EPFL

Low-intensity Transcranial Ultrasound Stimulation

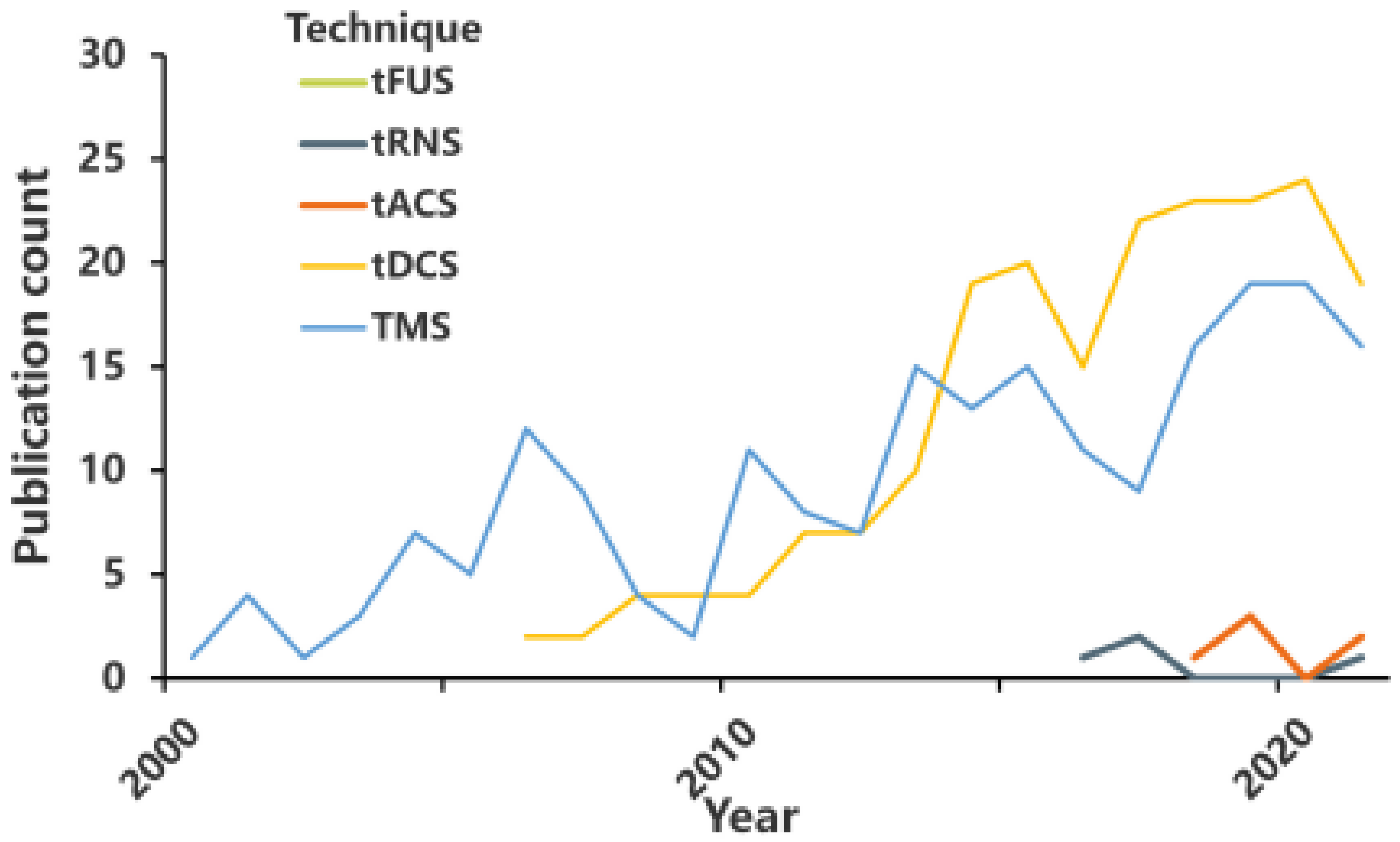
Estelle Raffin, PhD

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

The conventional NIBS techniques and their limitations

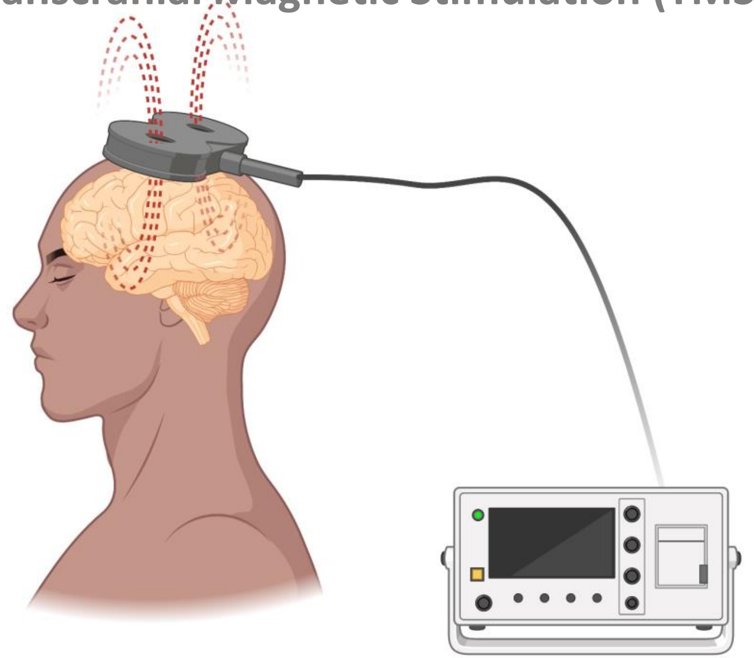
Conventional non-invasive brain stimulation techniques



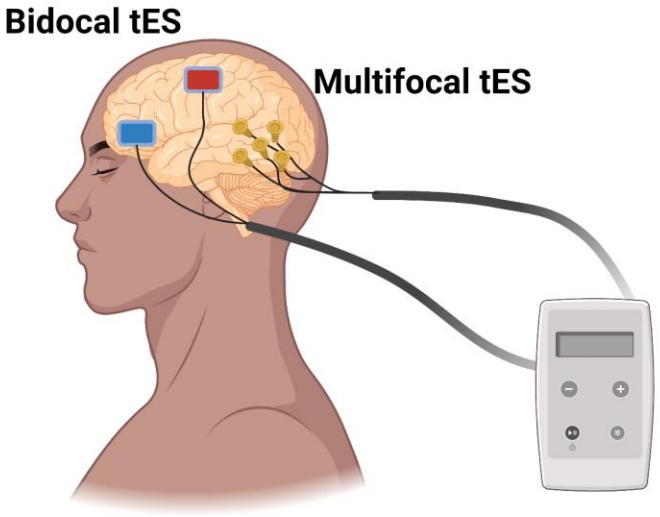
Xiong et al., 2022, Frontiers in Mol. Neurosciences

Conventional non-invasive brain stimulation techniques

Transcranial Magnetic Stimulation (TMS)

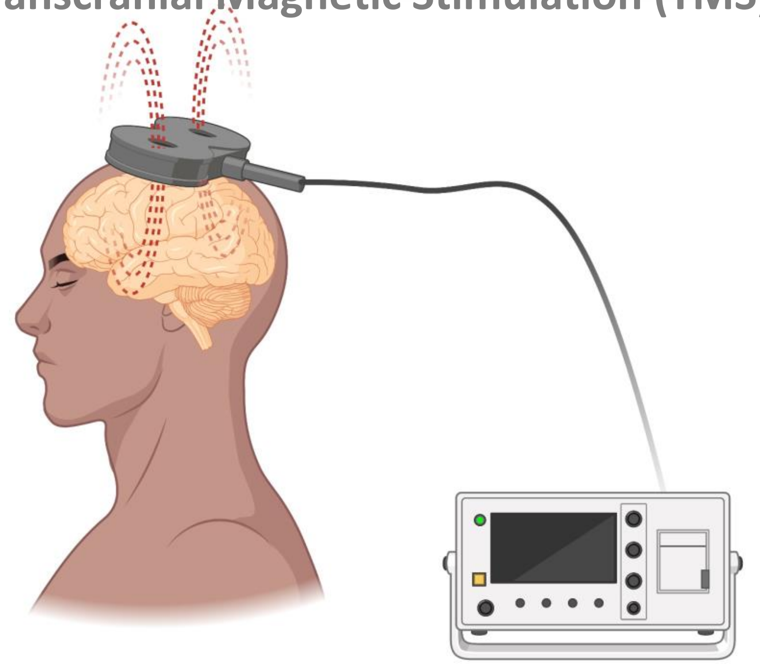


Transcranial Electric stimulation(tES)



Conventional non-invasive brain stimulation techniques

Transcranial Magnetic Stimulation (TMS)

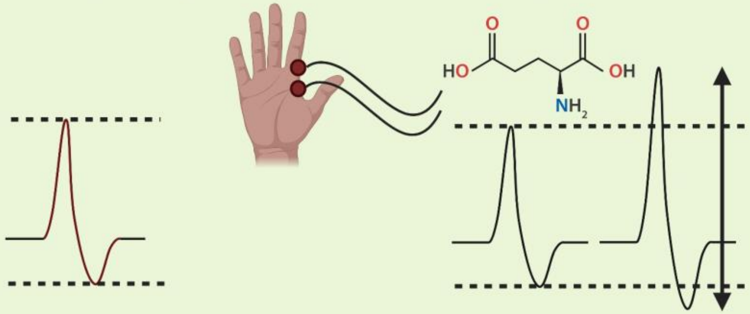


Single pulse

Probe corticospinal excitability

Double pulse

Probe cortical excitation/ inhibition

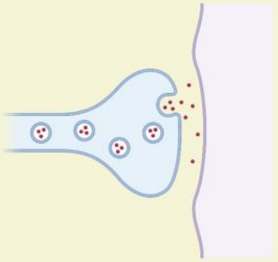


DIAGNOSTIC TOOL

Repeated

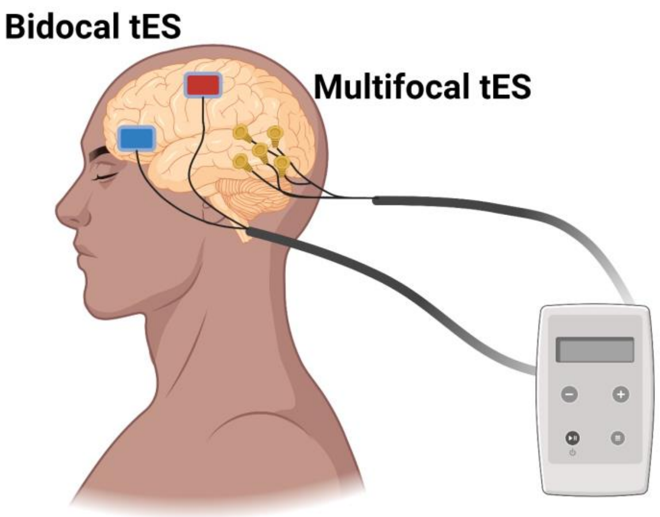
Modulate brain activity

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



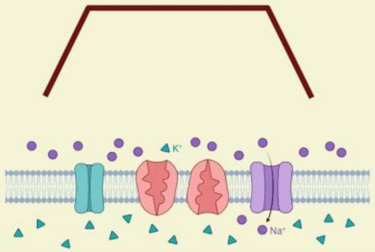
THERAPEUTIC TOOL

Transcranial Electric stimulation(tES)



tDCS

Continuous current
Anodal: Excitatory
Cathodal: Inhibitory



tACS

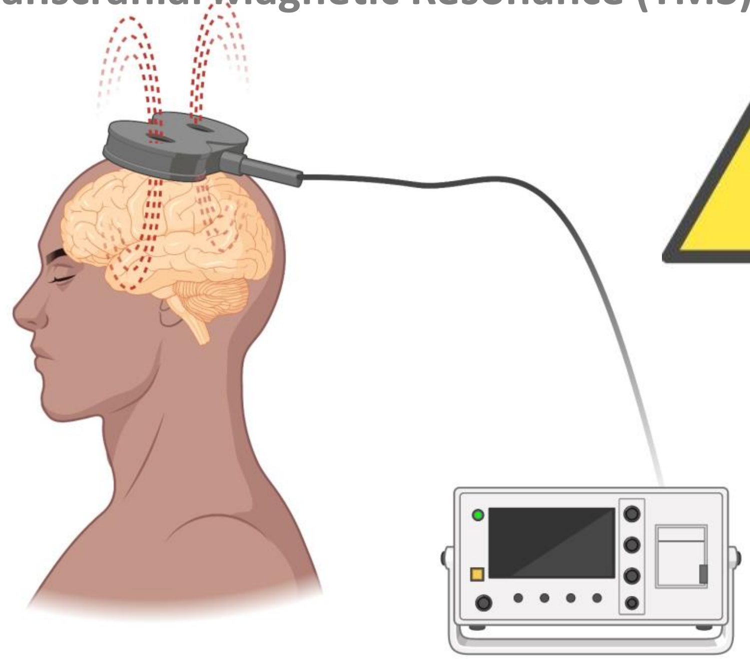
Alternative current
Frequency-dependent effects (Hz)

tRNS

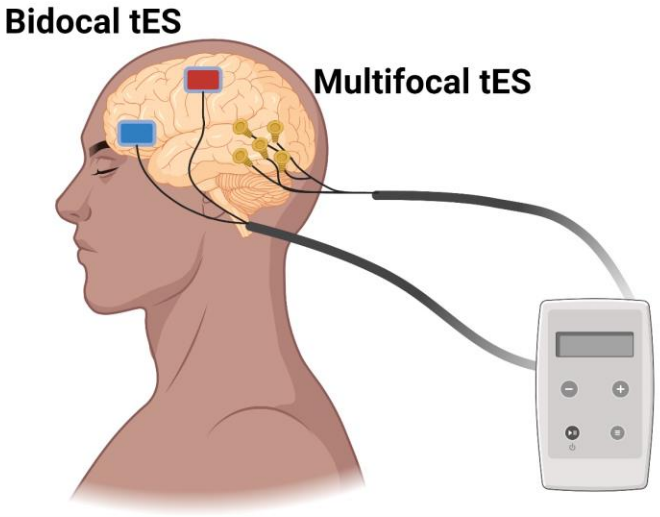
Alternative current
Random frequencies (1-640Hz)

Conventional non-invasive brain stimulation techniques

Transcranial Magnetic Resonance (TMS)

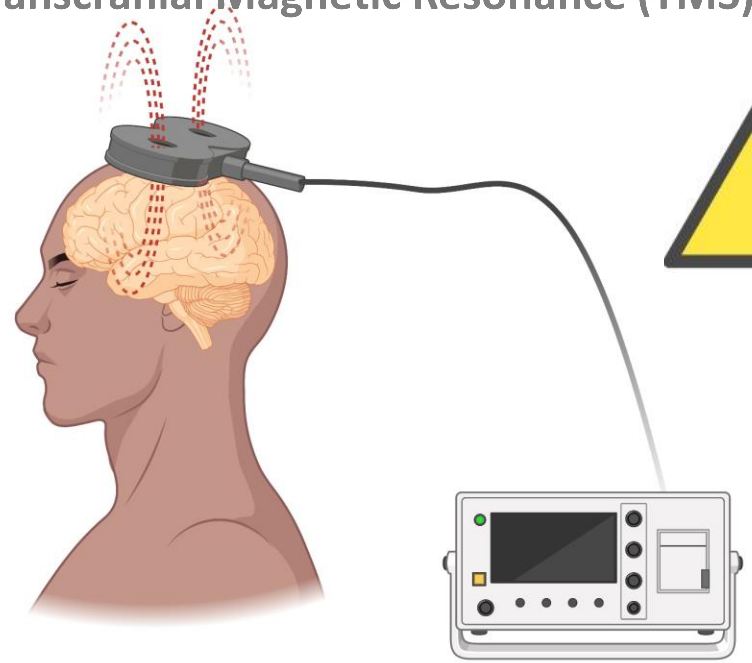


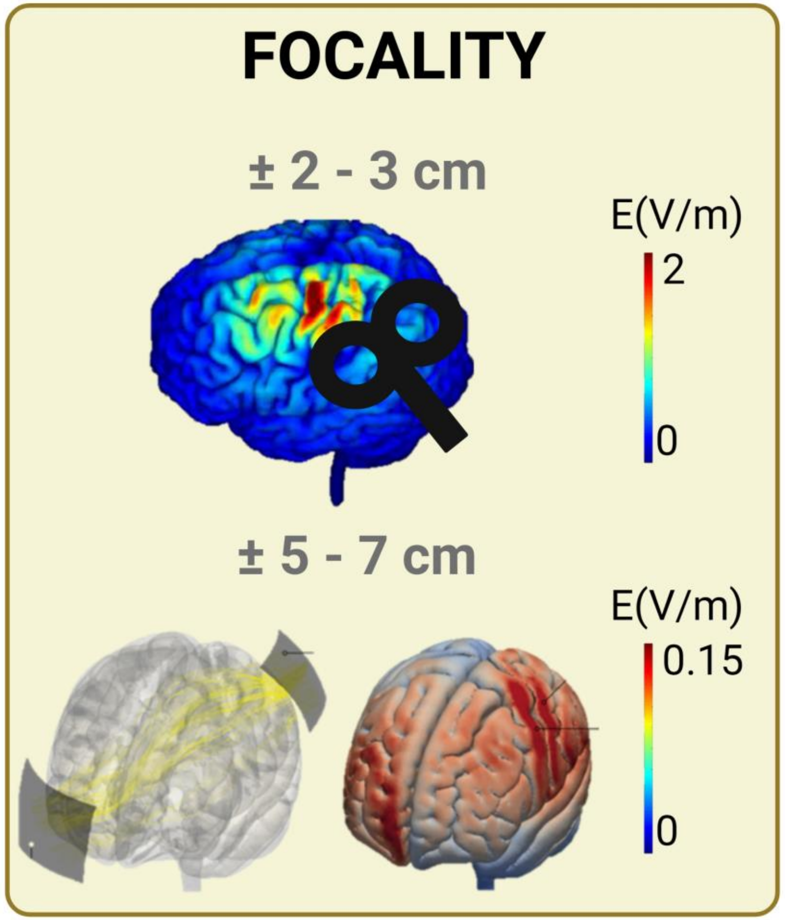
Transcranial Electric stimulation(tES)



Conventional non-invasive brain stimulation techniques

Transcranial Magnetic Resonance (TMS)





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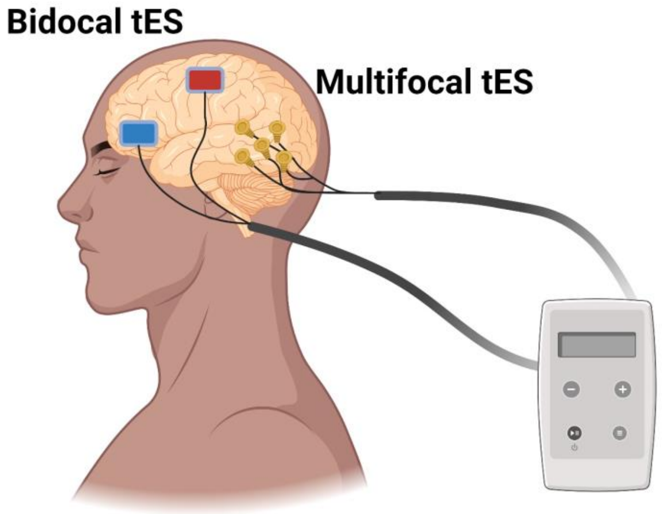
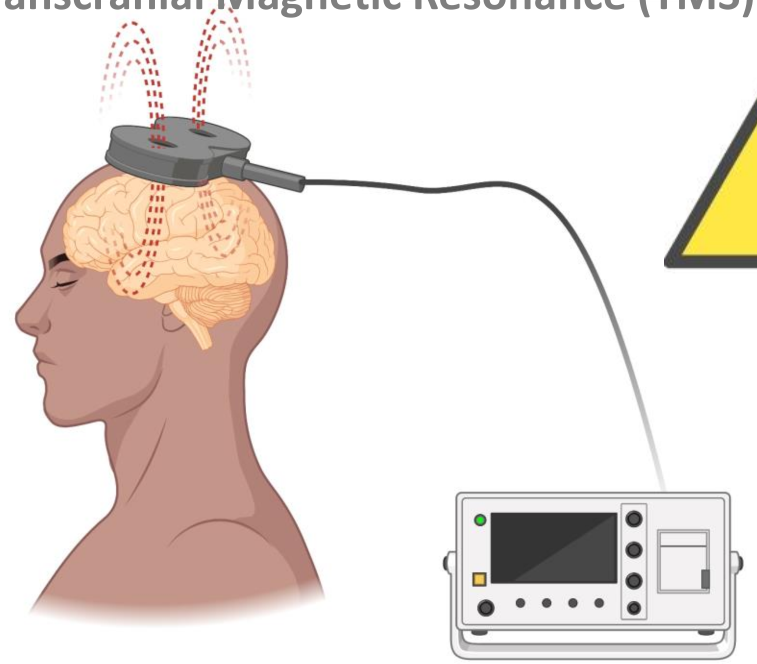


Karabanov, Raffin et al., 2021, Front. Neuro

Transcranial Magnetic Resonance (TMS)



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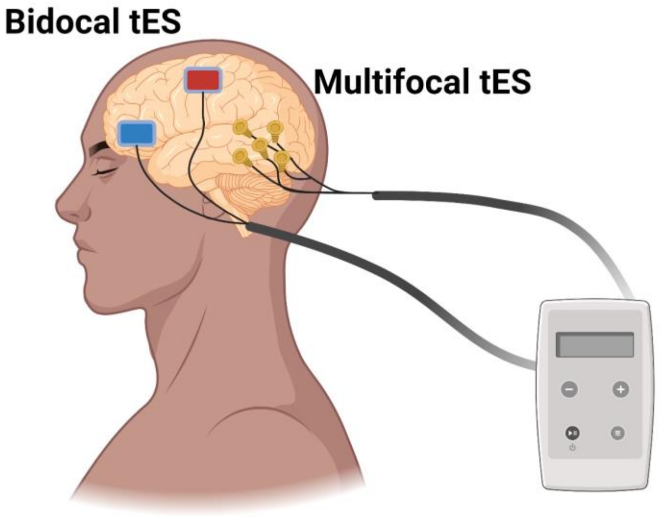
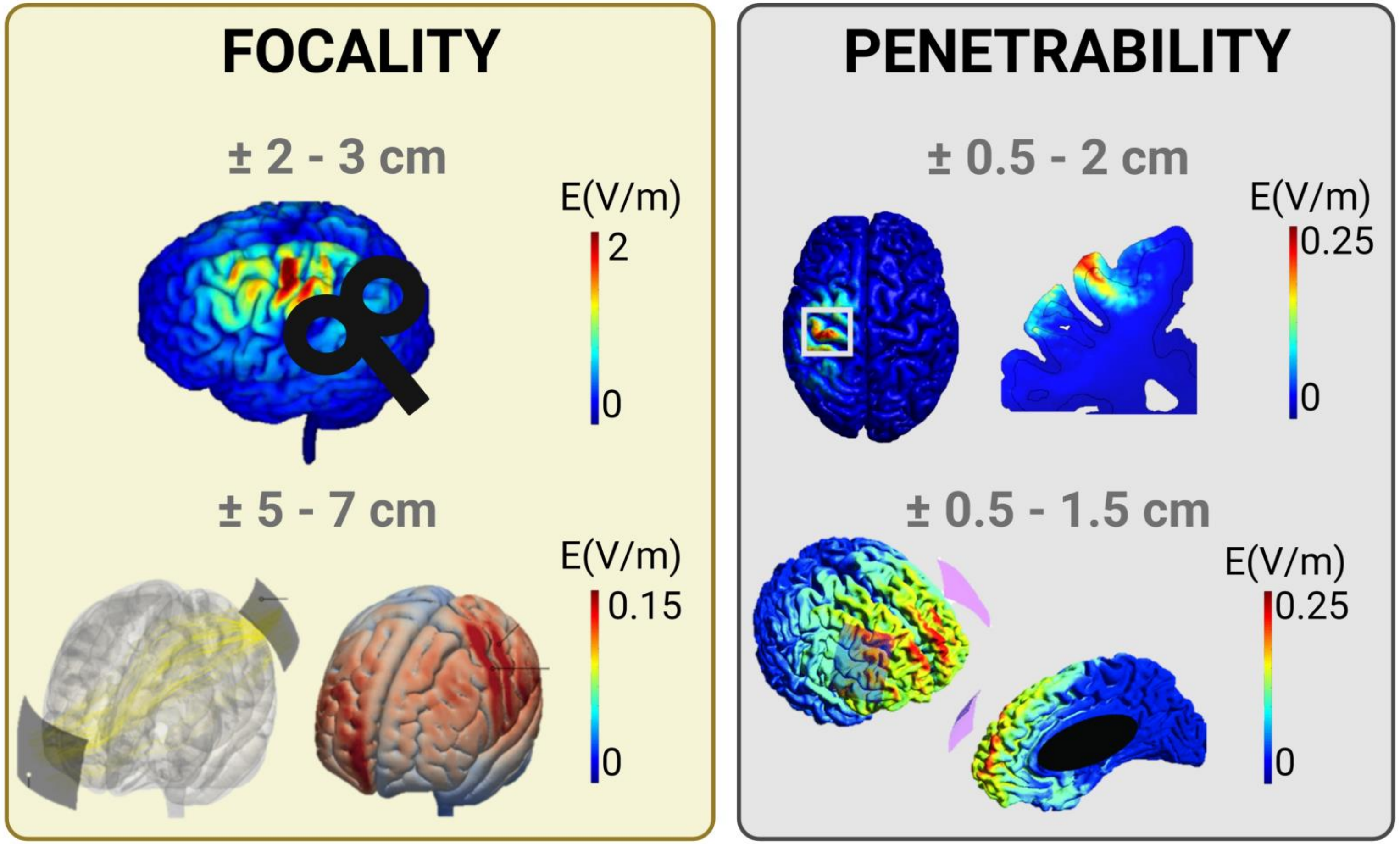
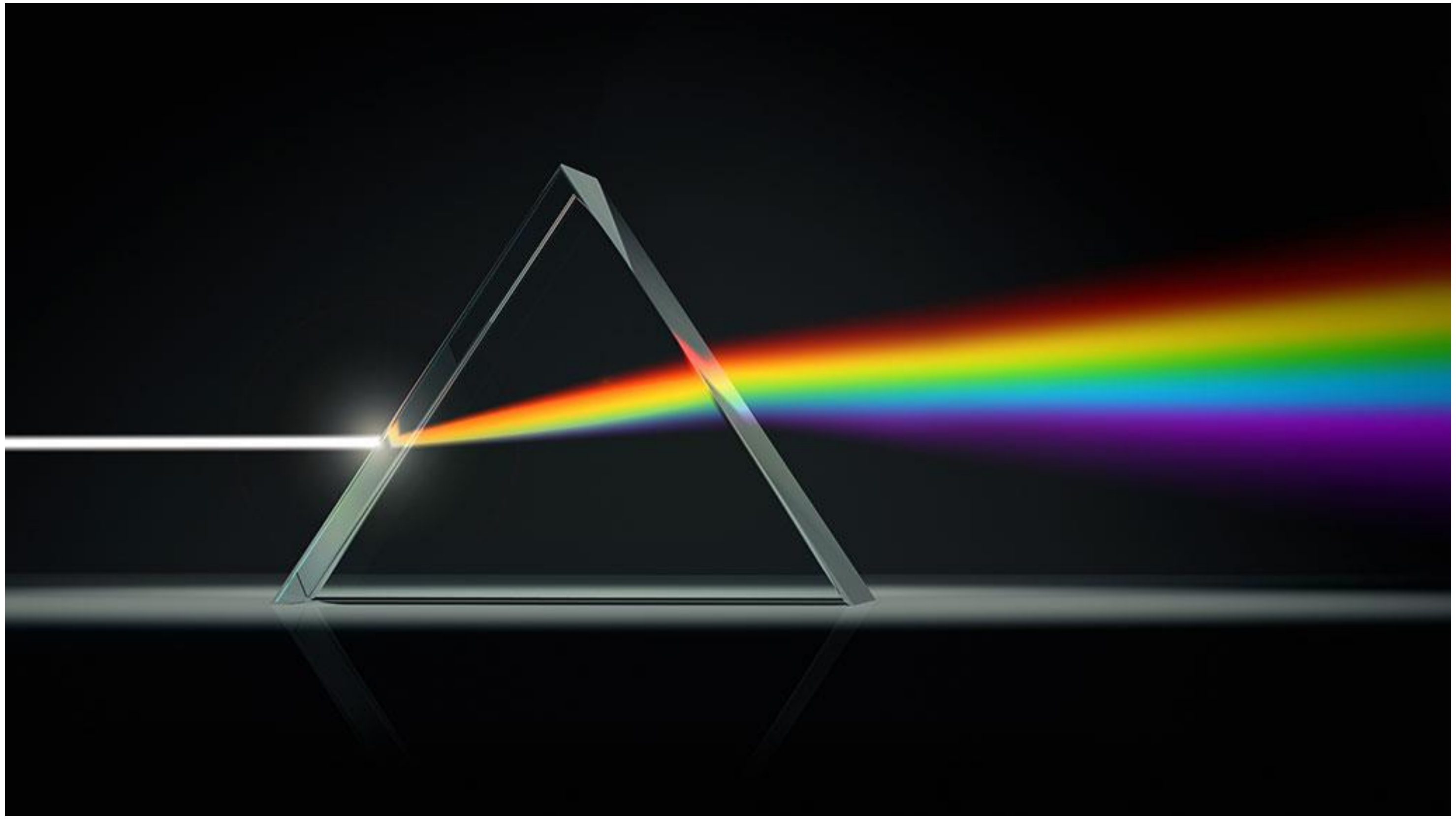




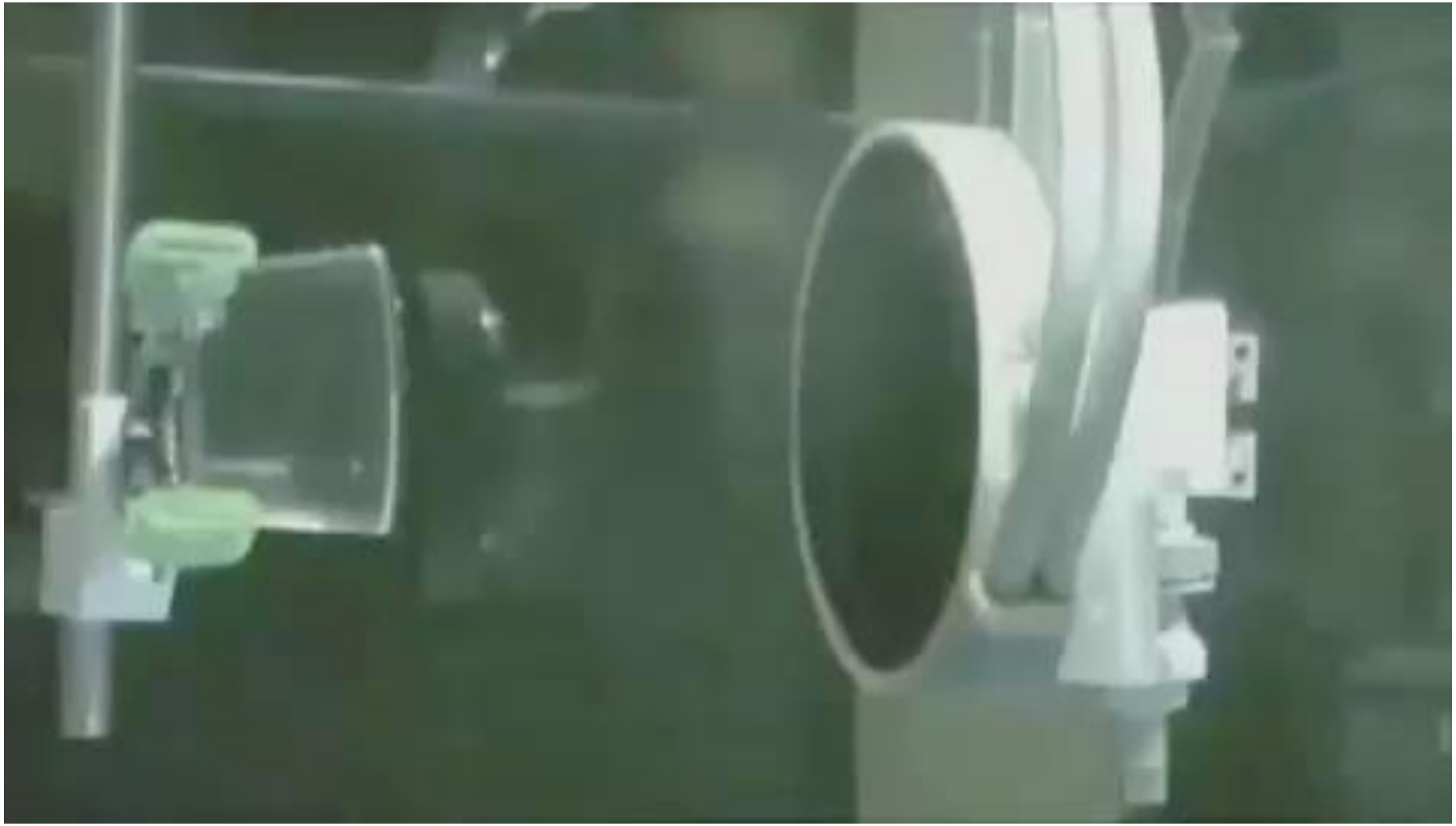
Romero et al., 2019, Nat. Com., Karabanov, Raffin et al., 2021, Front. Neuro

Other opportunities to remotely transfer energy

Other opportunities to remotely transfer energy

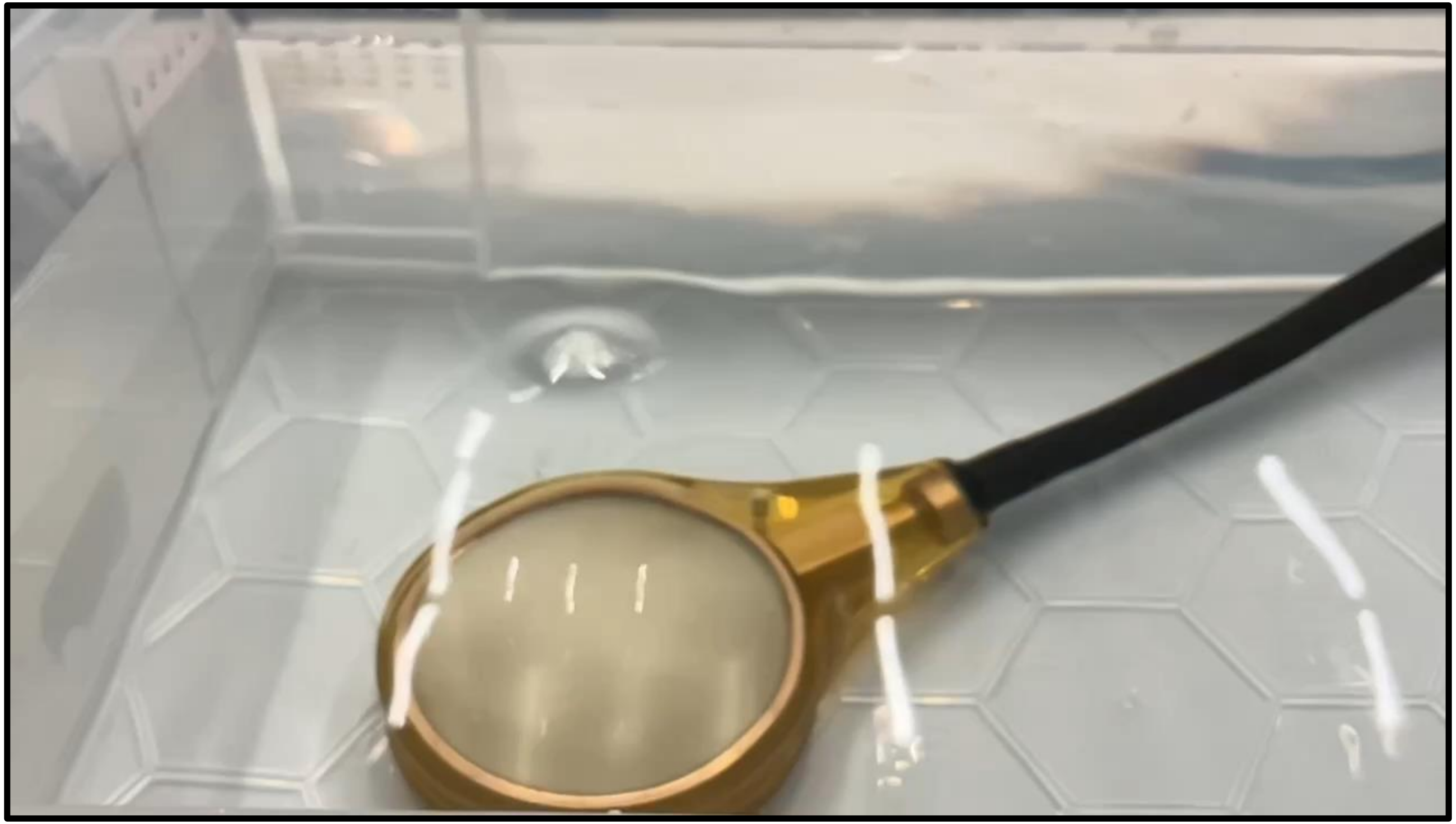


Other opportunities to remotely transfer energy



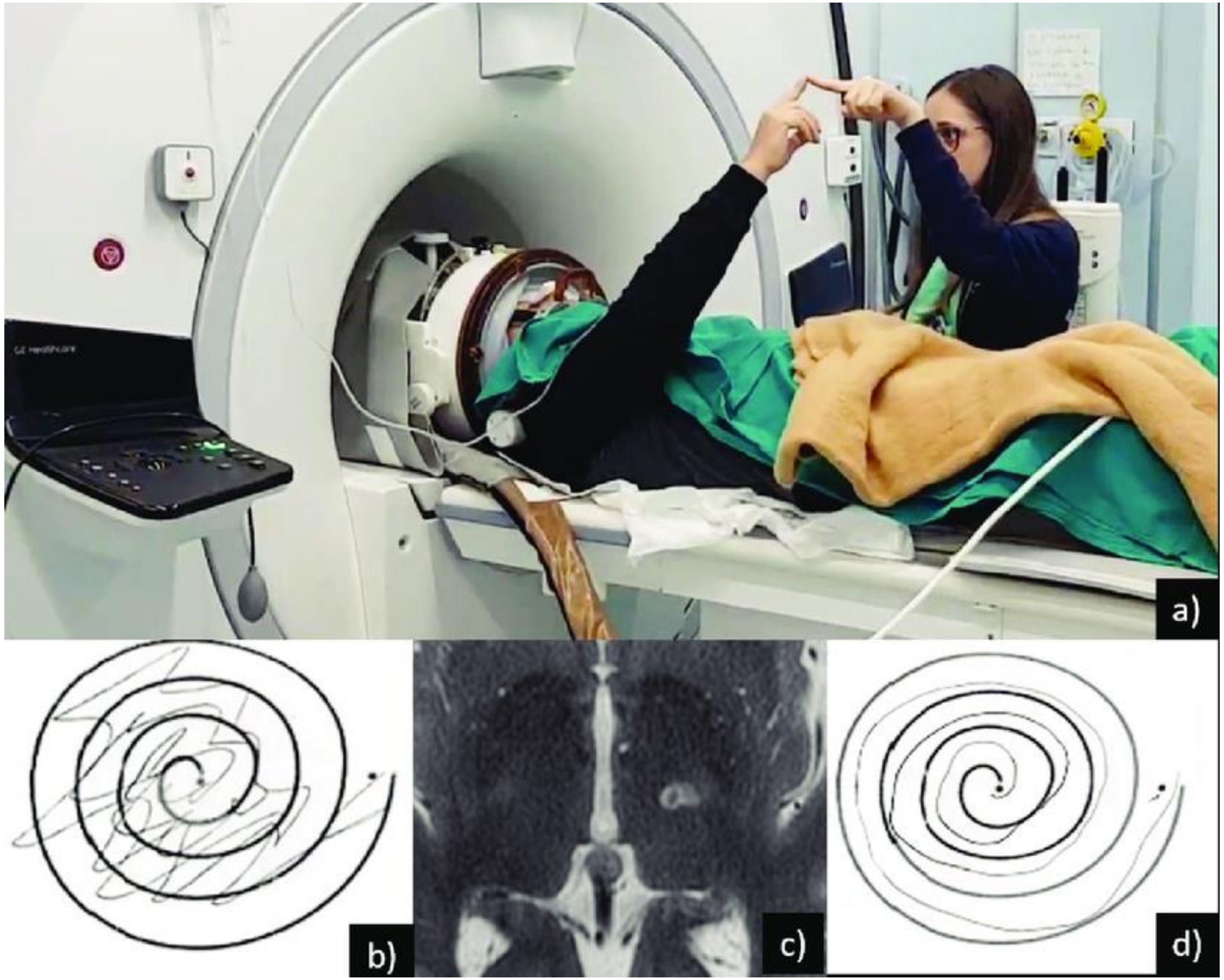
Dr Yoav Medan TEDMED 2011

Sound waves



High-intensity TUS for thalamotomy

Palombo et al., 2021,



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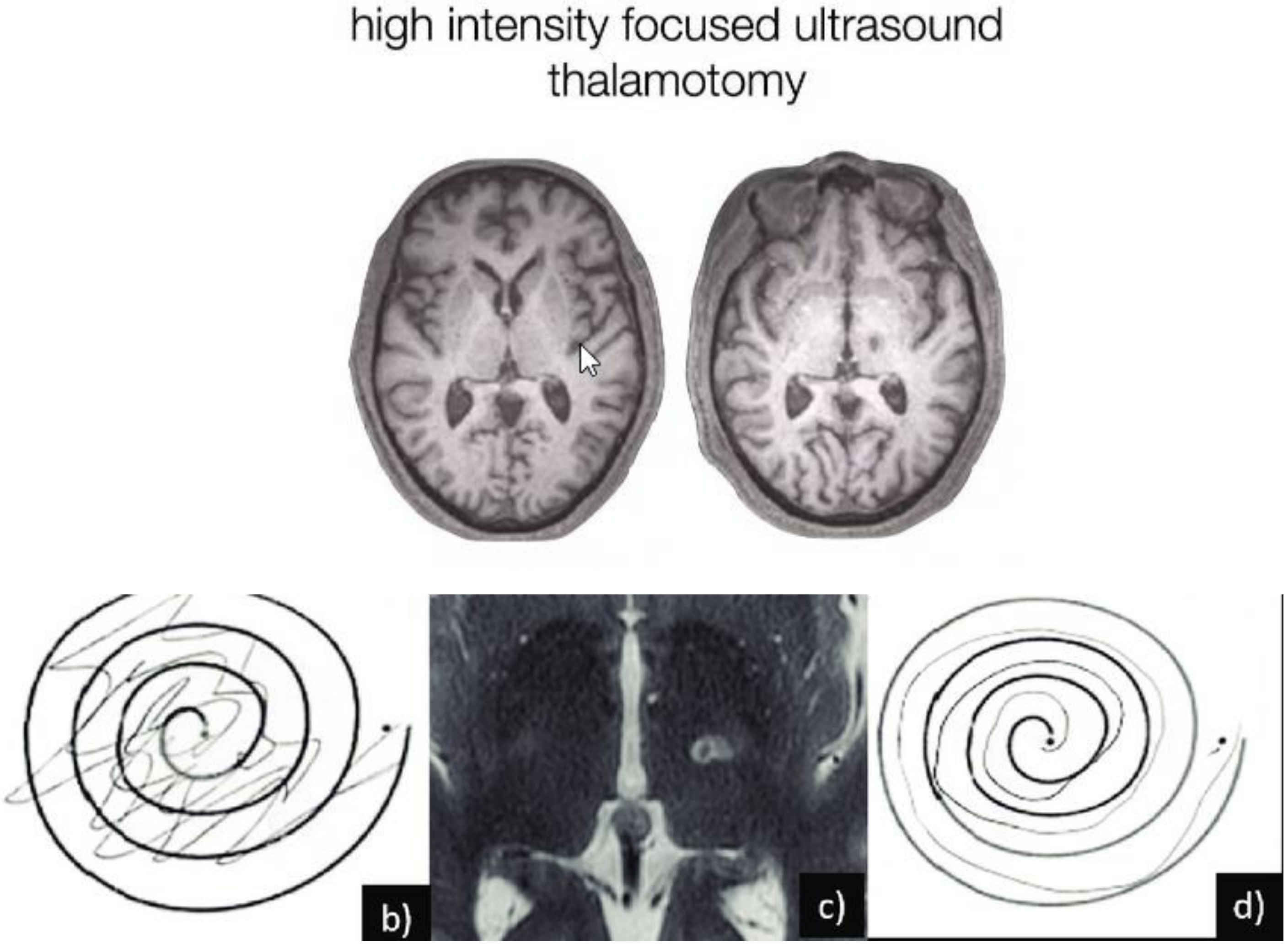


High-intensity TUS

Other 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 od 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

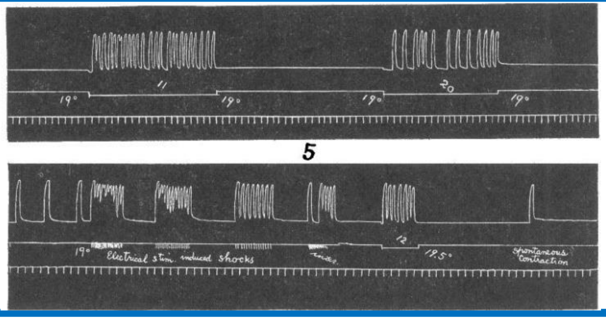
US for neuromodulation

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

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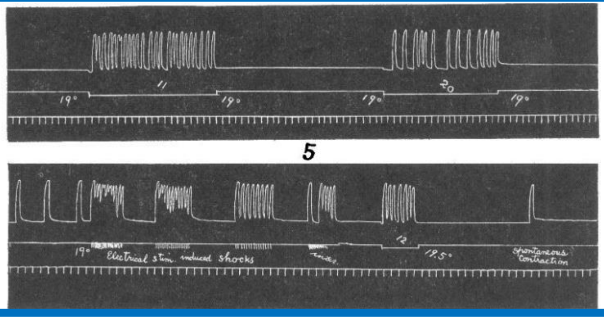

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Science • Volume 127, Issue 3289, Pages 83 - 84 • 1958

Production of reversible changes in the central nervous system by ultrasound

Fry F.J.[a], Ades H.W.[b], Fry W.J.[a]

Save all to author list

[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 | 1950 | 1960-90s | 2010 | 2014

US can excite nerve fibers in isolated turtle and frog muscle

US transiently suppresses amplitude of VEP in cats

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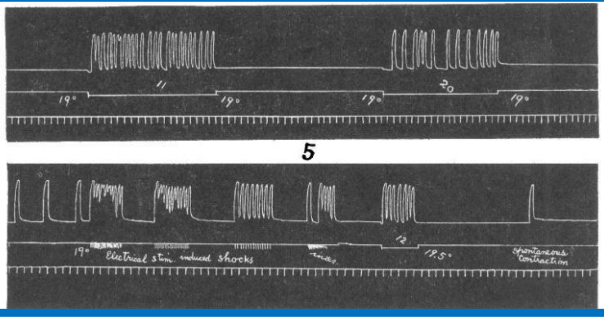

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1929 | **1950** | **1960-90s** | **2010** | **2014**

US can excite nerve fibers in isolated turtle and frog muscle

US transiantly suppresses amplitude of VEP in cats

Stimulation of inner ear structures and auditory nerve

US for neuromodulation

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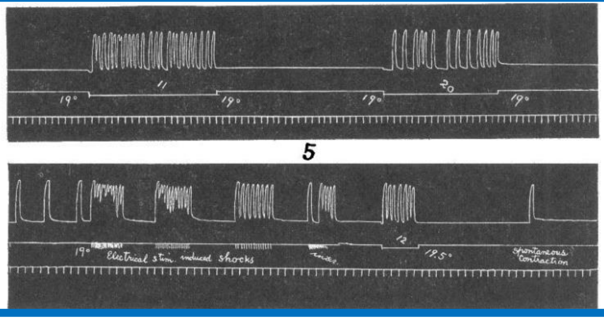

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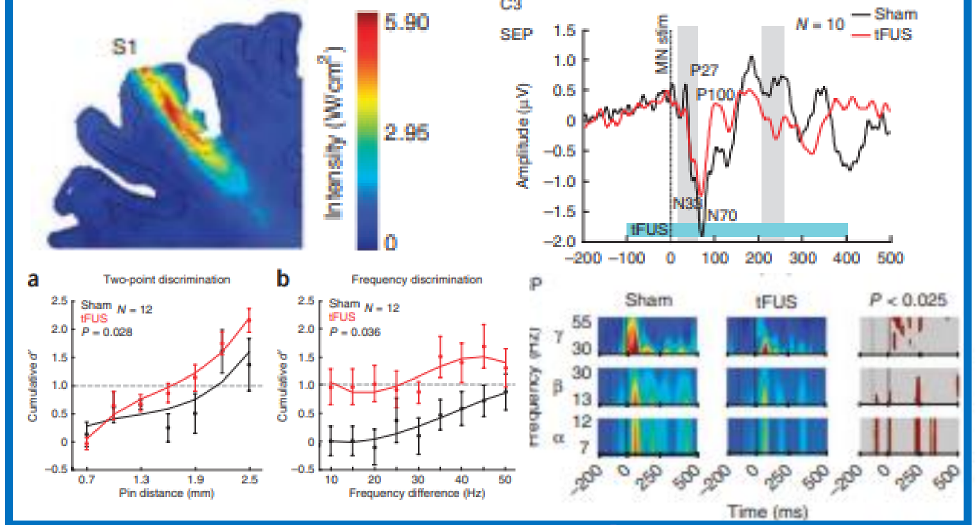
TECHNICAL REPORTS

nature neuroscience

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

Wynn Legon[1], Tomokazu F Sato[1], Alexander Opitz[1,2], Jerel Mueller[3], Aaron Barbour[1], Amanda Williams[1] & William J Tyler[1,3,4]



1929

1950

1960-90s

2010

2014

US can excite nerve fibers in isolated turtle and frog muscle

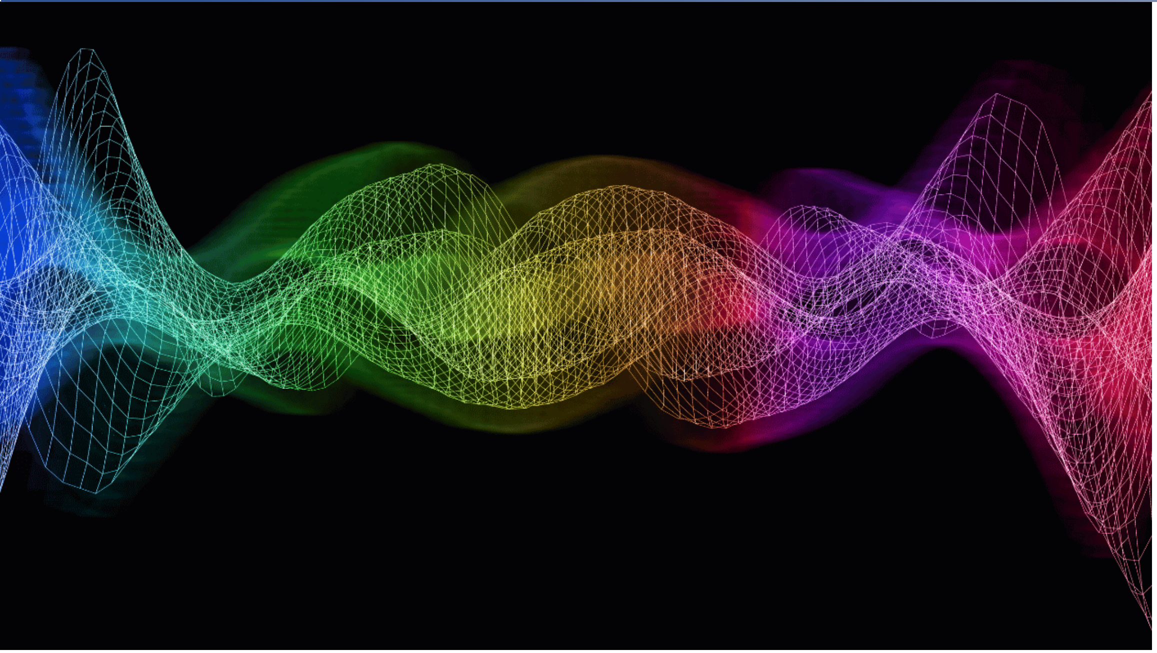
US transiantly suppresses amplitude of VEP in cats

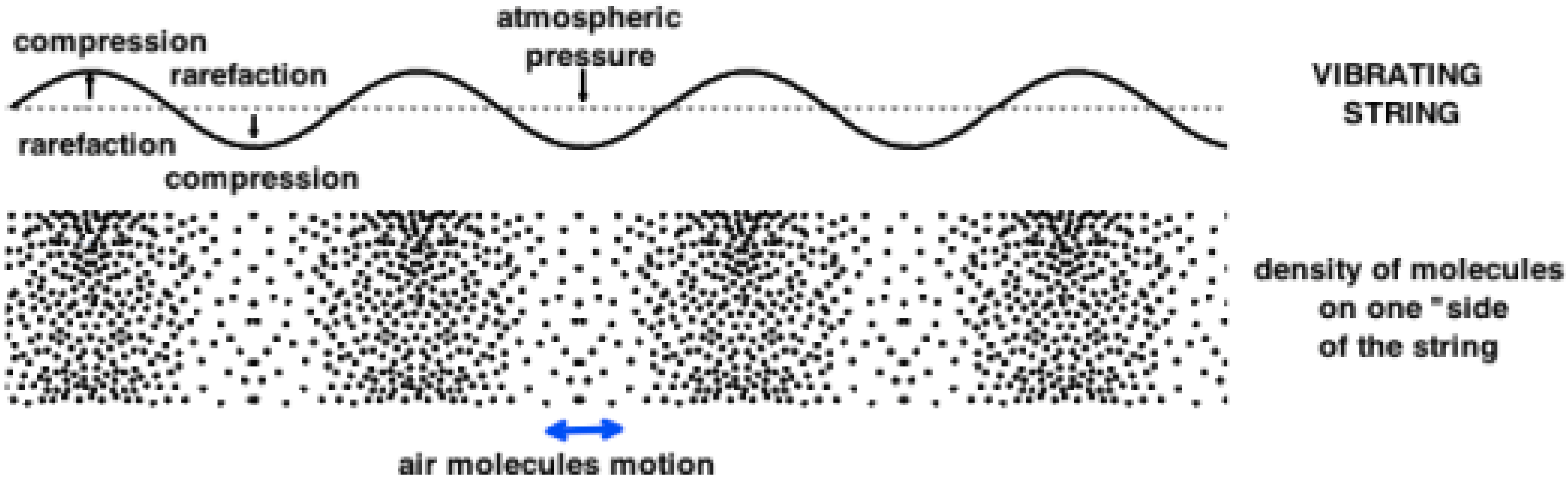
US excited neural activity of hippocampus and motor cortex in rat

US modulates the activity in human S1

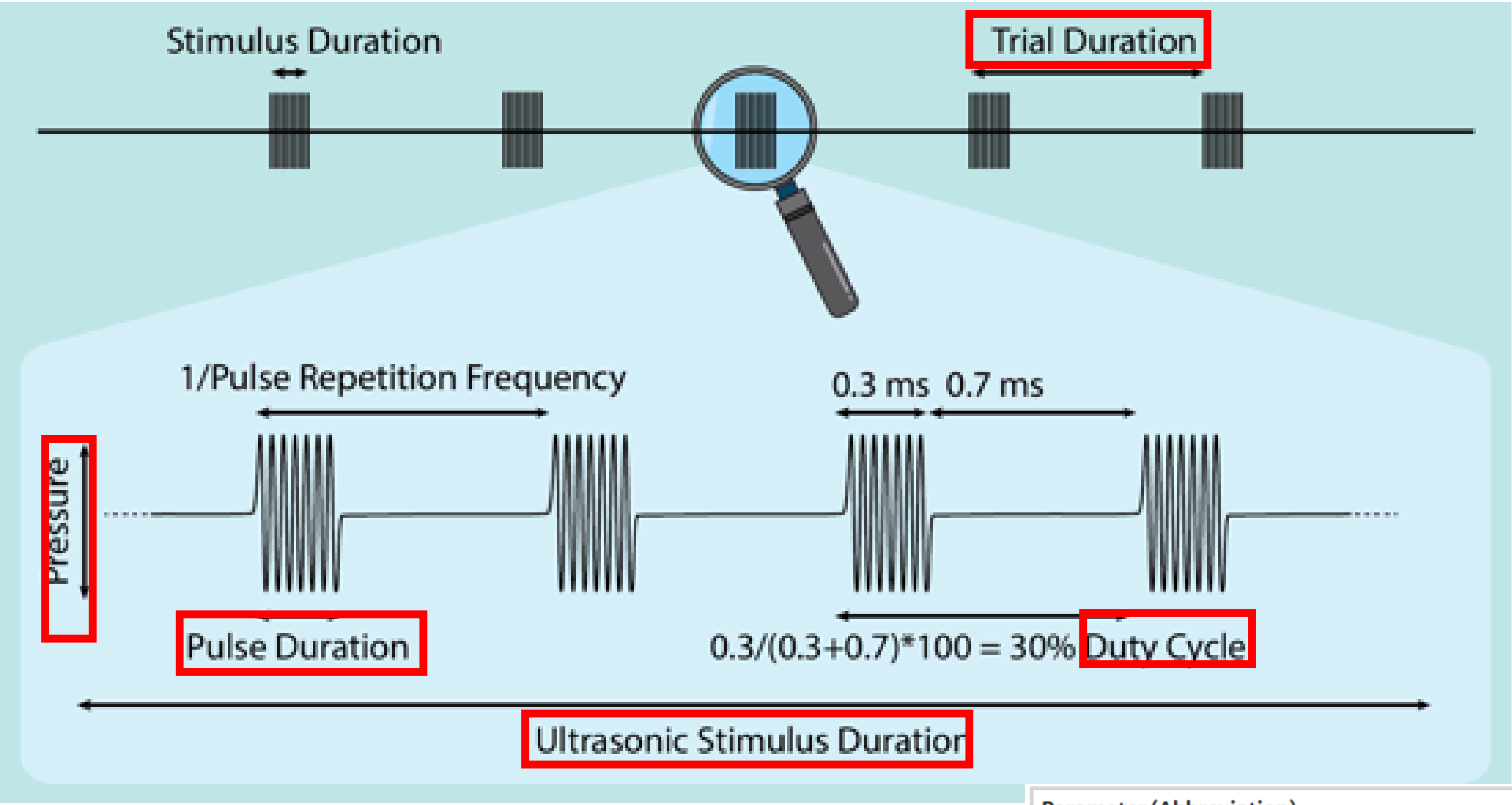
Mechanisms of TUS

US mechanisms



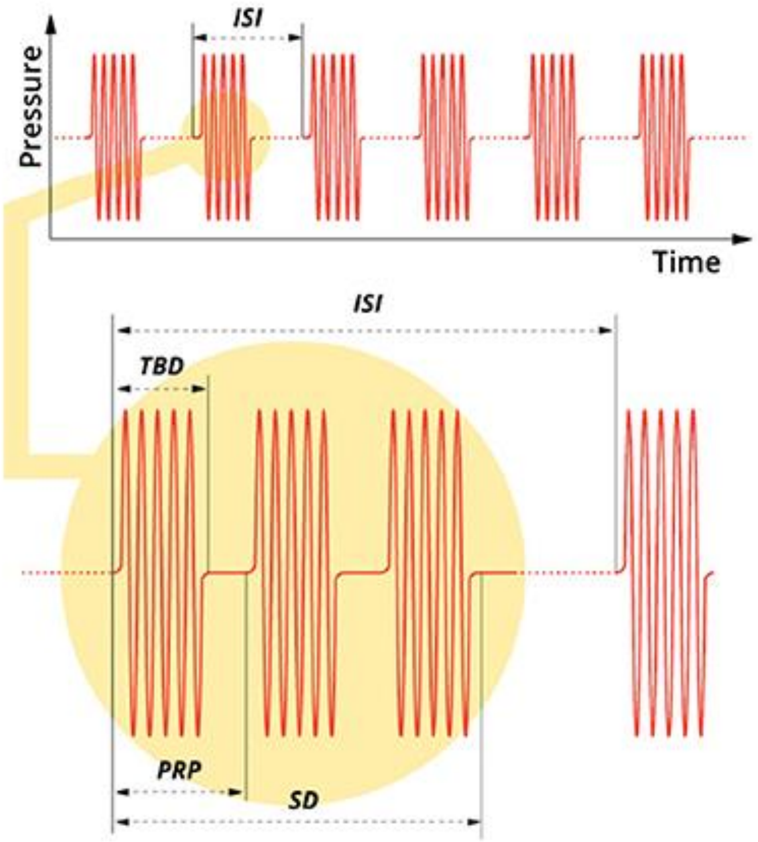


US mechanisms



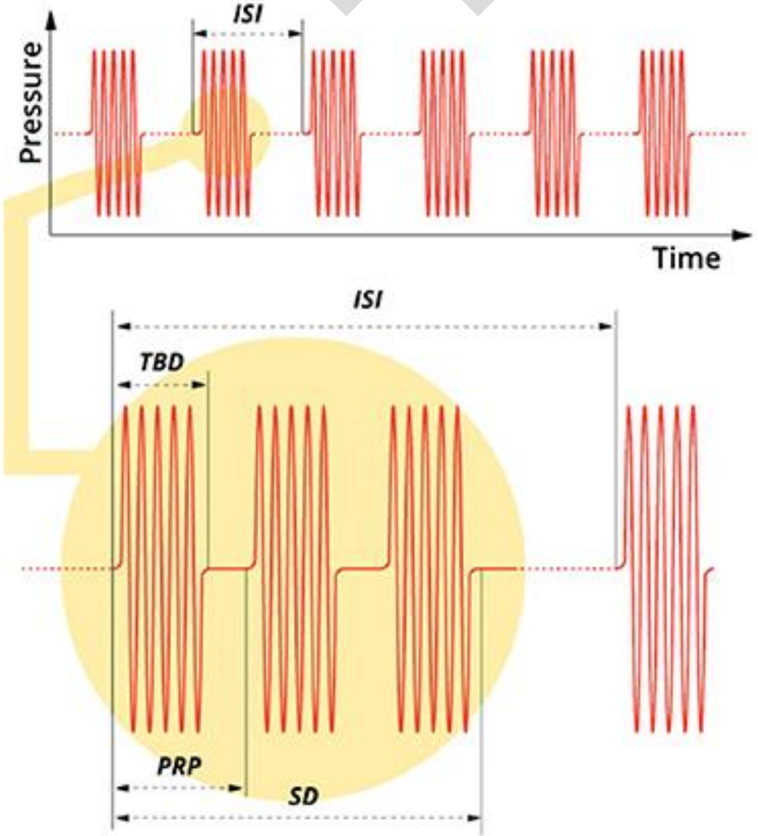
Parameter (Abbreviation)	Unit	Synonym
Fundamental frequency (FF)	kHz, MHz	Center frequency (f_c)
Pulse duration (PD)	ms	Tone burst duration (TBD), Pulse length (PL)
Pulse repetition interval (PRI)	ms	Pulse repetition period (PRP)
Pulse repetition frequency (PRF)	Hz, kHz	-
Duty cycle (DC)	%	Duty factor (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 enveloppe

Fundamental frequency



Acoustic Radiation Force (ARF) ← Amplitude enveloppe   Fundamental frequency ✗

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

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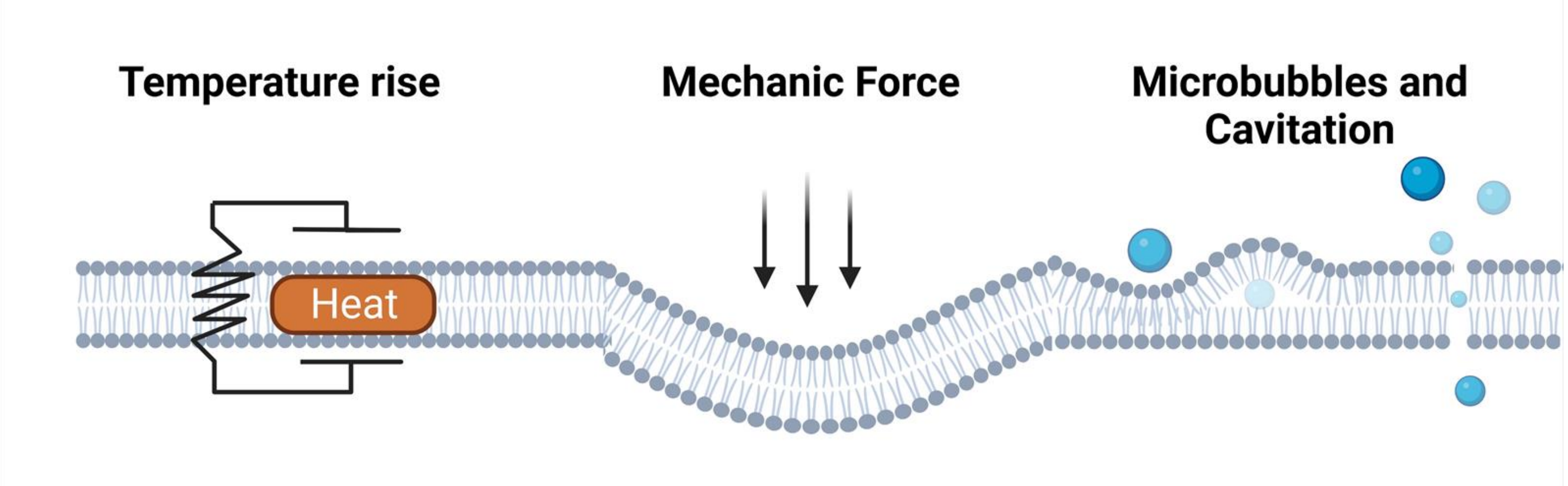

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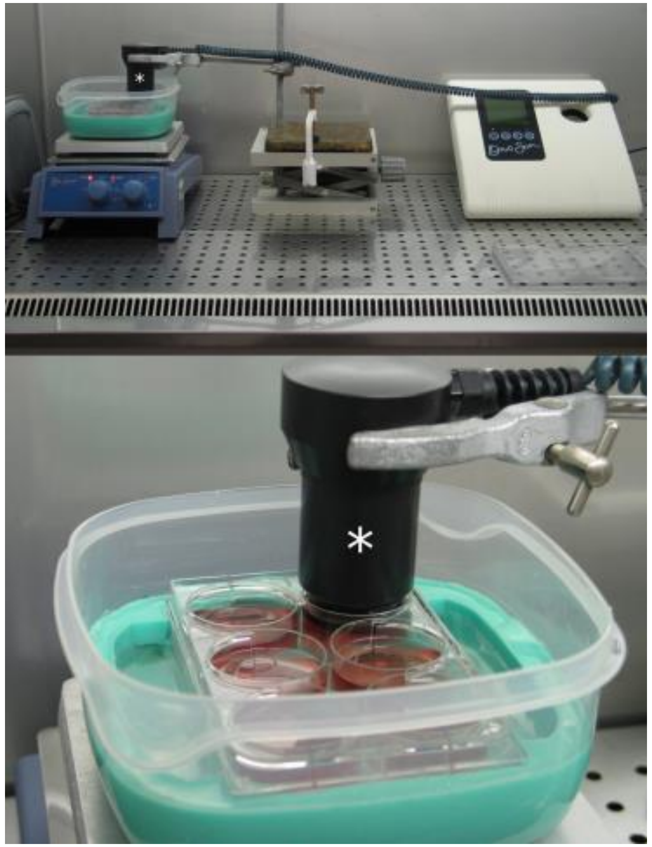

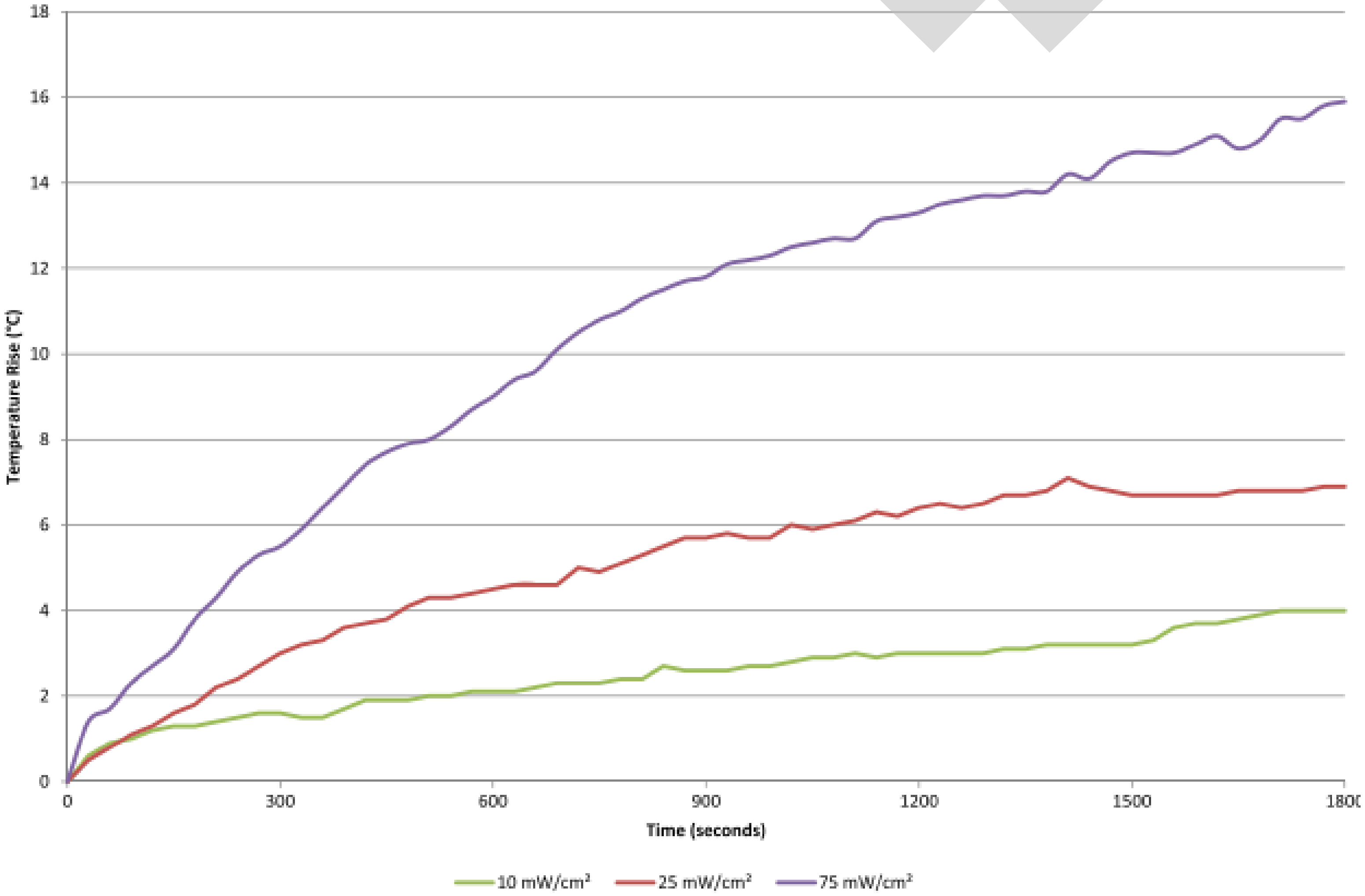

Patel et al., 2015, J Ultrasound therapeutics

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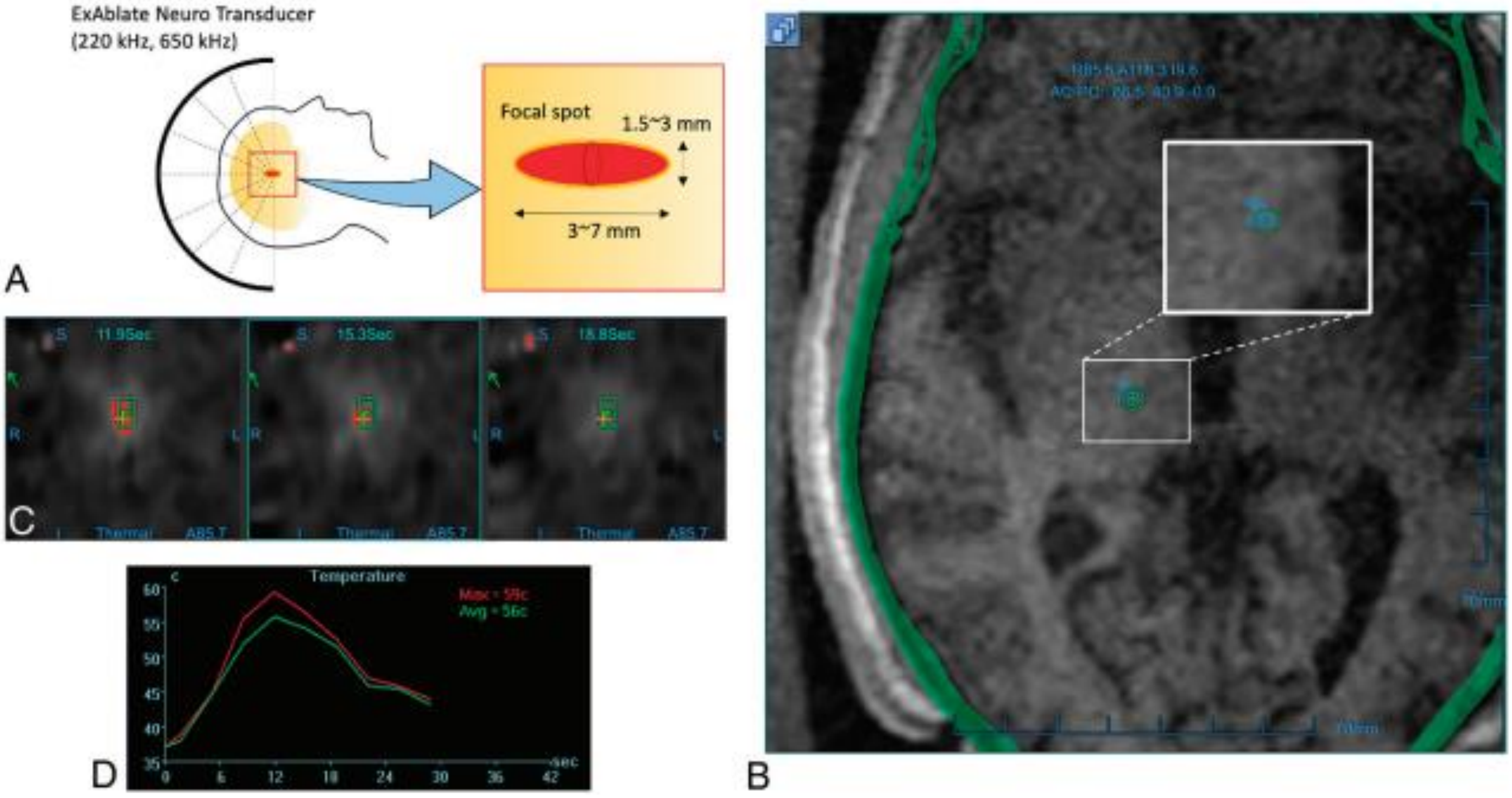
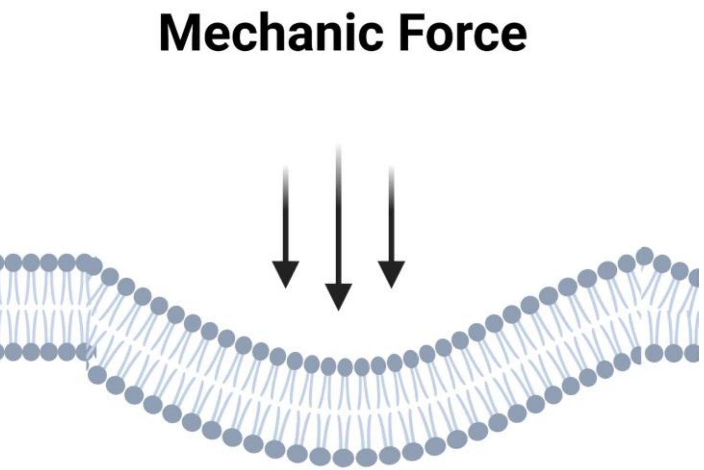


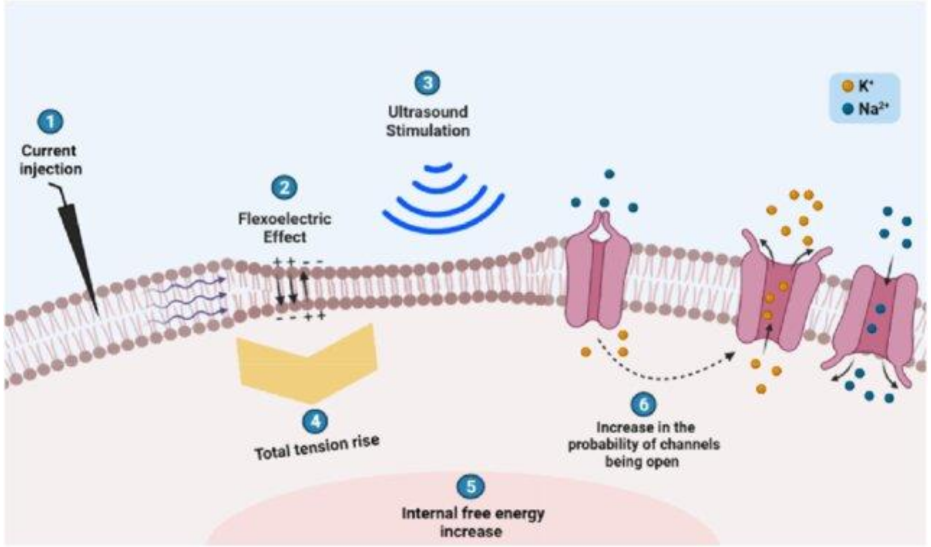
Mattay et al., 2024, AJNR

Acoustic Radiation Force (ARF) ← Amplitude enveloppe   Fundamental frequency

Hypothesis 1: US compresses the neural membrane bilayers and leads to a capacitive current which activates neurons



➔ Flexoelectricity: curvature-induced membrane polarization

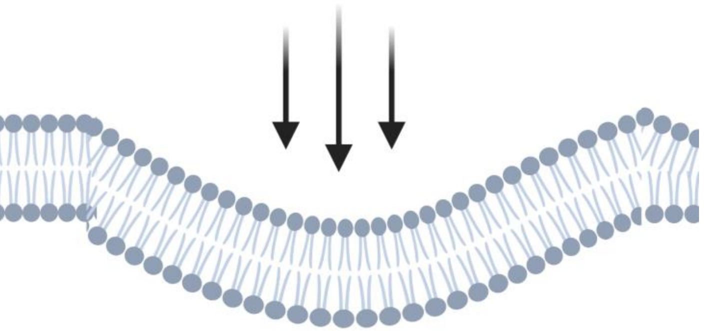


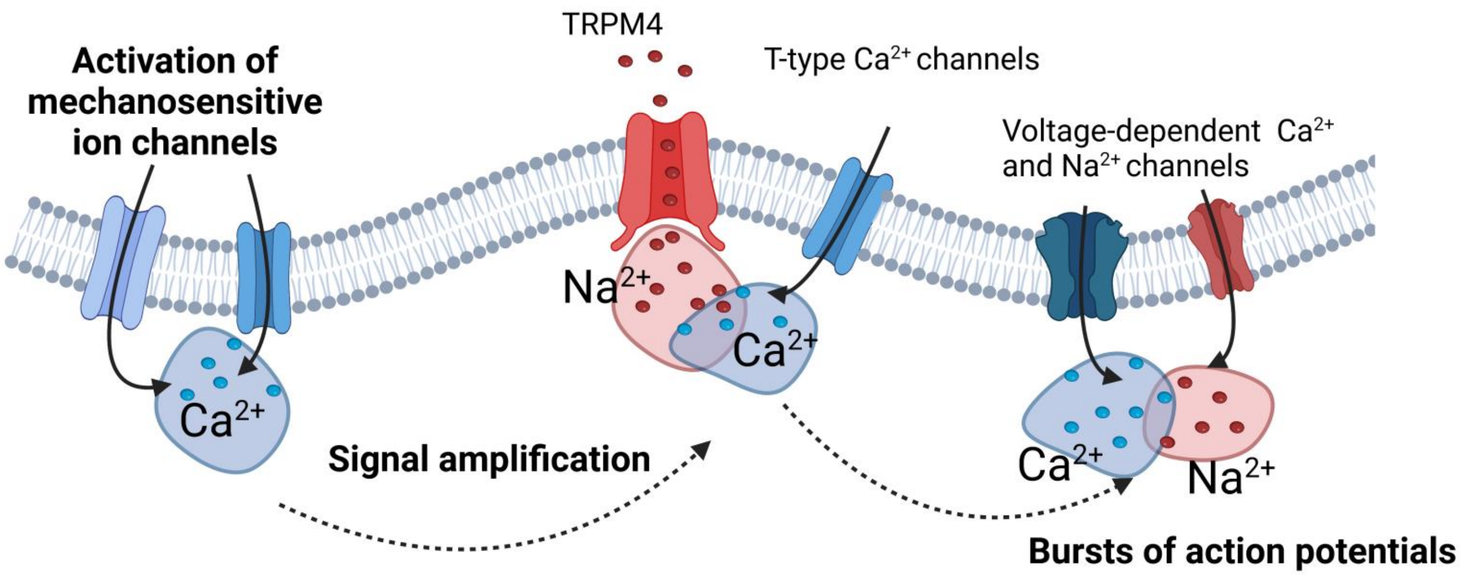
Badawe, 2023, Helyon

Acoustic Radiation Force (ARF) ← Amplitude enveloppe Fundamental frequency

Hypothesis 2: US indirectly manipulates mechanosensitive calcium channels in the membrane

Mechanic Force

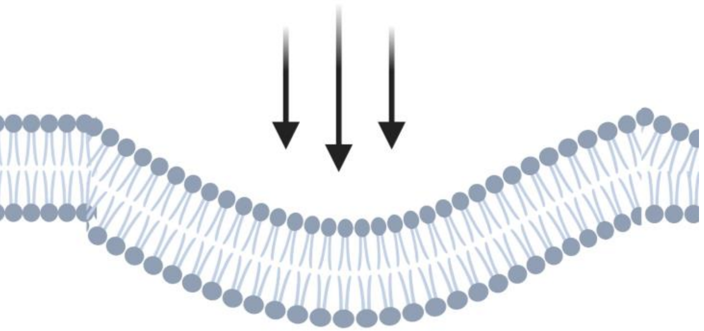


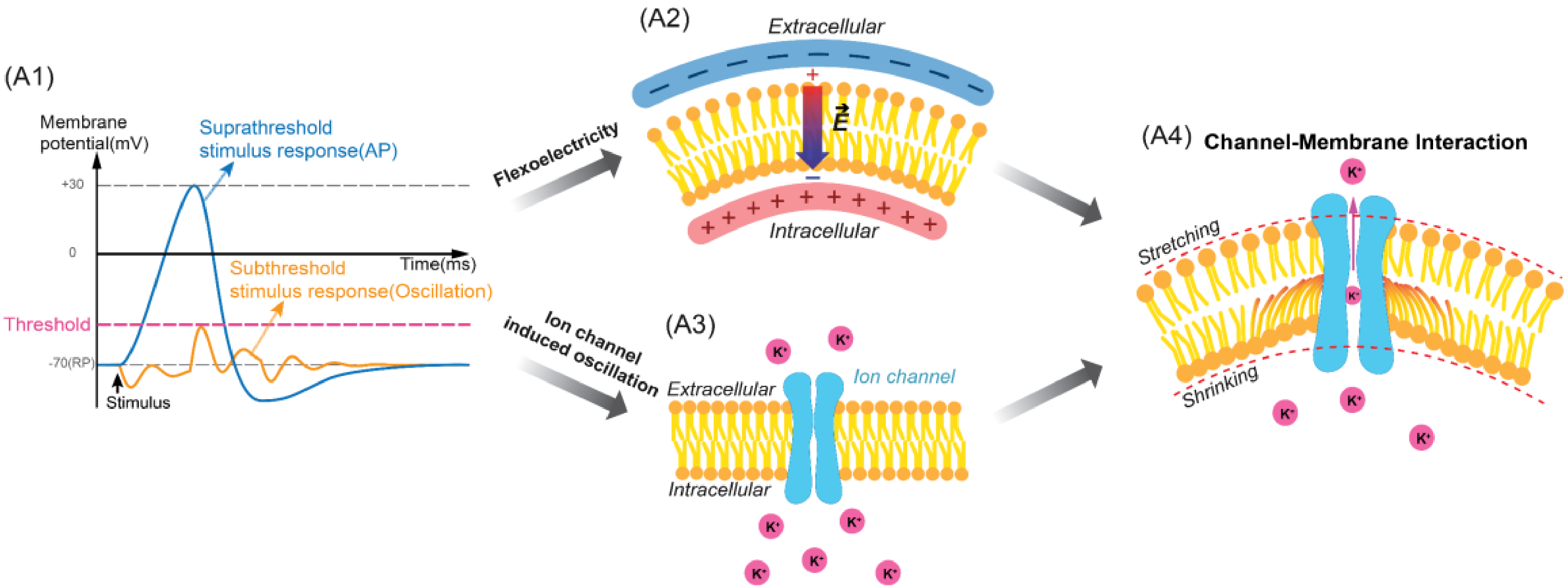


Acoustic Radiation Force (ARF) ← Amplitude enveloppe ~~Fundamental frequency~~

The Channel-membrane interaction (CMI) hypothesis

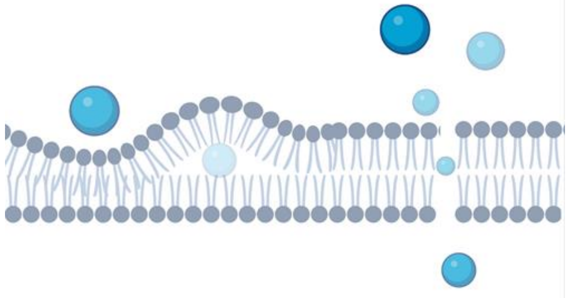
Mechanic Force

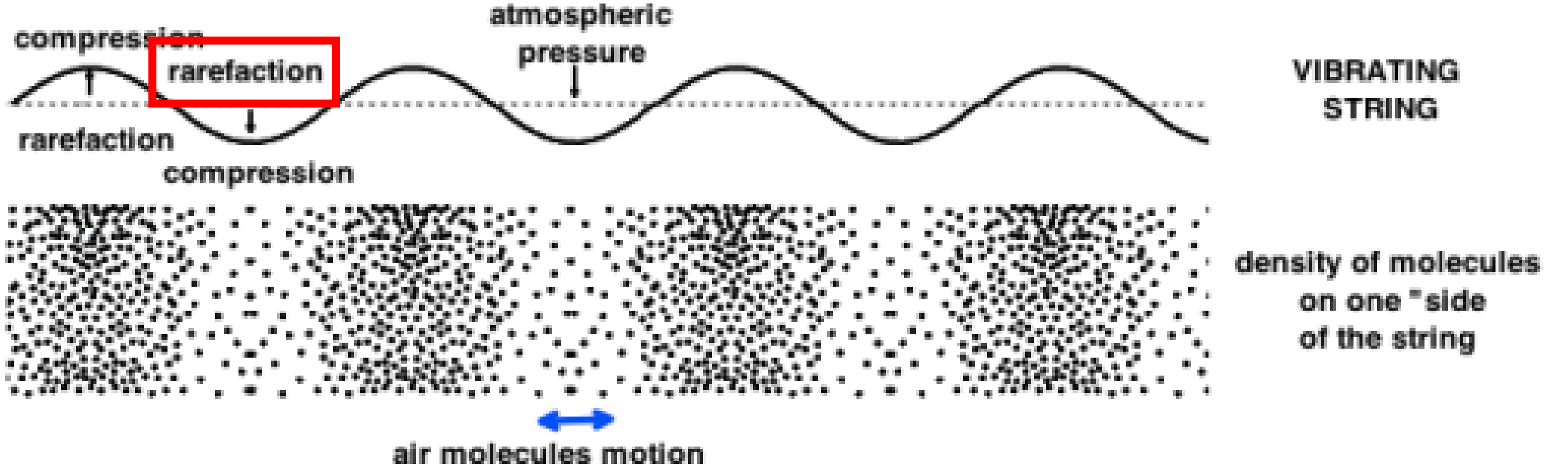




Acoustic Radiation Force (ARF) ← Amplitude enveloppe   Fundamental frequency

Microbubbles and Cavitation





➔ Caused by the ultrasonic **negative pressure** during the rarefaction phase of an acoustic wave propagation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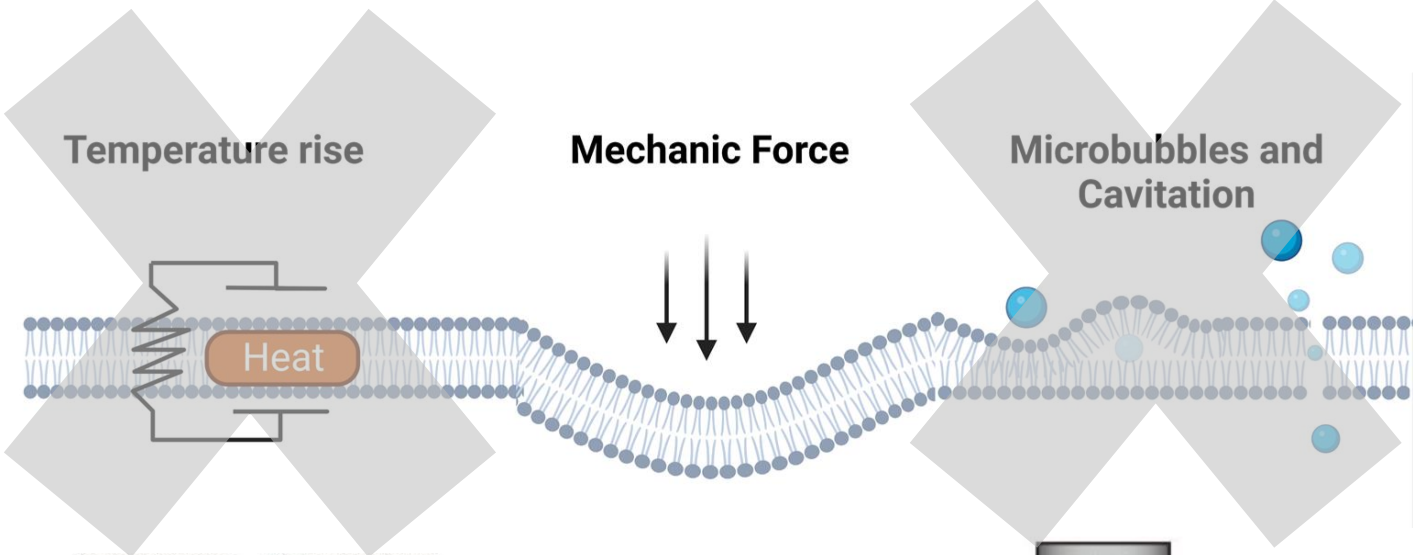
SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

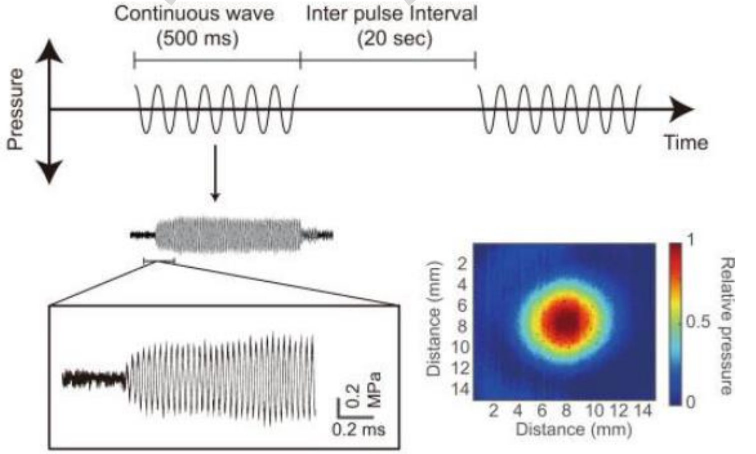
ORIGINAL ARTICLE | BRIEF REPORT

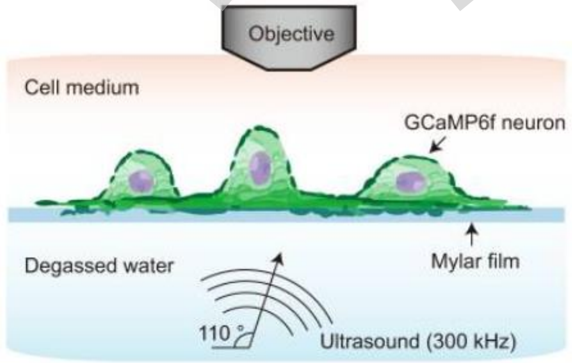
Ultrasound Blood–Brain Barrier Opening and Aducanumab in Alzheimer's Disease

Authors: Ali R. Rezai, 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., +8, and Marc W. Haut, Ph.D. Author Info & Affiliations

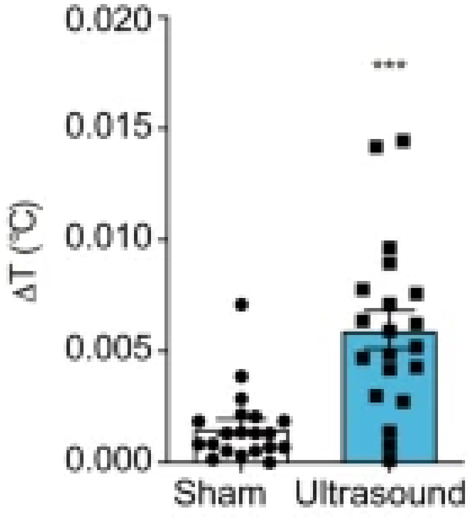
Published January 3, 2024 | N Engl J Med 2024;390:55-62 | DOI: 10.1056/NEJMoa2308719 | VOL. 390 NO. 1



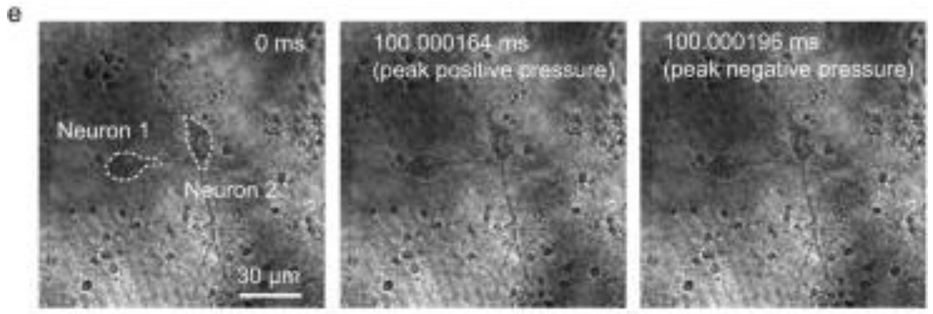




Fiber optic thermometer

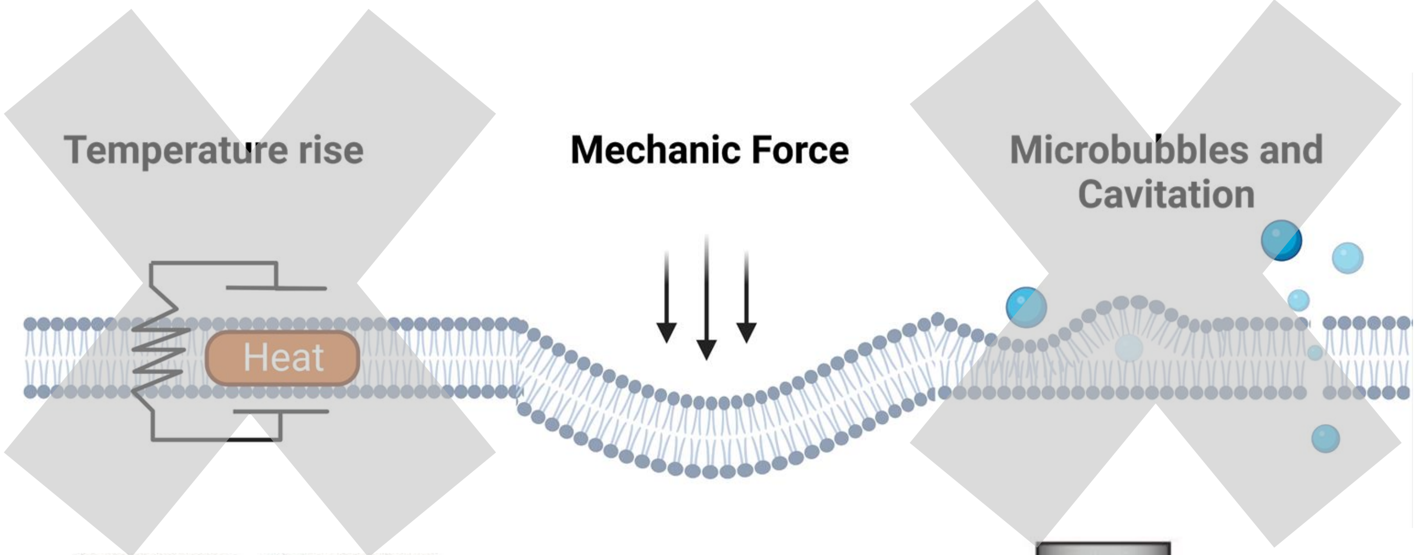


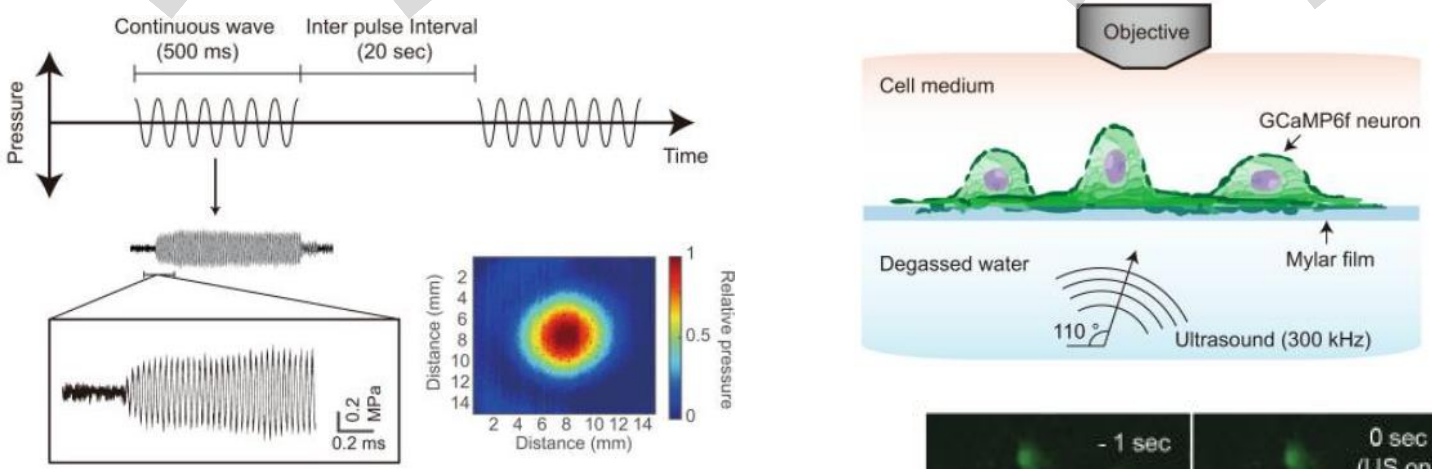
Fiber optic thermometer & Ultra-high speed camera



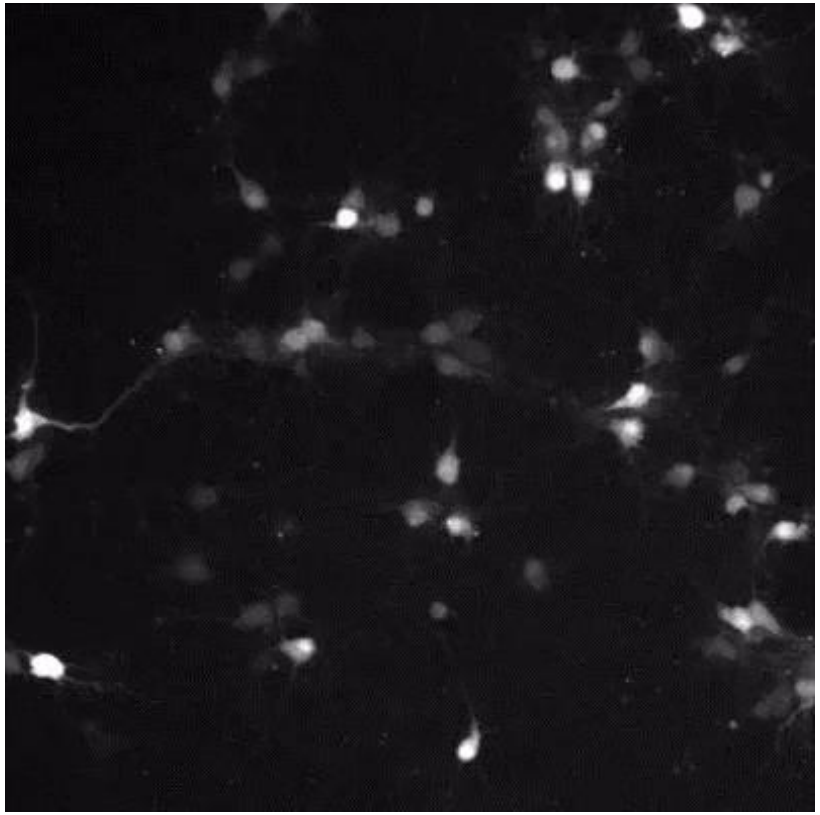
Yoo et al., 2022

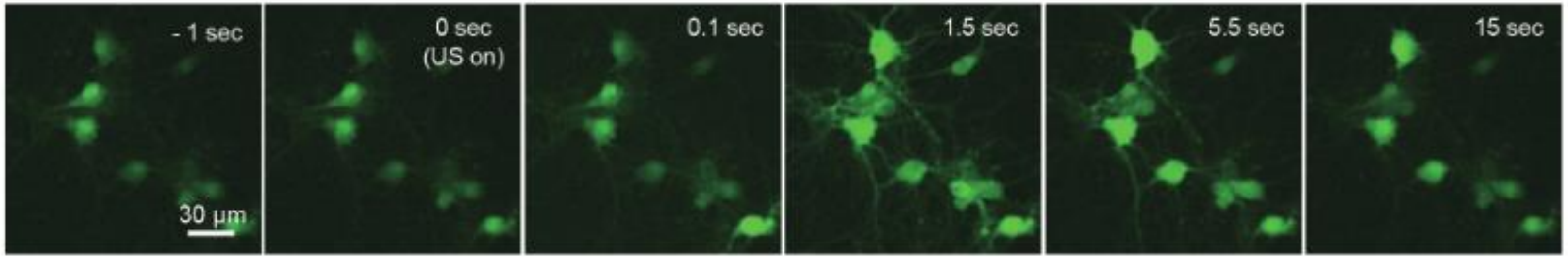
US mechanisms





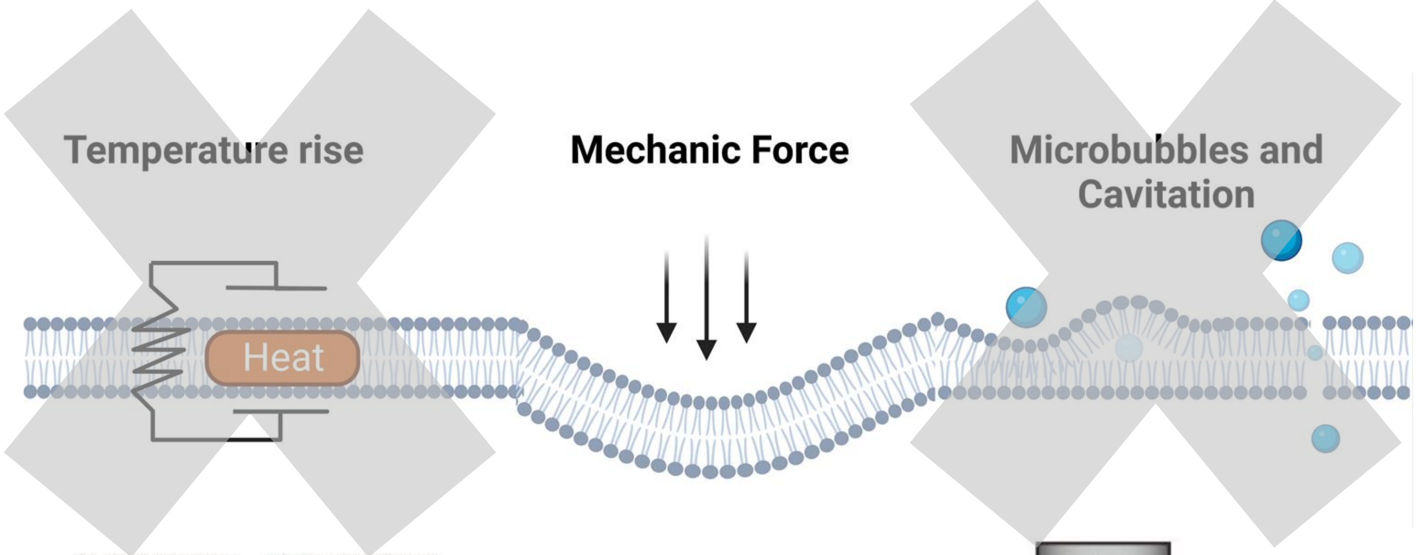
Neural calcium response, recorded by epifluorescence imaging

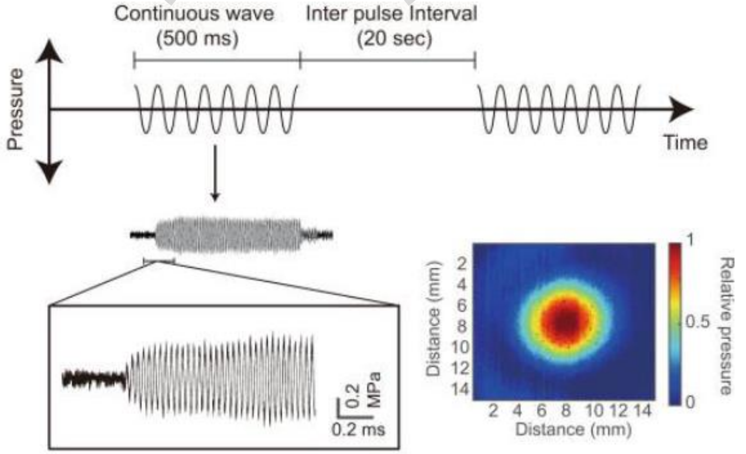


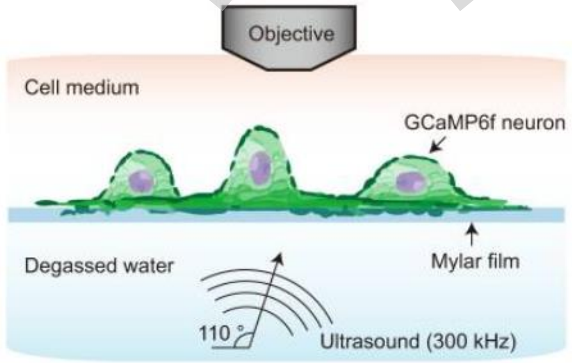


Yoo et al., 2022

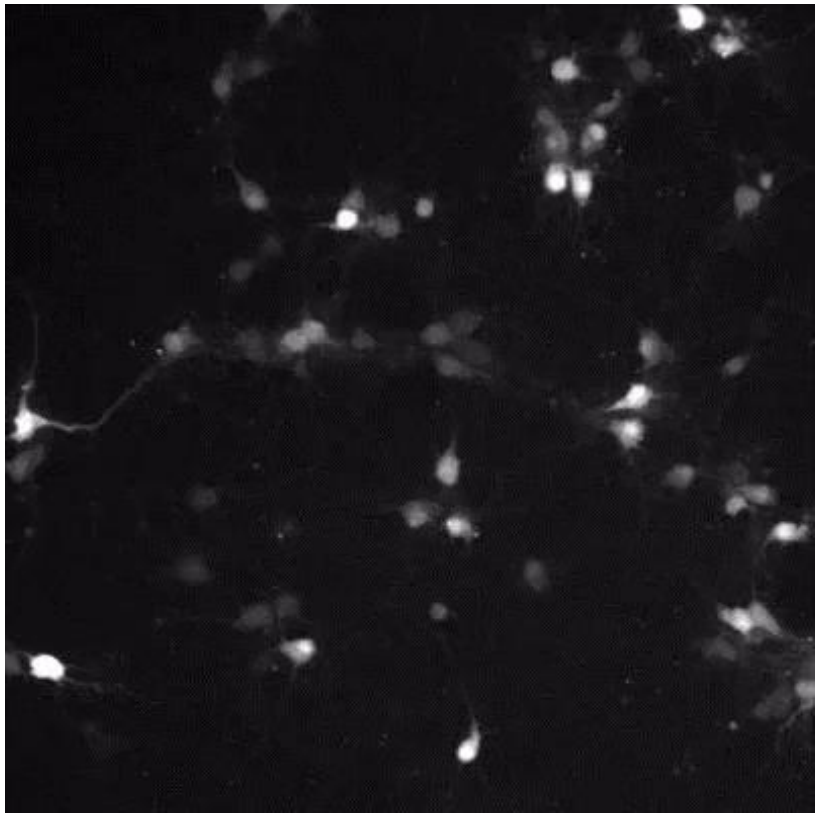
US mechanisms

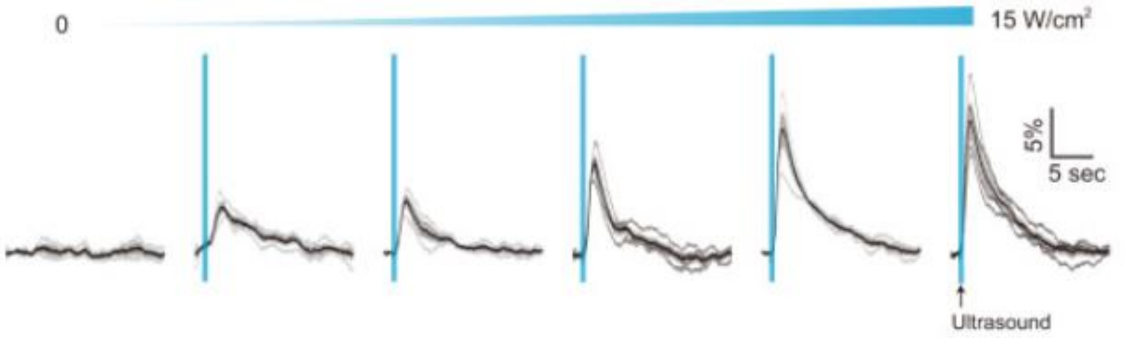






Neural calcium response, recorded by epifluorescence imaging

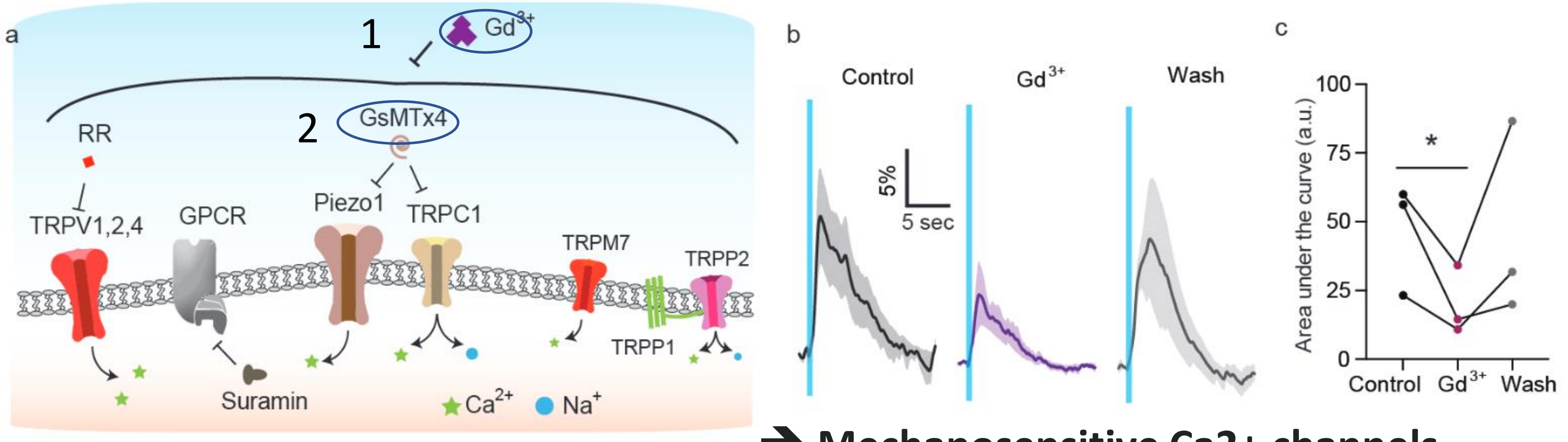




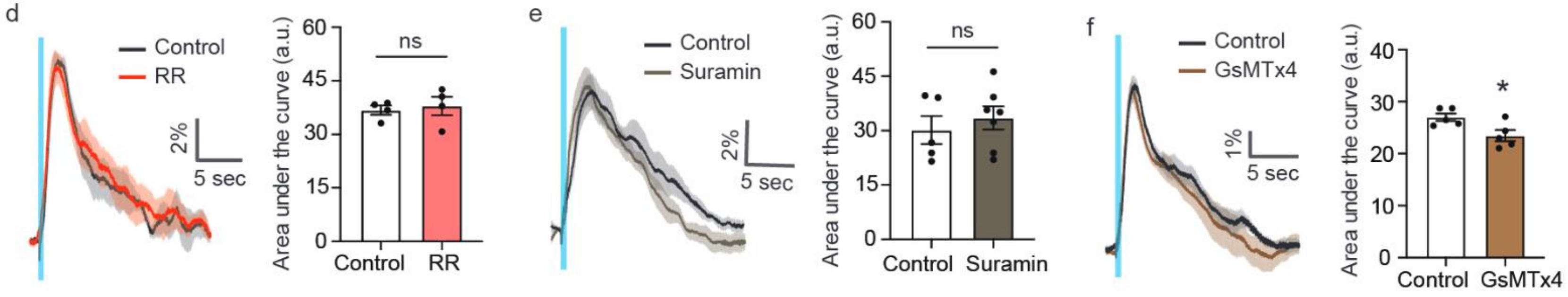
Quantification of calcium responses as function of ultrasound intensity

Yoo et al., 2022

Pharmacological inhibition of mechanosensitive receptors

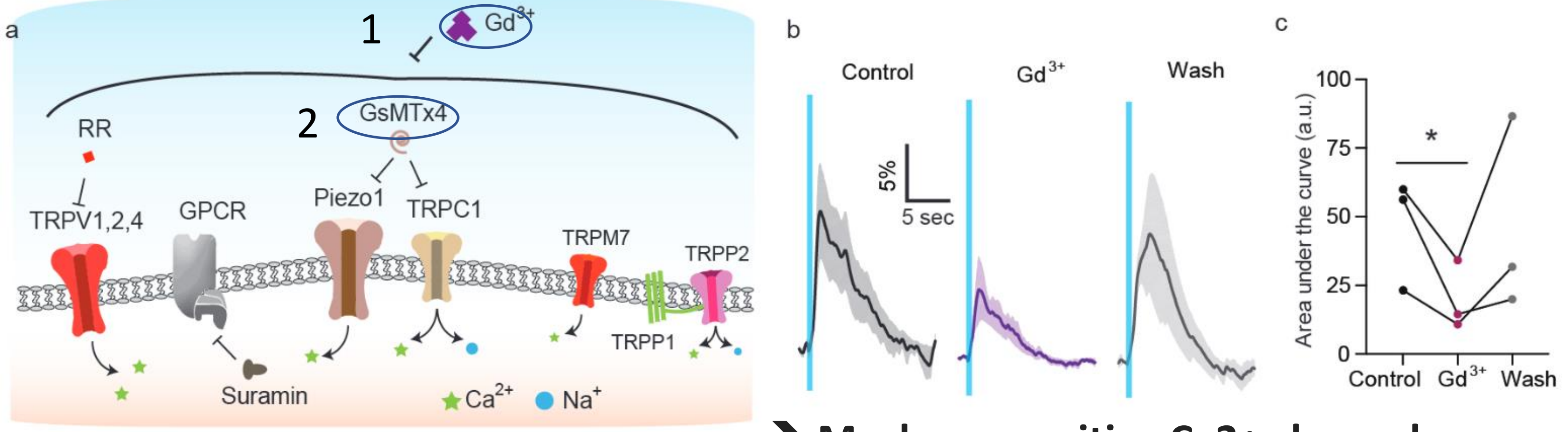


➔ **Mechanosensitive Ca2+ channels**

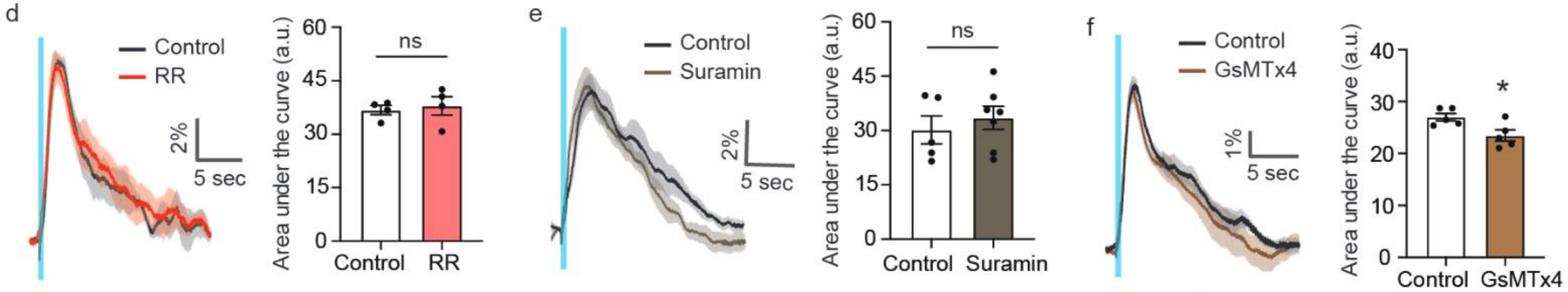


Yoo et al., 2022

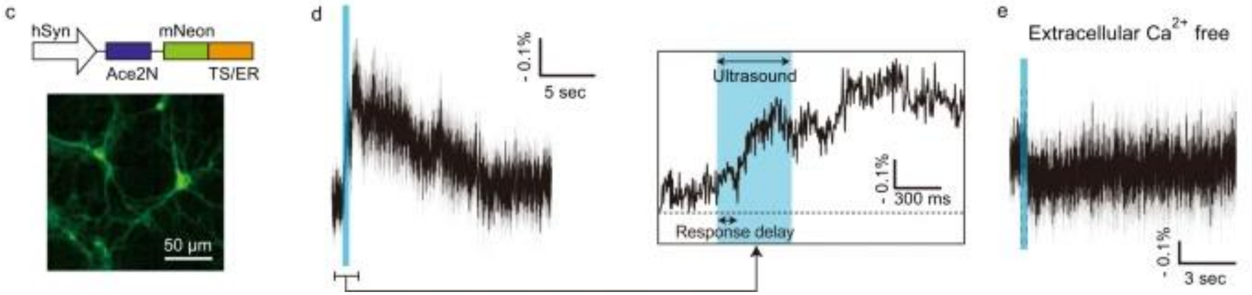
Pharmacological inhibition of mechanosensitive receptors



➔ **Mechanosensitive Ca2+ channels**

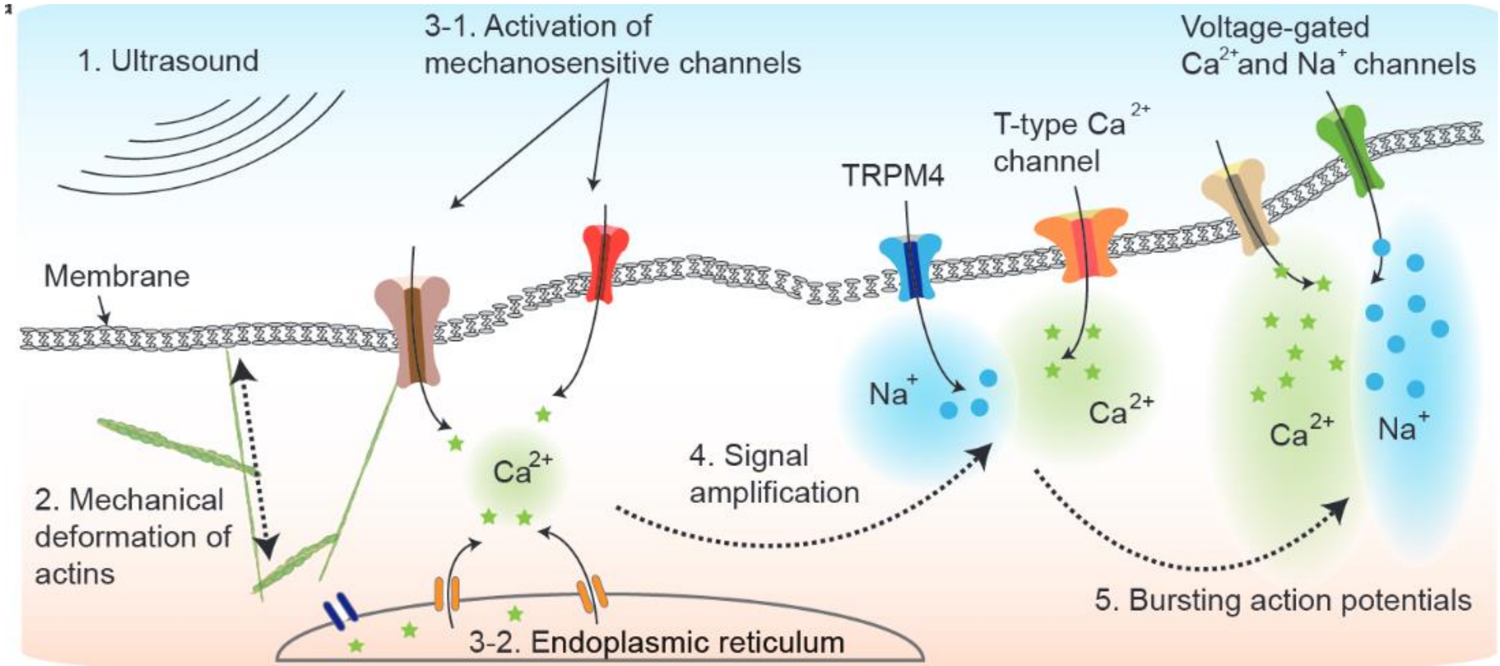


Transmembrane voltage imaging using the genetically encoded voltage indicator Ace2N



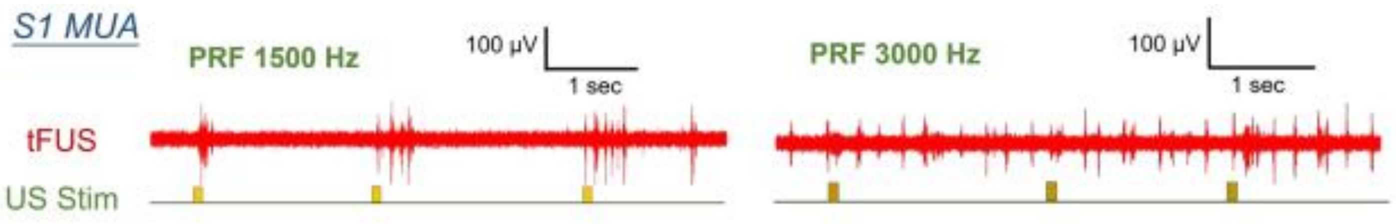
Yoo et al., 2022

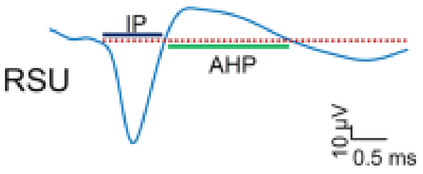
➔ **Role of mechanosensitive Ca2+ channels, amplified by Voltage-dependent Ca2+ and Na2+ channels**



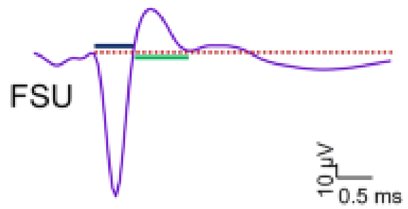
- Opening of specific **calcium-permeable mechanosensitive ion channels**.
- Calcium ions accumulate until they trigger the opening of **calcium-sensitive sodium channels.**
- This leads to depolarization of the cell membrane and the opening **of voltage-gated calcium channels**,
- Leading to the large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

➔ At the neuron's level

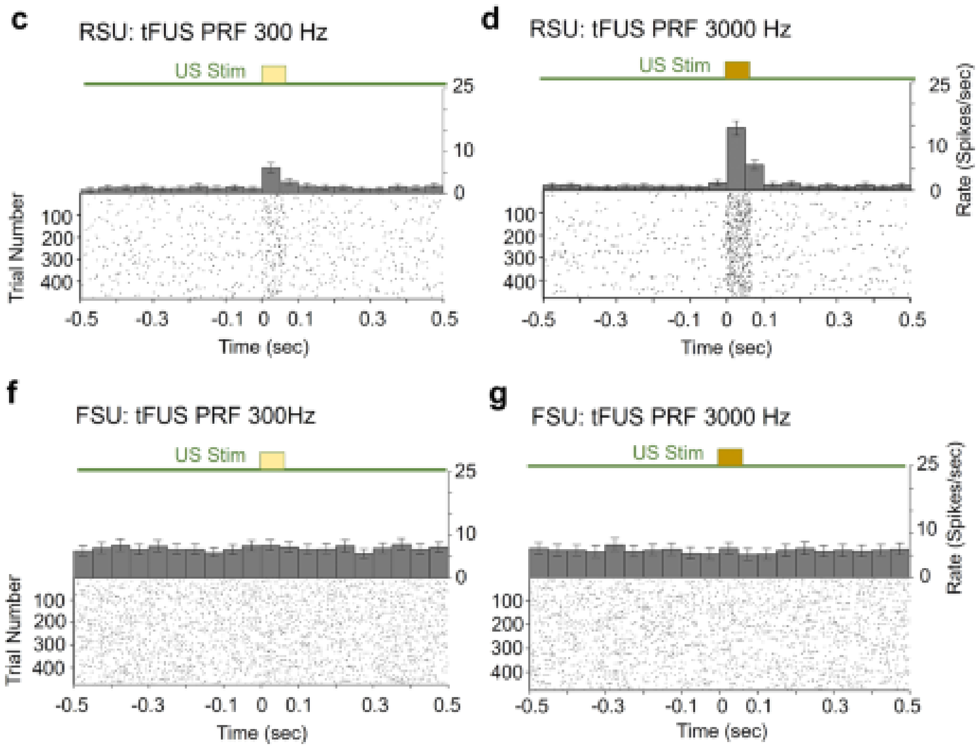


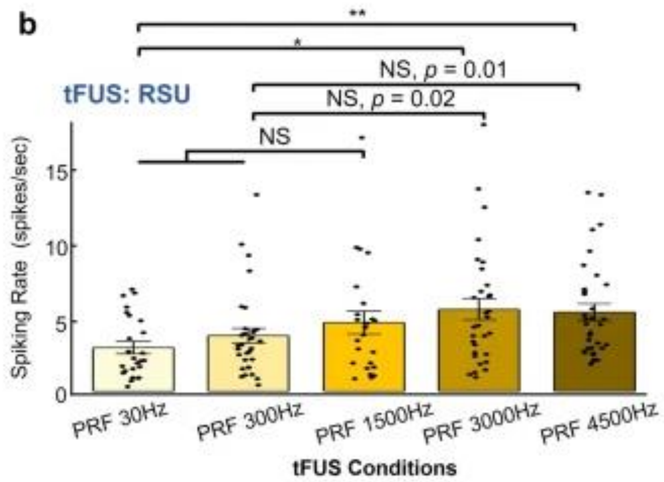


➔ Excitatory



➔ Inhibitory



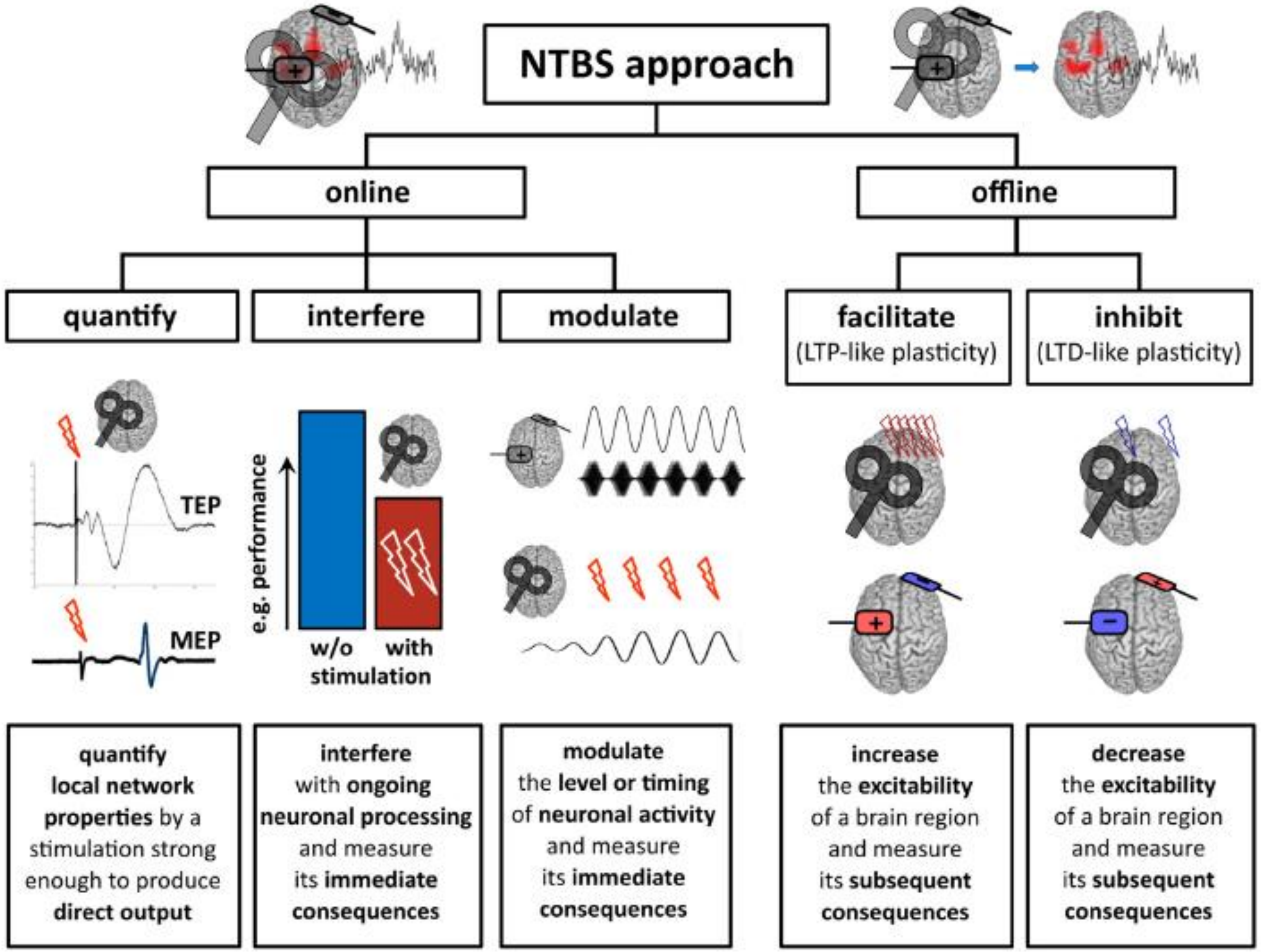


- RSU responses are time locked to TUS, FSU are delayed
- RSU spiking rates increase with increasing PRF

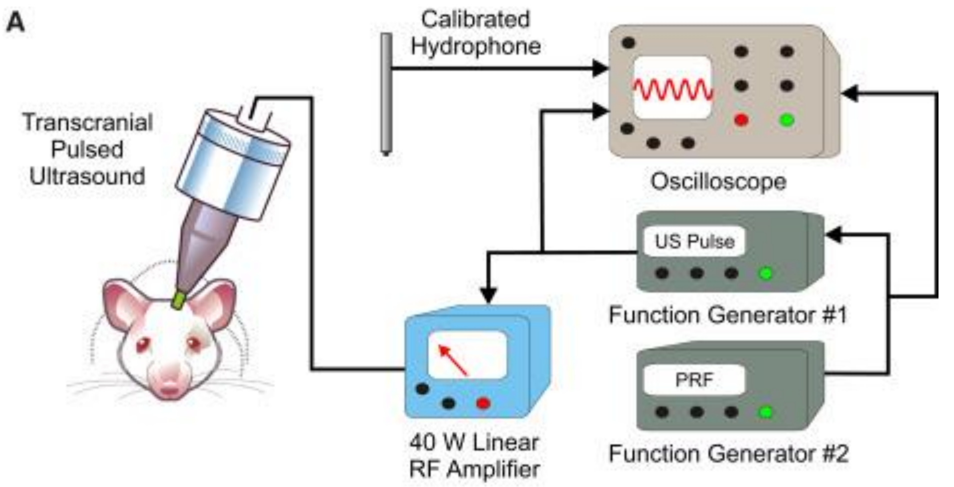
Yu et al., 2021, Nature Communications

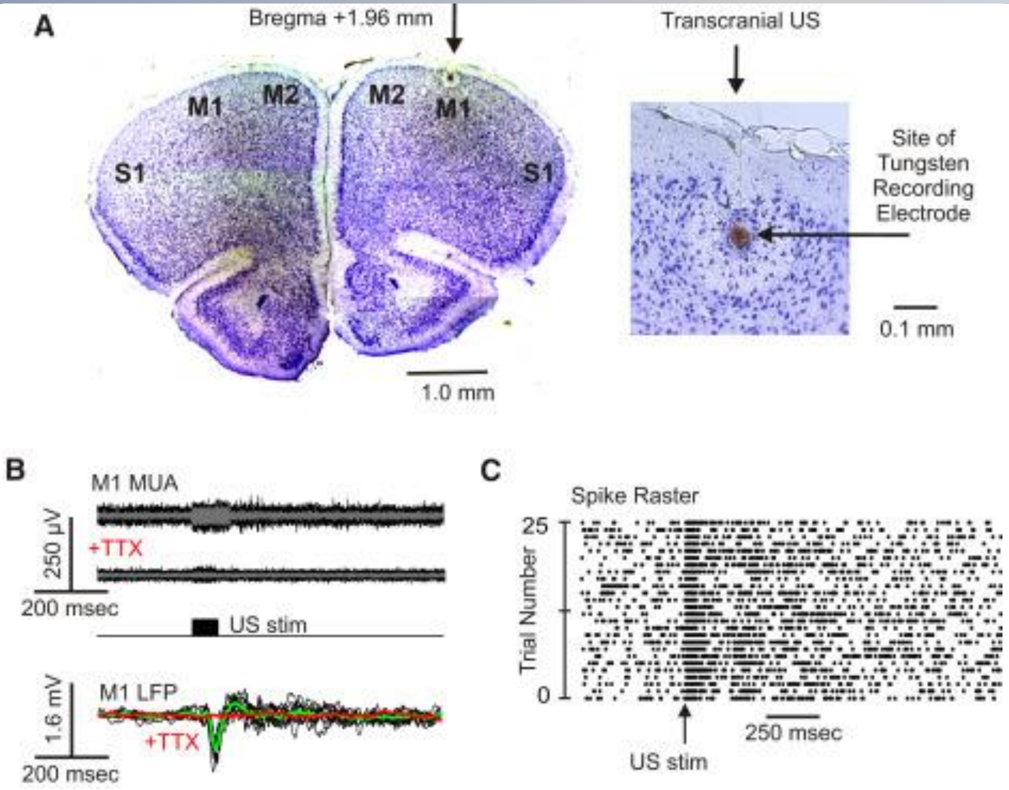
TUS for Neuromodulation

In vitro & Animal work

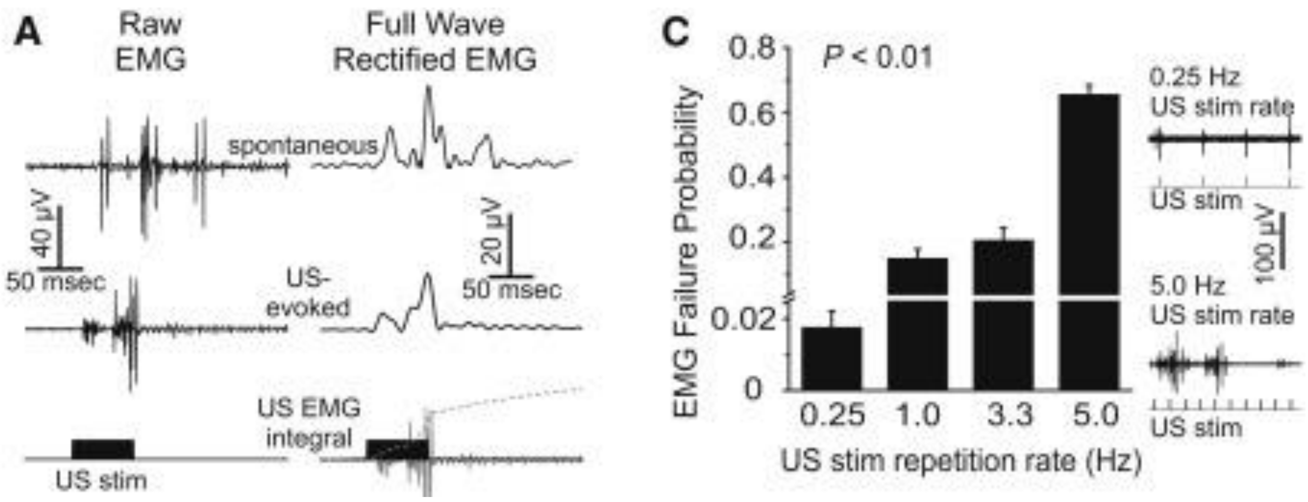

NTBS approach
online
offline
quantify
interfere
modulate
facilitate
(LTP-like plasticity)
inhibit
(LTD-like plasticity)
TEP
MEP
e.g. performance
w/o
with
stimulation
quantify
local network
properties by a
stimulation strong
enough to produce
direct output
interfere
with ongoing
neuronal processing
and measure
its immediate
consequences
modulate
the level or timing
of neuronal activity
and measure
its immediate
consequences
increase
the excitability
of a brain region
and measure
its subsequent
consequences
decrease
the excitability
of a brain region
and measure
its subsequent
consequences

Online protocols



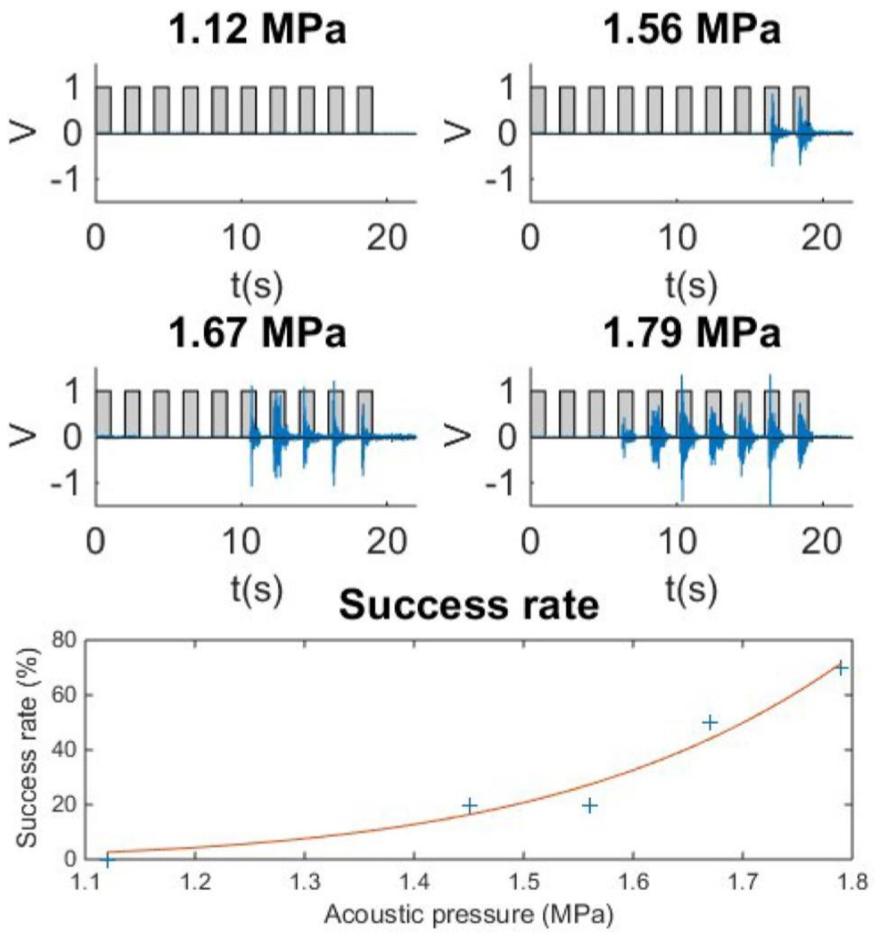


➔ Pulsed US triggers cortical action potentials to drive peripheral muscle contractions



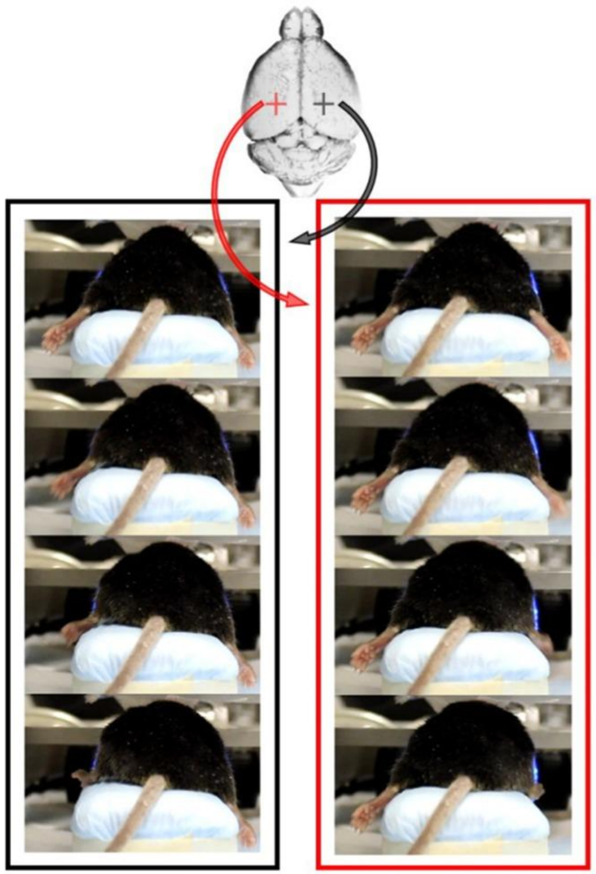
Tufail et al., 2010, Neurons

Online protocols

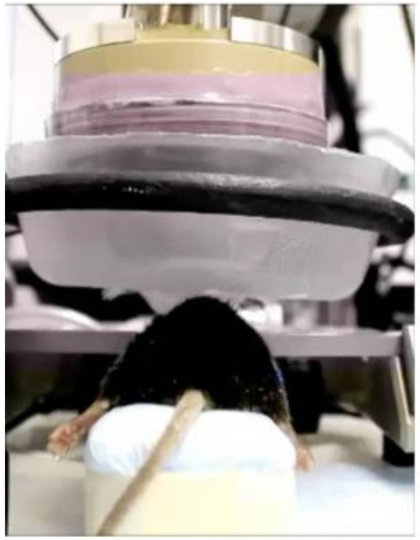


(a)

US MEP?



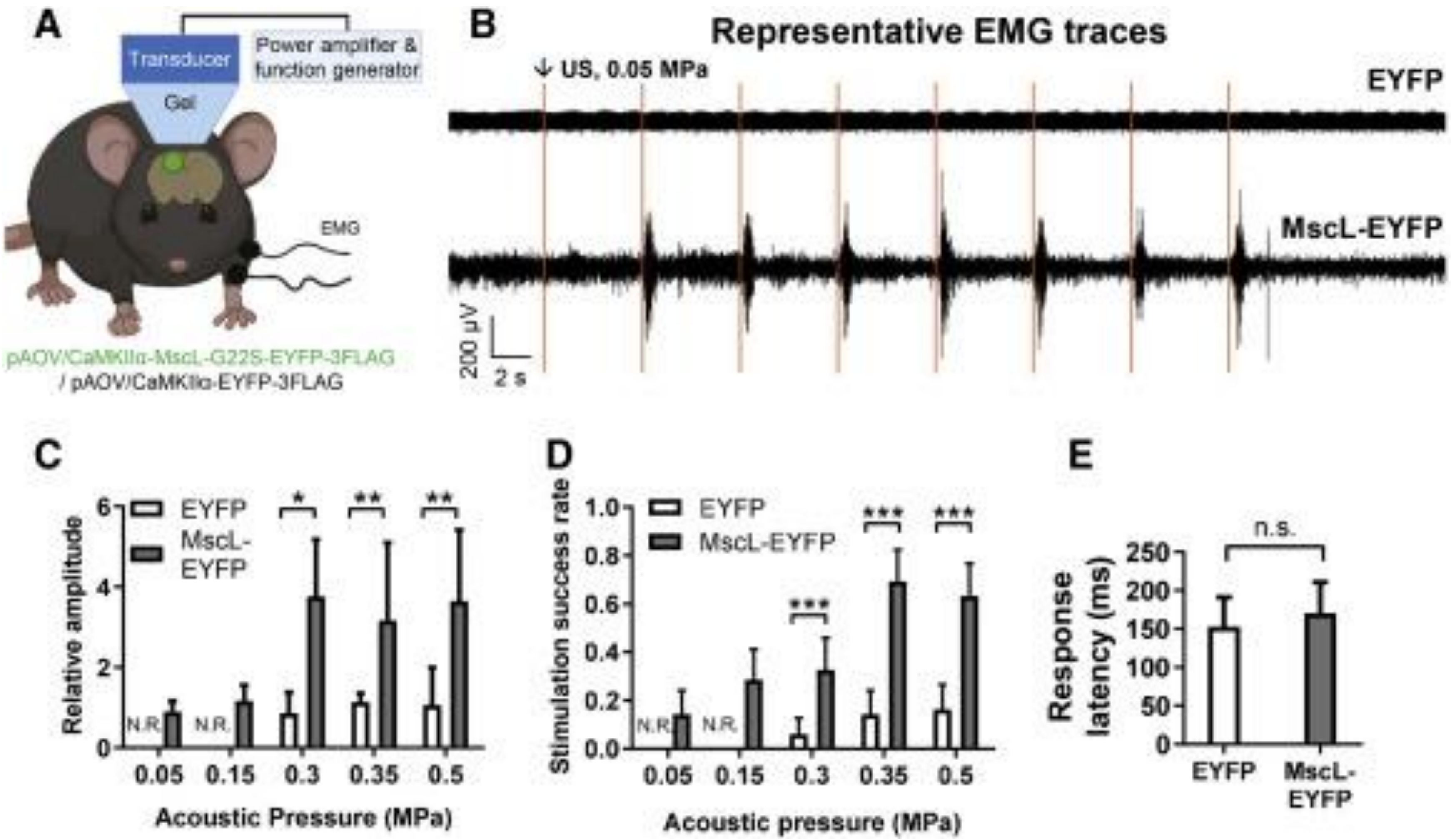
(b)



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

Kamimura et al., 2016, Neurons

Online protocols

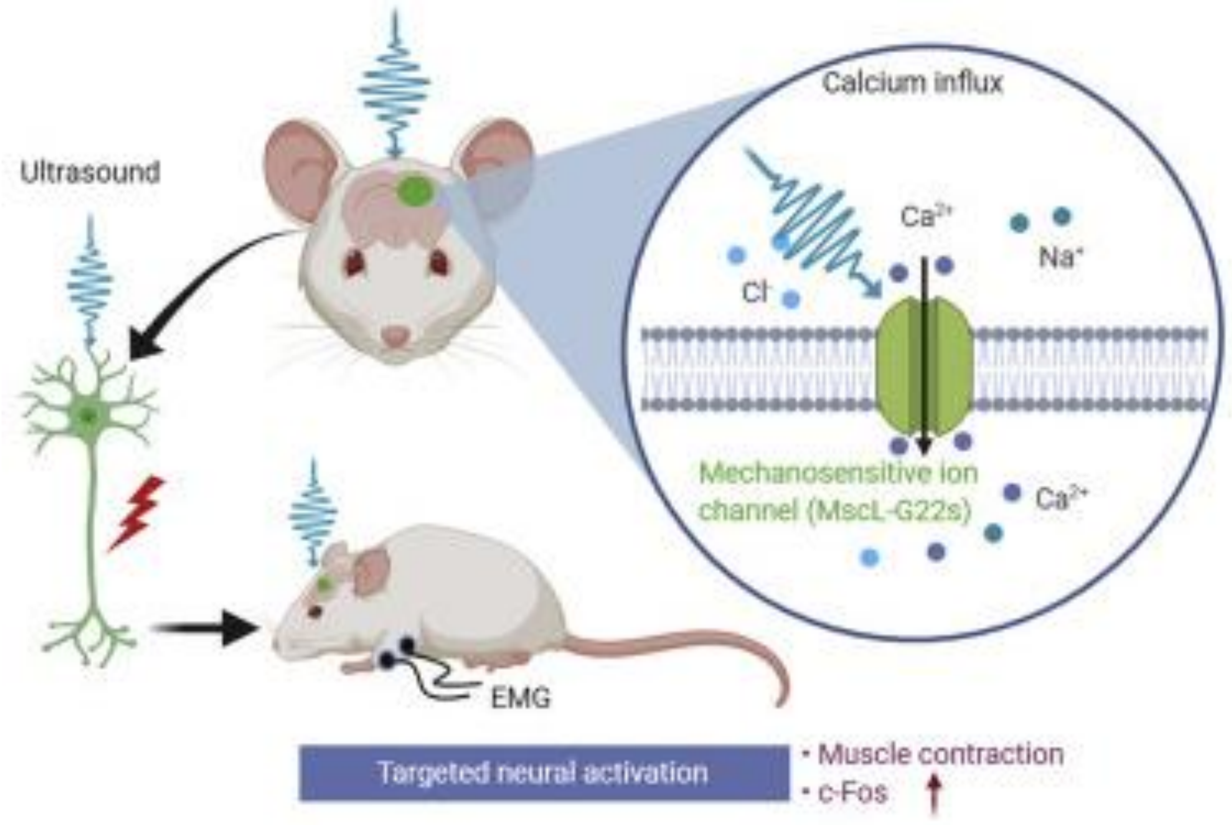


Qiu et al., 2020, Cell Reports

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

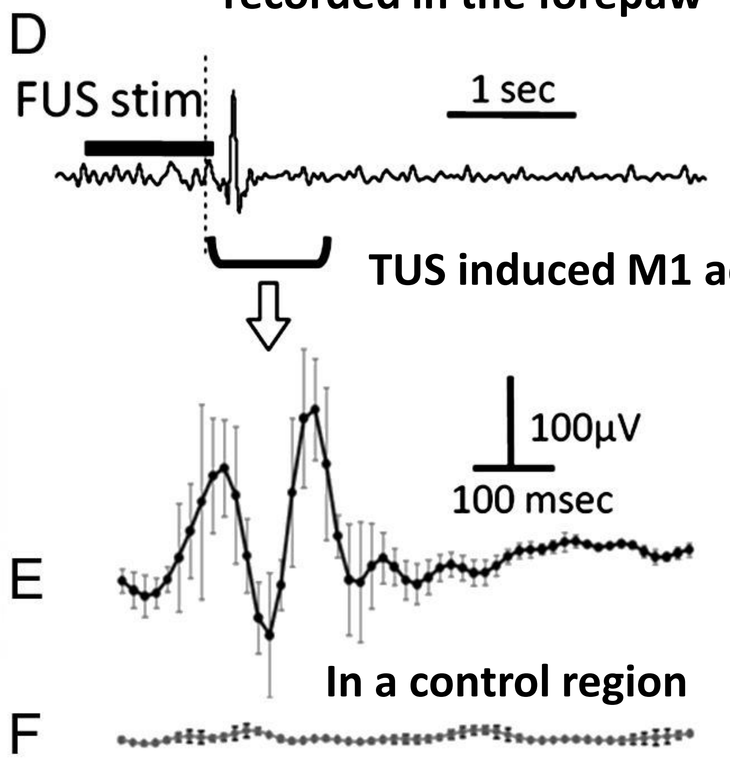


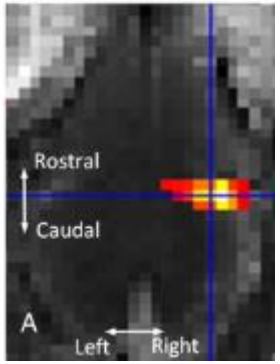
Kim et al., 2014, Brain Stim.

TUS induced motion recorded in the forepaw

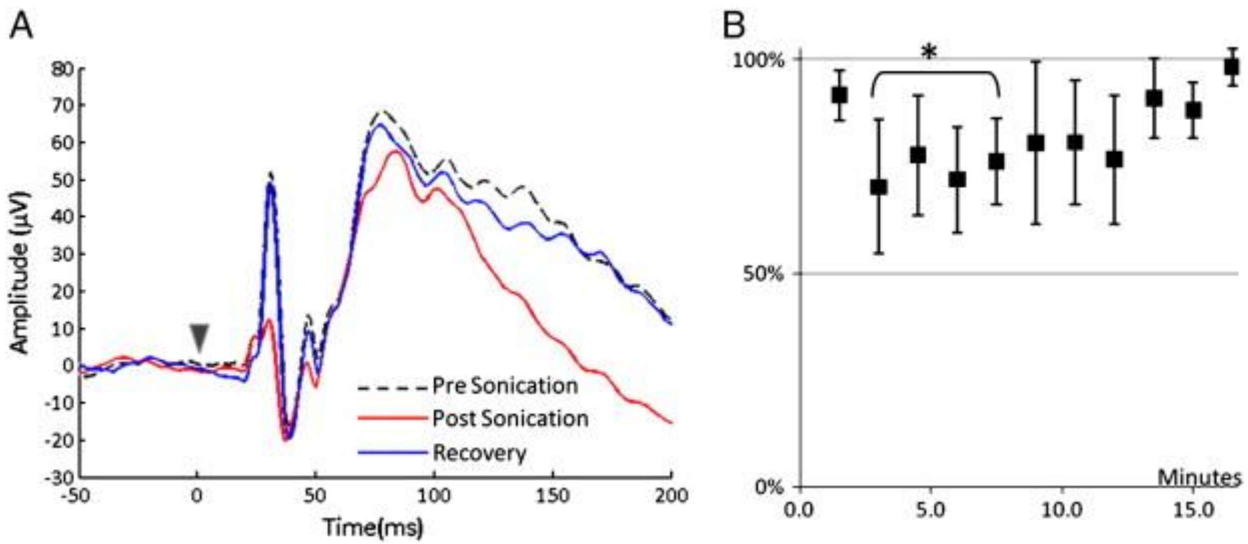
TUS induced M1 activation

In a control region

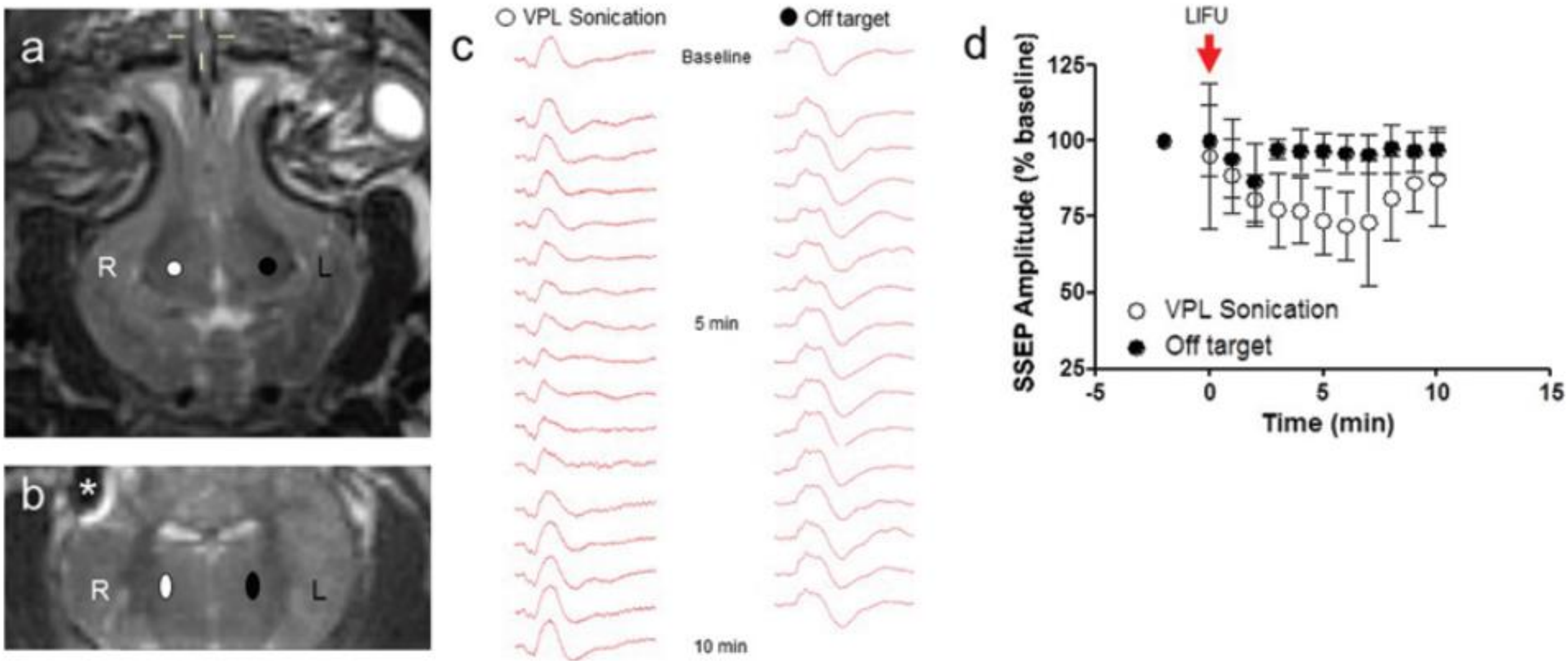




VEP recordings

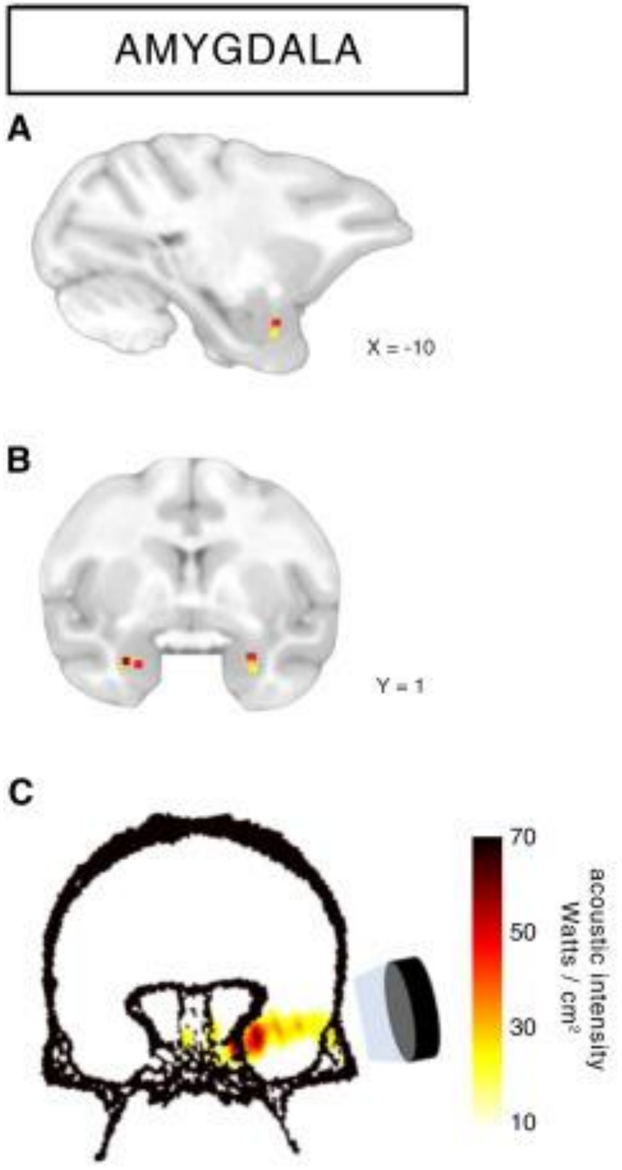


Yoo et al., 2011, NeuroImage

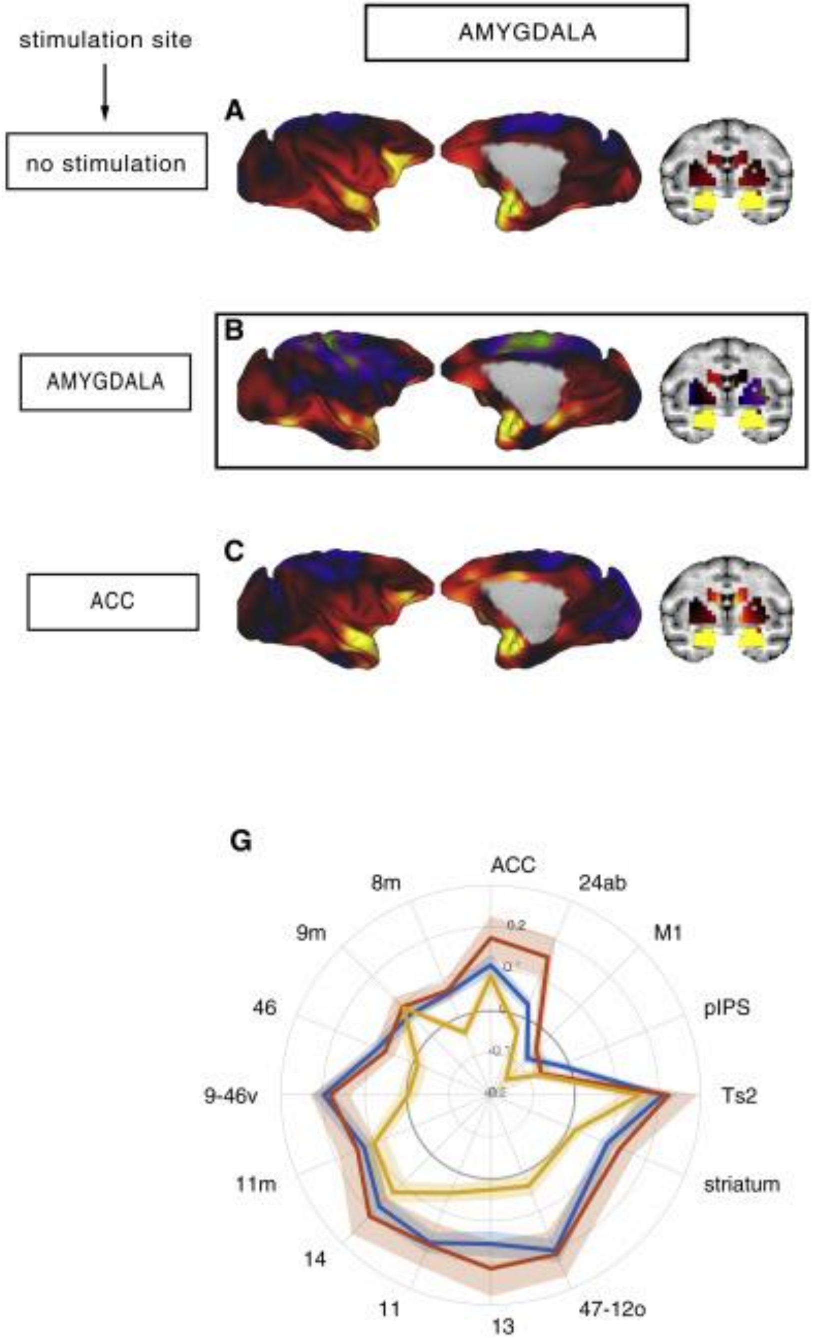


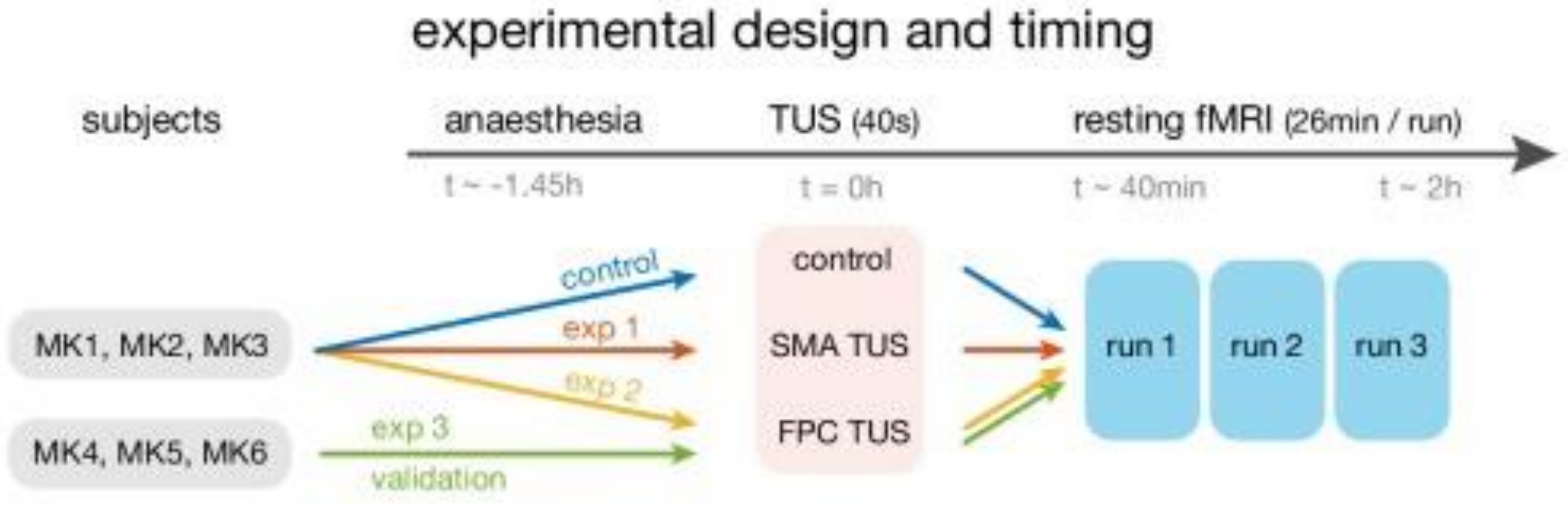
Dallaplazza et al., 2017, J Neurosurgery.

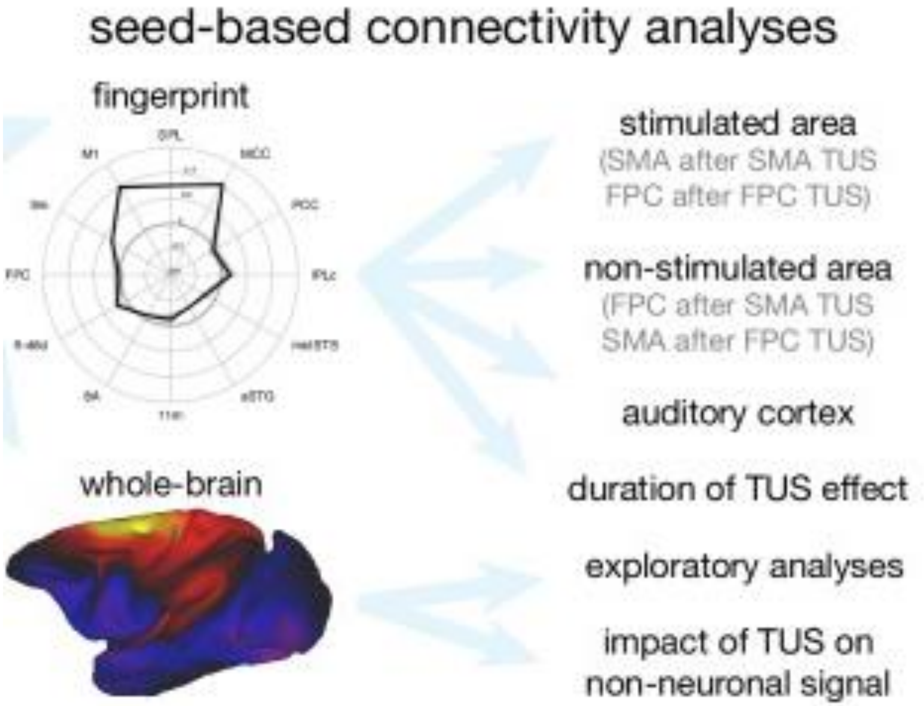
Towards offline neuromodulation



Folloni et al., 2019, Neuron

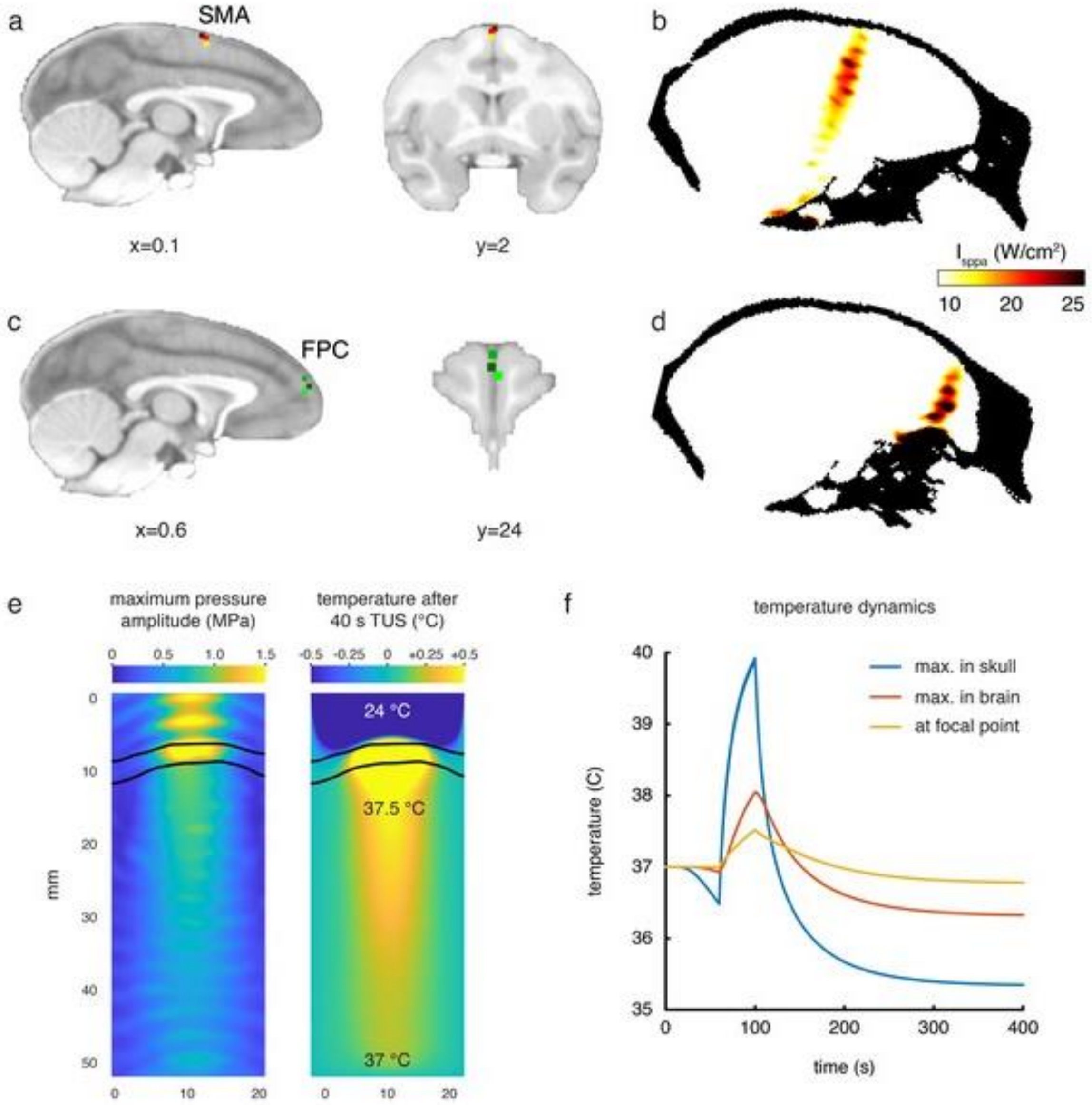


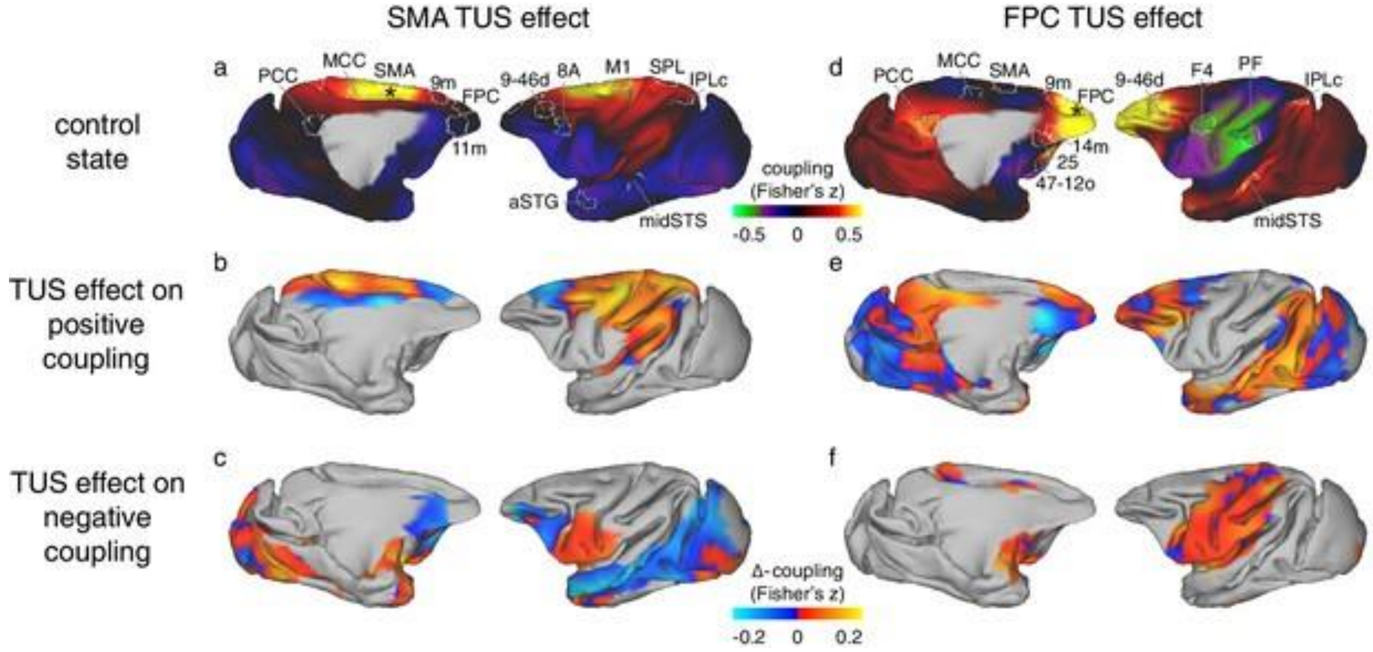




Verhaguen et al., 2018, eLife

Towards offline neuromodulation





Verhagen et al., 2018, Sci. Rep.

TUS for Neuromodulation

Human work

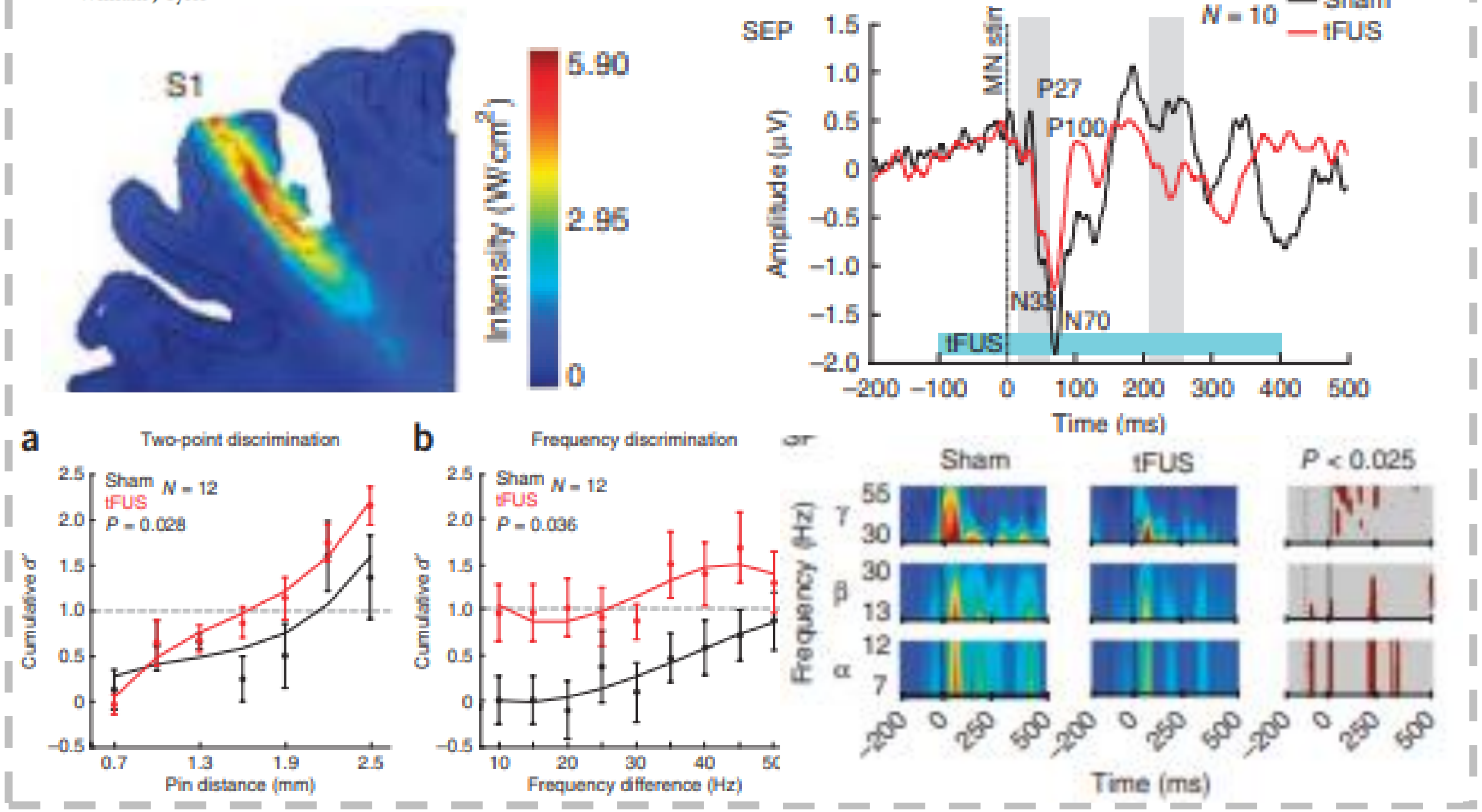
US in humans – Online neuromodulation

TECHNICAL REPORTS

nature neuroscience

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

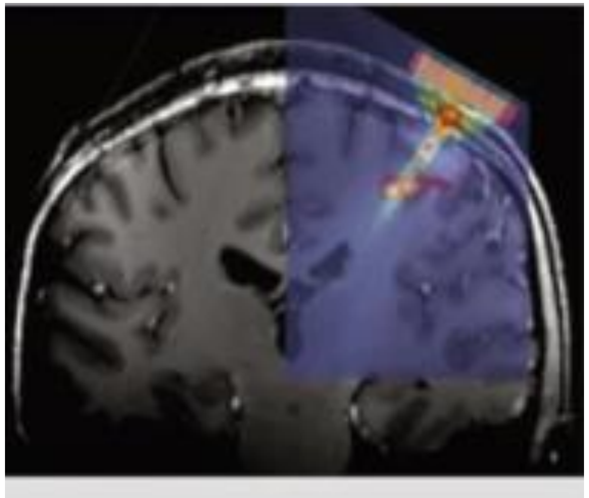
Wynn Legon[1], Tomokazu F Sato[1], Alexander Opitz[1,2], Jerel Mueller[3], Aaron Barbour[1], Amanda Williams[1] & William J Tyler[1,3,4]



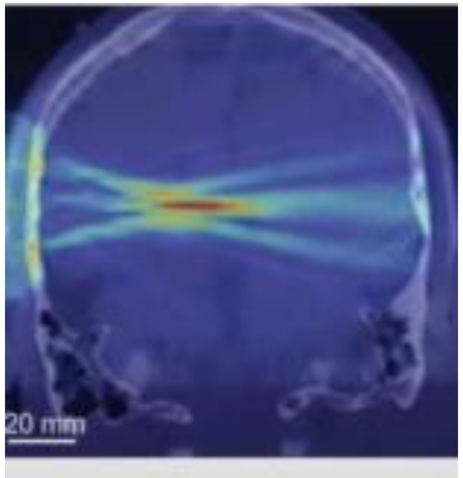
Legon et al., 2014, Nature Neurosc.

US in humans

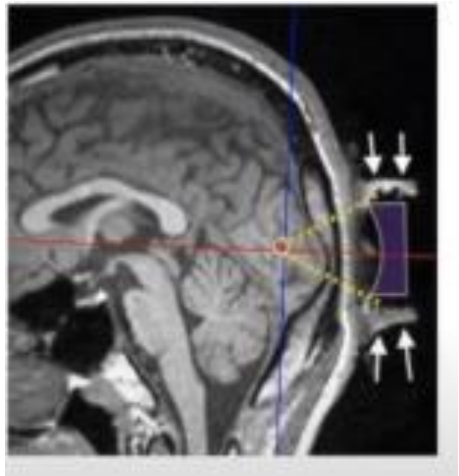
Primary motor cortex

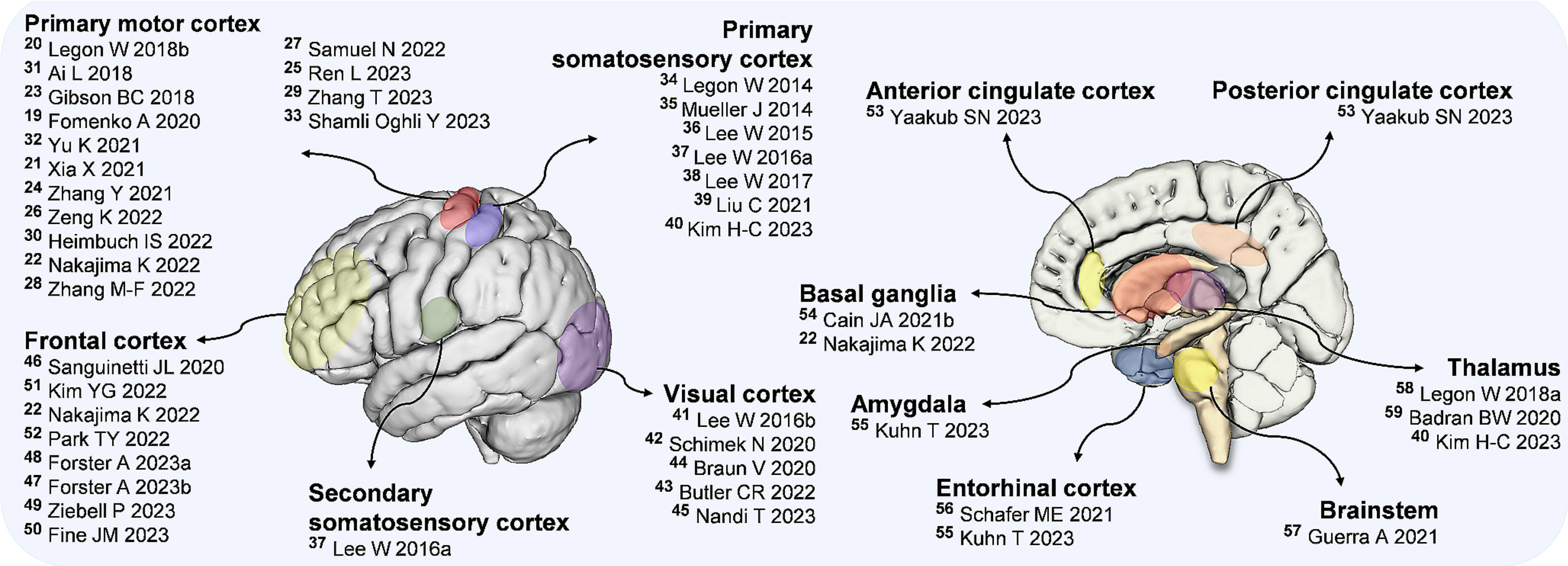


Thalamus



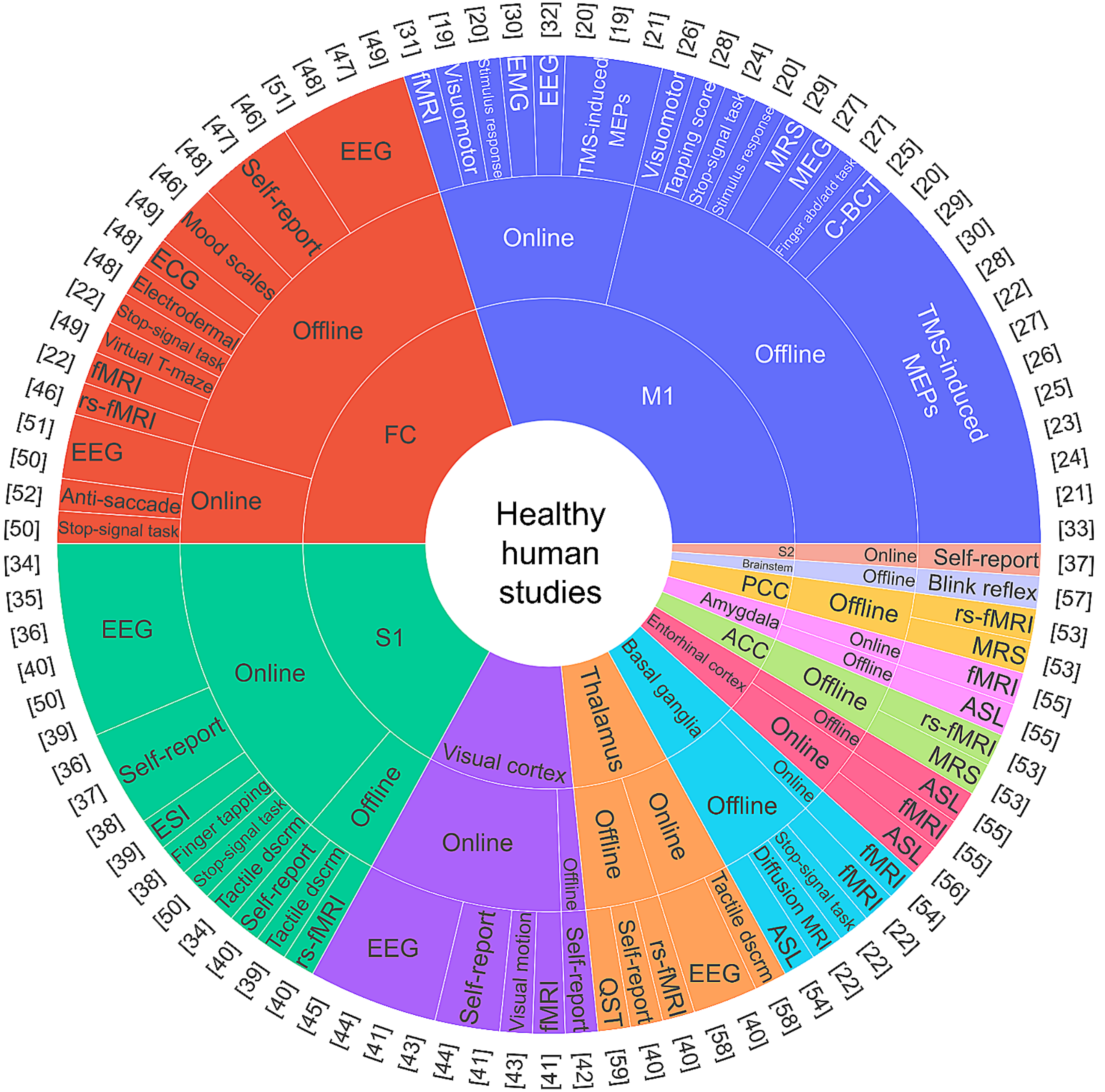
Primary visual cortex





Lee et al., 2024, BEL

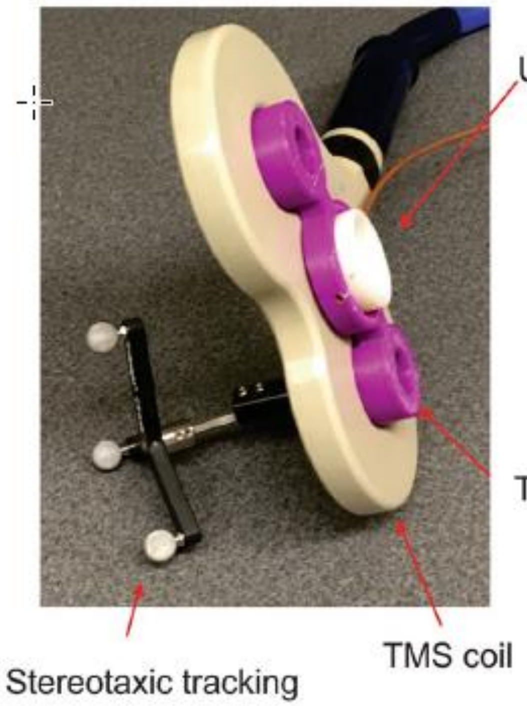
US in humans

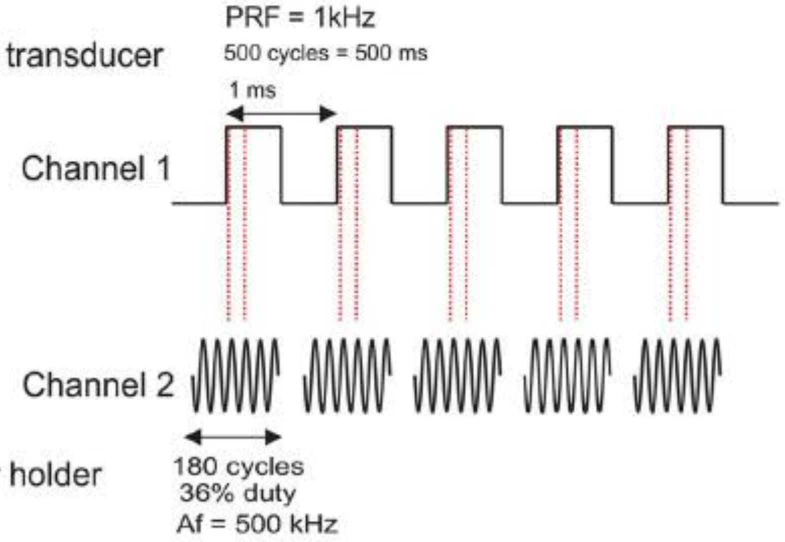


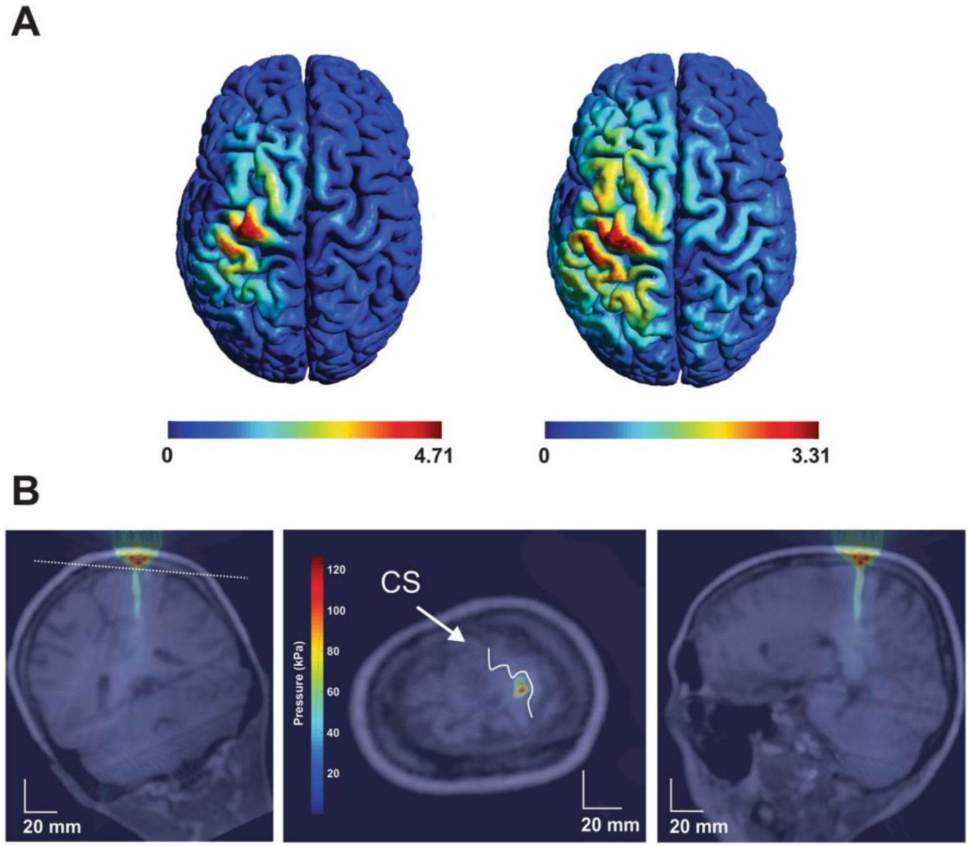
- 34 Legon W 2014
- 35 Mueller J 2014
- 36 Lee W 2015
- 37 Lee W 2016a
- 41 Lee W 2016b
- 38 Lee W 2017
- 58 Legon W 2018a
- 20 Legon W 2018b
- 31 Ai L 2018
- 23 Gibson BC 2018
- 46 Sanguinetti 2020
- 42 Schimek 2020
- 44 Braun V 2020
- 59 Badran 2020
- 19 Fomenko 2020
- 56 Schafer 2021
- 39 Liu C 2021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

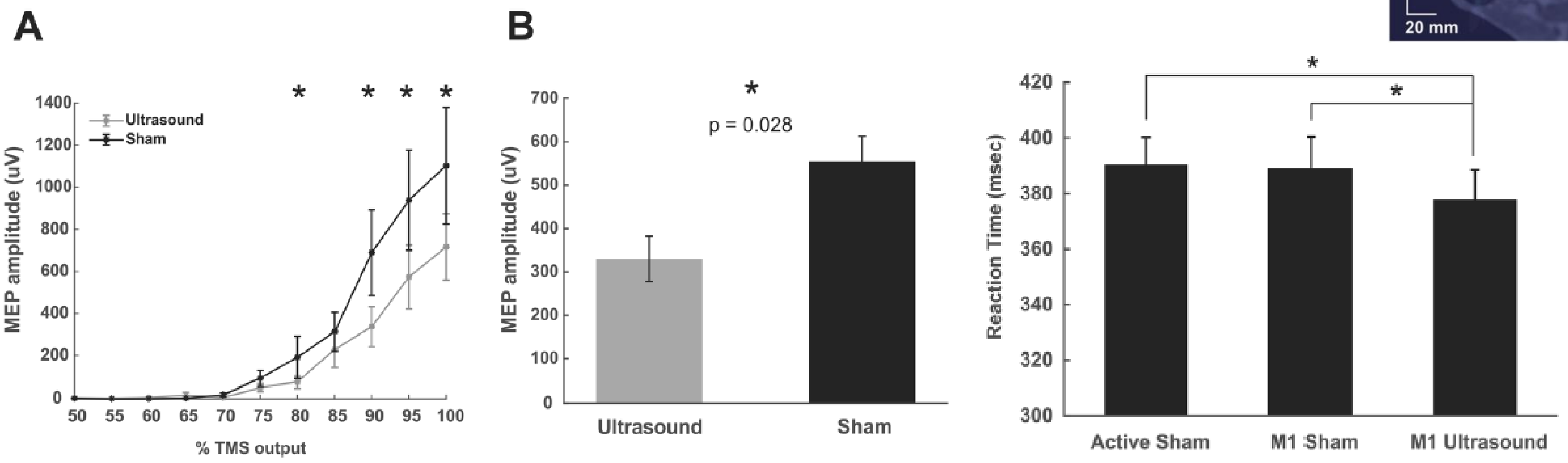
Lee et al., 2024, BEL

US in humans – Online neuromodulation









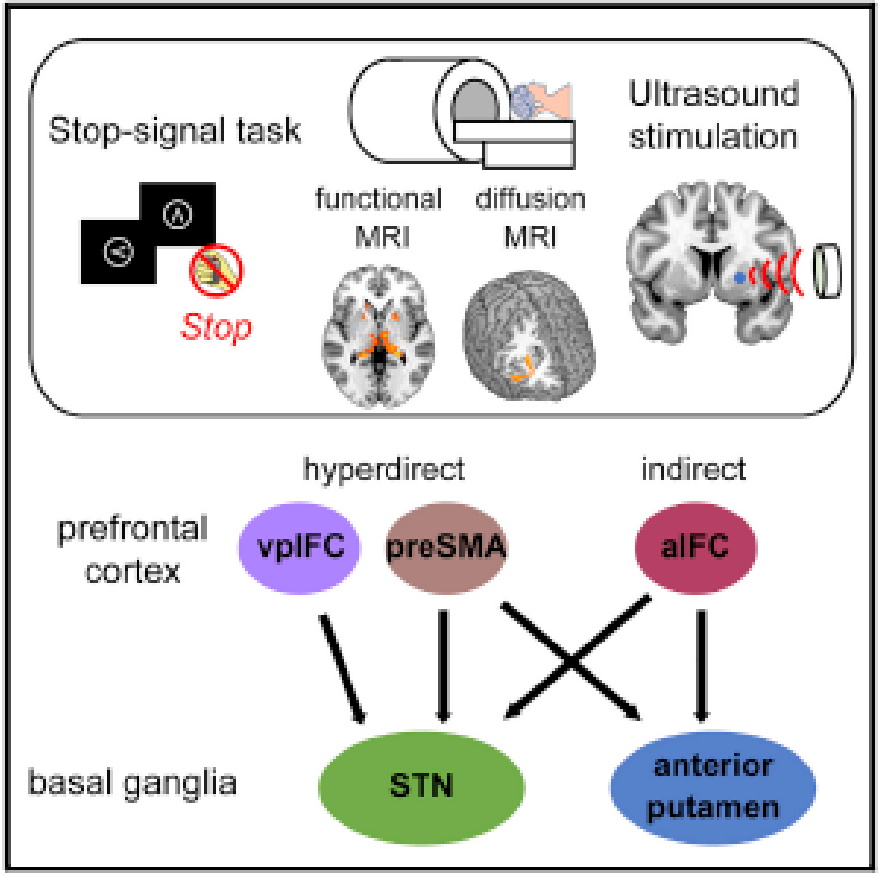
Legon et al., 2018, Scientific Reports

Cell Reports

Article

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

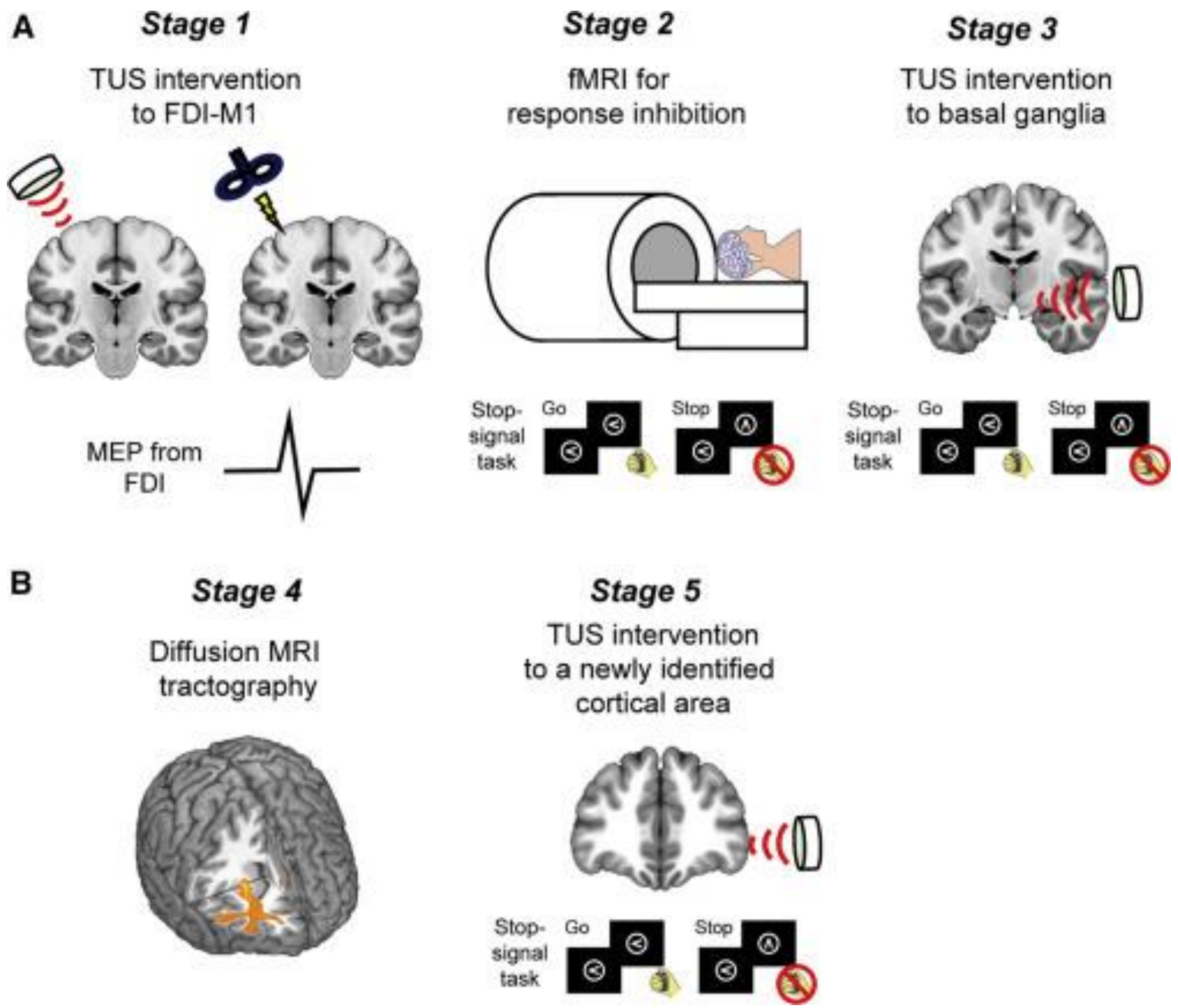
tosada@juntendo.ac.jp (T.O.), skonishi@juntendo.ac.jp (S.K.)

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.

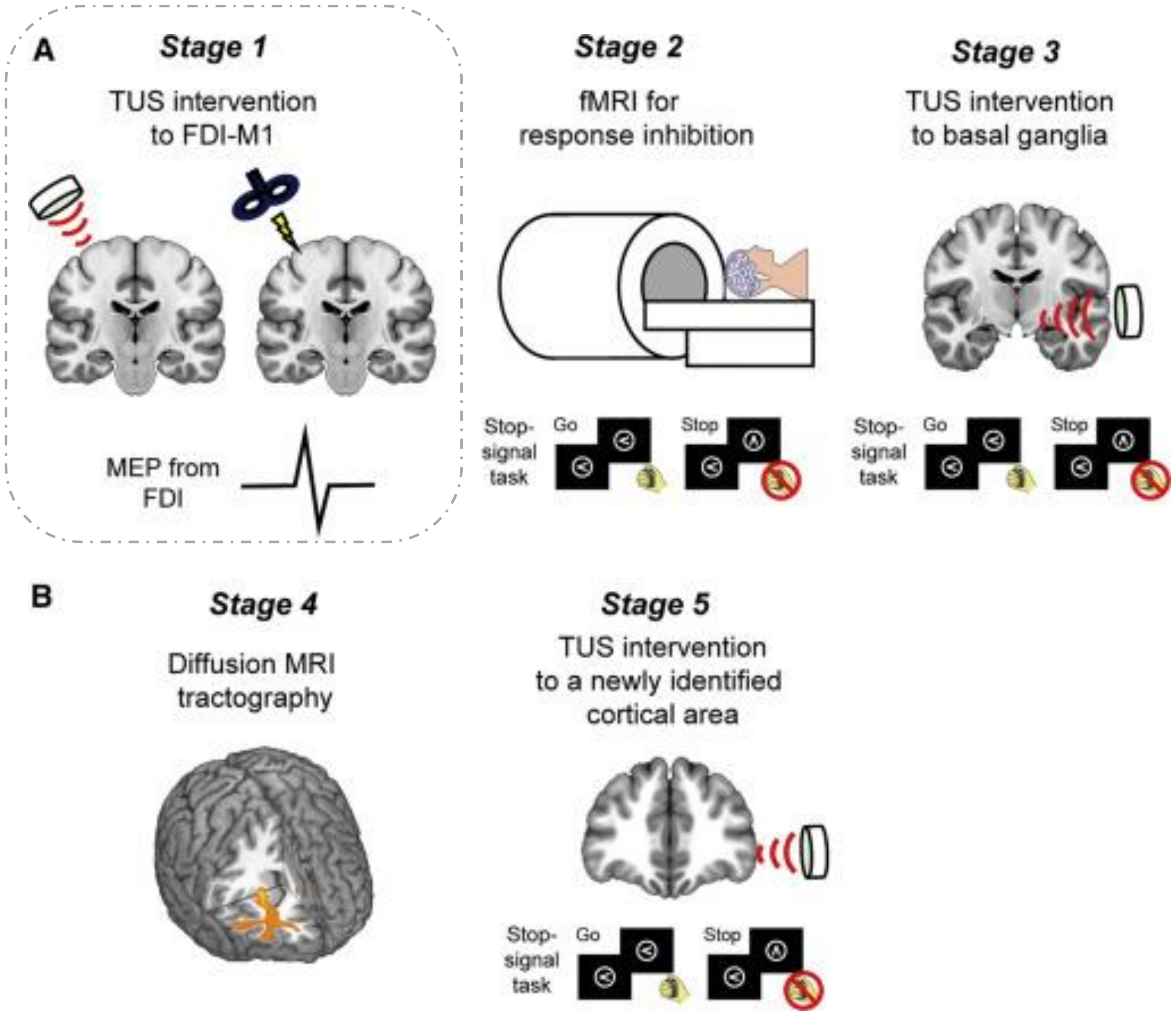
Nakajima et al., 2022, Cell Reports

Towards offline neuromodulation

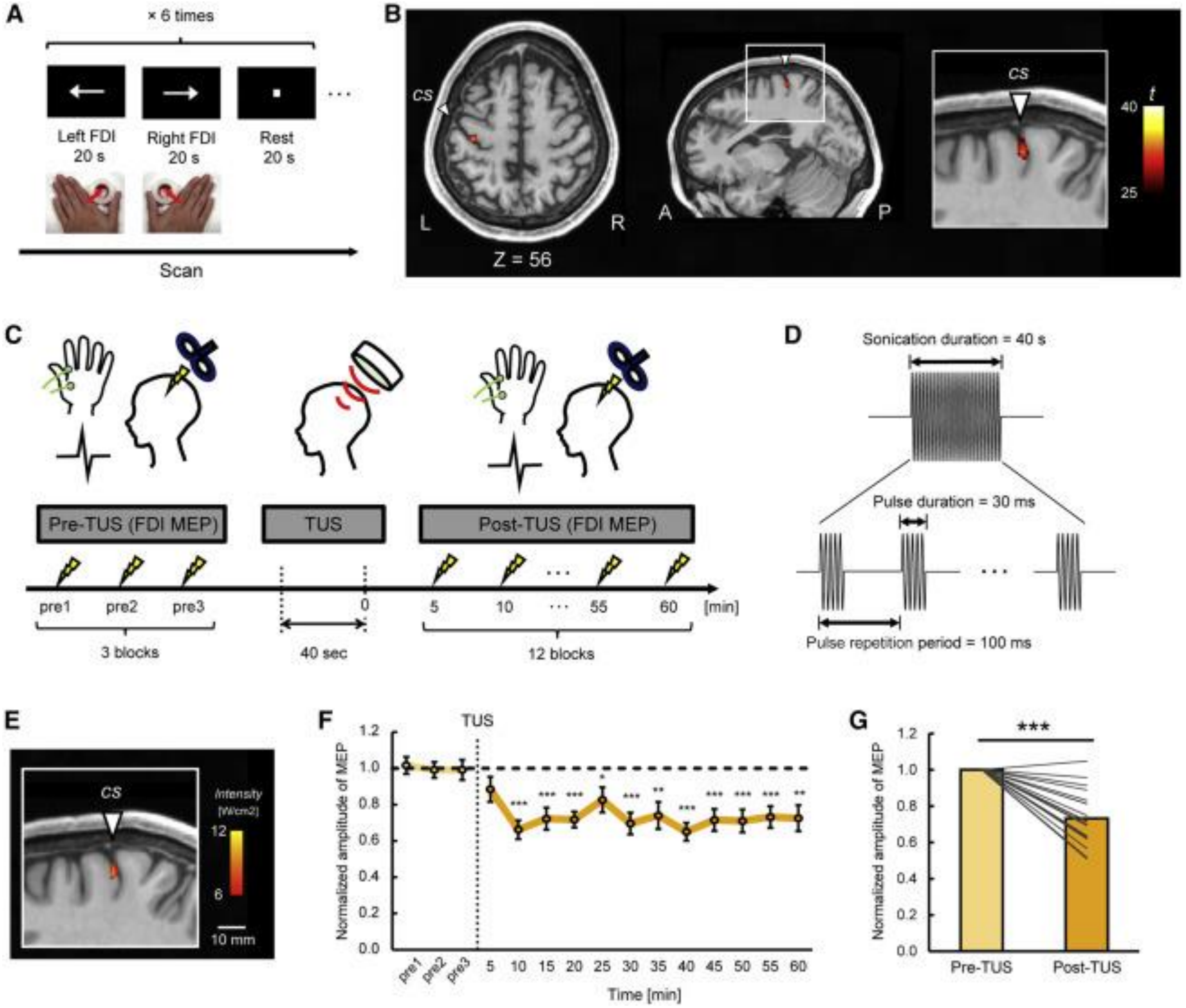


Nakajima et al., 2022, Cell Reports

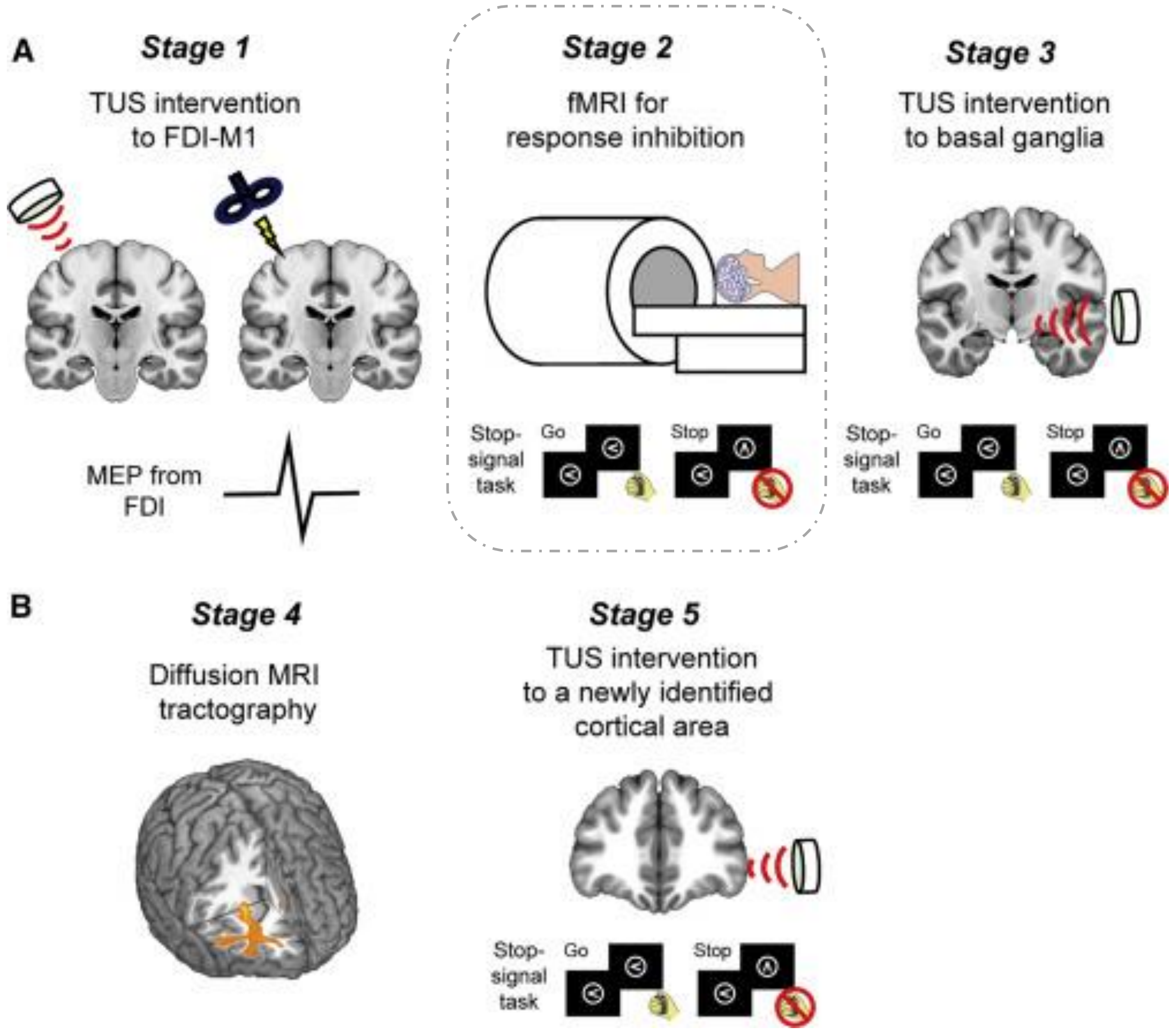
Towards offline neuromodulation



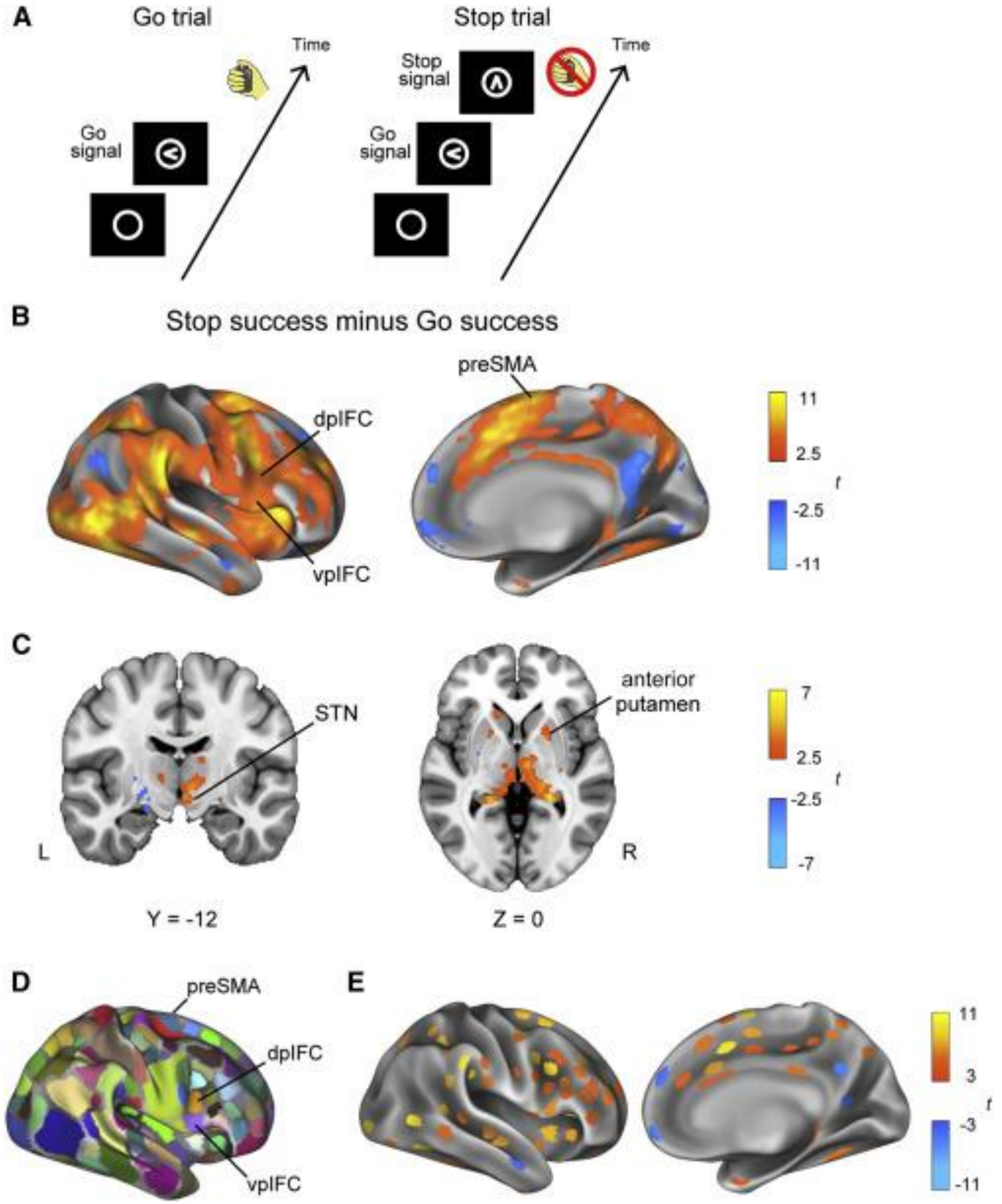
Nakajima et al., 2022, Cell Reports



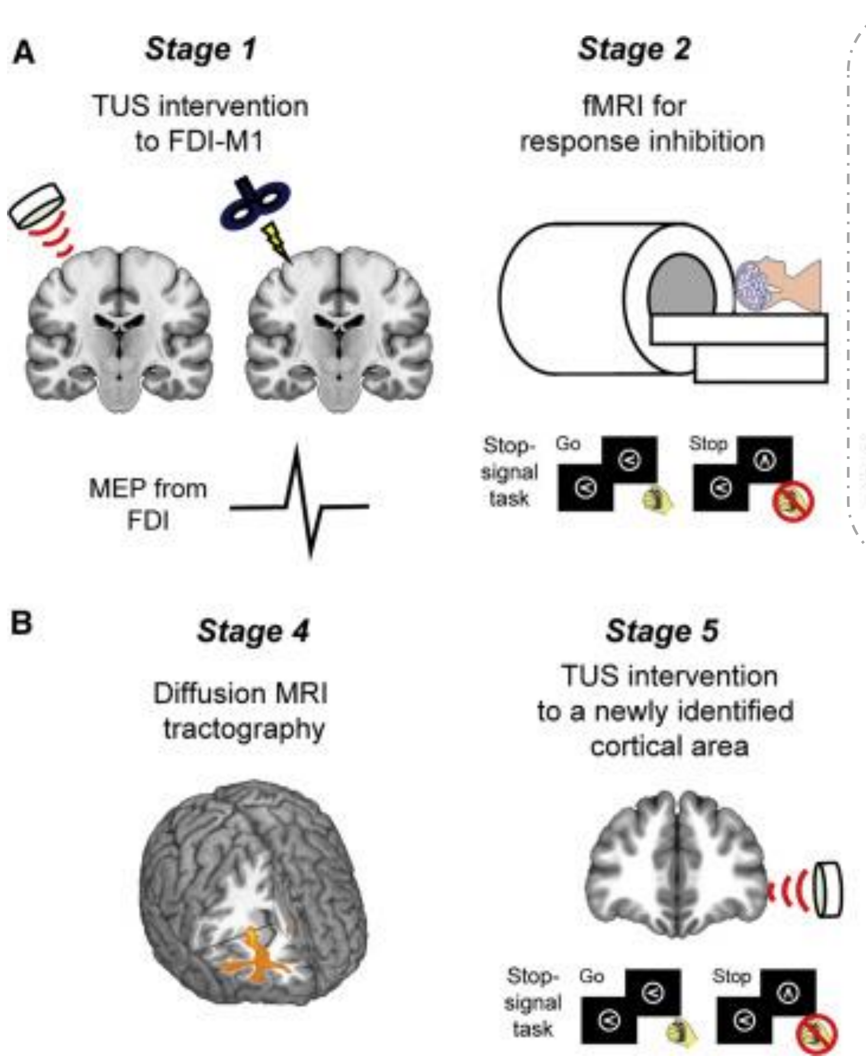
Towards offline neuromodulation

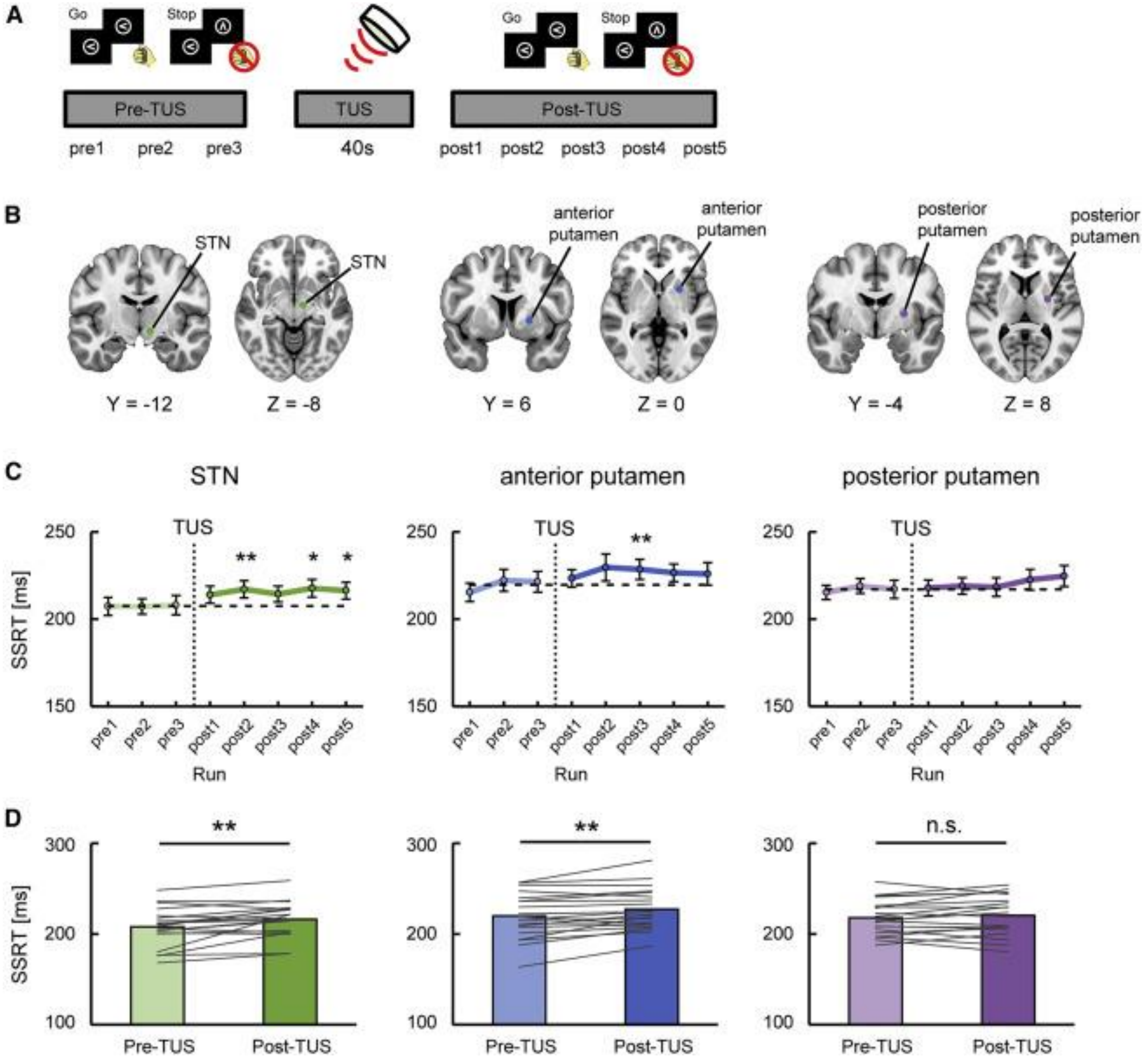


Nakajima et al., 2022, Cell Reports



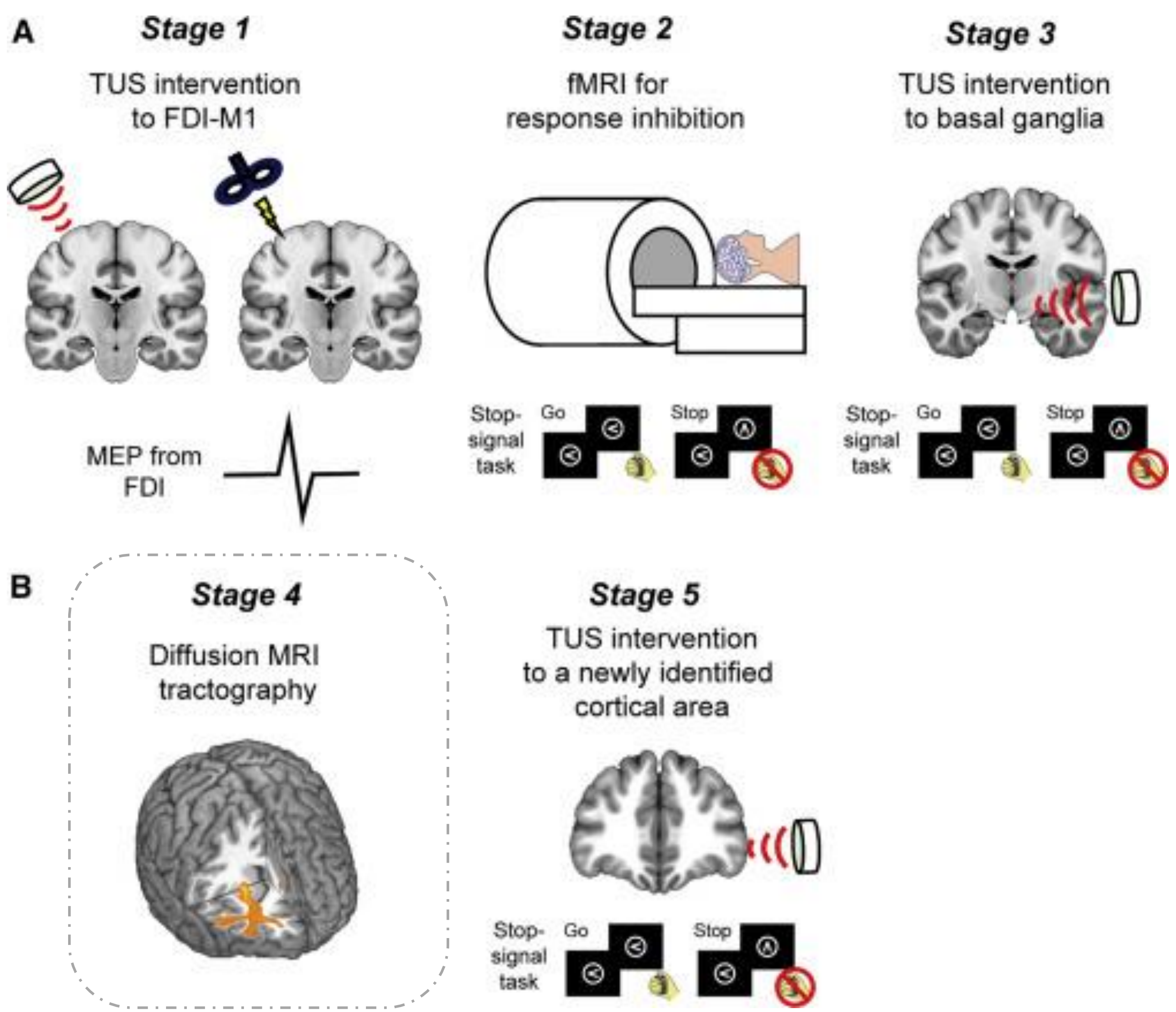
Towards offline neuromodulation



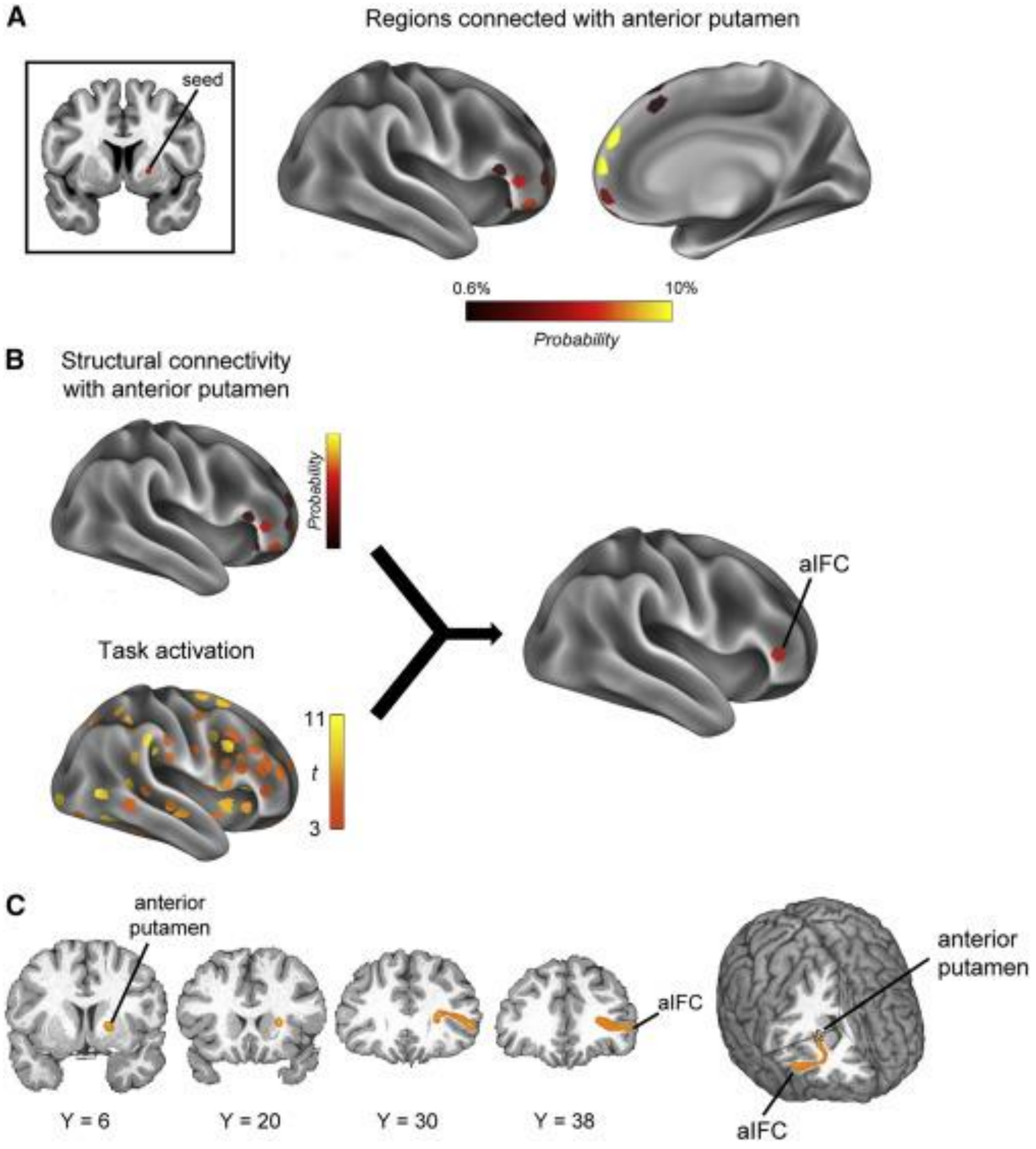


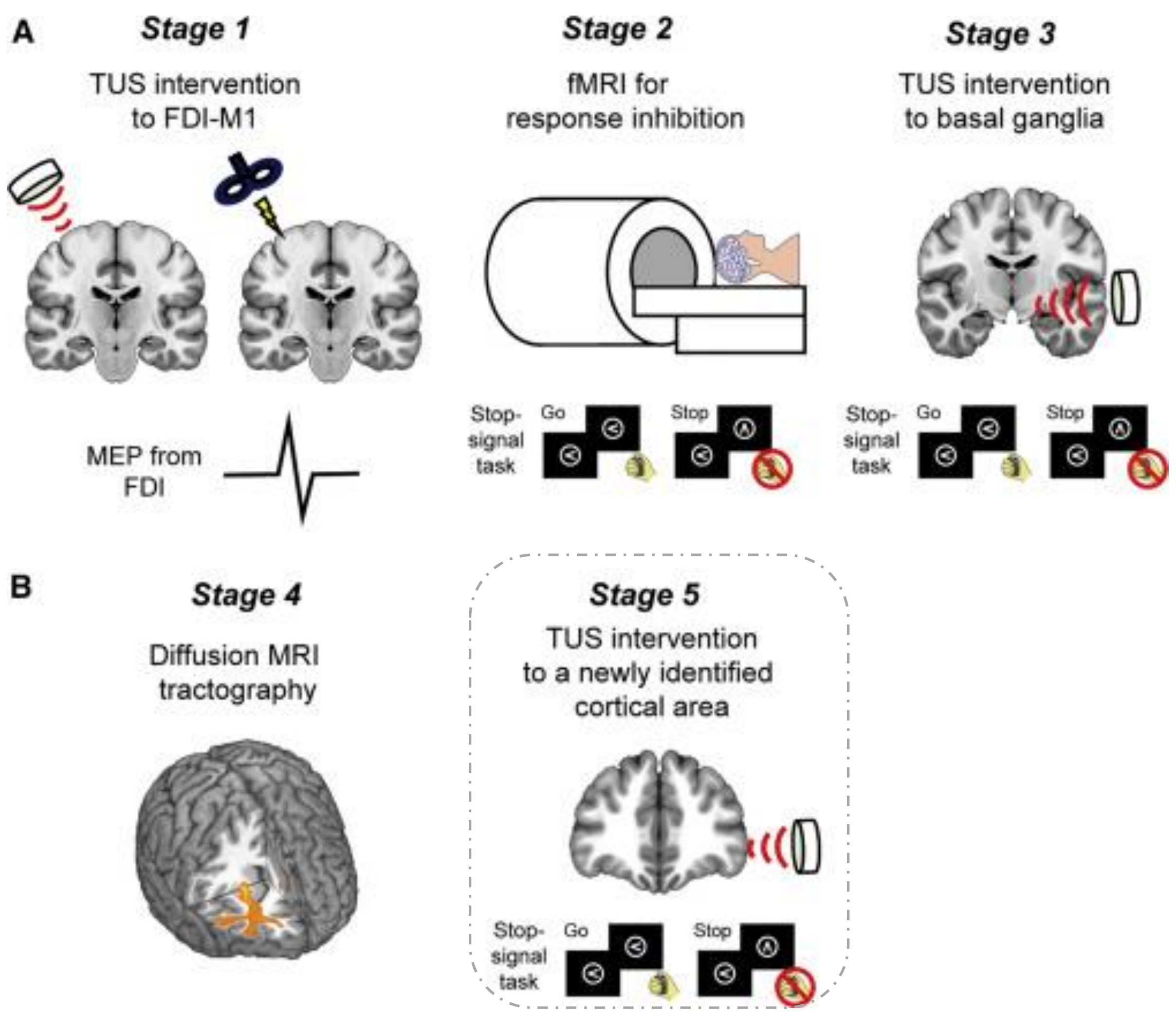
Nakajima et al., 2022, Cell Reports

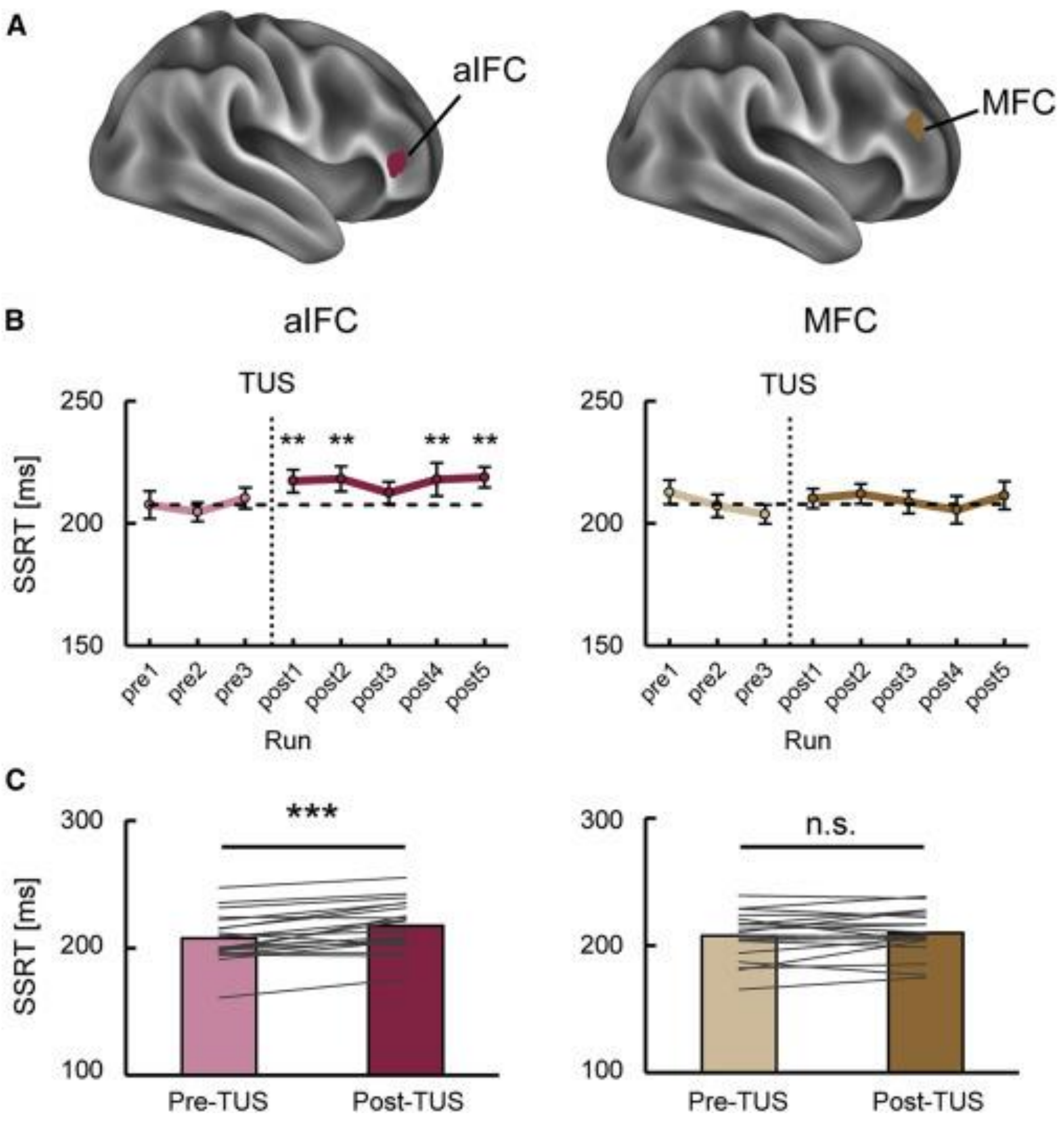
Towards offline neuromodulation



Nakajima et al., 2022, Cell Reports





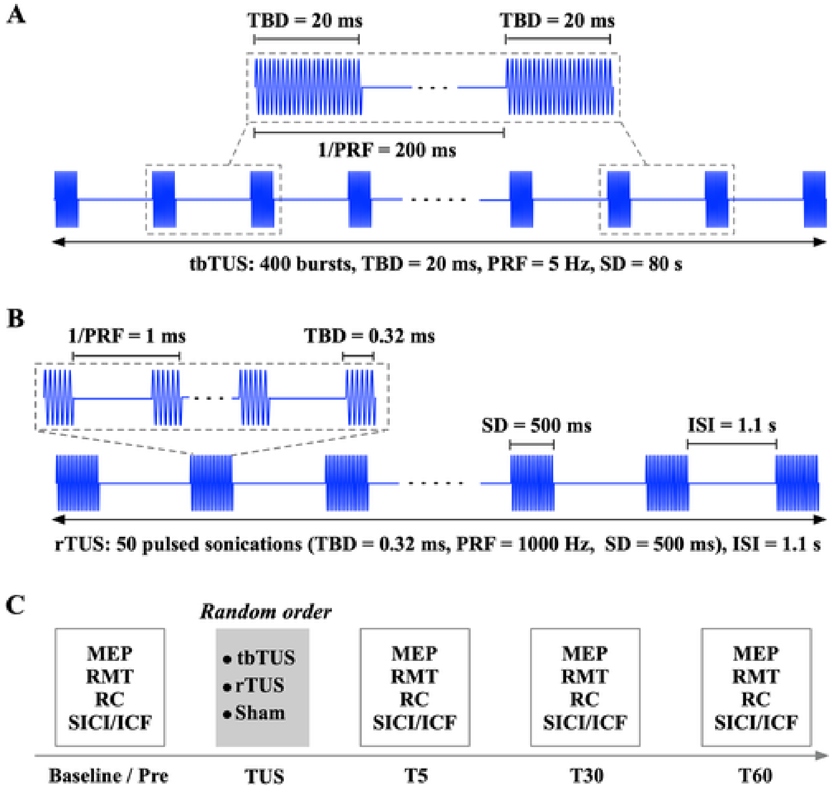


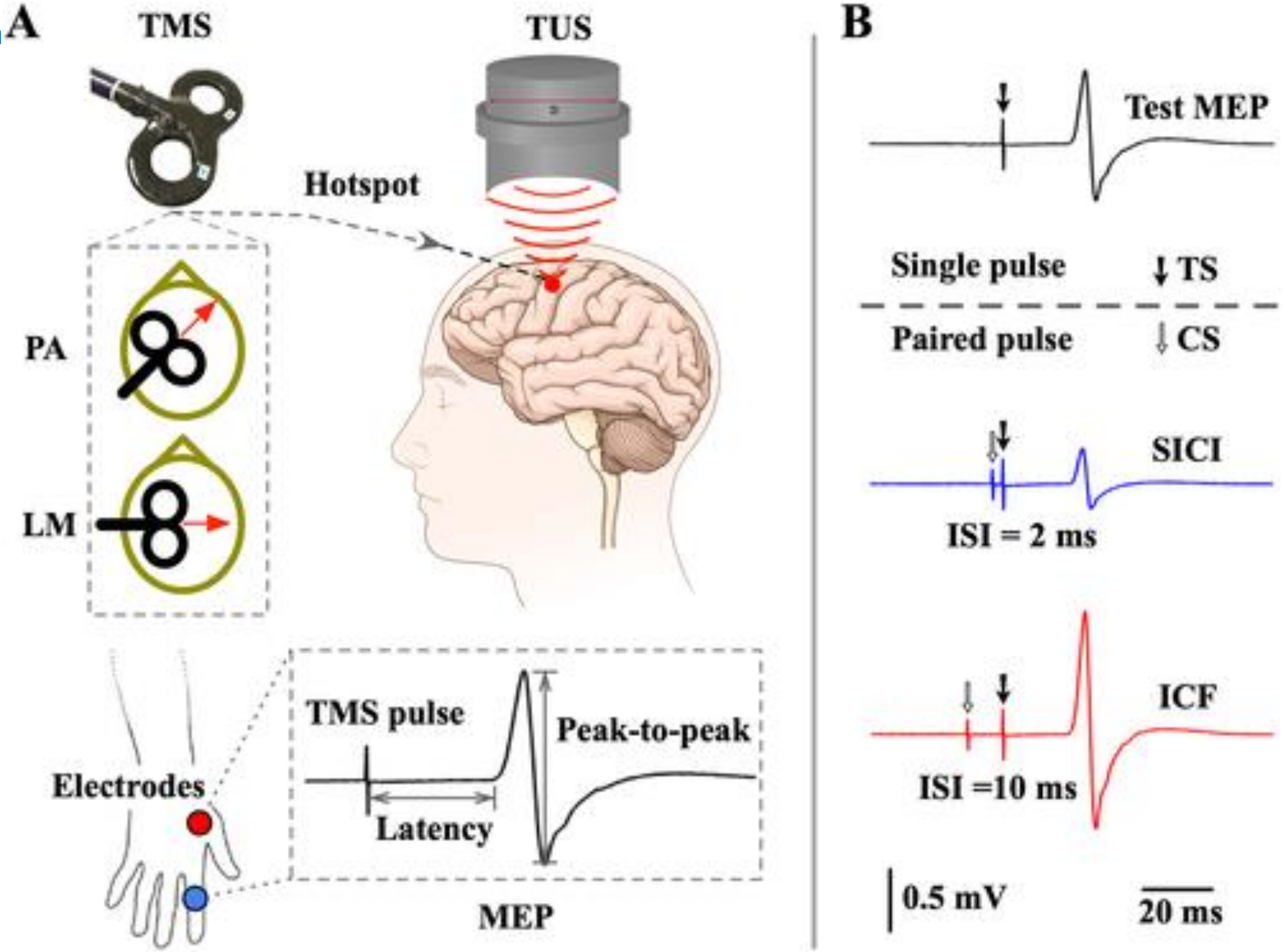
Nakajima et al., 2022, Cell Reports

> Ann Neurol. 2022 Feb;91(2):238-252. doi: 10.1002/ana.26294. Epub 2022 Jan 12.

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

Ke Zeng [1], Ghazaleh Darmani [1], Anton Fomenko [1], Xue Xia [1] [2], Stephanie Tra
Jean-François Nankoo [1], Yazan Shamli Oghli [1] [3], Yanqiu Wang [1] [2], Andres M
Robert Chen [1] [5]



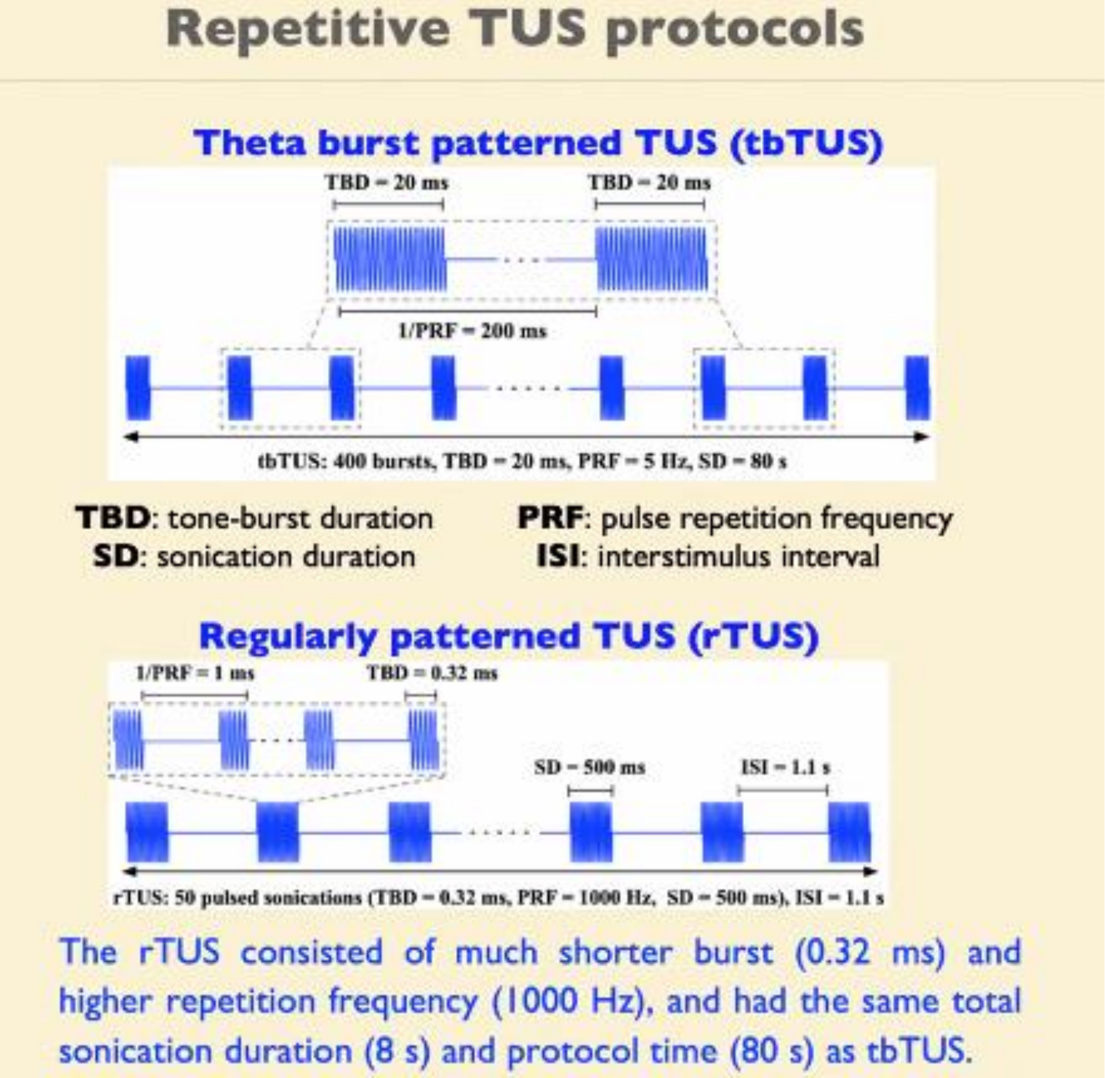


Zheng et al., 2022, Annals Neurol.

› Ann Neurol. 2022 Feb;91(2):238-252. doi: 10.1002/ana.26294. Epub 2022 Jan 12.

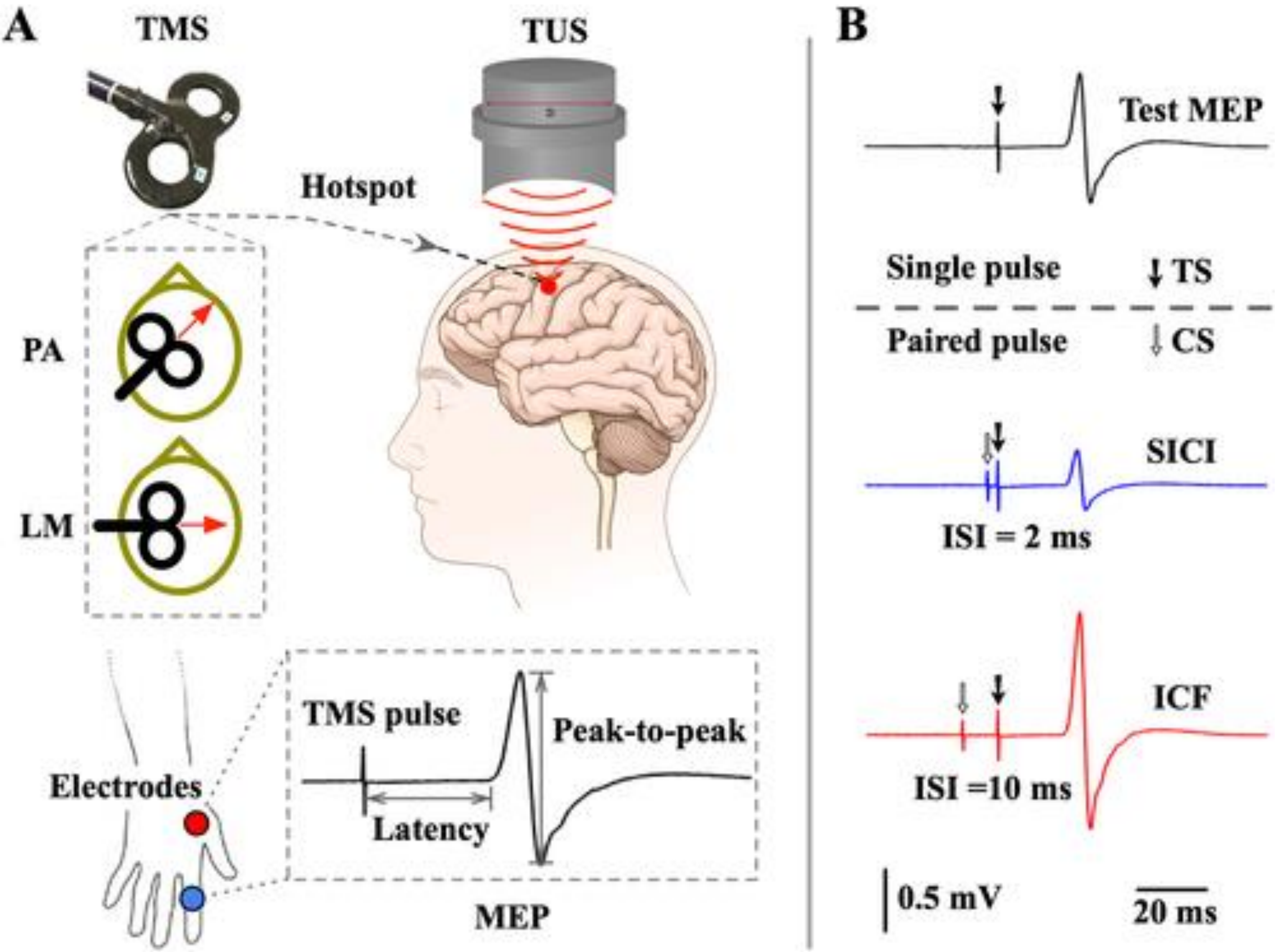
Induction of Human Motor Cortex Plasticity by Theta Burst Transcranial Ultrasound Stimulation

Ke Zeng [1], Ghazaleh Darmani [1], Anton Fomenko [1], Xue Xia [1 2], Stephanie Tran [1 3], Jean-François Nankoo [1], Yazan Shamli Oghli [1 3], Yanqiu Wang [1 2], Andres M Lozano [1 4], Robert Chen [1 5]



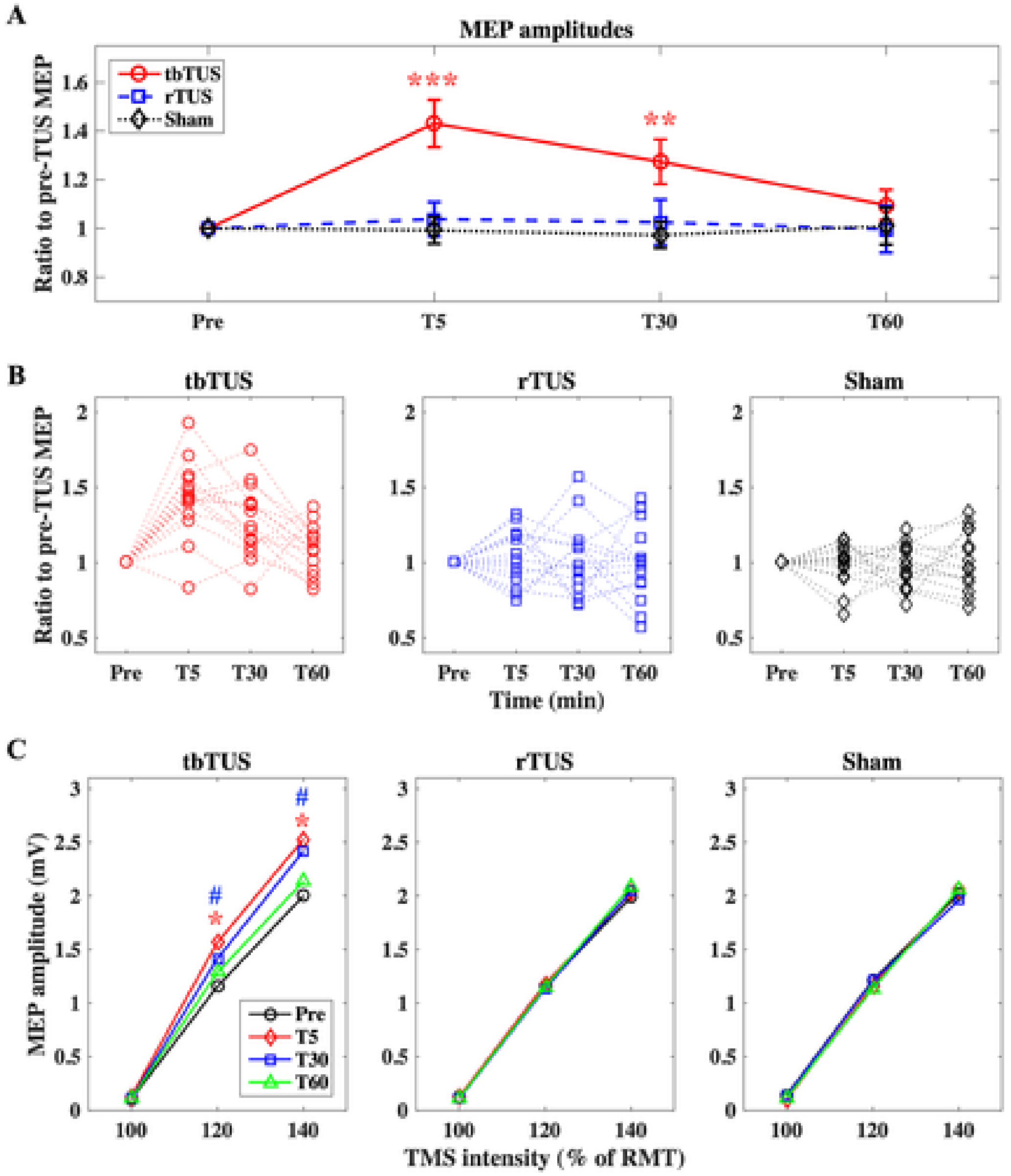
Zheng et al., 2022, Annals Neurol.

Towards offline neuromodulation



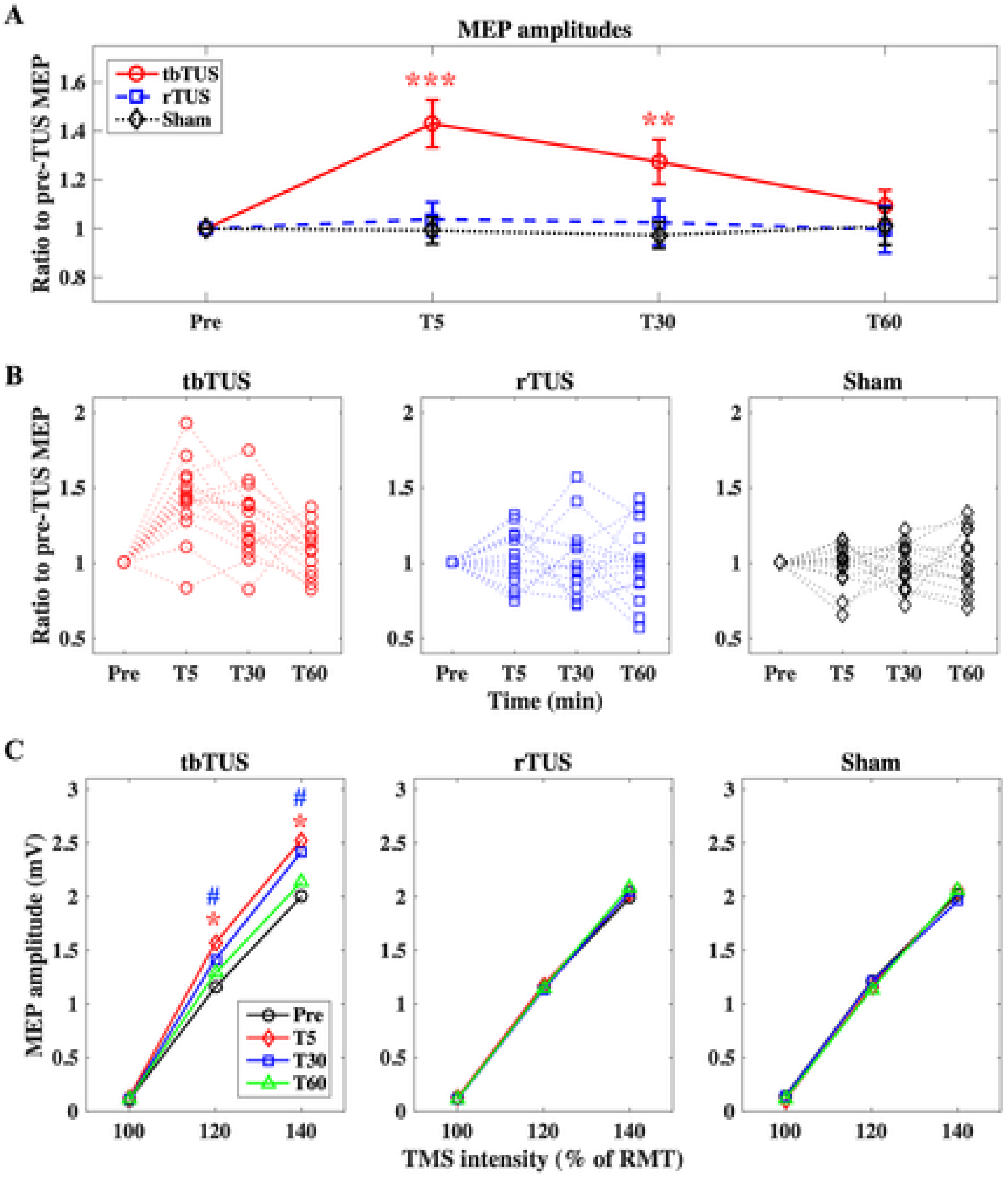
Zeng et al., 2022, Annals of Neurol.

Towards offline neuromodulation

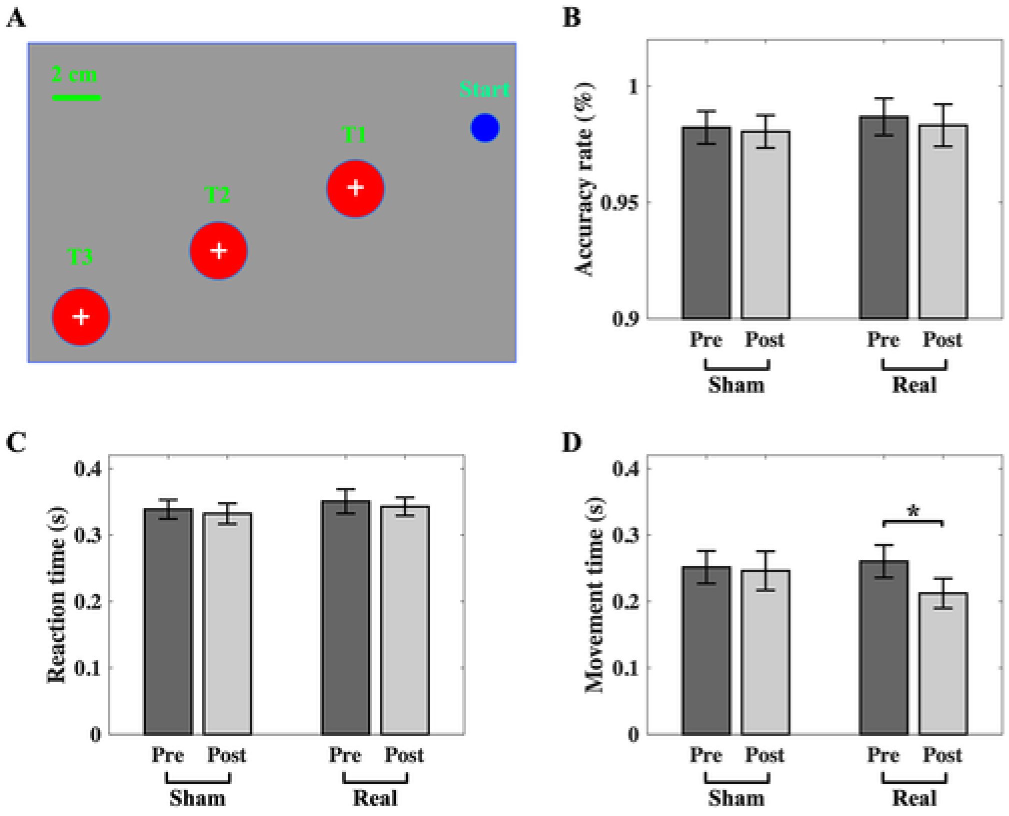


Zeng et al., 2022, Annals of Neurol.

Towards offline neuromodulation

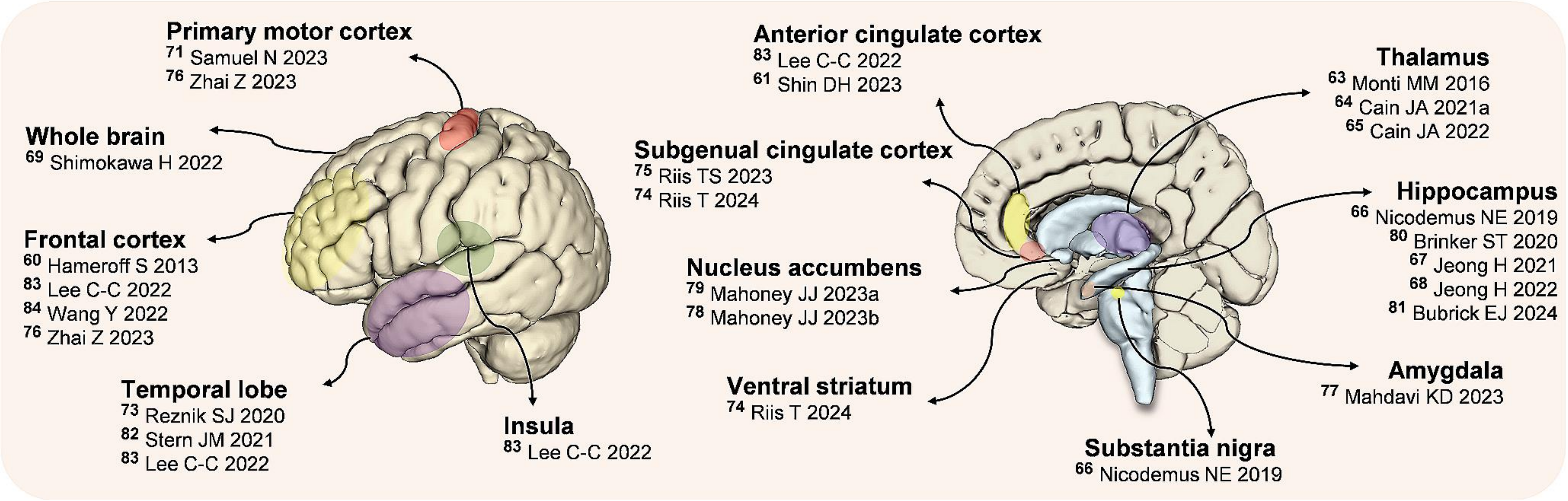


Zeng et al., 2022, Annals of Neurol.



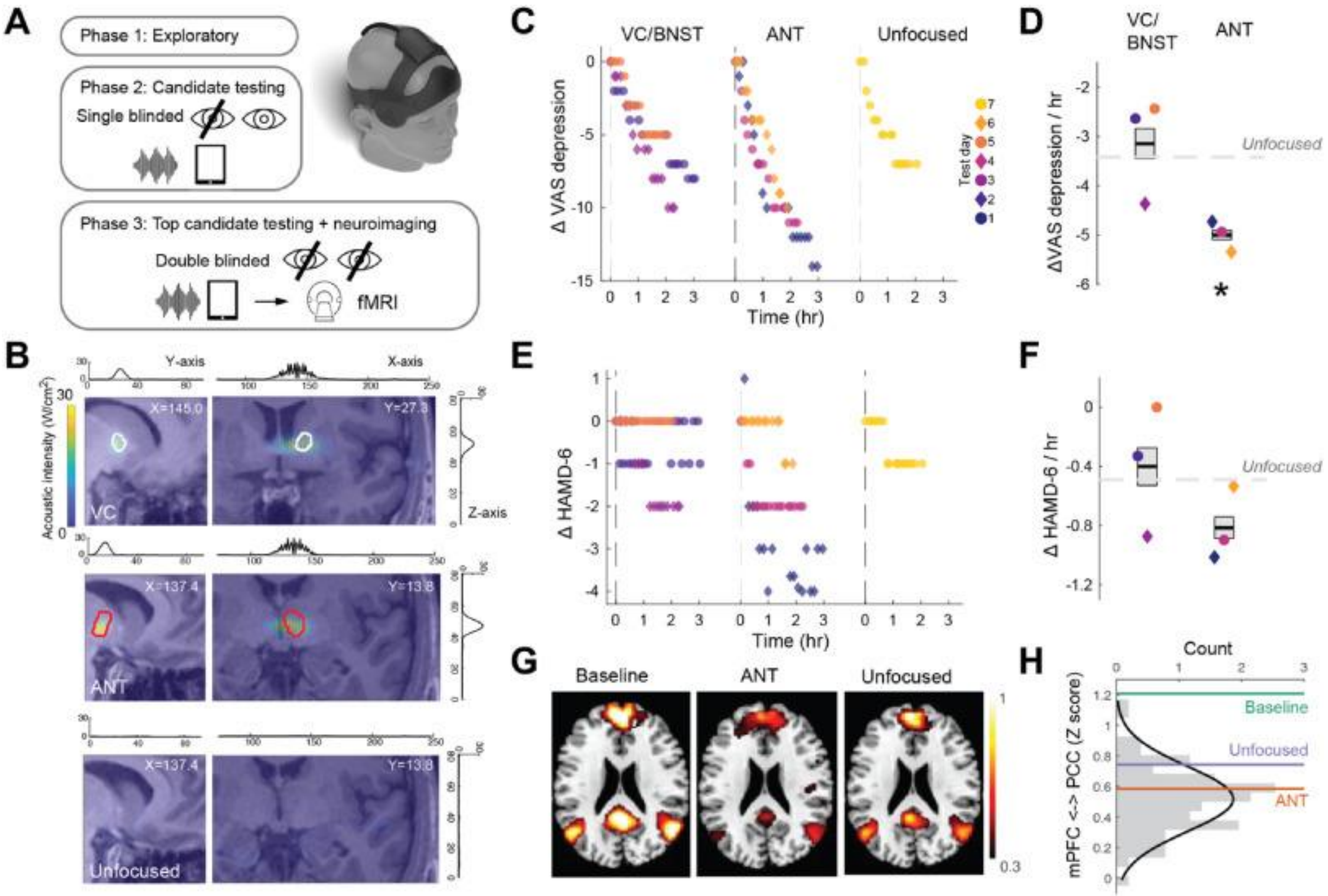
Clinical applications

Clinical studies

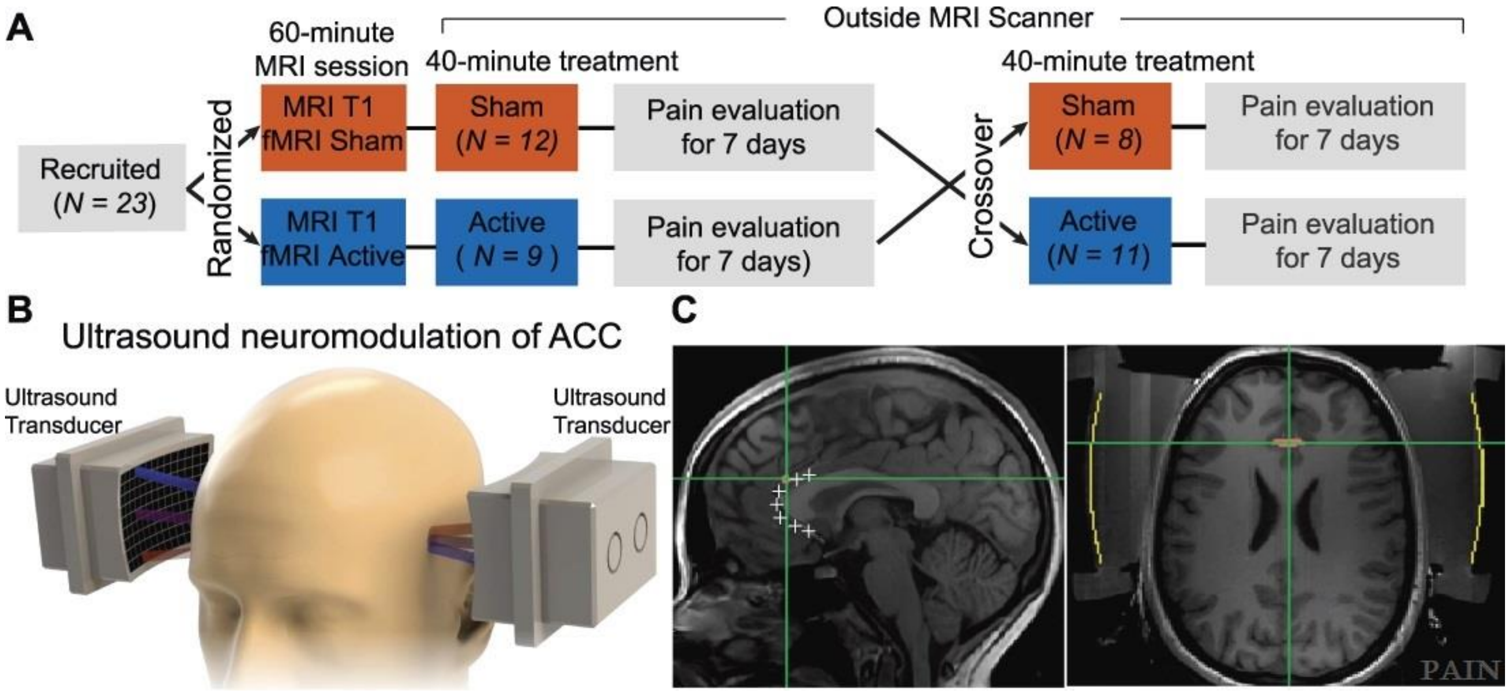


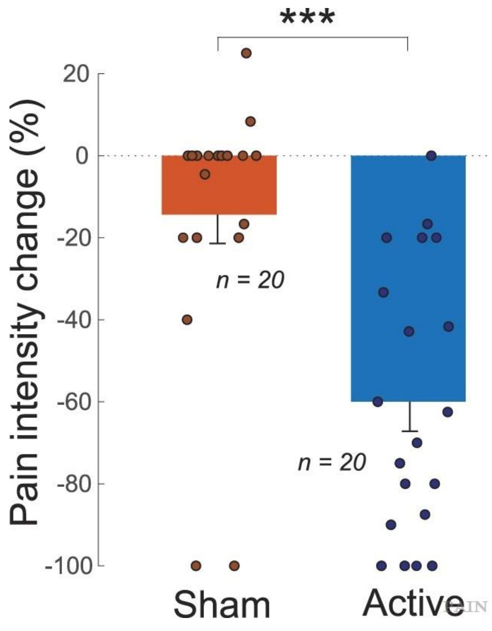
Lee et al., 2024, BEL

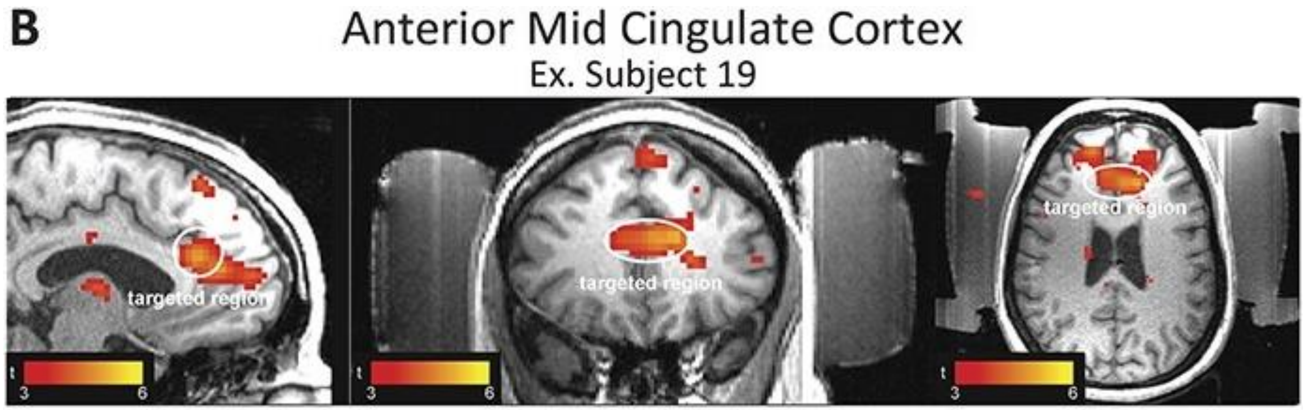
TUS for depression

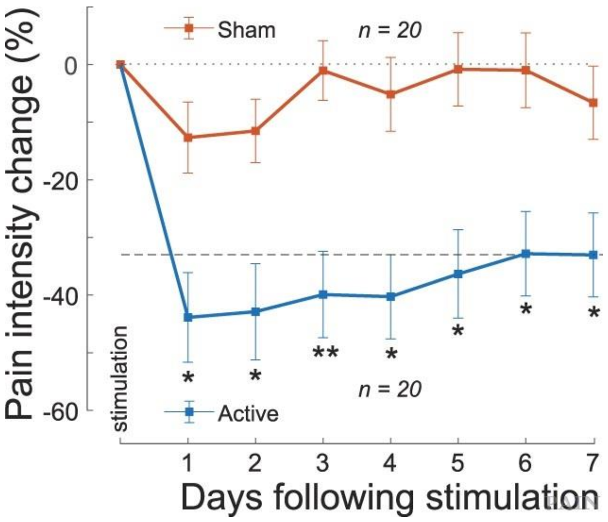


TUS for chronic pain





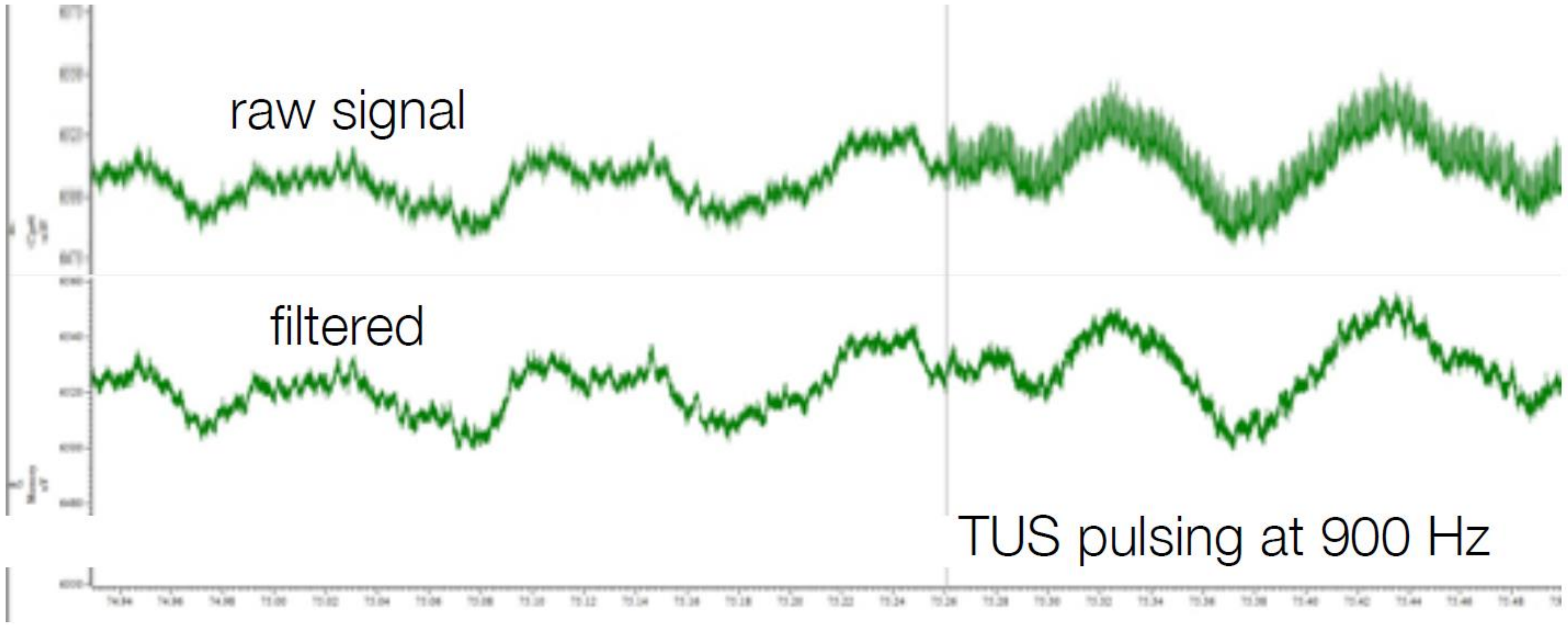




Multimodal experiments

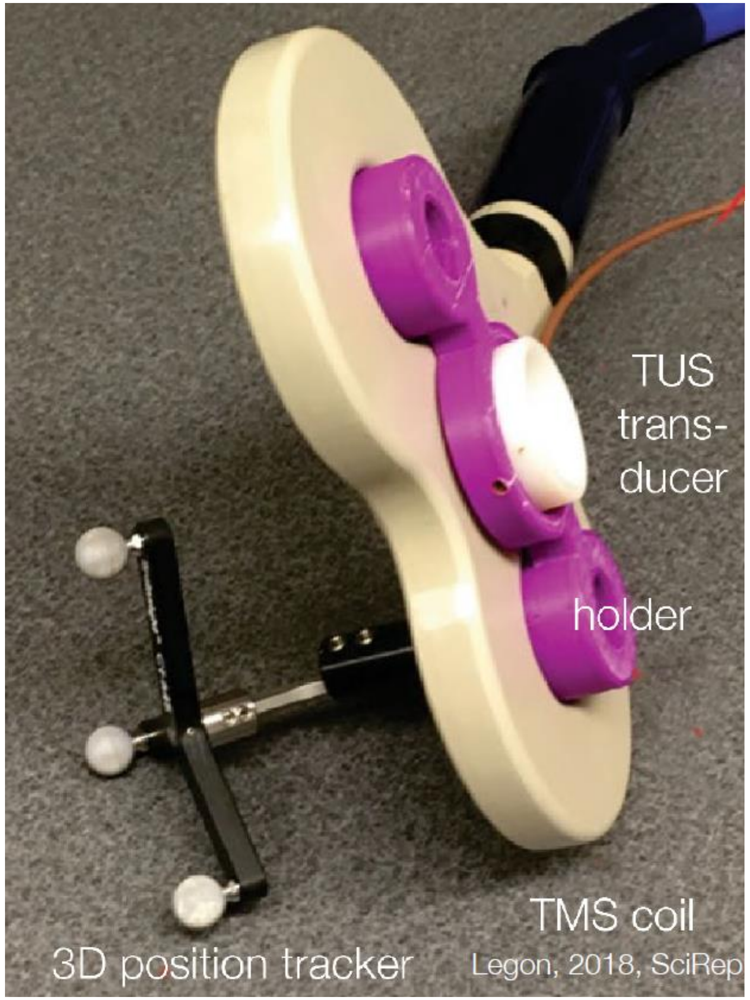
Combining TUS with EEG

TUS pulsing artefact on EEG

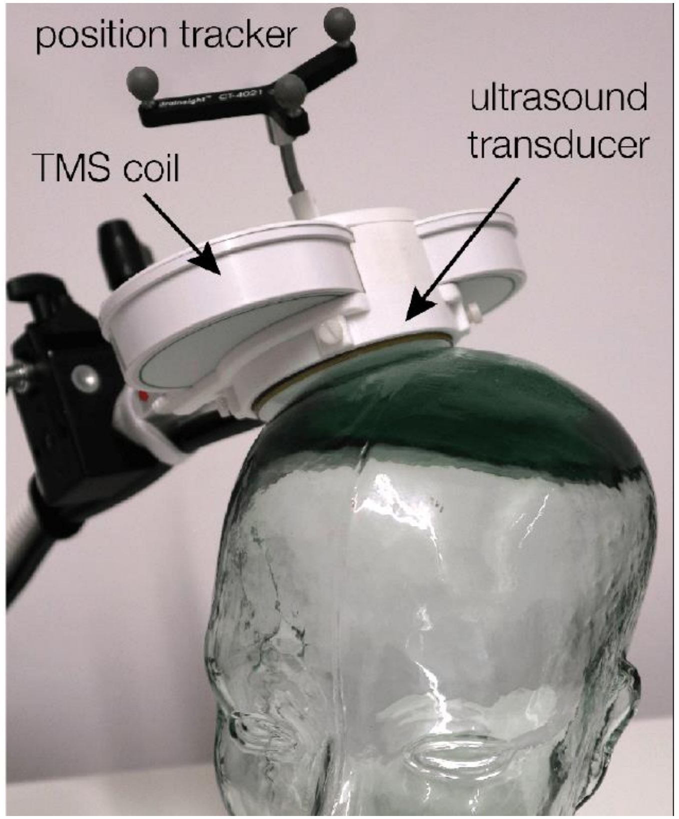


Fomenko, 2021, unpublished

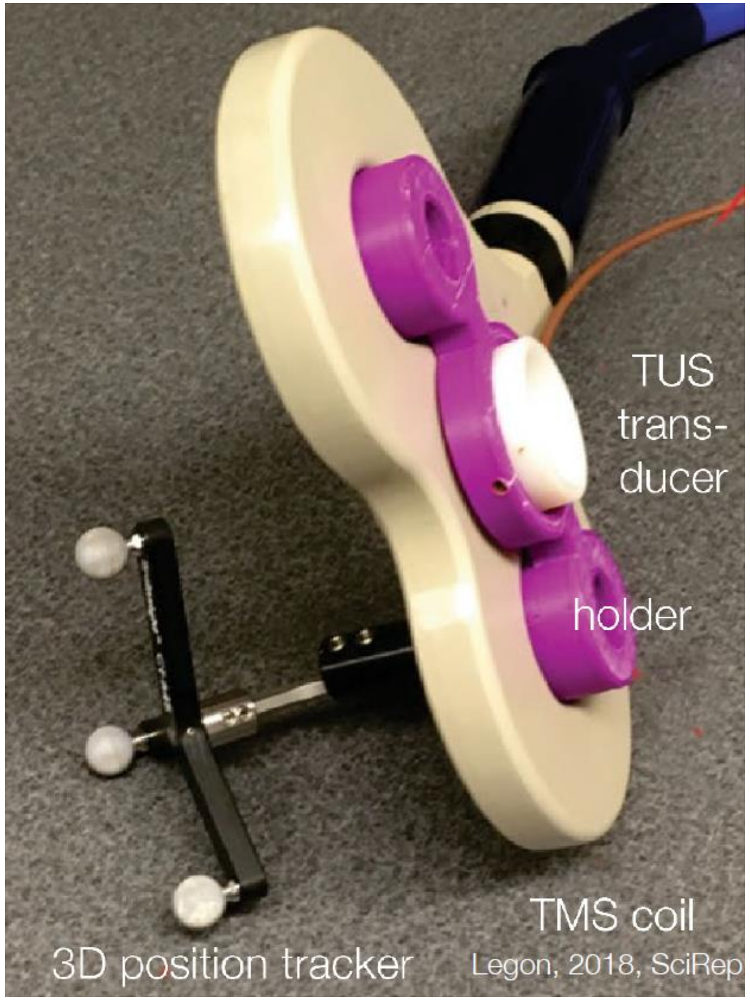
Combining TUS with TMS



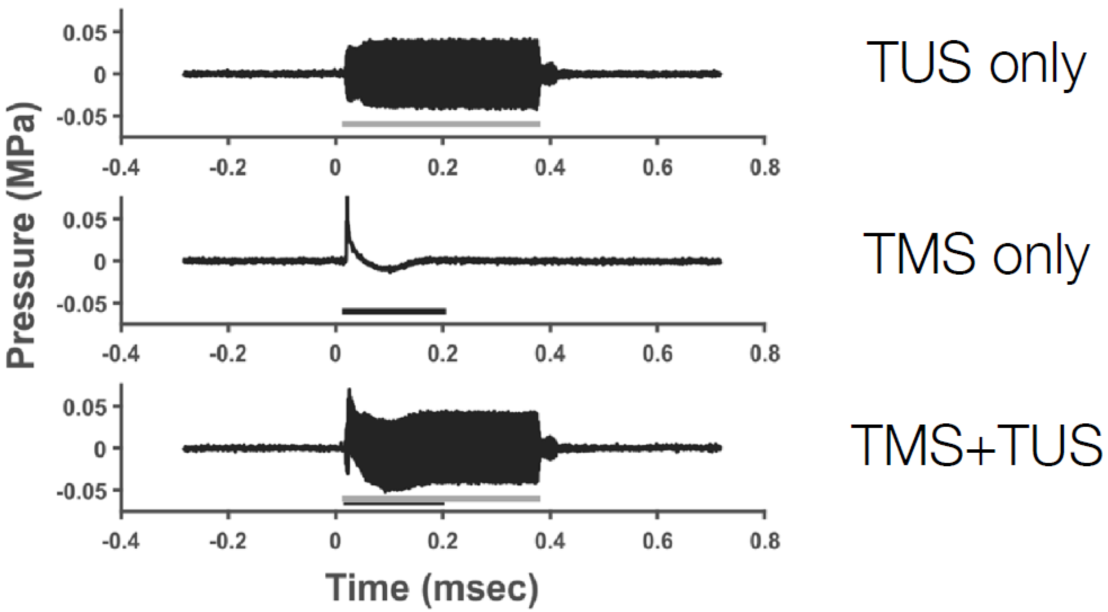
NeuroFUS + TMS
Brainbox system



Multimodal TUS studies



TMS artefact on TUS pressure measurement



Legon, 2018, SciRep

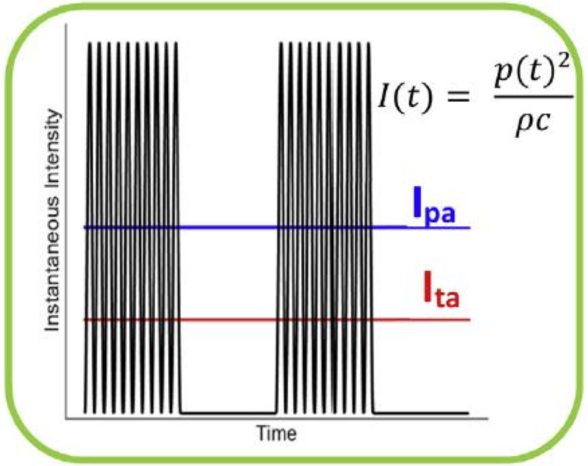
Designing experiments

- 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/cm2 from IEC standard 60601-2-5 for physiotherapy US equipment)

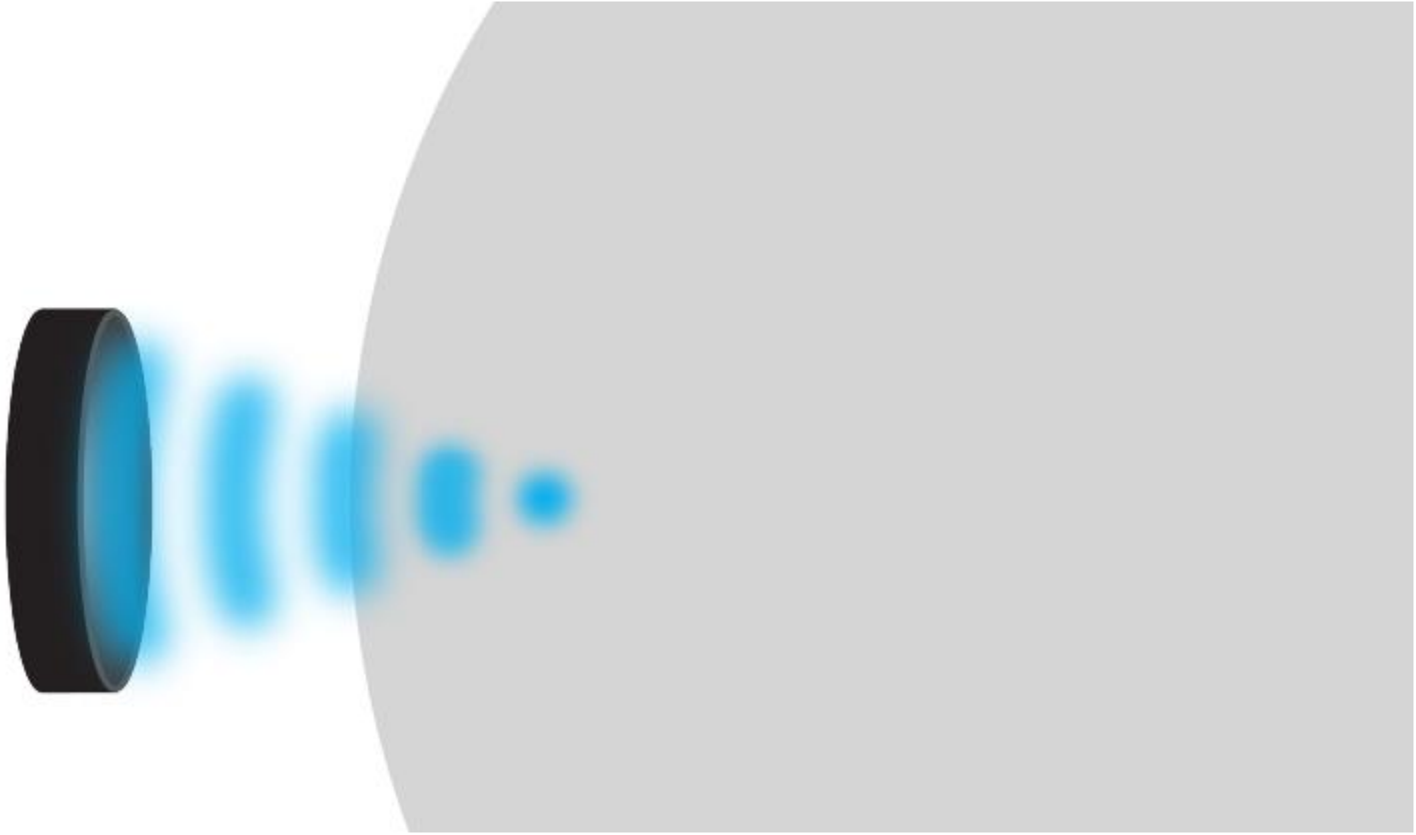
Bioeffects	ITRUSST parameters and levels
Mechanical	
	MI or MI_{tc} ≤ 1.9 in the brain and in the skin
Thermal	Any of:
	Maximum exposure time depending on the level of TIC*: 80 min 1.5 < TIC ≤ 2.0 40 min 2.0 < TIC ≤ 2.5 10 min 2.5 < TIC ≤ 3.0 160 sec 3.0 < TIC ≤ 4.0 40 sec 4.0 < TIC ≤ 5.0 10 sec 5.0 < 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.).

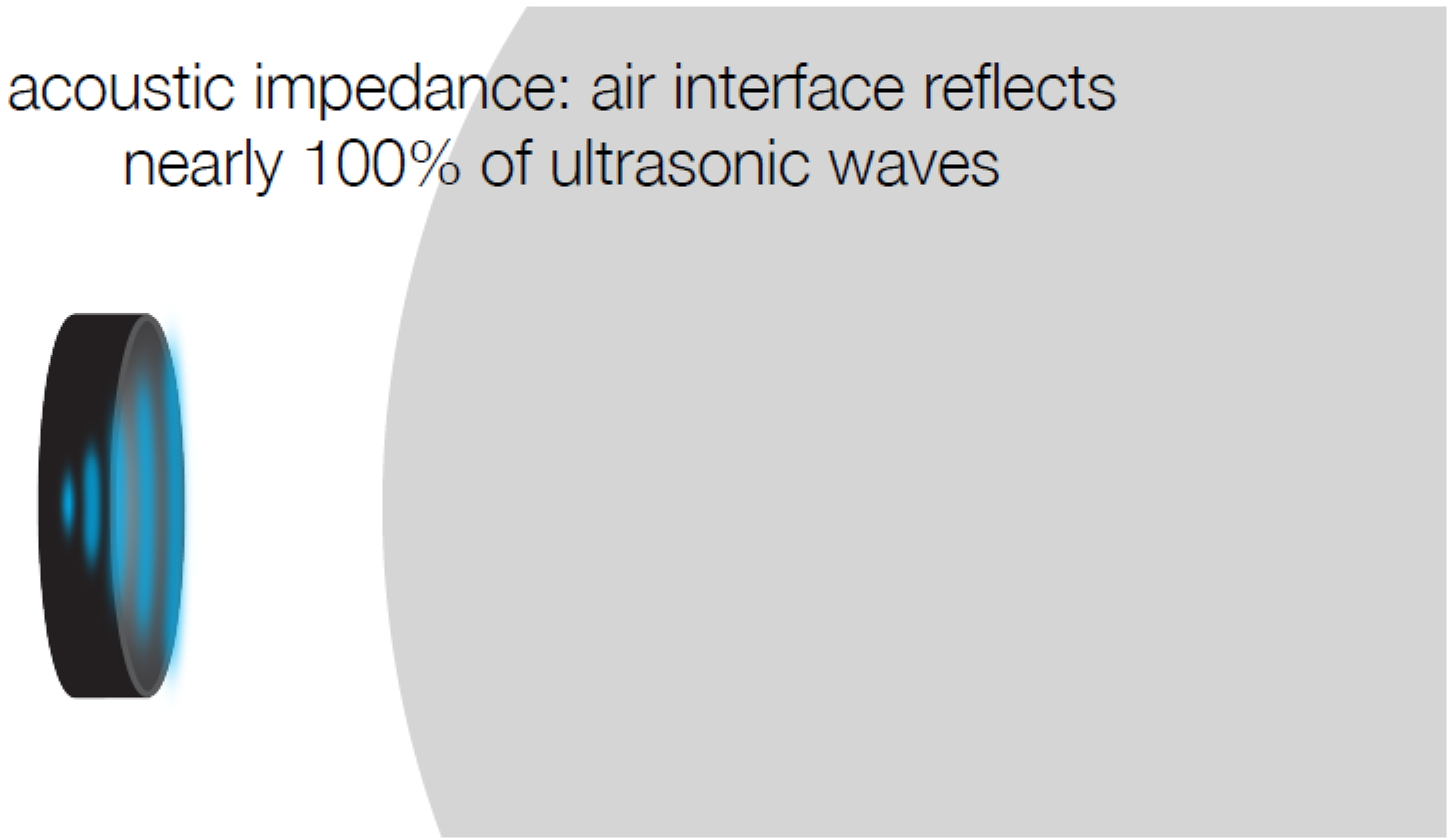
Aubry, et al. iTRUSST 2023

The coupling method

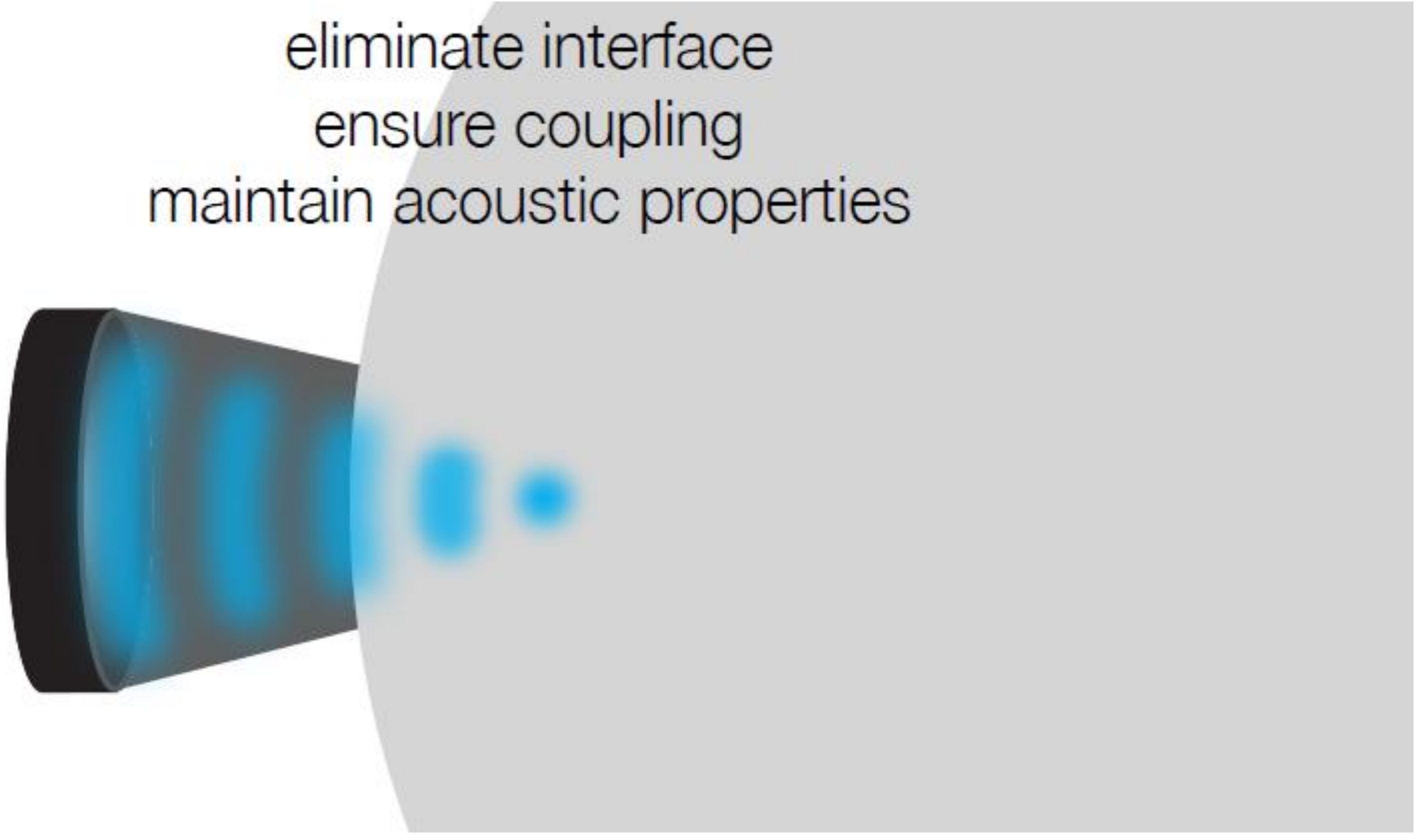
The coupling method



The coupling method



The coupling method



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

Verhagen et al, 2019, eLife

The coupling method

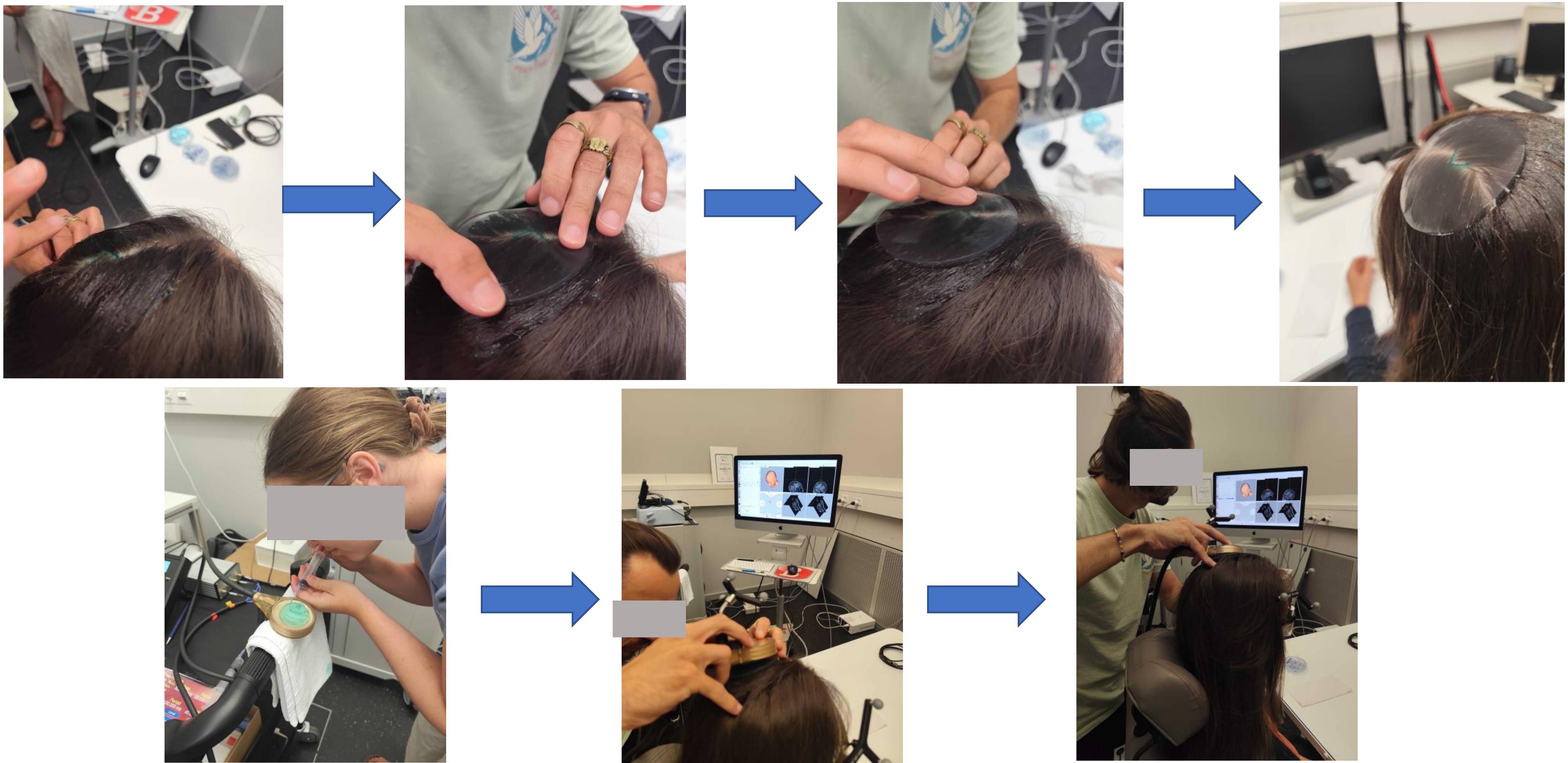
The coupling method

The coupling method

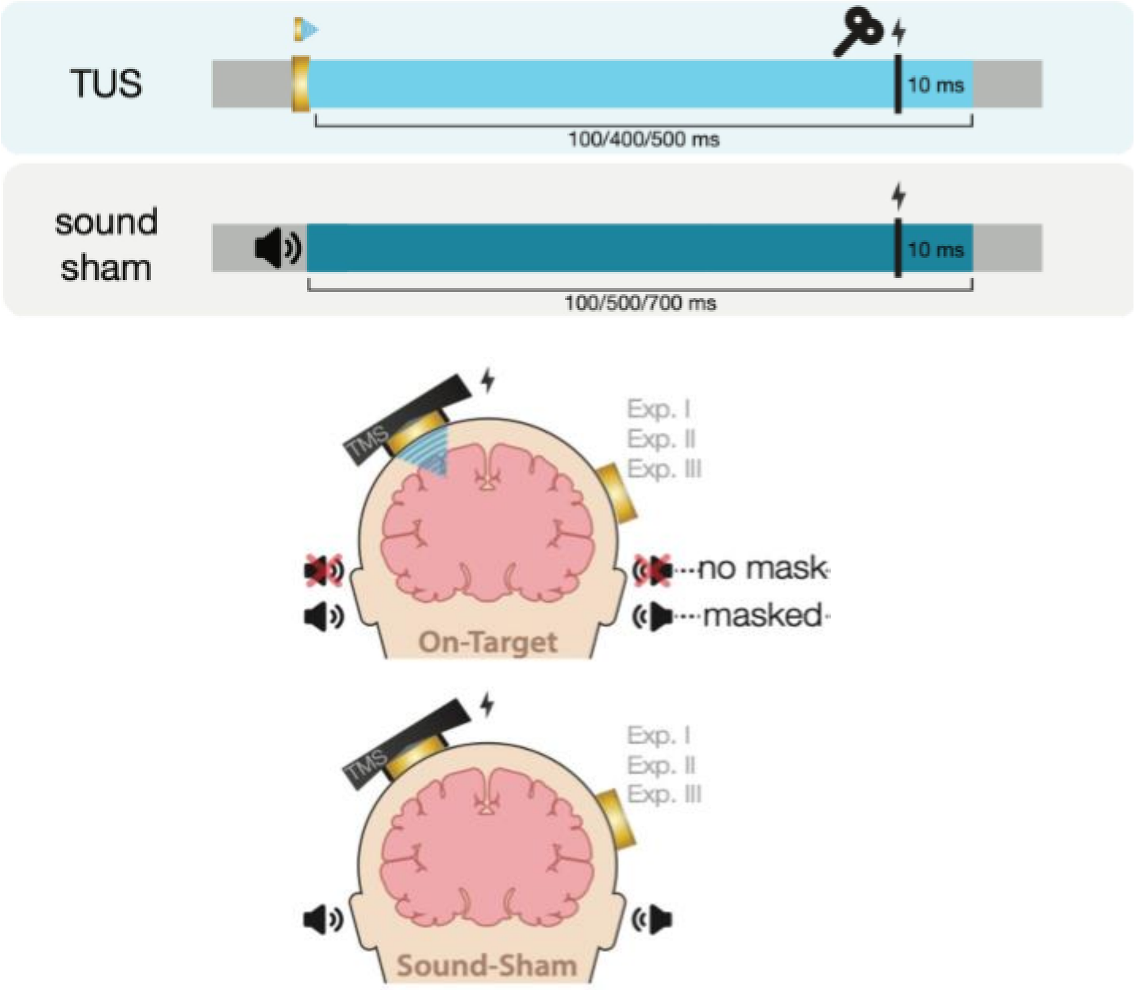
coupling media:
safety + efficacy

- 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

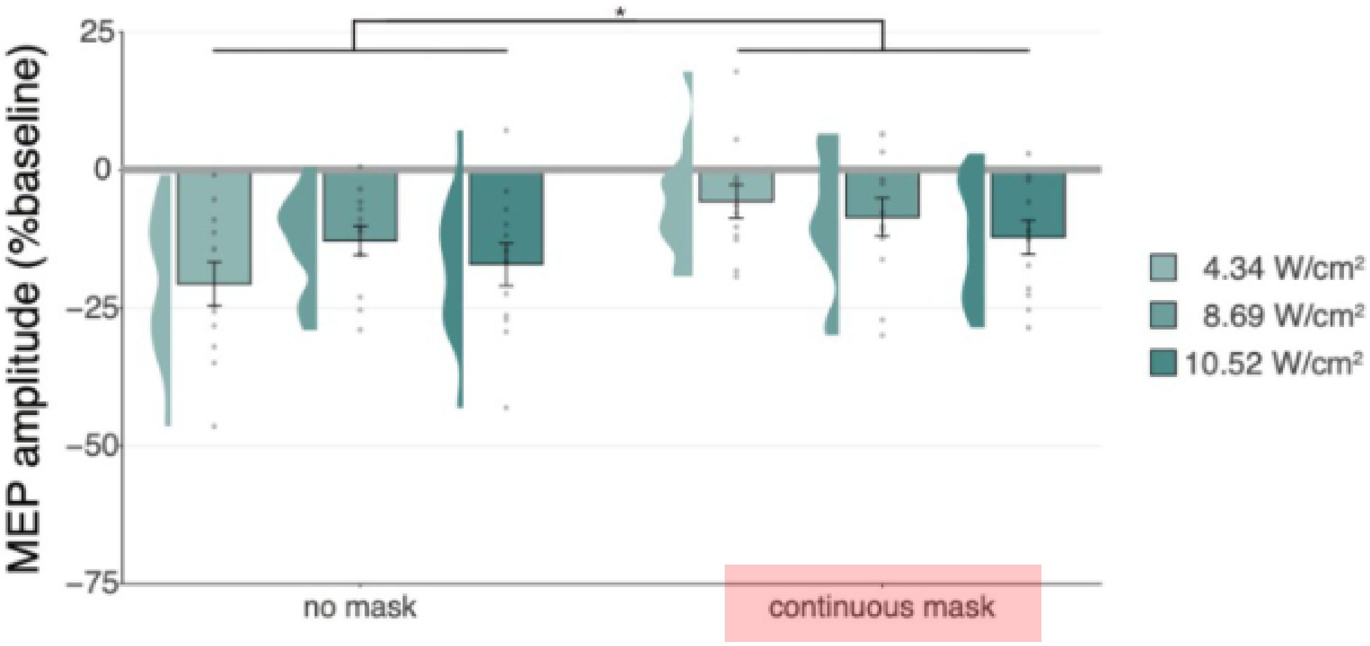


The auditory confound



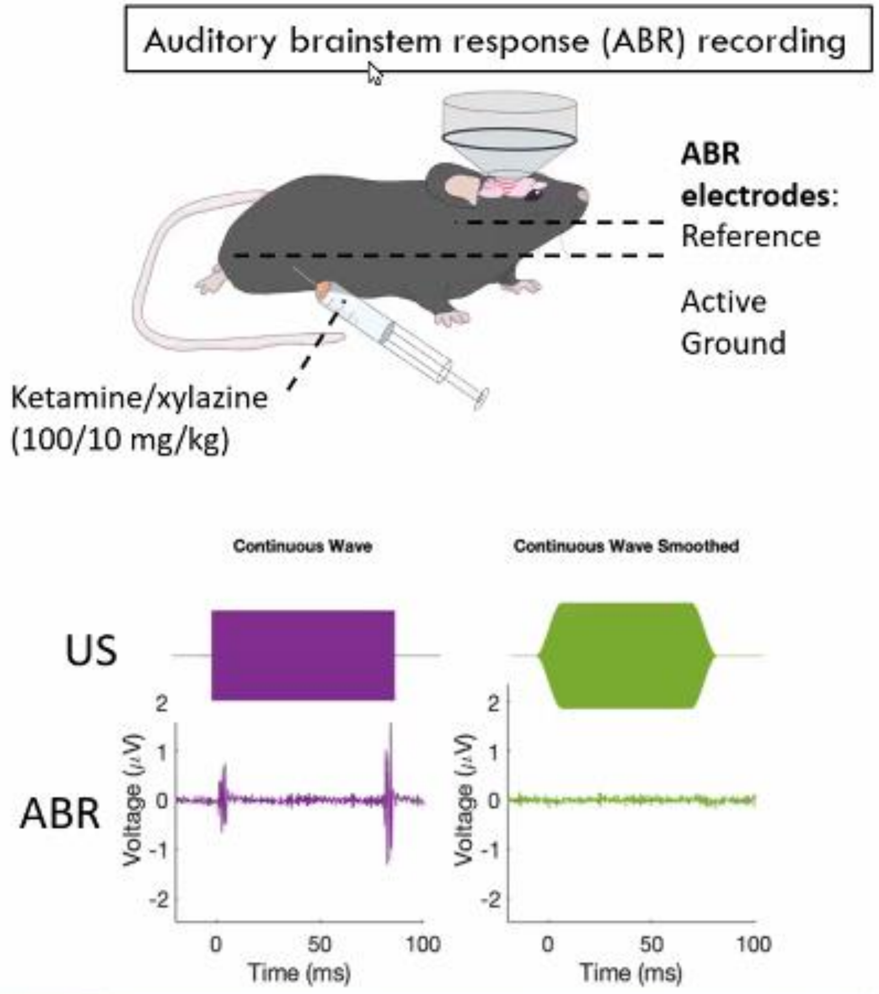
Sign. MEP inhibition

No effect



Kop et al., 2023, eLlife

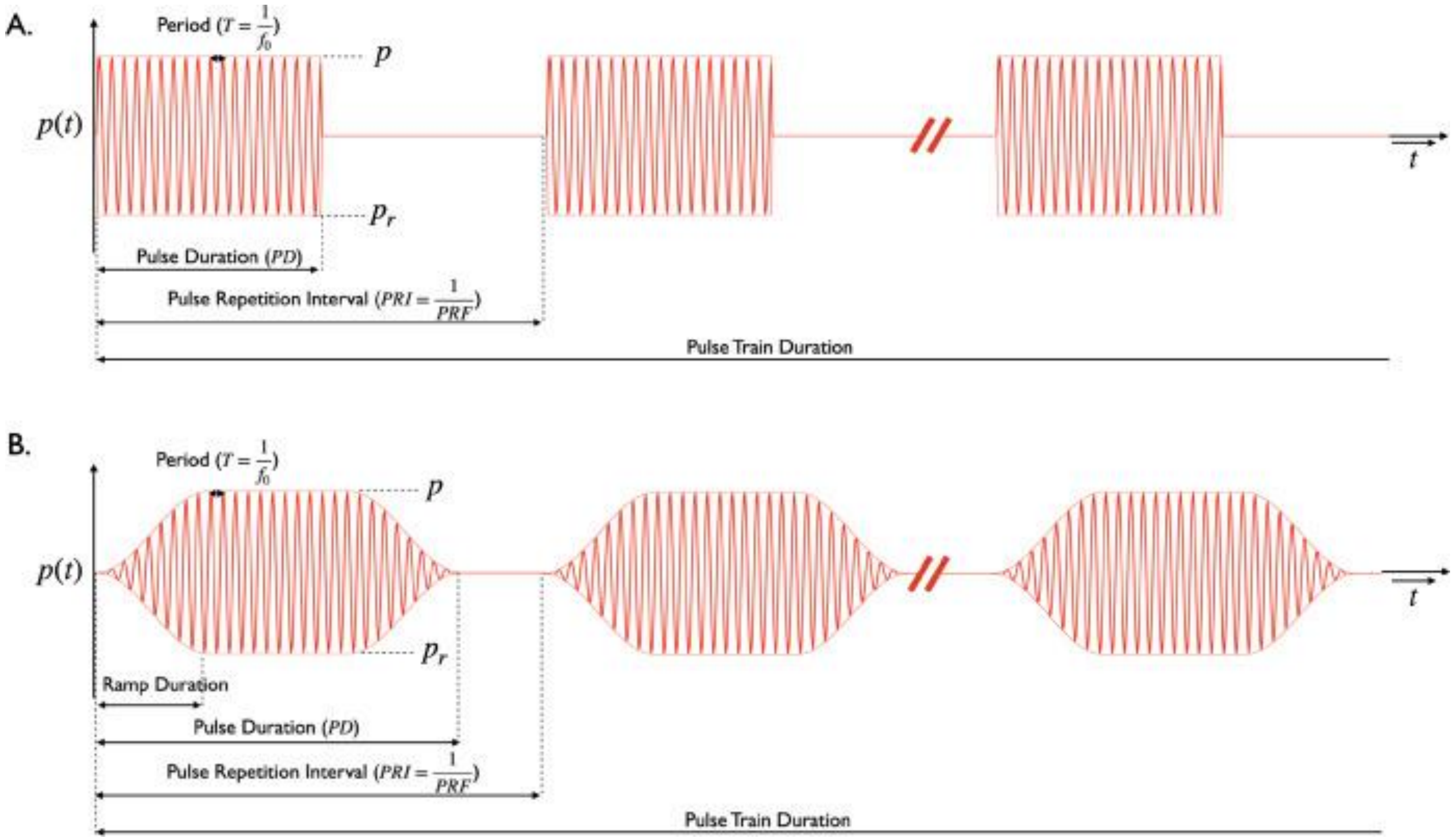
The auditory confound ➔ can be eliminated with smoothed wave



- Smoothed wave can eliminate the auditory effects

Mohammadjavadi M, Ye P P, Xia A, et al. Elimination of peripheral auditory pathway activation does not affect motor responses from ultrasound neuromodulation[J]. Brain stimulation, 2019, 12(4): 901-910.

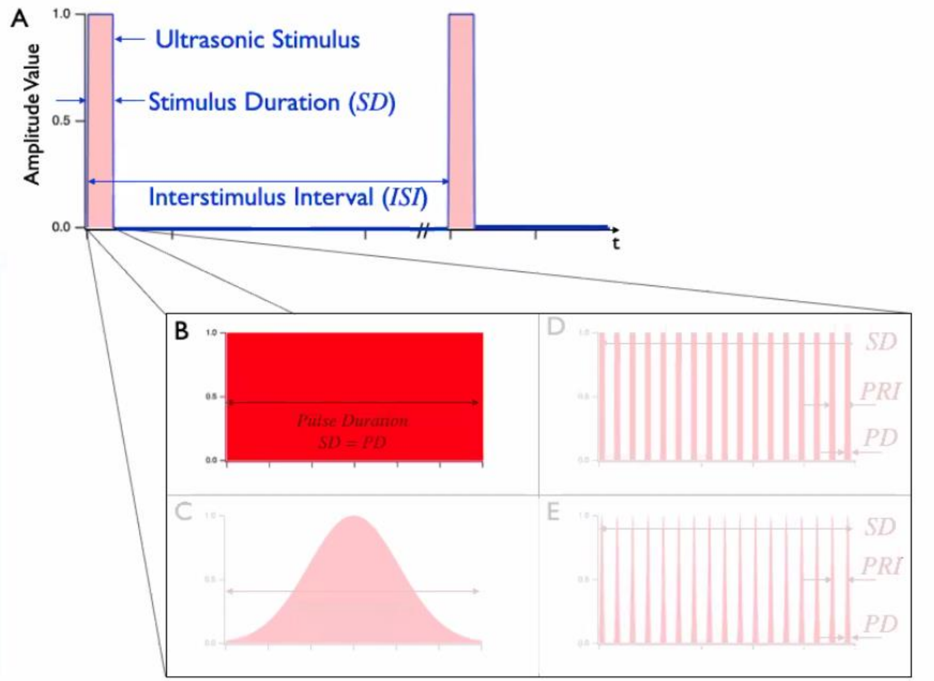
The auditory confound



Martin et al., 2024, Brain Stim.

The parameters' space

Temporal characteristics



Intensity characteristics

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
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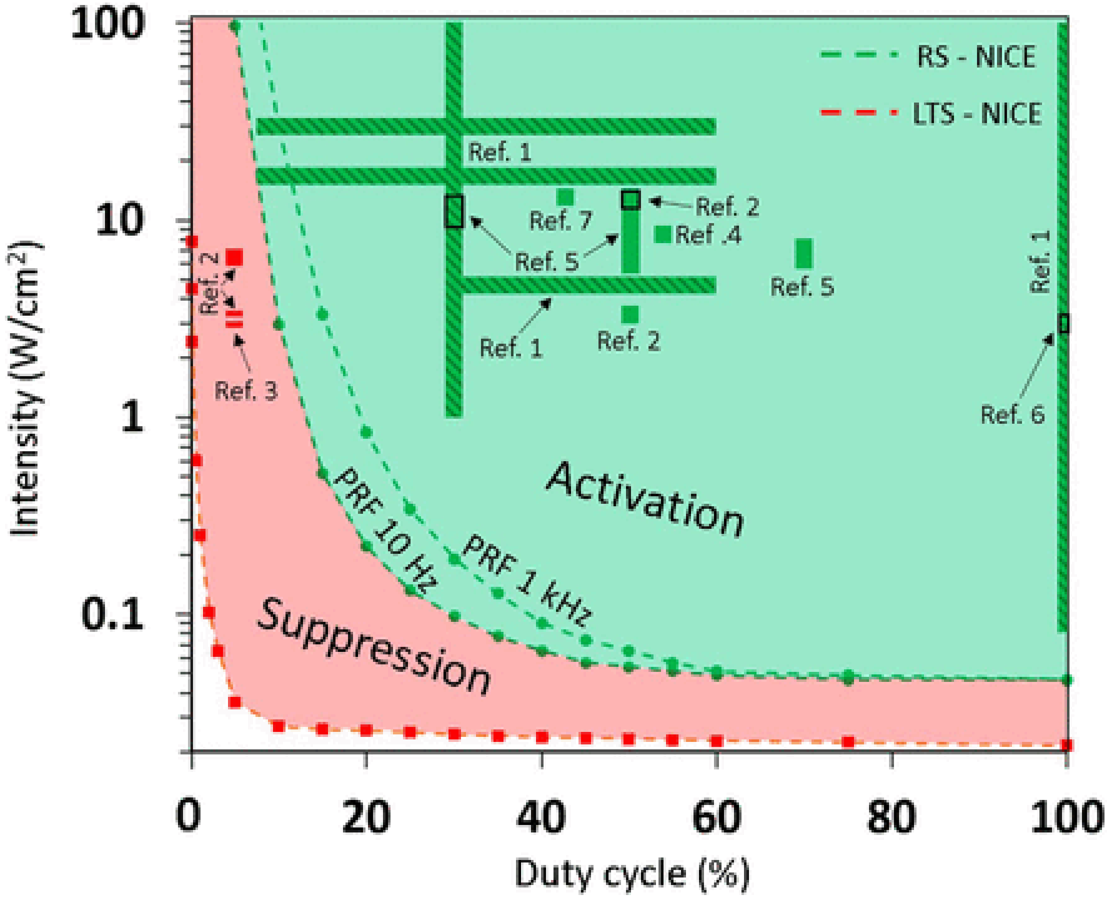


Plaskin, 2016

Delivering the proper dose

Deliver deterministic intensity (through the skull)

Skull aberrations:

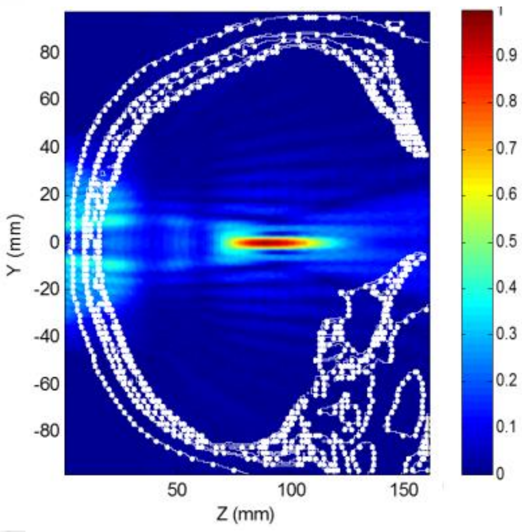
Dephasing

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

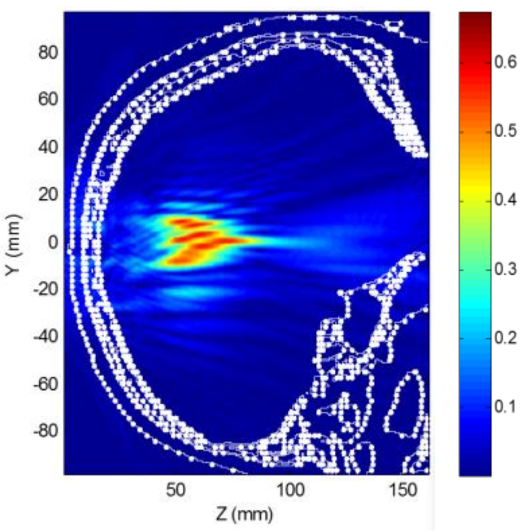
Attenuation

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

Homogeneous beam

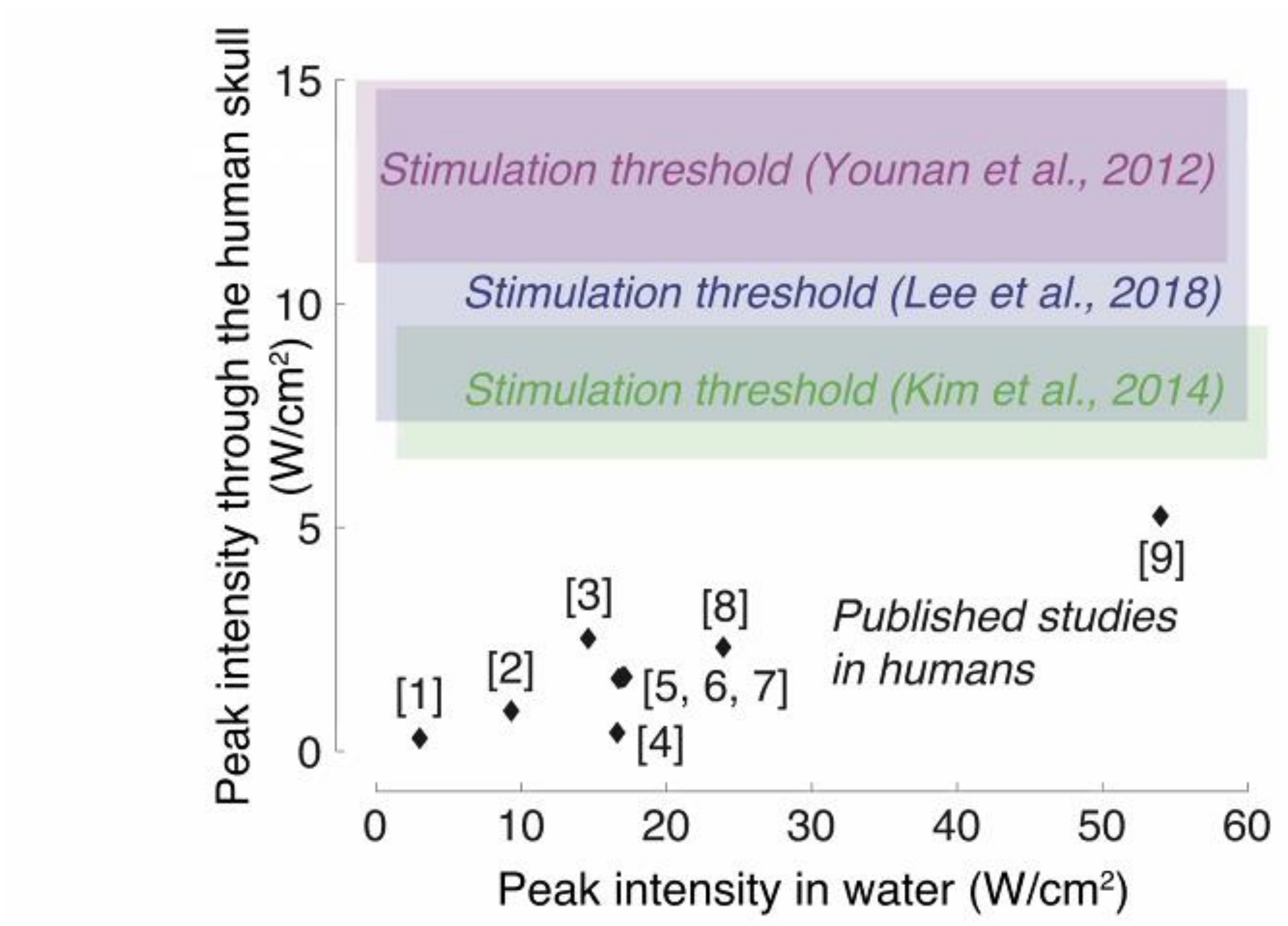


Skull aberrated beam



Delivering the proper dose

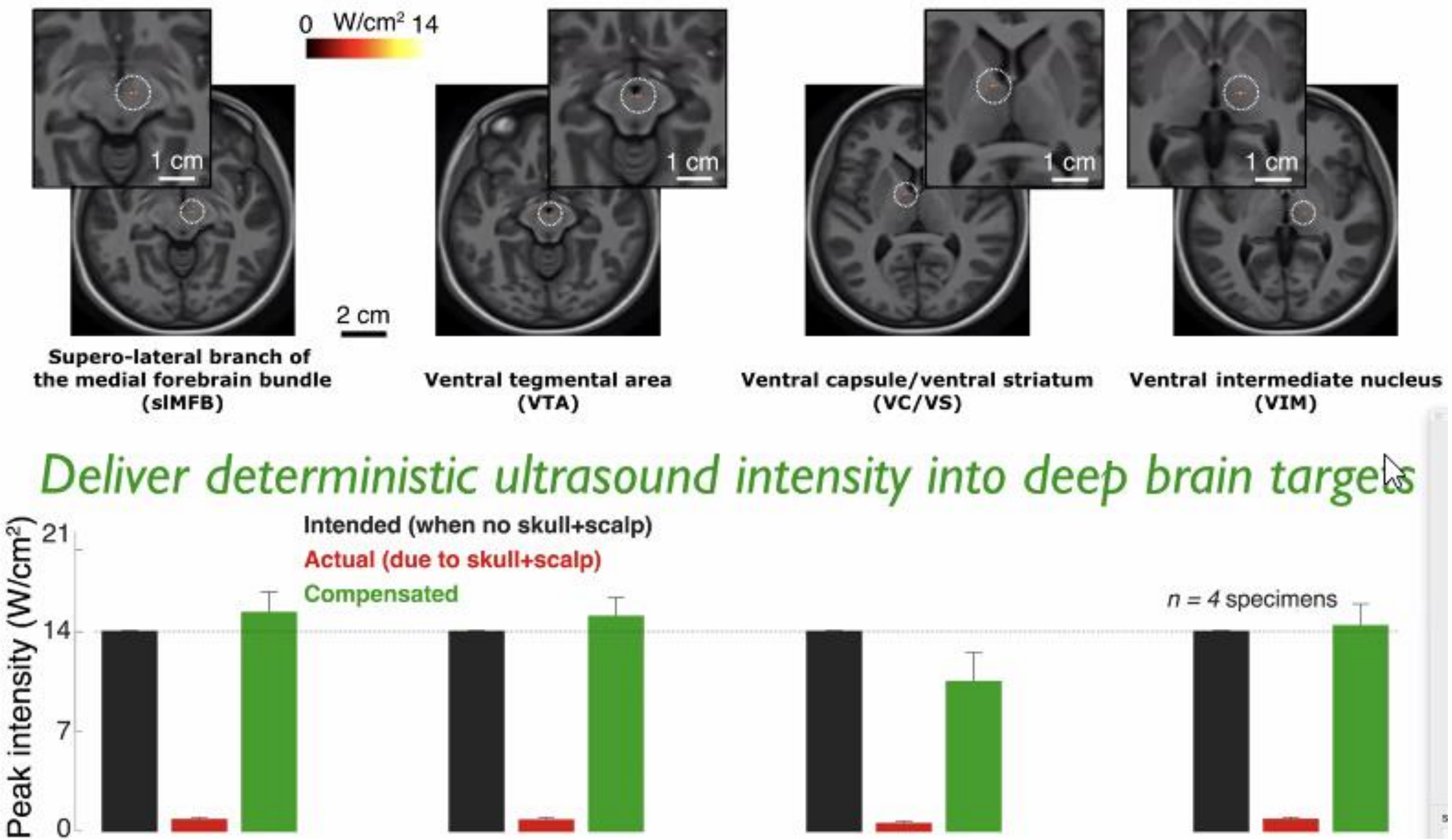
➔ TUS studies in humans have delivered inadequate intensity



Riis, Webb, Kubanek, 2021, Ultrasonics

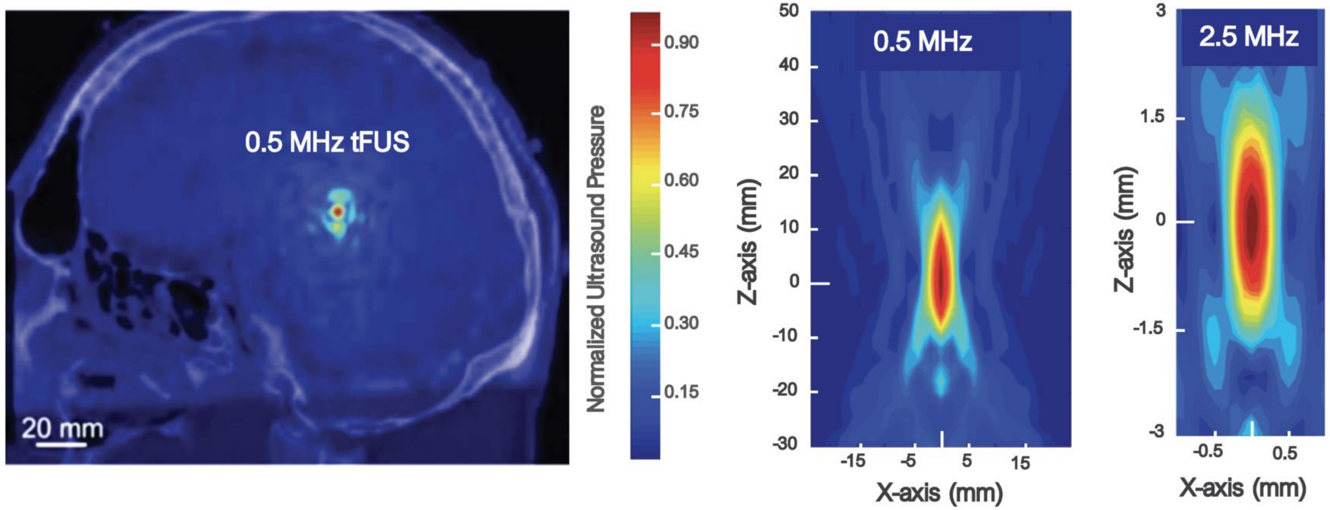
Delivering the proper dose

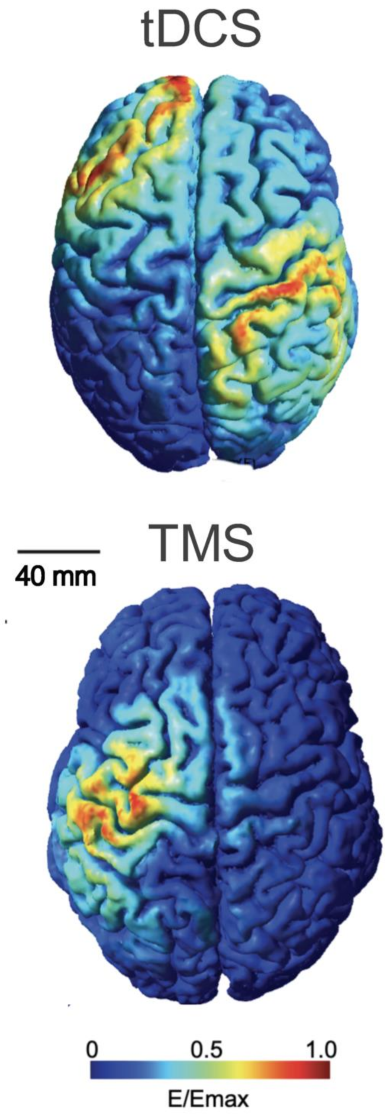
➔ Human system that compensates for attenuation accurately



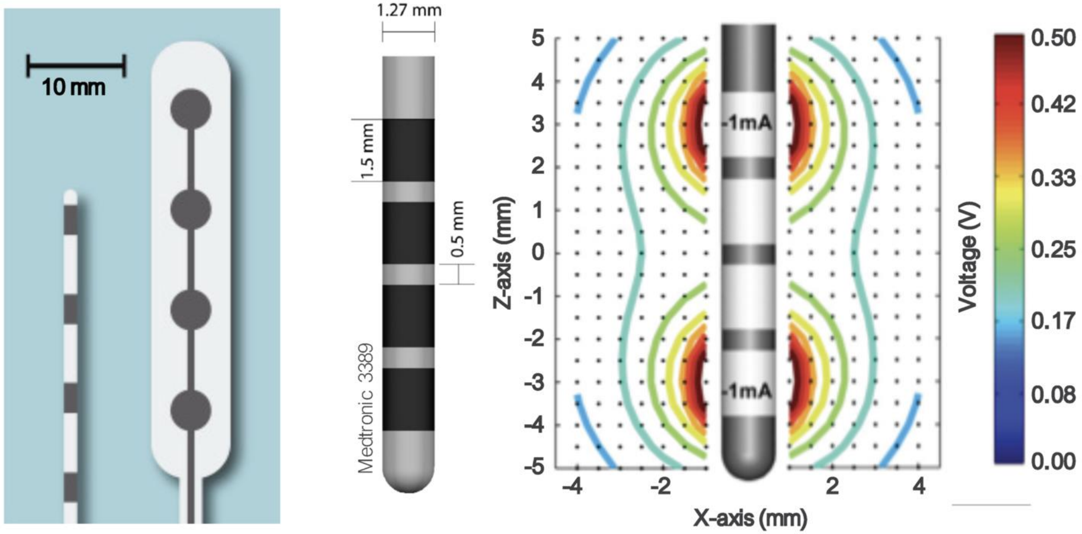
Targeting

Noninvasive Neuromodulation by Focused Ultrasound

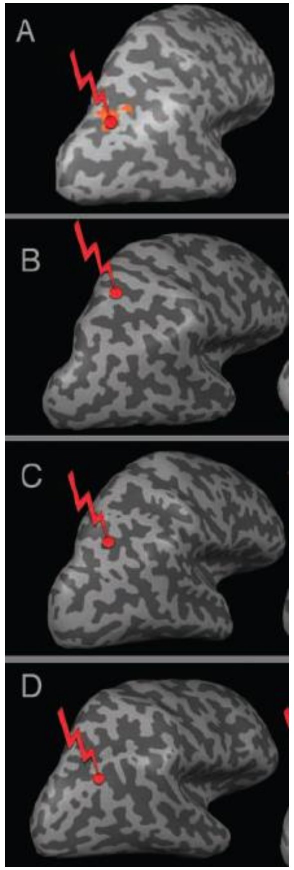




Surgically Implanted SCS and DBS Electrodes



Targeting: Anatomic/Functional planning

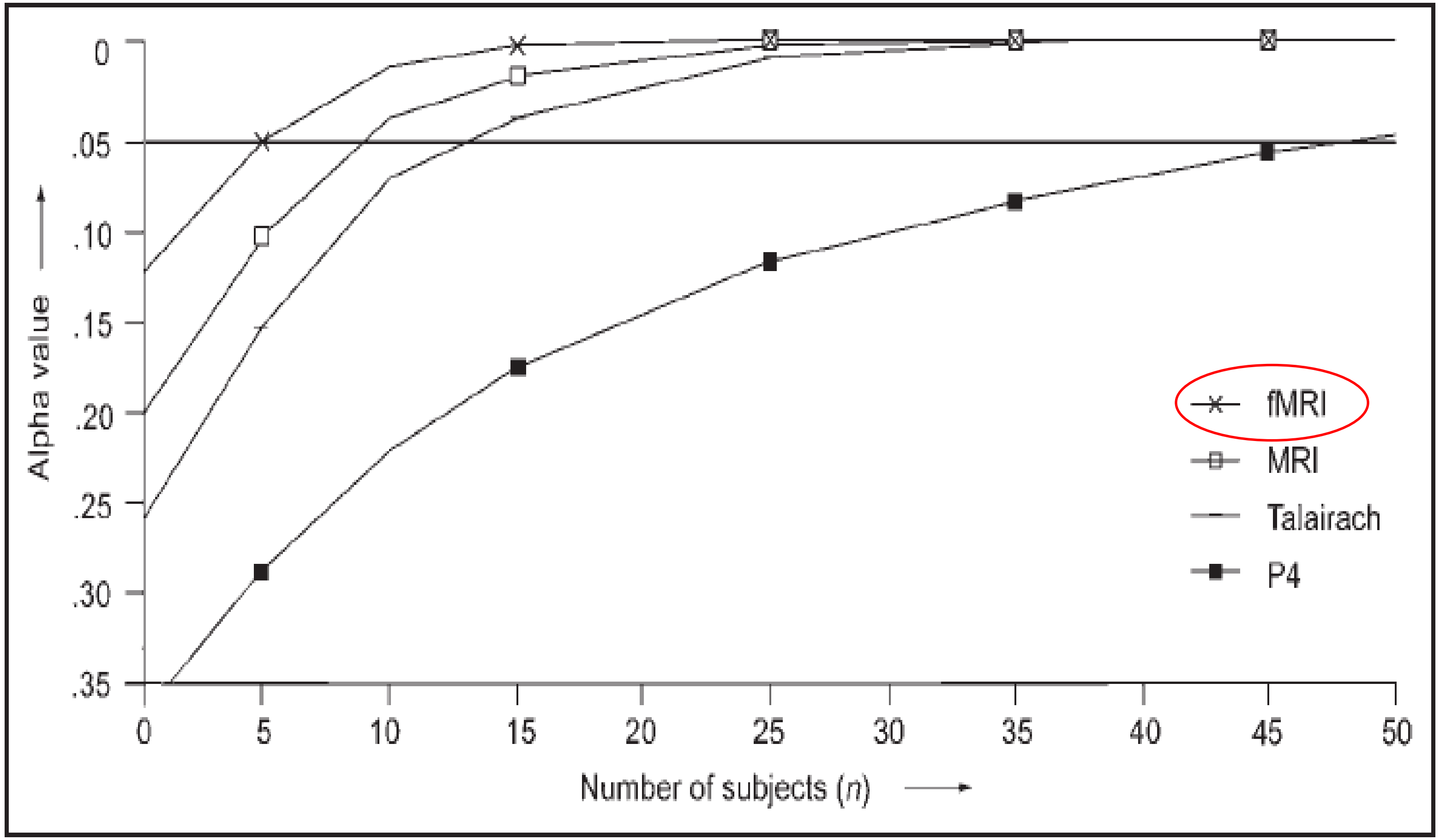


fMRI

sMRI

Talairach

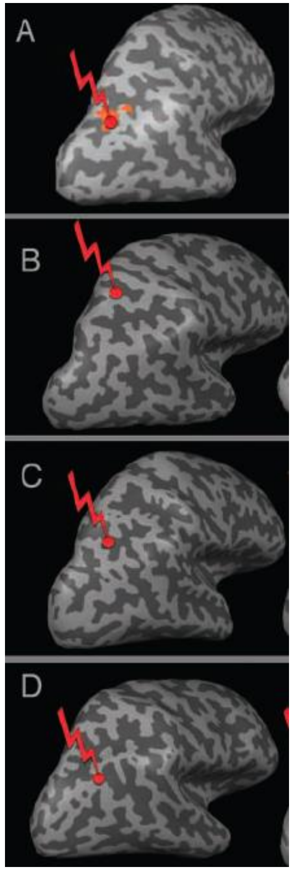
10-20 EEG



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

Sack, 2009

Targeting: Anatomic/Functional planning

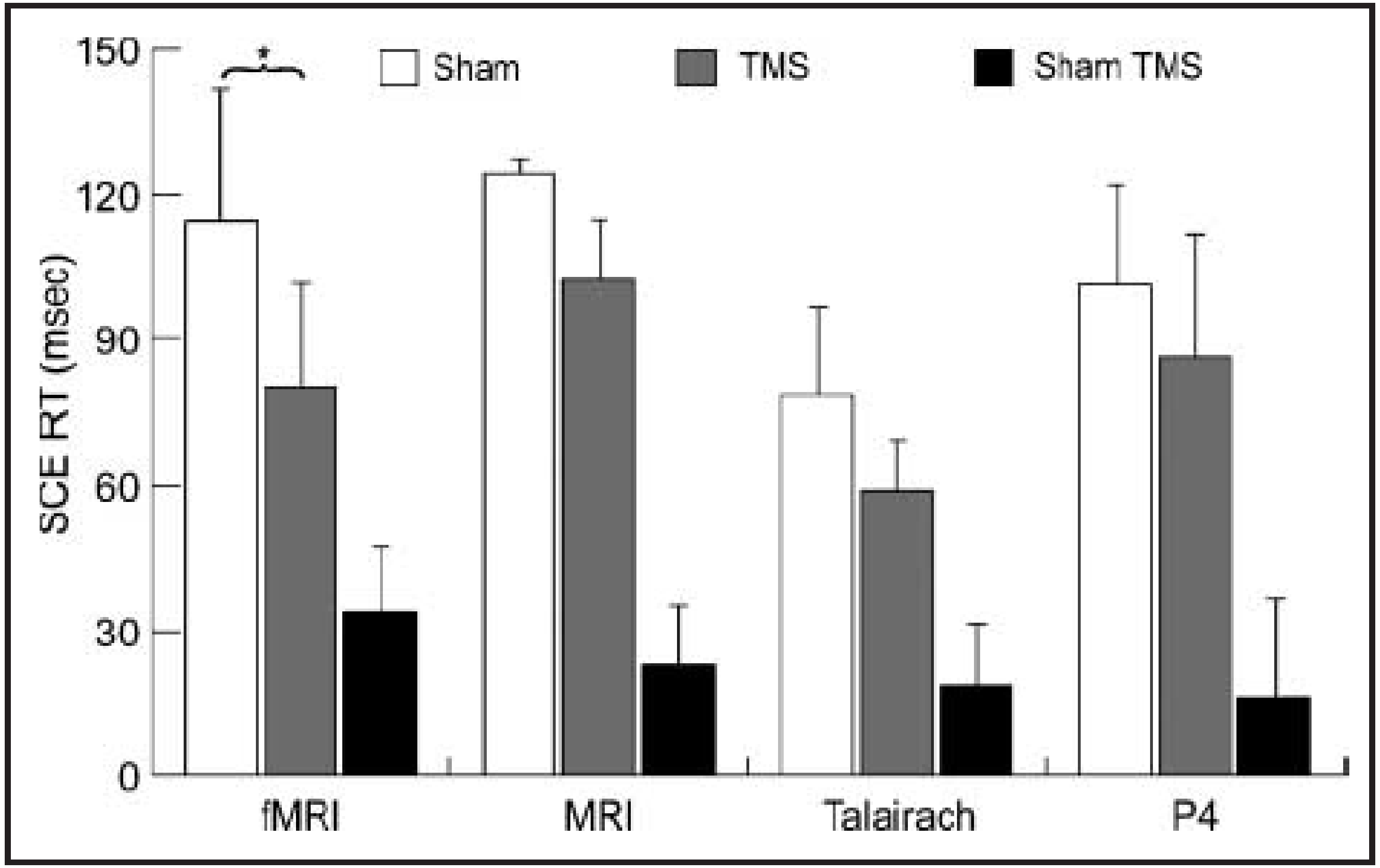


fMRI

sMRI

Talairach

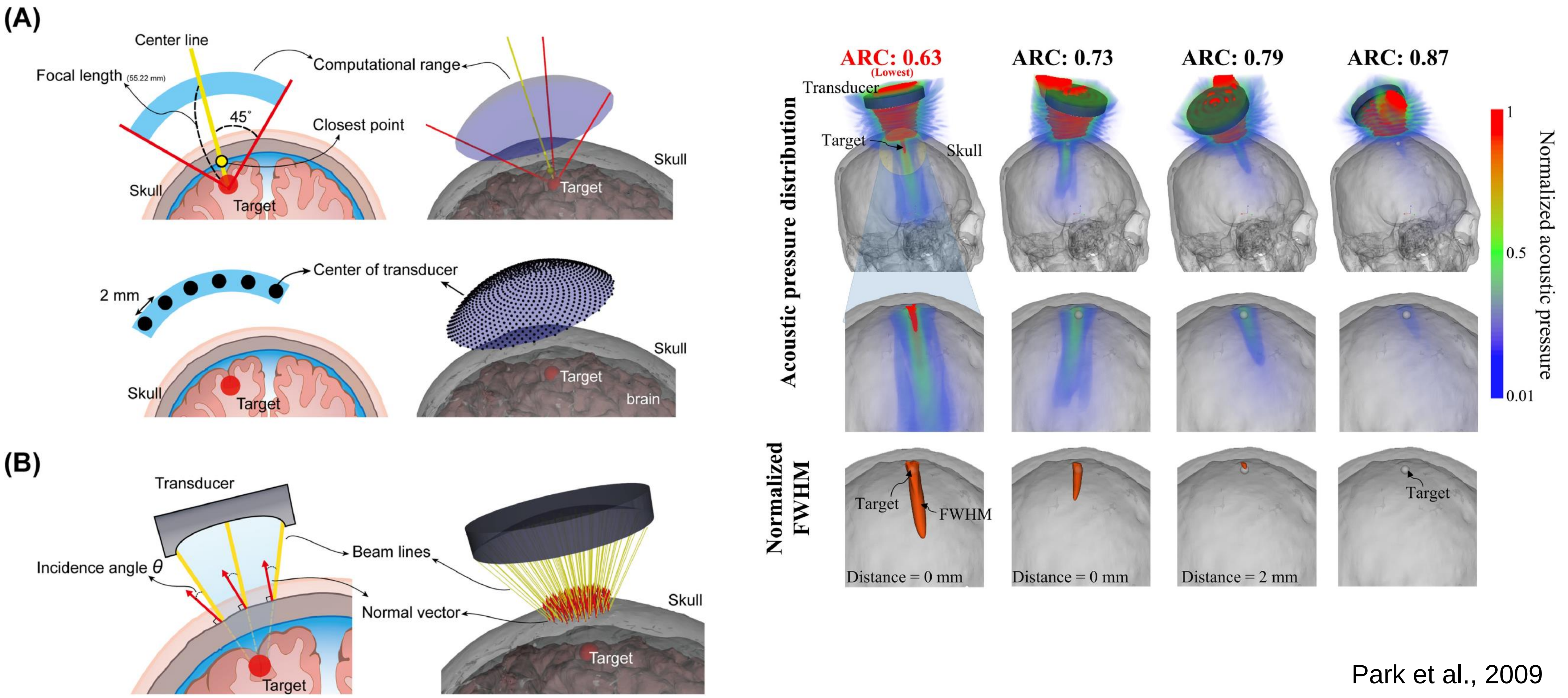
10-20 EEG



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

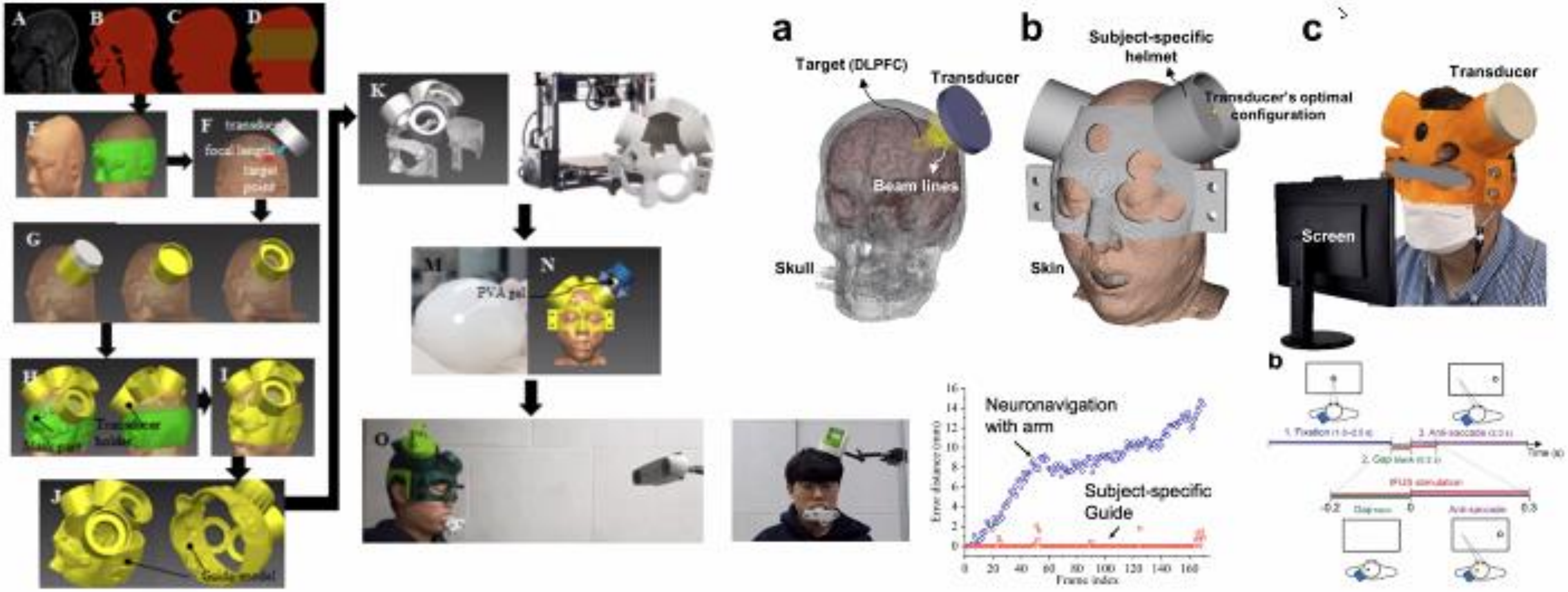
Sack, 2009

Targeting: Optimal Sonication Path



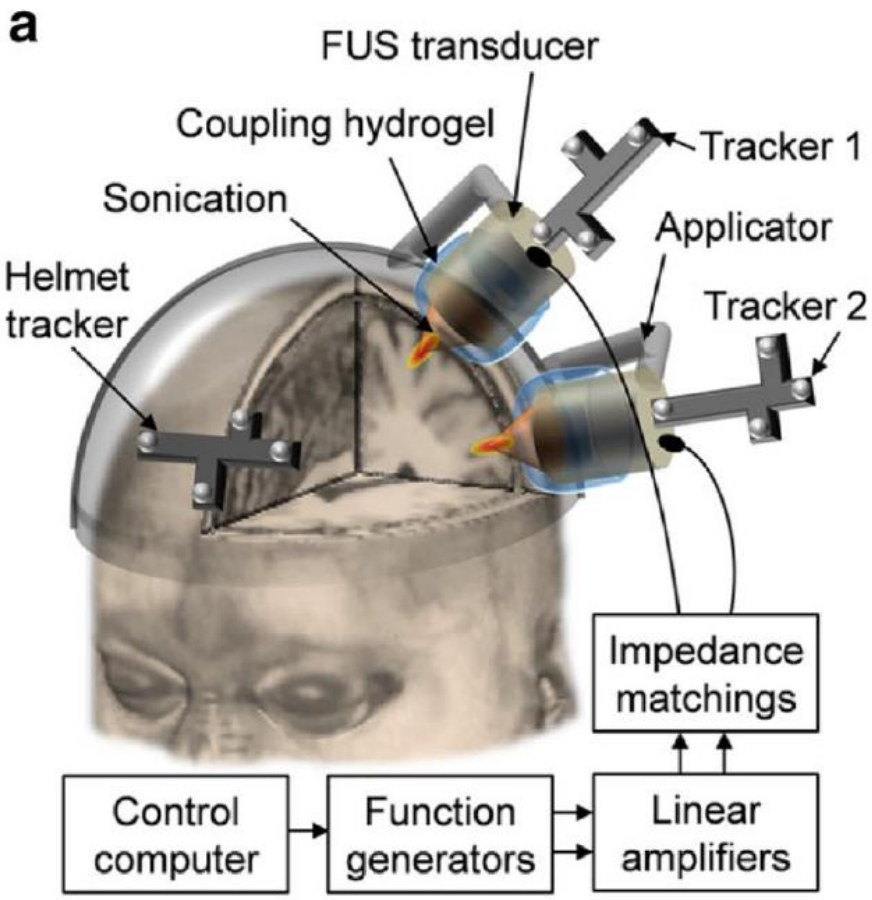
Park et al., 2009

Navigation: 3D printed Helmet-type Guide



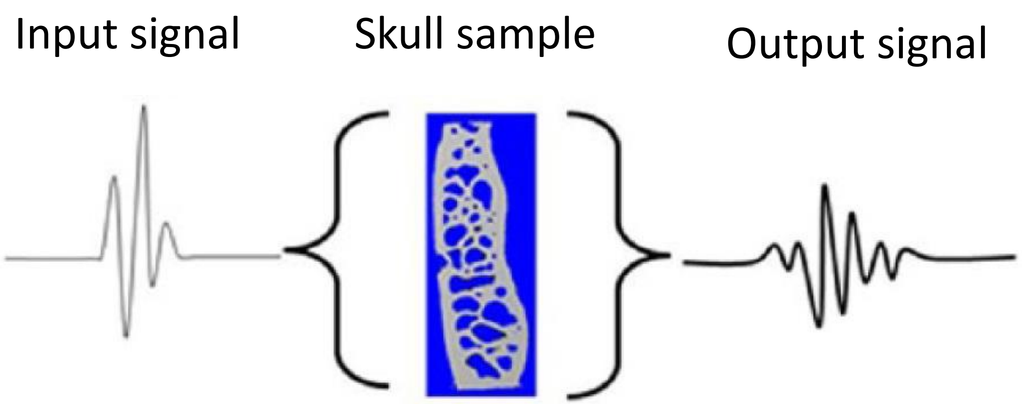
Joe et al. 2019 Comput Methods Programs Biomed

Navigation: 3D printed Helmet-type Guide



Lee, 2016, BMCNeurosci

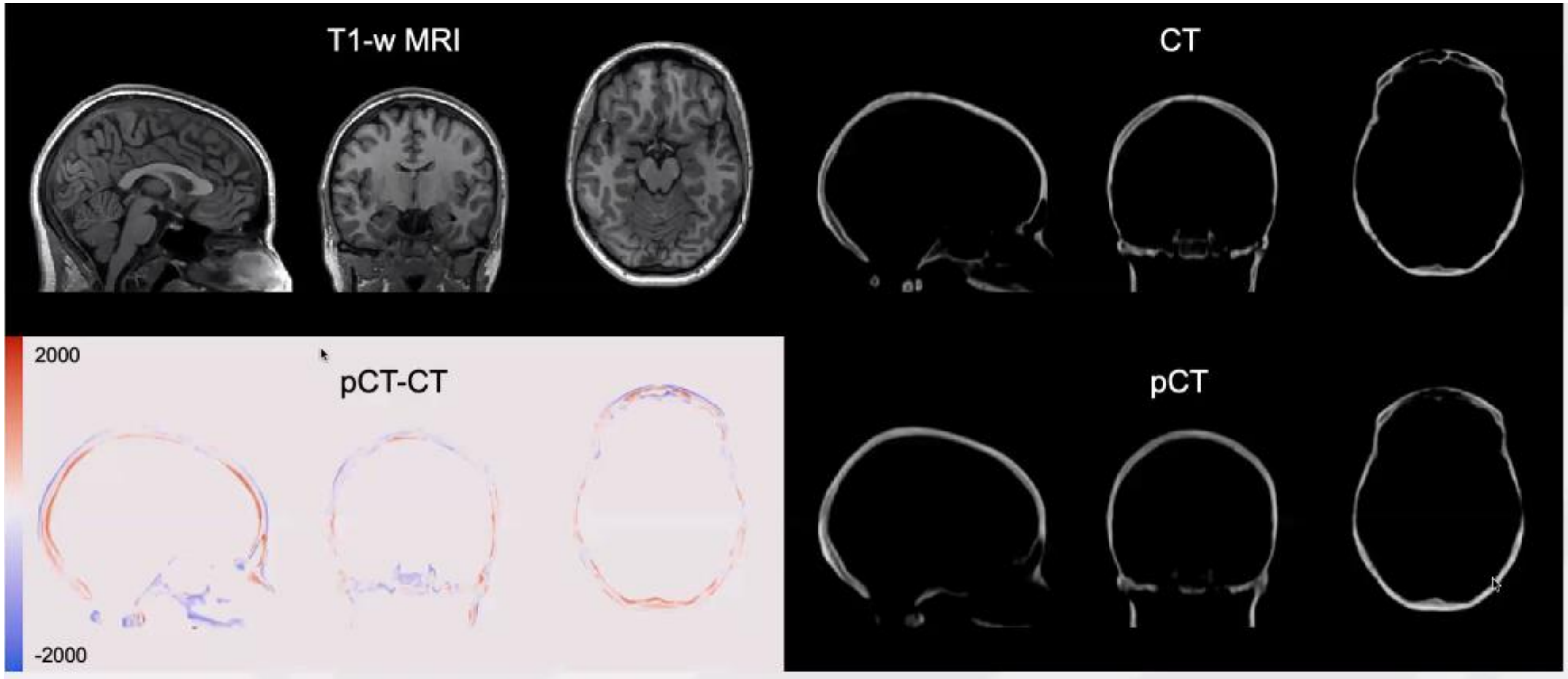
US simulations: to estimate dose + target



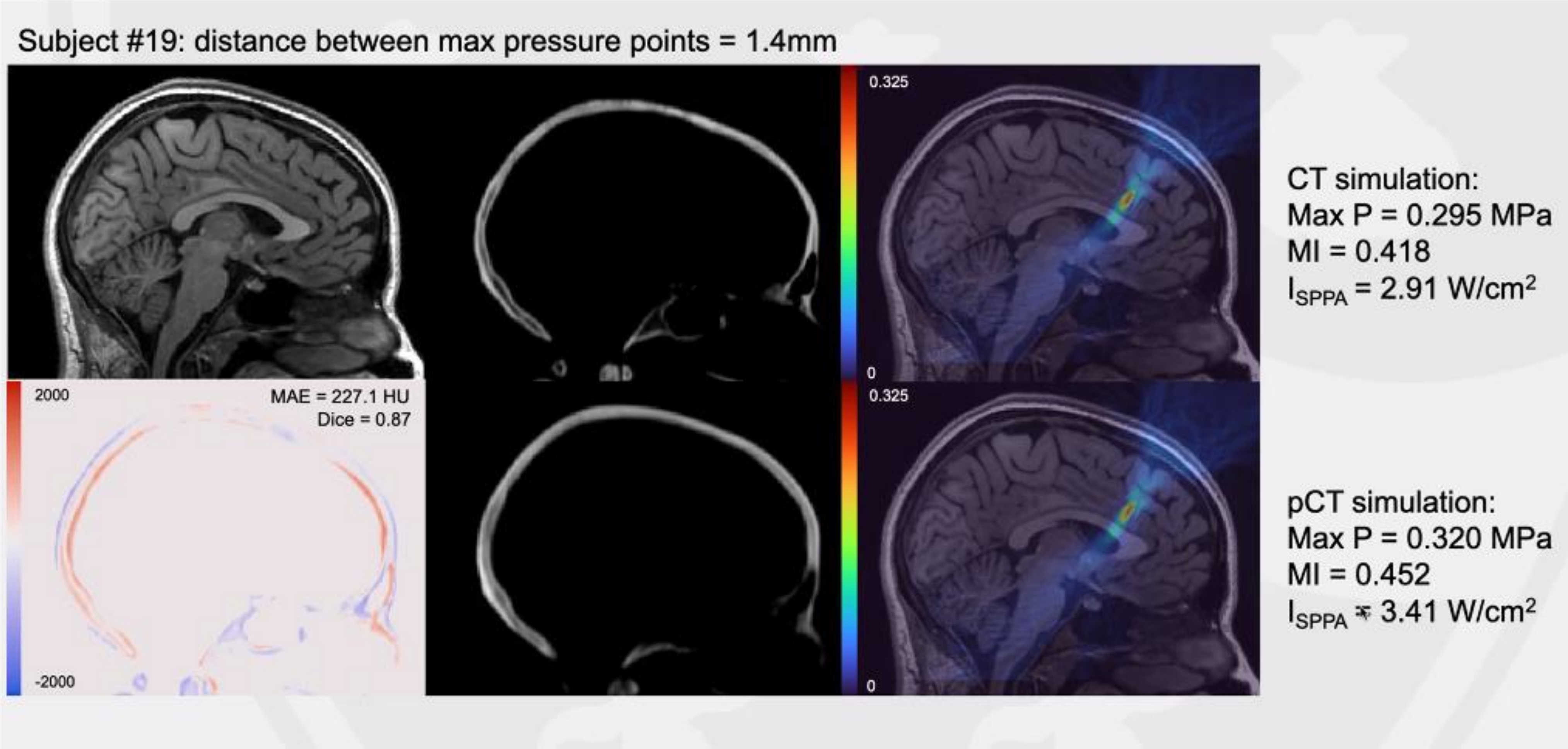
Variation in tissue composition and thickness

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 ($dB/MHz^y cm$)
$\rho_{min} = 1000$	$c_{min} = 1500$	$\alpha_{min} = 1.9$
$\rho_{max} = 1900$	$c_{max} = 3100$	$\alpha_{max} = 18.1$
		$\alpha_{water} = 0.0022$

Transducer: Brainbox NeuroFUS CTX-500

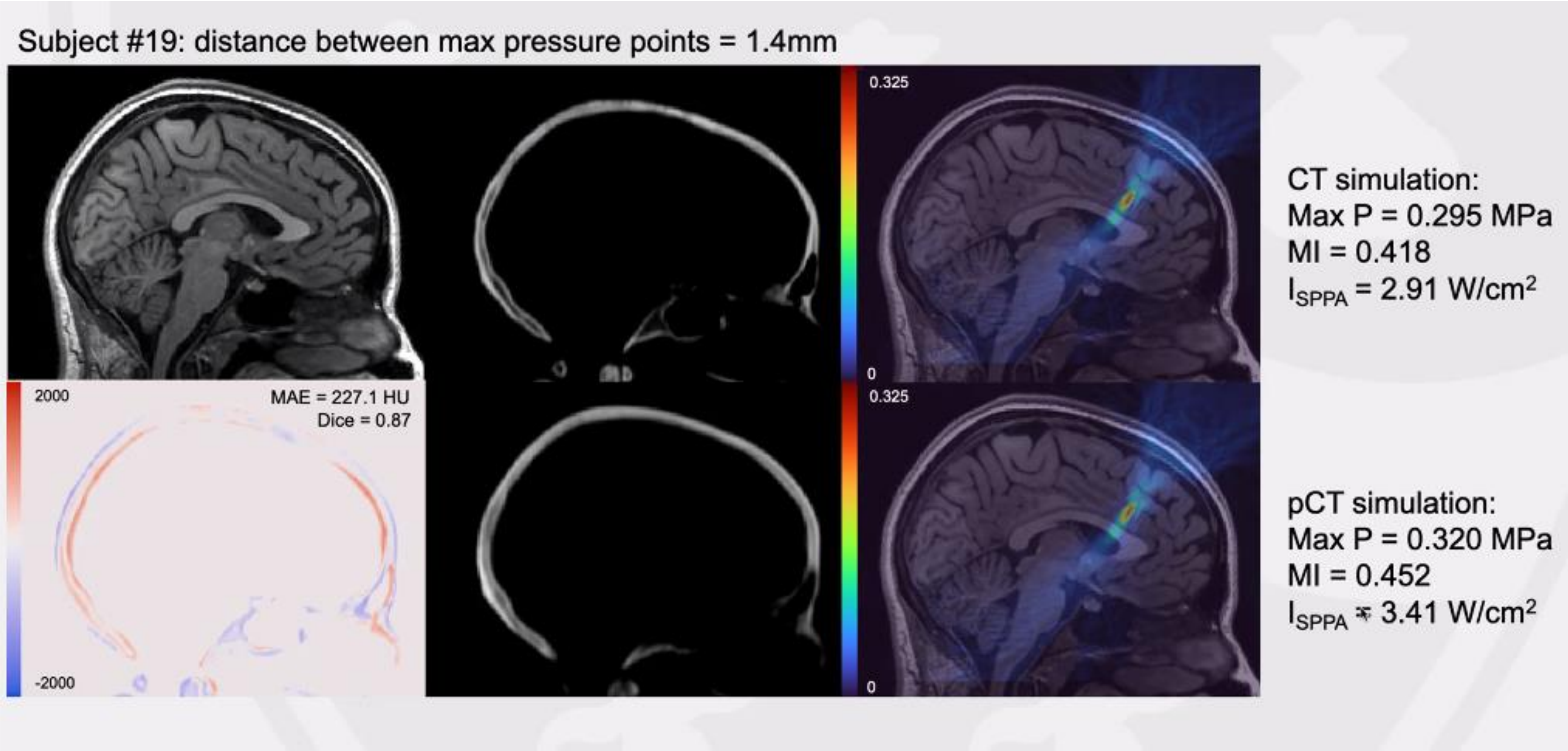
- 500 kHz 4-element annular transducer defined with kArray
- Pulse length = 20 ms
- Pulse repetition frequency = 5 Hz

k-Wave grid:

- Grid size 256 × 256 × 256
- Grid spacing set to λ/3 = 1 mm

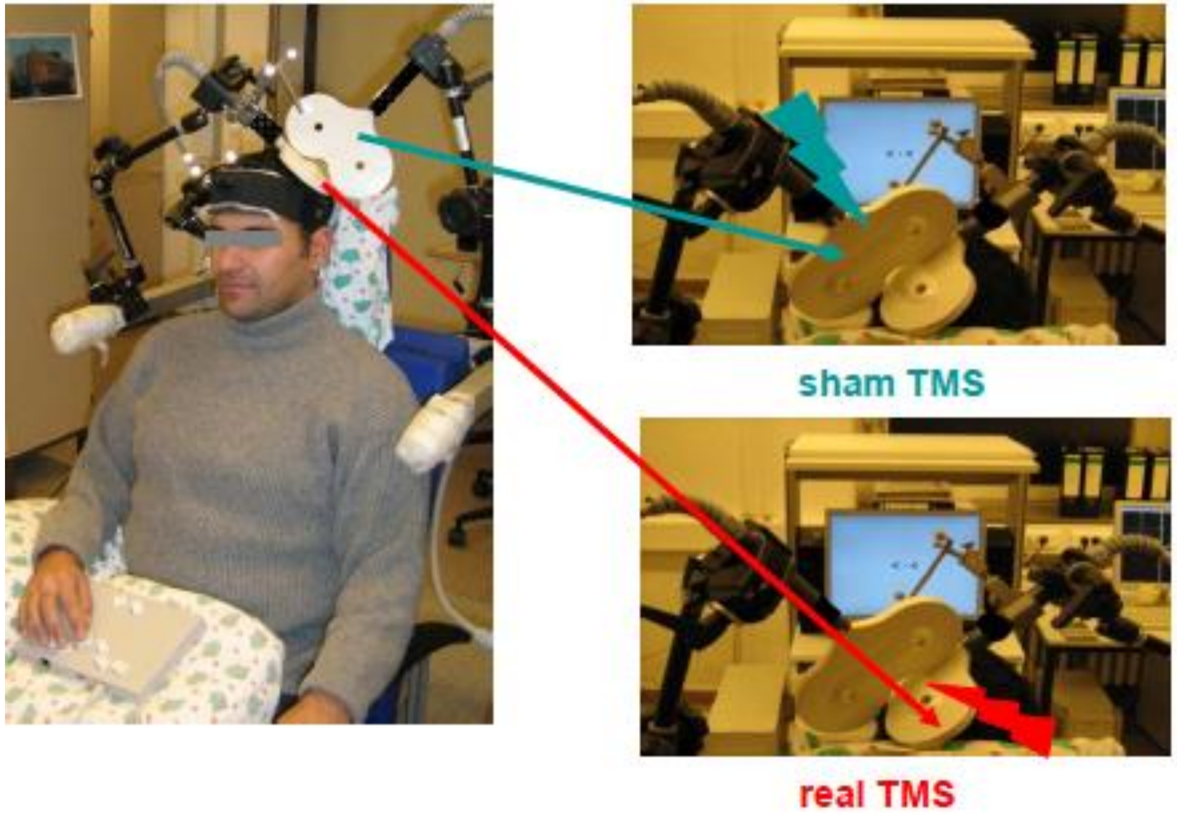
(k-Wave MATLAB Toolbox: Treeby and Cox, 2010; Treeby et al., 2012)
(CT acoustic mapping equations: Marsac et al., 2017; Mueller et al., 2017)

US simulations



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)

Image courtesy of Gesa Hartwigsen

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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Brain stimulation wish-list

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

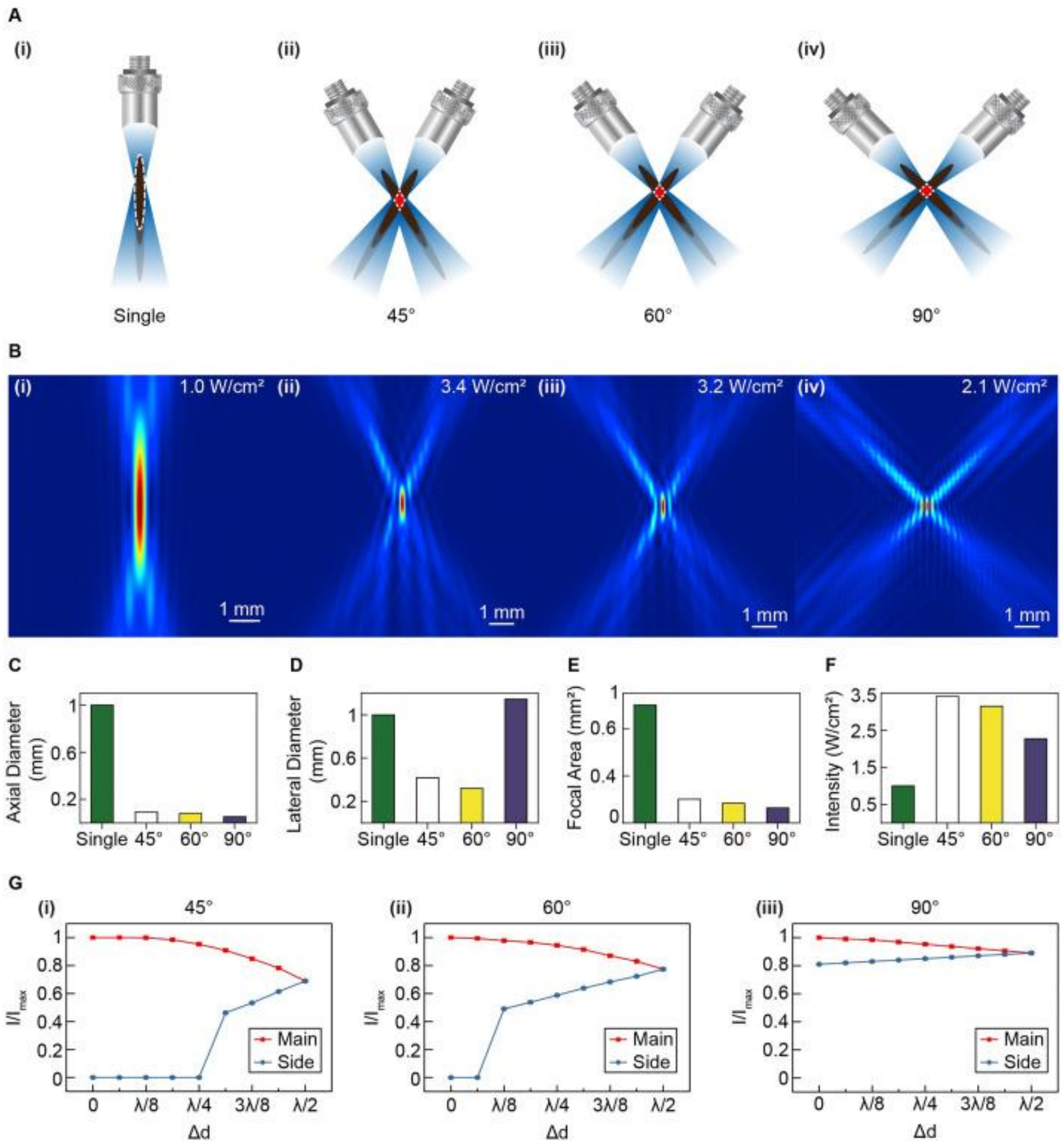
Brain stimulation wish-list

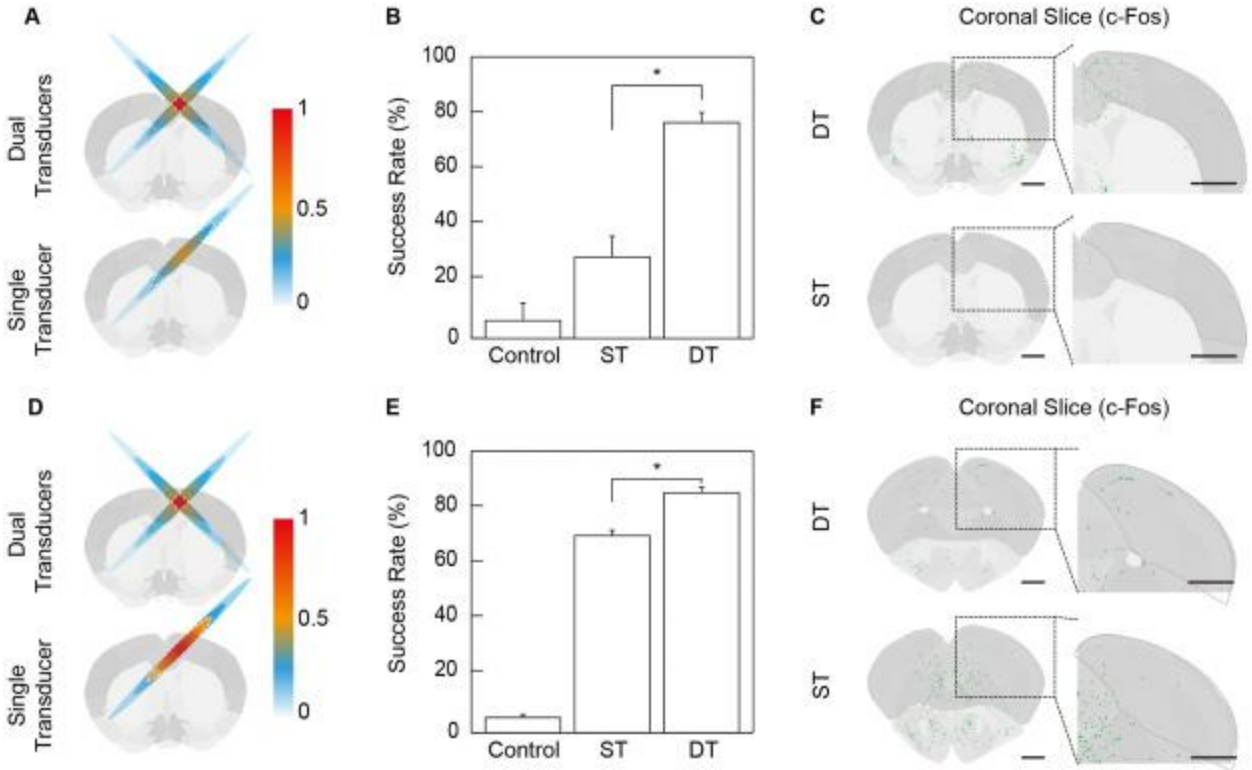
- Non-invasive √
- Focal √
- Surface & Deep √
- Long-lasting √
- Robust & effective √
- Measurable √
- Relevant for behaviour √

- Mechanisms ?!
- Physiology ?!
- Species differences ?!
- Temporal specificity ?!
- Sham control ?!
- Oscillatory modulation ?!
- Targeted connectivity ?!

Thank you

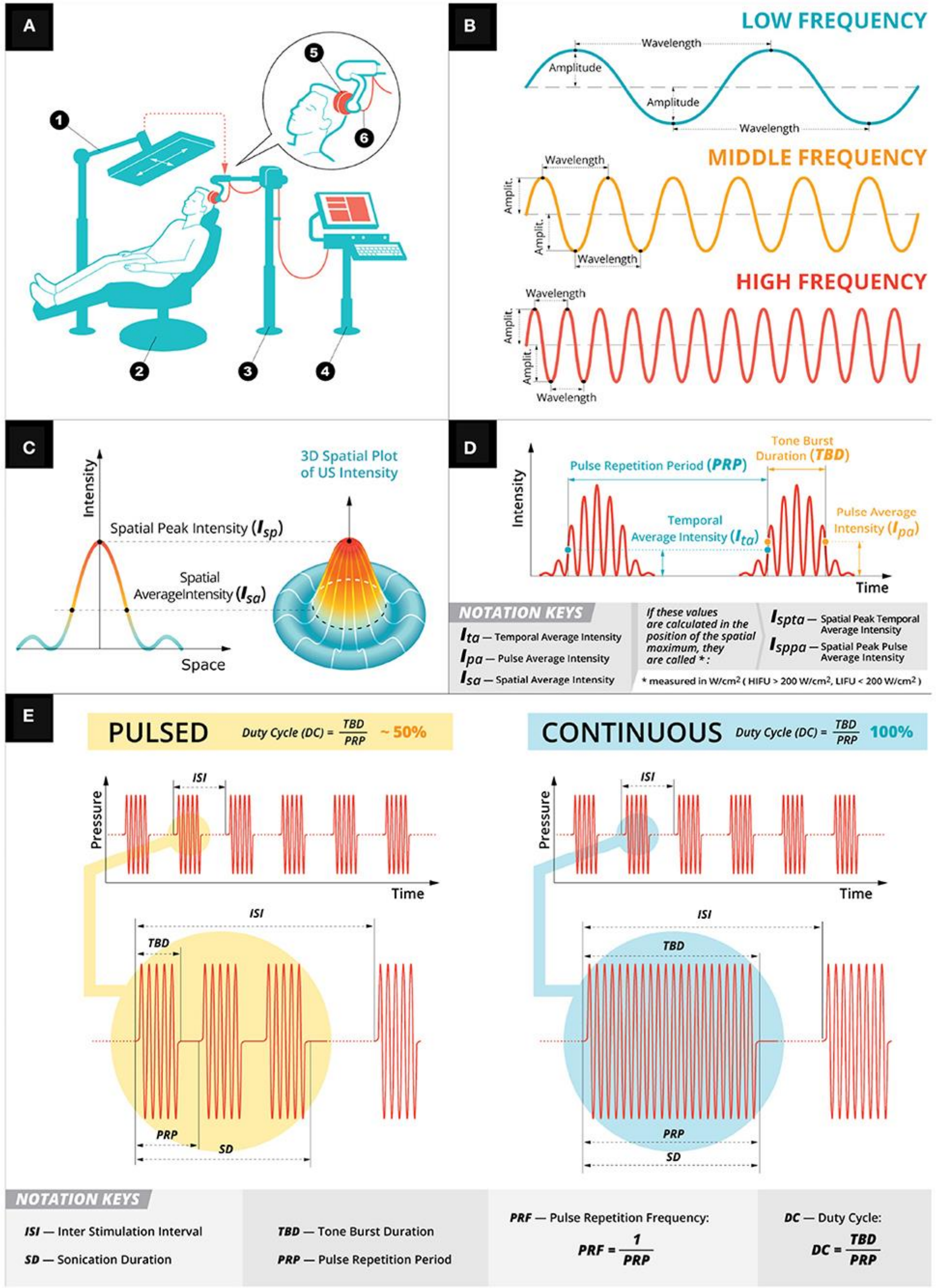
Current challenges

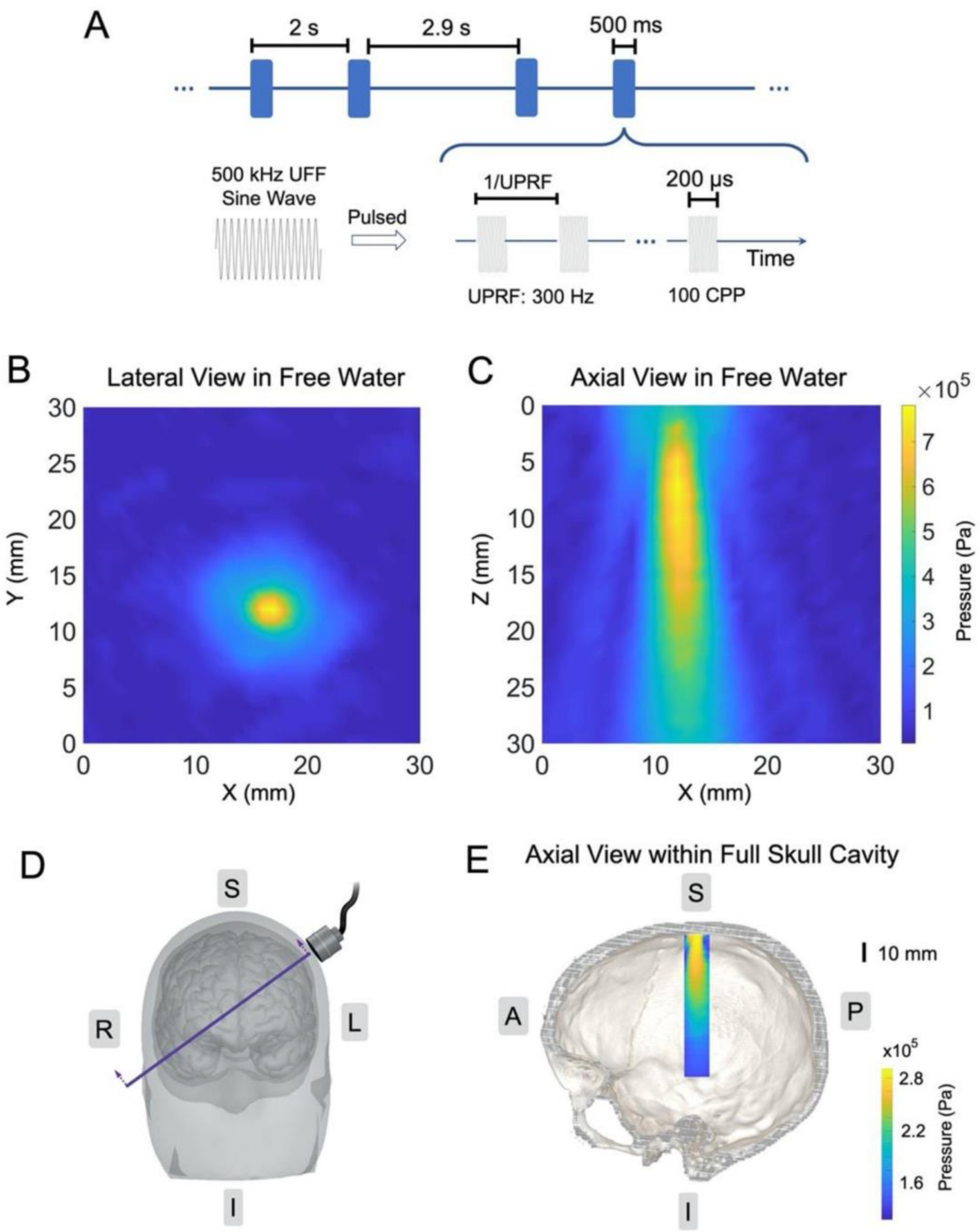


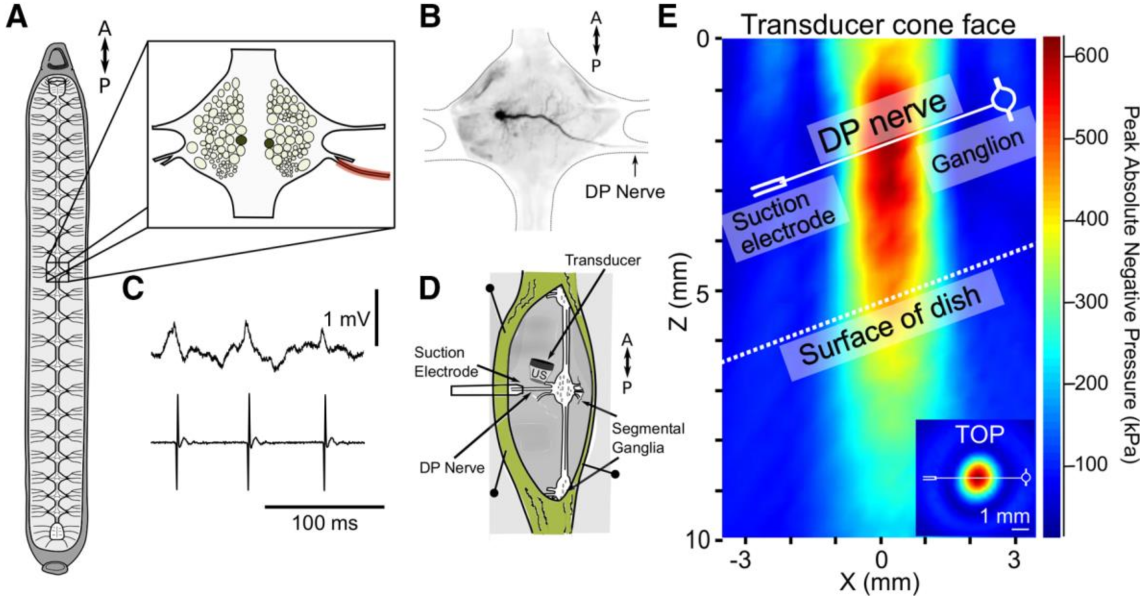


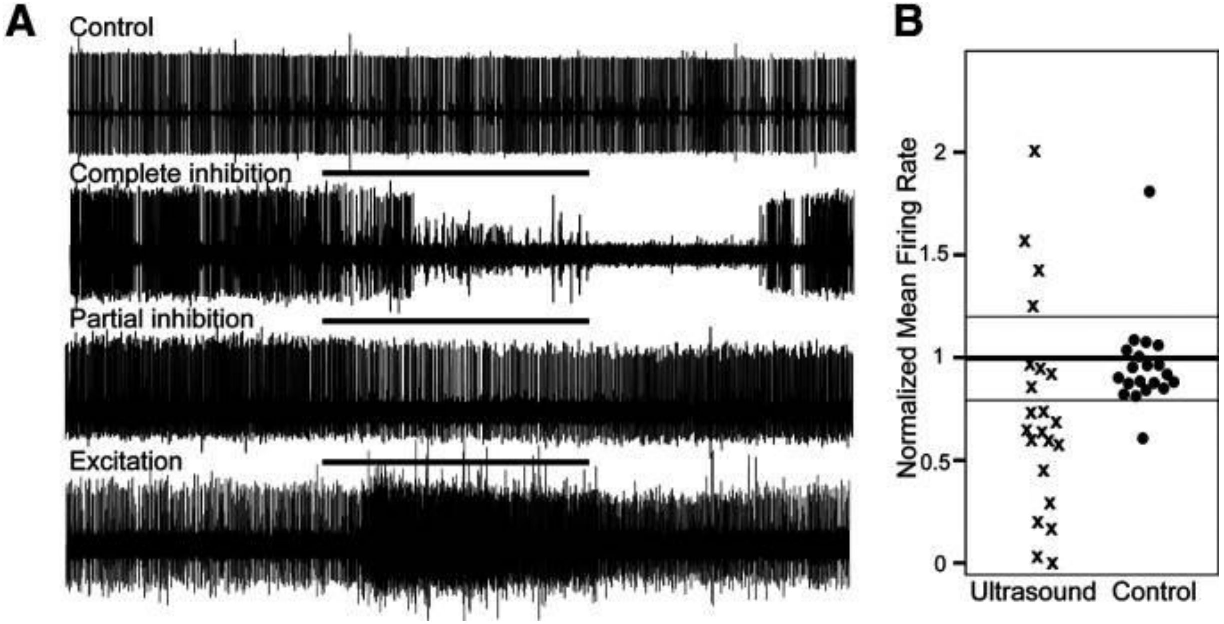
Kim et al., 2021, Brain Stim.

US mechanisms



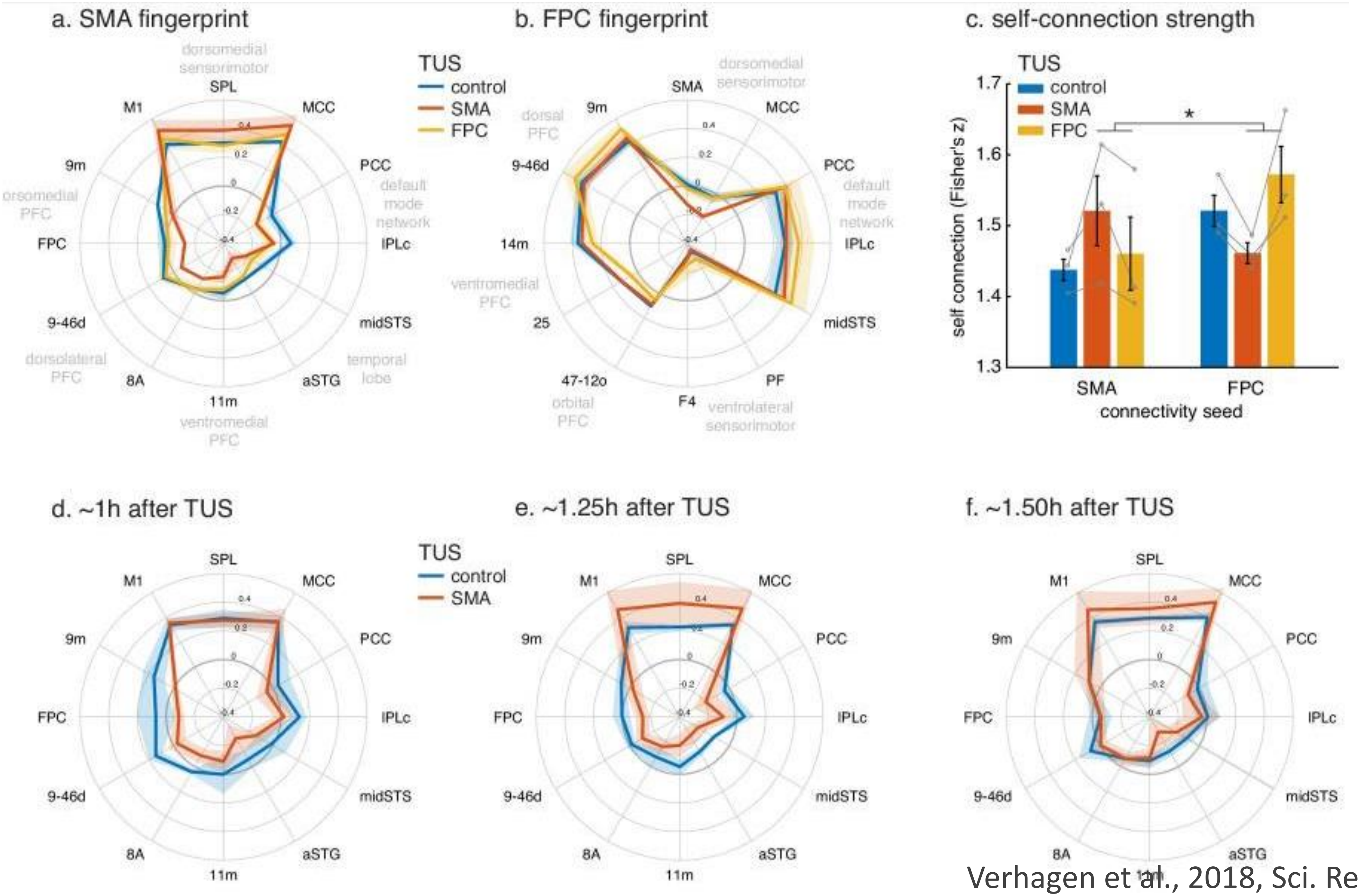






	Wire device	Ultrasound Regular saline	Ultrasound Ca^{2+}- free saline	Laser	Control	Bath heating
Max heat increase (°C)	4.9	3.4	3.4	2.1	0	2.0
Diameter of heat focus (mm)	8.5	6.8	6.8	1.2	n/a	n/a
Number of nerves tested	9	13	9	13	20	4

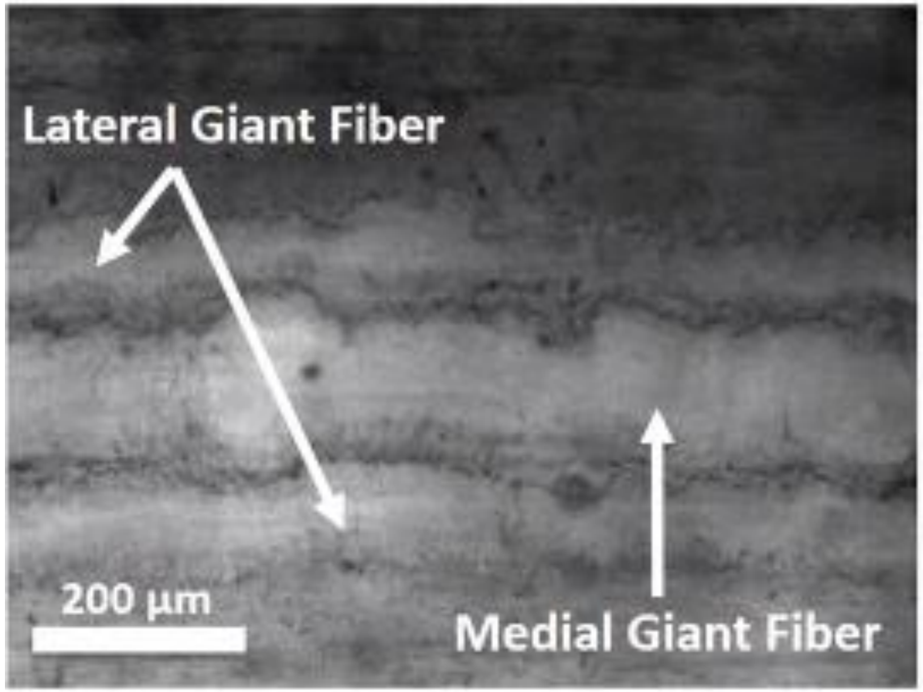
Collins et al., 2021, eNeuro

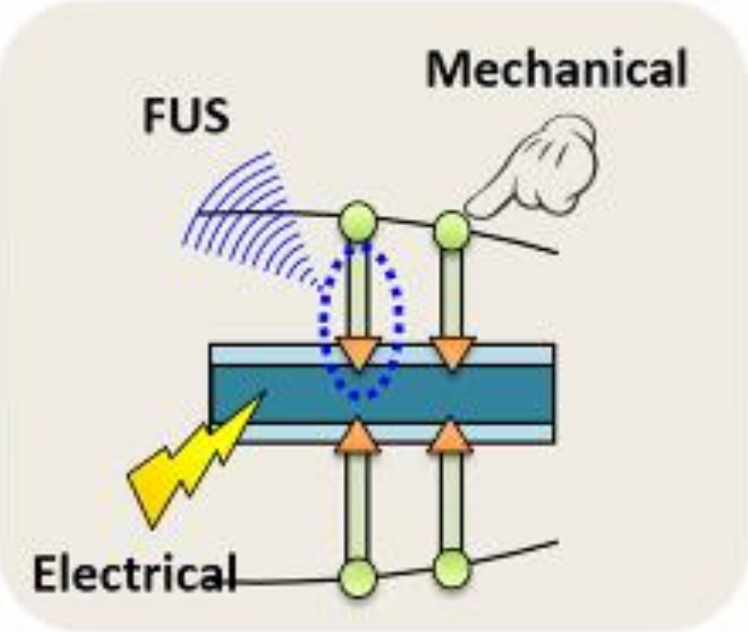


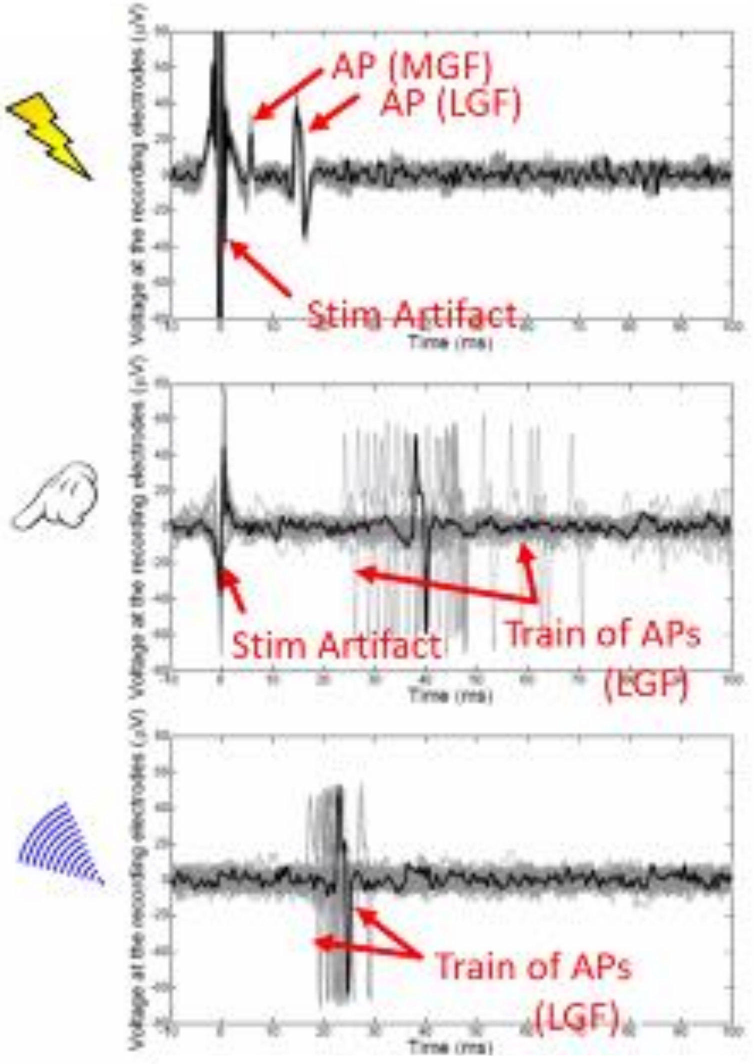
Verhagen et al., 2018, Sci. Rep.

US for Neuromodulation

FUS-induced APs in *in-vivo* giant axons[5,6]







FUS Parameters

- f = 1.1 MHz
- Single- & Repetitive- Pulses
- Pulse duration: 20 - 640 µs
- *PRF*: 25-125 Hz
- p = 2.5 – 7.3 MPa

Vion et al., Sci Res, 2019