Adaptive focusing for deep brain ultrasound stimulation: application to psychiatric disorders

Physics for Medicine PARIS

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Inserm ESPCI PARIS PSL cnrs

Physics for Medicine PARIS

Disclosure

JF Aubry

- **holds 5 patents on transcranial ultrasound focusing**
- **was the PI in a sponsored research agreement with Insightec**
- **is a member of FUSMobile’s scientific advisory board and holds ordinary options in the company**
- **is a co-founder of SonoMind**

Back to the 1950s: ultrasound neurostimulation emerges (reduction of evoked potentials)

Production of Reversible Changes in the Central Nervous System by Ultrasound

For the past several years an intensive research effort has been in progress at the Bioacoustics Laboratory of the University of Illinois on the production of selective lesions in the tissues of the central nervous system by high intensity ultrasound (*1*). Considerable information has been obtained concerning the dosage conditions required for the production of such lesions, and neuroanatomical studies utilizing this technique are now in progress. Relatively recent electrophysiological investigations indicate that *reversible* suppression of transmission along neural pathways can be accomplished by applying a controlled dosage of ultrasonic radiation at various sites along these pathways (*2*). By irradiating with ultrasound in the lateral geniculate nucleus it is possible to suppress temporarily the potential usually evoked in the visual cortex in response to a light stimulus. It should be noted that this effect is produced by a dosage of ultrasound which does not cause any histologically observable lesion in the tissue. This ultrasonic technique of producing reversible changes offers unique opportunities for three-dimensional mapping of central nervous system function.

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

Bipolar recording electrodes are placed in the appropriate cortical areas on both hemispheres to detect the evoked potentials. The focused ultrasonic beam source is used to irradiate the region of one of the lateral geniculate nuclei of the animal (cat) since these nuclei are sites of synaptic stations along the visual pathway. The ultrasonic energy must be transmitted from the irradiator to the brain through degassed Ringer's solution and the intervening skull bone must be removed.

Stimulation of the eye by light is repeated at fixed time intervals before, during, and after ultrasonic irradiation, and continuous electrical recording is in progress during the course of the experiment. A series of three light flashes, with approximately 3 seconds between flashes, is used to stimulate the eye of the animal. This series of flashes is repeated at variable intervals of time before, during, and after exposure to the ultrasonic radiation. The focus of the sound beam is placed successively in and around the region of the lateral geniculate nucleus. With a suitably chosen sound level and with an exposure time in the range from 20 to 120 seconds, it has been possible to produce reversible suppressions of various components of the elicited electrical response in the visual cortex. The type of result illustrated in Fig. 1 has been obtained in a number of animals. Figure 1 shows the cortical potentials (two electrodes) evoked by a flash of light (i) before ultrasonic irradiation, (ii) at the termination of the ultrasonic exposure period, and (iii) subsequent to irradiation. At the termination of the ultrasonic irradiation period the amplitude of the primary response (upper record) was reduced to less than one-third of its original value. The amplitude of the secondary response (upper record) was reduced to practically zero. Complete recovery of the primary and secondary response was apparent 30 minutes after exposure.

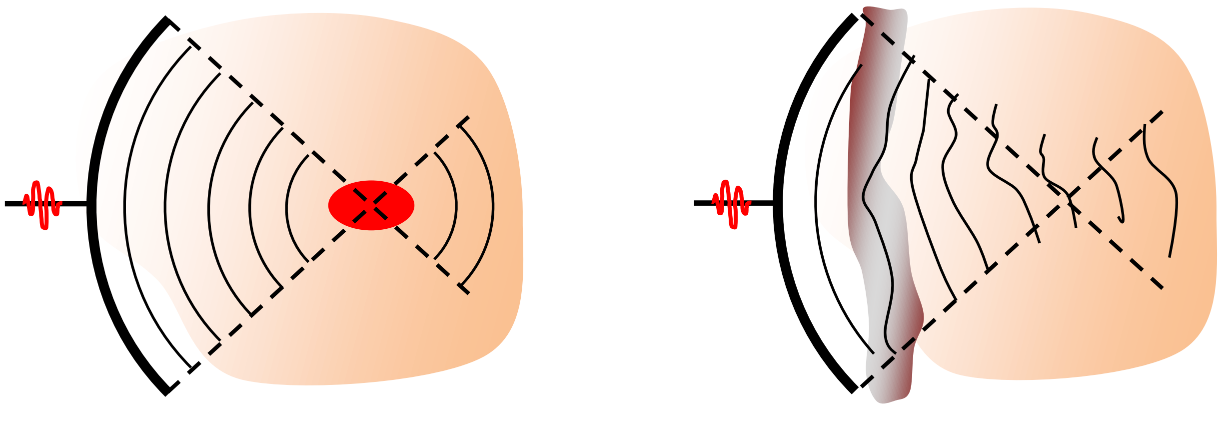
Experiments are in progress to quantify further the conditions for producing controlled reversibility and to determine the site or sites (synapses, axons, cell bodies) of action of the sound (*3*).

F. J. Fry

*Bioacoustics Laboratory,**
University of Illinois, Urbana

Fry, Ades & Fry, Science, 1958

« intervening skull must be removed »



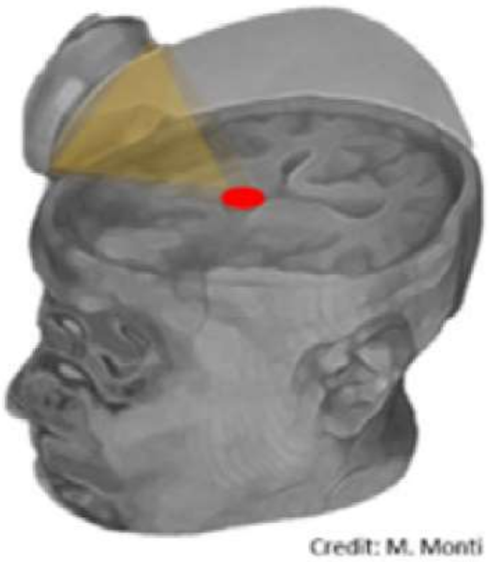
No skull: Good focusing

With skull : defocusing

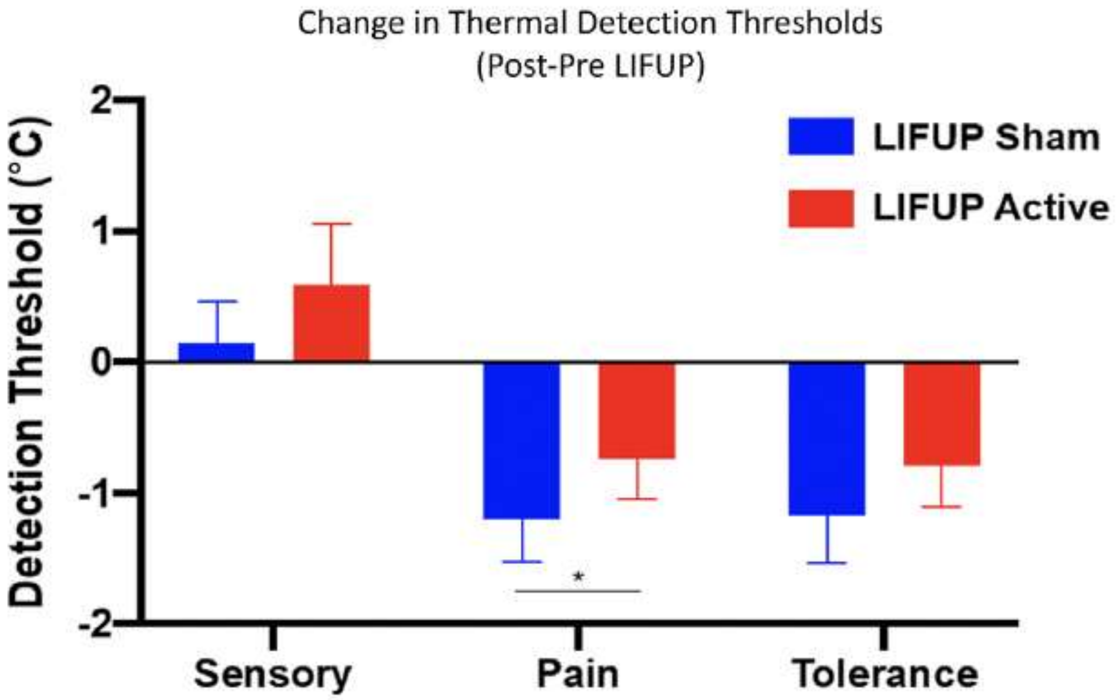
Many TUS studies on humans

Authors	Study Number	Year	Title
Mueller et al.	1	2014	Transcranial Focused Ultrasound Modulates Intrinsic and Evoked EEG Dynamics
Legon et al.	2	2014	Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans
Lee et al.	3	2015	Image-Guided Transcranial Focused Ultrasound Stimulates Human Primary Somatosensory Cortex
Lee et al.	4	2016	Transcranial focused ultrasound stimulation of human primary visual cortex
Lee et al.	5	2016	Simultaneous acoustic stimulation of human primary and secondary somatosensory cortices using transcranial focused ultrasound
Ai et al.	6	2016	Transcranial focused ultrasound for BOLD fMRI signal modulation in humans
Legon et al	7	2018	Transcranial focused ultrasound neuromodulation of the human primary motor cortex
Legon et al.	8	2018	Neuromodulation with single-element transcranial focused ultrasound in human thalamus
Ai et al.	9	2018	Effects of transcranial focused ultrasound on human primary motor cortex using 7T fMRI: a pilot study
Braun et al.	10	2020	Transcranial ultrasound stimulation in humans is associated with an auditory confound that can be effectively masked
Sanguinetti et al.	11	2020	Transcranial Focused Ultrasound to the Right Prefrontal Cortex Improves Mood and Alters Functional Connectivity in Humans
Badran et al.	12	2020	Sonication of the anterior thalamus with MRI-Guided transcranial focused ultrasound (tFUS) alters pain thresholds in healthy adults: A double-blind, sham-controlled study
Fine et al,	13	2020	Response inhibition is driven by top-down network mechanisms and enhanced with focused ultrasound
Fomenko et al.	14	2020	Systematic examination of low-intensity ultrasound parameters on human motor cortex excitability and behavior
Yu et al.	15	2020	Transcranial Focused Ultrasound Neuromodulation of Voluntary Movement-related Cortical Activity in Humans
Cain et al	16	2021	Real time and delayed effects of subcortical low intensity focused ultrasound
Liu et al.	17	2021	Transcranial Focused Ultrasound Enhances Sensory Discrimination Capability through Somatosensory Cortical Excitation
Monti et al.	18	2016	Non-Invasive Ultrasonic Thalamic Stimulation in Disorders of Consciousness after Severe Brain Injury: A First-in-Man Report
Brinker et al.	19	2020	Focused Ultrasound Platform for Investigating Therapeutic Neuromodulation Across the Human Hippocampus
Reznik et al.	20	2020	A double-blind pilot study of transcranial ultrasound (TUS) as a five-day intervention: TUS mitigates worry among depressed participants
Cain et al.	21	2021	Ultrasonic thalamic stimulation in chronic disorders of consciousness
Stern et al.	22	2020	Safety of Focused Ultrasound Neuromodulation in Humans with Temporal Lobe Epilepsy

650kHz neurostimulation (right anterior thalamus)



measuring sensory, pain, and tolerance thresholds to a thermal stimulus applied to the left forearm



0.57°C increase in the thermal pain threshold (1.3% compared to the 45.3°C threshold)

Badran et al., Brain Stimulation (2020)

Many TUS studies on humans… that neglect the effect of the skull on the acoustic beam

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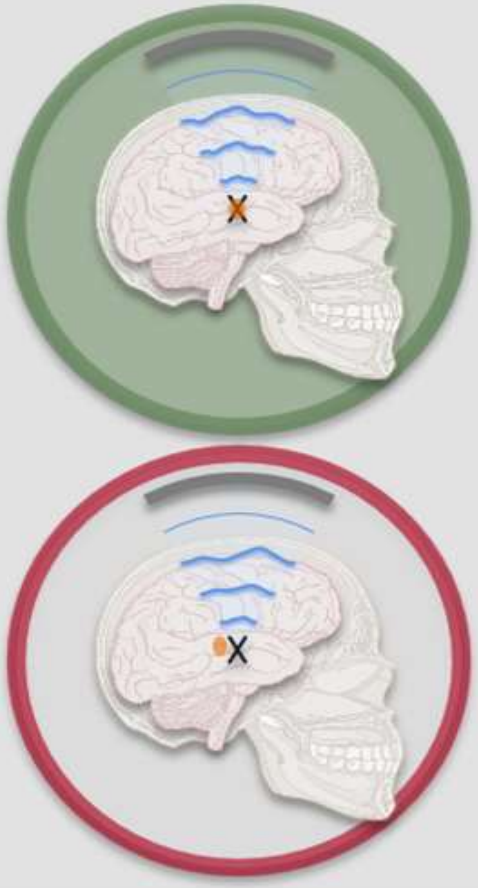
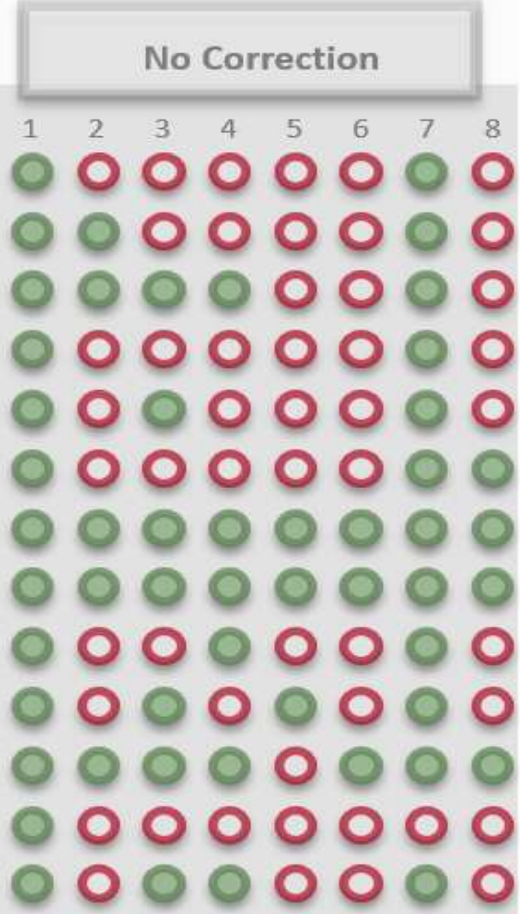
Impact of the skull on the precision of the targeting

TARGET ENGAGEMENT
(at least one point of the 50% isodose hits the target)

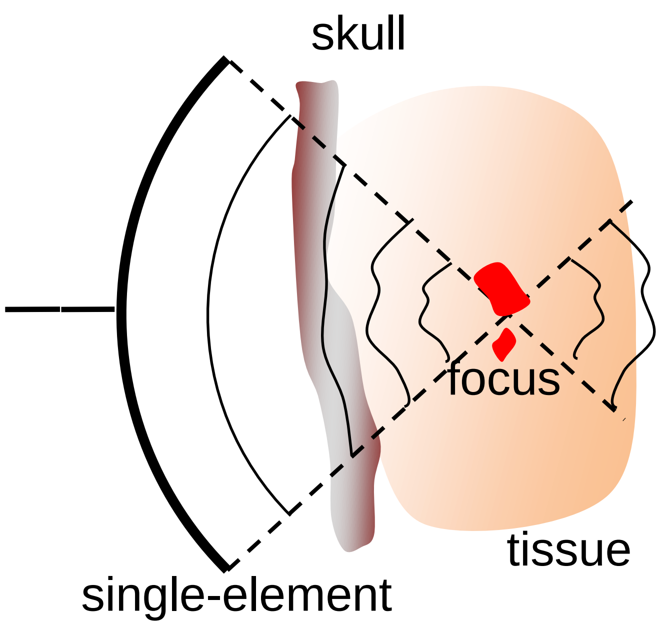


STUDY	AUTHOR, YEAR	TUS TARGET
1	Monti, 2016	Right Thal.
2	Ai, 2016	Left Caudate
3	Legon, 2018	Left Thal.
4	Badran, 2020	Right Thal.
5	Brinker, 2020	Left HPC
6	Cain, 2021 (1)	Left Pallidus
7	Jeong, 2021	Right HPC
8.1	Lee, 2022	Left PM Gyrus
8.2		Left HPC
8.3		Right Insula
8.4		Left AC gyrus
9	Stern, 2021	Left HPC
10	Cain, 2021 (2)	Left Thal.



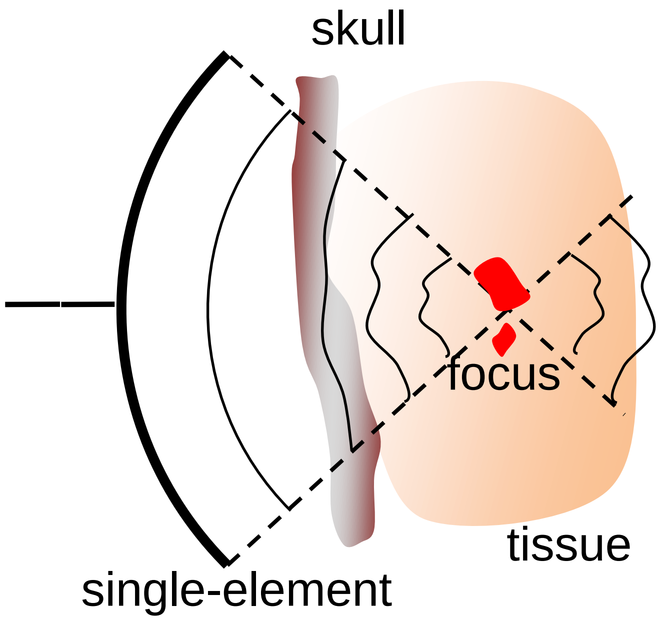
TOTAL	53/104 (51%)
TARGETING ERROR BETWEEN INITIAL TARGET AND MAXIMUM PRESSURE LOCATION	5.1 mm (± 3.6mm)

Challenge #1: focusing ultrasound waves through human skulls

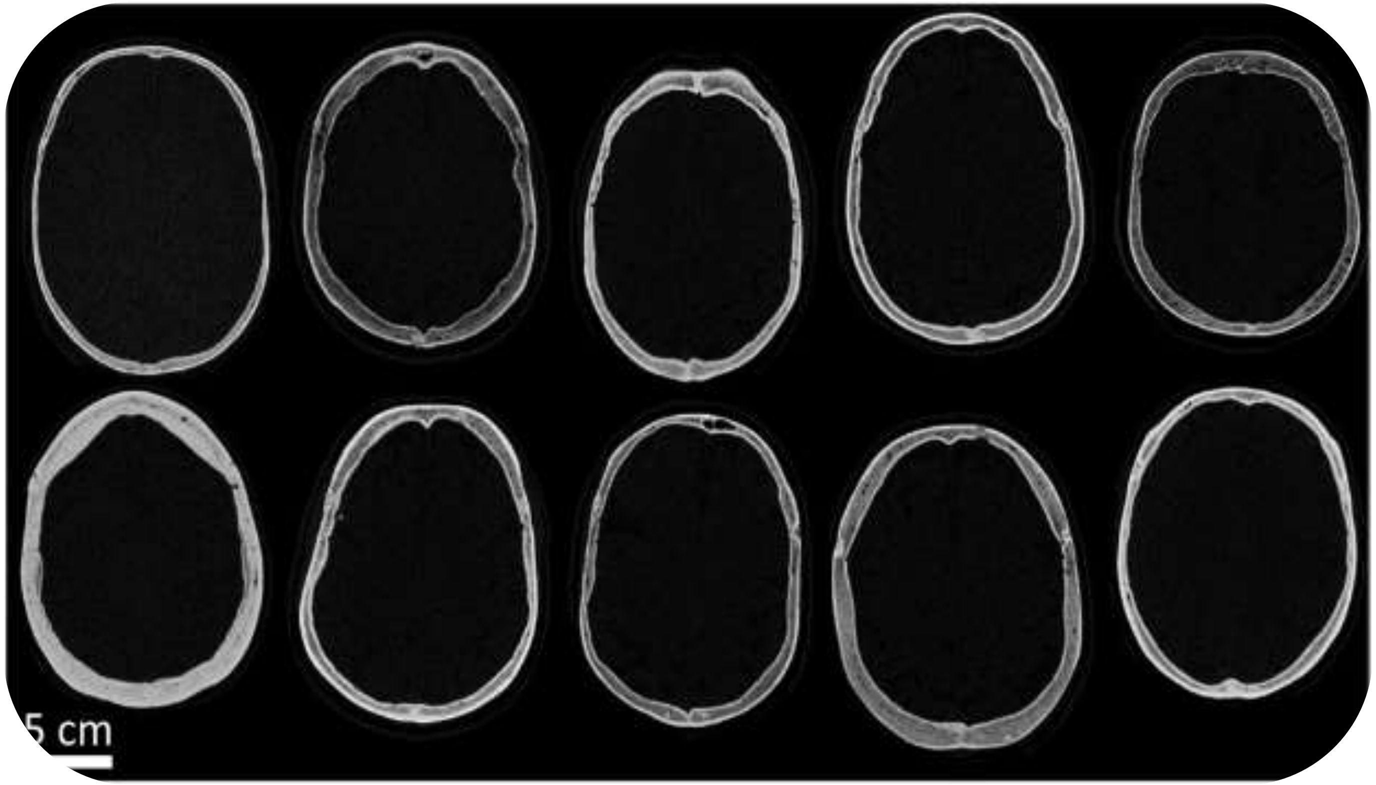


Abberration induced
by the skull

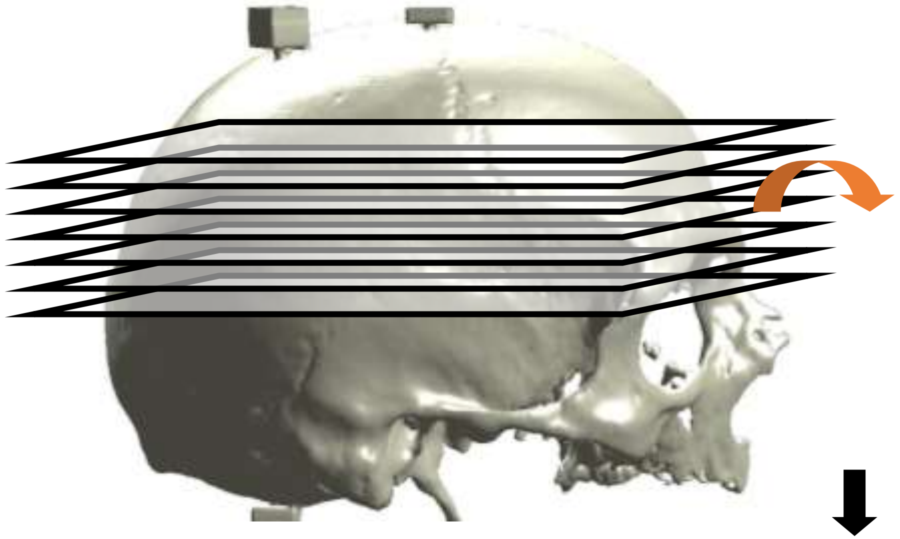
Challenge #1: focusing ultrasound waves through human skulls



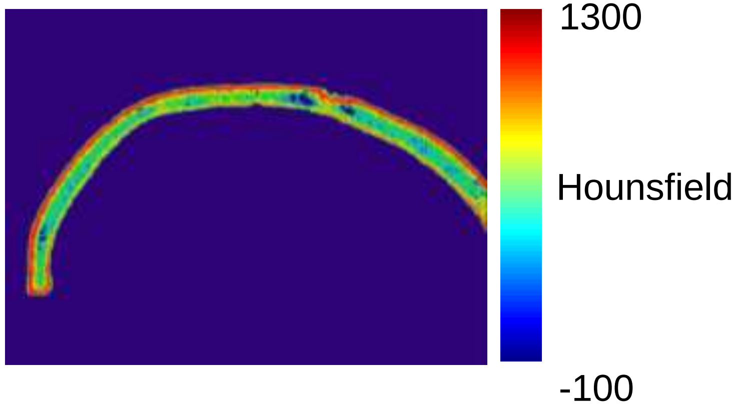
Abberration induced
by the skull



Focusing ultrasound waves through human skulls



CT Scan



Acoustical properties of the skull

Speed of sound

Density

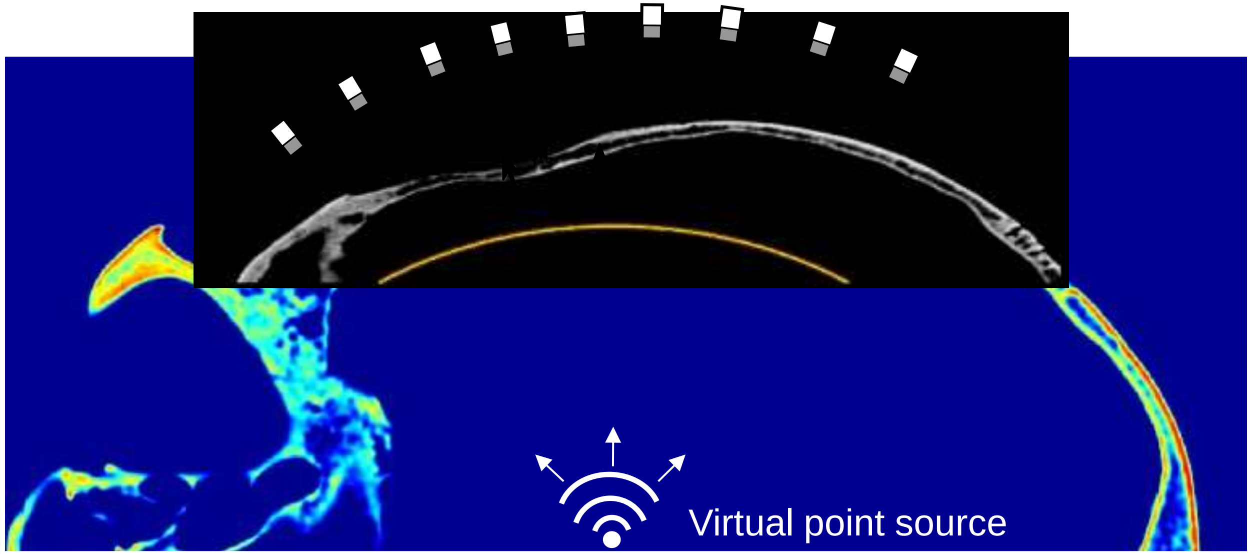
Absorption

$$\rho(r)\,div\left(\frac{\overrightarrow{grad}\,p(r,t)}{\rho(r)}\right)-\frac{1}{c^{2}(r)}\frac{\partial^{2}p(r,t)}{\partial t^{2}}=0$$

Aubry JF et al, “Experimental demonstration of non invasive transskull adaptive focusing based on prior CT scans”, Journal of the Acoustical Society of America, 113 (1), pp 84-94, 2003.

Clement GT and Hynynen K: A non-invasive method for focusing ultrasound through the human skull. Phys Med Biol 47:1219–1236, 2002.

Focusing ultrasound waves through human skulls



With aberration correction

- Focal spot: 1.5mm diameter
- Focused with submillimeter accuracy

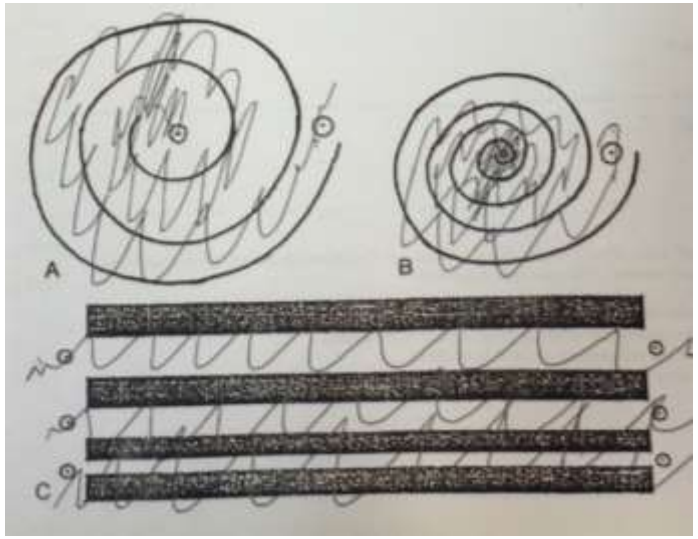
Without correction

With correction

Kyriakou A et al. "A review of numerical and experimental compensation techniques for skull-induced phase aberrations in transcranial focused ultrasound." *International journal of hyperthermia* (2014)

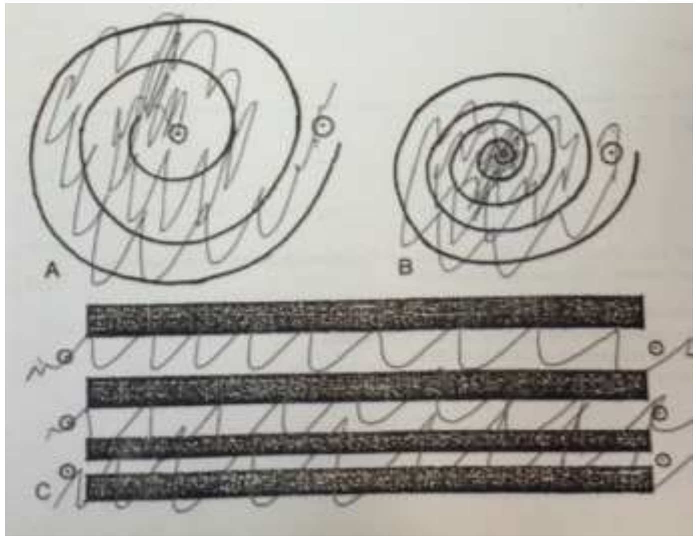
Bancel T et al. "Comparison between ray-tracing and full-wave simulation for transcranial ultrasound focusing on a clinical system using the transfer matrix formalism." *IEEE transactions on ultrasonics, ferroelectrics, and frequency control* (2021)

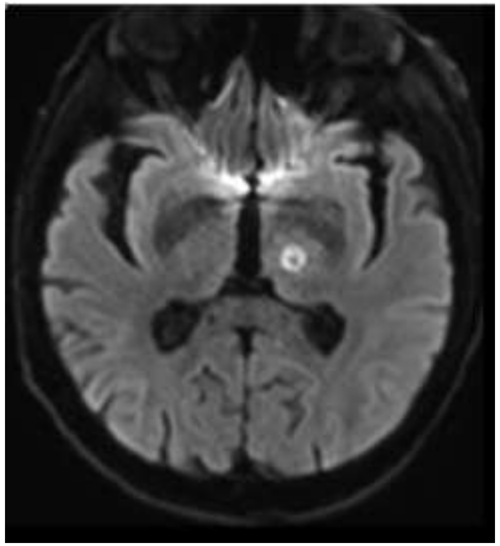
Treatment of Essential Tremor by thermal ablation with focused ultrasound

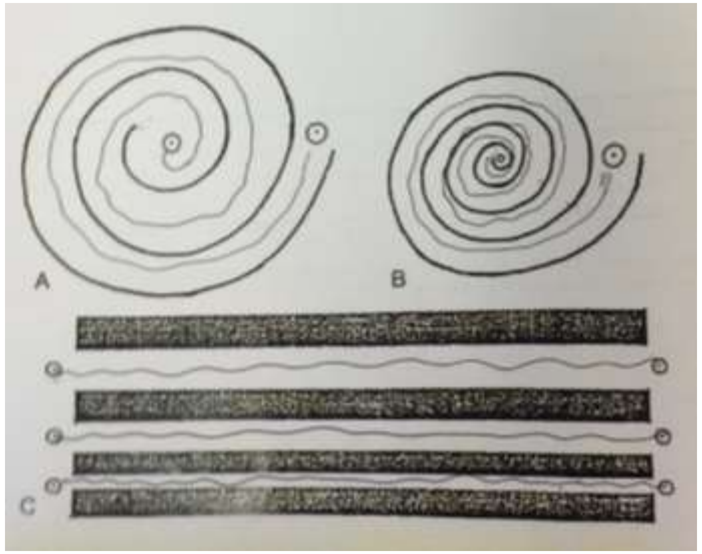


Treatment at la Pitié Salpêtrière hospital, Paris, France

Treatment of Essential Tremor by thermal ablation with focused ultrasound

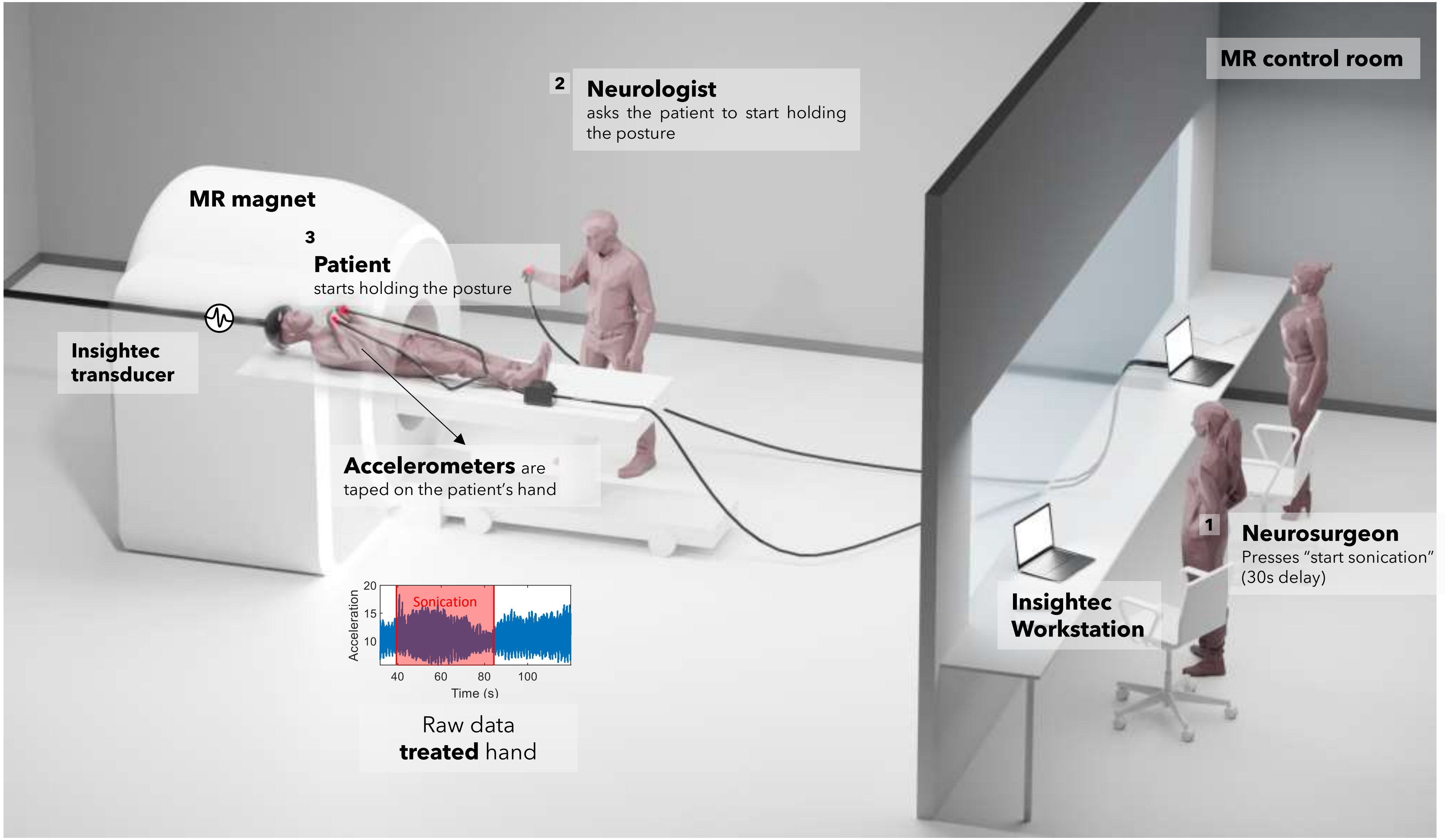






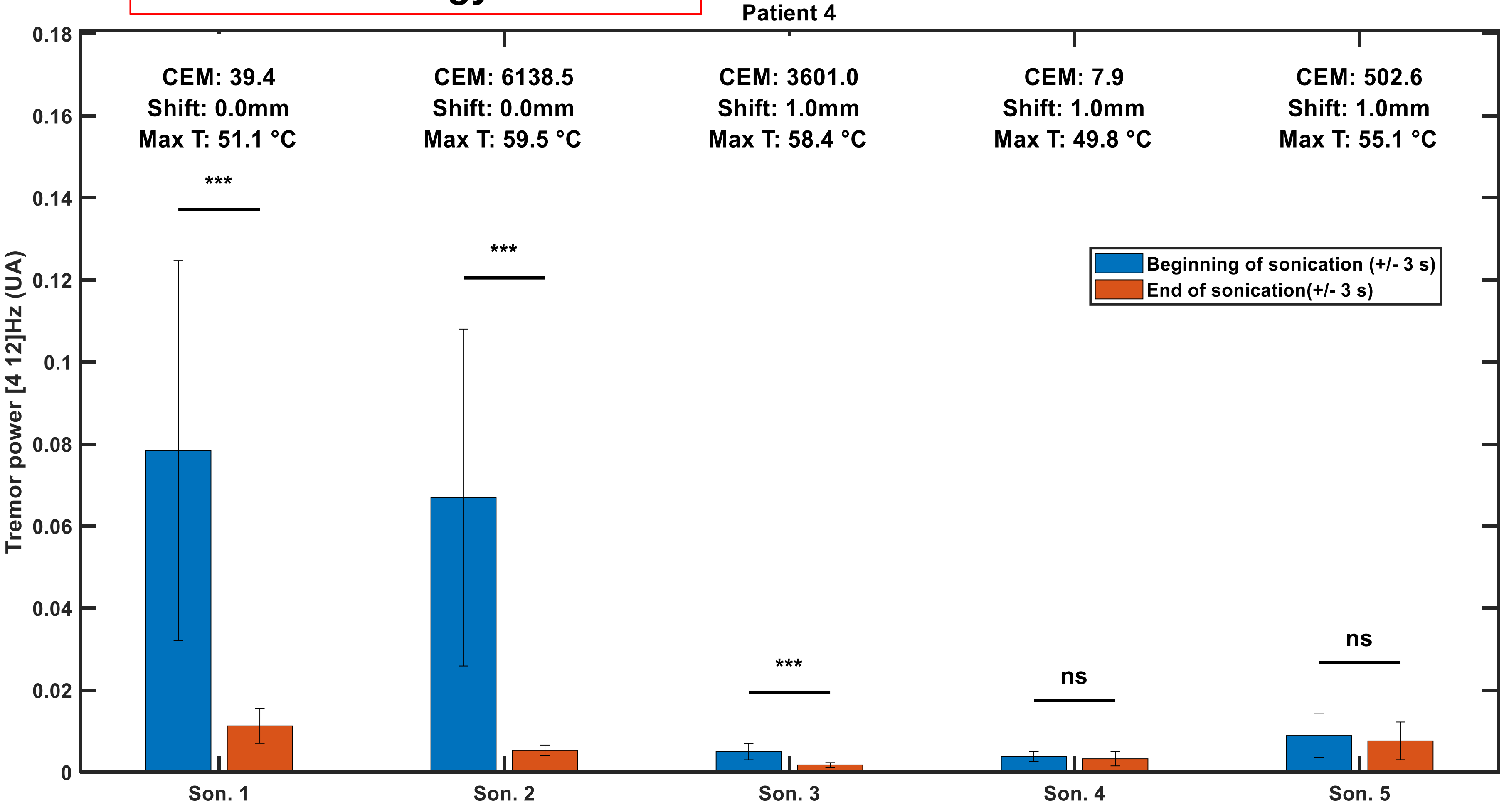
Treatment at la Pitié Salpêtrière hospital, Paris, France

Tremor assessment during treatment



Effect of high intensity focused ultrasound

Acoustic Energy : 20 000 J



More than 90% reduction in tremor power

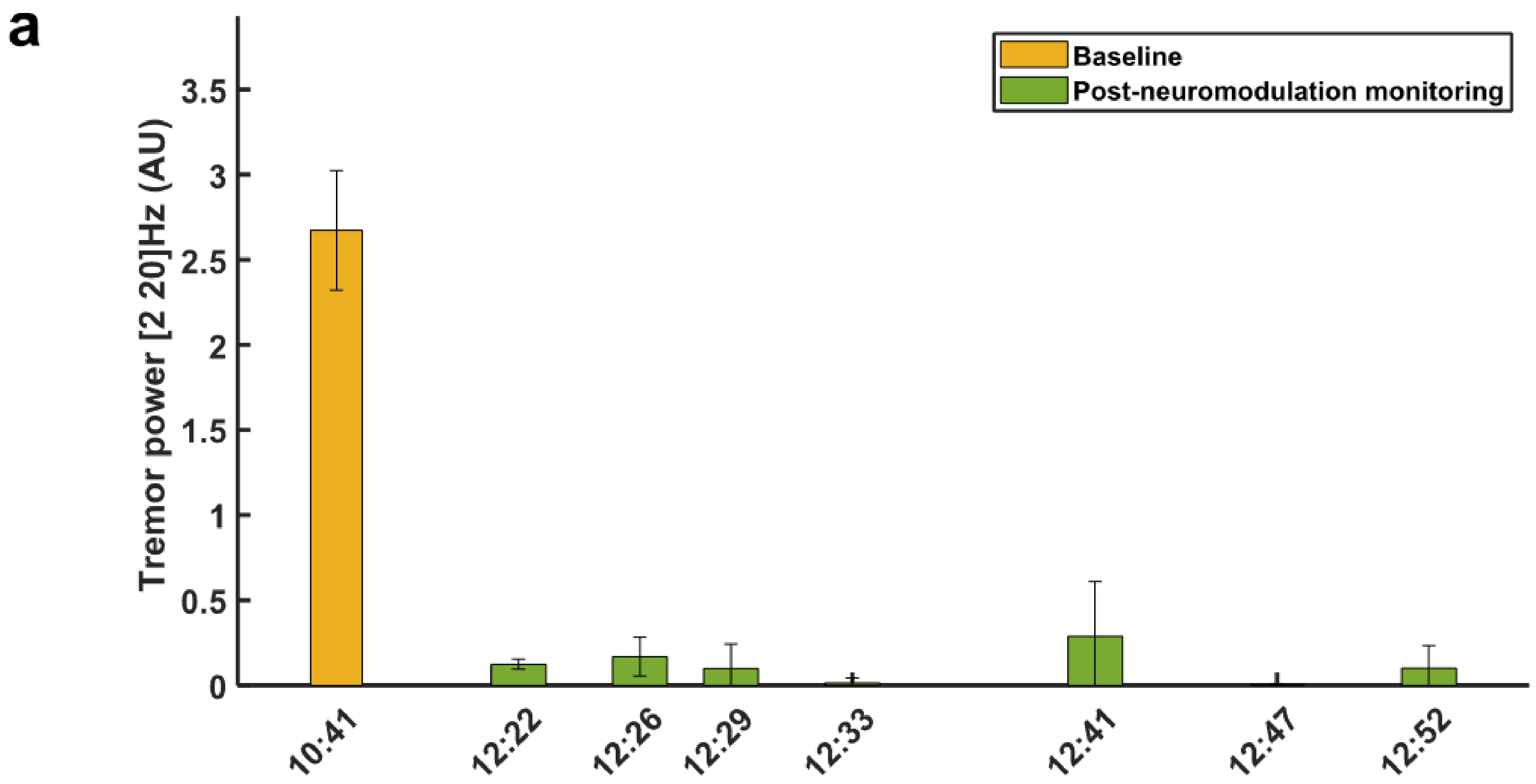
Neuromodulation in the thalamus with Exablate Neuro

Acoustic Energy : 8 J

Neuromodulation in the thalamus with Exablate Neuro

Acoustic Energy : 8 J

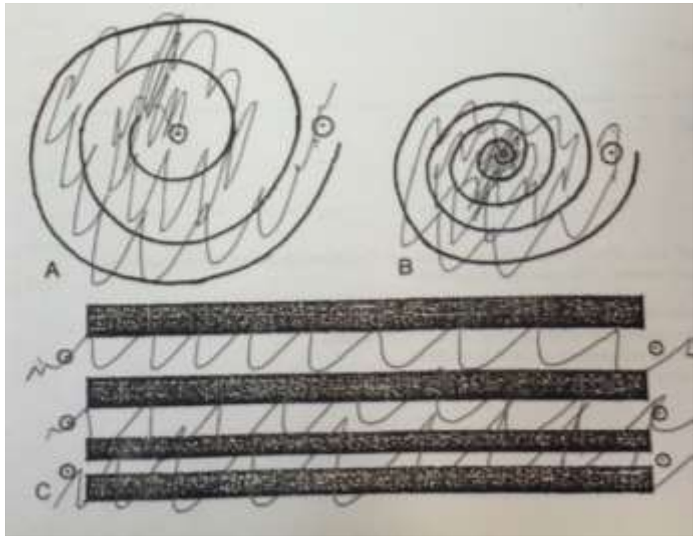
T. Bancel et al.

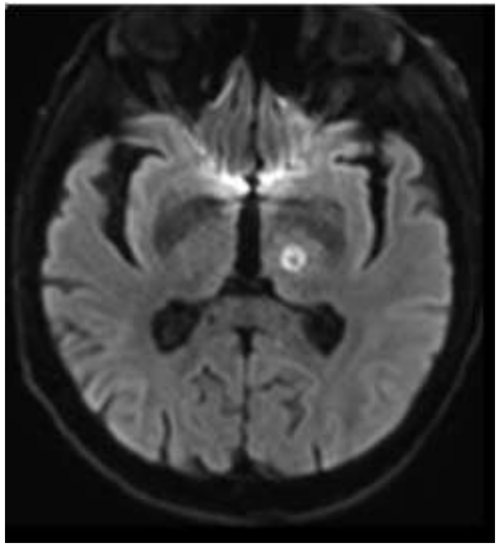


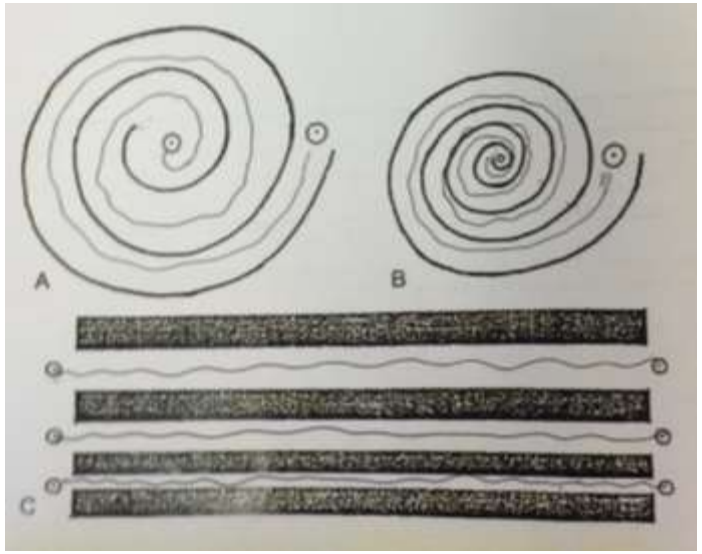
96% reduction in tremor power for 30min

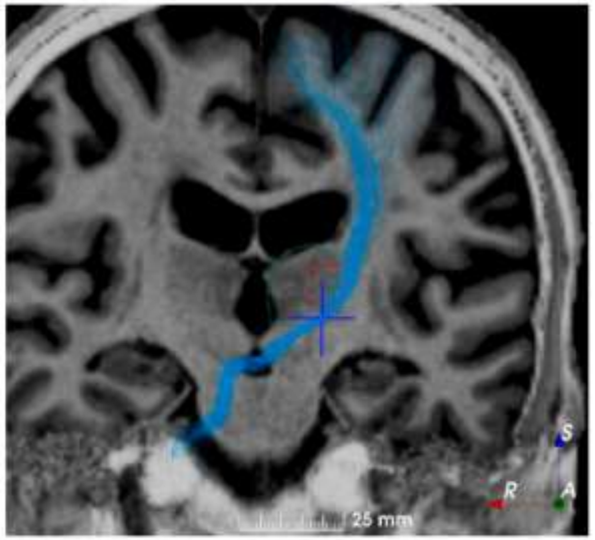
Bancel et al, Sustained reduction of essential tremor with low-power non-thermal transcranial focused ultrasound stimulations in humans, Brain Stimulation 2024

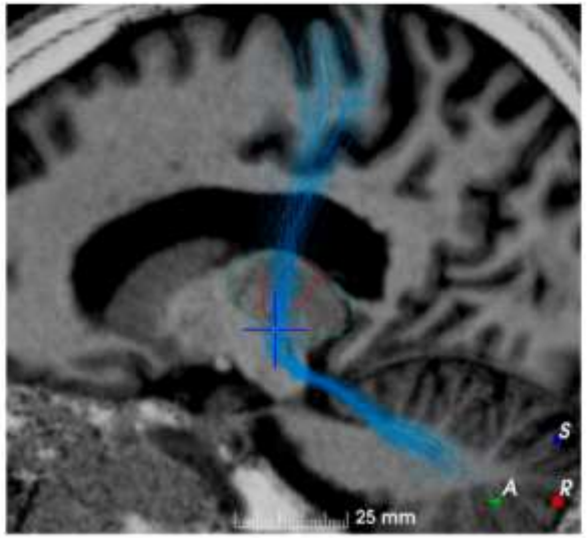
Treatment of Essential Tremor by thermal ablation with focused ultrasound





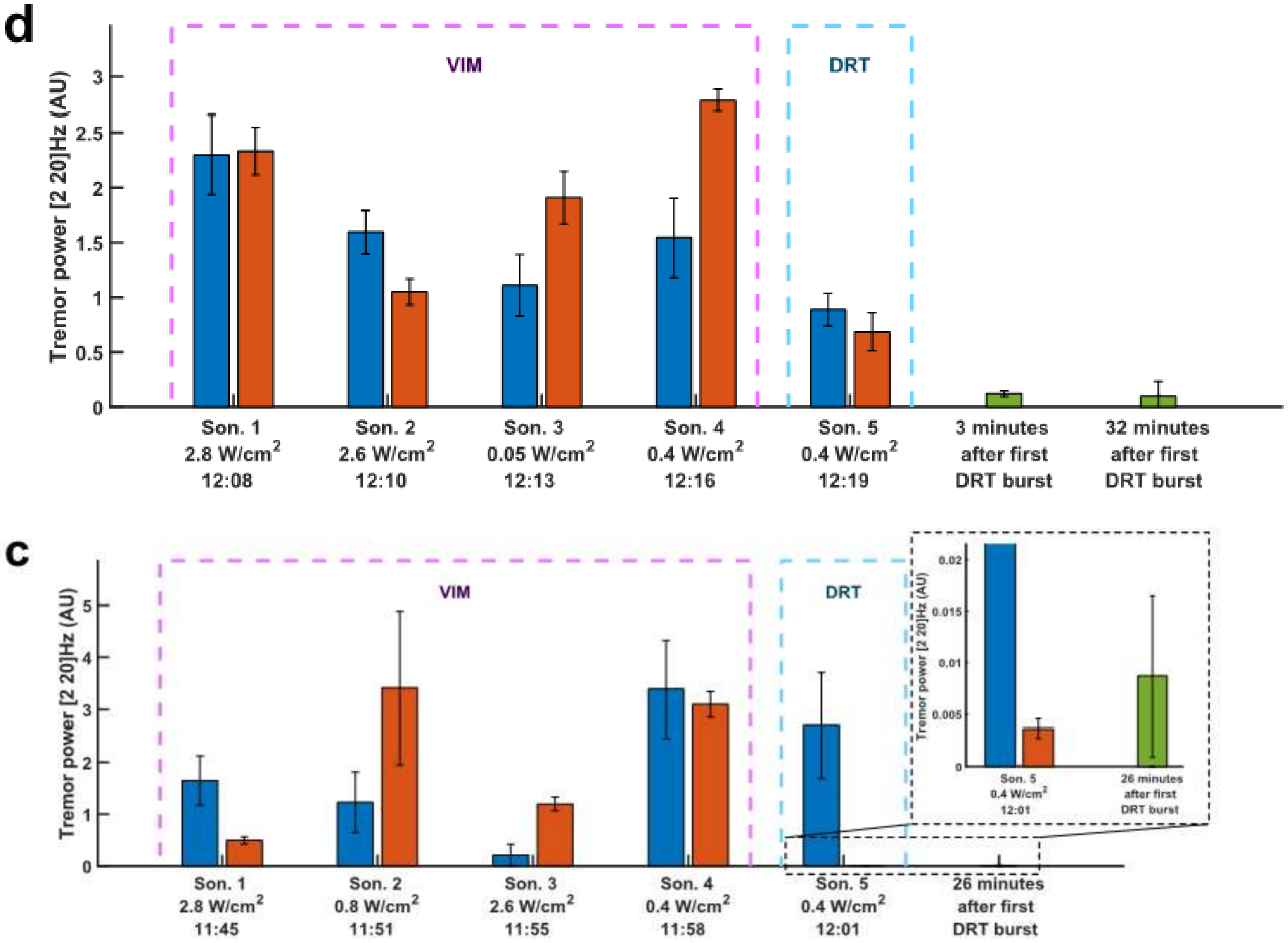






Treatment at la Pitié Salpêtrière hospital, Paris, France

Neuromodulation in the thalamus with Exablate Neuro



Bancel et al, Sustained reduction of essential tremor with low-power non-thermal transcranial focused ultrasound stimulations in humans, Brain Stimulation 2024

Neuromodulation in the Nuc Accumbens with Exablate Neuro

Mahoney, James J., et al. "Low-intensity focused ultrasound targeting the nucleus accumbens as a potential treatment for substance use disorder: safety and feasibility clinical trial." *Frontiers in Psychiatry* 14 (2023): 1211566.

Opioids

Alcohol

Cocaine

Neuromodulation in the Nuc Accumbens with Exablate Neuro

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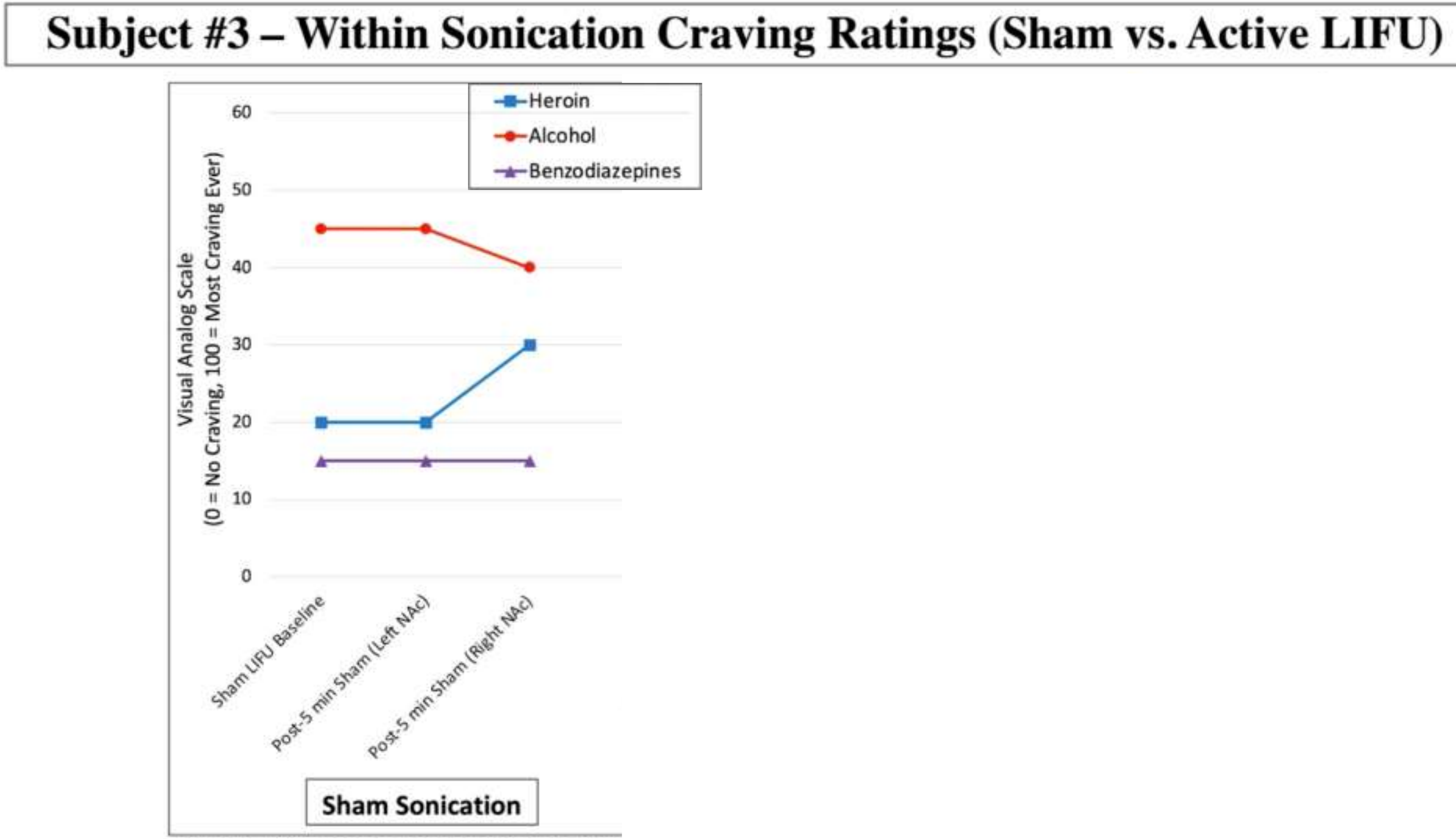
Opioids

Alcohol

Cocaine



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Neuromodulation in the Nuc Accumbens with Exablate Neuro

WVU Rockefeller Neuroscience Institute

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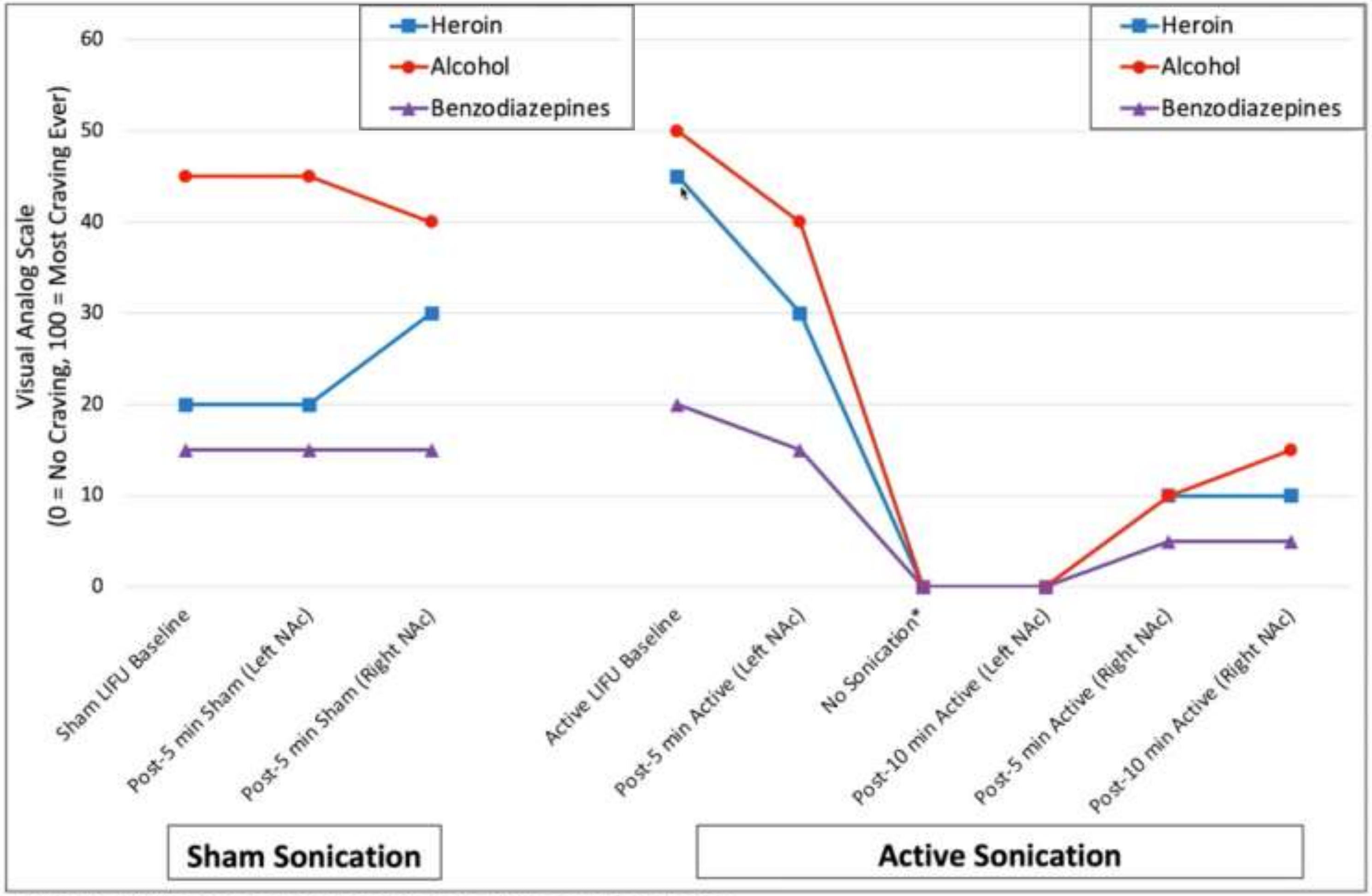
Opioids

Alcohol

Cocaine

Subject #3 – Within Sonication Craving Ratings (Sham vs. Active LIFU)



*Additional VAS assessment completed during 5-minute pause in sonication

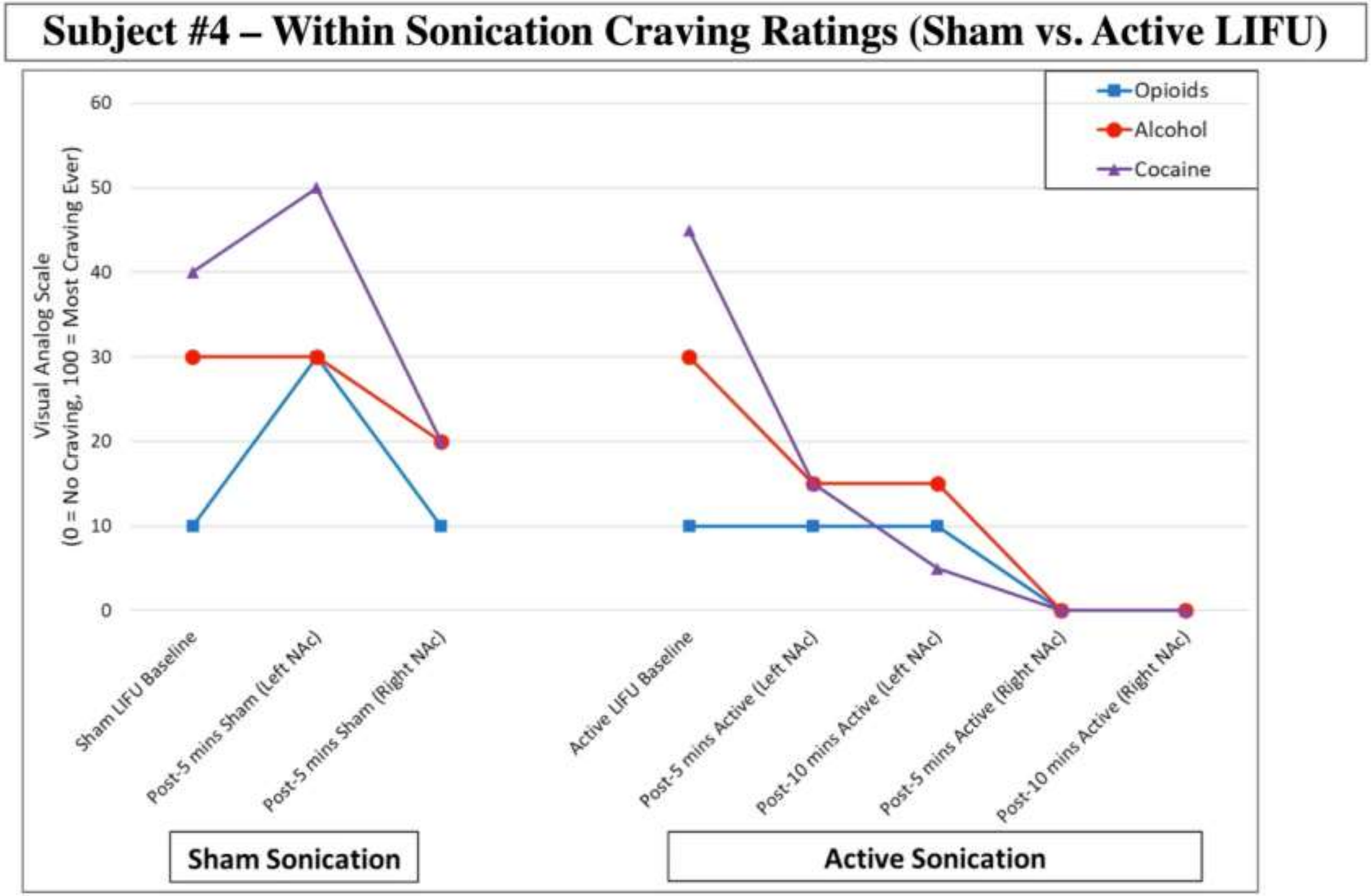
Neuromodulation in the Nuc Accumbens with Exablate Neuro

Mahoney, James J., et al. "Low-intensity focused ultrasound targeting the nucleus accumbens as a potential treatment for substance use disorder: safety and feasibility clinical trial." *Frontiers in Psychiatry* 14 (2023): 1211566.

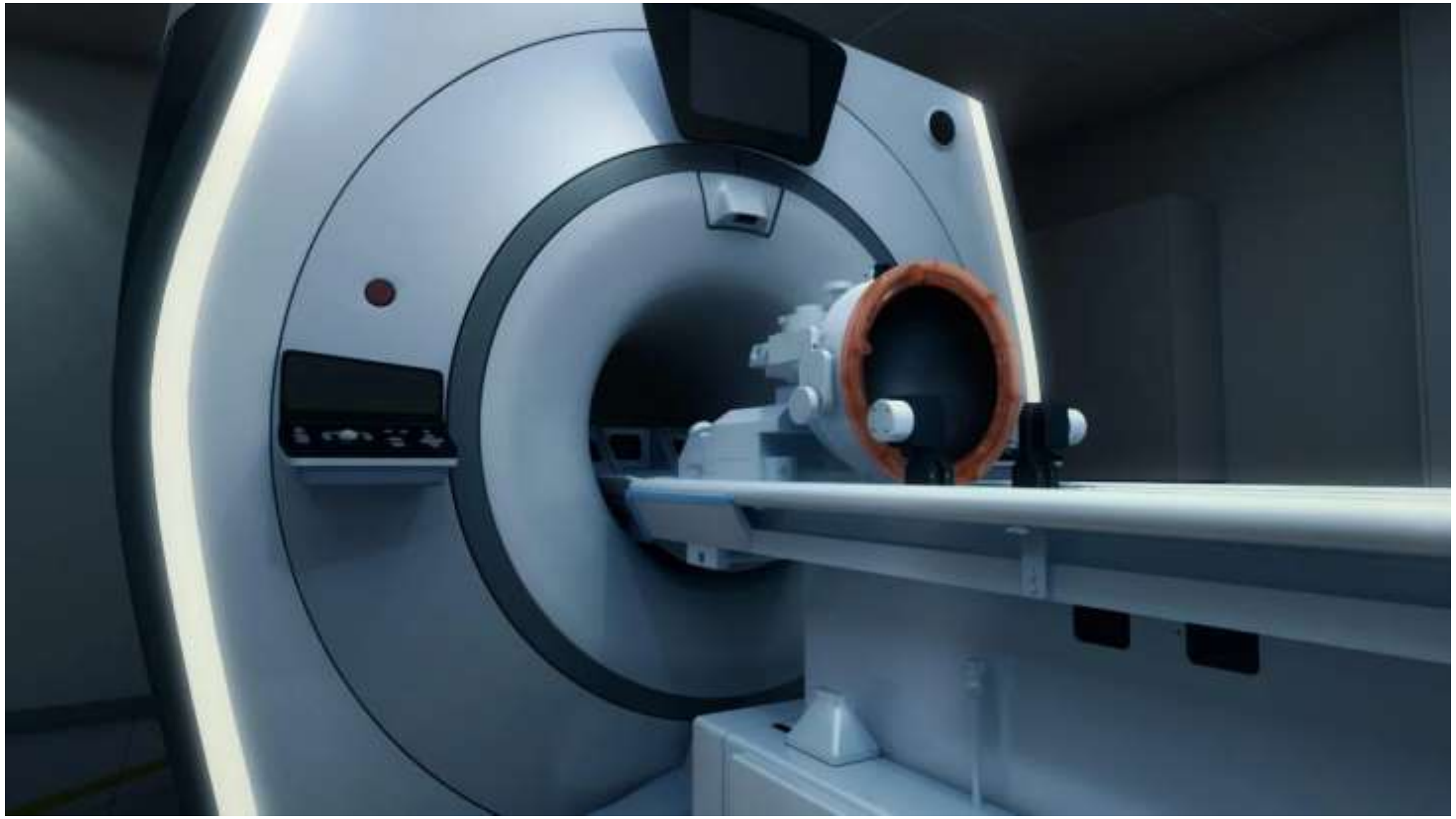
Opioids

Alcohol

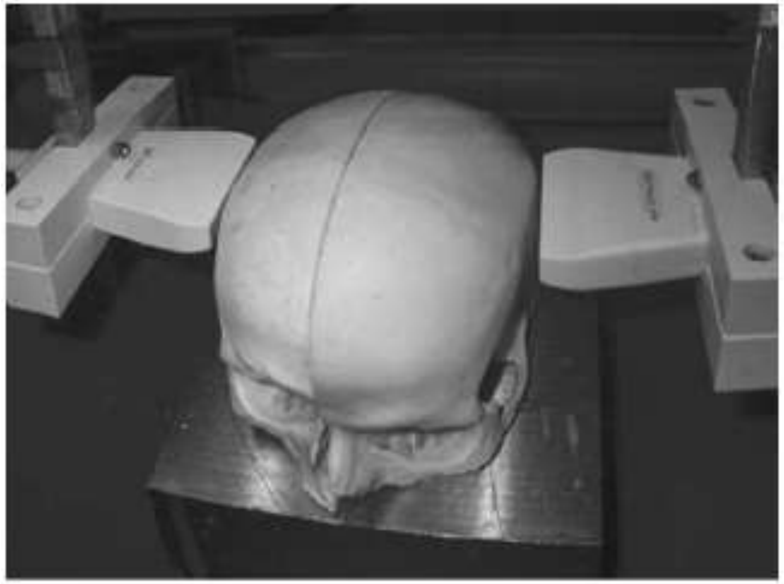
Cocaine



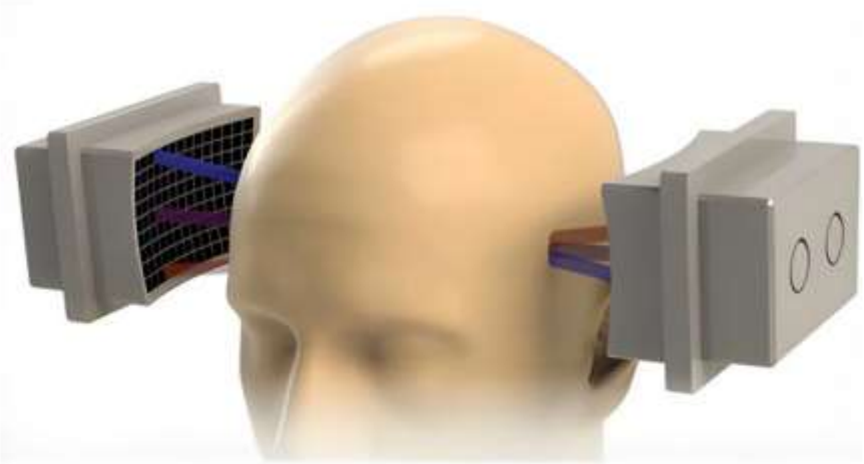
Strong target engagement with aberration correction. What is the price to pay?



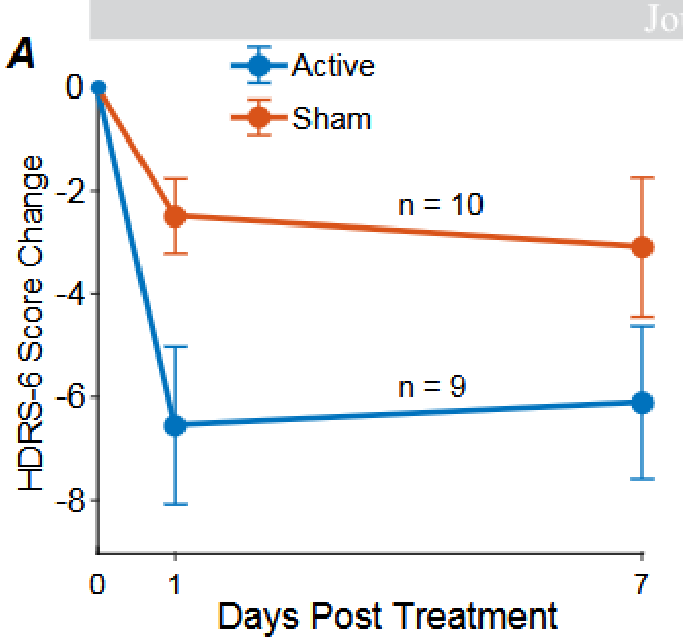
Decreasing the number of elements from 1024 to 256

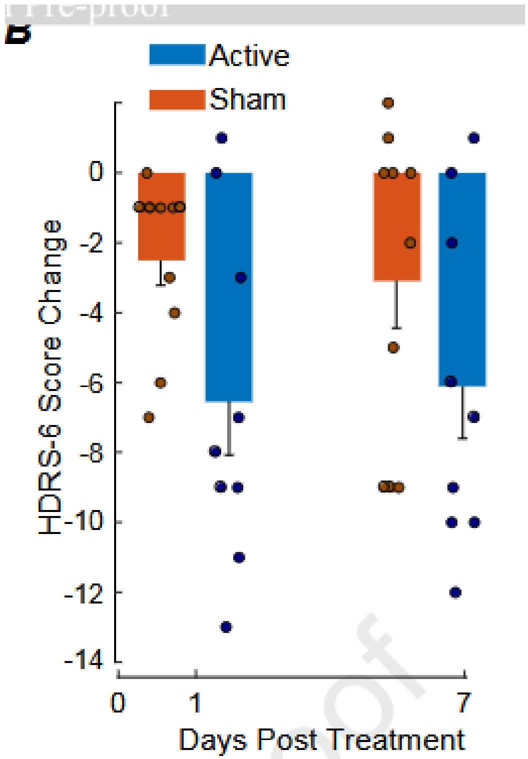


Vignon F, Aubry J-F, Tanter M, Margoum A, & Fink, M (2006). Adaptive focusing for transcranial ultrasound imaging using dual arrays. *The Journal of the Acoustical Society of America*



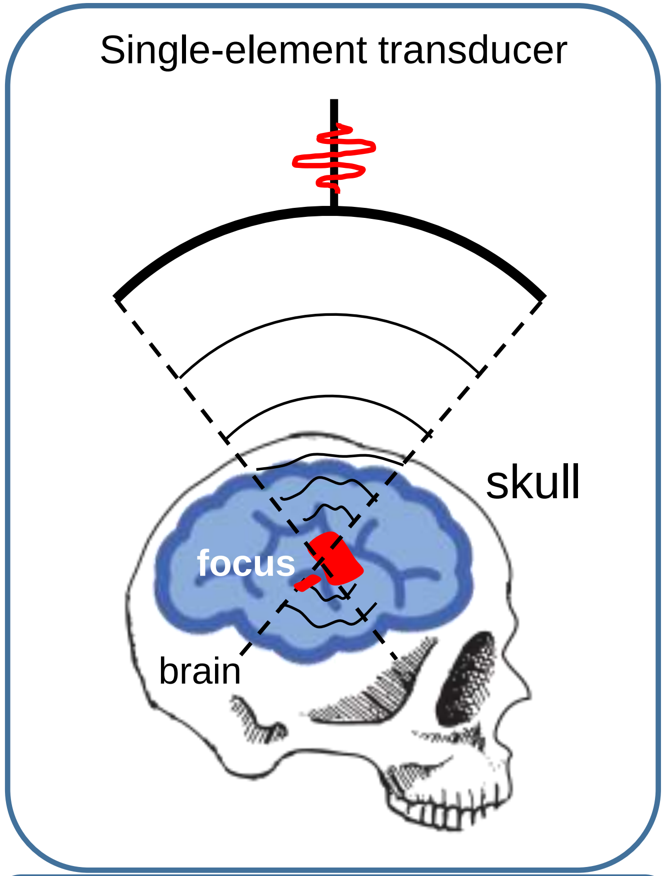
Riis, T., Feldman, D., Losser, A., Mickey, B., & Kubanek, J. (2023). Device for multifocal delivery of ultrasound into deep brain regions in humans. *IEEE TBME*



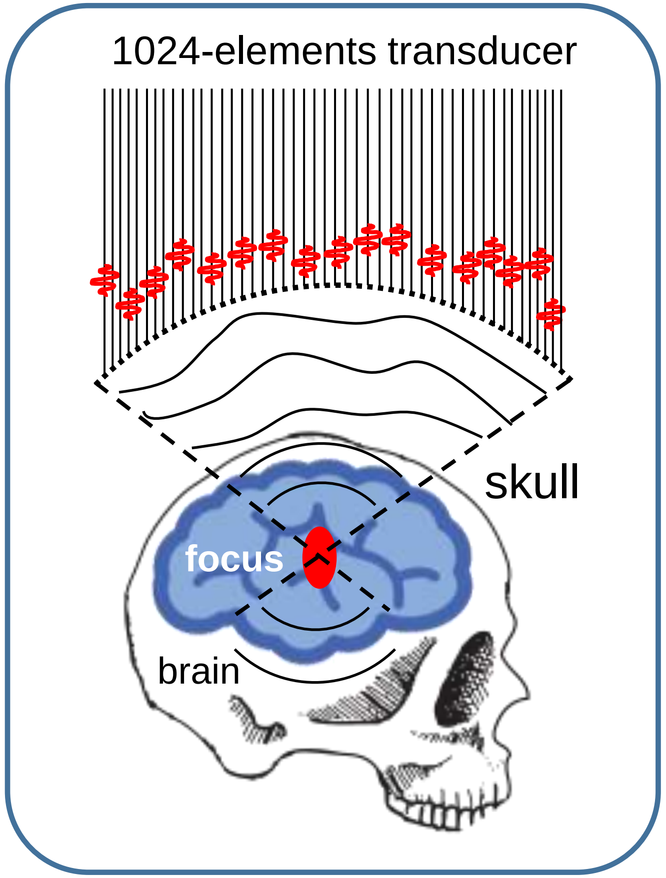


Riis, T., et al. "Noninvasive modulation of subcallosal cingulate and depression with focused ultrasonic waves." *Biological Psychiatry* (2024).

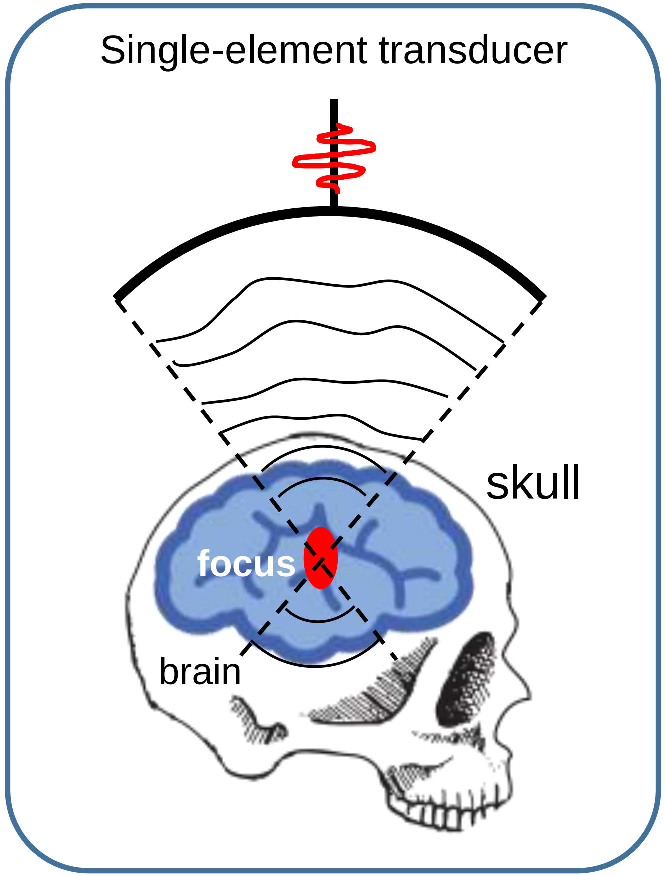
Transcranial focusing: the next revolution



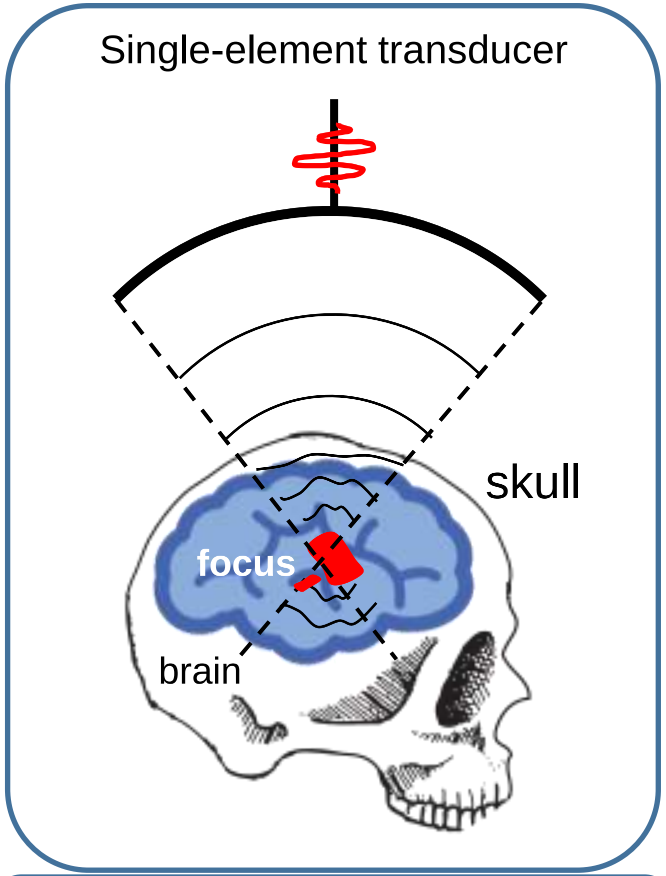
Single element transcranial Focused Ultrasound without correction



Multielement Transcranial Focused Ultrasound



Transcranial focusing: the next revolution



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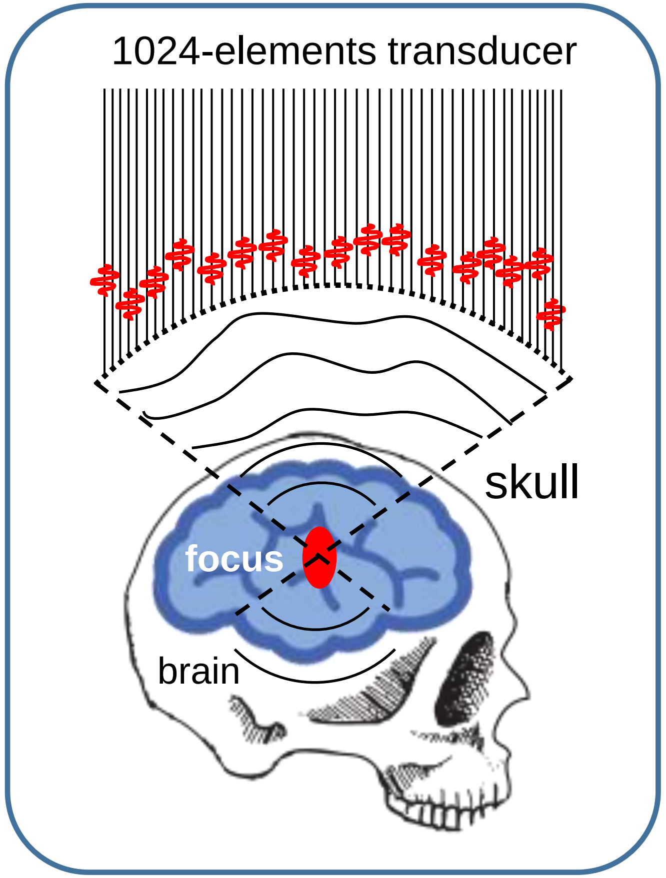
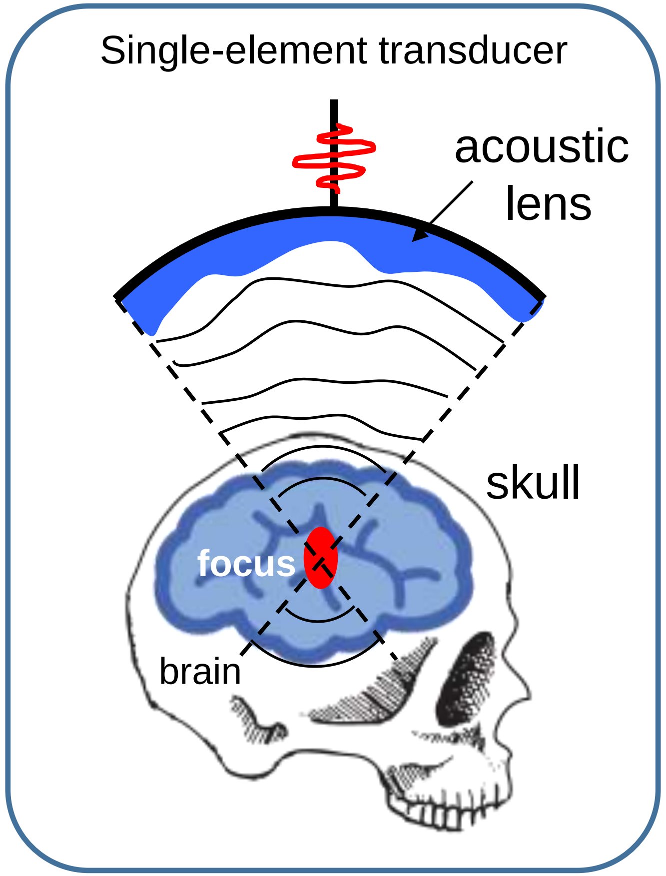


Multielement Transcranial Focused Ultrasound



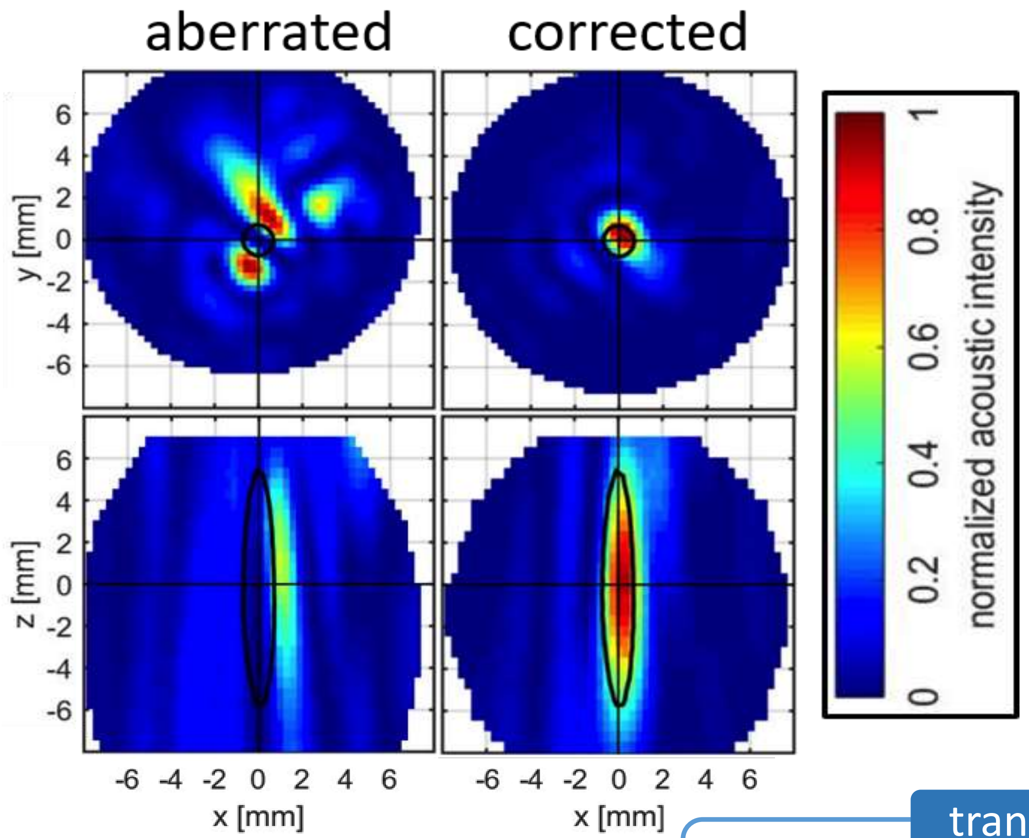
Transcranial Focused Ultrasound with acoustic lens

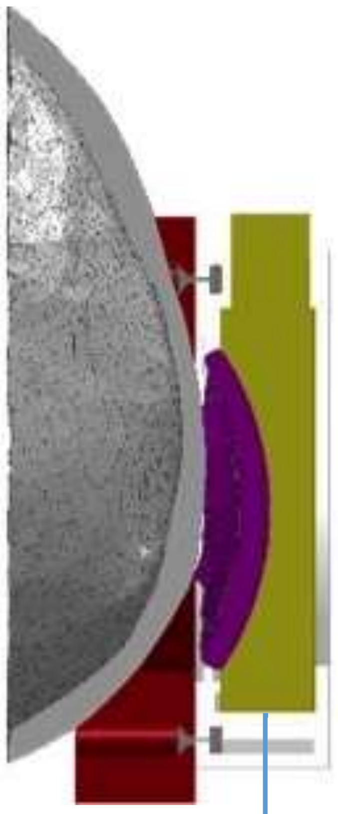
Aubry et al, WO 2017001781 Patent, July 2015

Maimbourg et al, 3D-printed adaptive acoustic lens as a disruptive technology for transcranial ultrasound therapy using single-element transducers, Physics in Medicine & Biology 2018

Maimbourg et al, Steering capabilities of an acoustic lens for transcranial therapy, IEEE TBME 2019

Technological breakthrough: towards low cost transcranial focusing





transducer

single-element with a 61mm radius of curvature and a 67mm aperture (H101 MR, Sonic Concepts, USA) operated at 914kHz.

Maimbourg et al, 3D-printed adaptive acoustic lens as a disruptive technology for transcranial ultrasound therapy using single-element transducers, Physics in Medicine & Biology 2018

Maimbourg et al, Steering capabilities of an acoustic lens for transcranial therapy, IEEE TBME 2019

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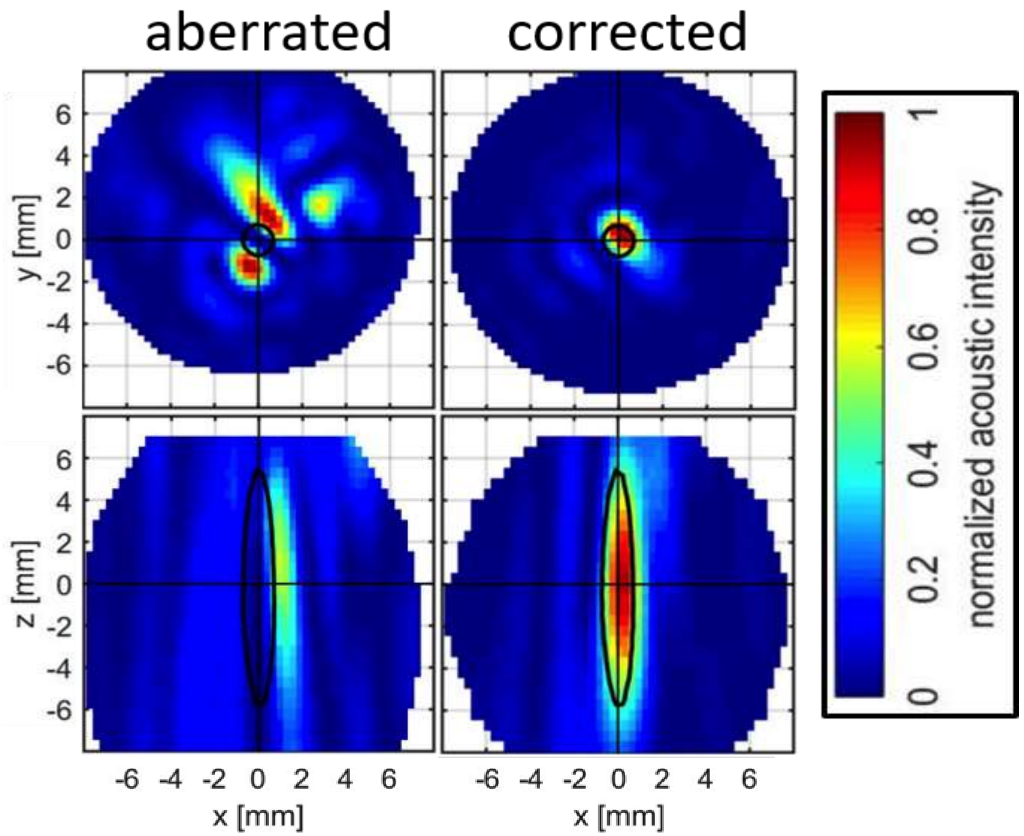
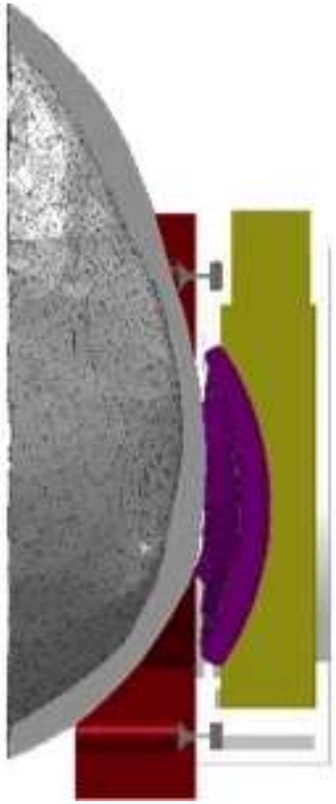




	skull A	skull B	skull C	mean ± std
aberrated	1.2W/cm^2	1.3W/cm^2	1.3W/cm^2	1.3 ± 0.1 W/cm^2
corrected	18W/cm^2	12W/cm^2	9.2W/cm^2	13 ± 4.5 W/cm^2

Maimbourg et al, 3D-printed adaptive acoustic lens as a disruptive technology for transcranial ultrasound therapy using single-element transducers, Physics in Medicine & Biology 2018

Maimbourg et al, Steering capabilities of an acoustic lens for transcranial therapy, IEEE TBME 2019

Impact of the lens on the precision of the targeting

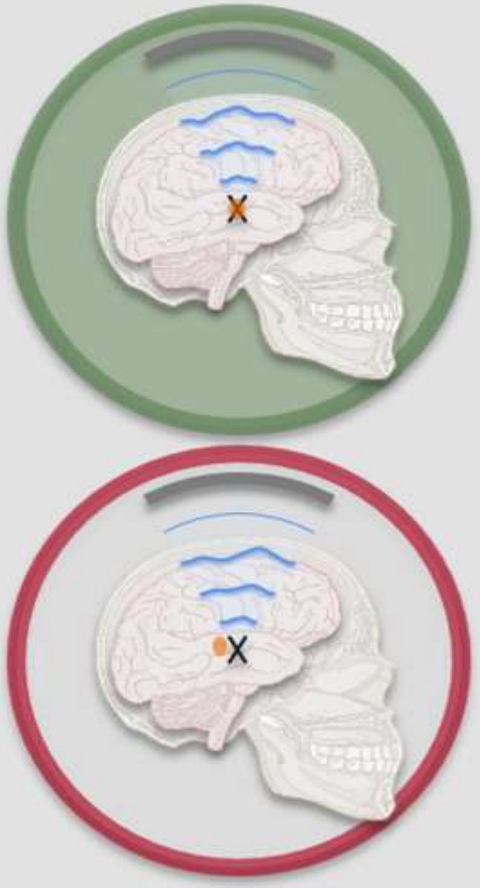
TARGET ENGAGEMENT
(at least one point of the 50% isodose hits the target)

STUDY	AUTHOR, YEAR	TUS TARGET	No Correction 1	2	3	4	5	6	7	8
1	Monti, 2016	Right Thal.	●	○	○	○	○	○	●	○
2	Ai, 2016	Left Caudate	●	●	○	○	○	○	●	○
3	Legon, 2018	Left Thal.	●	●	●	●	○	○	●	○
4	Badran, 2020	Right Thal.	●	○	○	○	○	○	●	○
5	Brinker, 2020	Left HPC	●	○	●	○	○	○	●	○
6	Cain, 2021 (1)	Left Pallidus	●	○	○	○	○	○	●	●
7	Jeong, 2021	Right HPC	●	●	●	●	●	●	●	●
8.1	Lee, 2022	Left PM Gyrus	●	●	●	●	●	●	●	●
8.2		Left HPC	●	○	○	●	○	○	●	○
8.3		Right Insula	●	○	●	○	●	○	●	○
8.4		Left AC gyrus	●	●	●	●	○	●	●	●
9	Stern, 2021	Left HPC	●	○	○	○	○	○	○	○
10	Cain, 2021 (2)	Left Thal.	●	○	●	●	○	○	●	○

	TOTAL 53/104 (51%)
TARGETING ERROR BETWEEN INITIAL TARGET AND MAXIMUM PRESSURE LOCATION	5.1 mm (± 3.6mm)

Impact of the lens on the precision of the targeting

TARGET ENGAGEMENT
(at least one point of the 50% isodose hits the target)



STUDY	AUTHOR, YEAR	TUS TARGET	No Correction 1	2	3	4	5	6	7	8	Correction with an Acoustic Lens 1	2	3	4	5	6	7	8
1	Monti, 2016	Right Thal.	●	○	○	○	○	○	●	○	●	●	●	●	●	●	●	●
2	Ai, 2016	Left Caudate	●	●	○	○	○	○	●	○	●	●	●	●	●	●	●	●
3	Legon, 2018	Left Thal.	●	●	●	●	○	○	●	○	●	●	●	●	●	●	●	●
4	Badran, 2020	Right Thal.	●	○	○	○	○	○	●	○	●	●	●	●	●	●	●	●
5	Brinker, 2020	Left HPC	●	○	●	○	○	○	●	○	●	●	●	●	●	●	●	●
6	Cain, 2021 (1)	Left Pallidus	●	○	○	○	○	○	●	●	●	●	●	●	●	●	●	●
7	Jeong, 2021	Right HPC	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
8.1	Lee, 2022	Left PM Gyrus	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
8.2		Left HPC	●	○	○	●	○	○	●	○	●	●	●	●	●	●	●	●
8.3		Right Insula	●	○	●	○	●	○	●	○	●	●	●	●	●	●	●	●
8.4		Left AC gyrus	●	●	●	●	○	●	●	●	●	●	●	●	●	●	●	●
9	Stern, 2021	Left HPC	●	○	○	○	○	○	○	○	●	●	●	●	●	●	●	●
10	Cain, 2021 (2)	Left Thal.	●	○	●	●	○	○	●	○	●	●	●	●	●	●	●	●

	No Correction		Correction with an Acoustic Lens
TOTAL	53/104 (51%)		104/104 (100%)
TARGETING ERROR BETWEEN INITIAL TARGET AND MAXIMUM PRESSURE LOCATION	5.1 mm (± 3.6mm)	VS	1.5 mm (± 1.7mm)

Comparison with measurements:
Gimeno et al. (2019) IEEE IUS: 4.4 mm (± 3.2mm) without correction

Unpublished Result, Manuscript under preparation.

Neuronavigated, lens-based aberration correction for precise deep brain stimulation

SonoMind

Electromagnetic compatibility and electrical safety

Certified by a notified body:
LCIE Bureau Veritas

BUREAU VERITAS 1828
BUREAU
VERITAS
Shaping a World of Trust

- radiation emission
- electrostatic discharge
- RF electromagnetic fields
- leakage current
- dielectric strength test of solid insulating materials
- excessive temperatures in the equipment
- proximity fields from RF wireless communications

Neuronavigated, lens-based aberration correction for precise deep brain stimulation

SonoMind

Mechanical safety

==> Mechanical Index < 1.9

(associated with the absence of mechanical risks according to standards for ultrasound imaging)

SonoMind

Thermal safety

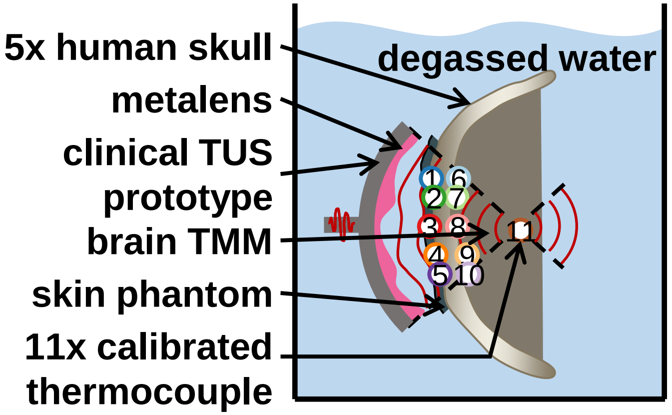
Calibrated measurements in free water

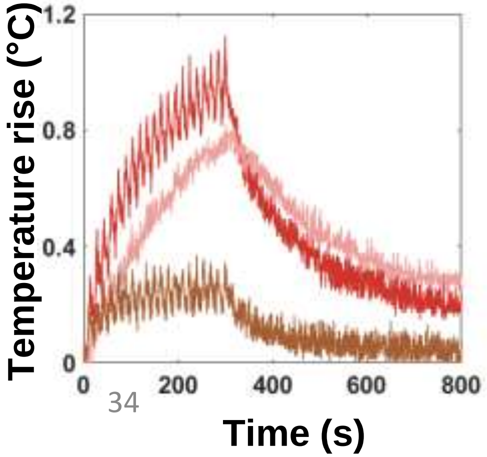
==> Cranial Thermal Index < 2

Measurements on 5 ex vivo skulls

==> Thermal Rise < 2°C

(safe according to standards for MRI and implantable devices)





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Regulatory requirements for human studies

Low-intensity focused ultrasound stimulation in stroke: An intensity escalation phase I safety and feasibility study

Ziping Huang, MS[1,2*]; Charalambos C. Charalambous, PhD[1*]; Mengyue Chen, MS[3]; Taewon Kim, PhD[4,5]; Estate Sokhadze, PhD[1]; Allen Song, PhD[6]; Sin-Ho Jung, PhD[7]; Shashank Shekhar, MD[1]; Jody Feld, PhD[1,8]; Xiaoning Jiang, PhD[3]; Wuwei Feng, MD, MS[1,2]

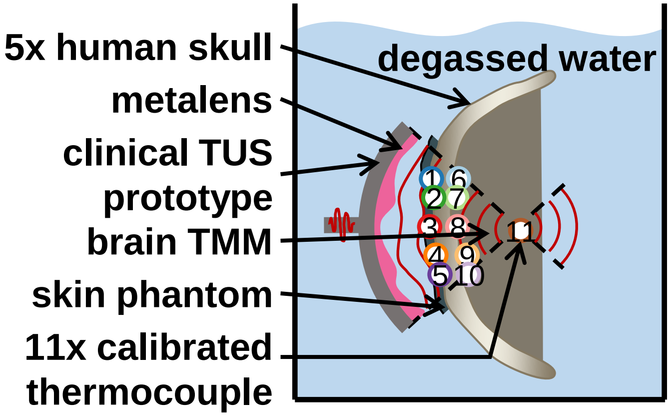
[1]Department of Neurology, Duke University School of Medicine
[2]Department of Biomedical Engineering, Duke University
[3]Department of Mechanical and Aerospace Engineering, North Carolina State University
[4]Department of Physical Medicine and Rehabilitation, Penn State College of Medicine
[5]Department of Kinesiology, Pennsylvania State University
[6]Duke Brain Imaging and Analysis Center, Duke University School of Medicine
[7]Department of Biostatistics and Bioinformatics, Duke University School of Medicine
[8]Department of Orthopaedic Surgery, Duke University School of Medicine
*These authors contributed equally to this work.

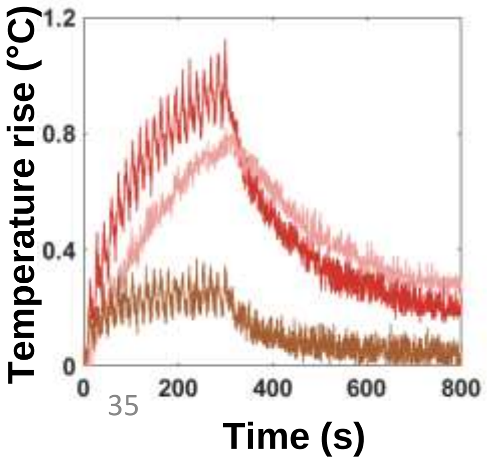
Although no stopping rules were met, one participant (4 W/cm²) suffered a first-degree scalp burn with mild pain sensation that resolved on the next day.

Thermal safety

Calibrated measurements in free water
==> Cranial Thermal Index < 2

Measurements on 5 ex vivo skulls
==> Thermal Rise < 2°C
(safe according to standards for MRI and implantable devices)





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Neuronavigated, lens-based aberration correction for precise deep brain stimulation

SonoMind

On going clinical trial on drug resistant depression

GHU PARIS PSYCHIATRIE & NEUROSCIENCES

Dr M. Plaze

Dr D. Attali

Physics for Medicine PARIS

Work supported by:

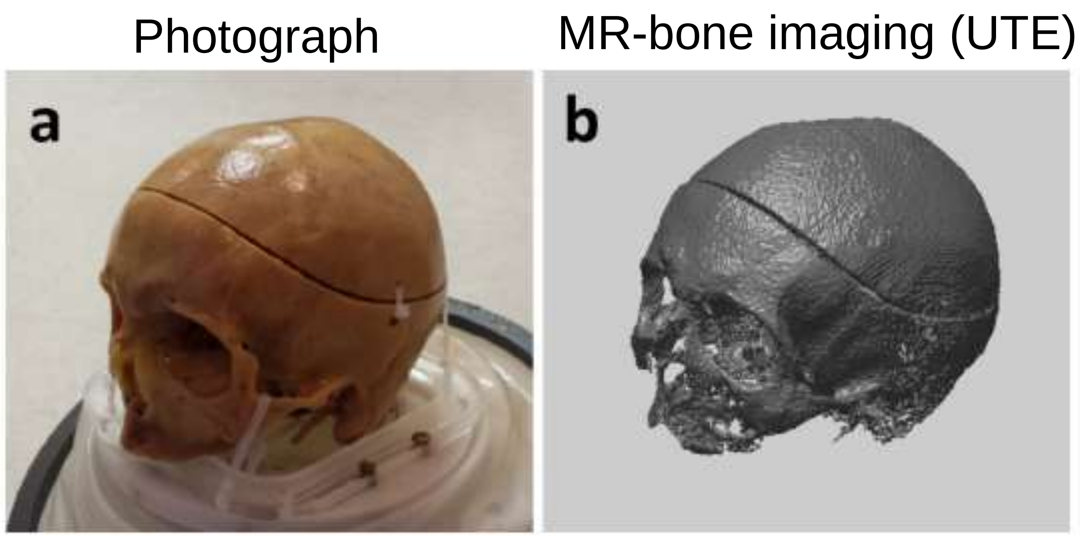
Focused Ultrasound Foundation
Center of excellence

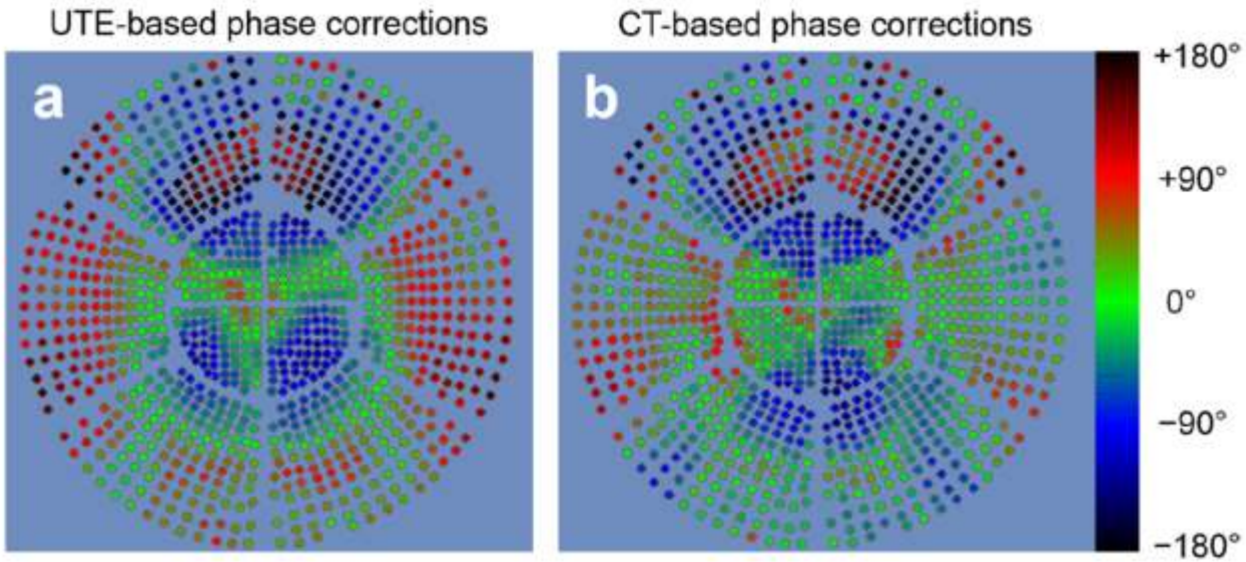
National Agency for Research

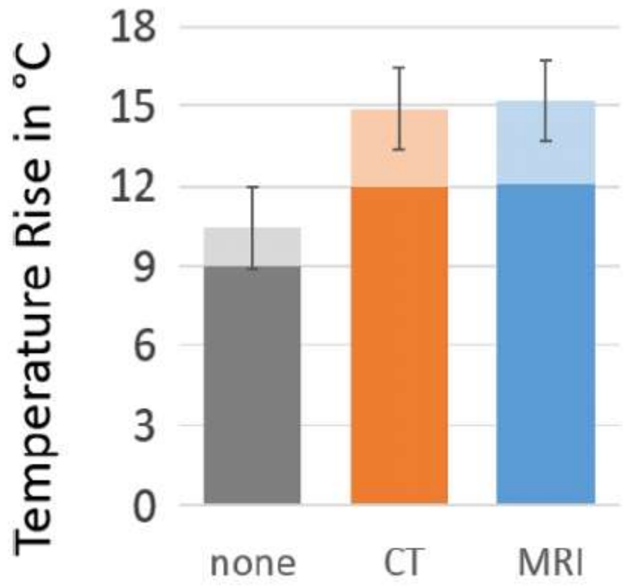
ANR-10-EQPX-15

Fondation Bettencourt Schueller

MR skull imaging correction as an alternative to CT based correction





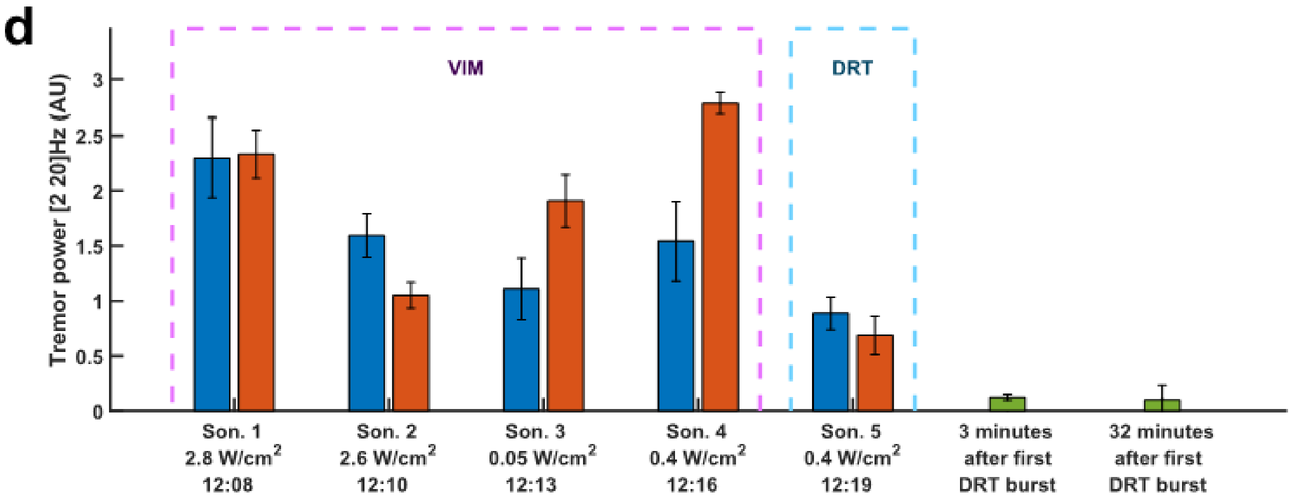


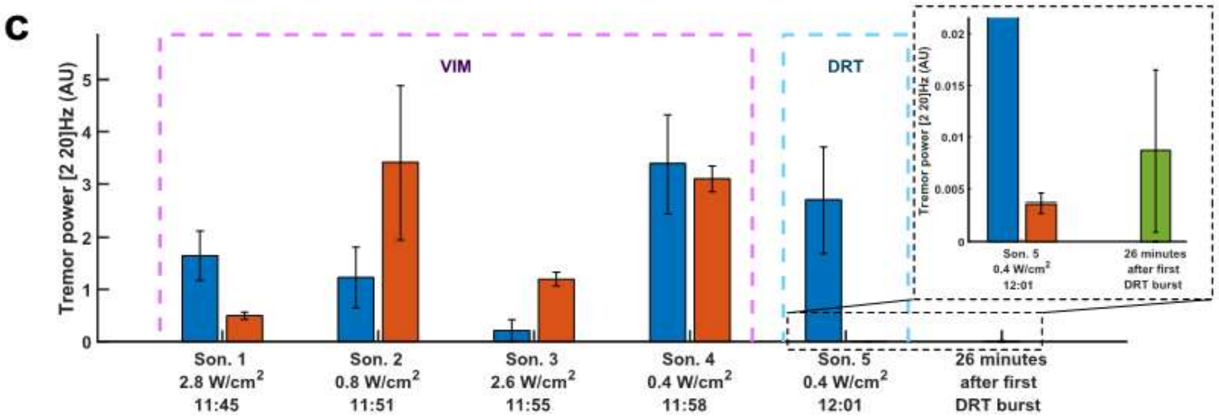
G. W. Miller et al, Medical physics, 2015

Physics for Medicine PARIS

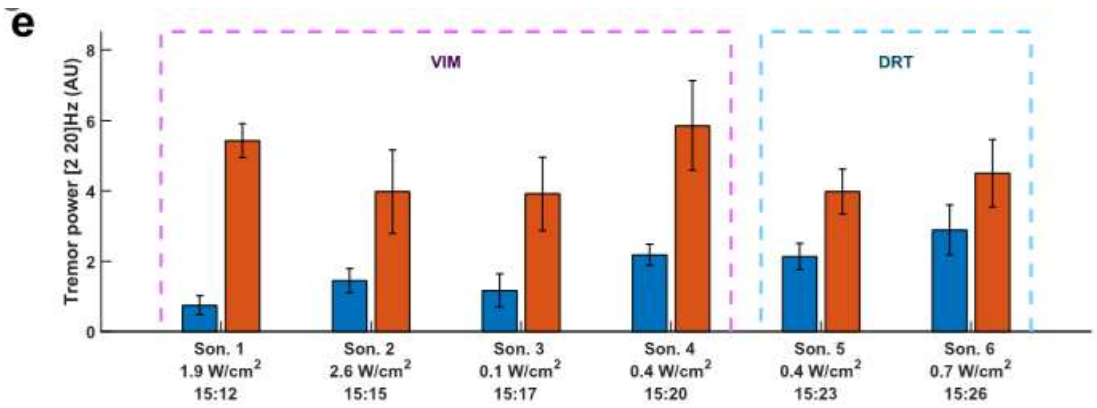
Neuromodulation in the thalamus with Exablate Neuro

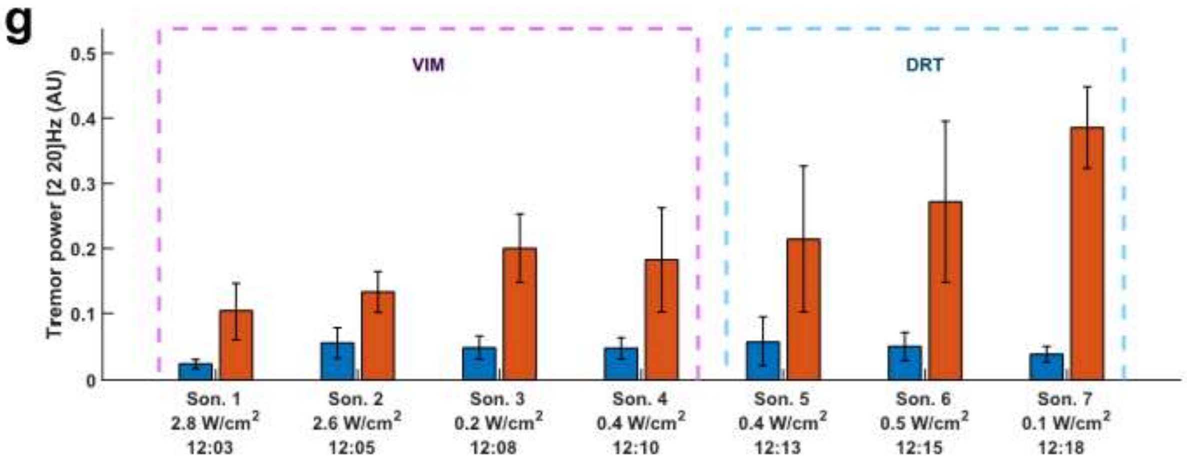
Responders





Non-responders ??

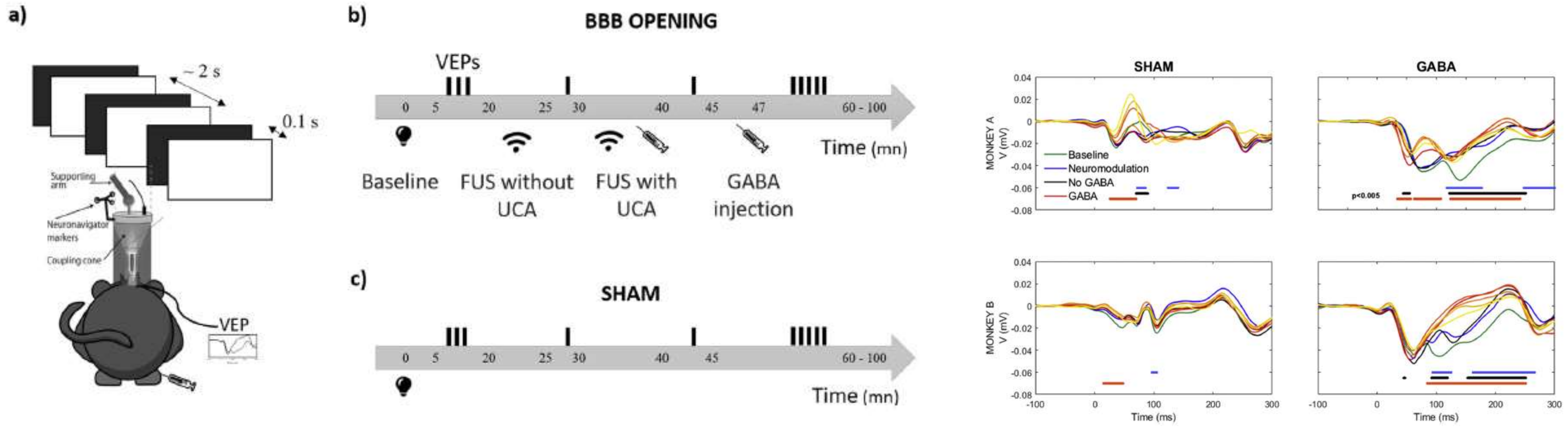




Bancel et al, Sustained reduction of essential tremor with low-power non-thermal transcranial focused ultrasound stimulations in humans, Brain Stimulation 2024

Bonus: BBB opening and neuromodulation

Non-invasive ultrasonic modulation of visual evoked response by GABA delivery through the blood brain barrier



Constans, C. et al Non-invasive ultrasonic modulation of visual evoked response by GABA delivery through the blood brain barrier. *Journal of Controlled Release*, *318*, 223-231.

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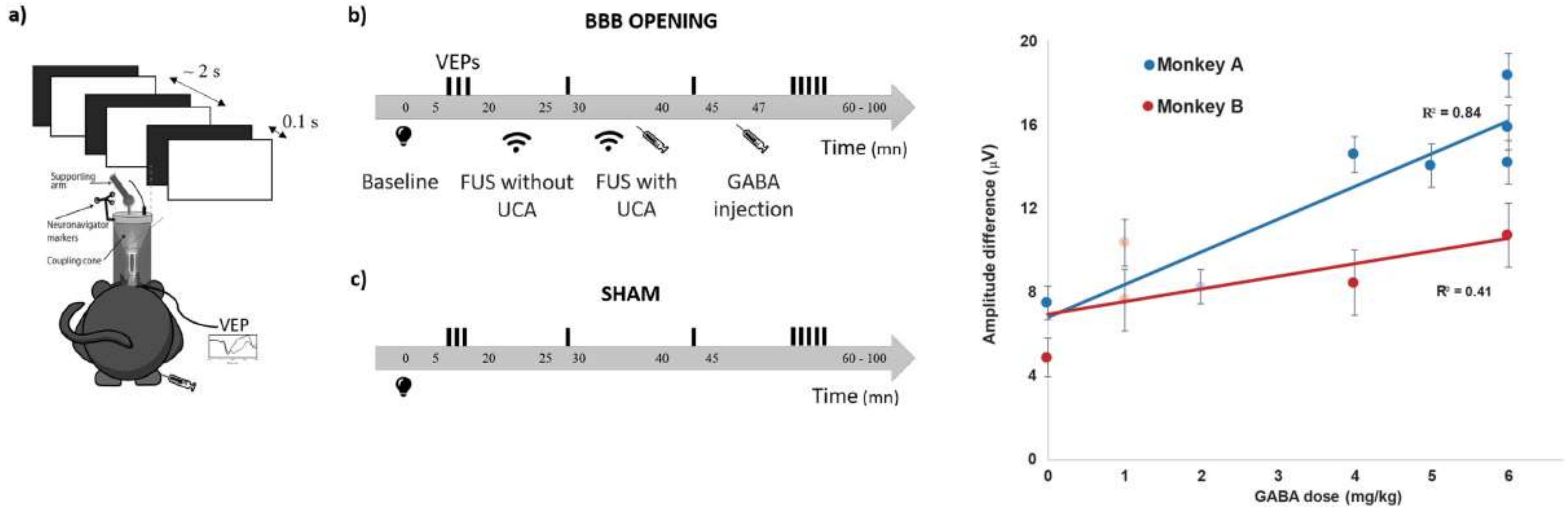

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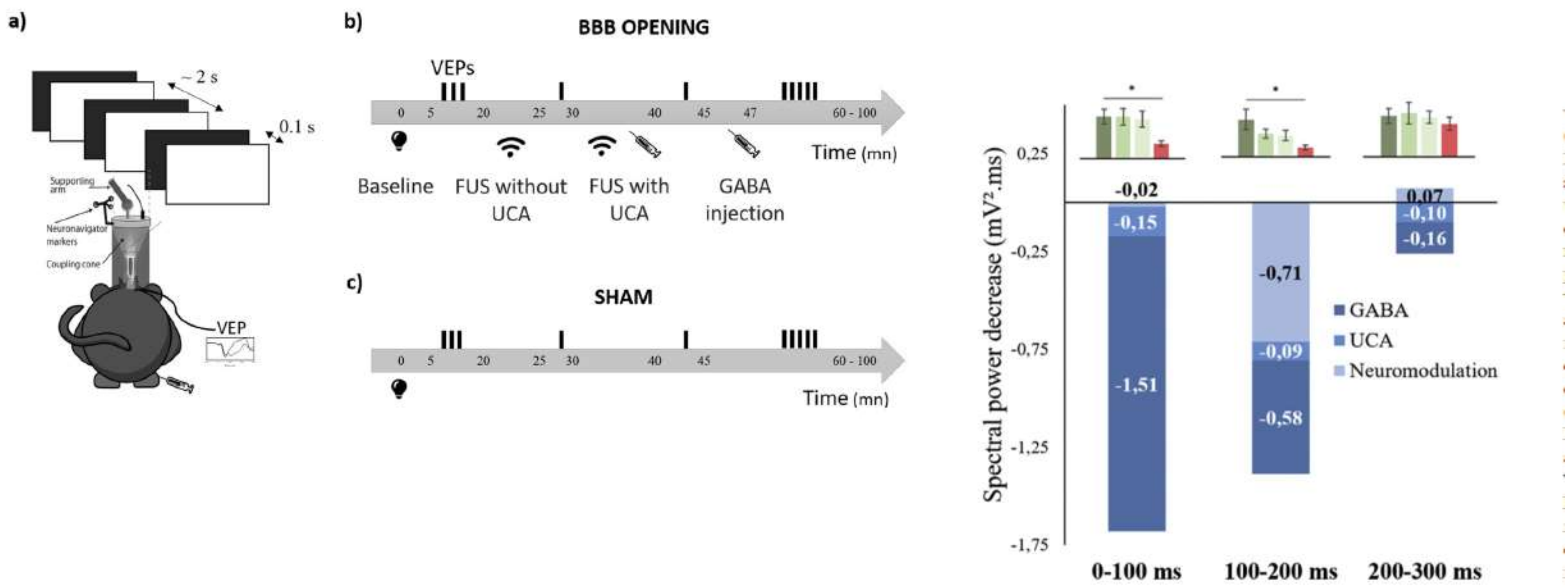
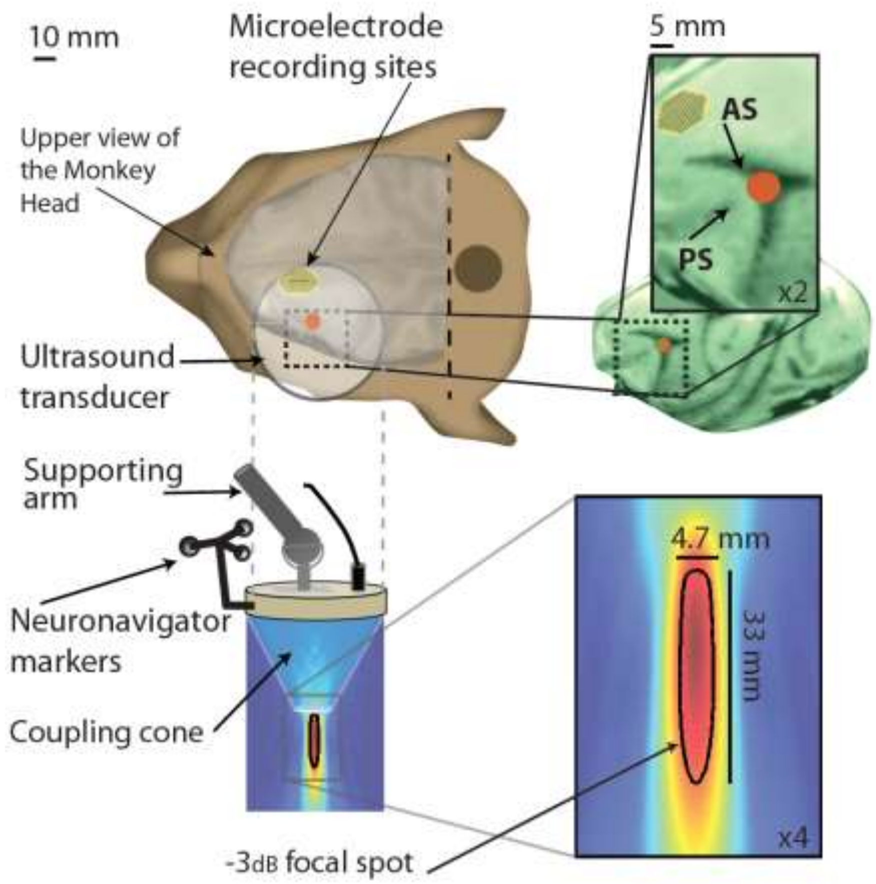
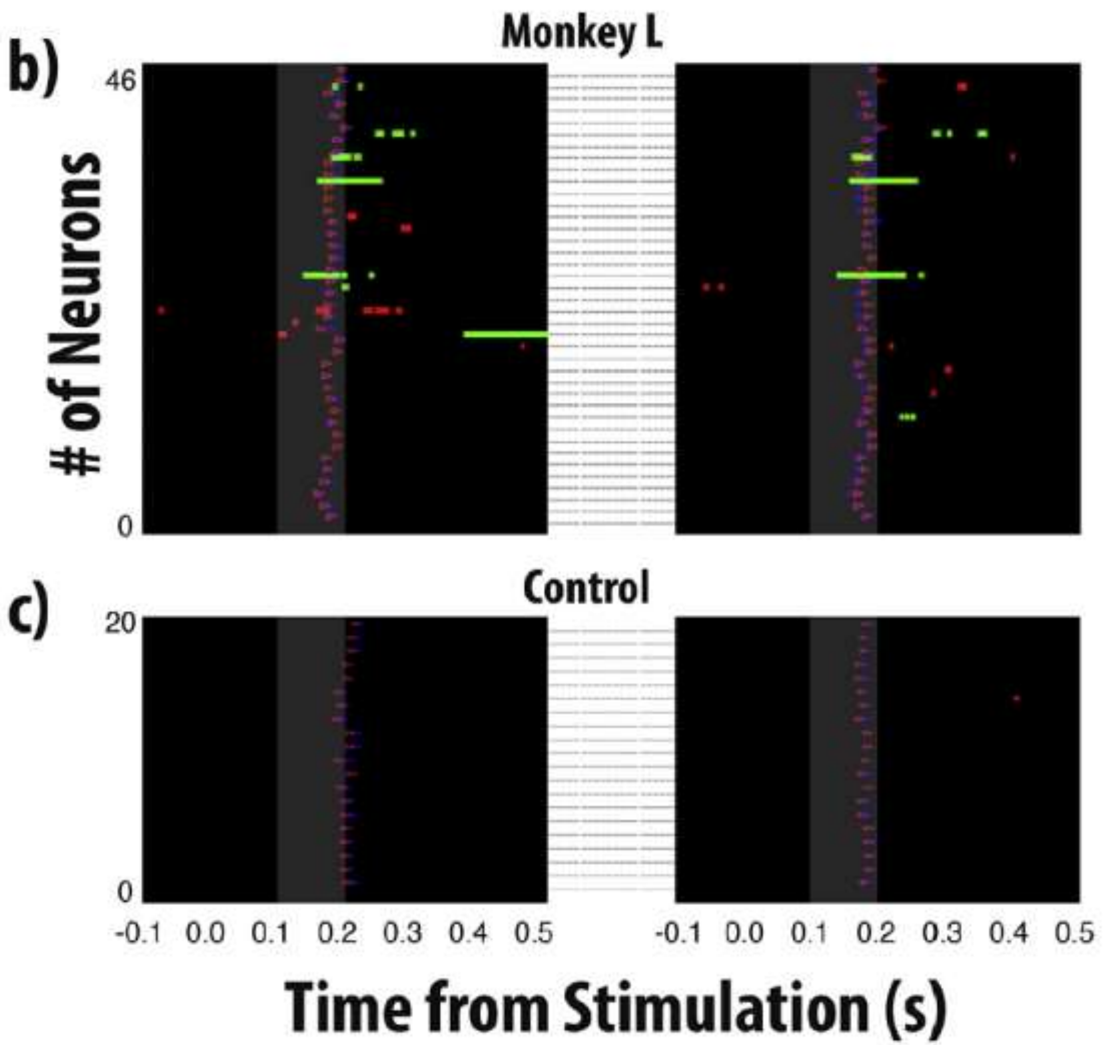


Constans, C. et al Non-invasive ultrasonic modulation of visual evoked response by GABA delivery through the blood brain barrier. *Journal of Controlled Release*, *318*, 223-231.

Neuromodulation on awake animals : microelectrodes recording

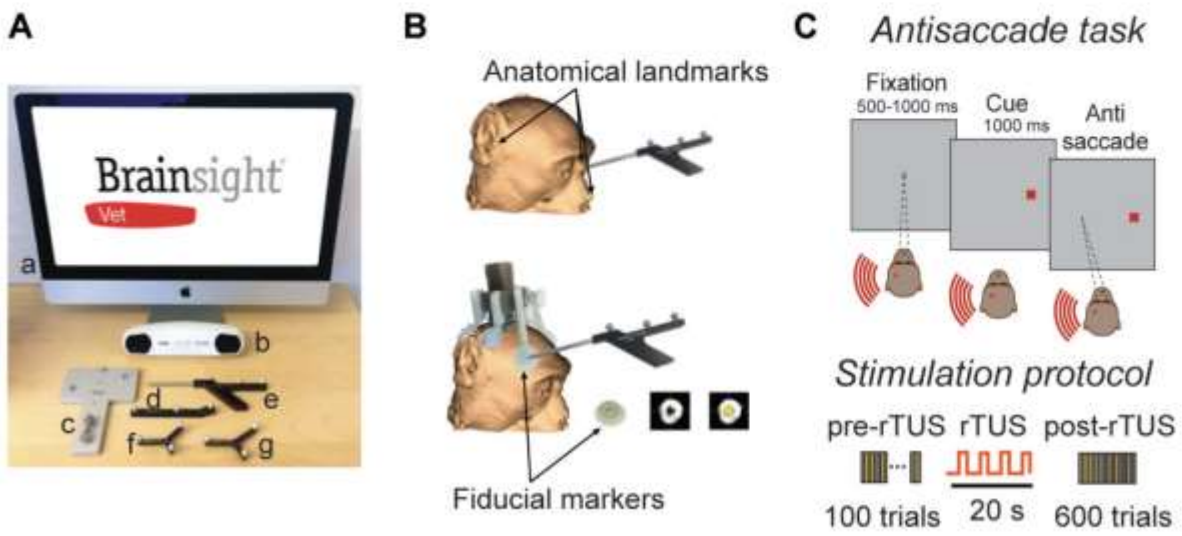
Stimulation site: Frontal Eye Field
Microelectrodes recording site: Supplementary Eye Field

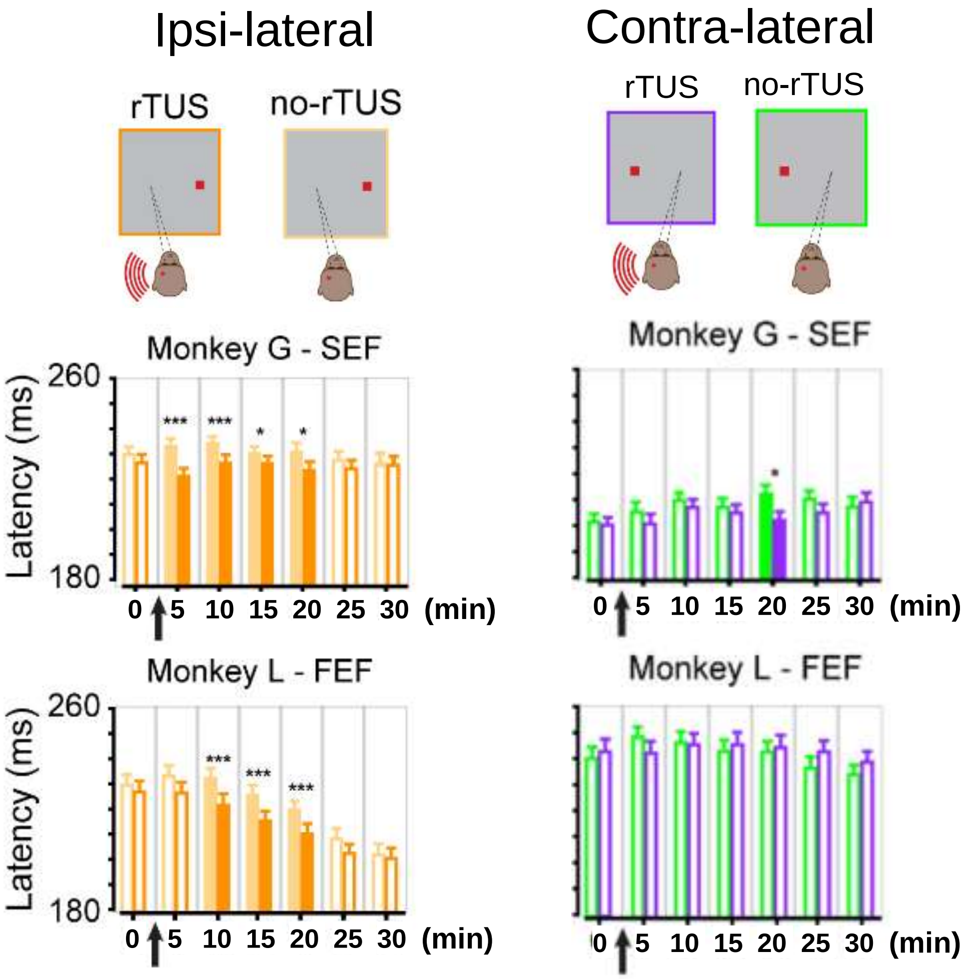




Wattiez et al, Neurostimulation (2017)

Long-lasting and reversible effects on oculomotor performance in non-human primates





Pouget et al, Neuronavigated Repetitive Transcranial Ultrasound Stimulation induces long-lasting and reversible effects on oculomotor performance in non-human primates." Frontiers in Physiology 11 (2020).