

Neurex Symposium
10/02/2023

Focused ultrasound (FUS) and indirect neuromodulation

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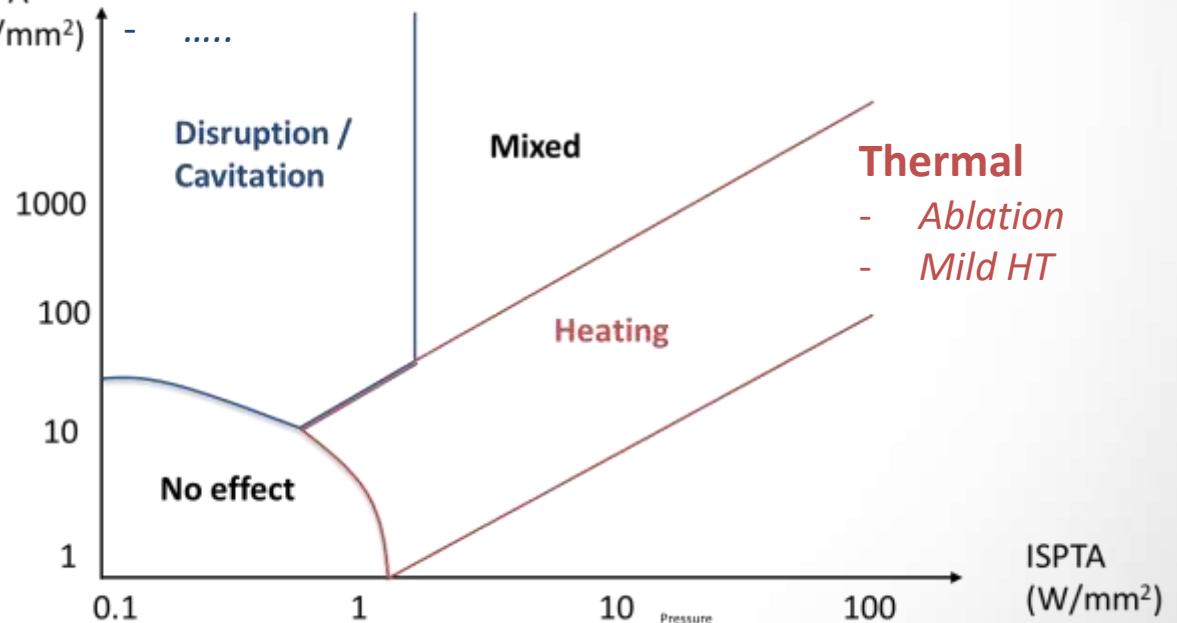
Therapeutic Ultrasound : Mechanisms of action



Non-Thermal

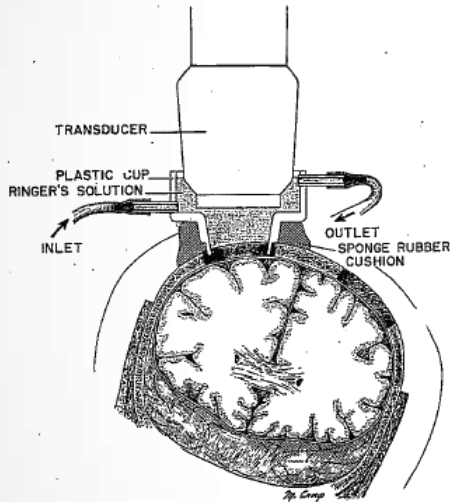
- Drug delivery (sonoporation, permeation)
- Histotripsy
- Neuromodulation
-

ISPPA
(W/mm²)



Adapted From Kieran et al., AIP Conf. Proc. 911, 185 (2007)

The first therapeutic Ultrasound device: 1953



1953
Frontal lobotomy on 20 patients
(craniotomy)

Courtesy B. Larrat, CEA/Neurospin



The Fry Brothers

1950s~1970s



A PRECISION FOCUSED-ULTRASOUND GENERATOR
For
NEUROPHYSIOLOGICAL and
NEUROLOGICAL RESEARCH*



RADIONICS, INC., as the
prime manufacturer of this
device in 1955, now offers an
improved line of equipment,
including a variety of generators,
transducers and focusing systems,
applicator cones, calibration
thermocouple devices, and
auxiliary calibration instruments.

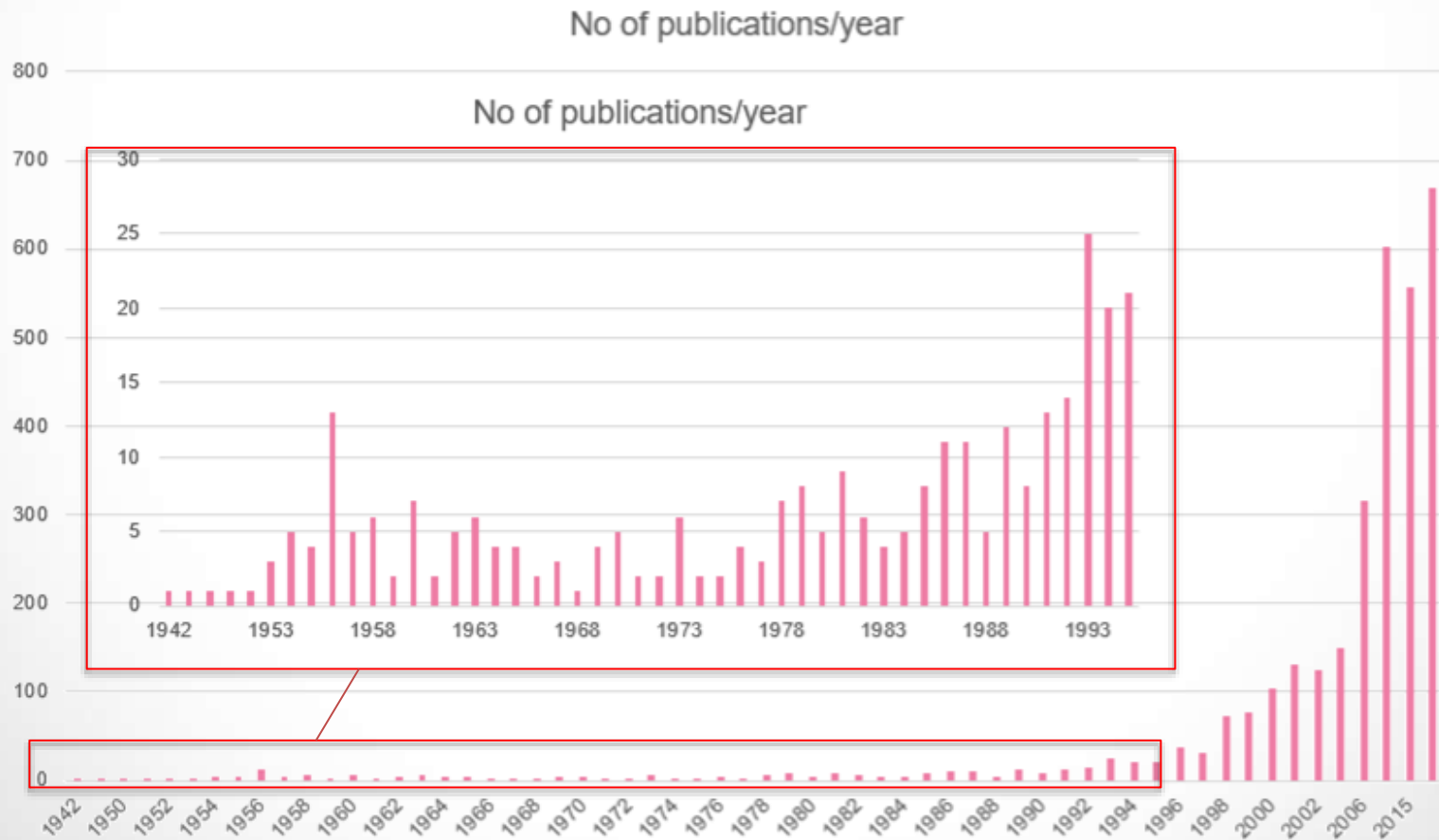
Improved pre-calibrated sound
heads will be added as time
develops, and there is no possibility
of obsolescence of any existing
equipment in the foreseeable
future. For further information,
write us.

*Based on Radionics' In-
strumentation, including
of generators, focusing
transducers, and pre-
calibrated sound heads, for
use in calibration of
test equipment. Con-
struction requires a
specialist.

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RADIONICS, INC.
75 CAMBRIDGE STREET • BURLINGTON, MASS.
Developers and Builders of Apparatus for Medical Research since 1939

Therapeutic Ultrasound Timeline



Gail Ter Haar, History of Focused Ultrasound, ISTU 2020

Common clinical indications



11

New indications

Gastrointestinal	<ul style="list-style-type: none"> Inflammatory bowel disease Irritable bowel syndrome
Miscellaneous	<ul style="list-style-type: none"> Heterotopic ossification Infection Kaposi's sarcoma
Musculoskeletal	<ul style="list-style-type: none"> Osteopenia
Neurological	<ul style="list-style-type: none"> Mood disorder
Ophthalmological	<ul style="list-style-type: none"> Retinal impairment Retinal injury
Women's Health	<ul style="list-style-type: none"> Hyperplasia of the vulva Lichen sclerosis

Development stage

● Preclinical
 ● Clinical

Source: *fusfoundation*

FUS and brain

**Thermal
Ablation**

- Tremor (essential, Parkinsonian)
- Brain cancer
- Neurodegenerative disorders
- Epilepsy
- Depression
- ...

**FUS-induced
neuromodulation**

**Localized drug
delivery**

FUS and brain

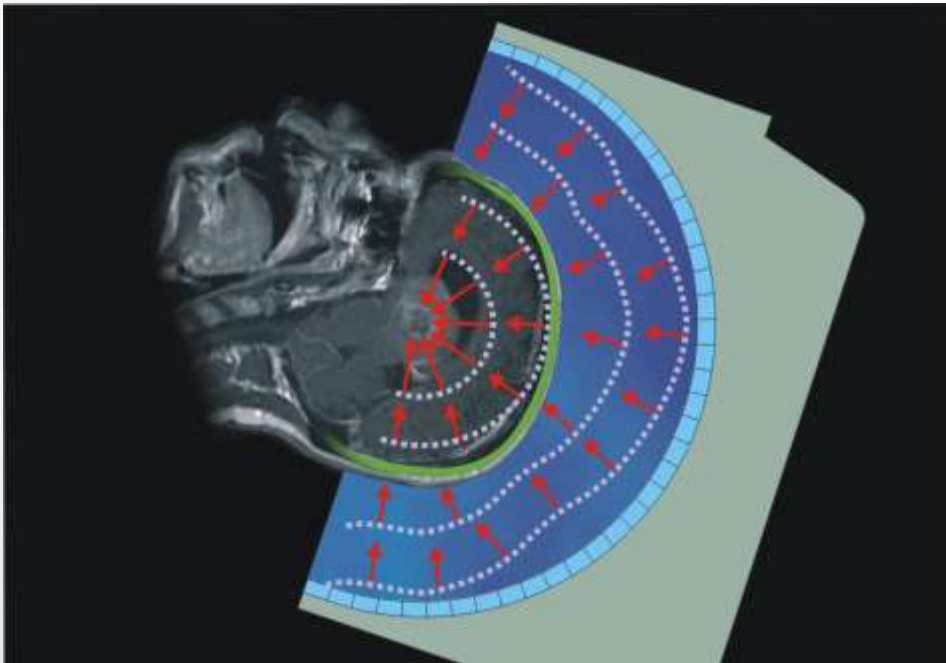
**Thermal
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**FUS-induced
neuromodulation**

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delivery**

Thermal FUS: Transcranial approach



*InSightec
Exablate
Neuro*

Thermal FUS: Transcranial approach

Videos from the FUS Foundation



Awake, no anesthesia

No incisions

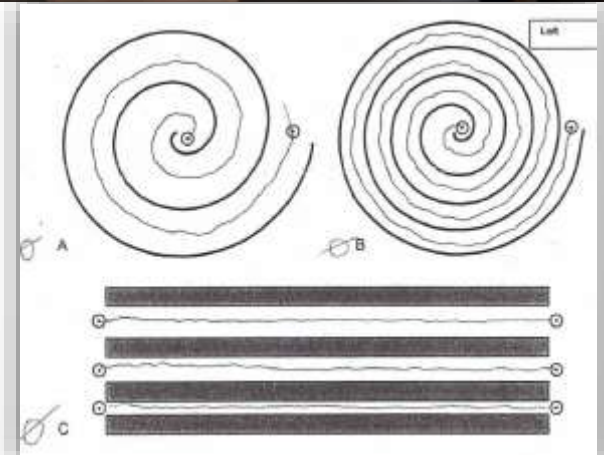
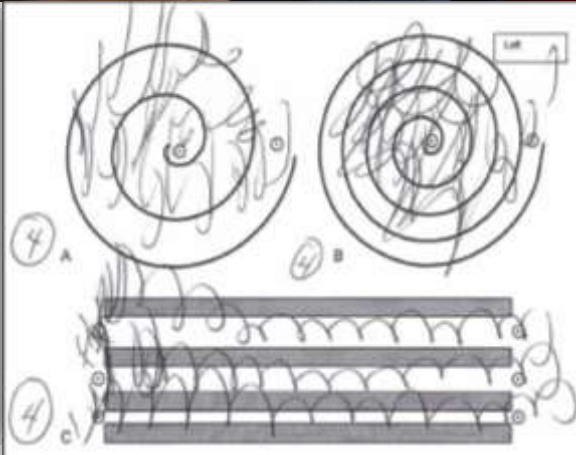
No burr holes

No electrodes

No infection

No blood clots

No brain damage



FUS ablation and psychiatry

Molecular Psychiatry

<https://doi.org/10.1038/s41380-020-0737-1>

IMMEDIATE COMMUNICATION



Magnetic resonance-guided focused ultrasound capsulotomy for refractory obsessive compulsive disorder and major depressive disorder: clinical and imaging results from two phase I trials

Benjamin Davidson^{1,2,3} · Clement Hamani^{1,2,3} · Jennifer S. Rabin^{2,3,4} · Maged Goubran^{2,3,5,6} · Ying Meng^{1,2,3} · Yuexi Huang³ · Anusha Baskaran^{2,3} · Sachie Sharma^{2,3} · Miracle Ozzoude^{2,3} · Margaret Anne Richter^{2,3,7,8} · Anthony Levitt^{2,3,8} · Peter Giacobbe^{2,3,8} · Kullervo Hynynen^{2,3,5,6} · Nir Lipsman^{1,2,3}

Received: 11 December 2019 / Revised: 1 April 2020 / Accepted: 15 April 2020

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FUS ablation and psychiatry



- Preliminary study that illustrates feasibility and safety of the proposed approach
- Encouraging clinical results (N=12)
- 4/16 patients excluded due to non accessibility of the target (ExAblate is designed for targeting the thalamus)

FUS and brain

**Thermal
Ablation**

**FUS-induced
neuromodulation**

- Tremor (essential, Parkinsonian)
- Brain cancer
- Neurodegenerative disorders
- Epilepsy
- Depression
- ...

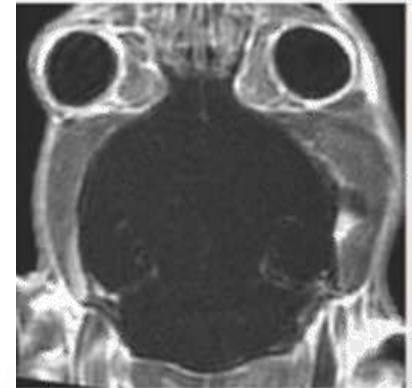
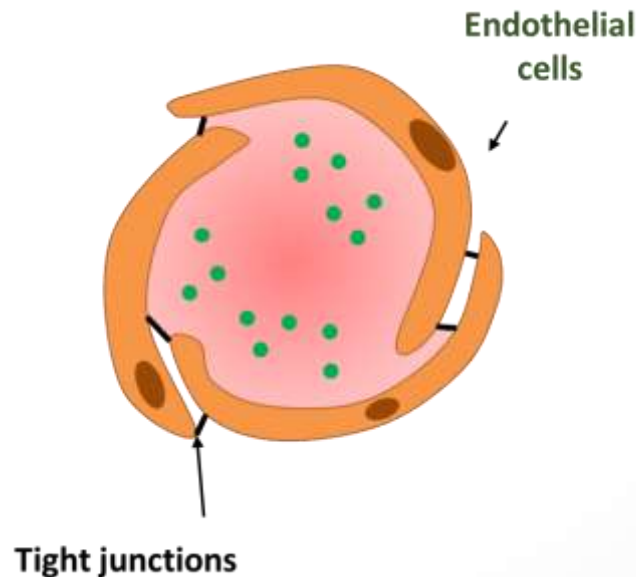
**Localized drug
delivery**

The challenge of treating brain diseases

Most pharmacological treatment strategies for central nervous system (CNS) disorders are ineffective



- > 95% of drugs do not cross the **Blood-brain barrier (BBB)**.
- Global failure of pharmacological therapy of the central nervous system.



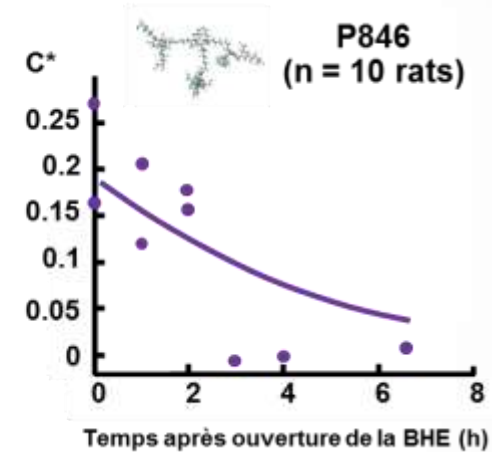
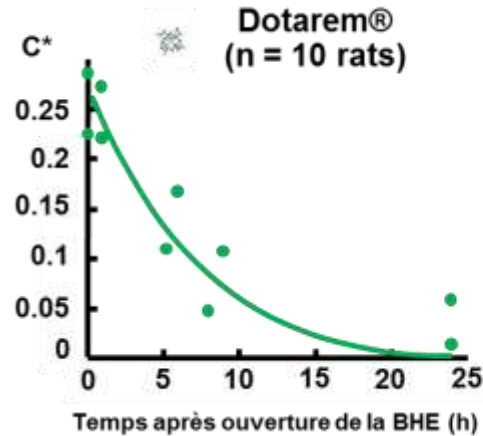
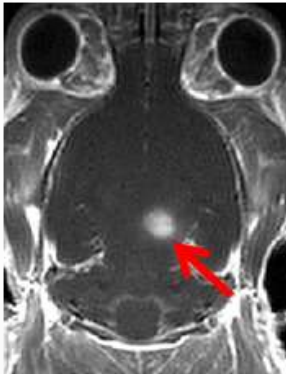
Blood-brain barrier (BBB)

BBB Opening using ultrasound



Brain blood barrier opening video from Queensland Brain Institute -

BBB Opening using ultrasound



Marty et al., J Cereb Blood Flow Metab, 2012

- ✓ Transient and reversible
- ✓ Highly localized
- ✓ Safe when cavitation is properly monitored

BBB opening: Indications (Oncology)

Courtesy B. Larrat, CEA/Neurospin

Clinical trial registration n°	Indication	Drug	Device	Phase	Primary outcome measures
NCT03712293	GBM	Temozolomide	ExAblate®	N/A	Safety
NCT04440358	rGBM	Carboplatin	ExAblate®	Phase I/II	Safety/Feasibility
NCT04417088	rGBM	Carboplatin	ExAblate®	Phase I/II	Safety/Feasibility
NCT03616860	GBM	Temozolomide	ExAblate®	N/A	Safety
NCT03551249	GBM	Temozolomide	ExAblate®	N/A	Safety
NCT04998864	GBM	Temozolomide	ExAblate®	N/A	Safety/Feasibility
NCT02343991	Brain tumor	Liposomal doxorubicin or temozolomide	ExAblate®	N/A	Safety
NCT02253212	rGBM	Carboplatin	SonoCloud-1®	Phase I/II	Safety
NCT03744026	rGBM	Carboplatin	SonoCloud-9®	Phase I/II	Safety/Feasibility
NCT04614493	GBM	Temozolomide	SonoCloud-9®	Phase II	Efficacy (PFS)
NCT04528680	rGBM	Abraxane® (Phase I) Carboplatin/ Abraxane® (Phase II)	SonoCloud-9®	Phase I/II	Safety/Efficacy (1-year survival rate)
NCT03626896	rGBM	N/A	NaviFUS®	N/A	Safety
NCT04446416	rGBM	Bevacizumab	NaviFUS®	N/A	Safety/Efficacy (PFS-6 months)

GBM: glioblastoma, rGBM: recurrent glioblastoma, PFS: progression-free survival,

BBB opening: Indications (Neurodegenerative diseases)

NCT04118764	Non-invasive Blood-brain Barrier Opening in Alzheimer's Disease Patients Using Focused Ultrasound (safety)	Columbia University, NYC	Neuronavigation
NCT03671889	ExAblate Blood-Brain Barrier (BBB) Disruption for the Treatment of Alzheimer's Disease (safety)	InSightec, multicentric, USA	MR-guided
NCT03321487	Blood-Brain Barrier Opening Using MR-Guided Focused Ultrasound in Patients With Amyotrophic Lateral Sclerosis (safety => BBBo in motor cortex)	InSightec, Sunnybrook Health Science Center, Toronto, Canada	MR-guided
NCT04370665	Blood-Brain-Barrier Disruption With Cerezyme in Patient's With Parkinson's Disease	InSightec, Sunnybrook Health Science Center, Toronto, Canada	MR-guided

BBB opening and psychiatry?





Behavioural Brain Research

Volume 342, 16 April 2018, Pages 57–61



Short communication

Antidepressant effects of focused ultrasound induced blood-brain-barrier opening

Skyler J. Mooney^a  , José N. Nobrega^{c d}, Anthony J. Levitt^{b c},
Kullervo Hynynen^{a e}

Show more 

=> Neurogenesis ?

=> Long-term changes in neural excitability?

“neuromodulatory potential of FUS-mediated BBB opening”

BBB opening and psychiatry?

PLOS ONE

OPEN ACCESS PEER-REVIEWED

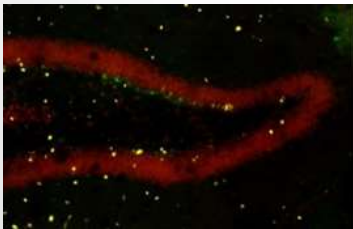
RESEARCH ARTICLE

Focused Ultrasound-Induced Neurogenesis Requires an Increase in Blood-Brain Barrier Permeability

Skyler J. Mooney , Kairavi Shah, Sharon Yeung, Alison Burgess, Isabelle Aubert, Kullervo Hynynen

Published: July 26, 2016 • <https://doi.org/10.1371/journal.pone.0159892>

Sonicated

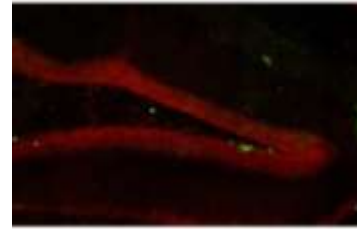


Control



With microbubbles
(BBB open)

Sonicated



Control



Without microbubbles

Non-invasive BBB Opening using Ultrasound

MR-guided



*InsighTech (Israel),
ExAblate Neuro*

Neuronavigation

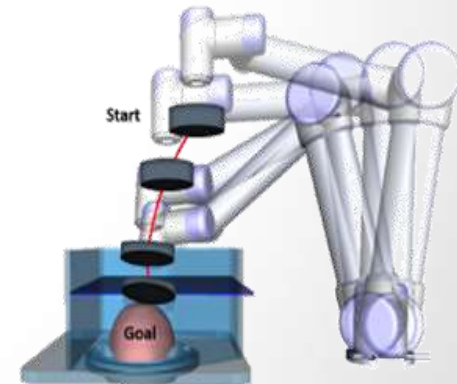
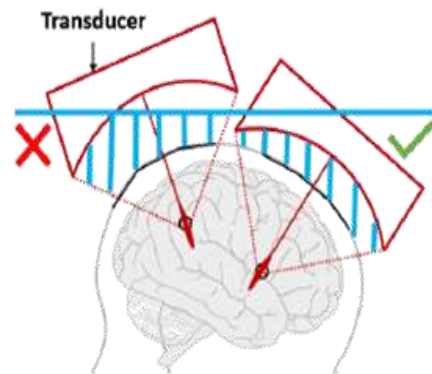
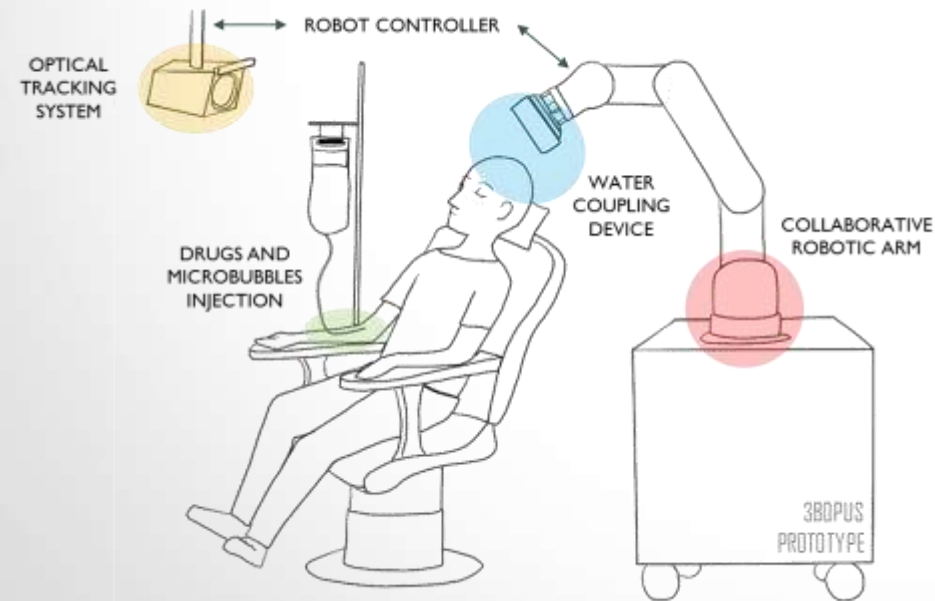


*NaviFUS (Taiwan)
Columbia University (NY, USA)*

Major challenge = BBB opening on extended volumes

The Therasonic device

New FUS device for opening BBB, robotized, neuronavigated, outside MRI



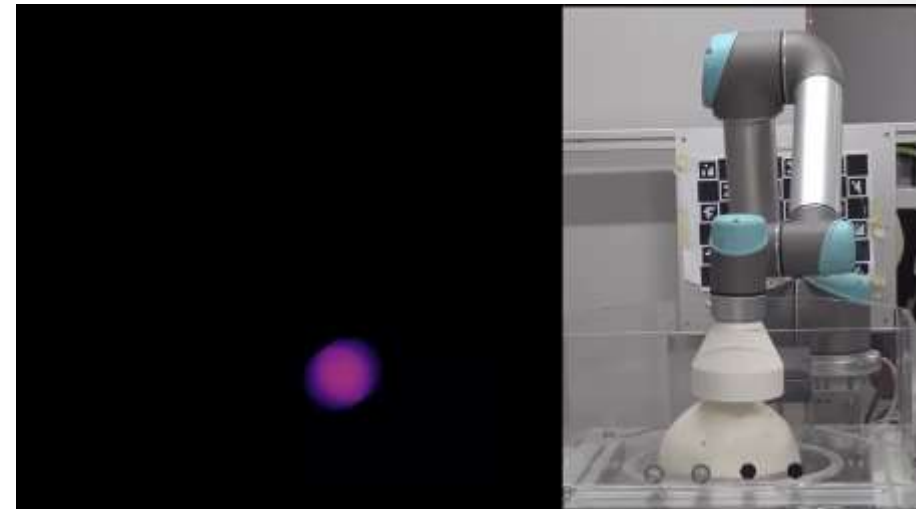
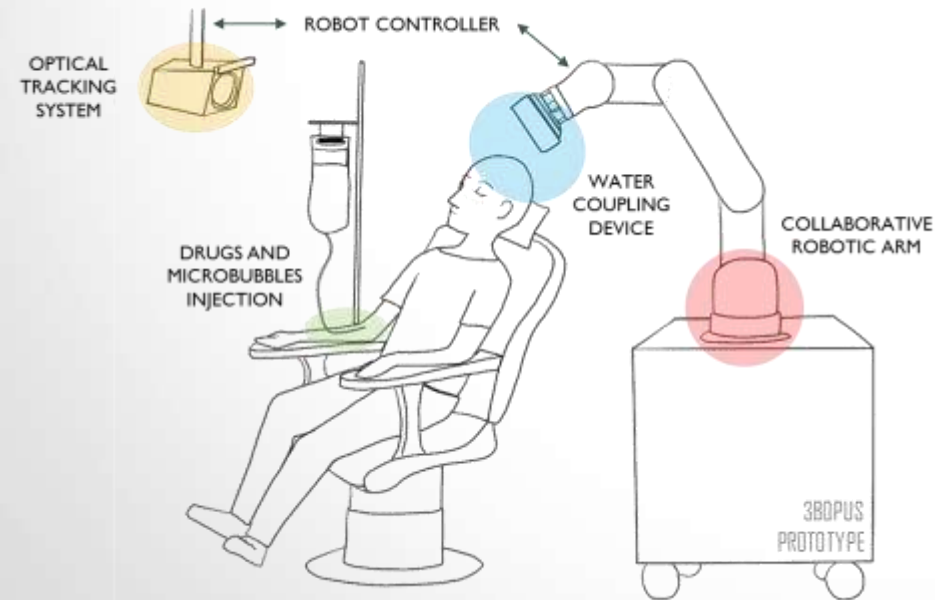
Thomas et al., IEEE EMBC 2021

The Therasonic device

New FUS device for opening BBB, robotized, neuronavigated, outside MRI



Volumetric BBB opening



Thank you!



*TechnoFUS joint laboratory
ICube- Image Guided Therapy*

Information Sciences
and Technology for Healthcare | HealthTech

The interdisciplinary thematic institutes
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funded under the Excellence Initiative program 