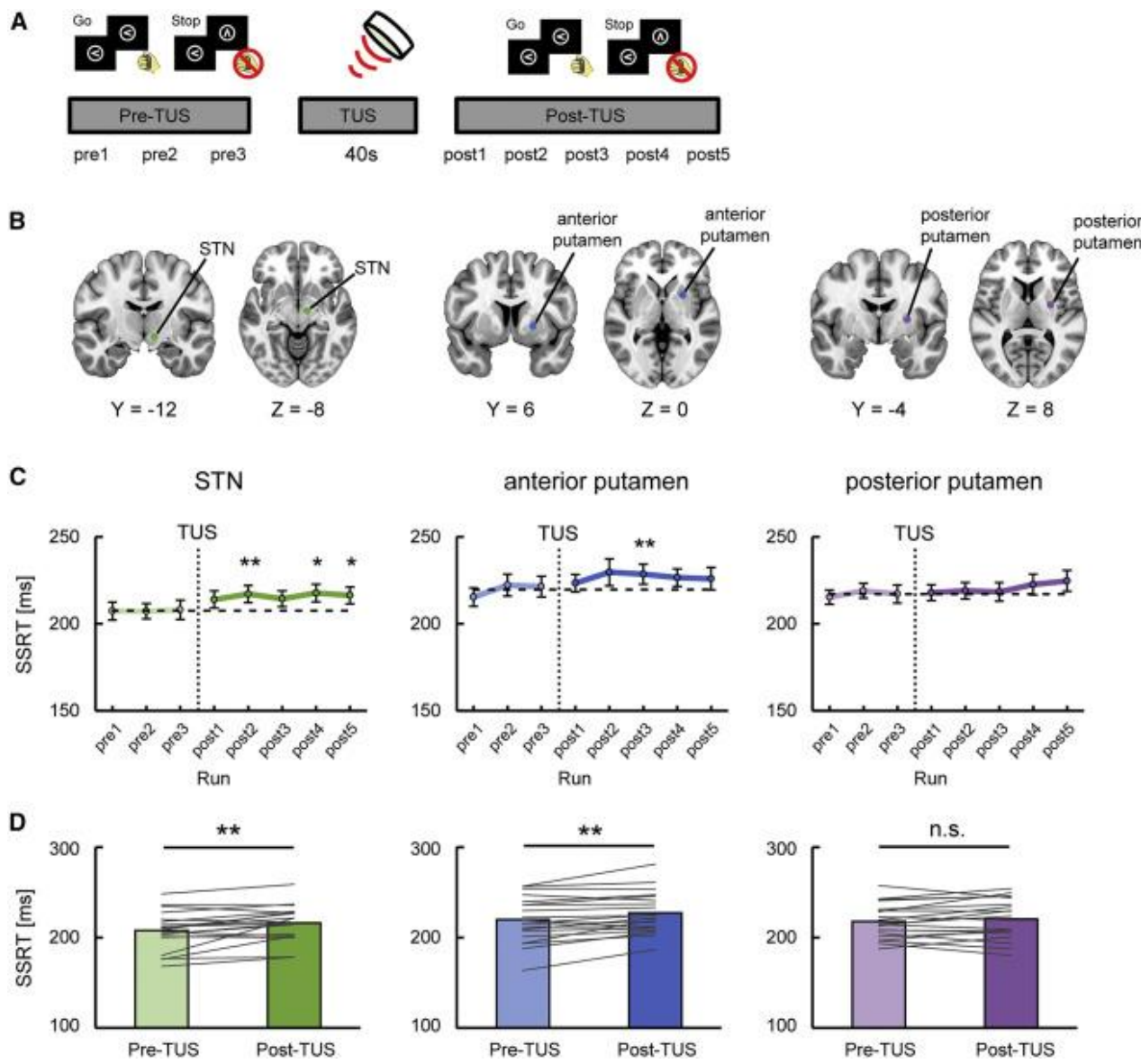
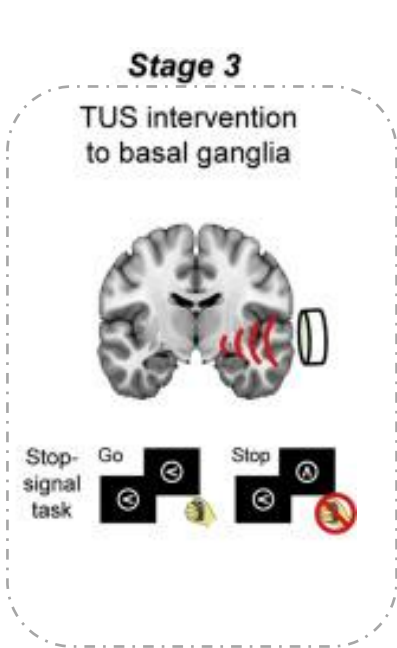
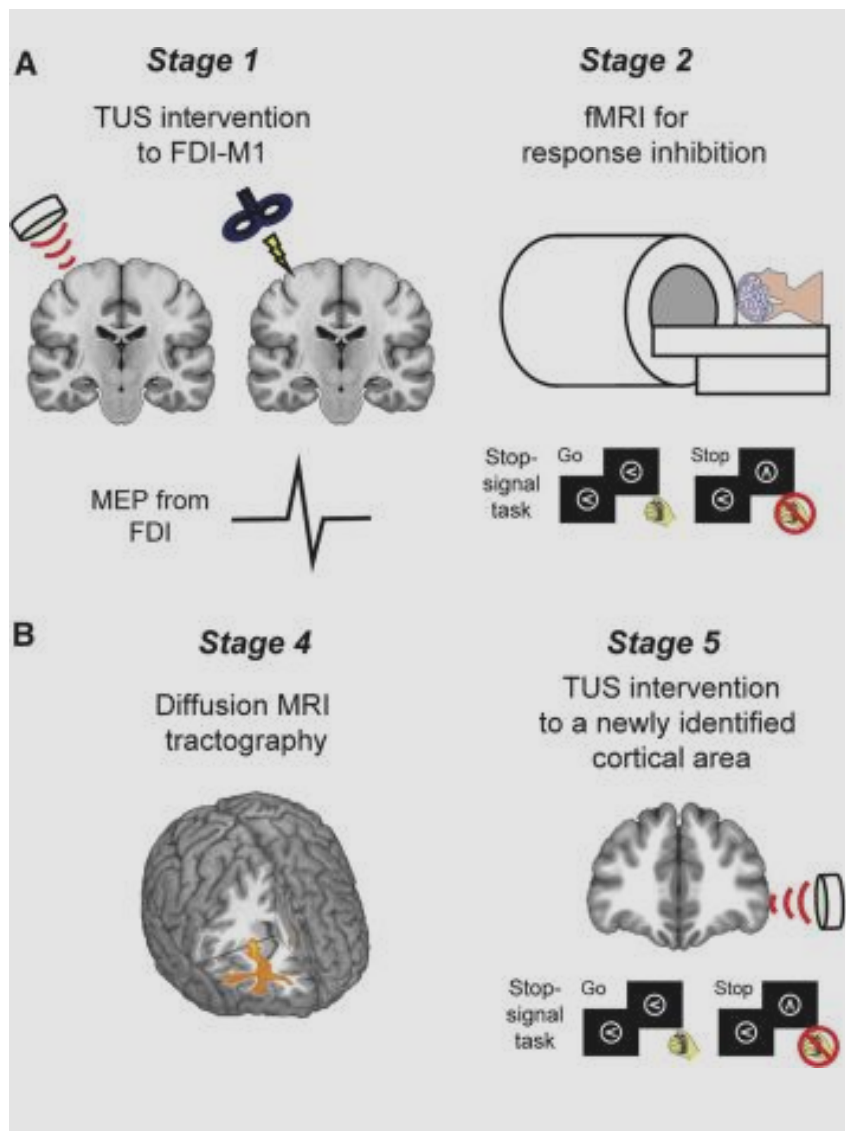


Towards offline neuromodulation

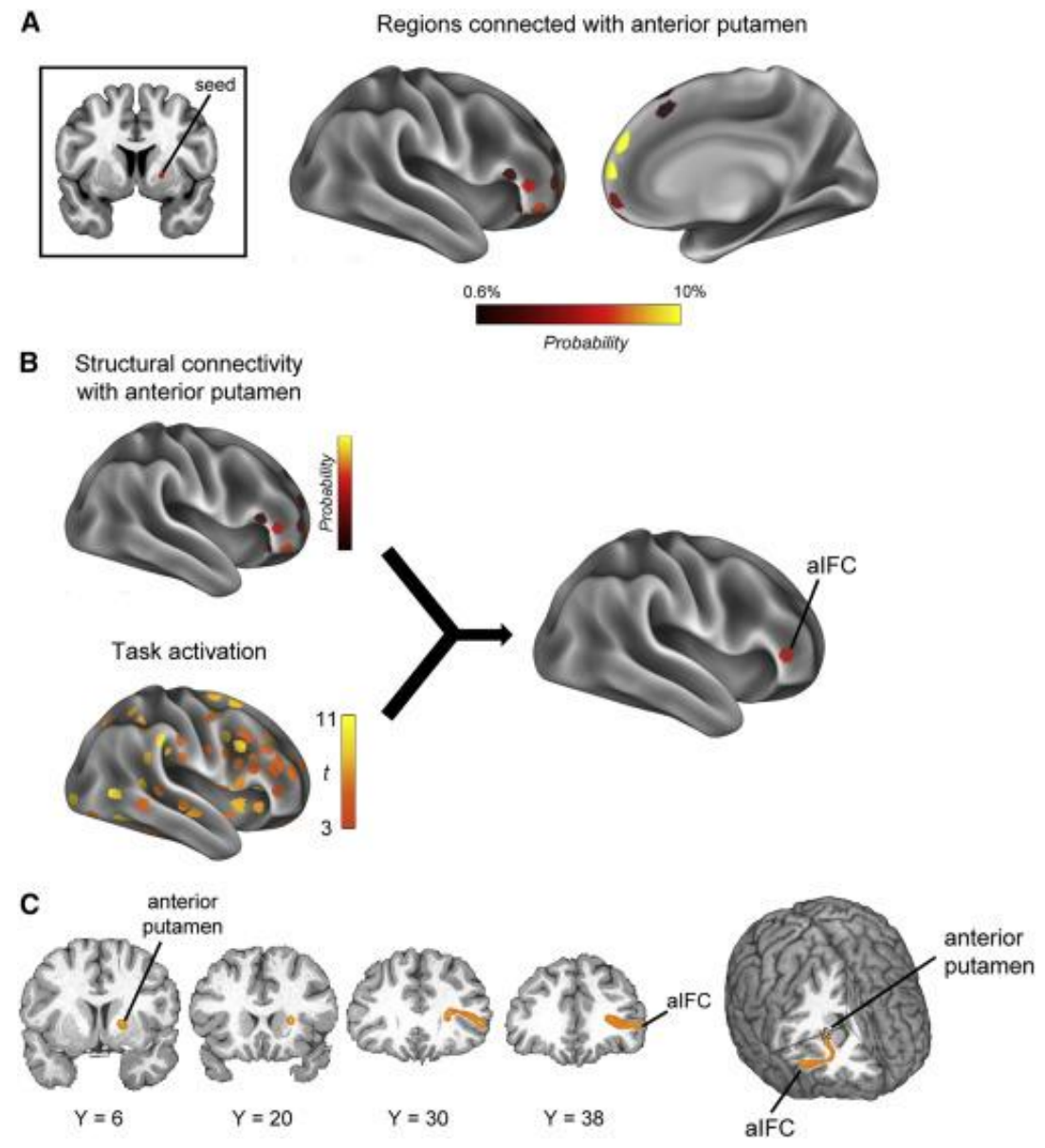
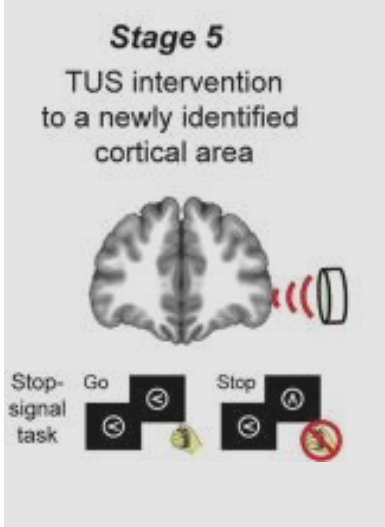
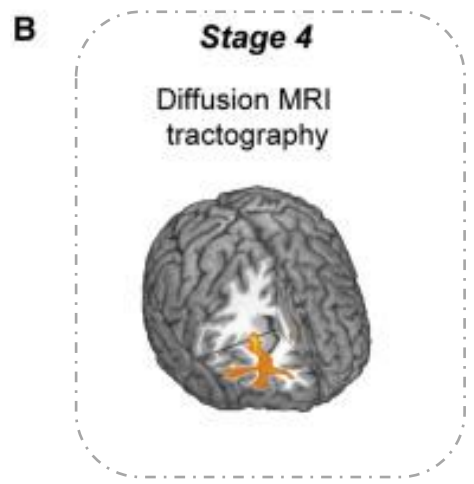
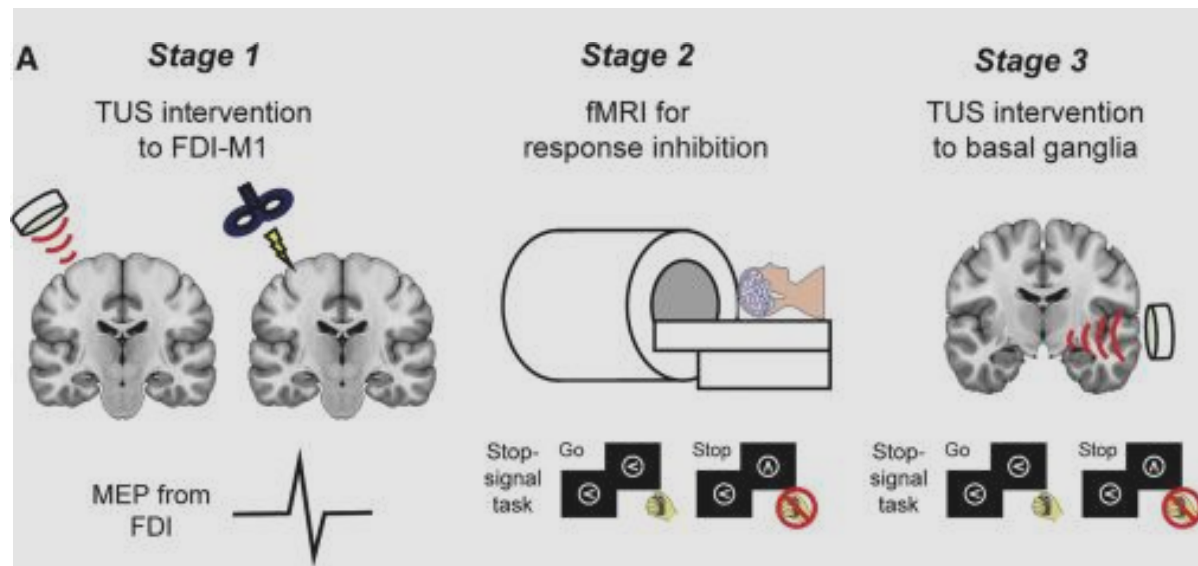


Nakajima et al.,
2022, Cell Reports

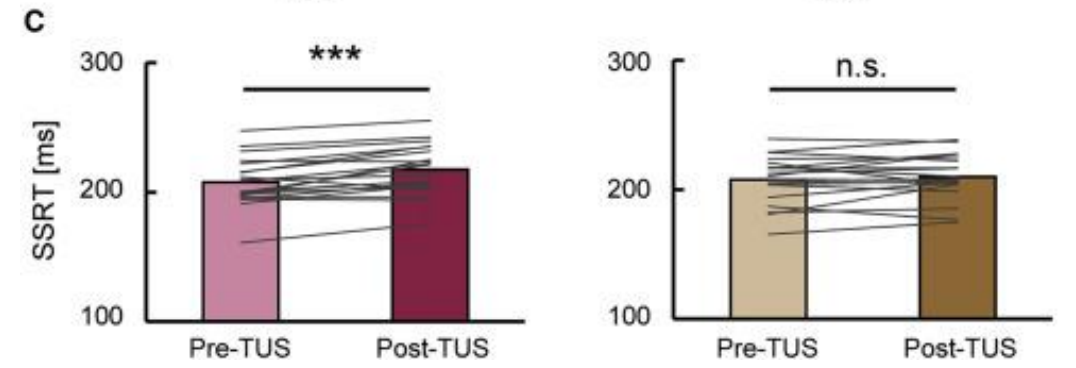
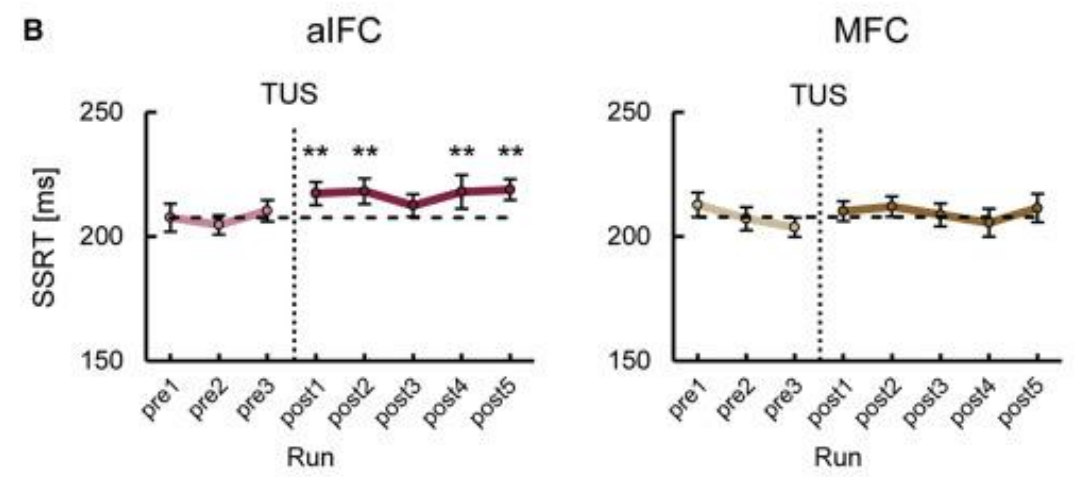
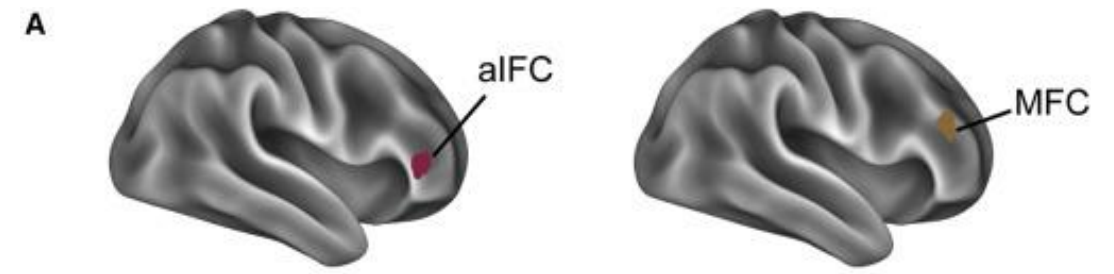
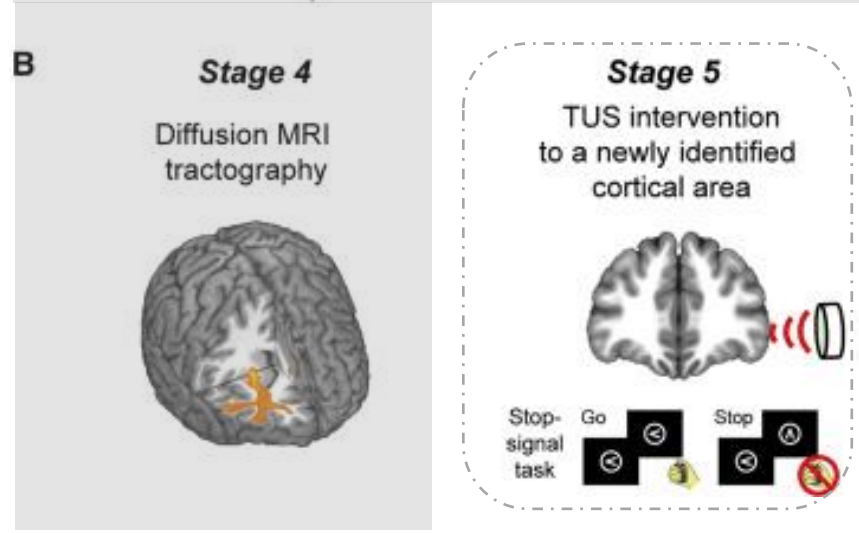
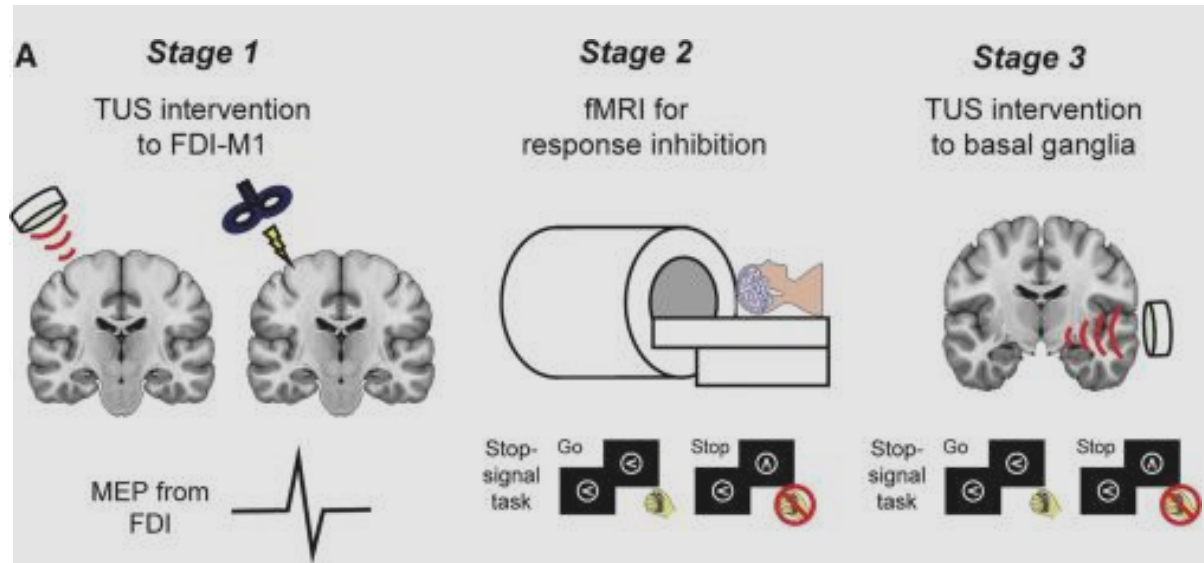




Nakajima et al., 2022, Cell Reports



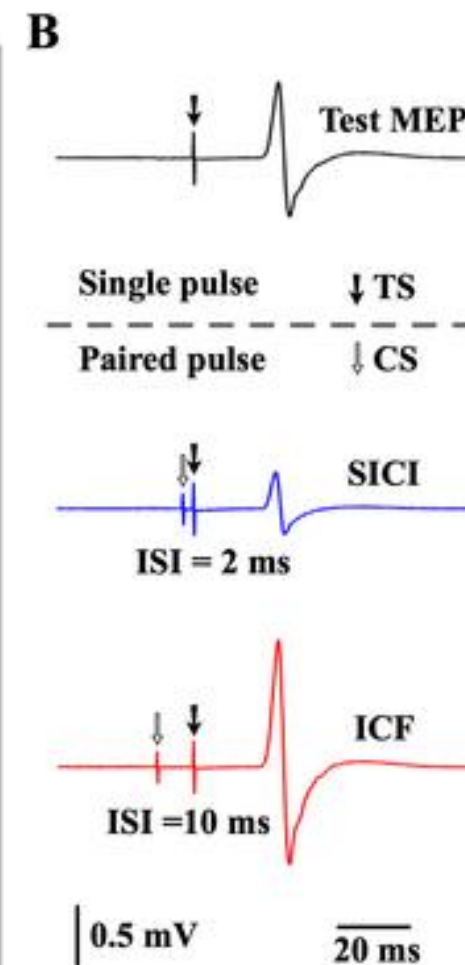
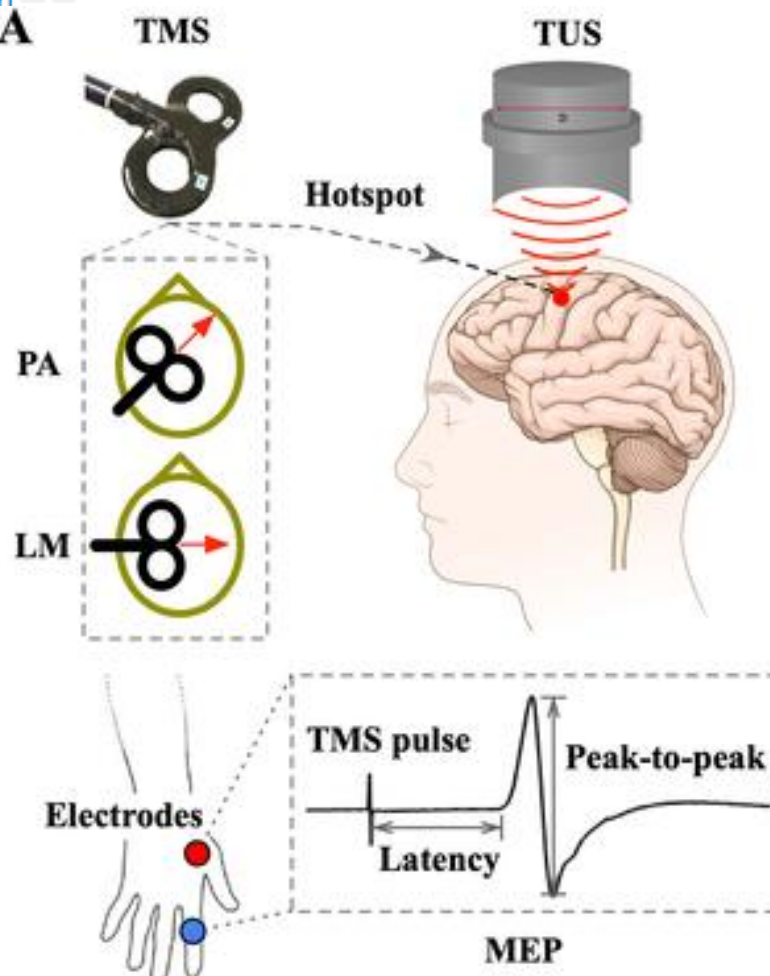
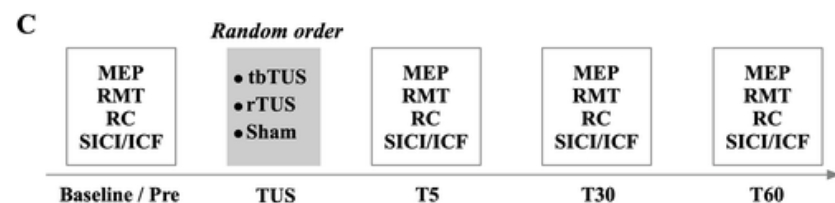
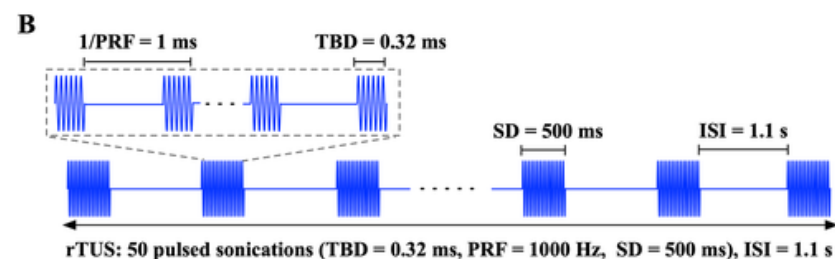
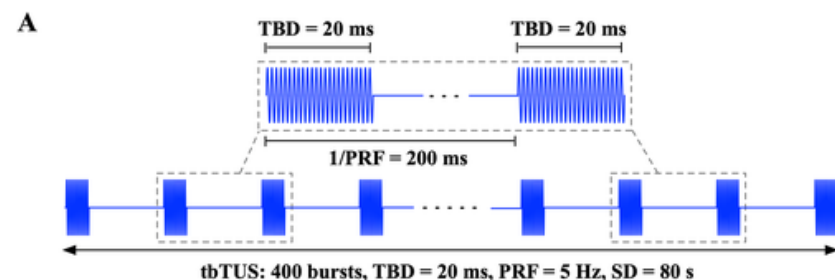
Towards offline neuromodulation



Nakajima et al.,
2022, Cell Reports

Induction of Human Motor Cortex Plasticity by Theta Burst Transcranial Ultrasound Stimulation

Ke Zeng¹, Ghazaleh Darmani¹, Anton Fomenko¹, Xue Xia^{1 2}, Stephanie Tran^{1 3}, Jean-François Nankoo¹, Yazan Shamli Oghli^{1 3}, Yanqiu Wang^{1 2}, Andres M Robert Chen^{1 5}

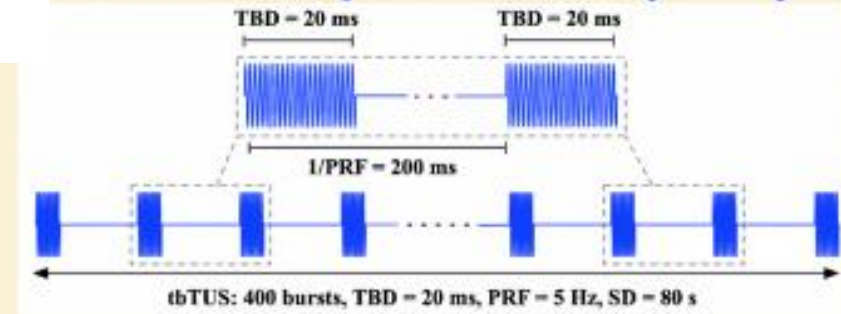


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Repetitive TUS protocols

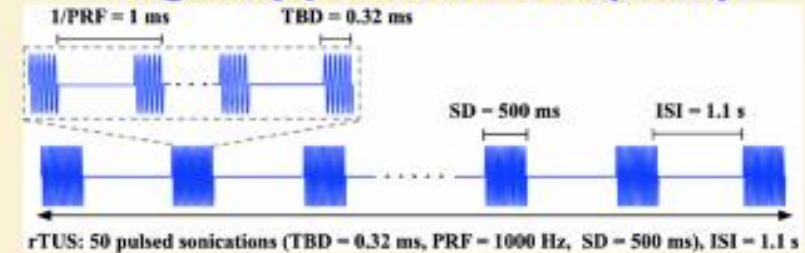
Theta burst patterned TUS (tbTUS)



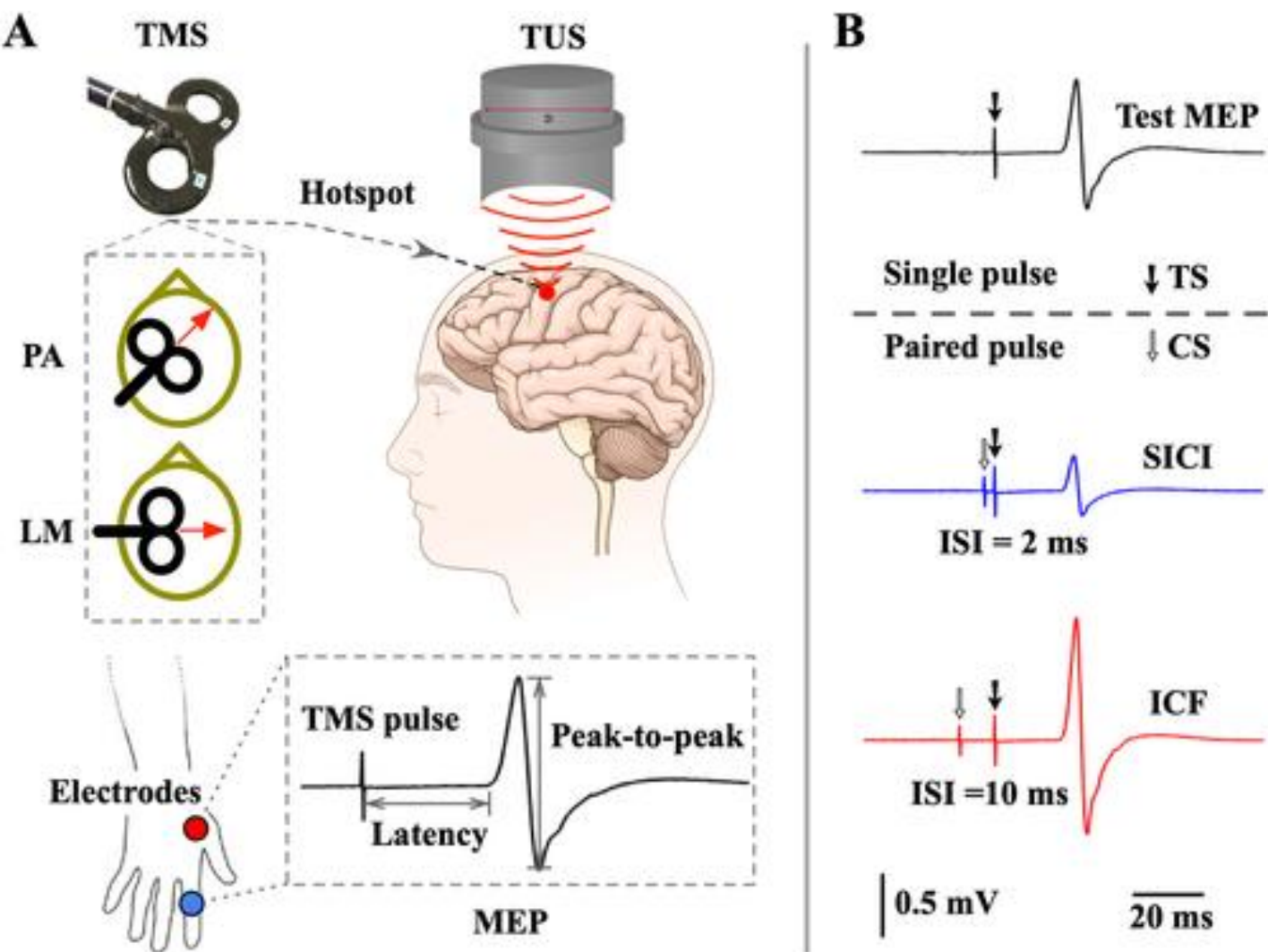
TBD: tone-burst duration
SD: sonication duration

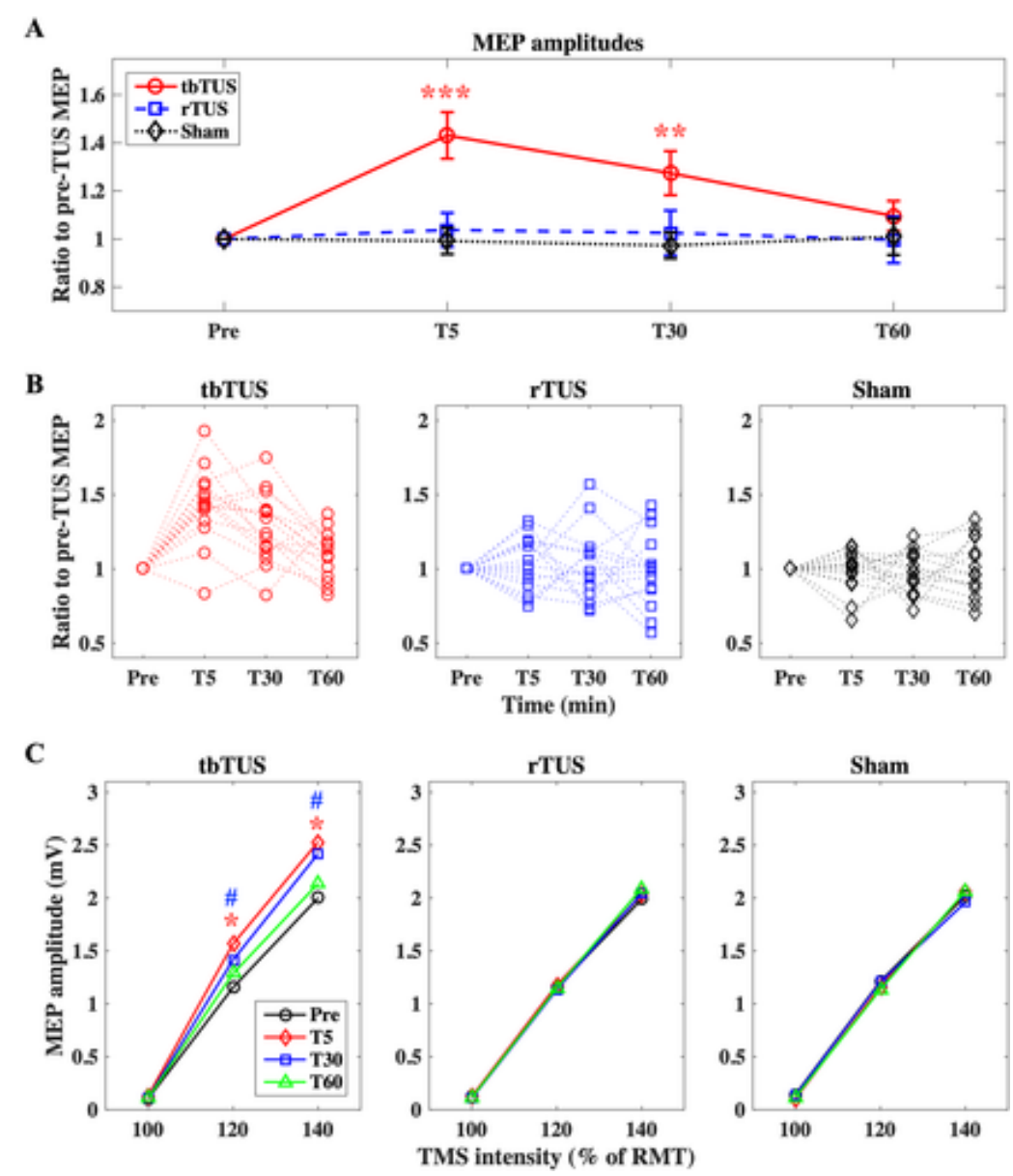
PRF: pulse repetition frequency
ISI: interstimulus interval

Regularly patterned TUS (rTUS)

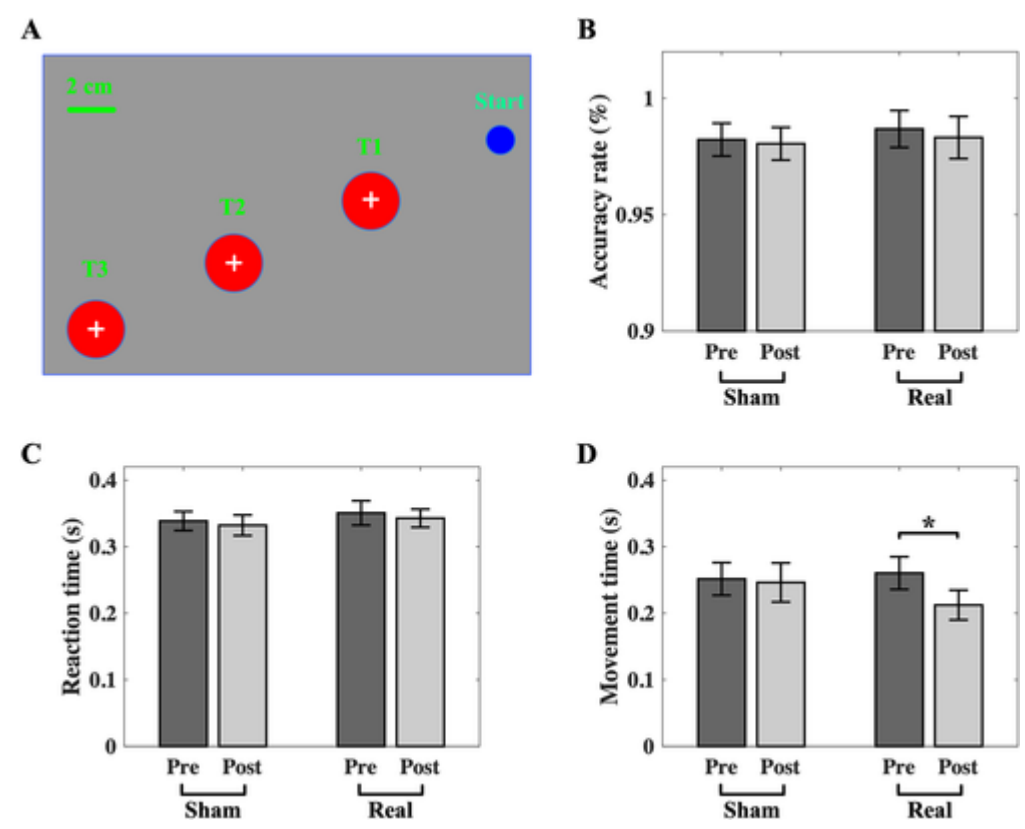
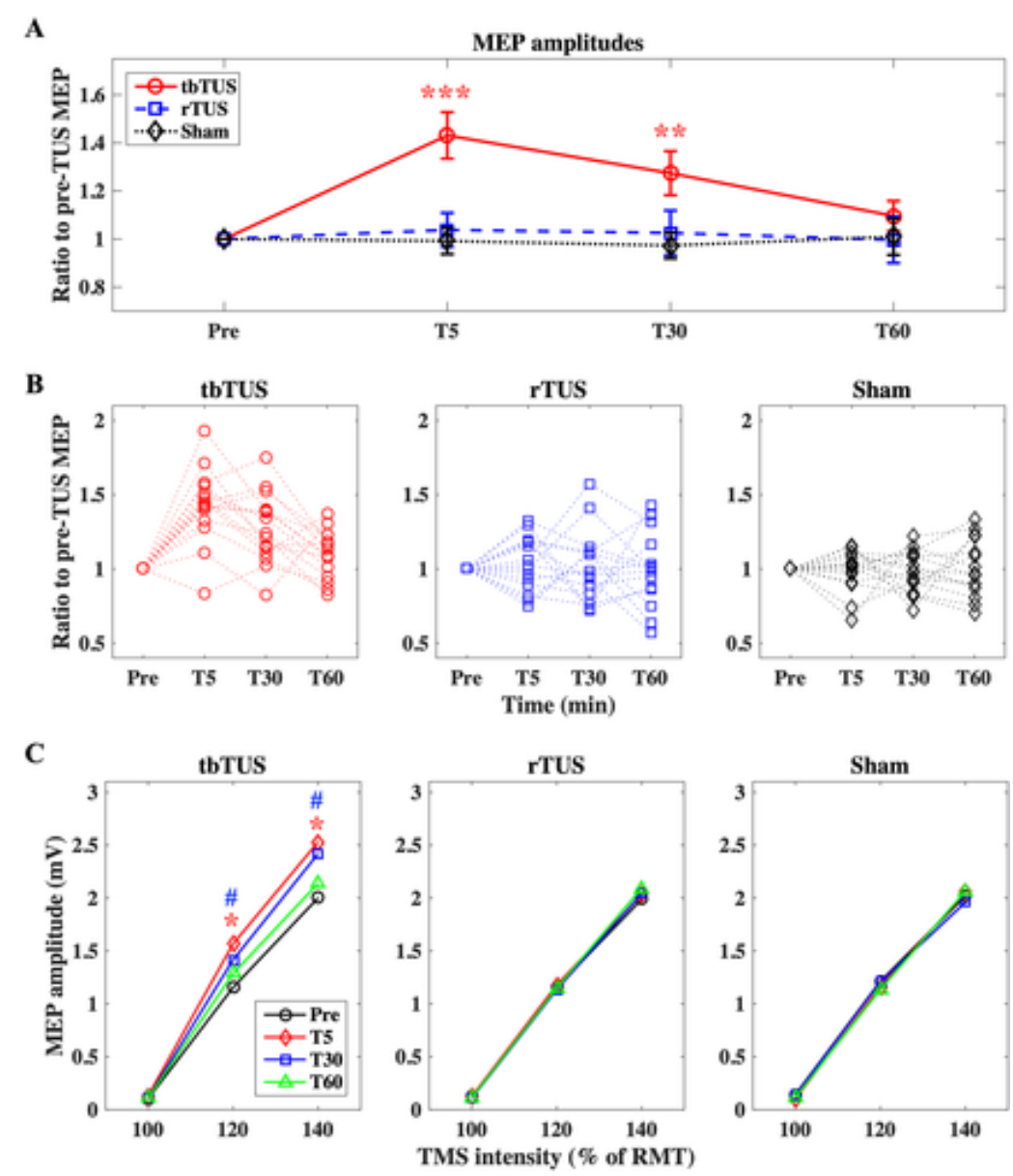


The rTUS consisted of much shorter burst (0.32 ms) and higher repetition frequency (1000 Hz), and had the same total sonication duration (8 s) and protocol time (80 s) as tbTUS.



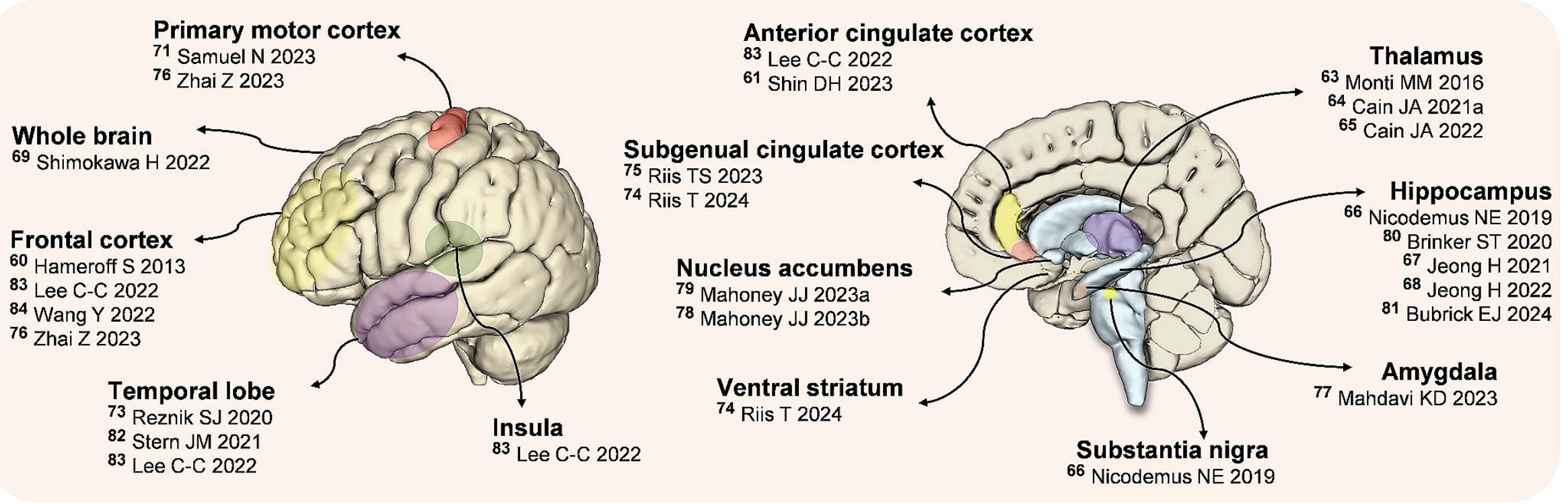


Towards offline neuromodulation

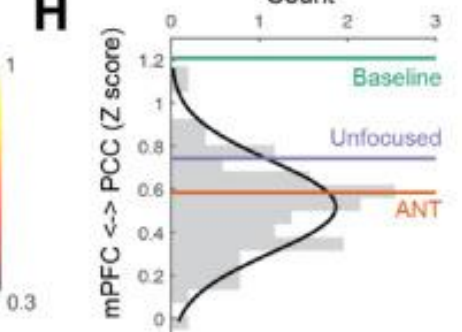
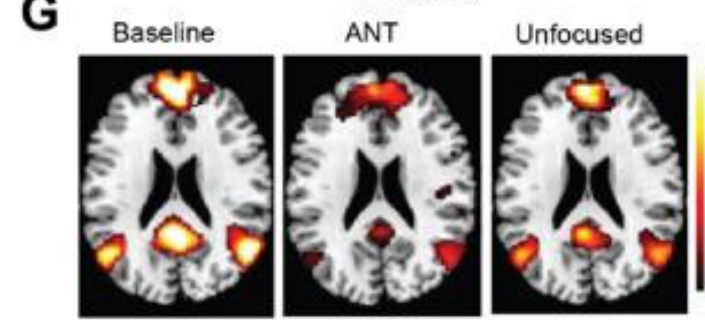
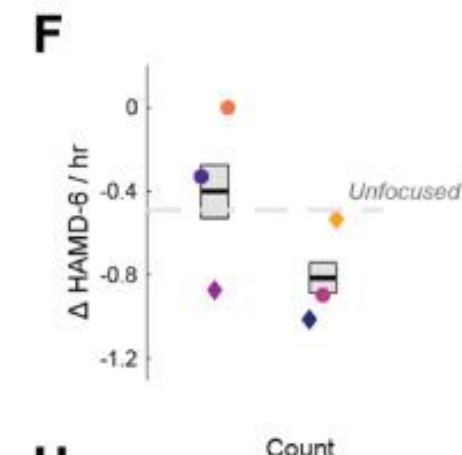
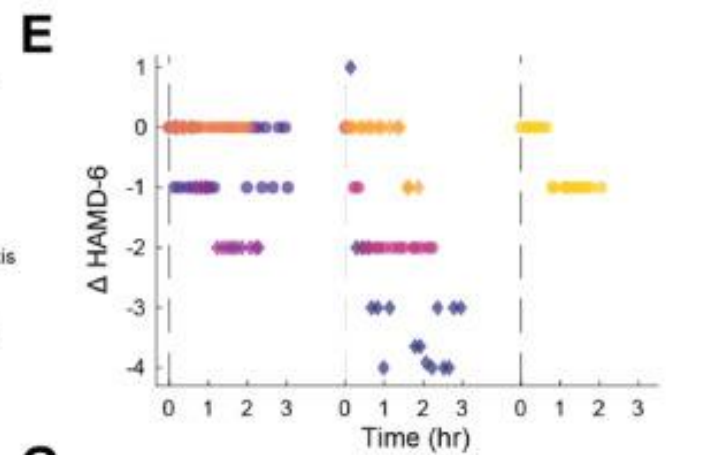
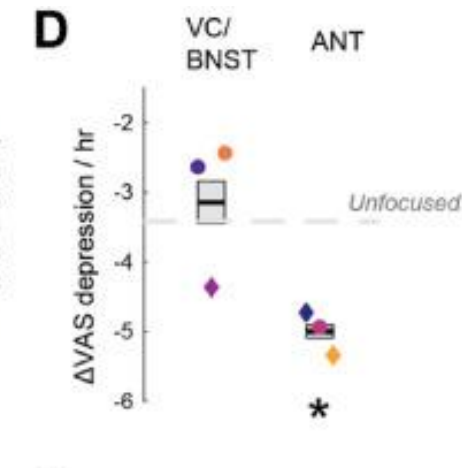
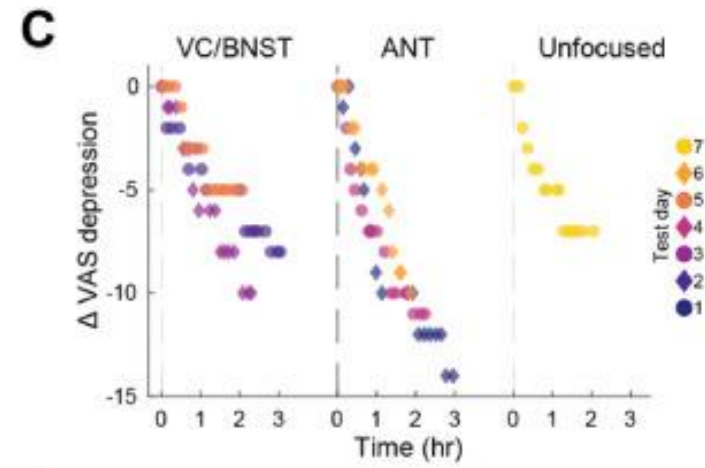
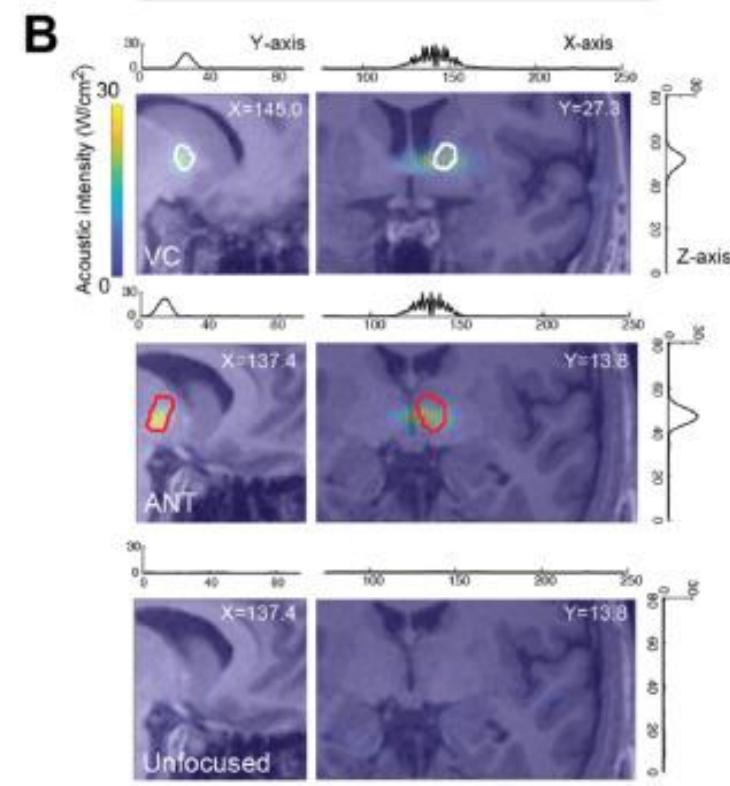
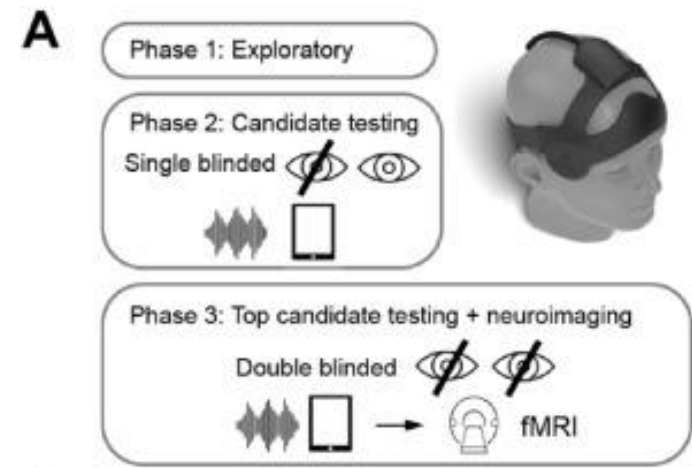


Clinical applications

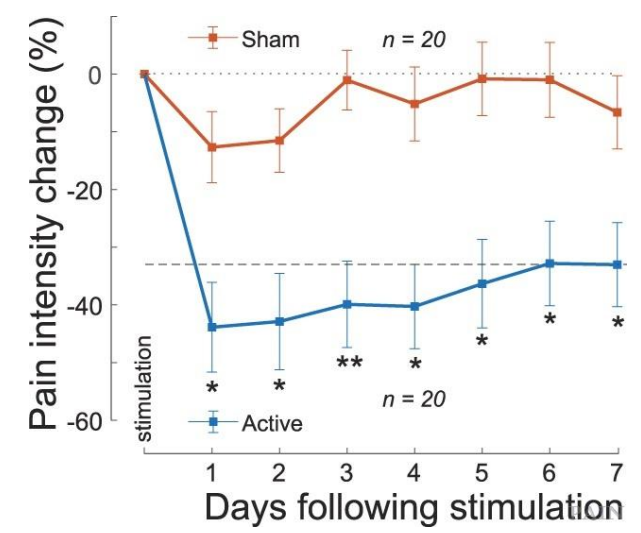
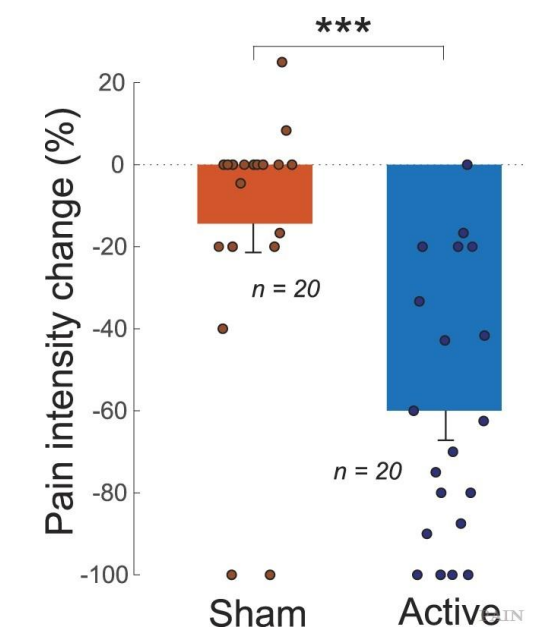
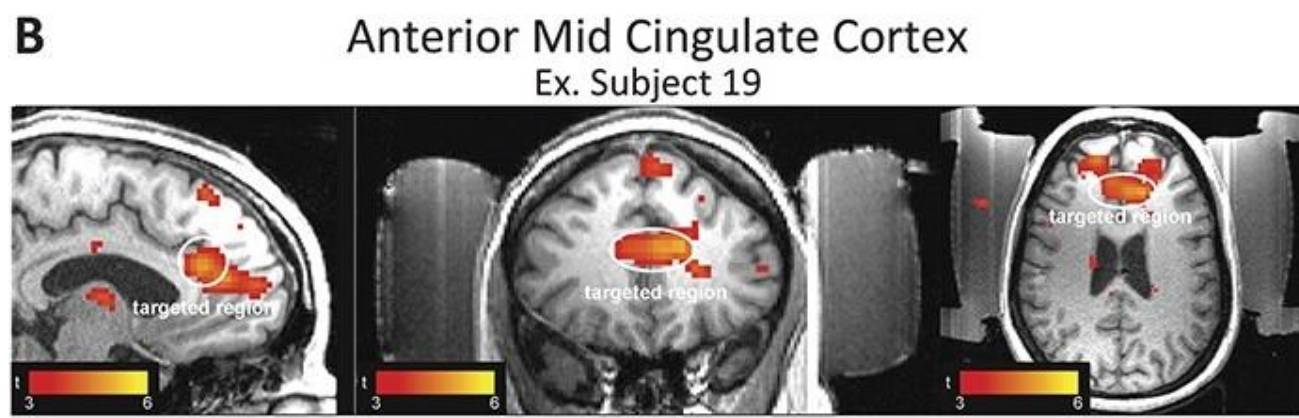
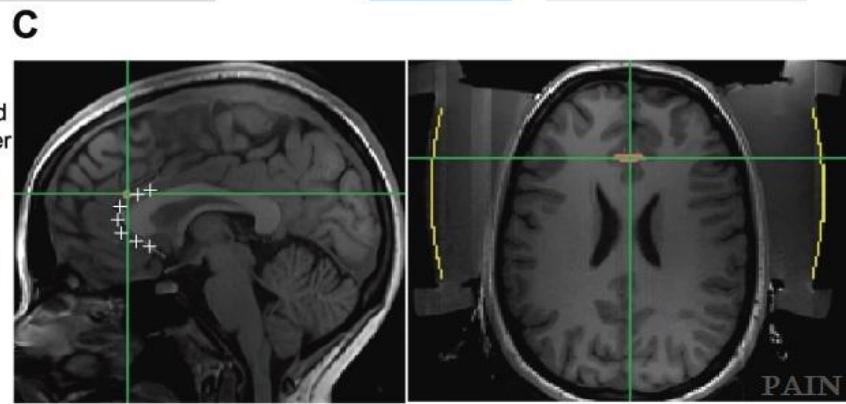
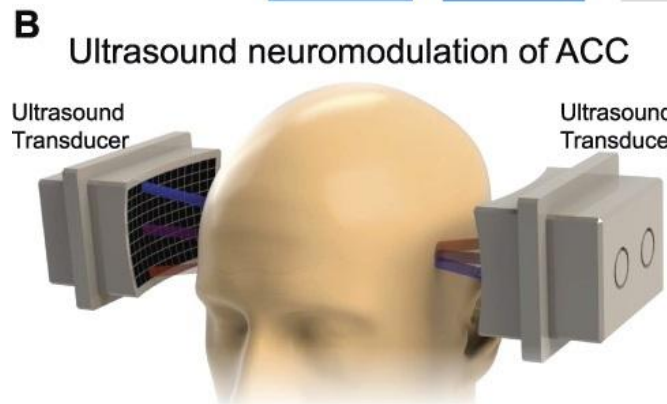
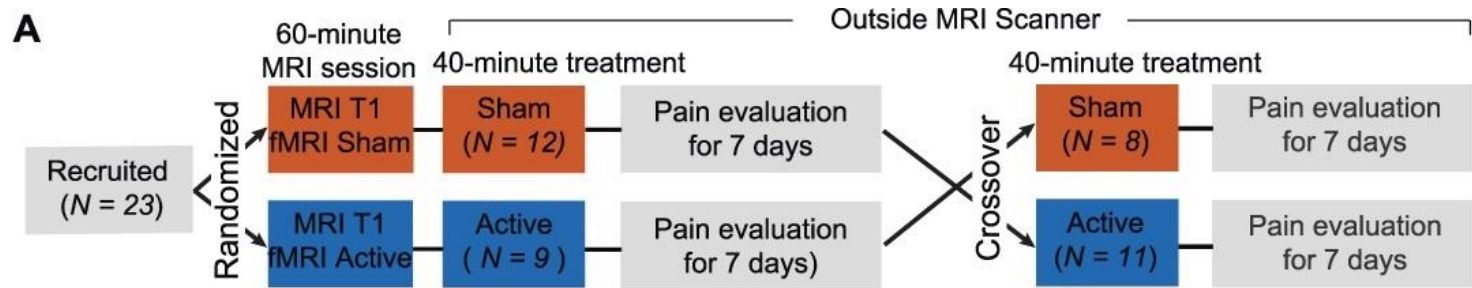
Clinical studies



TUS for depression



TUS for chronic pain

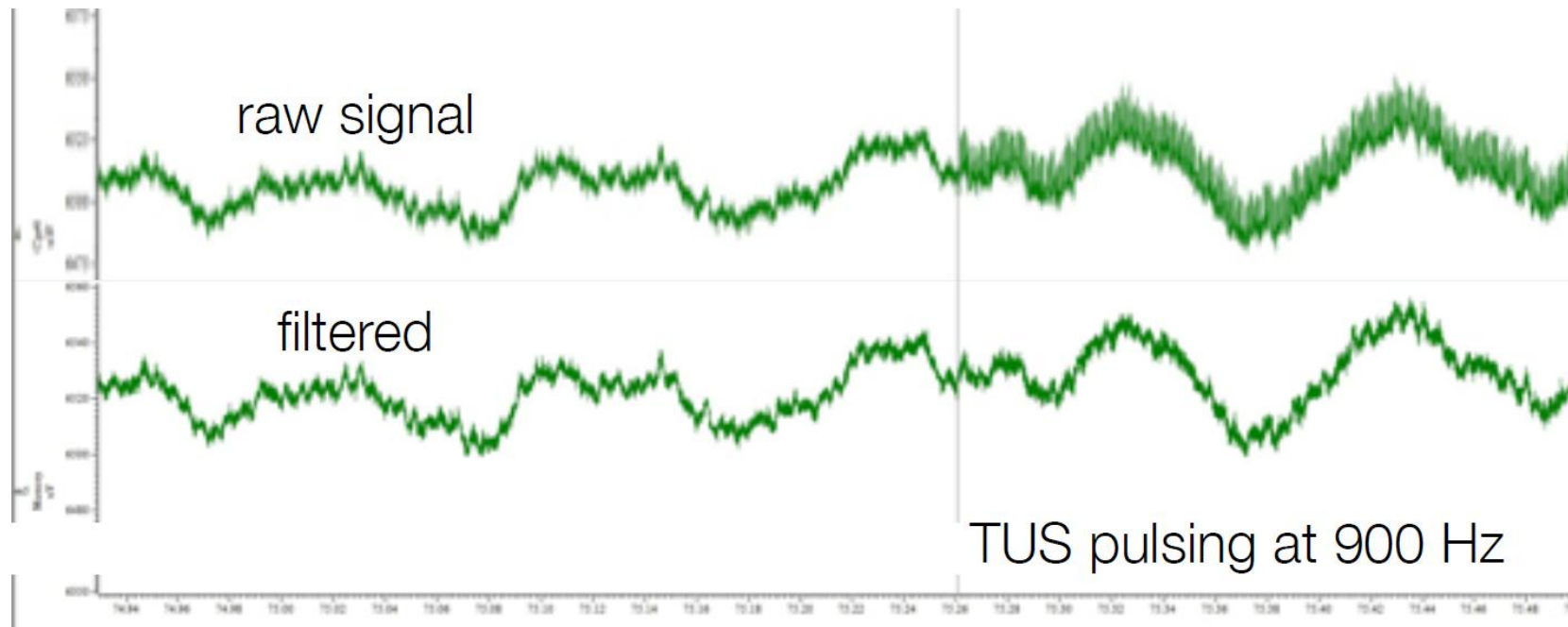


Multimodal experiments

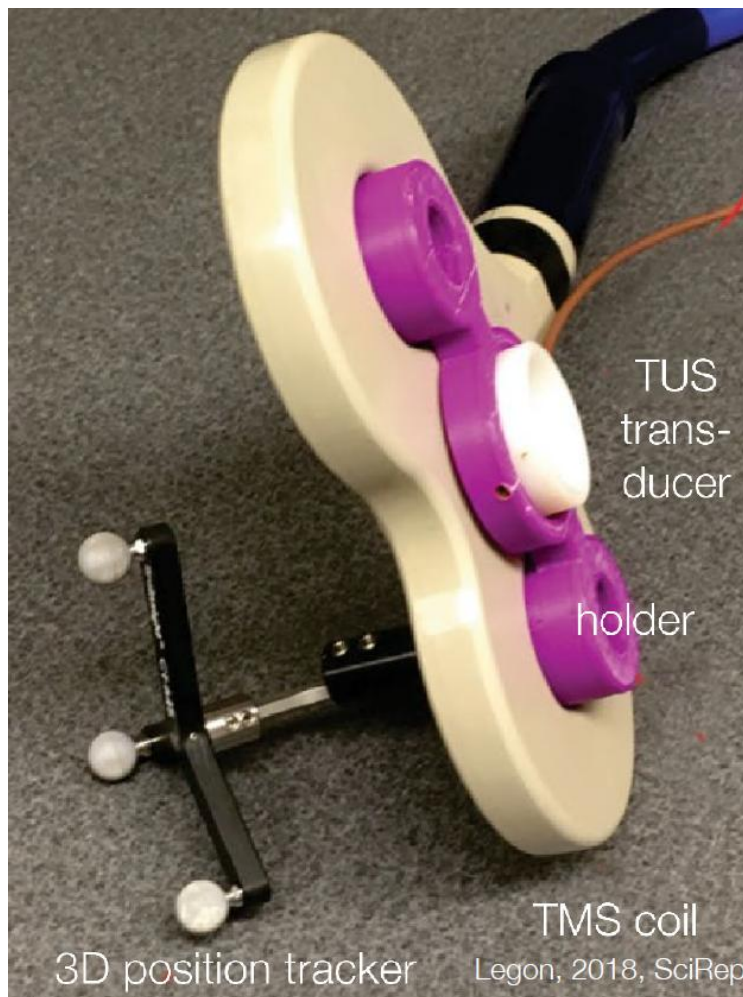
Combining TUS with EEG



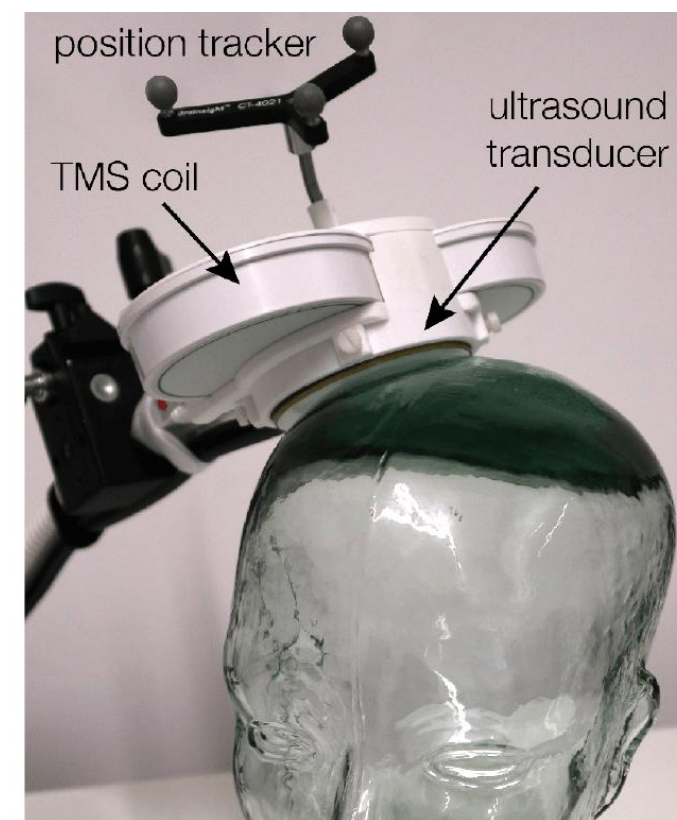
TUS pulsing artefact on EEG

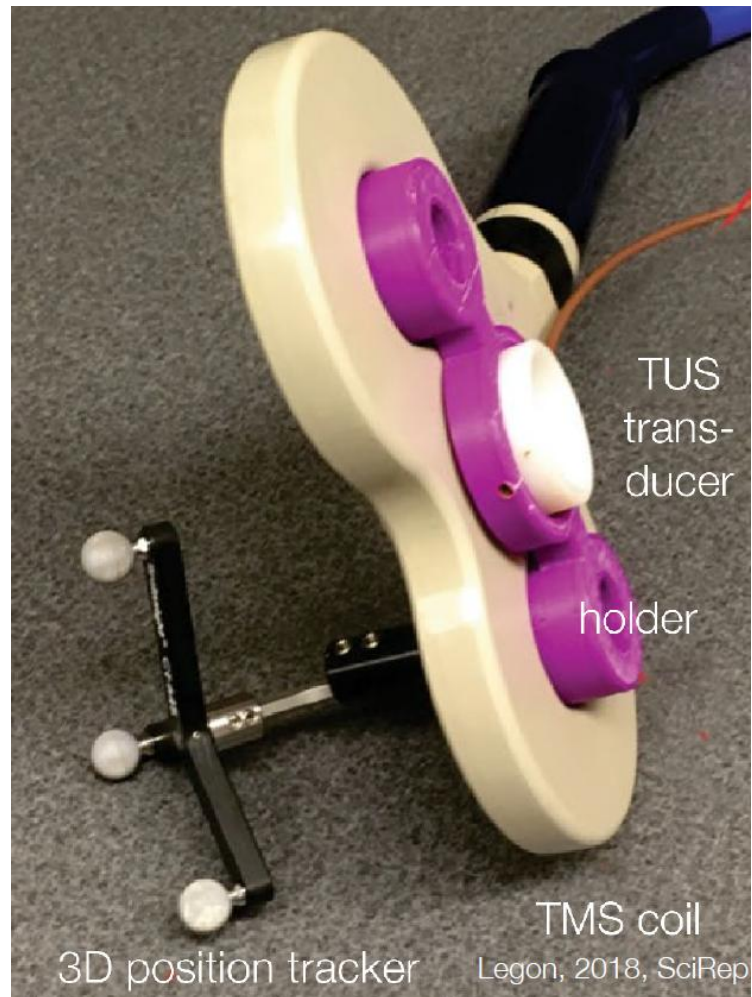


Combining TUS with TMS

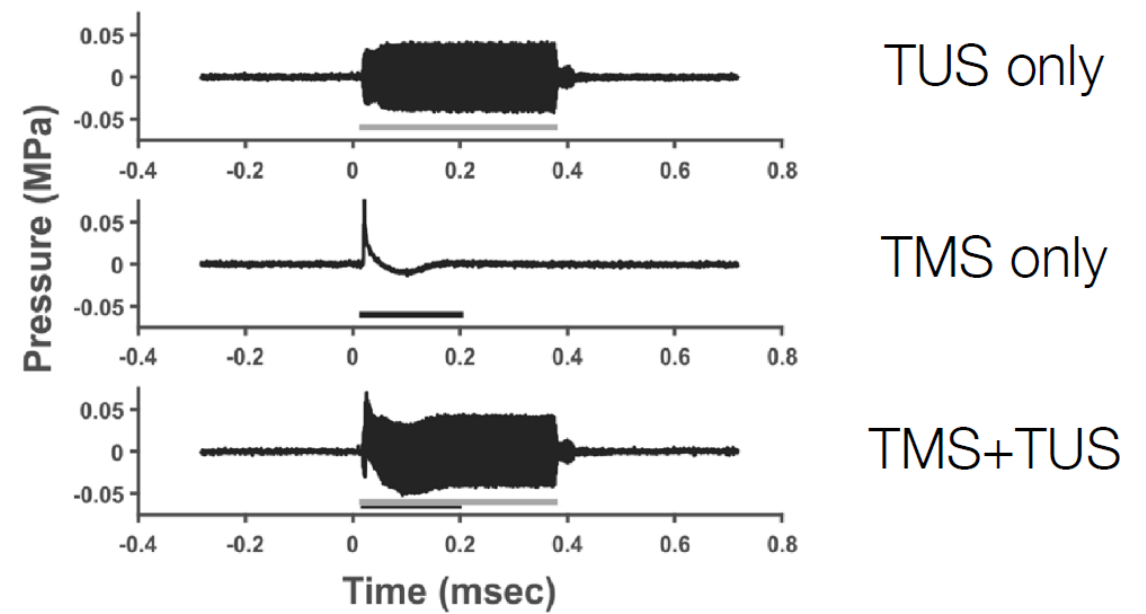


NeuroFUS + TMS Brainbox system





TMS artefact on TUS pressure measurement



Designing experiments

- Safety
- The coupling method
- The auditory confound
- The parameters' space
- Delivering the proposer dose
- Targeting
- Simulations
- Reporting
- The control condition
- Etc...

Safety

Risk of cavitation

- I_{sppa} (spatial peak pulse average intensity) is the pulse average intensity, calculated at the position of the spatial maximum
- MI (mechanical index) gives an estimation of the likelihood of inertial cavitation

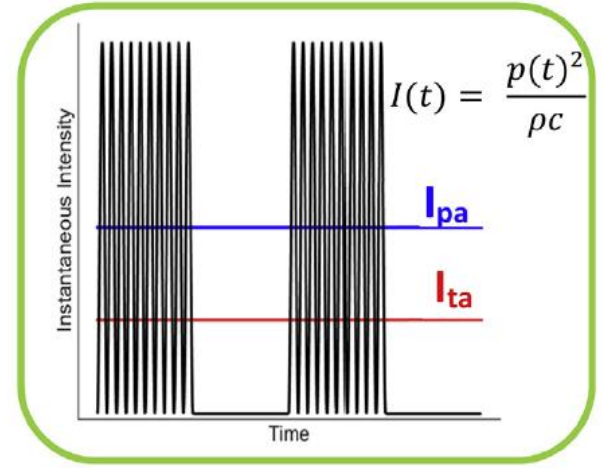
Risk of thermal bio-effects

- I_{spta} (spatial peak temporal average intensity) is the temporal average intensity, calculated at the position of the spatial maximum
- TI (thermal index) is the steady-state temperature increase in soft tissue during ultrasound sonication
- TIC (thermal index for cranial bone) is a modification of TI, when the skull is close to the transducer face

Table 1
Allowed limits for MI, TI, I_{spta} and I_{sppa} according to the FDA guidelines for diagnostic ultrasound. The limit for TI also applies to TIC when bone is close by.

I_{spta} (mW/cm ²)	I_{sppa} (W/cm ²)	MI	TI
720	190	1.9	6

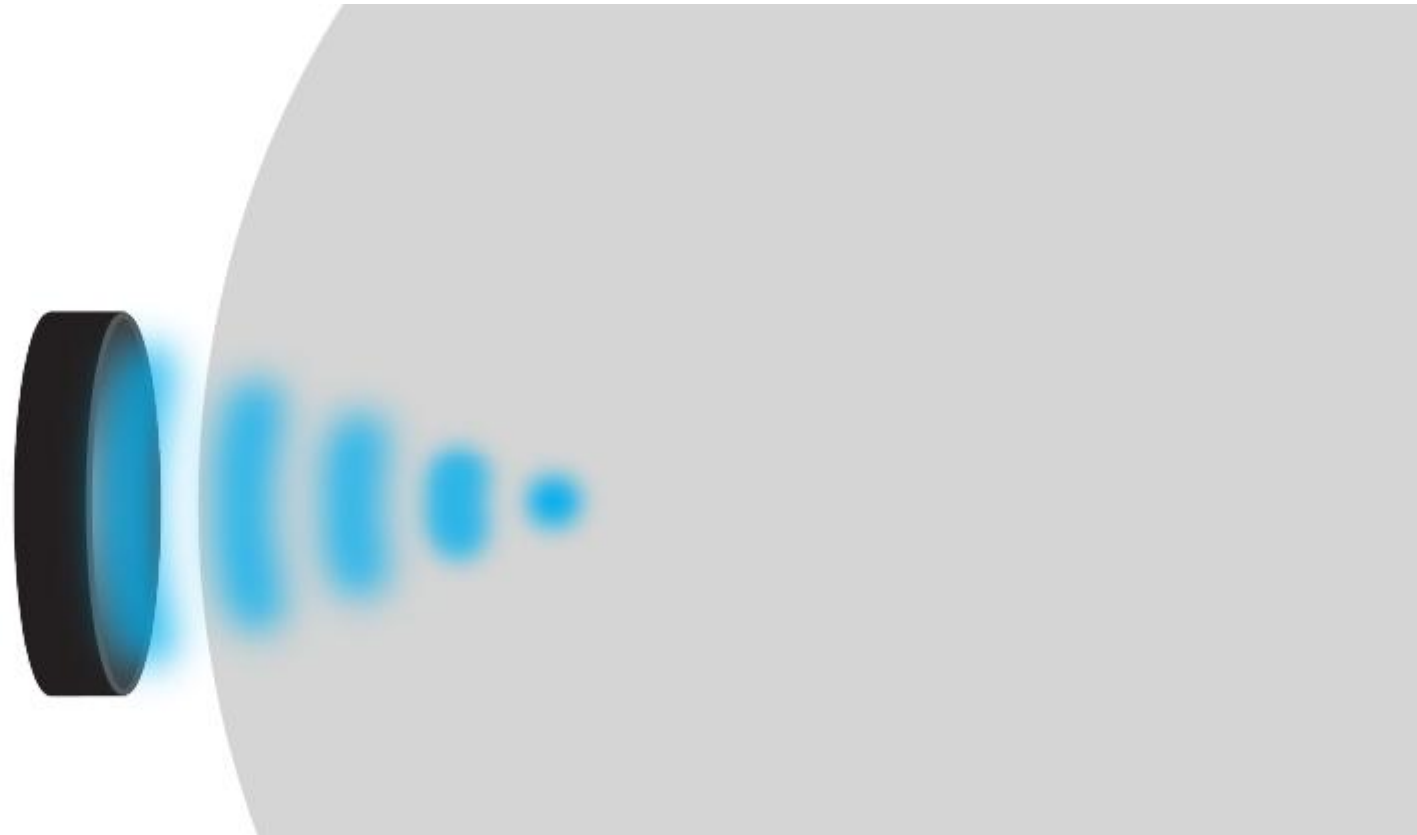
($I_{spta} < 3W/cm^2$ from IEC standard 60601-2-5 for physiotherapy US equipment)



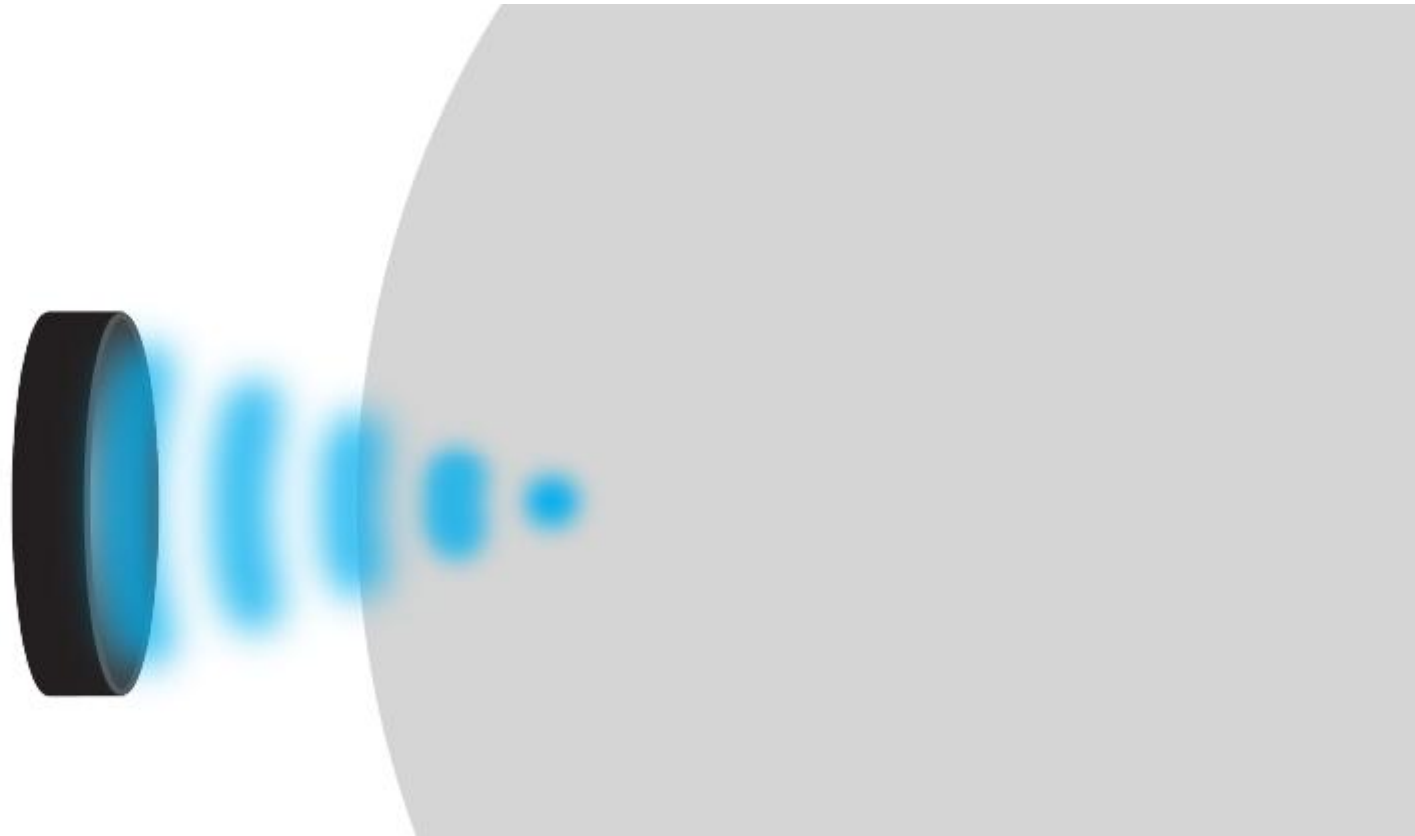
Bioeffects	ITRUSST parameters and levels
Mechanical	MI or $MI_{tc} \leq 1.9$ in the brain and in the skin
Thermal	Any of: Maximum exposure time depending on the level of TIC*: 80 min 1.5 < TIC ≤ 2.0 40 min 2.0 < TIC ≤ 2.5 10 min 2.5 < TIC ≤ 3.0 160 sec 3.0 < TIC ≤ 4.0 40 sec 4.0 < TIC ≤ 5.0 10 sec 5.0 < TIC ≤ 6.0 Temperature rise due to ultrasound ≤ 2° Celsius at any time in soft tissue Thermal dose ≤ 0.25 CEM43 in soft tissue

Table 1: Summary of the parameters and levels considered by iTRUSST to be safe. * It is the responsibility of the operator/manufacturer to determine which thermal index corresponds best to the configuration: TIS, TIB, TIC (see section 2.2.A.).

The coupling method



The coupling method



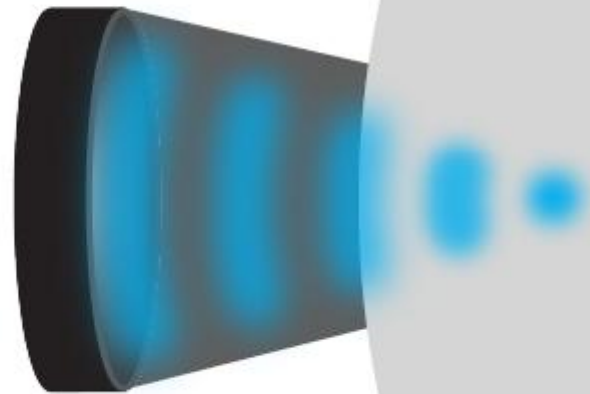
The coupling method

acoustic impedance: air interface reflects
nearly 100% of ultrasonic waves

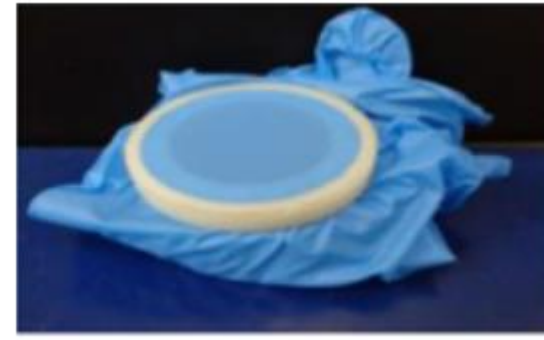


The coupling method

eliminate interface
ensure coupling
maintain acoustic properties



The coupling method



Lime et al, 2017, ResBiomedEng

Ultrasound stimulation

A single element ultrasound transducer (H115-MR, diameter 64 mm, Sonic Concept, Bothell, WA, USA) with 51.74 mm focal depth was used with a coupling cone filled with degassed water and sealed with a **latex membrane (Durex)**. The resonance frequency of the ultrasonic wave was set at 250 kHz with 30 ms bursts of ultrasound generated every 100 ms, controlled through a digital function generator (Handyscope HS5, TiePie engineering, Sneek, The Netherlands). The stimulation

The coupling method



The coupling method



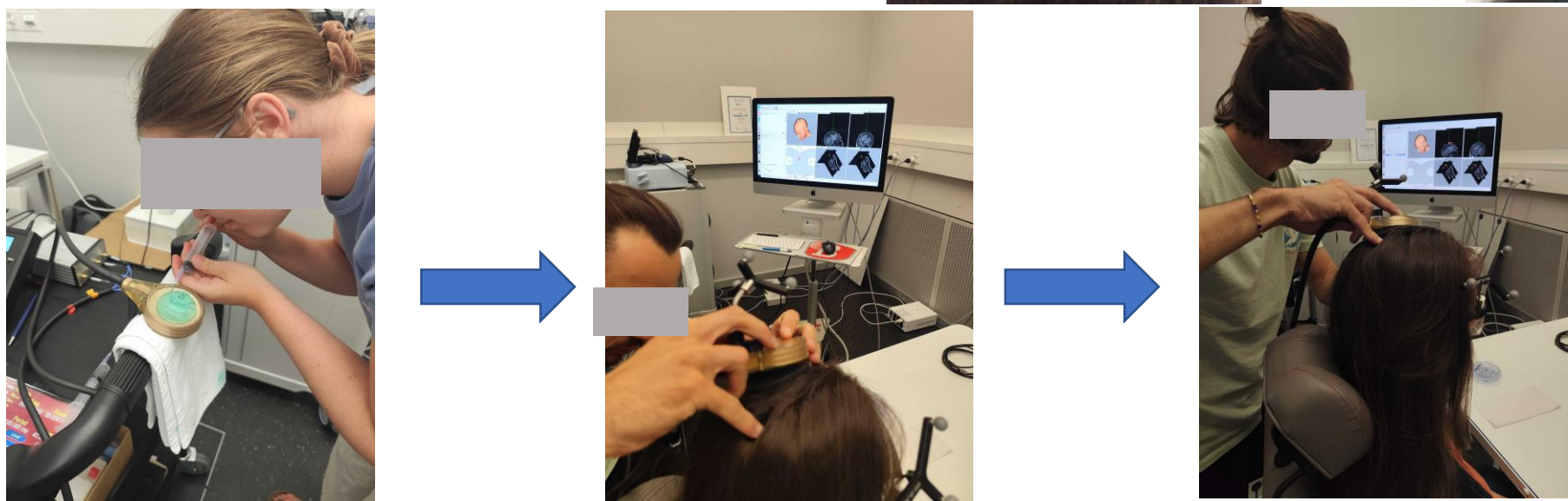
The coupling method

coupling media: safety + efficacy

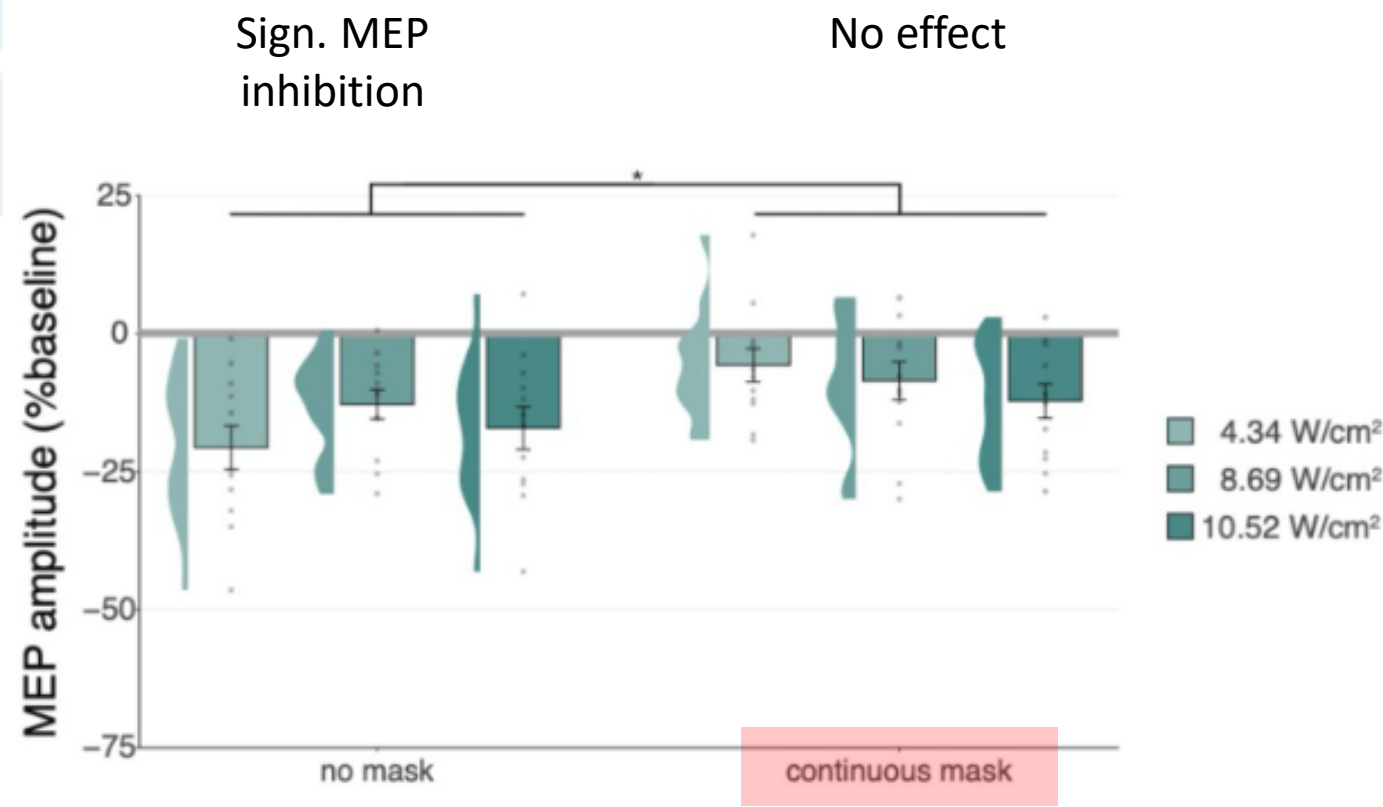
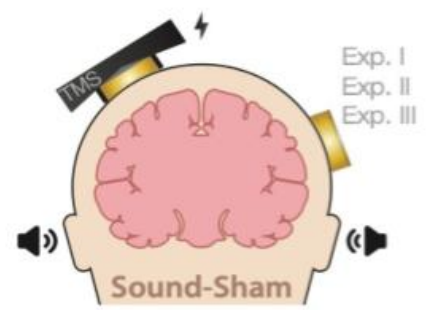
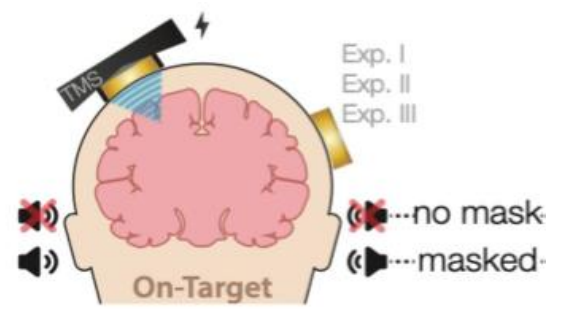
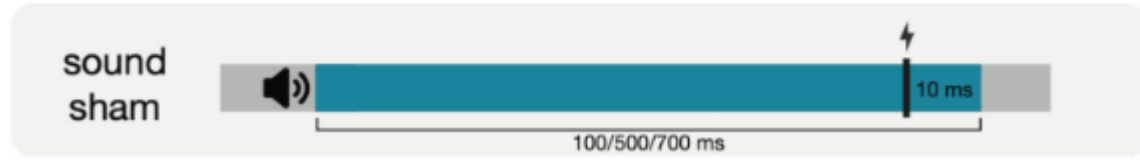
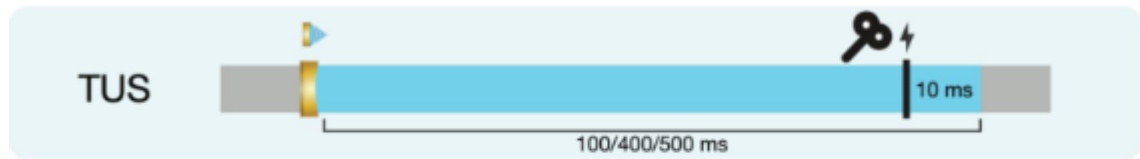
- ▶ low absorption
- ▶ acoustic impedance similar to, or higher than, that of treated tissue
- ▶ low cost (consumable)
- ▶ durable
- ▶ hypo-allergenic
- ▶ disinfectable
- ▶ heat conductive



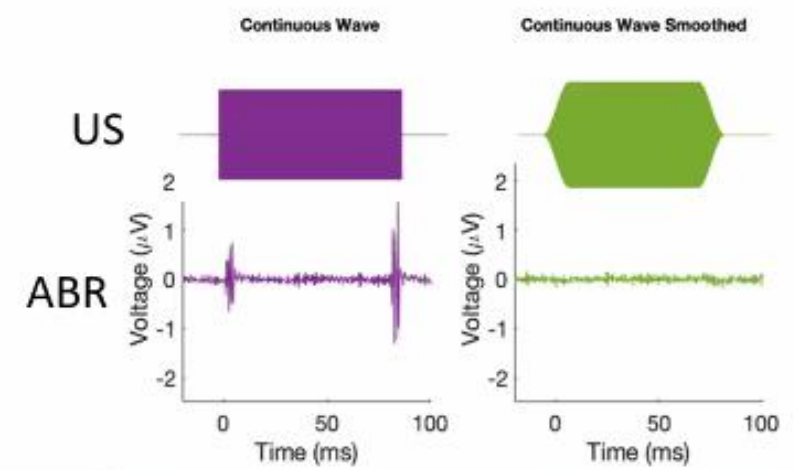
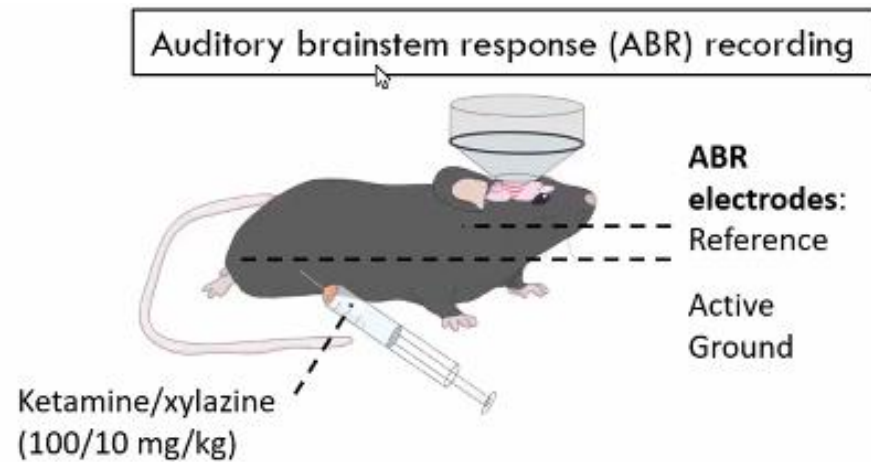
The coupling method



The auditory confound

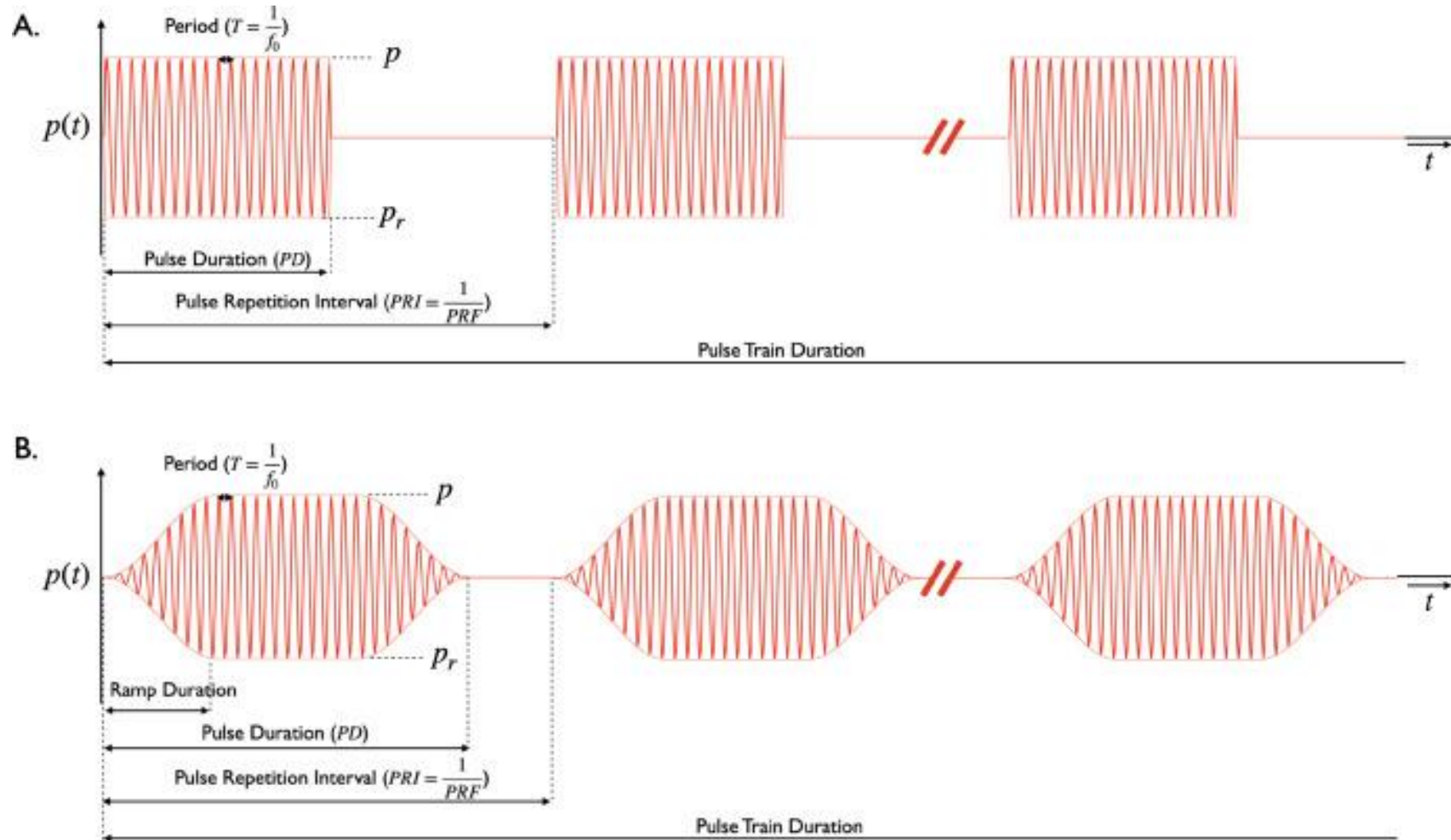


The auditory confound → can be eliminated with smoothed wave



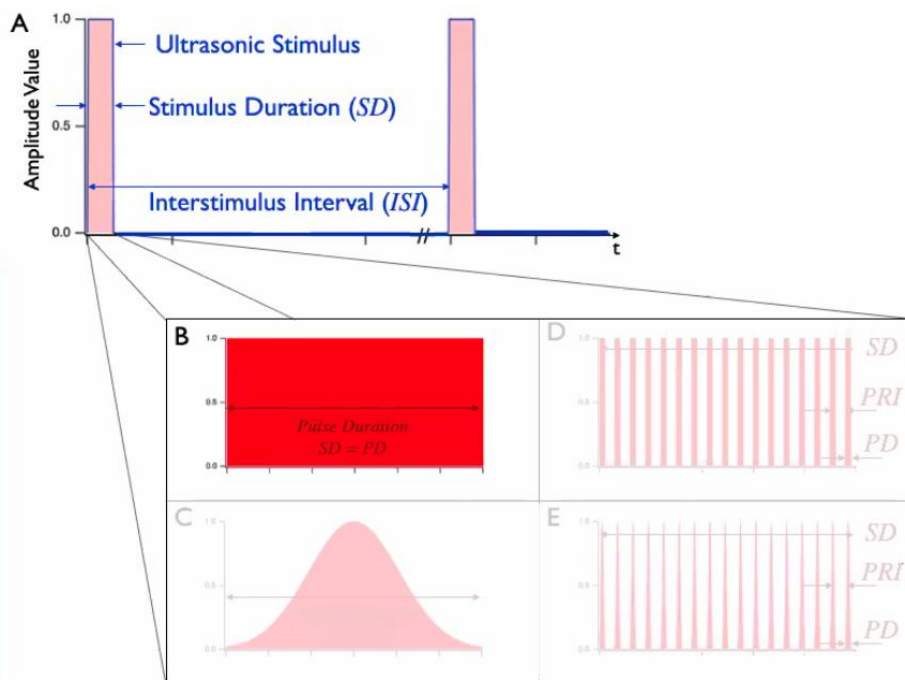
- Smoothed wave can eliminate the auditory effects

The auditory confound



The parameters' space

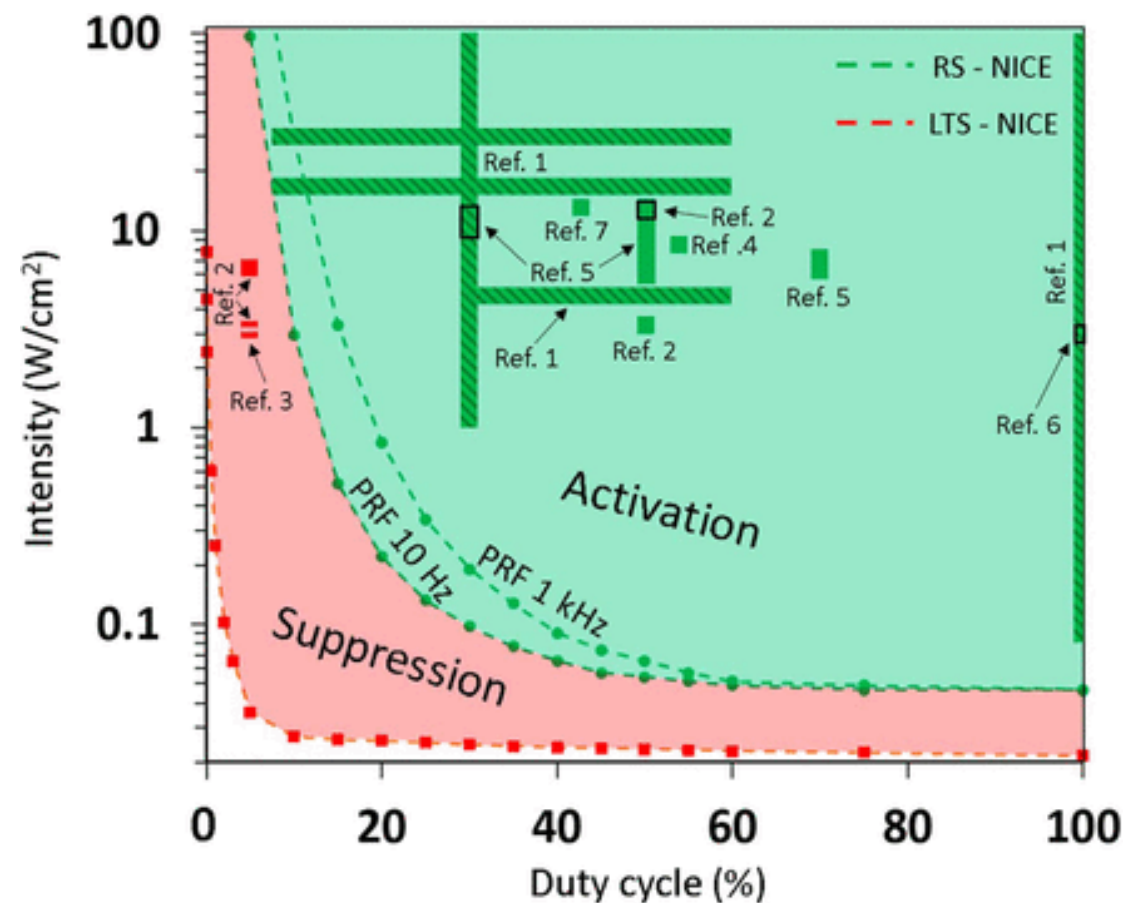
Temporal characteristics



Intensity characteristics

Table 1
Allowed limits for MI, TI, I_{spca} and I_{sppa} according to the FDA guidelines for diagnostic ultrasound. The limit for TI also applies to TIC when bone is close by.

I_{spca} (mW/cm ²)	I_{sppa} (W/cm ²)	MI	TI
720	190	1.9	6



Delivering the proper dose

Deliver deterministic intensity (through the skull)

Skull aberrations:

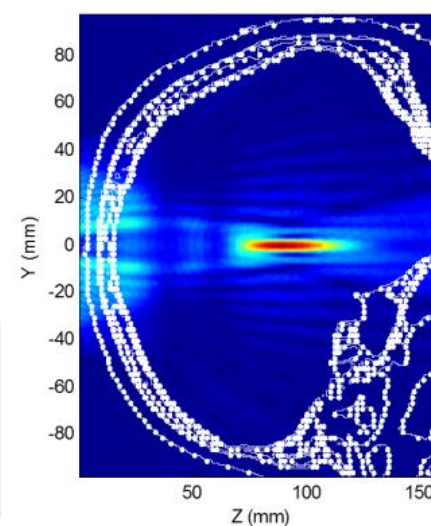
Dephasing

- compensation critical for sharp focus
- compensation possible if CT scans available

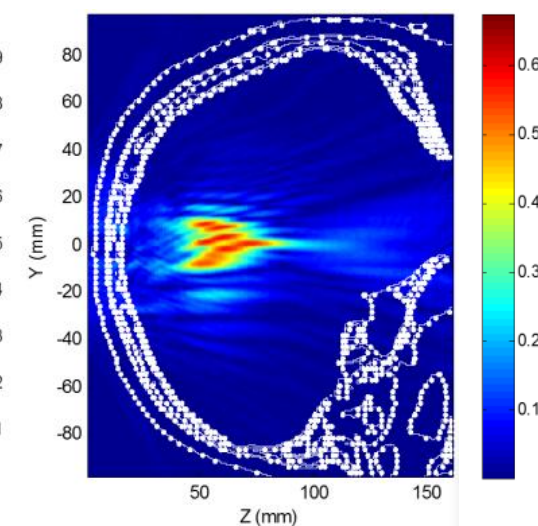
Attenuation

- compensation critical for deterministic intensity at target
- existing CT-based approaches incapable to address

Homogeneous beam

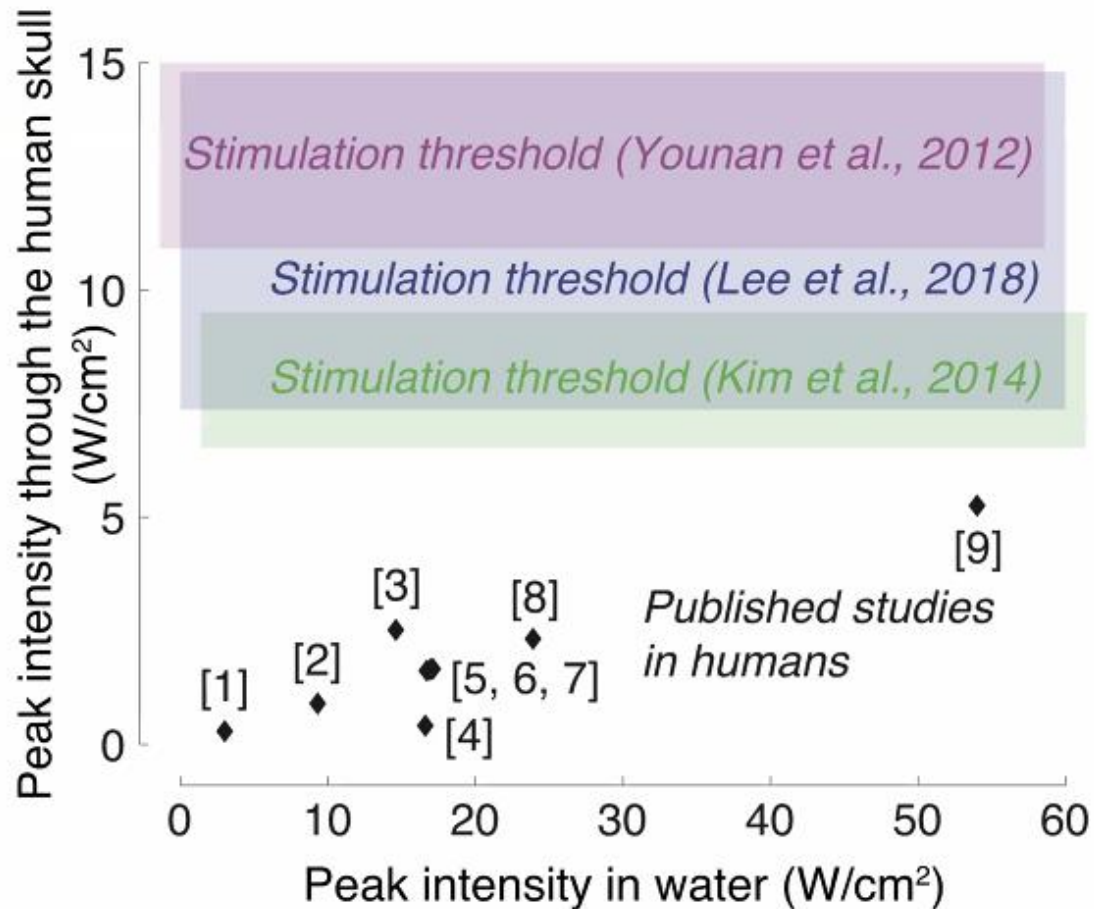


Skull aberrated beam



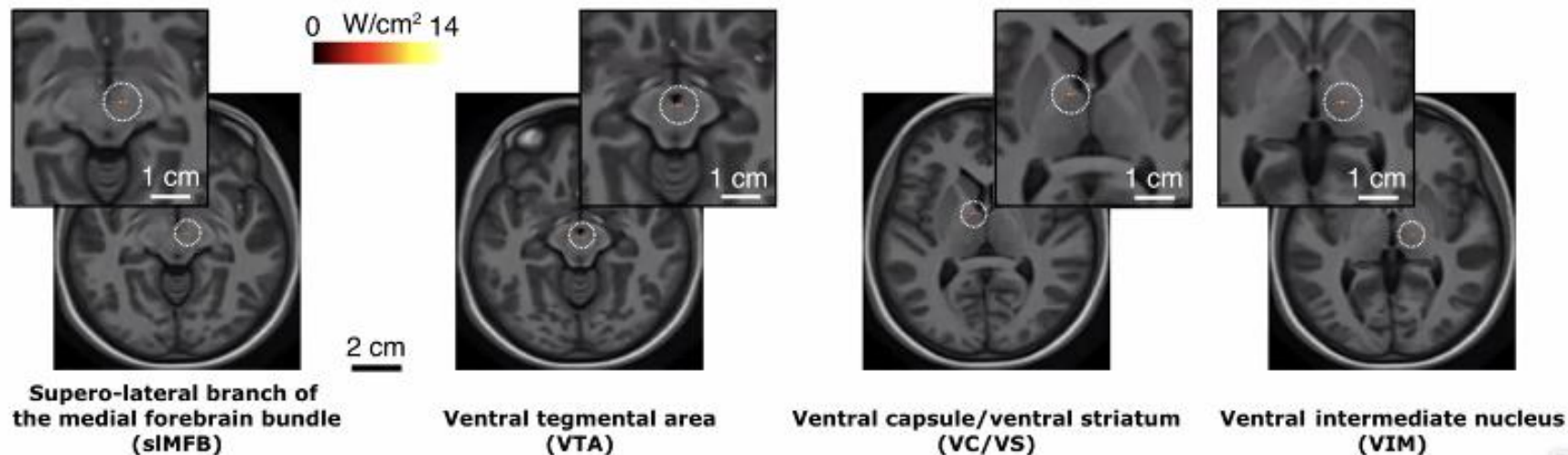
Delivering the proper dose

➔ TUS studies in humans have delivered inadequate intensity

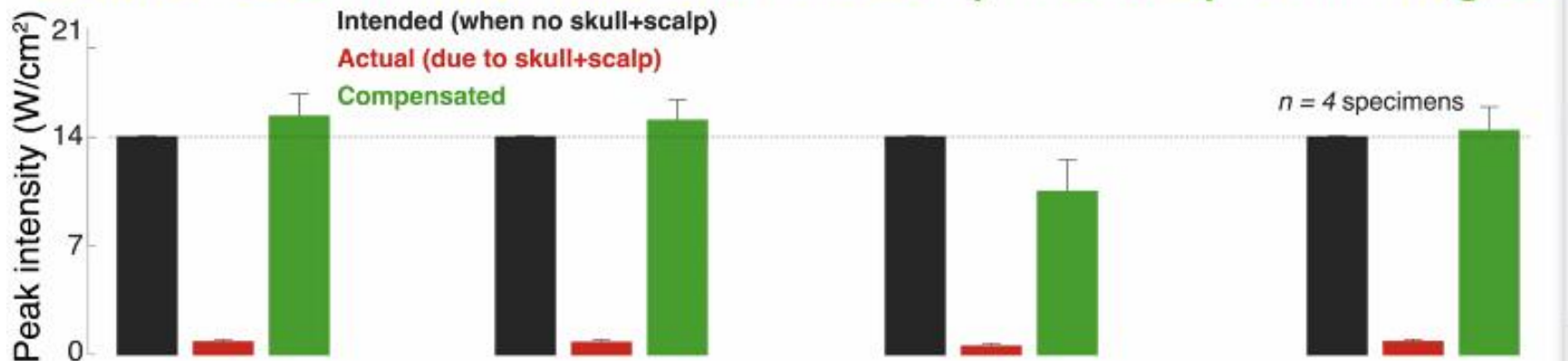


Delivering the proper dose

➔ Human system that compensates for attenuation accurately

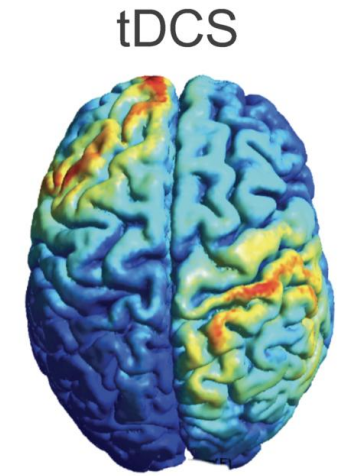
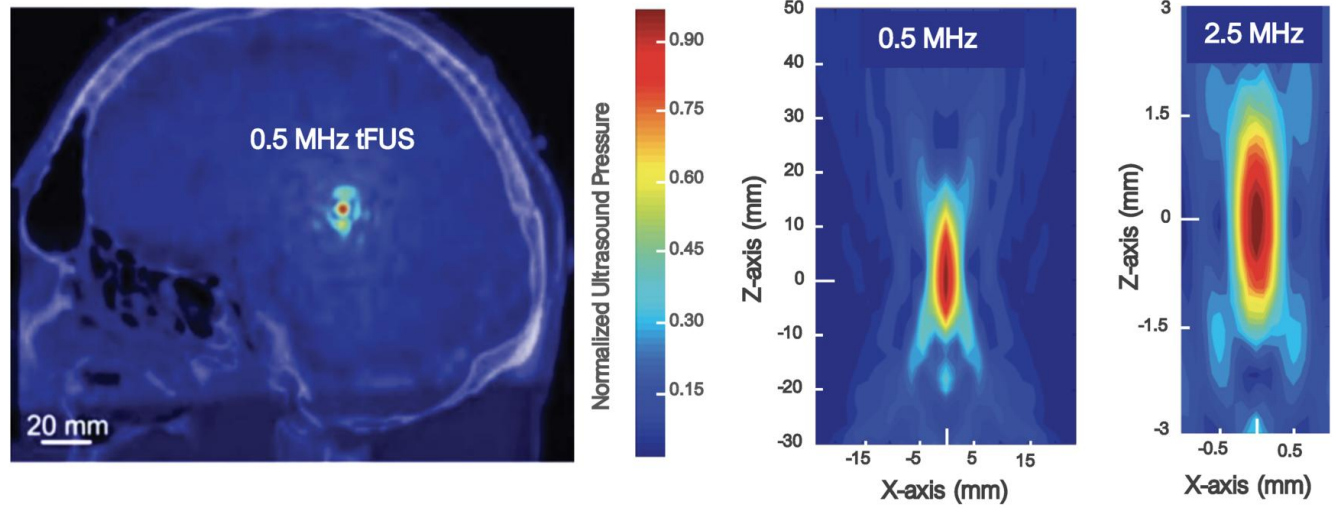


Deliver deterministic ultrasound intensity into deep brain targets

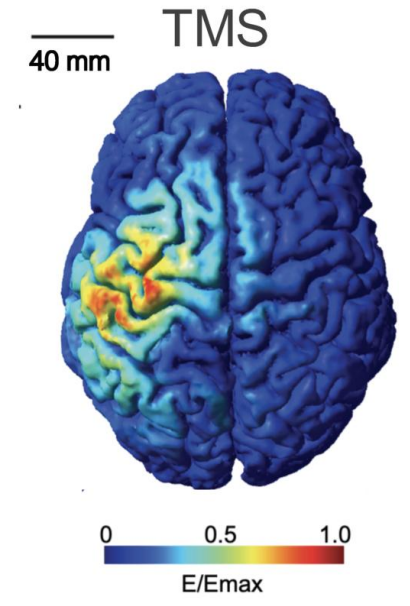
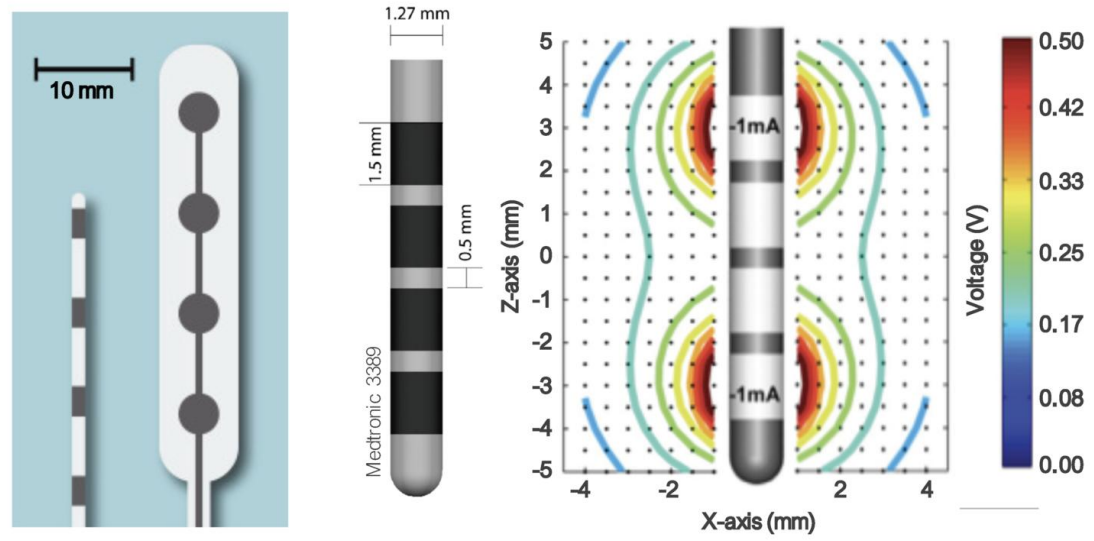


Targeting

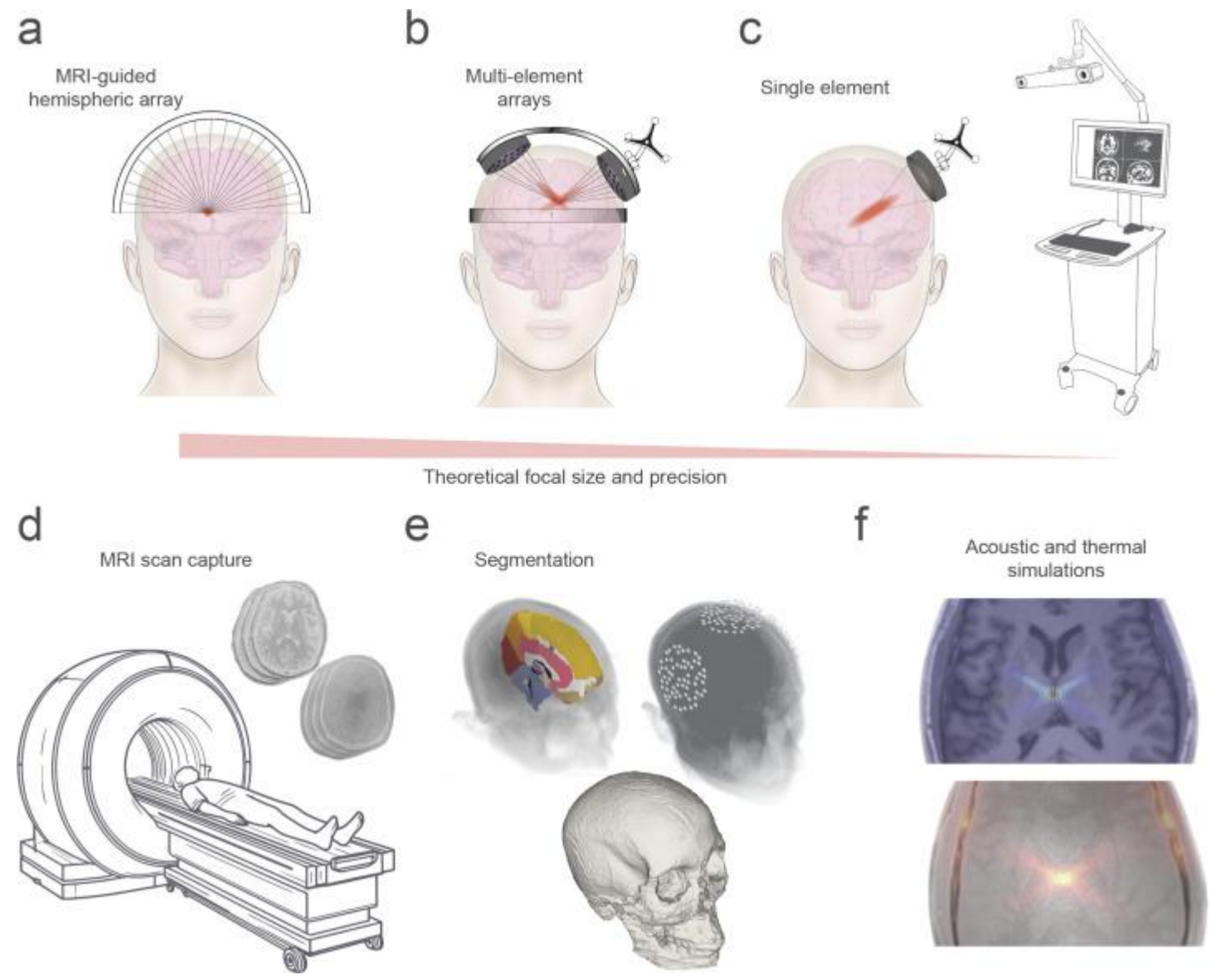
Noninvasive Neuromodulation by Focused Ultrasound



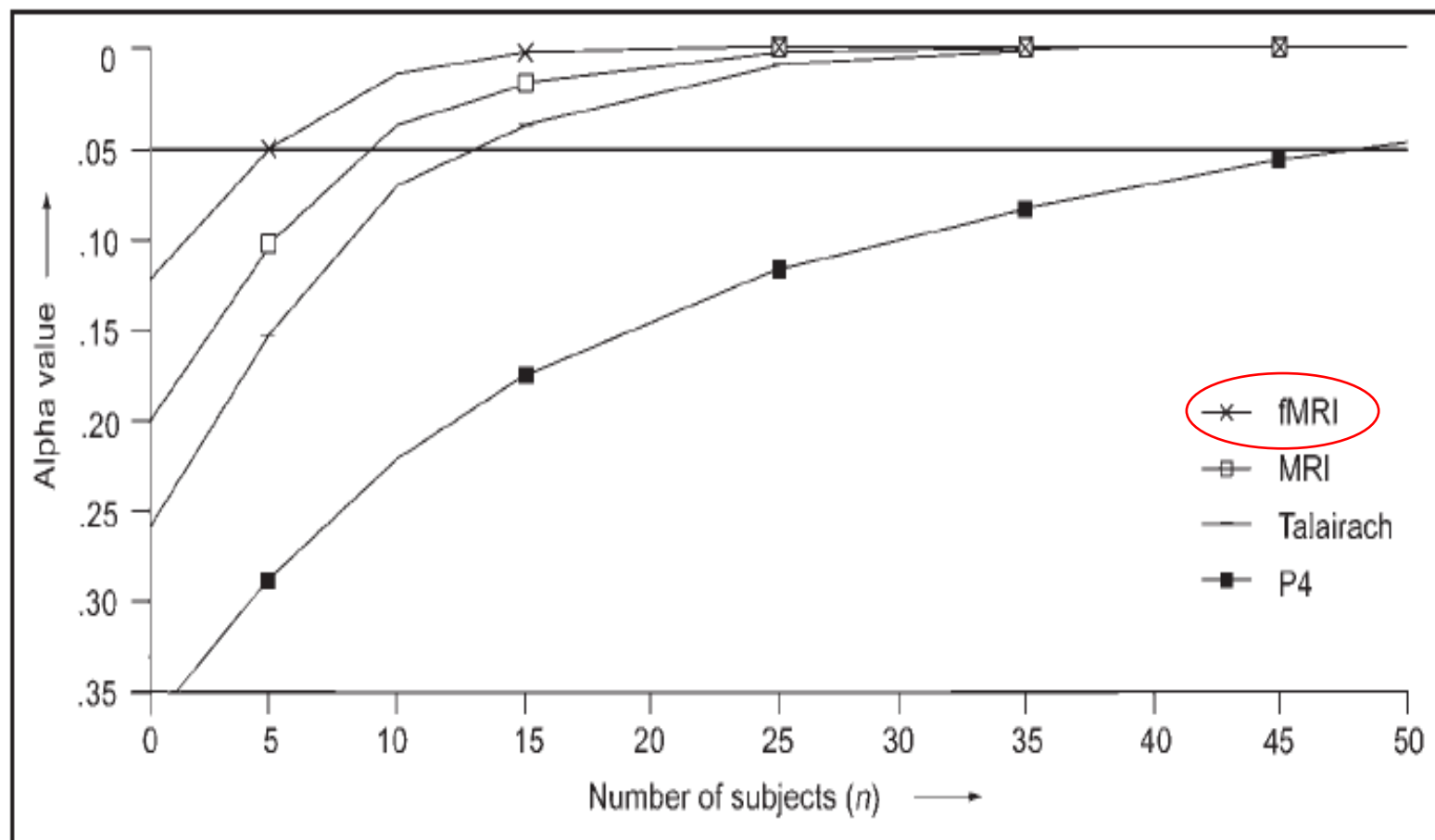
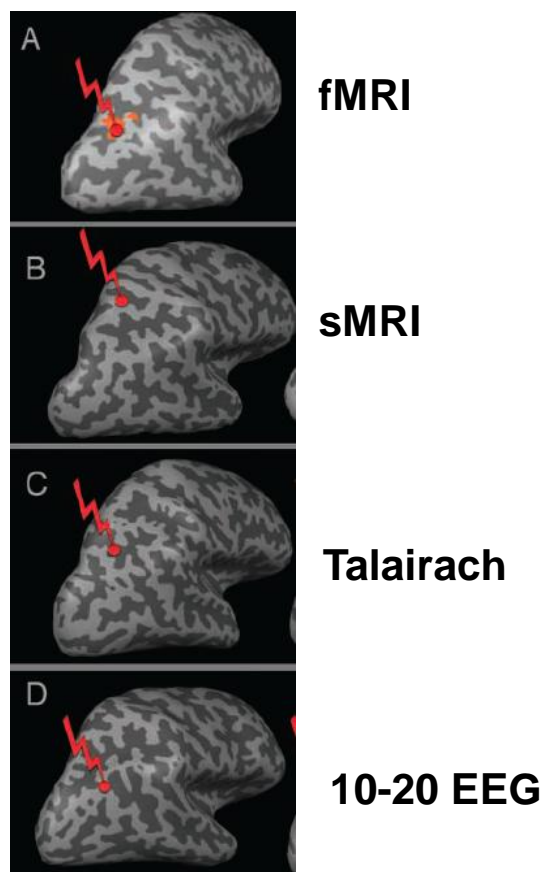
Surgically Implanted SCS and DBS Electrodes



Targeting

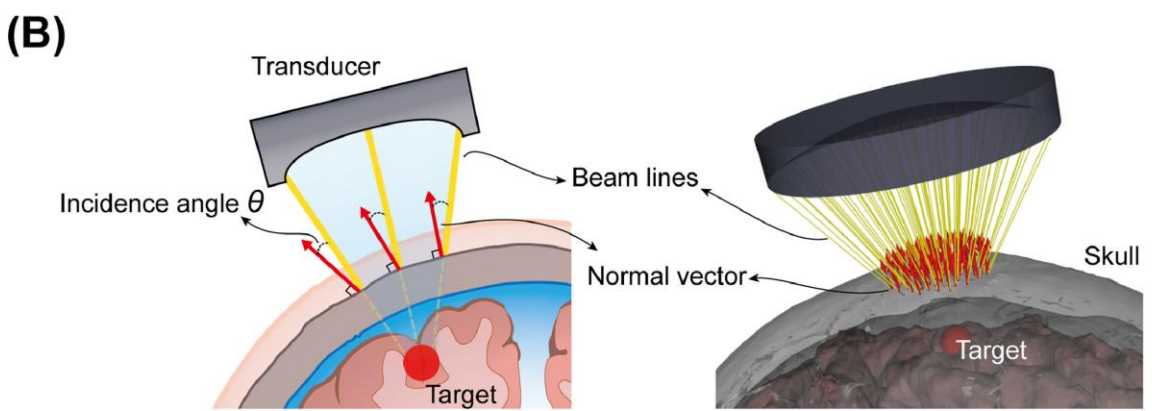
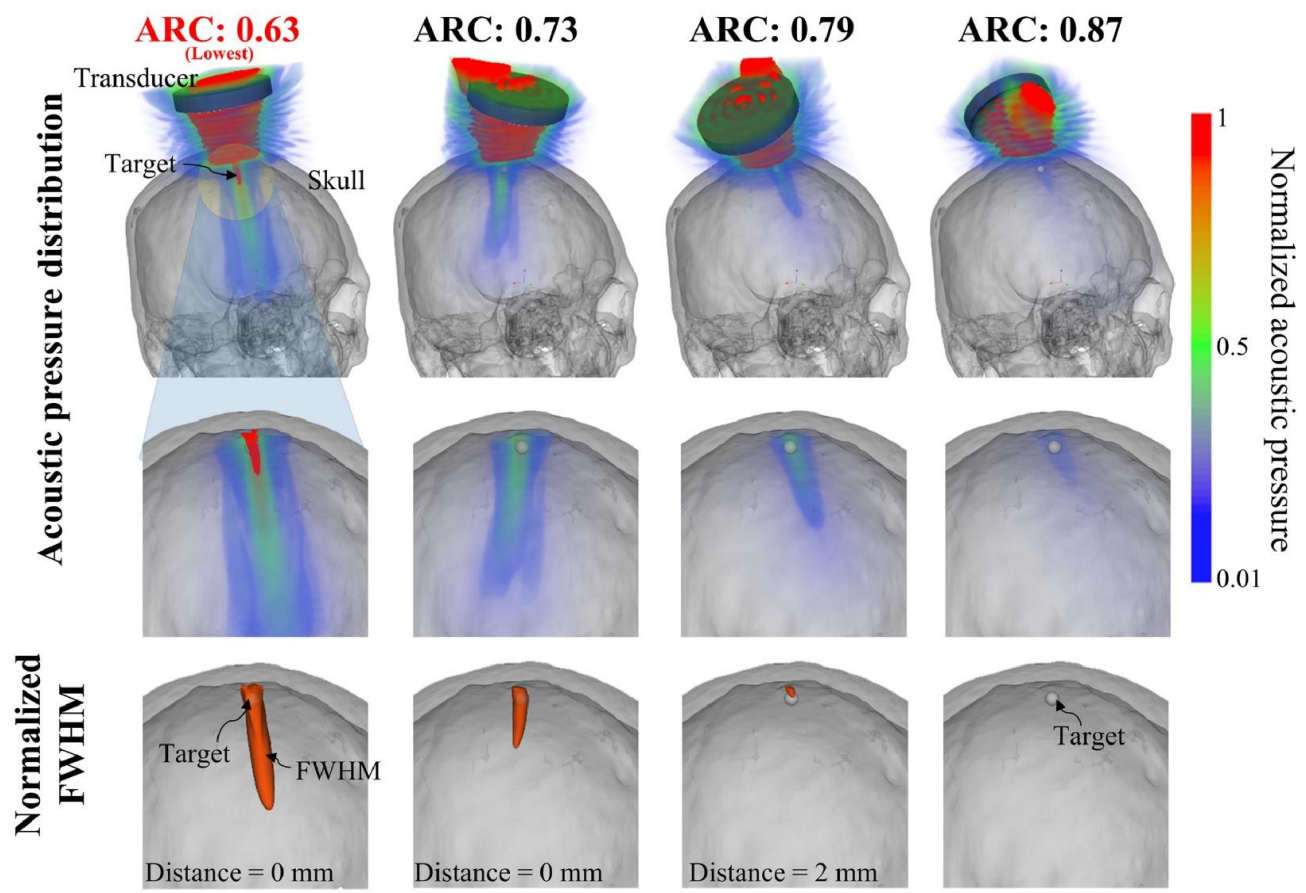
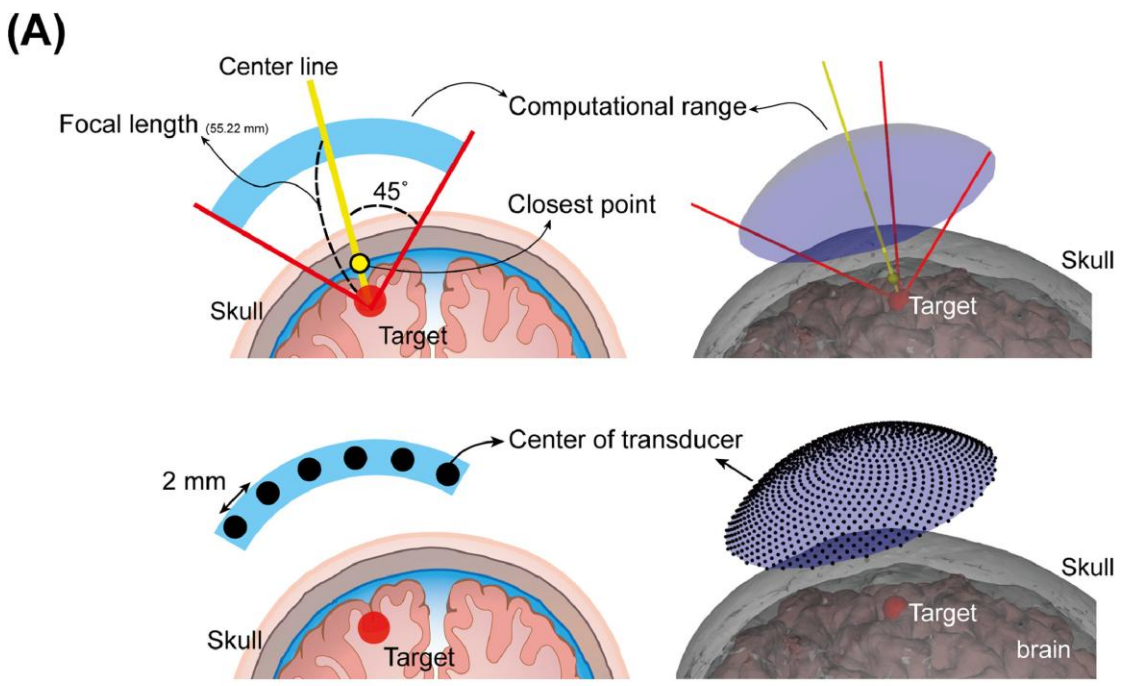


Targeting: Anatomic/Functional planning

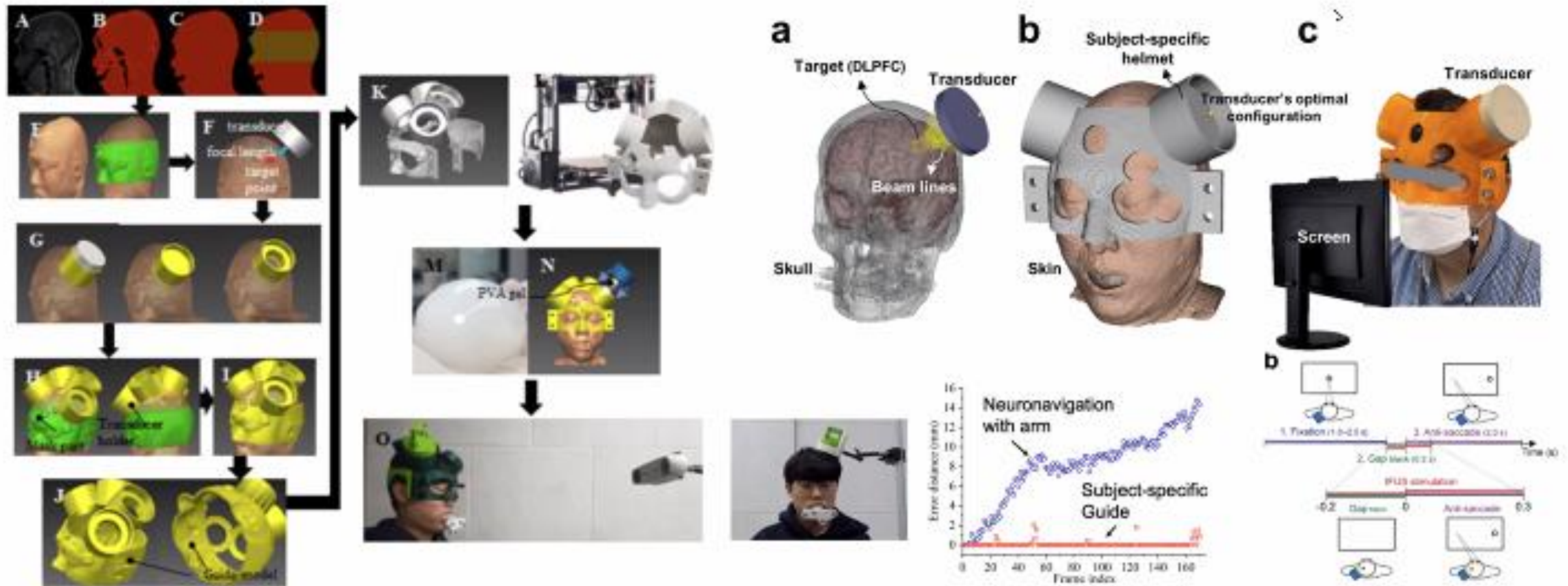


Individual placement based on neuronavigation and **individual functional activity peaks** improves **study power**.

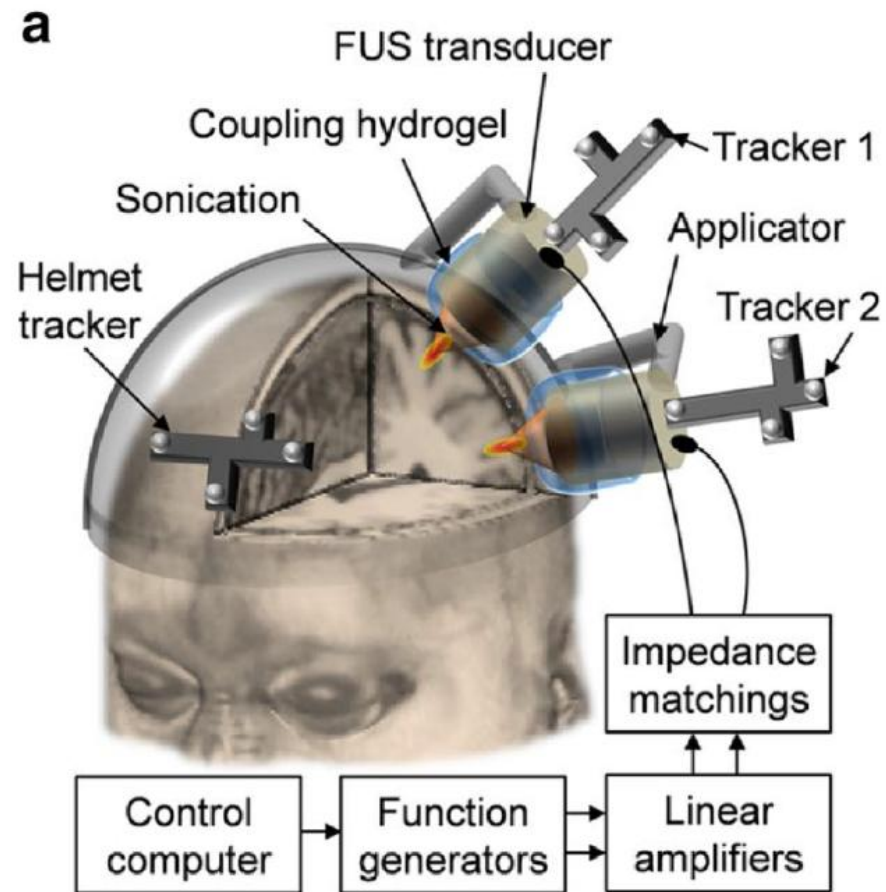
Targeting: Optimal Sonication Path



Navigation: 3D printed Helmet-type Guide



Navigation: 3D printed Helmet-type Guide

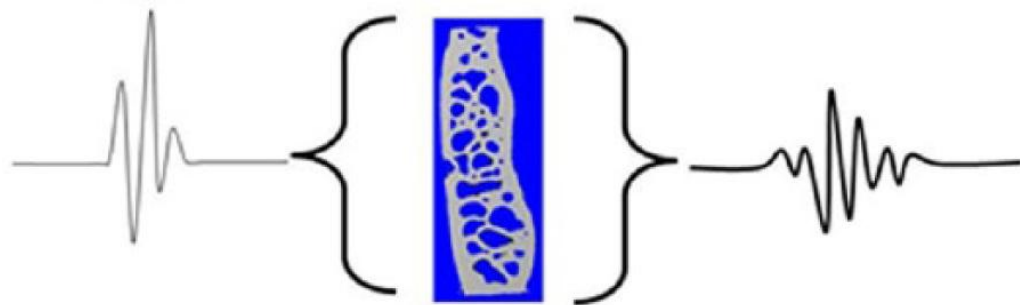


US simulations: to estimate dose + target

Input signal

Skull sample

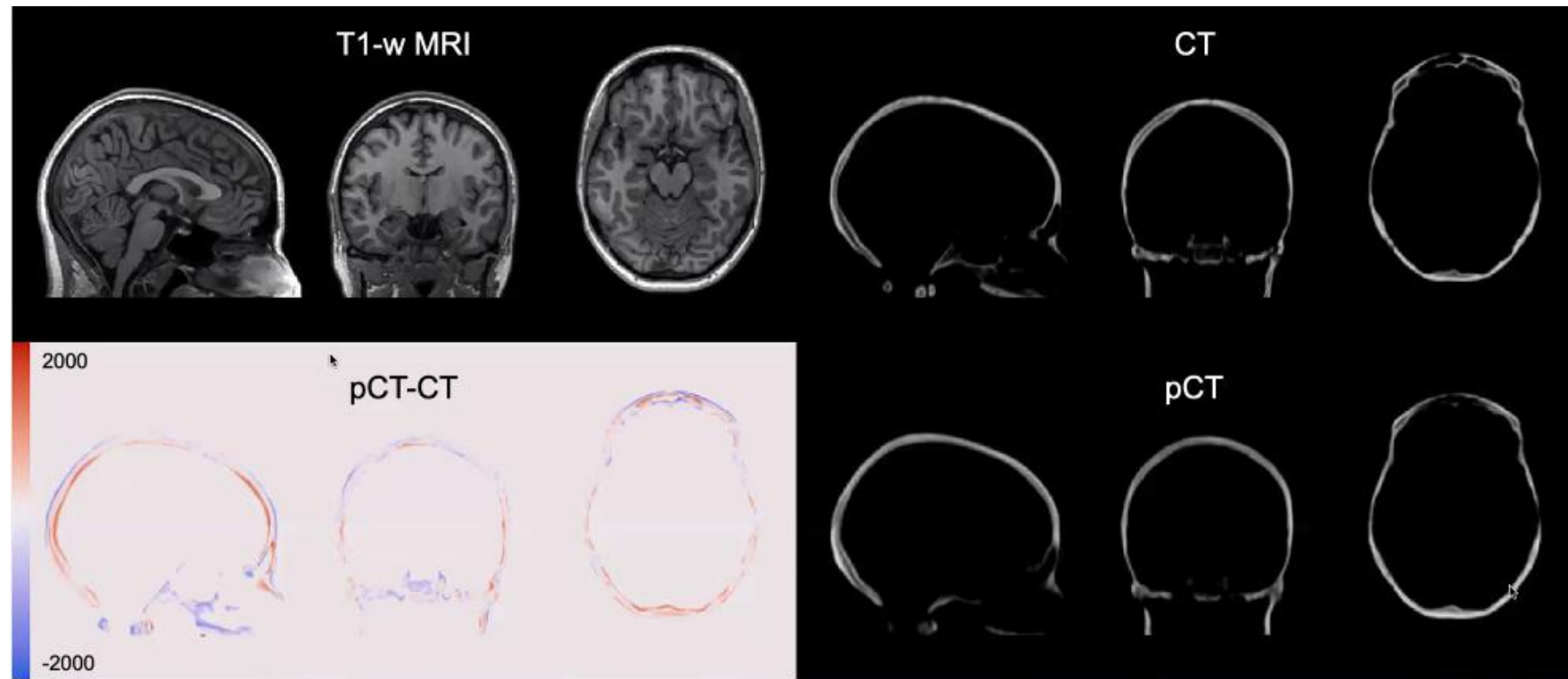
Output signal



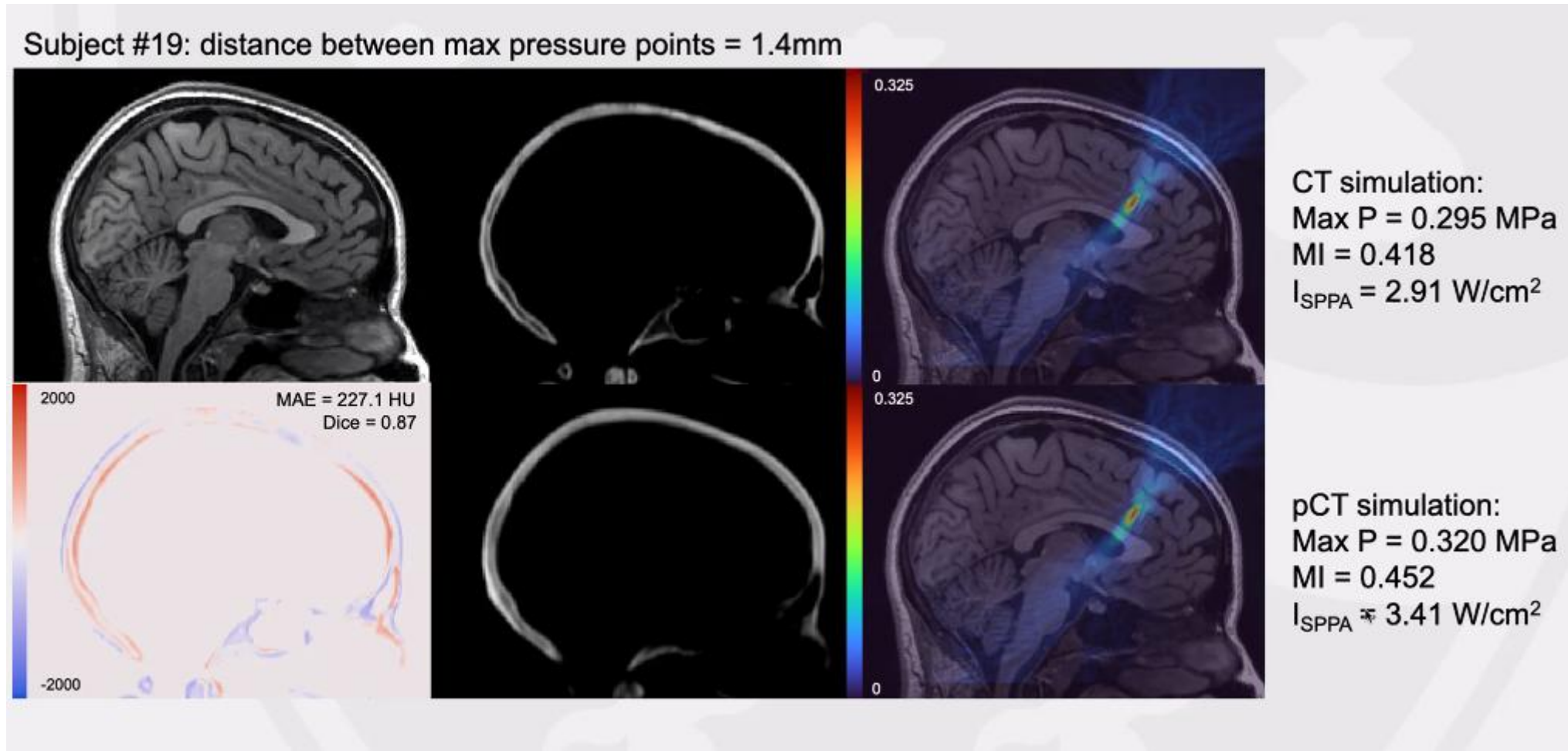
Variation in tissue composition and thickness

Methods to image the skull:

- Ultra-short echo time (UTE) MRI to image bone
- Methods to generate pseudo-CT (pCT) from MRIs:
 - Multi-atlas co-registration
 - Convolutional neural networks



US simulations: to estimate dose + target



US simulations: to estimate dose + target

Acoustic simulations in k-Wave

Skull acoustic properties linearly mapped from CT HU

Non-skull: treated as water

$$\rho = \rho_{min} + (\rho_{max} - \rho_{min}) \frac{HU - HU_{min}}{HU_{max} - HU_{min}}$$

$$c = c_{min} + (c_{max} - c_{min}) \frac{\rho - \rho_{min}}{\rho_{max} - \rho_{min}}$$

$$\alpha = \alpha_{min} + (\alpha_{max} - \alpha_{min}) \left(1 - \frac{HU - HU_{min}}{HU_{max} - HU_{min}}\right)^{0.5}$$

Density (kg/m ³)	Sound speed (m/s)	Absorption (dB/MHz ² cm)
$\rho_{min} = 1000$	$c_{min} = 1500$	$\alpha_{min} = 1.9$
$\rho_{max} = 1900$	$c_{max} = 3100$	$\alpha_{max} = 18.1$
		$\alpha_{water} = 0.0022$

Transducer: Brainbox NeuroFUS CTX-500

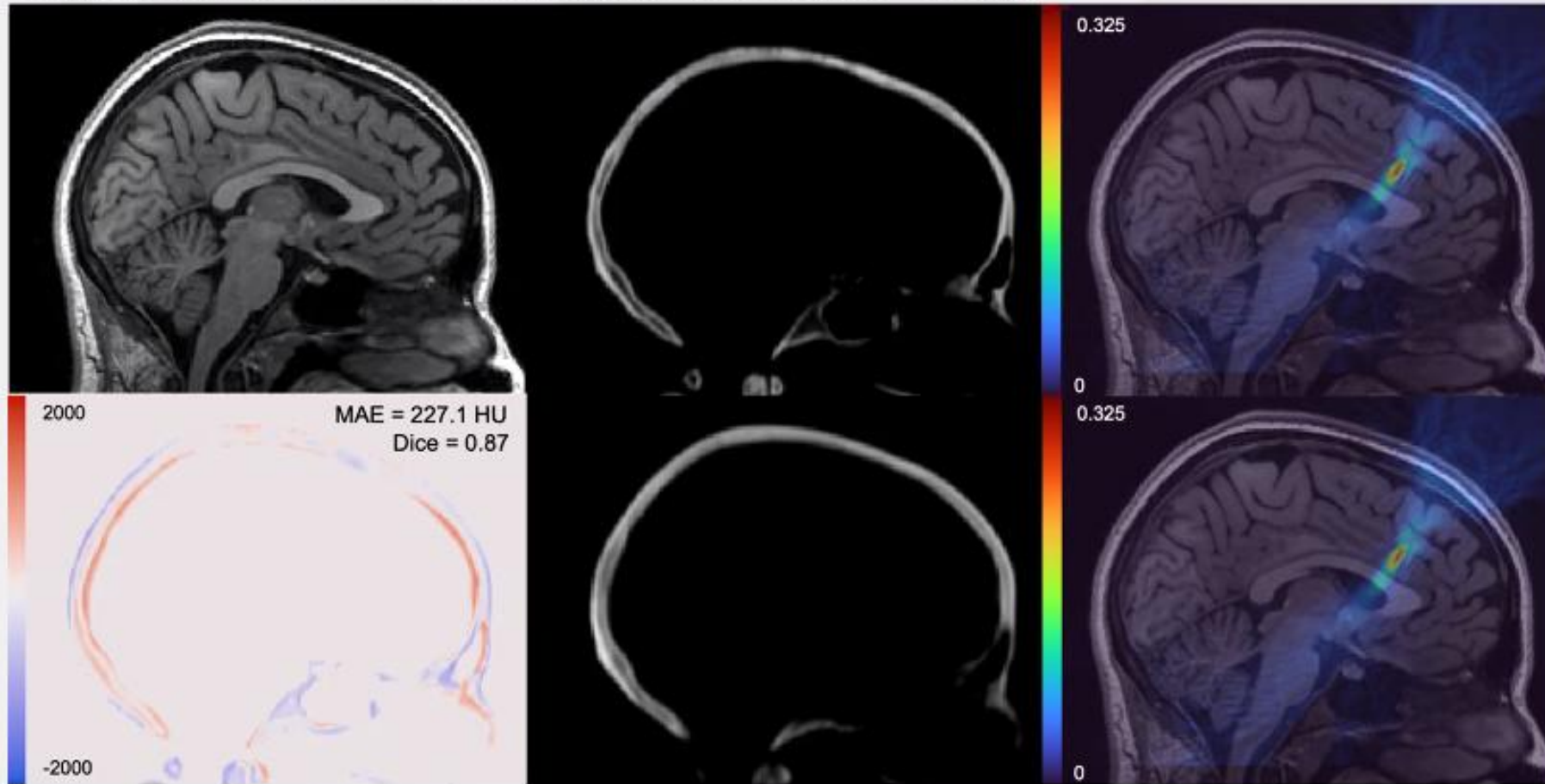
- 500 kHz 4-element annular transducer defined with kArray
- Pulse length = 20 ms
- Pulse repetition frequency = 5 Hz

k-Wave grid:

- Grid size 256 × 256 × 256
- Grid spacing set to $\lambda/3 = 1$ mm

US simulations

Subject #19: distance between max pressure points = 1.4mm

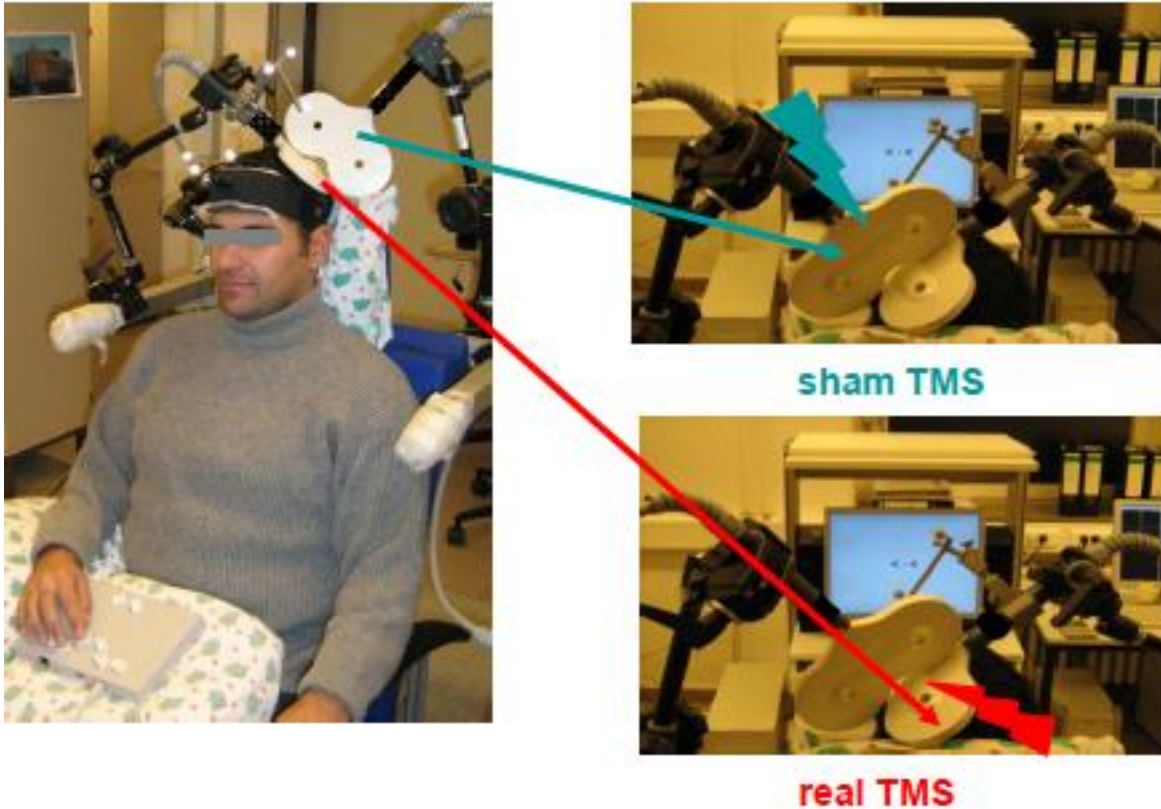


CT simulation:
 Max P = 0.295 MPa
 MI = 0.418
 $I_{SPPA} = 2.91 \text{ W/cm}^2$

pCT simulation:
 Max P = 0.320 MPa
 MI = 0.452
 $I_{SPPA} \approx 3.41 \text{ W/cm}^2$

The importance of a control condition

A sham TUS should control for noise, sensations, attention, placebo effects...



- Active Control site (demonstrating anatomical specificity)
- Time Control (demonstrating temporal specificity)

Clear and standardised reporting in papers:

Transducer and drive system description

- Transducer manufacturer and model number (Section 'Transducer Description')
- Transducer centre frequency (Section 'Transducer description')
- Transducer geometry (e.g., radius of curvature and aperture diameter) (Section 'Transducer description')
- Drive system components, including manufacturer and model number (e.g., signal generator and amplifier or integrated driving system) (Section 'Drive system description')

Drive system settings (Section 'Drive system settings')

- Operating frequency
- Output level settings
- Focal position settings
- Description of transducer coupling method

Free field acoustic parameters (Section 'Parameters to report')

- Reference position for measurements
- Spatial-peak pressure amplitude
- Position of spatial-peak pressure amplitude (relative to reference position)
- Size of focal volume (-3 dB and -6 dB axial and lateral widths)

Clear and standardised reporting in papers:

- ☐ Position of centre of focal volume (centre of -3 dB relative to reference position)
- ☐ Description of how free field parameters were obtained (including details of measurement equipment)

Pulse timing parameters (Section 'Pulse timing parameters')

- ☐ Pulse timing table

In situ estimates of exposure parameters

- ☐ Estimated *in situ* spatial-peak pressure amplitude (Section 'Estimated *in situ* pressure amplitude')
- ☐ Estimated *in situ* pressure amplitude at the target (Section 'Estimated *in situ* pressure amplitude')
- ☐ Estimated *in situ* mechanical index (Section 'Estimate of *in situ* mechanical index')
- ☐ One of the following thermal metrics: temperature rise, thermal index, or thermal dose (Section 'Thermal metrics')
- ☐ Description of how *in situ* estimates were obtained (Section 'Estimated *in situ* pressure amplitude')

Intensity parameters (optional)

- ☐ Spatial-peak pulse-average intensity (Section 'Spatial-peak pulse-average intensity')
- ☐ Spatial-peak time-average intensities (Section 'Spatial-peak time-average intensities')
- ☐ The acoustic impedance used for the conversion (Section 'Spatial-peak pulse-average intensity')

Clear and standardised reporting in papers:

Transducer and drive system description

- Transducer manufacturer and model number (Section 'Transducer Description')
- Transducer centre frequency (Section 'Transducer description')
- Transducer geometry (e.g., radius of curvature and aperture diameter) (Section 'Transducer description')
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Free field acoustic parameters (Section 'Parameters to report')

- Reference position for measurements
- Spatial-peak pressure amplitude
- Position of spatial-peak pressure amplitude (relative to reference position)
- Size of focal volume (-3 dB and -6 dB axial and lateral widths)

Brain stimulation wish-list

- Non-invasive ✓
- Focal ✓
- Surface & Deep ✓
- Long-lasting ✓
- Robust & effective ✓
- Measurable ✓
- Relevant for behaviour ✓

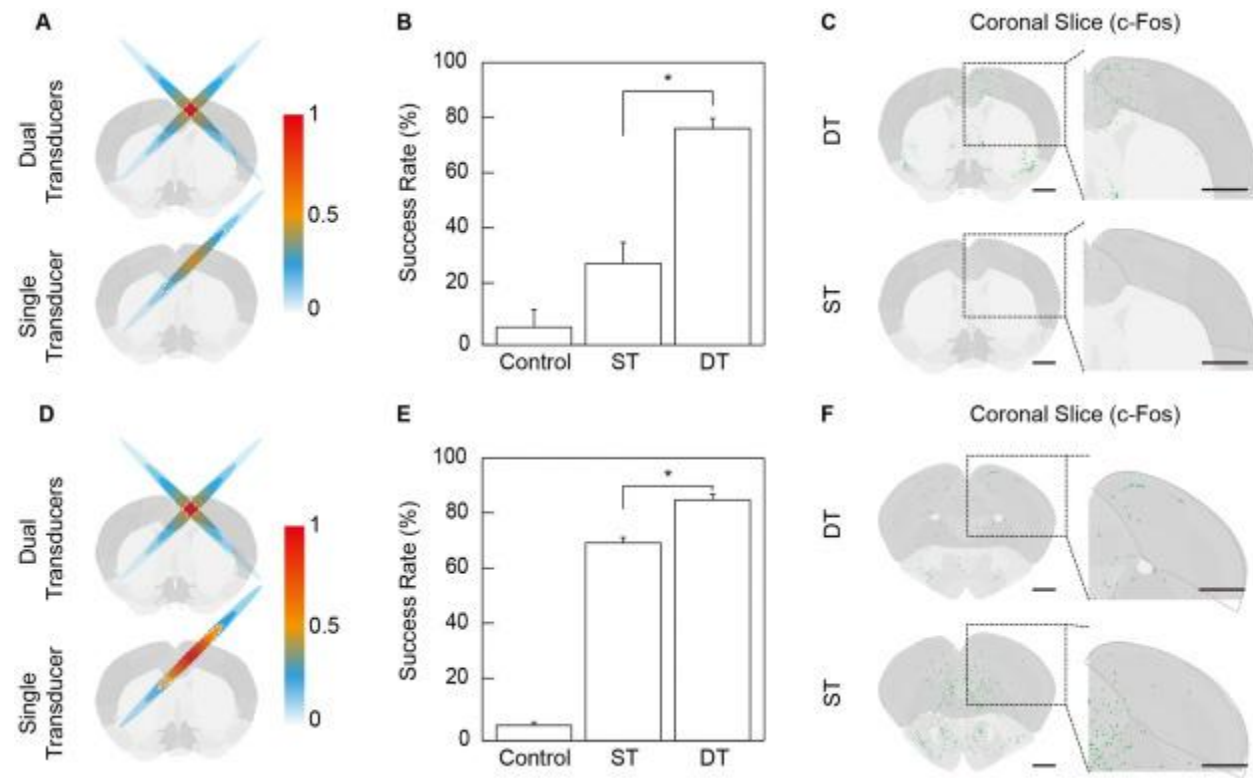
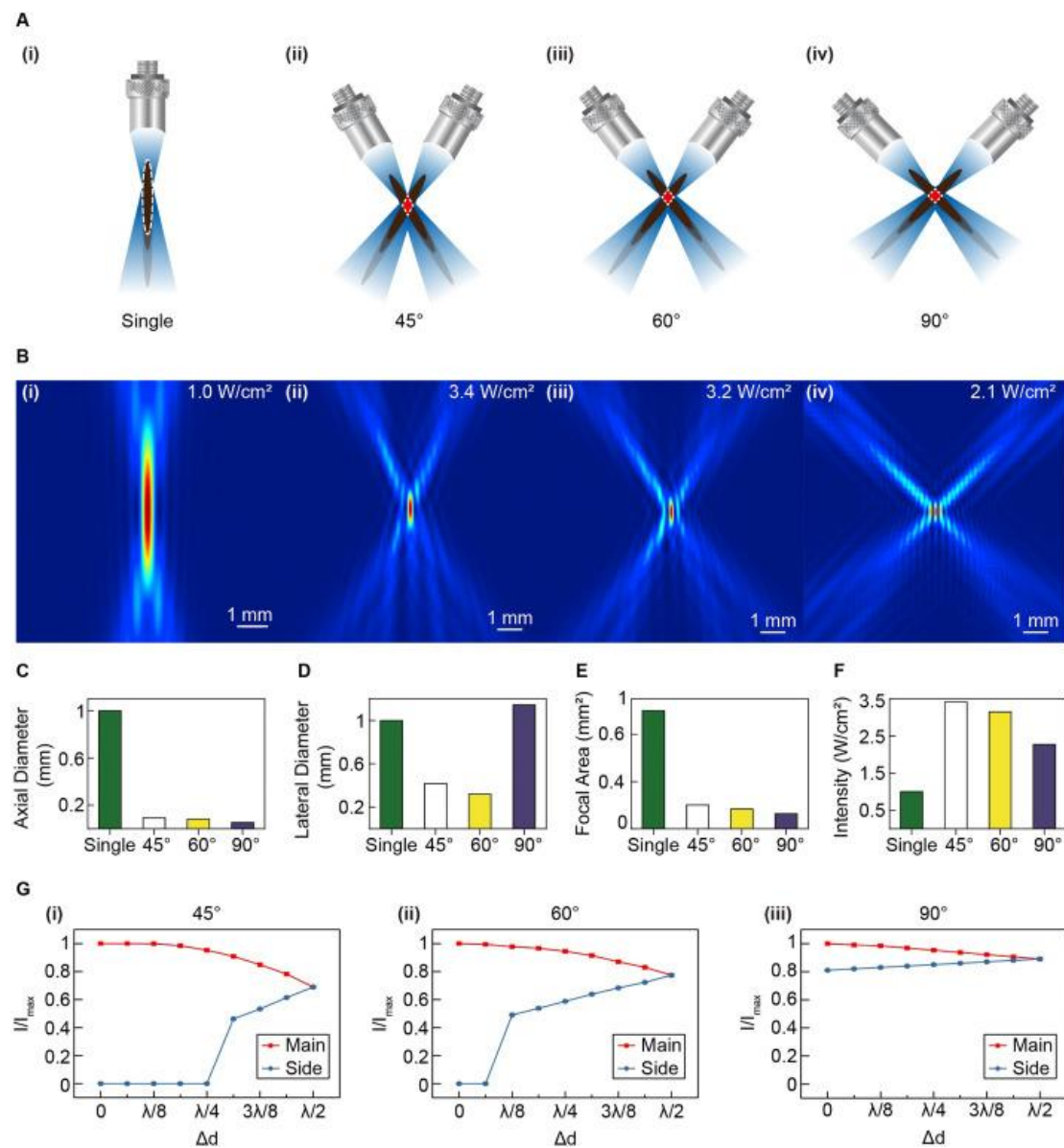
Brain stimulation wish-list

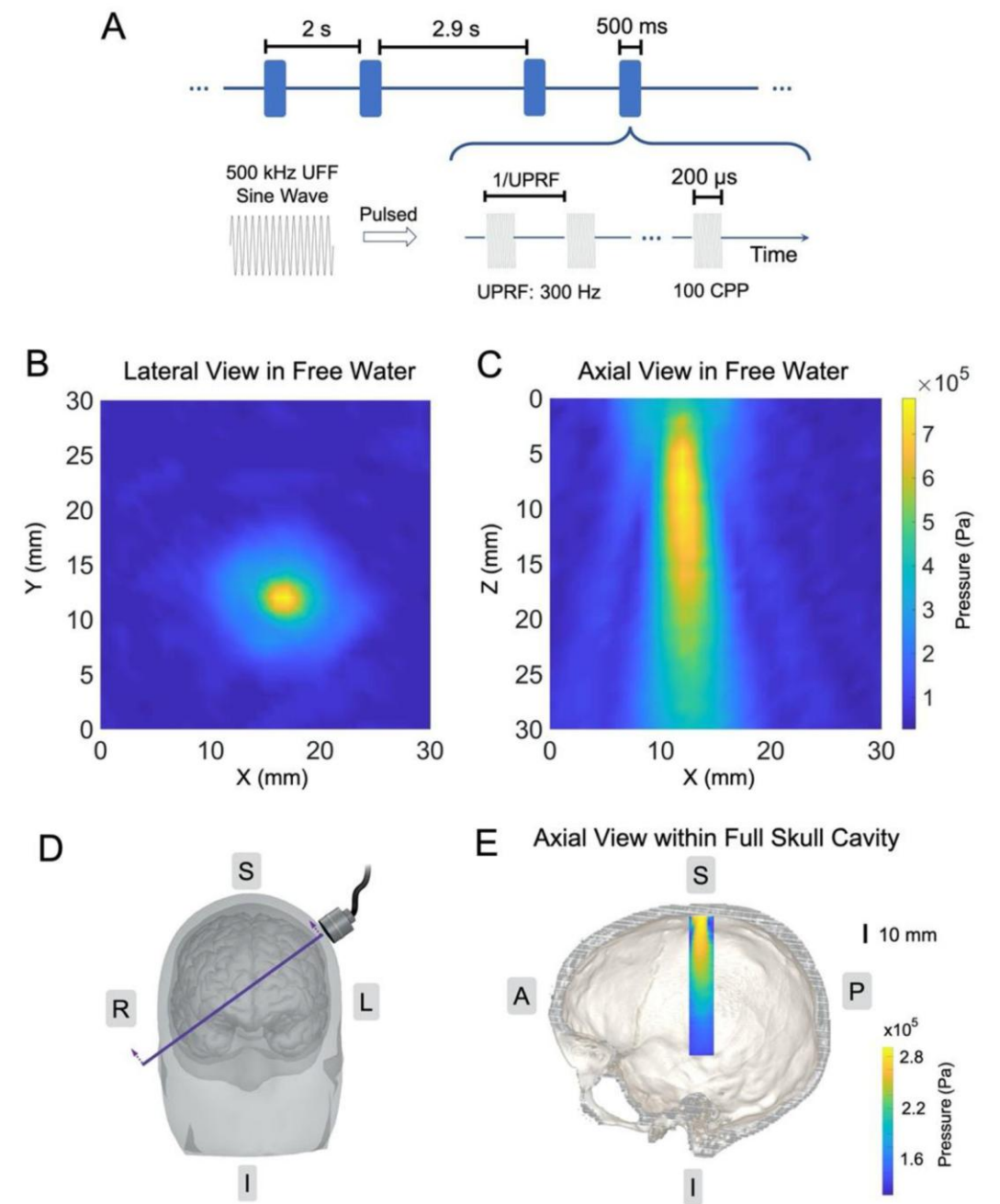
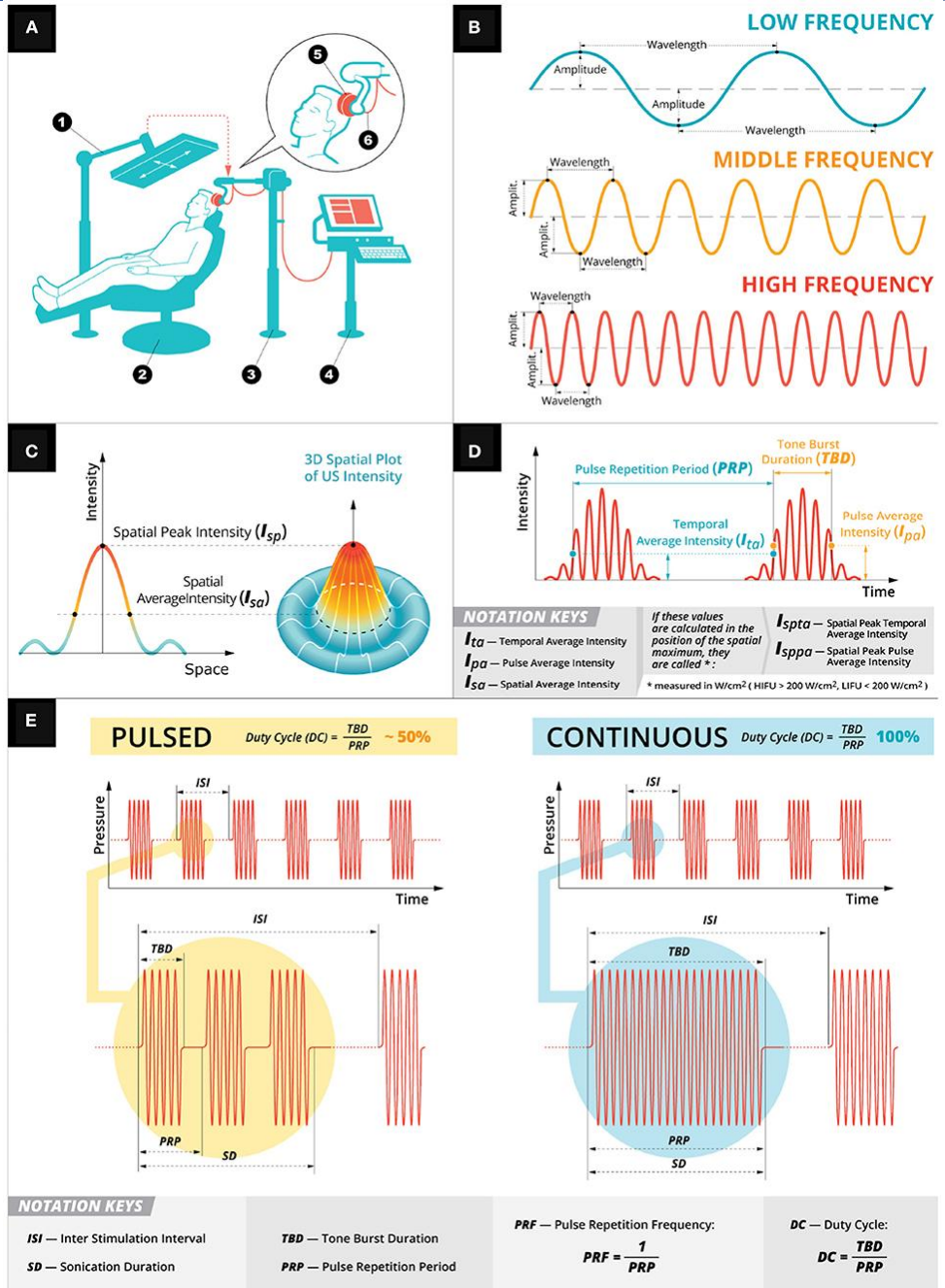
- Non-invasive ✓
- Focal ✓
- Surface & Deep ✓
- Long-lasting ✓
- Robust & effective ✓
- Measurable ✓
- Relevant for behaviour ✓
- Mechanisms ?!
- Physiology ?!
- Species differences ?!
- Temporal specificity ?!
- Sham control ?!
- Oscillatory modulation ?!
- Targeted connectivity ?!

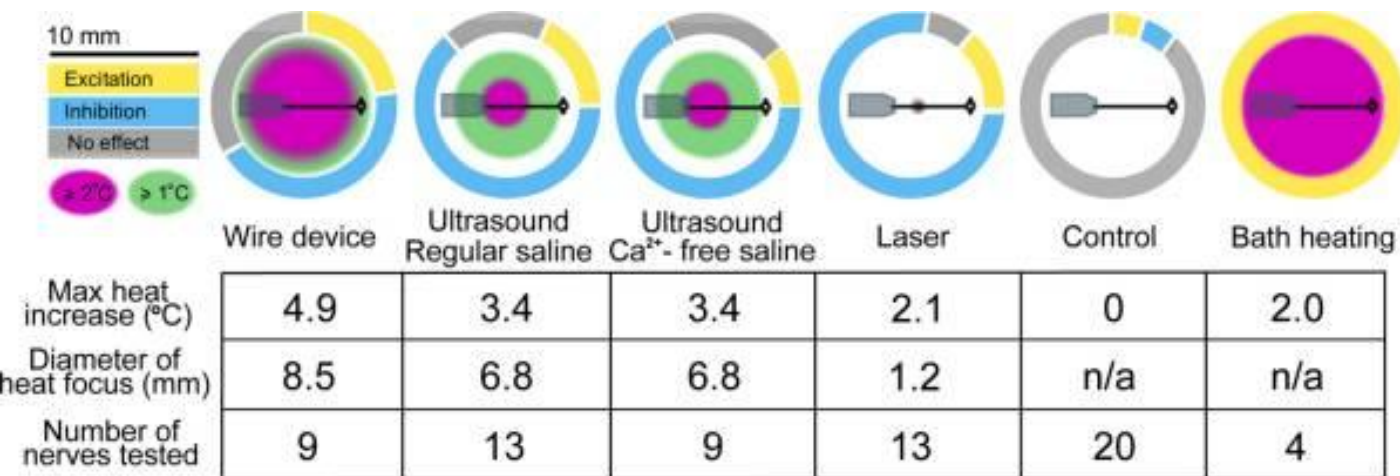
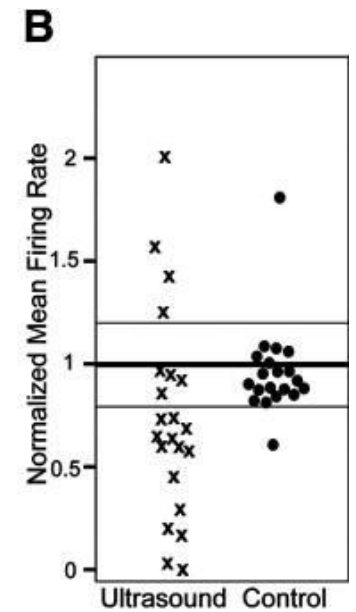
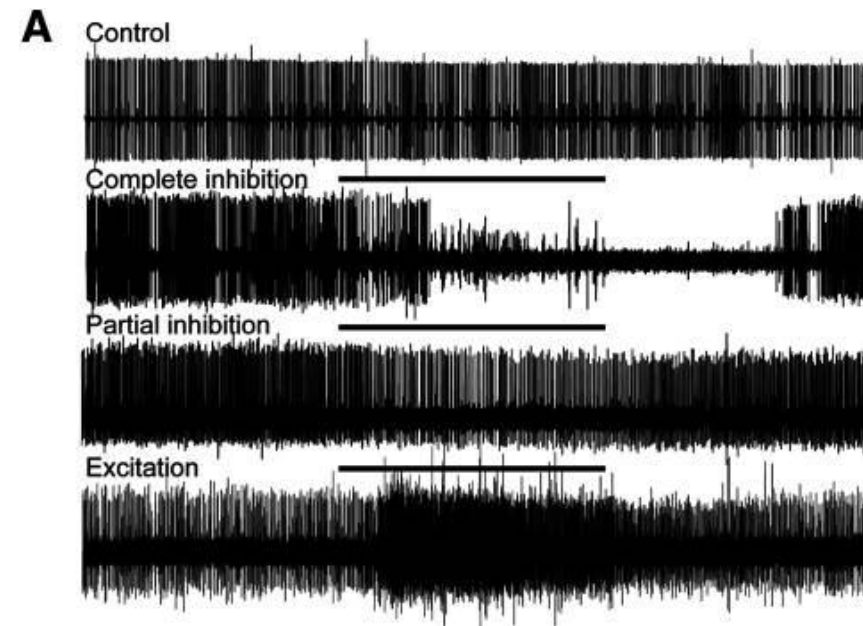
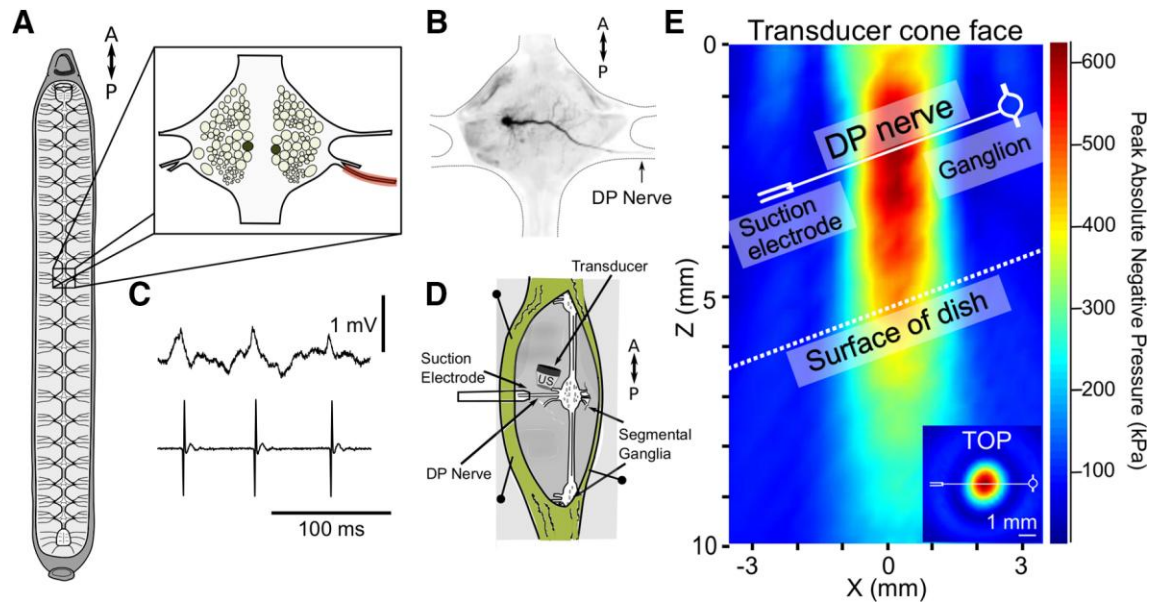
Thank you

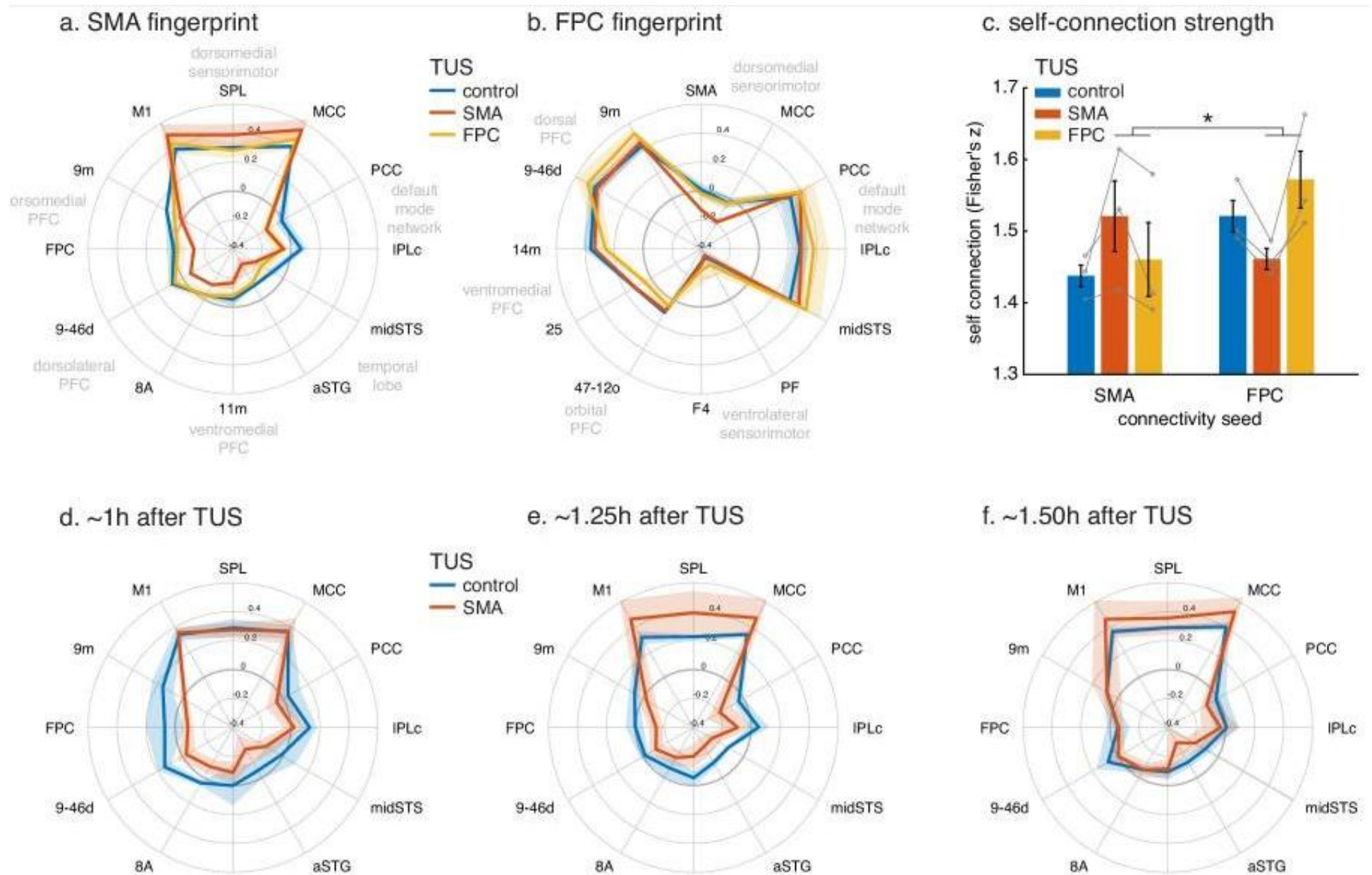


Current challenges

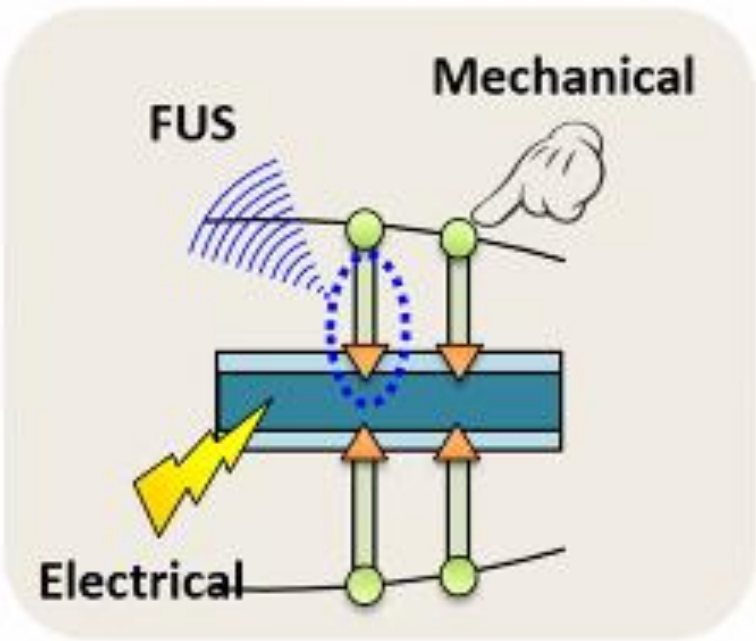
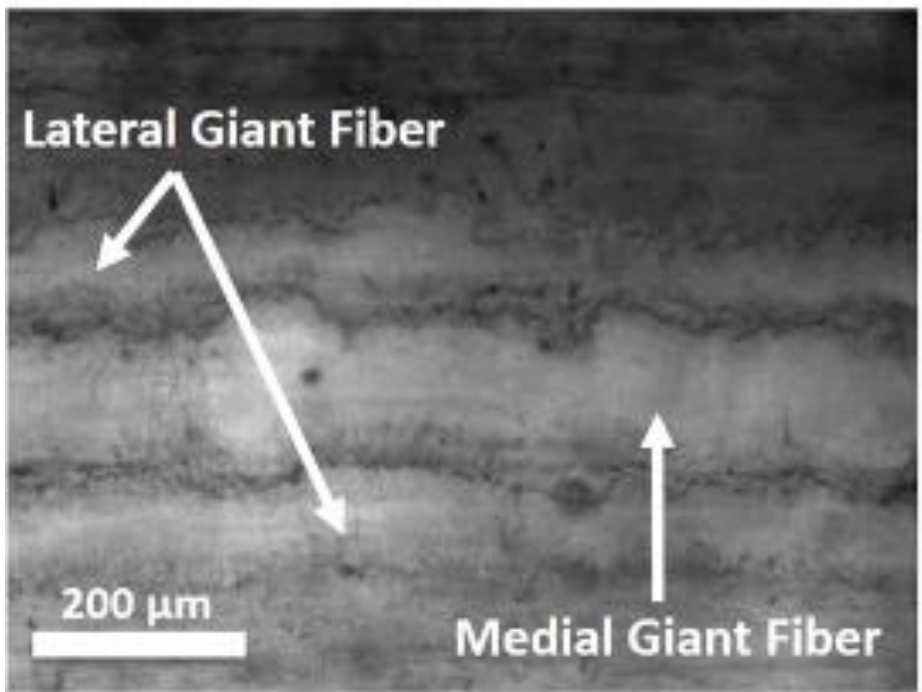






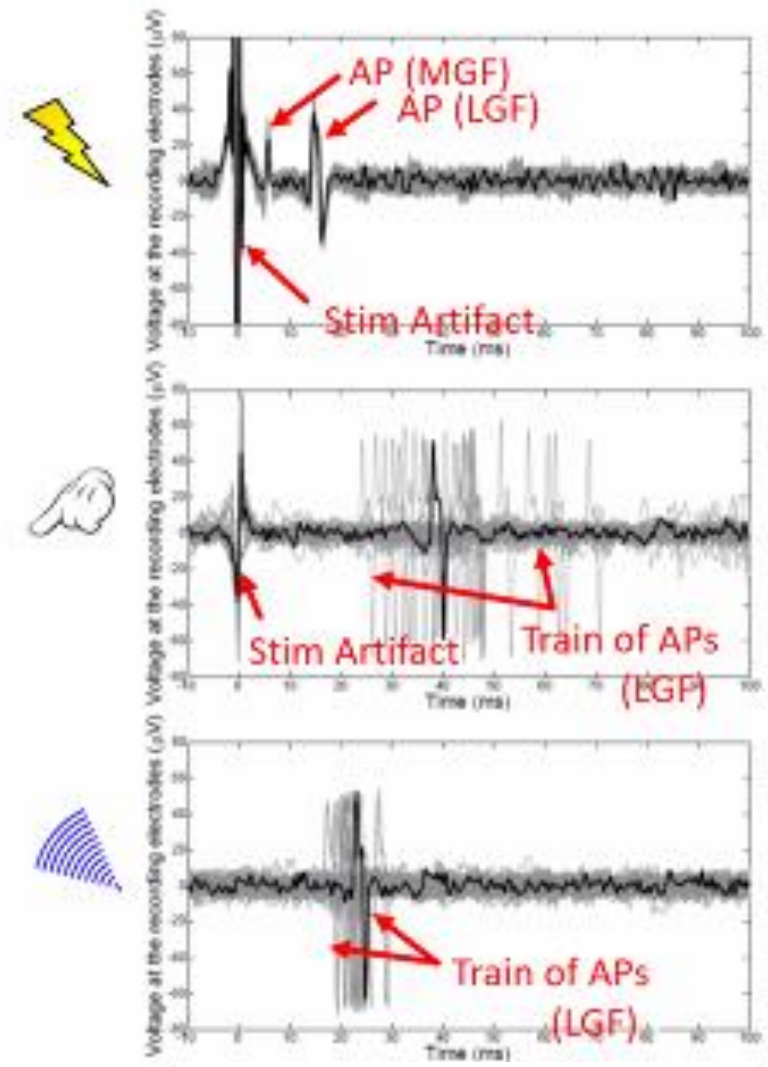


FUS-induced APs in *in-vivo* giant axons^{5,6}

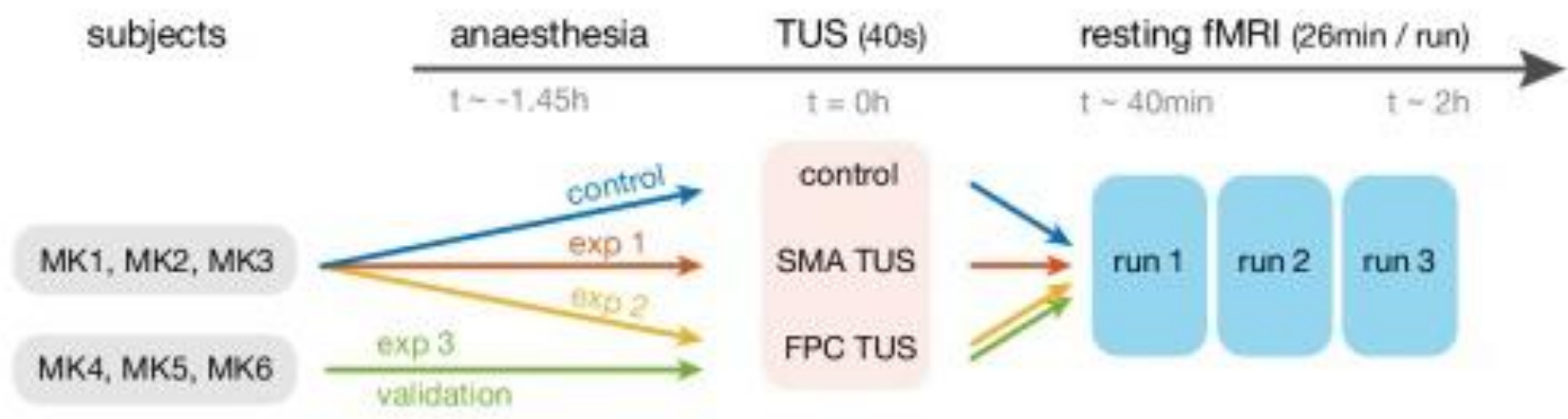


FUS Parameters

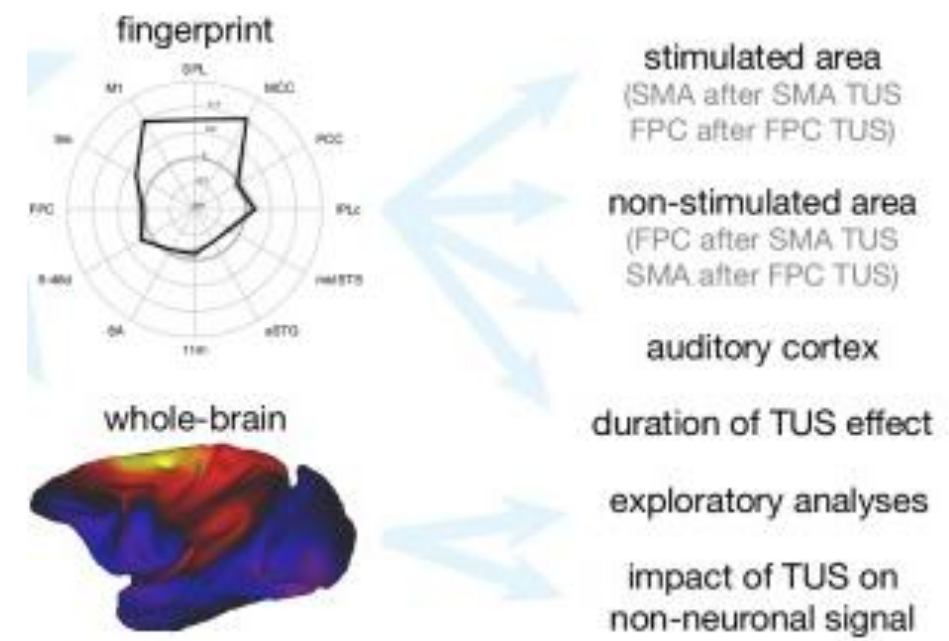
- $f = 1.1 \text{ MHz}$
- Single- & Repetitive- Pulses
- Pulse duration: 20 - 640 μs
 - $PRF: 25\text{-}125 \text{ Hz}$
- $p = 2.5 - 7.3 \text{ MPa}$



experimental design and timing



seed-based connectivity analyses



Towards offline neuromodulation

