

# Focused ultrasound beyond phased-arrays:
## Acoustic holograms for the brain

Noé Jiménez,

nojigon@upv.es

Bienal de Física 2019. Zaragoza (Spain), 14-19 July 2019.

# Who we are

## Instituto de Instrumentation para Imagen Molecular [I3M]

Joint institute CSIC – UPV, Universitat Politècnica de València (Spain)

About 50 researchers

- Detectors for Molecular Imaging Laboratory (DMIL)
- Magnetic Resonance Imaging Laboratory (MRILab)
- Medical Imaging Reconstruction Group (MIRG)
- Laser Acceleration of Ions and Applications (LAIA)
- Ultrasound Medical and Industrial Laboratory (UMIL)

## Ultrasound Medical and Industrial Laboratory (UMIL)

11 researchers

- Hybrid ultrasonic imaging techniques
- Focusing metamaterials and therapeutic ultrasonic beams
- Ultrasonic technology applied to odontology
- Industrial applications of ultrasound
- Transcranial propagation of therapeutic ultrasound

***Holograms to focus ultrasound in the CNS***



Sergio Jiménez-Gambín,



María C. Dejoz-Díez



José María Benlloch

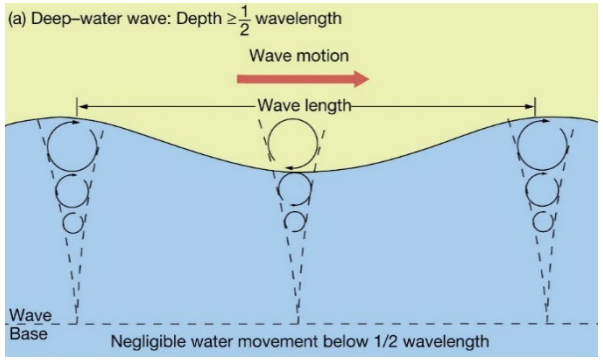


Francisco Camarena

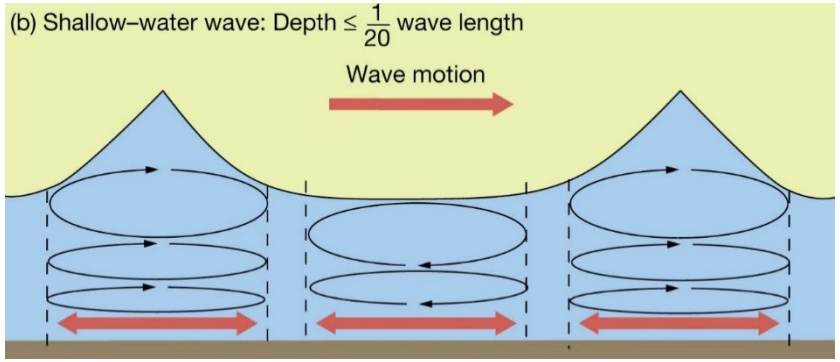
# Ultrasound capabilities in biomedical applications

## Small-amplitude waves

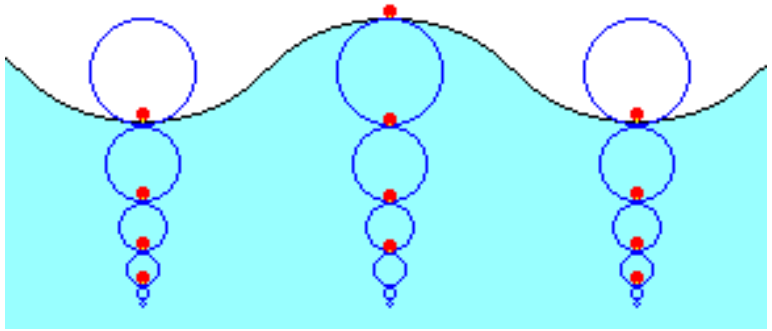
Deep-water wave




Shallow-water wave

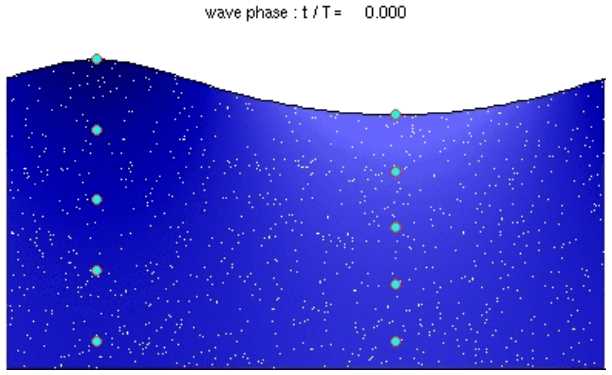



Steady motions

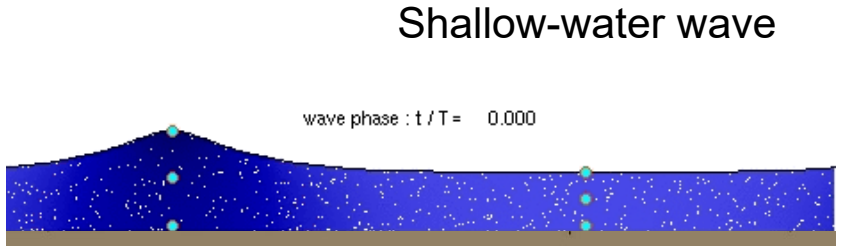


## High amplitude waves

Deep-water wave




Shallow-water wave




Irreversible processes



# Ultrasound capabilities in biomedical applications

**Interaction**

Acoustic waves carry energy and momentum

Under certain condition, both can be transferred to tissues

**Low amplitude ultrasound**

Small energy and momentum transfer: Ultrasound imaging and NDT

**High amplitude ultrasound**

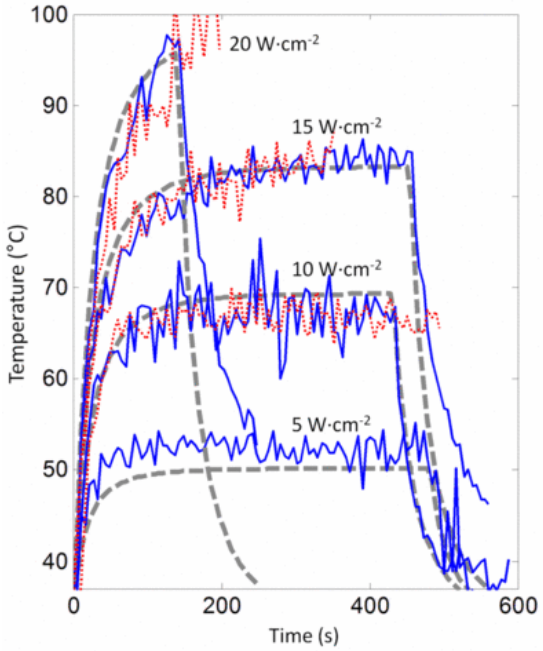
Waves interact with matter: therapeutic application / industrial applications

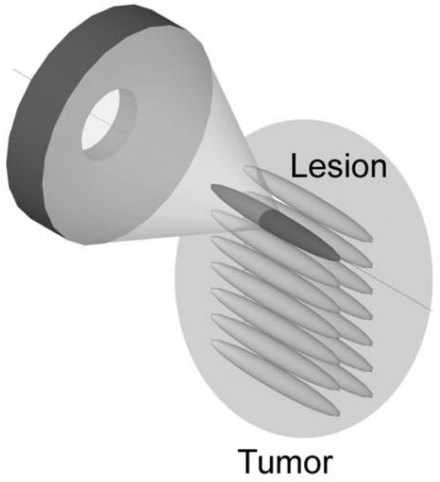
**Ultrasound effects on matter**

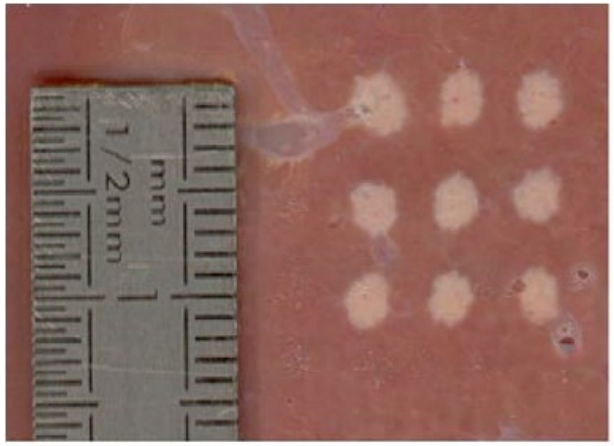
a) Thermal effects

- Temperature rise

**Temperature rise**



# Ultrasound capabilities in biomedical applications

**Interaction**

Acoustic waves carry energy and momentum

Under certain condition, both can be transferred to tissues

**Low amplitude ultrasound**

Small energy and momentum transfer: Ultrasound imaging and NDT

**High amplitude ultrasound**

Waves interact with matter: therapeutic application / industrial applications

**Ultrasound effects on matter**

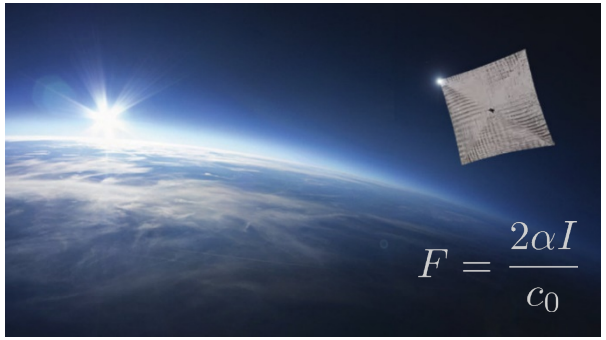
a) Thermal effects

- Temperature rise
- Sonoluminescence

b) Mechanical effects

- Acoustic radiation force
- Streaming in fluids and deformations in solids
- Cavitation (inertial and non-inertial)

**Acoustic radiation force**



# Ultrasound capabilities in biomedical applications

**Interaction**

Acoustic waves carry energy and momentum

Under certain condition, both can be transferred to tissues

**Low amplitude ultrasound**

Small energy and momentum transfer: Ultrasound imaging and NDT

**High amplitude ultrasound**

Waves interact with matter: therapeutic application / industrial applications

**Ultrasound effects on matter**

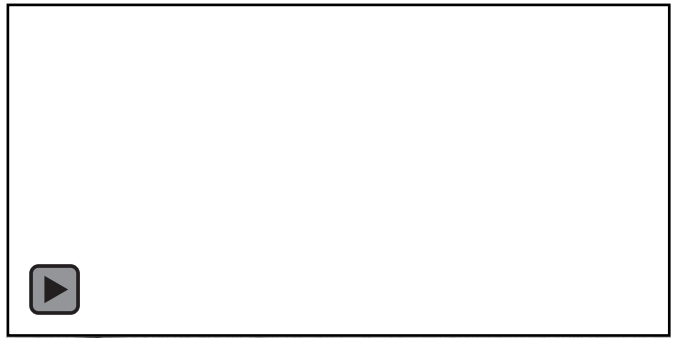
a) Thermal effects

- Temperature rise
- Sonoluminescence

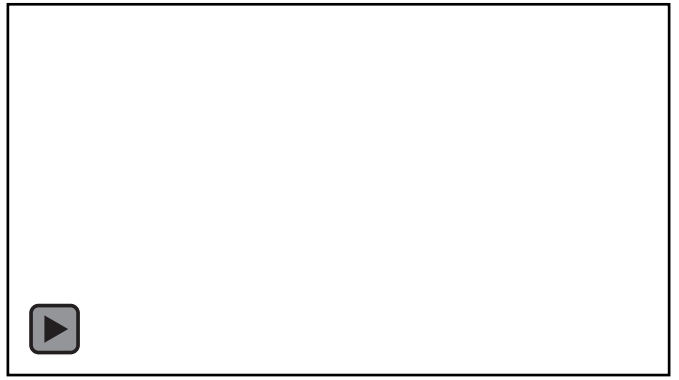
b) Mechanical effects

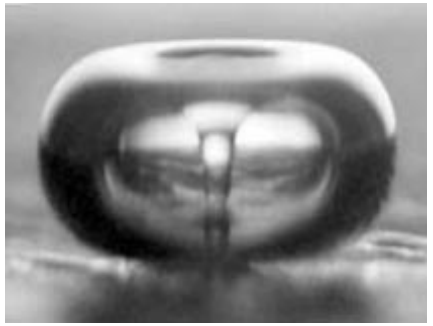
- Acoustic radiation force
- Streaming in fluids and deformations in solids
- Cavitation (non-inertial and inertial)

**Cavitation**



Physical Review Letters, 106, 134501 (2011)

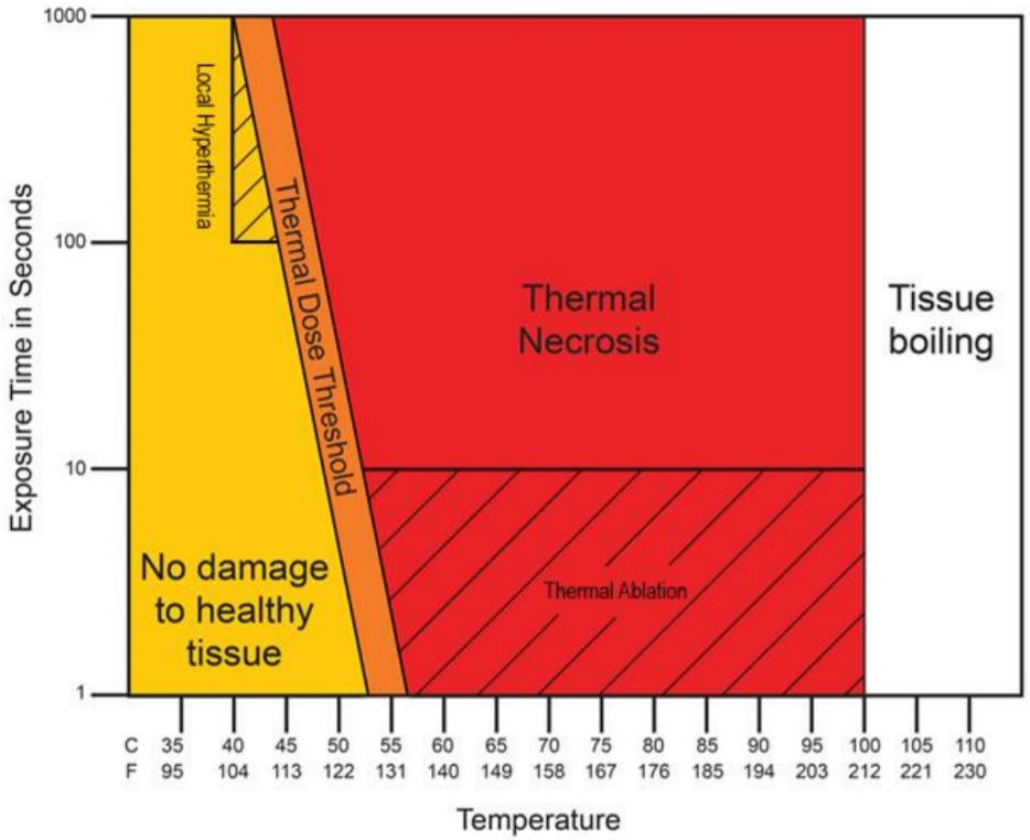




# Ultrasound capabilities in biomedical applications

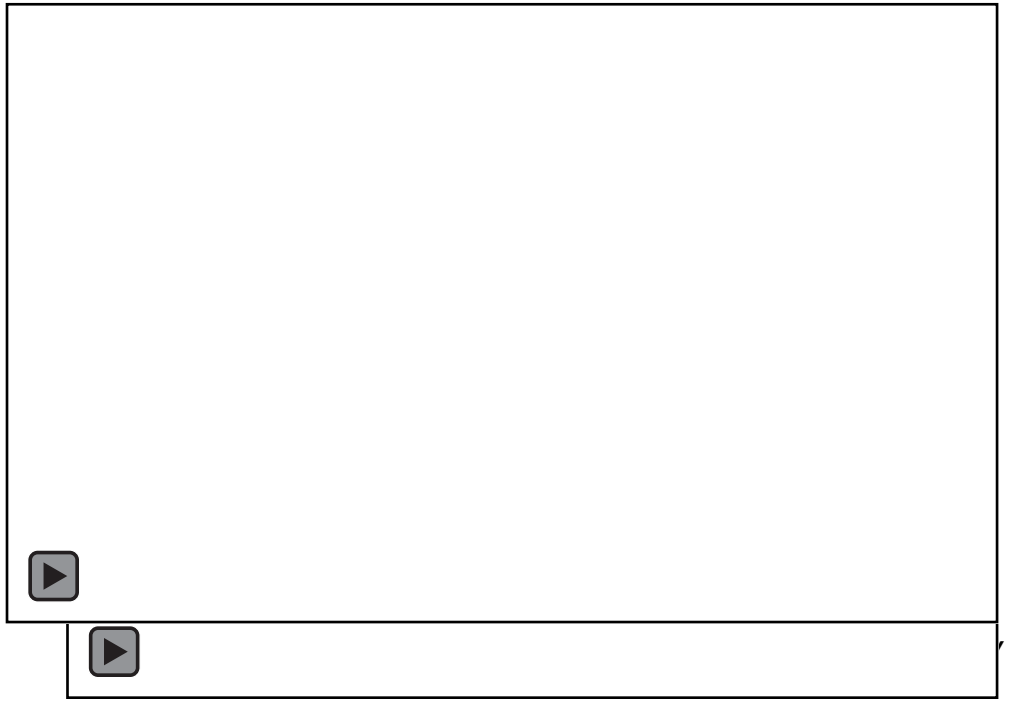
## **Finite-amplitude Ultrasound bio-effects:** Therapeutic applications

### Thermal effects




Focused Ultrasound Foundation

### Mechanical effects



*Gas microbubbles and cancer cells interact under the influence of low-energy, clinically safe ultrasound.*

# Ultrasound capabilities in biomedical applications

**Finite-amplitude Ultrasound bio-effects:** Therapeutic applications

## Tissue destruction

Thermal ablation

Mechanical Tissue Destruction

## Targeted Drug Delivery

Blood-Brain Barrier Disruption

Drug Delivery Vehicles

Increased Vascular Permeability

Local Hyperthermia

Sonoporation

Vasodilation

## Other Effects

Vasoconstriction

Clot Lysis

Neuromodulation

Immunomodulation

Sensitization to Chemotherapy

Sensitization to Radiotherapy

Amplification of Cancer Biomarkers

Angiogenesis

Blood Vessel Occlusion and Coagulation

Sonodynamic Therapy

Stem Cell Homing

# Neurological applications of ultrasound today

## State of the art: Neurological

Addiction
Anorexia Nervosa
Cerebral Cavernous Malform
Hydrocephalus
Neuroblastoma
Stroke

**Early Stage**

Focused ultrasound research is in the laboratory phase and is not yet available for patients.

**Clinical Trials**

Focused ultrasound for this condition is being researched in clinical trials.

Brain Tumors, Glioma and Metastatic
Alzheimer's Disease
Amyotrophic Lateral Sclerosis (ALS)
Dementia
Epilepsy
Dystonia, Holmes Tremor
Huntington's Disease
Migraine Headaches
Multiple Sclerosis
Painful Amputation Neuromas
Traumatic Brain Injury

Essential Tremor
Parkinson's Disease

**FDA Approved**

The US Food and Drug Administration has approved focused ultrasound for this condition. Patients can seek commercial treatment at participating sites.

**International Approval**

Focused ultrasound is approved to treat this condition outside the US. Patients can seek commercial treatment at participating international sites.

Depression
Neuropathic Pain
Obsessive-Compulsive Disorder
Trigeminal Neuralgia

Focused Ultrasound Foundation (updated 2019)

# Neurological applications of ultrasound today

## Thermal ablation

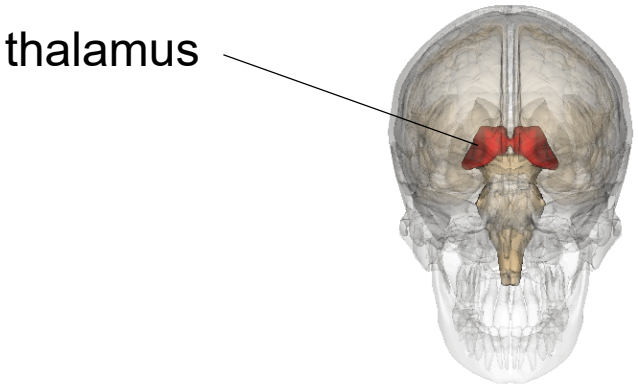
Thalamotomy for Essential Tremor

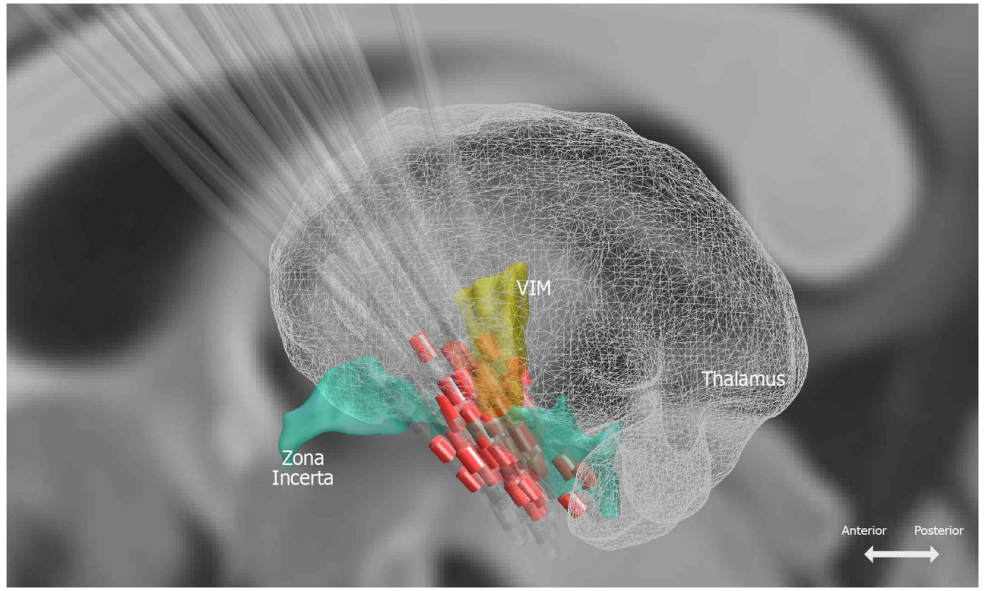
Problem:

Most common movement disorder, benign disease. Impair patients' ability to eat, shave, write, perform household activities, and function in the workplace.

Solution:

Ablation of the thalamus (ventralis intermedius) by High intensity focused US. Patient is awake and involves no anesthesia, no incisions in the scalp, and no burr holes through the skull or insertion of electrodes into the brain.




Al-Fatly (2019). *bioRxiv*, 575209

# Neurological applications of ultrasound today



**Th**

Th
Sy
Ma
Ult

Ex





# Neurological applications of ultrasound today

## Localized drug delivery at the CNS

Blood-brain barrier (BBB) opening

Problem:

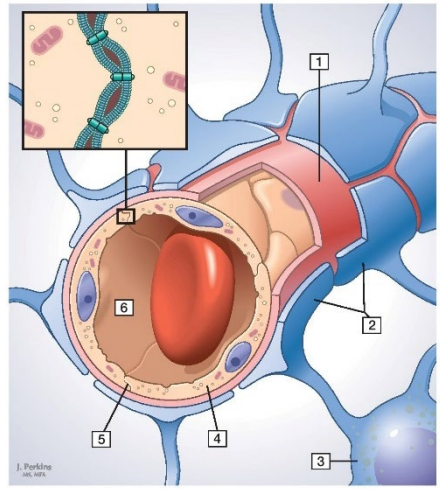
Endothelial tissue do not allow most large molecules to pass through the CNS to the brain tissue. Therapeutic drugs (95%) cannot be deliver.

Solution:

US is applied along with microbubbles to produce a mechanical effect on the tight junctions. BBB is opened locally, transiently and safely.

Application:

Treatments of Neurological disorders and pathologies, such as Alzheimer, Parkinson, etc…




Courtesy of EE Konofagou

# Focusing challenges

**(1) Beam steering**

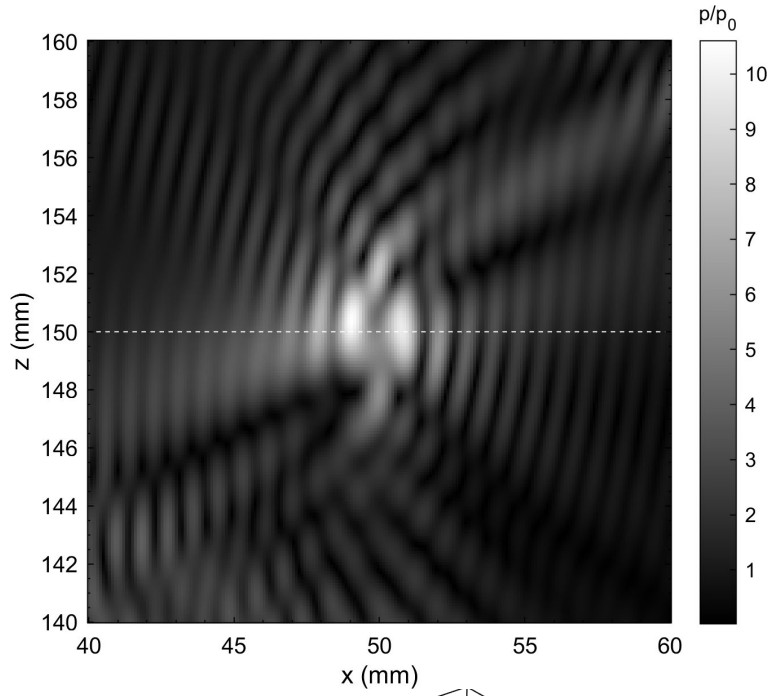
Phased arrays provide good focusing but…

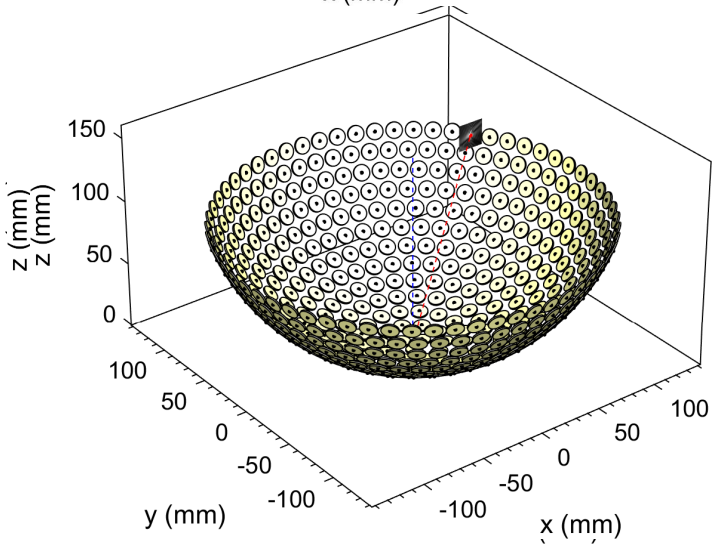
As elements are separated (much) more than half-wavelength

Steering capabilities are limited

**Example:**

- InsightTech's Exablate Neuro 4000
- 1024 elements covering the full head
- Good focusing near geometrical center (thalamus)
- Poor focusing over other CNS nuclei or cortex

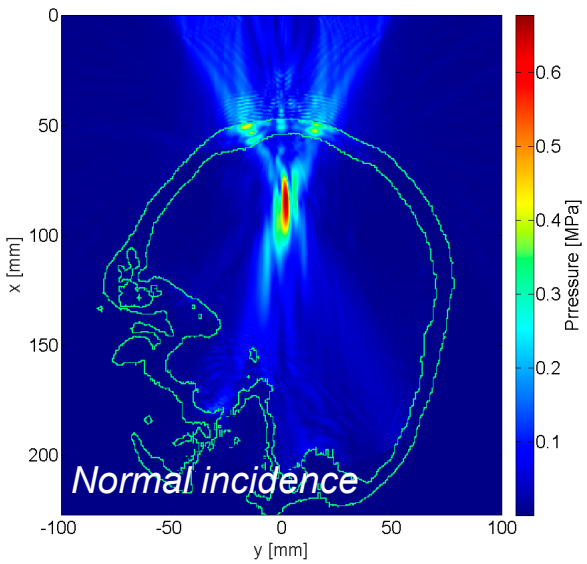


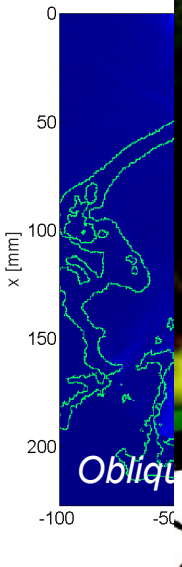



# Focusing challenges

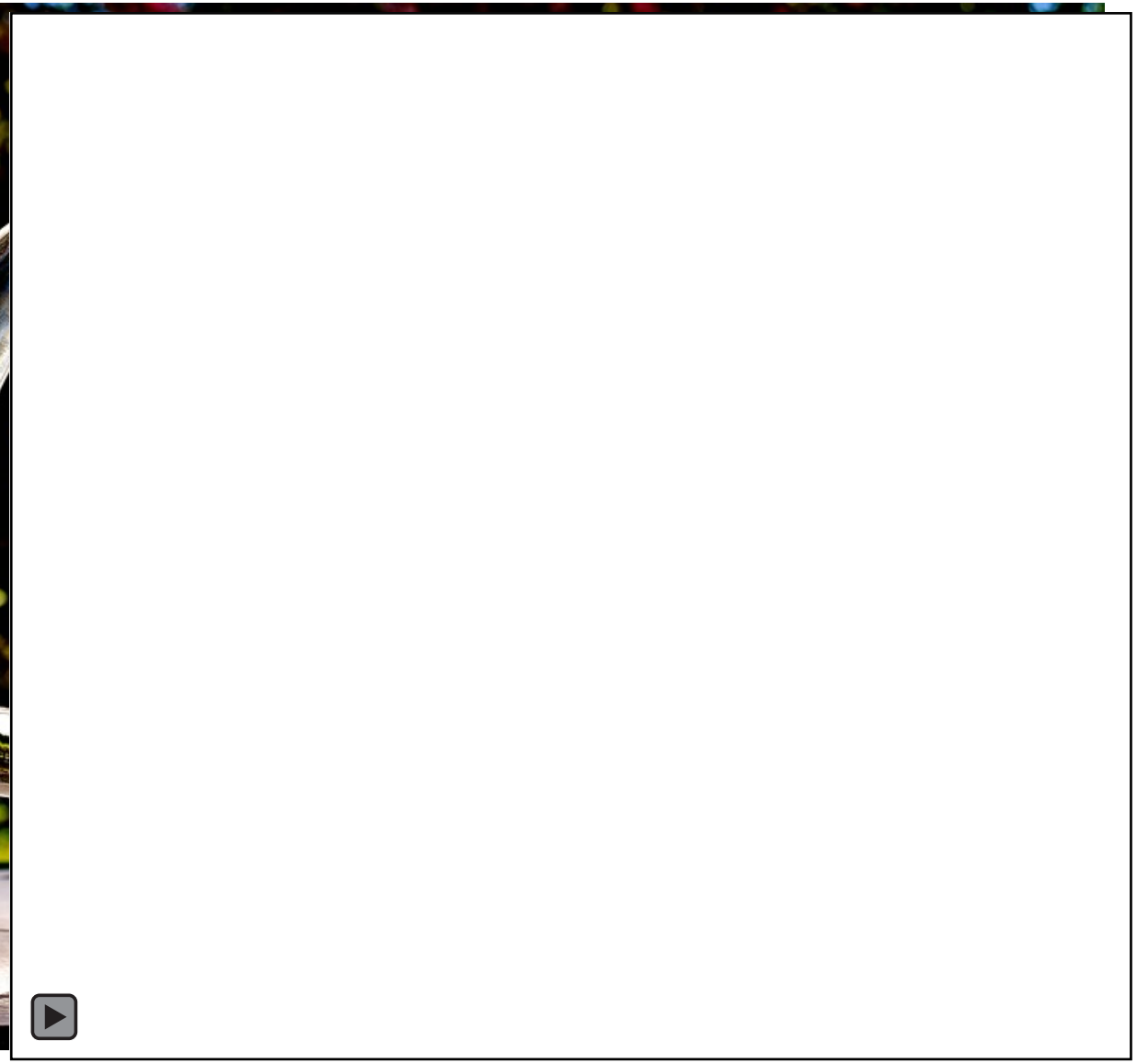
## (2) Transcranial aberrati

- Refraction
- Absorption
- Reflection
- Scattering
- Cavitation?



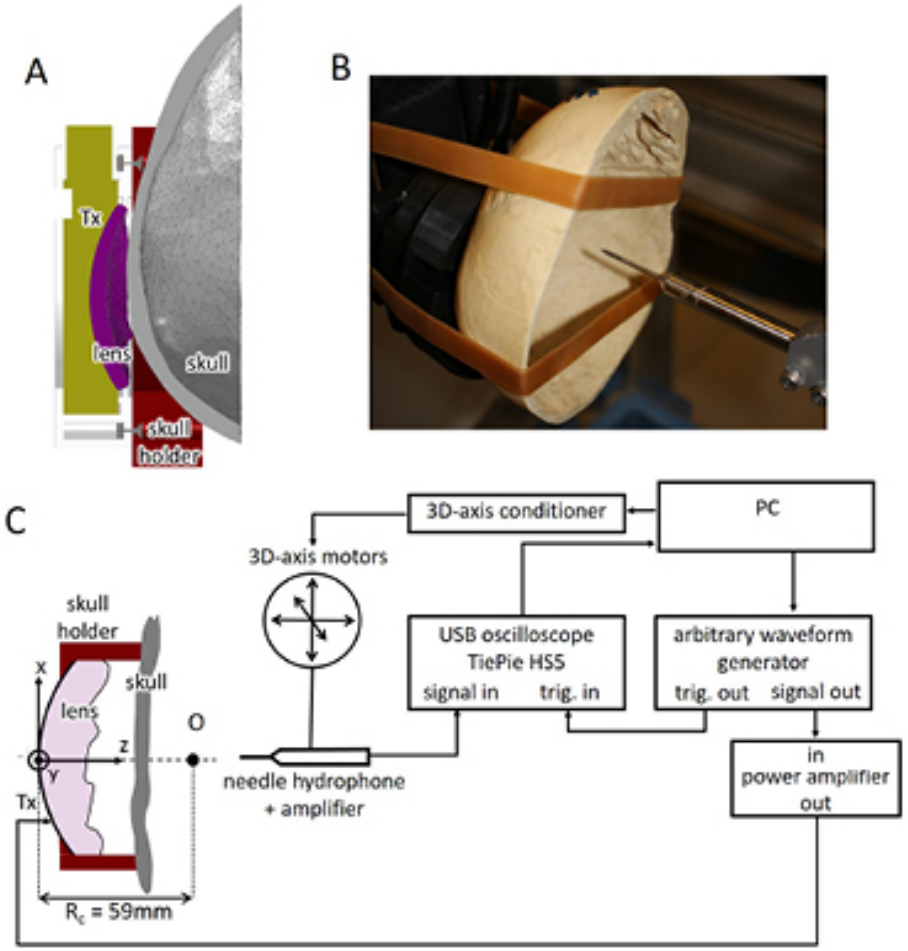


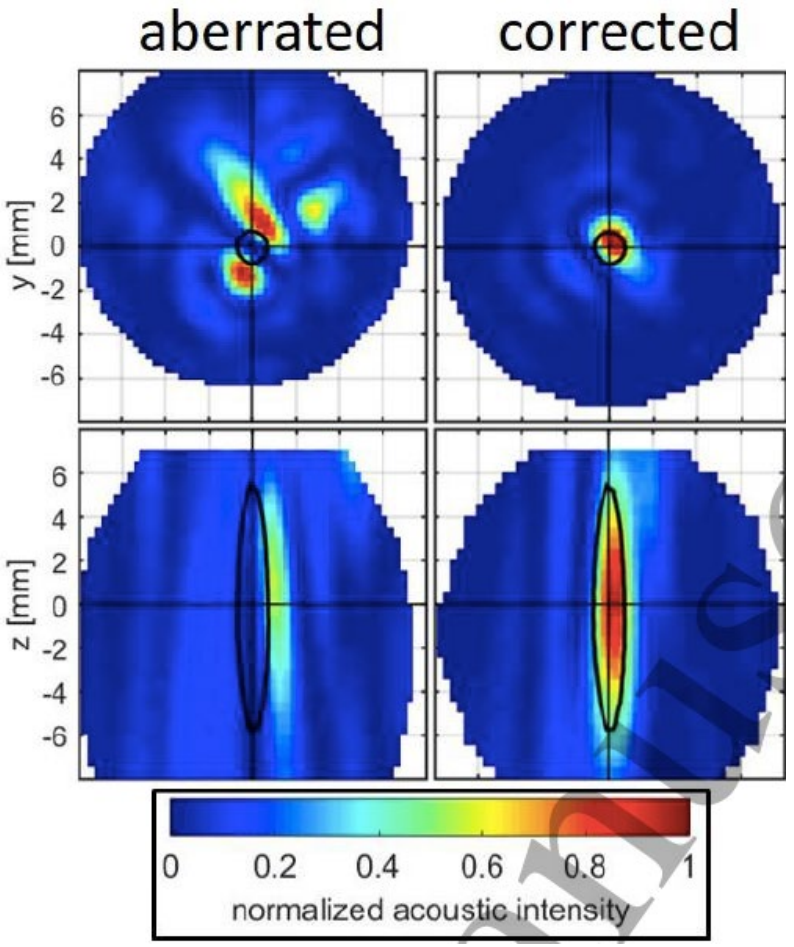



# Focusing challenges

## Lenses

- Single-element + phase lens approach



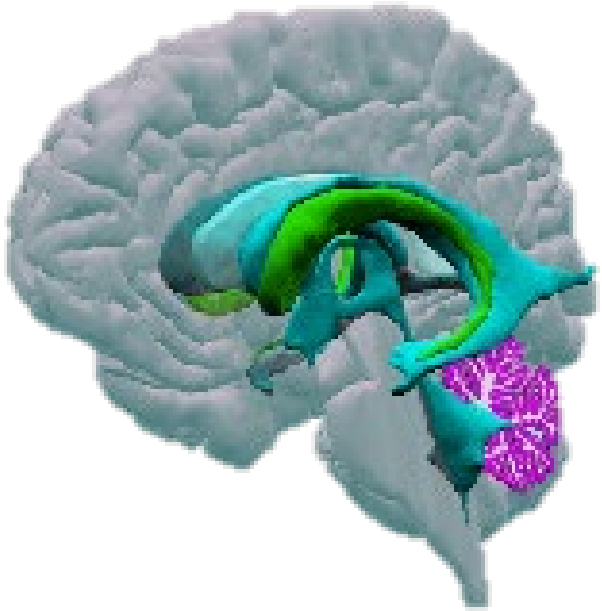



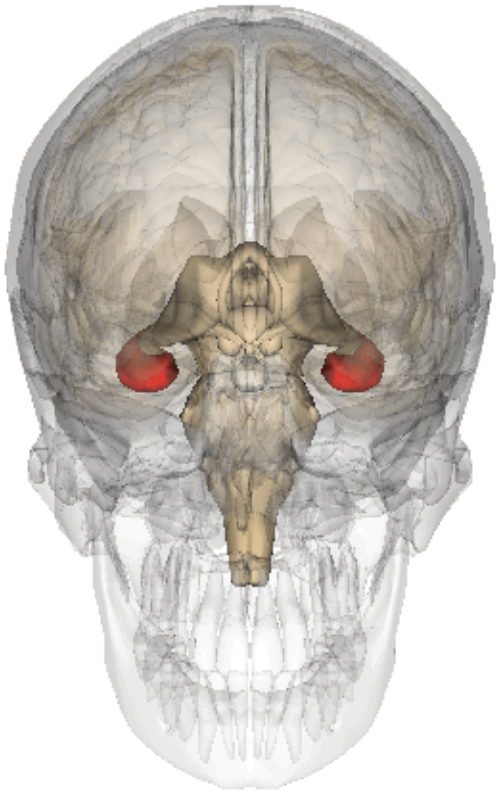

Maimburg et al. Physics in Medicine & Biology 63(2) 2018.

# Focusing challenges

**(3) Complex morphology**

Focus with a single shot over a CNS structure



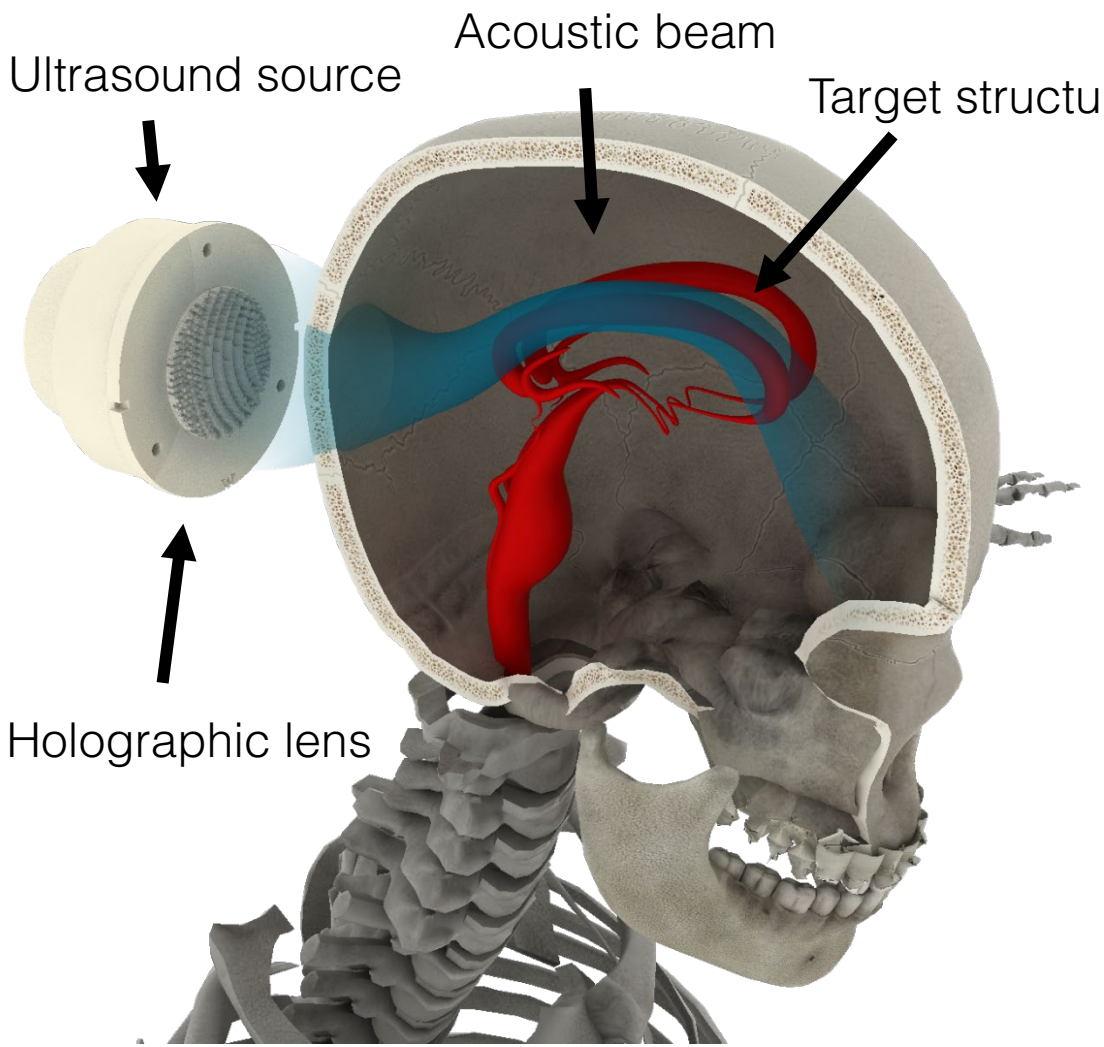


**Example**

- Hippocampus for Alzheimer's disease

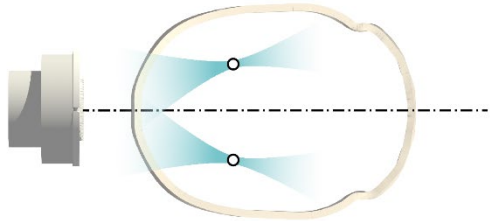
# Acoustic holograms for the brain

## Beyond phased-arrays: holographic lenses

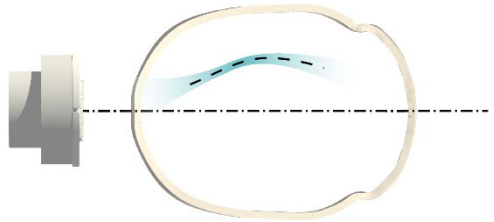



Configurations

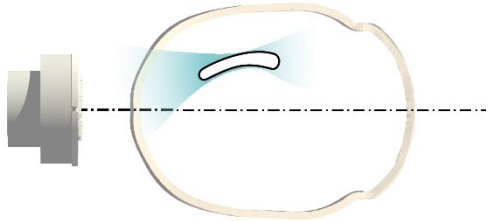
1) Multiple point



2) Self-bending beams

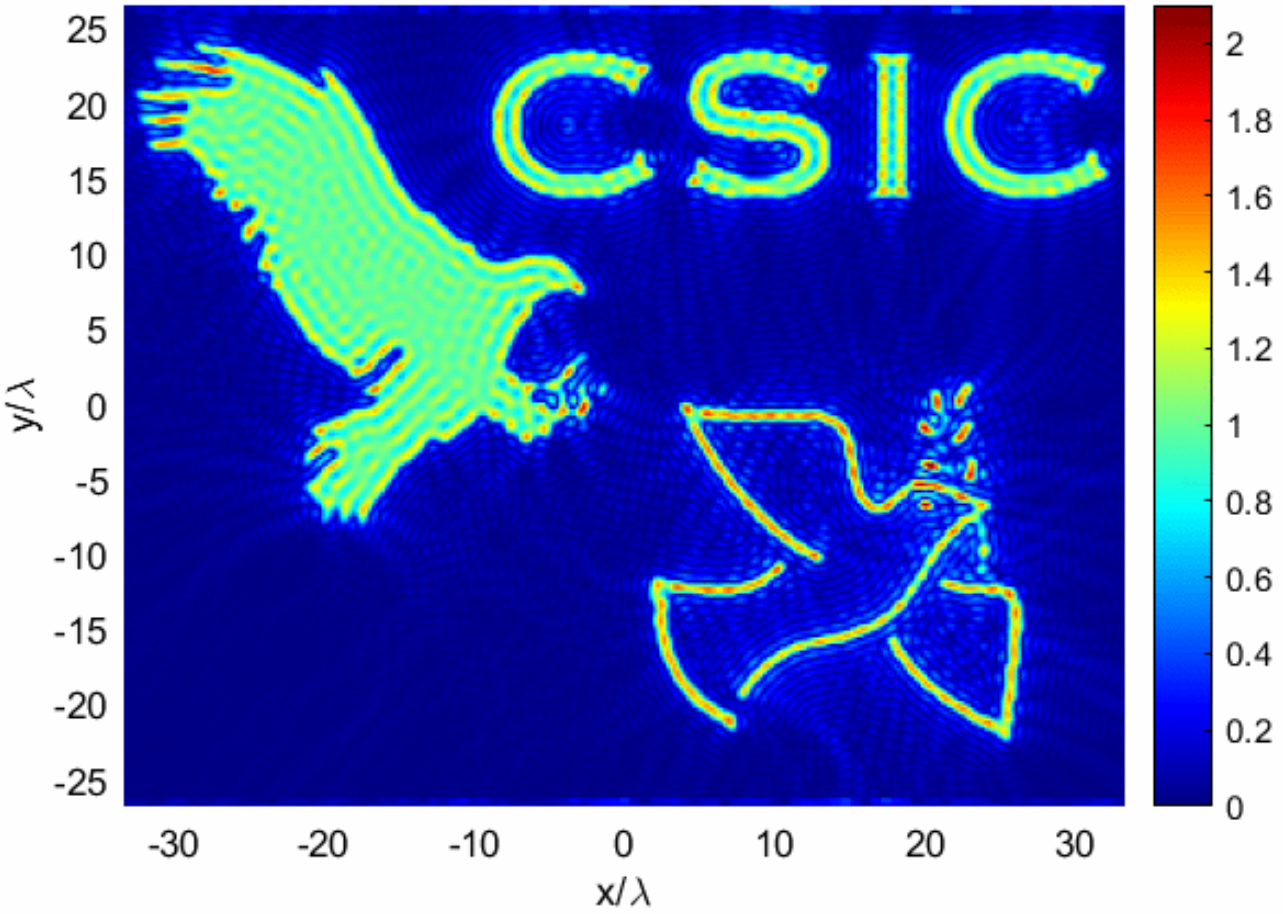


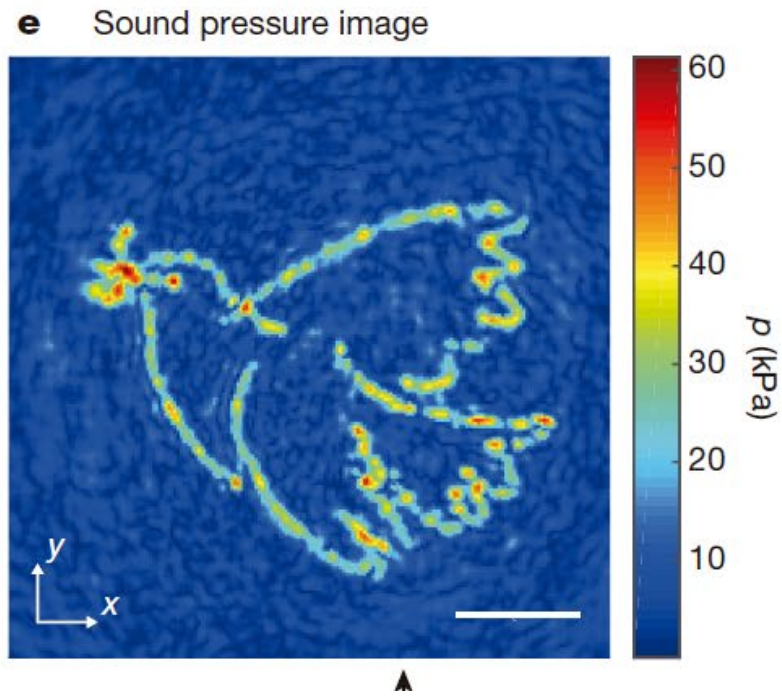
3) Volumetric treatments



# Acoustic holograms for the brain

## Holograms in free-media



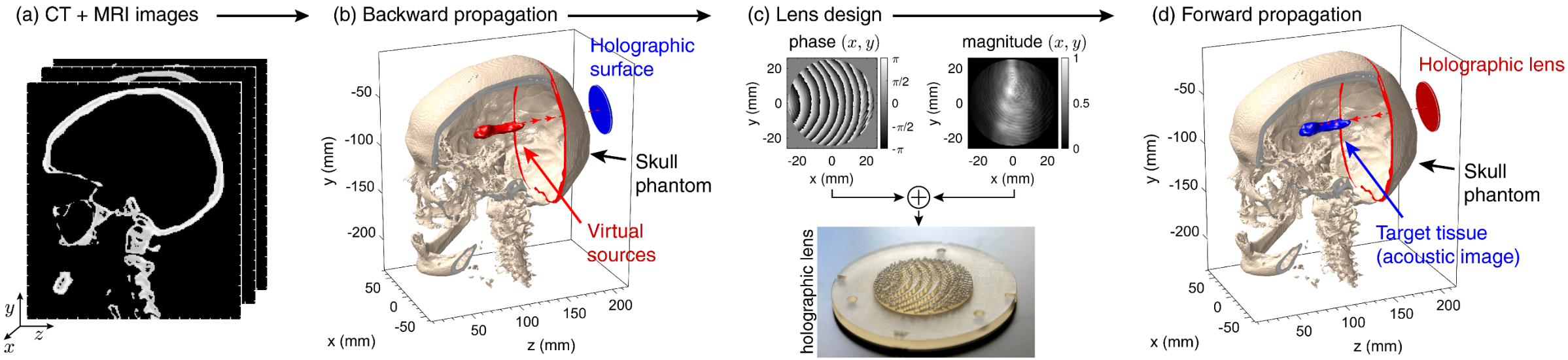




Melde, et al. Nature volume 537, 518–522 (2016)

# Acoustic holograms for the brain

## Protocol

1) **Treatment planning:** MRI (soft tissue segmentation) + X-ray CT (skull bone, 0.22 mm)
2) **Backward propagation:** Time-reversal simulation (phase conjugation)
3) **Lens design:** Phase-only method, manufacturing by 3D-print
4) **Forward propagation:** validation and treatment



# Acoustic holograms for the brain

**Semi-analytical methods: propagation in free media (water)**

- Rayleigh-Sommerfeld integral:

$$p(\mathbf{r},\omega) = \frac{i\omega\rho_0}{2\pi}\int_S \frac{v_0(\mathbf{r}_0)\exp\left(-ik_0\left|\mathbf{r}-\mathbf{r}_0\right|\right)}{\left|\mathbf{r}-\mathbf{r}_0\right|}dS,$$

**Simulation methods: propagation including the skull**

- Pseudo-spectral time-domain simulation with *k*-space corrector

$$\begin{aligned}\frac{\partial\rho}{\partial t} &= -\rho_0\nabla\cdot\mathbf{u} - \mathbf{u}\cdot\nabla\rho_0,\\ \frac{\partial\mathbf{u}}{\partial t} &= -\frac{1}{\rho_0}\nabla p,\\ p &= c_0^2\left(\rho + \mathbf{d}\cdot\nabla\rho_0 - \mathrm{L}\rho\right),\end{aligned}$$

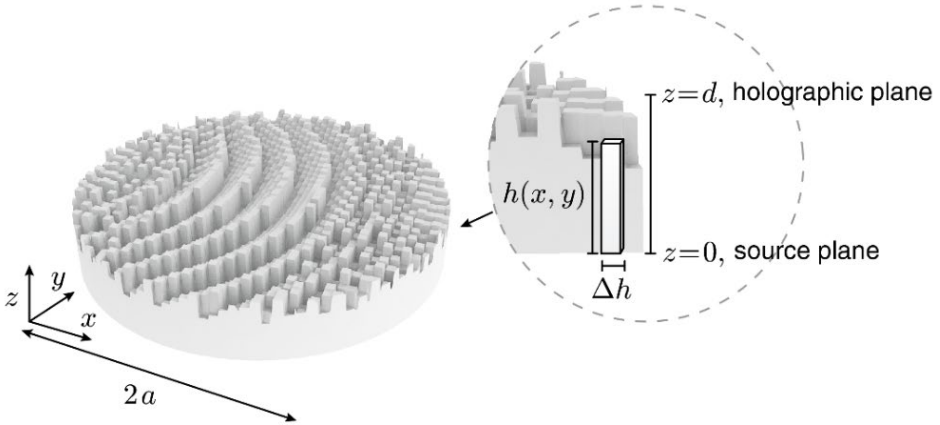
- Low numerical dispersion, explicit solver
- Soft-tissue absorption in the form: $\alpha(\omega) = \alpha_0\omega^{\gamma}$,
- Frequency power-law attenuation using the fractional Laplacian: $\mathrm{L} = \tau\frac{\partial}{\partial t}\left(-\nabla^2\right)^{\frac{\gamma}{2}-1} + \eta\left(-\nabla^2\right)^{\frac{\gamma+1}{2}-1}$,

# Acoustic holograms for the brain

## Lens design

- Fabry-Perot resonators

$$p(\mathbf{x}_0) = p_0 \frac{2Z\mathrm{e}^{-ik_0[d-h(\mathbf{x}_0)]}}{2Z\cos\left[k_L h(\mathbf{x}_0)\right] + i\left(Z^2+1\right)\sin\left[k_L h(\mathbf{x}_0)\right]},$$

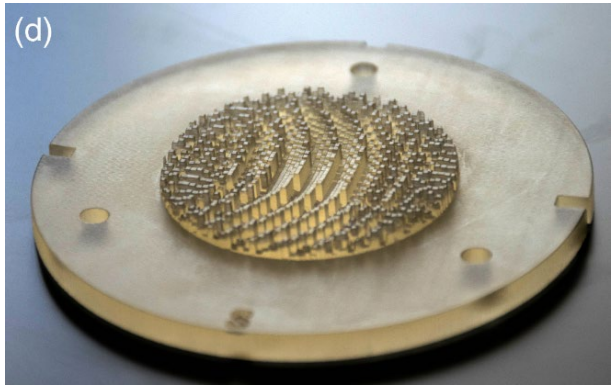



## From phase-and-magnitude to phase-only

- Direct method: bidirectional error diffusion: Tsang et. al. Opt. Express 21, 23680 (2013).
- Long computations: 20 hours E5-2680 2.80 GHz, 256 GB RAM, using a CPU parallel implementation
- Optimization methods using complete-skull simulations are intractable.

## Manufacturing

- Printing by stereo-lithography
- Objet30 Stratasys (10 μm)



# Acoustic holograms for the brain

## Experimental setup

- Ultrasound measurements in water-tank
- 3D, 5 µm resolution steeped Axis

## Flat ultrasound transducer

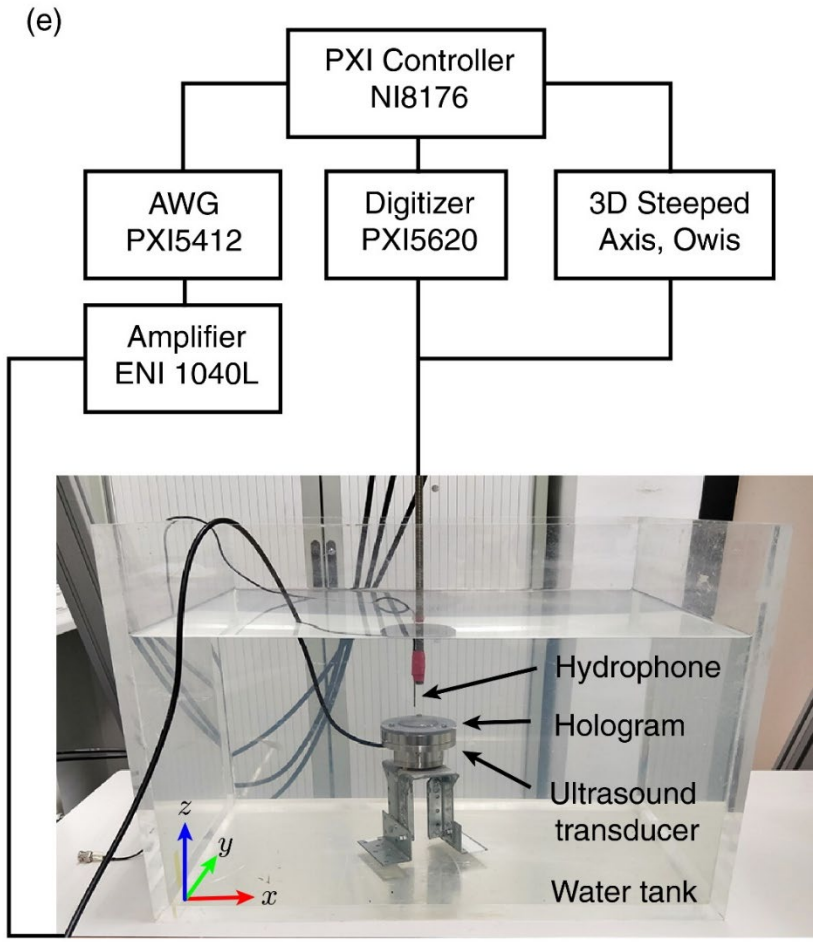
- Frequency: 1.1 MHz (1.4 mm wavelength)
- Aperture: 50 mm (36 wavelengths)

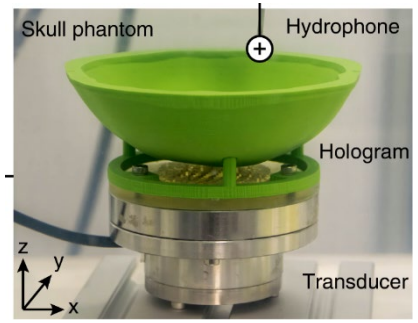
## Skull phantom

- 3D-printed skull using polylactic acid
- Simulations including PLA properties

## Verification

- Simulations including skull properties



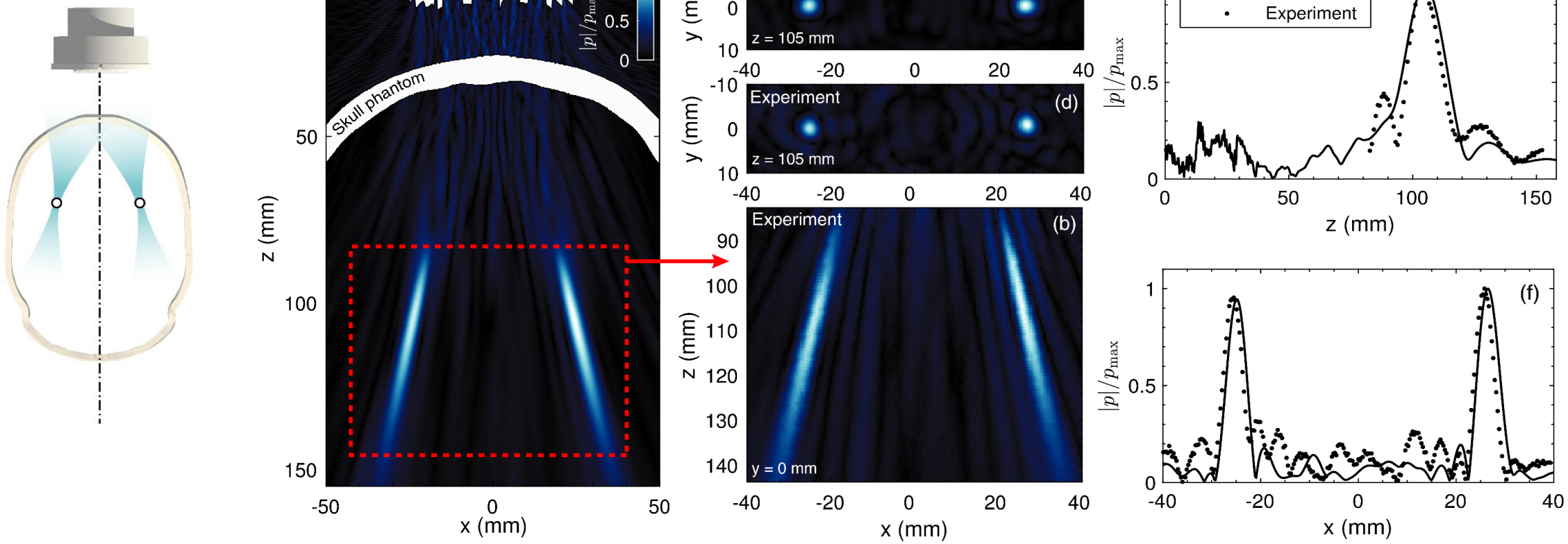





# Acoustic holograms for the brain

## Multiple target focusing

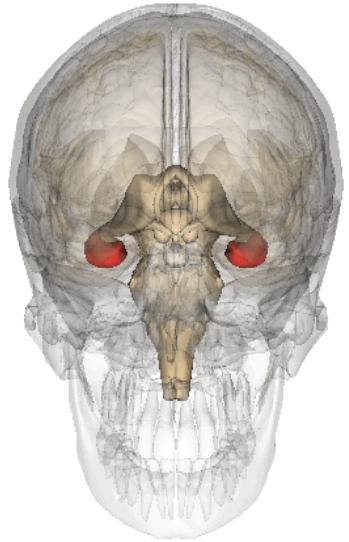
- The beam focus at each target simultaneously
- Hologram corrects skull aberrations
- Diffraction-limited focusing

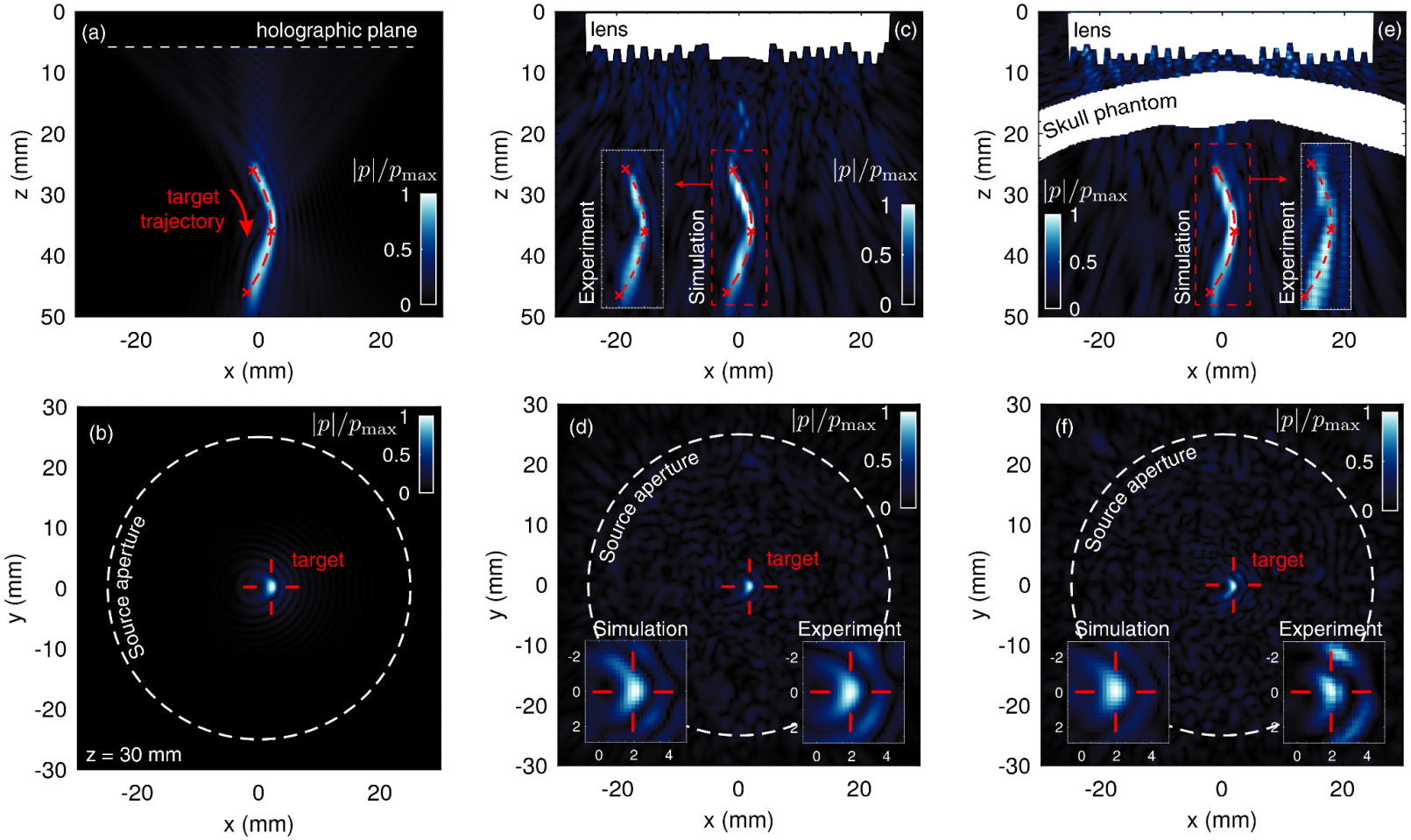


# Acoustic holograms for the brain

## Self-bending beams

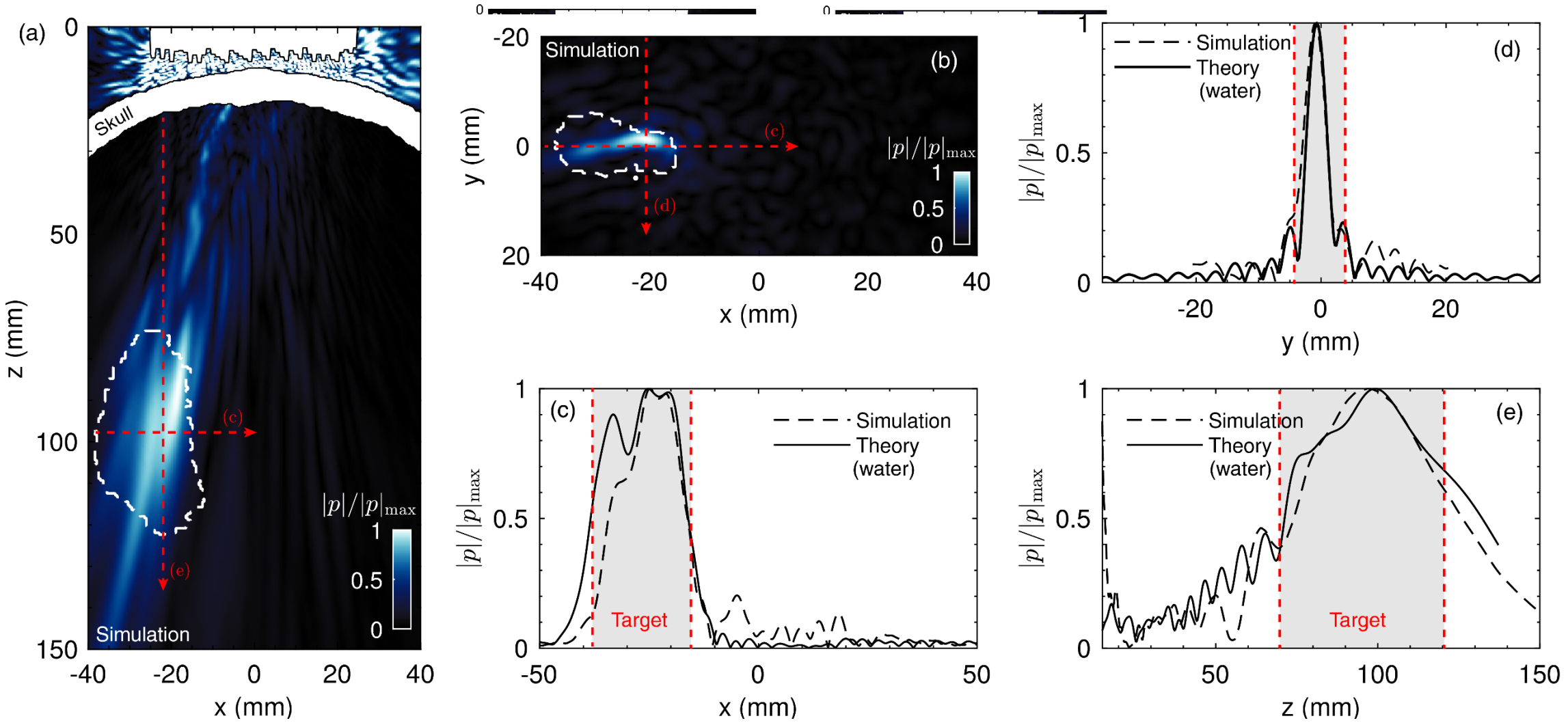
- The beam adapts to a target arbitrary curve
- Aberration free propagation
- Diffraction limited beam





# Acoustic holograms for the brain

## Volumetric focusing



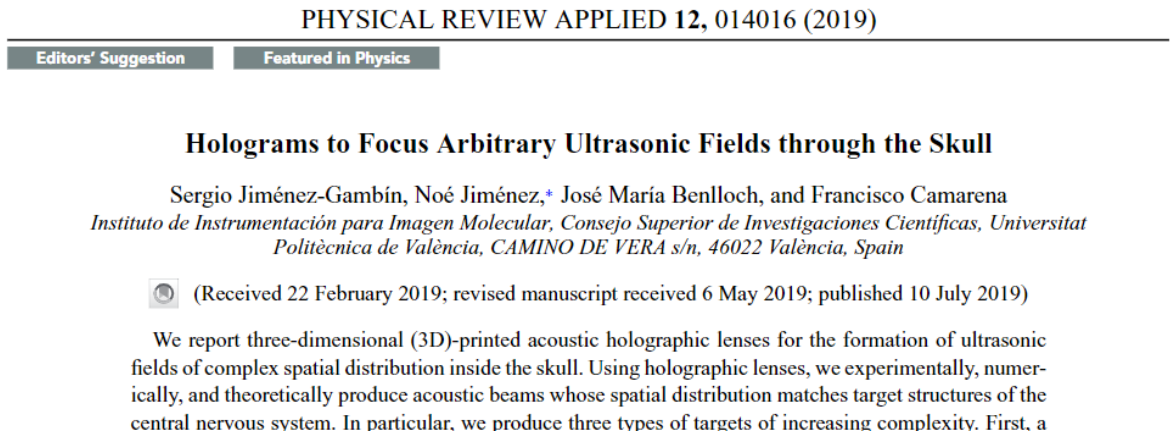
# Conclusions

## Transcranial focusing

- Promising biomedical applications
- From clinical trials to reimbursement
- Still focusing challenges for neurological applications

## Acoustic holograms for the brain

- Aberration correction
- Simultaneous multiple targets
- Beam-steering without strong diffraction-grating lobes
- Volumetric imaging matching target CNS



PHYSICAL REVIEW APPLIED **12,** 014016 (2019)

Editors' Suggestion | Featured in Physics

**Holograms to Focus Arbitrary Ultrasonic Fields through the Skull**

Sergio Jiménez-Gambín, Noé Jiménez,* José María Benlloch, and Francisco Camarena

*Instituto de Instrumentación para Imagen Molecular, Consejo Superior de Investigaciones Científicas, Universitat Politècnica de València, CAMINO DE VERA s/n, 46022 València, Spain*

(Received 22 February 2019; revised manuscript received 6 May 2019; published 10 July 2019)

We report three-dimensional (3D)-printed acoustic holographic lenses for the formation of ultrasonic fields of complex spatial distribution inside the skull. Using holographic lenses, we experimentally, numerically, and theoretically produce acoustic beams whose spatial distribution matches target structures of the central nervous system. In particular, we produce three types of targets of increasing complexity. First, a

## Results

- Patented technology

## Next steps

- On-going *in-vivo* experiments (BBBO) at Columbia University
- Metamaterials for subwavelength focusing
- From phased-arrays to **reconfigurable metasurfaces / holograms**

ueil | columbia
*Ultrasound Elasticity Imaging Laboratory*
*Columbia University*

# References

**Related publications**


- S. Jiménez-Gambín, et al. Holograms to focus arbitrary ultrasonic fields through the skull
  Physical Review Applied, 12 (1), pp. 014016, (2019)
  **Editors' Pick + Featured in APS and OIP Blog's**

- J Rodríguez-Sendra, et al. IEEE Trans on Ultrasonics Ferroelectrics and Frequency Control, Accepted, (2019)
- S Jiménez-Gambín, et al. Revista de Acústica, 50 (1-2), pp. 22-25, (2019)
- N. Jiménez, et al. Applied Physics Letters 112, 204101 (2018)
- N Jiménez, et al. Acta Acustica united with Acustica, 102 (5), pp. 876–892, (2016)
- N Jiménez, et al. Revista de Acústica, 43 (1), pp. 5-11, (2012)


**Patent**


- Método de fabricación de una lente y dispositivo de ultrasonidos que comprende dicha lente (approved 2018)



# Focused ultrasound beyond phased-arrays:
## Acoustic holograms for the brain

Noé Jiménez,

nojigon@upv.es

Bienal de Física 2019. Zaragoza (Spain), 14-19 July 2019.

# Acoustic holograms for the brain



# Acoustic holograms for the brain

