

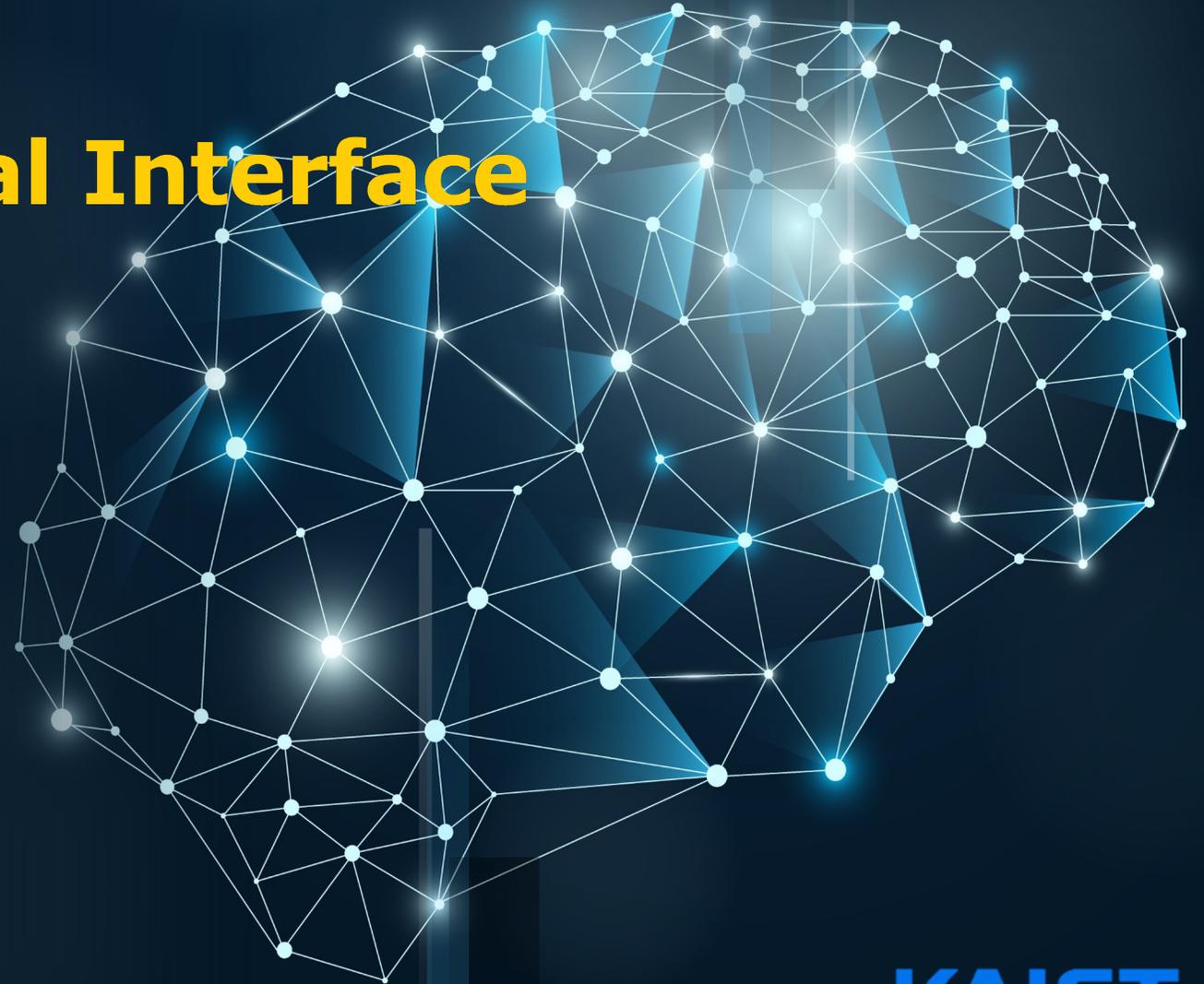
# Bi-directional Neural Interface

Ultrasound-mediated  
Neuromodulation

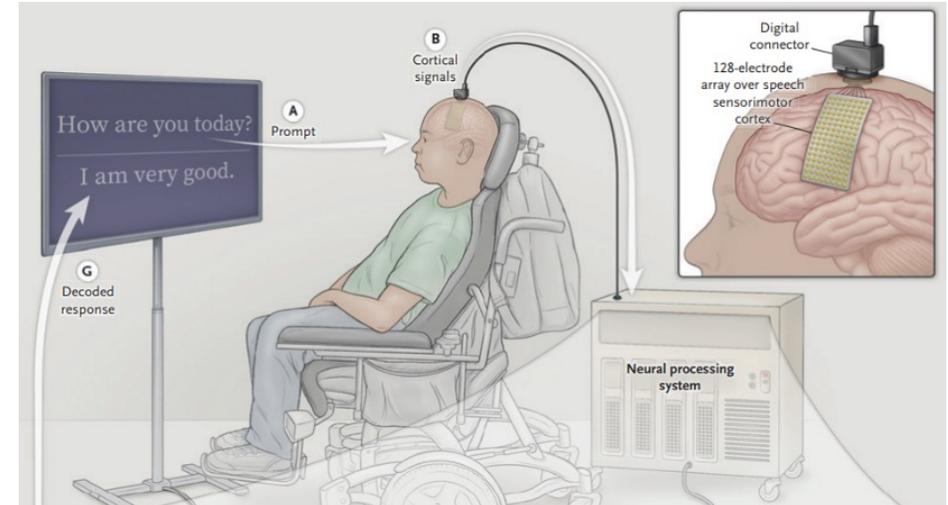
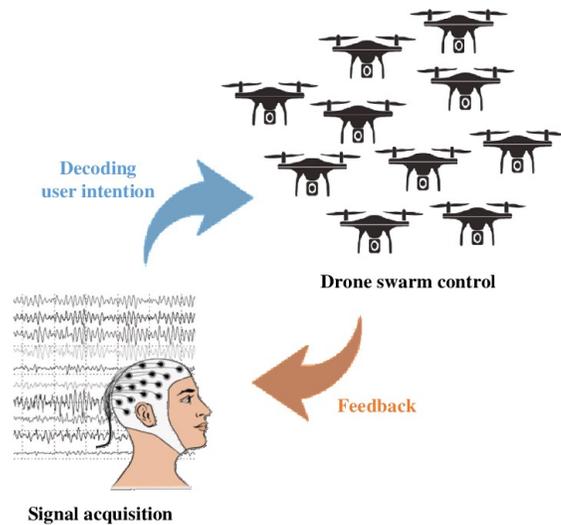
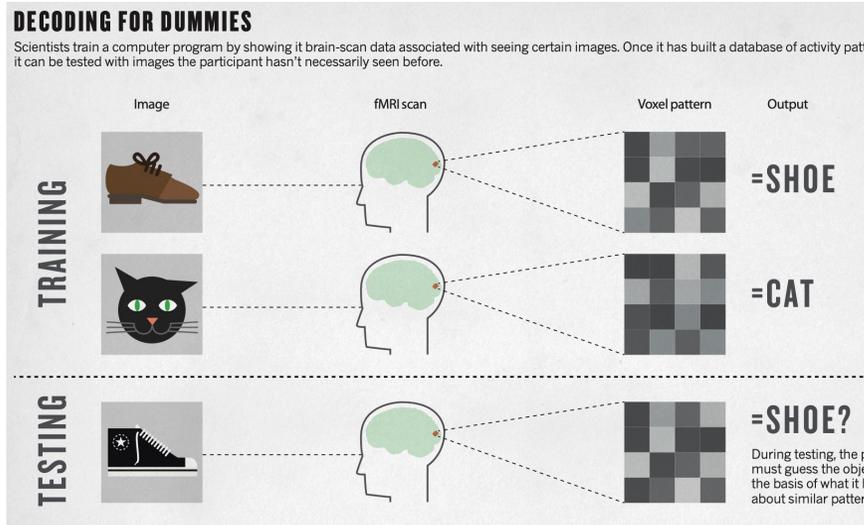
---

**Hyunjoo Jenny Lee, Ph.D.**

Associate Professor / KAIST Endowed Chair Professor  
School of Electrical Engineering  
Korea Advanced Institute of Science and Technology



# Brain Machine Interface - Decoding



Sources: Electrophysiological signals, fMRI image data

Applications: Treatment for paralyzed patients, Reading minds, Brain-to-X communications

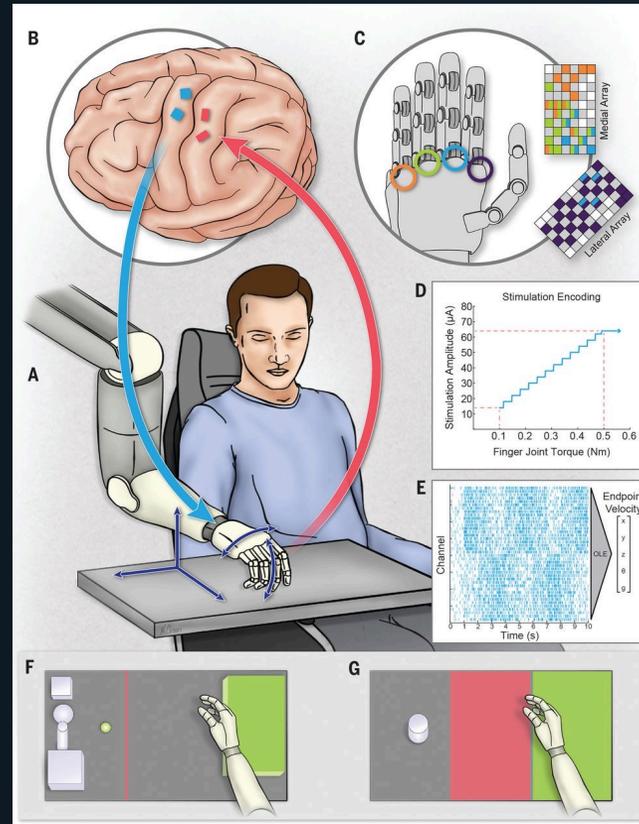
# Brain Machine Interface - Stimulation

## Therapeutics

**DEEP BRAIN STIMULATION**

Conditions treated by DBS:

- Addictions
- Anorexia nervosa
- Cluster headache
- Alzheimer's disease
- Refractory Aggression
- Essential Tremor
- Tourette Syndrome
- Obsessive compulsive disorder
- Parkinson's Disease
- Restless Leg Syndrome
- Treatment-Resistant Depression
- Dystonia
- Chronic pain
- Obesity
- Drug-resistant refractory epilepsy



## Brain-to-X communications



### TELEPATHIC SOLDIERS

A soldier wears a headset that picks up on behavioural brain signals, this connects to a computer device in their pocket

The small computer decodes the brain signals and sends an interpretation to the computer of a soldier nearby

Their computer relays the other soldier's brain signals to them via their headset and the two soldiers have communicated telepathically

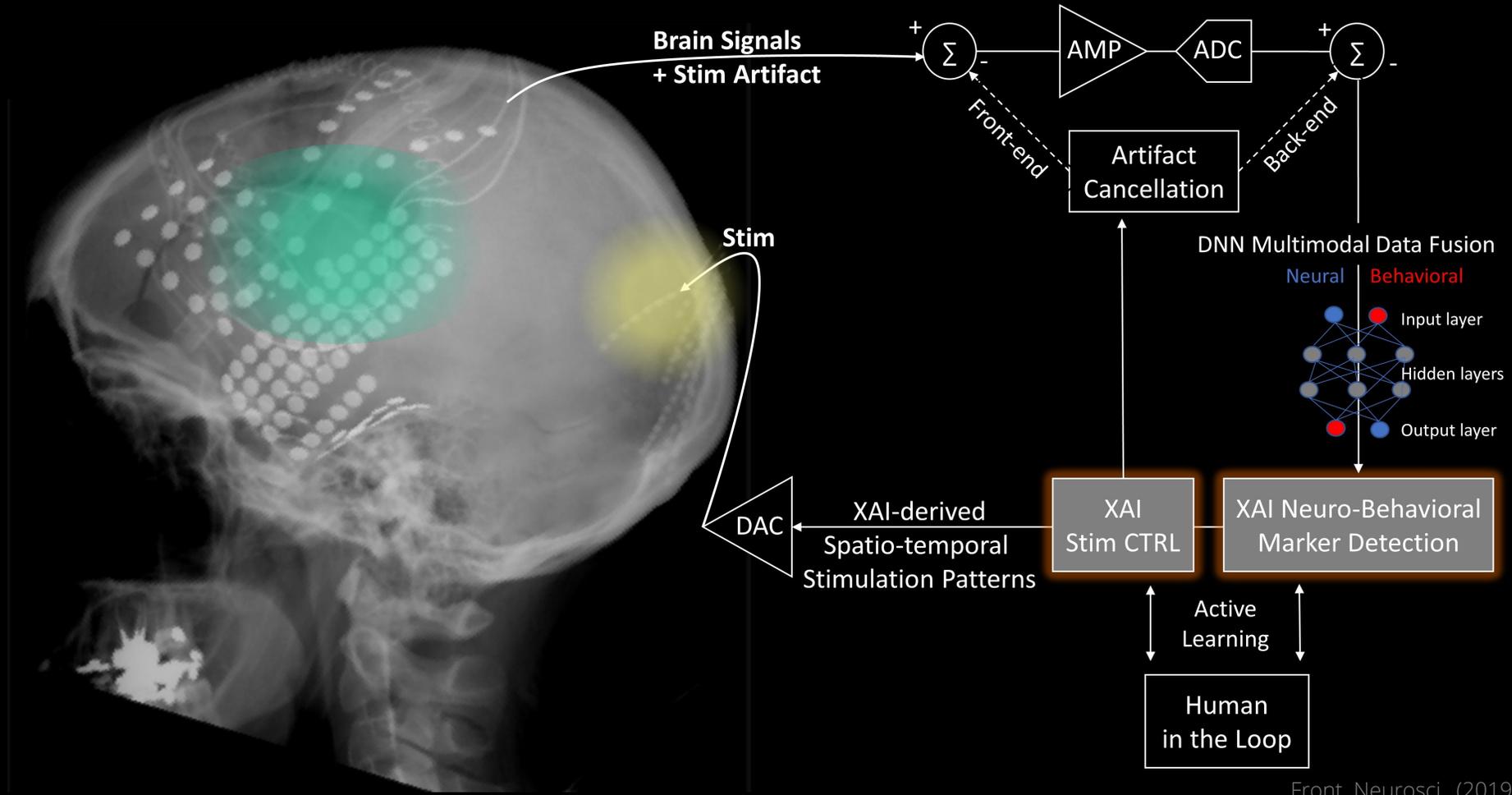
\* DOI: 10.1016/j.neurop.2022.03.001

# Future of BMI - **Bi-directional control**



\* Short clip from "The Entire History of You", Black Mirror Season 1 (Source: Youtube)

# Brain as a "black box"



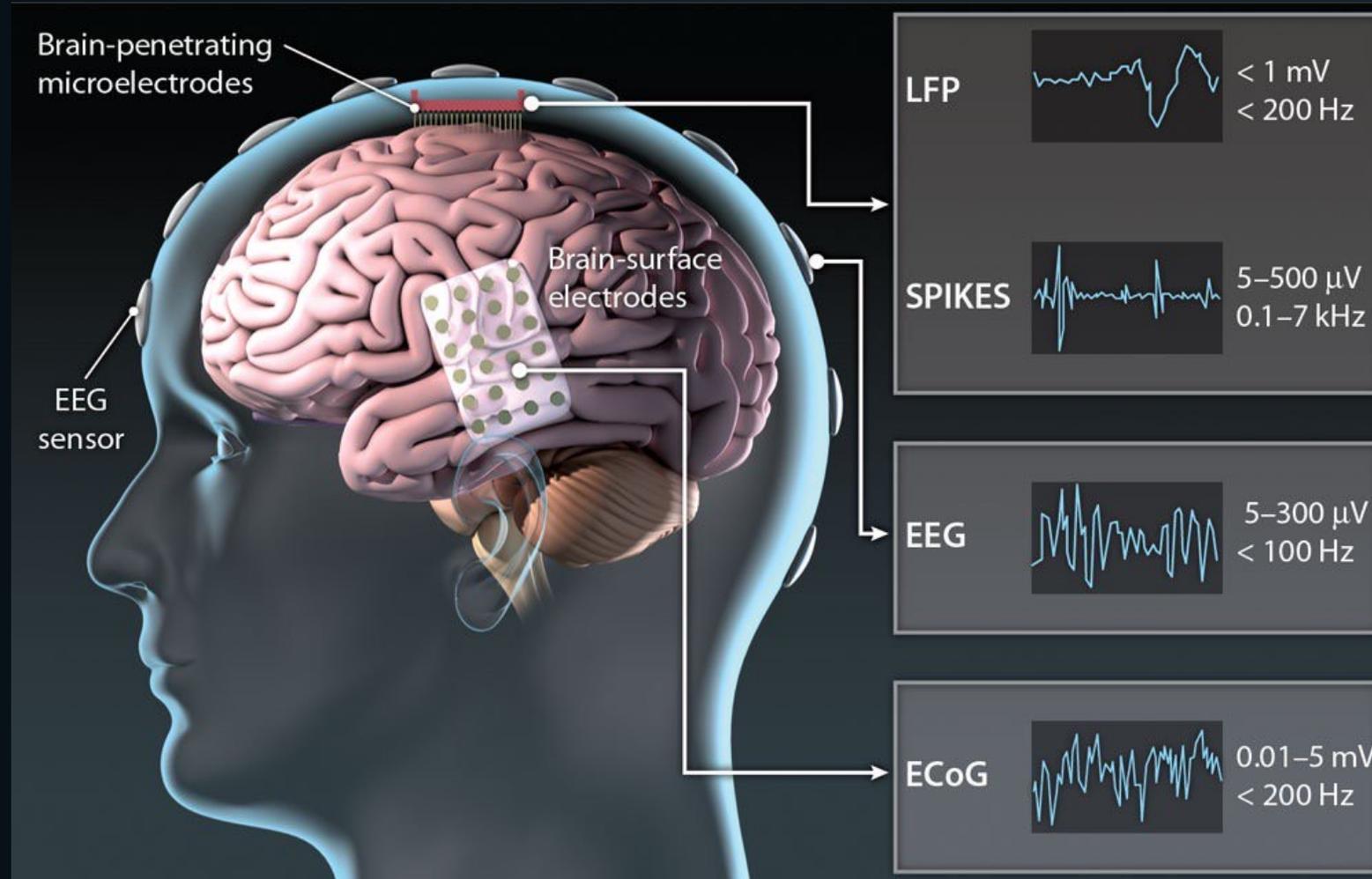
Front. Neurosci., (2019)



# **01** Brain-Machine Interface

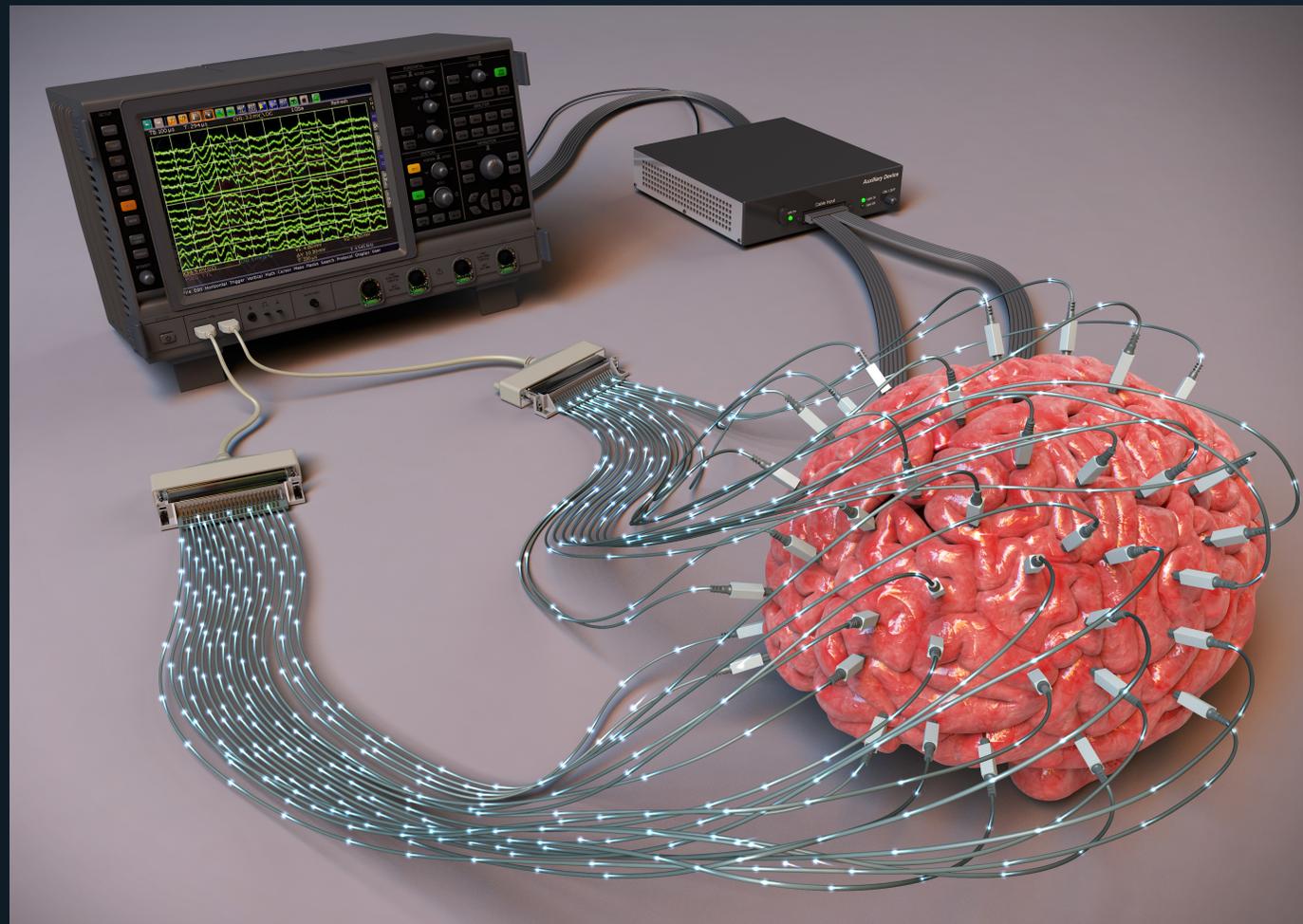
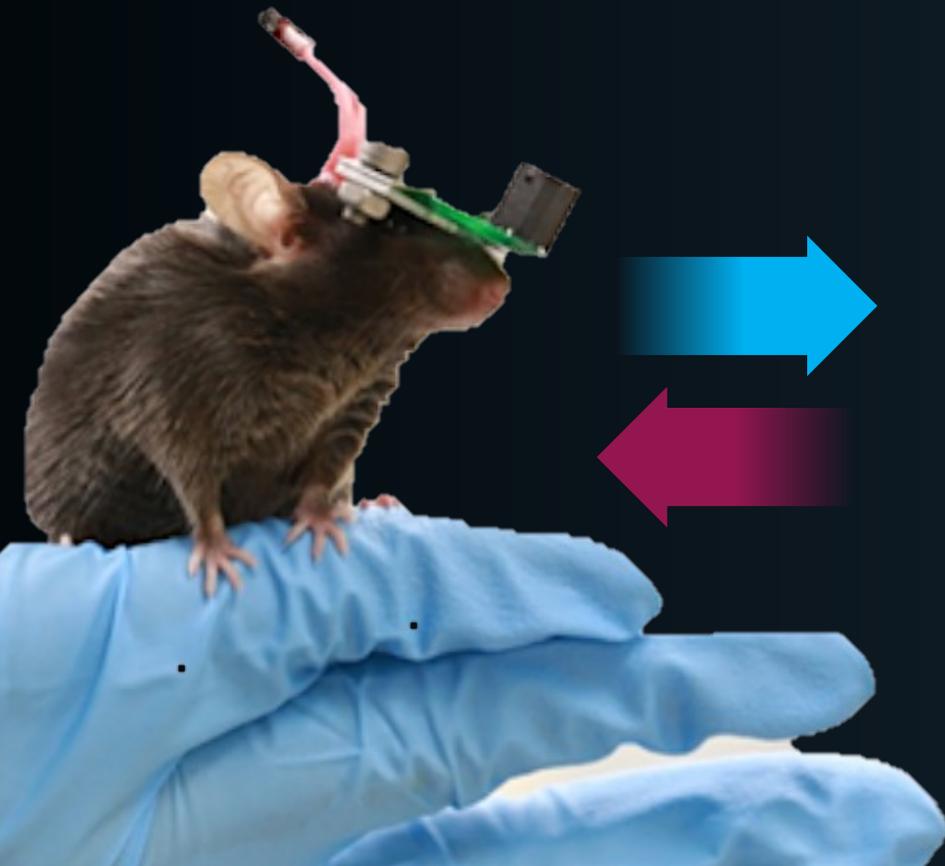
**Neural interface for monitoring**

# Neural recording

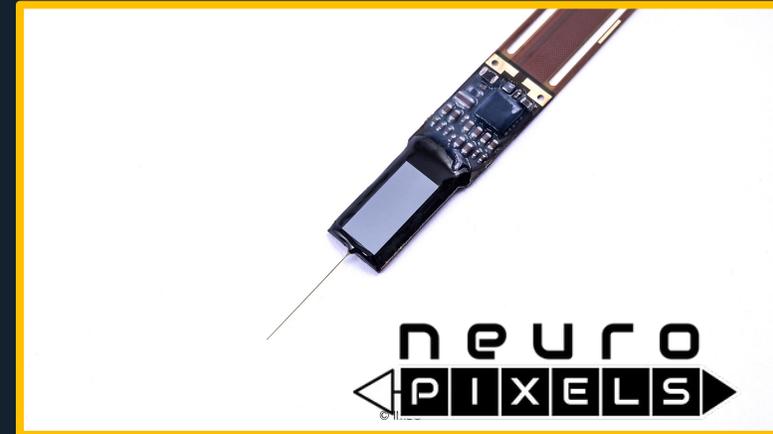
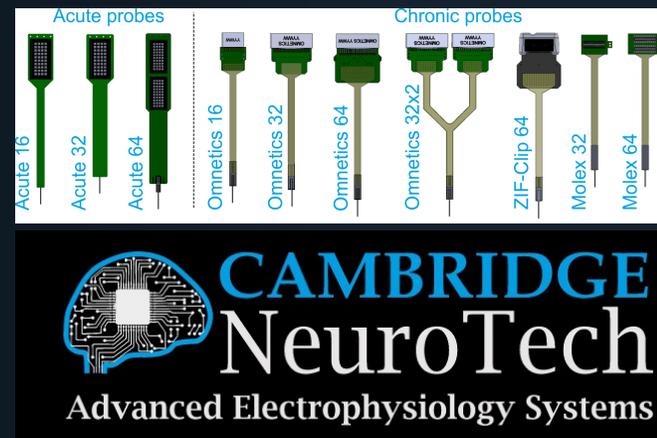
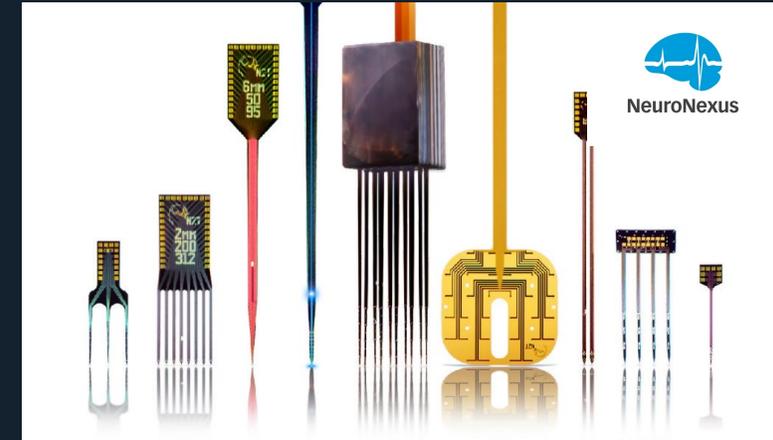
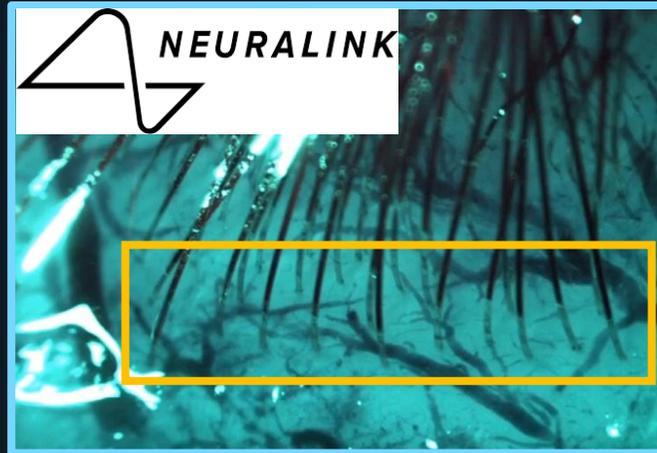
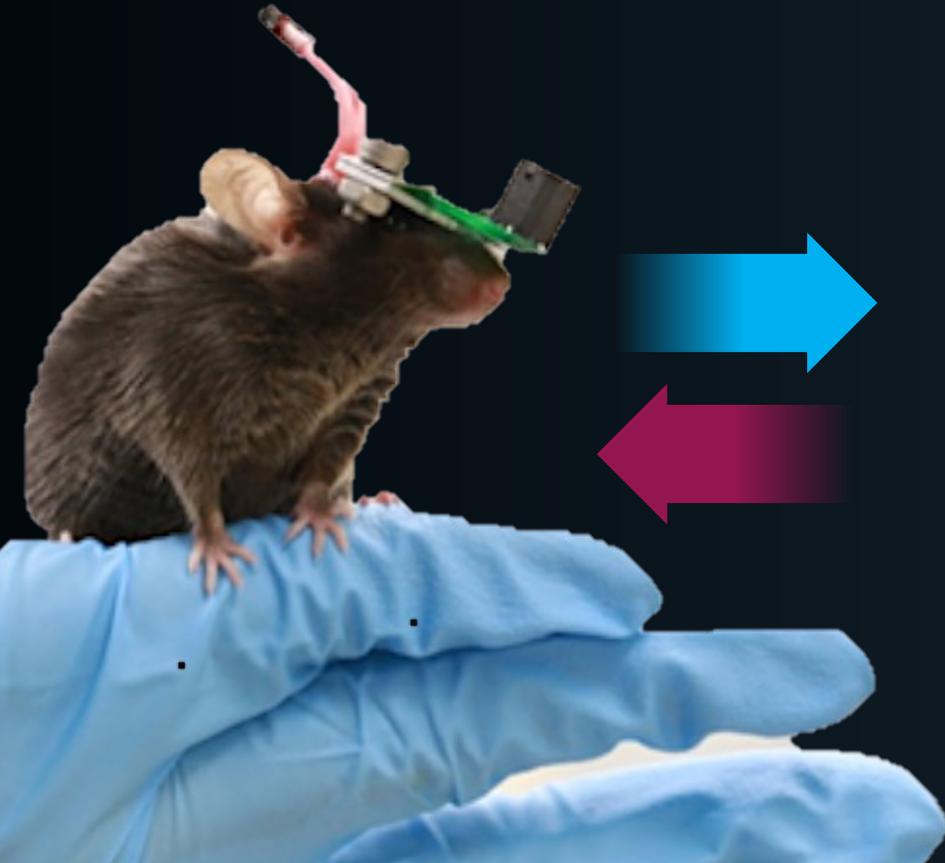


\*Science Translational Medicine 5 (210), 2013

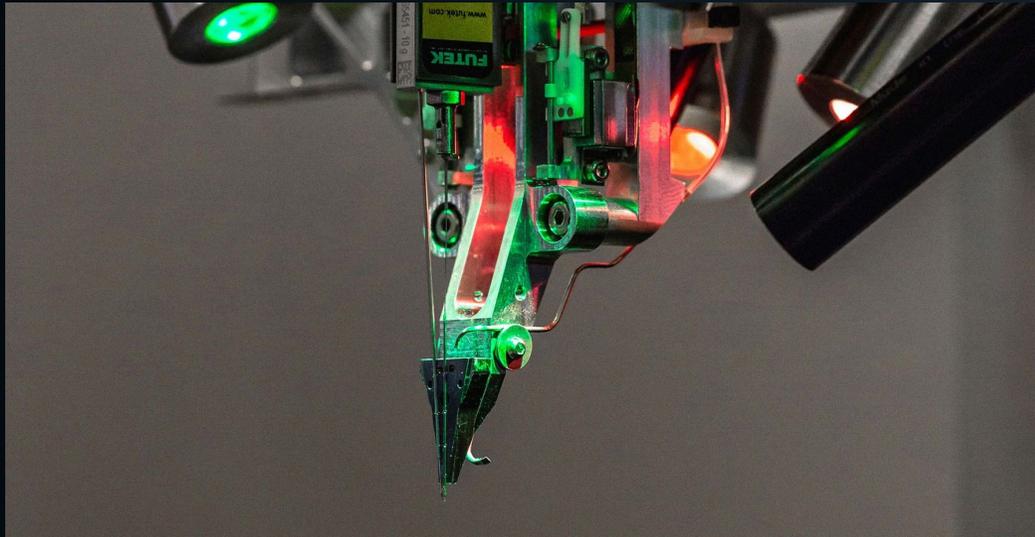
# Neurotechnology - Neurotools



# Neurotechnology - Neural probes



# Neurotechnology - Neuralinks



## LINK V0.9

1024 channels per Link

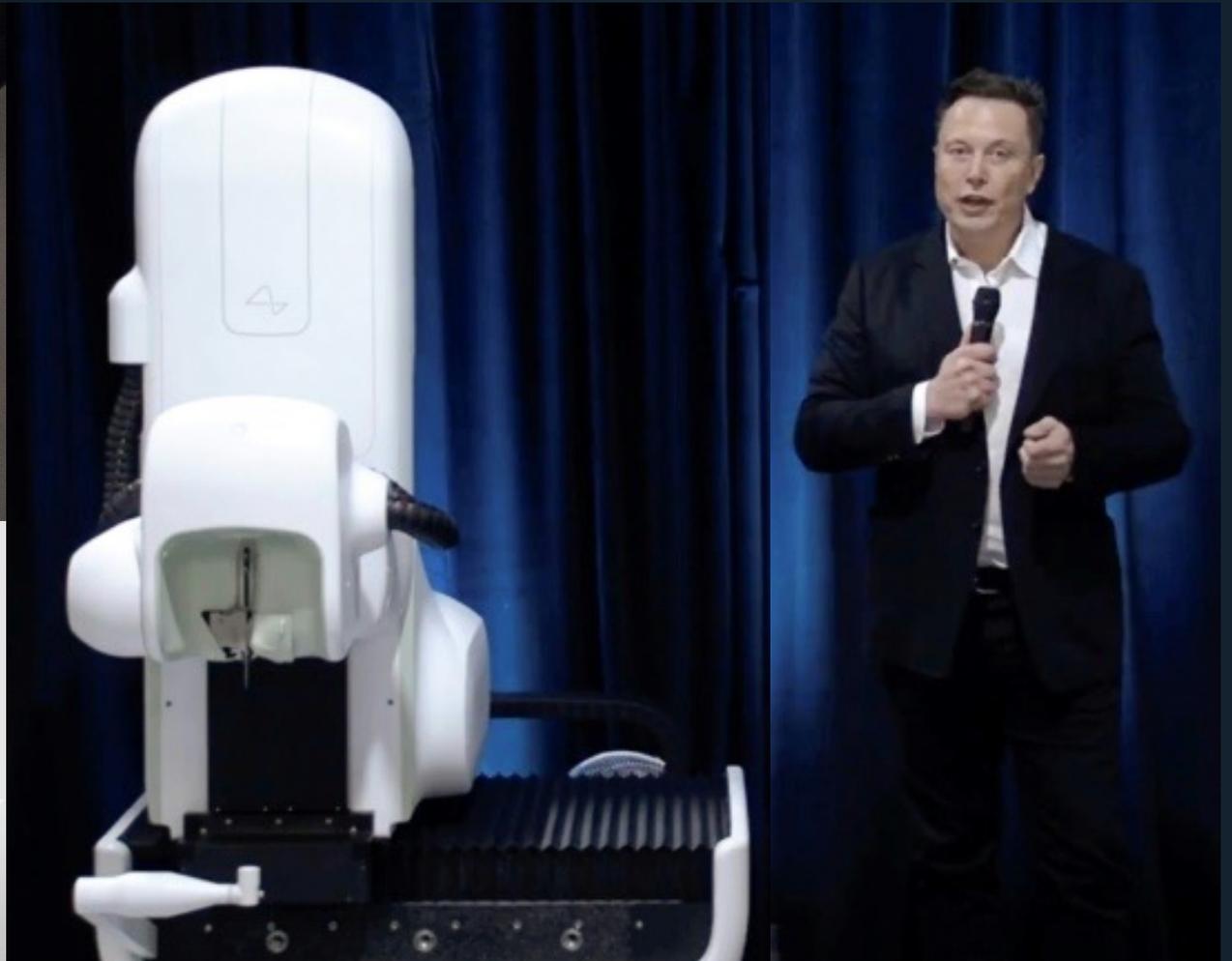
23 mm x 8 mm

Flush with skull (invisible)

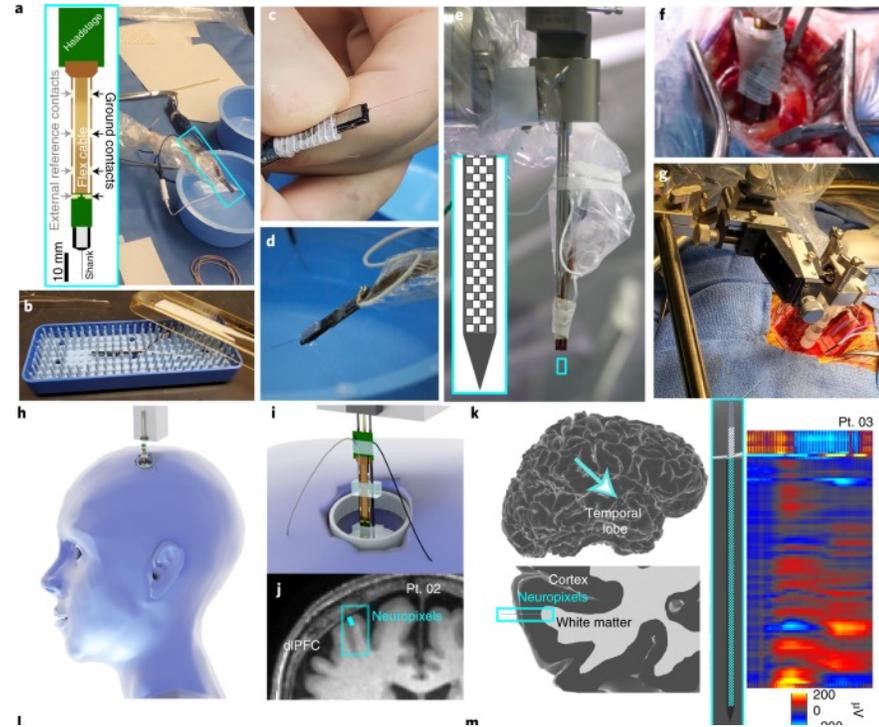
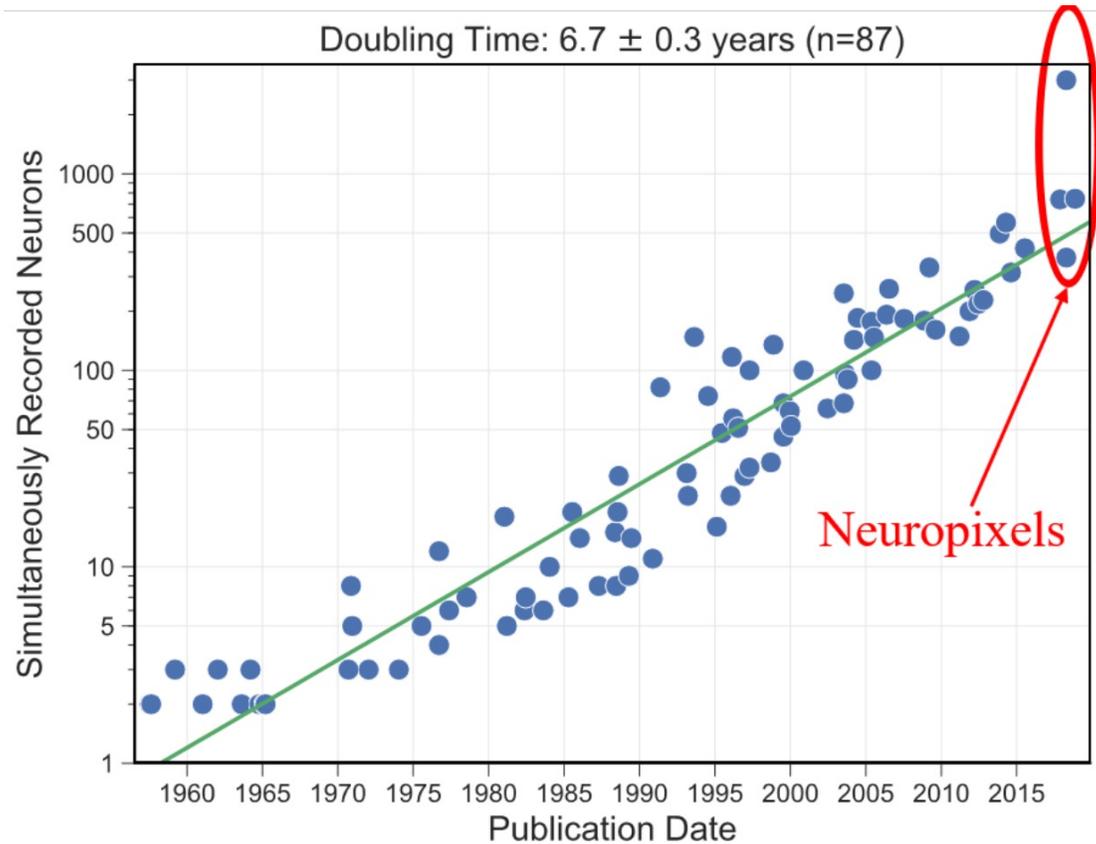
6-axis IMU, temperature, pressure, etc.

Megabit wireless data rate, post compression

All day battery life



# Trends in neural recording - Density



- Invented by Tim Harris at HHMI Janelia Research Campus
- Designed and fabricated by IMEC
- Tested by UCL and Allen Institute of Brain Science

\*<https://stevenson.lab.uconn.edu/scaling/> and Stevenson IH and Kording KP (2011) Nature Neuroscience, 14: 139-142

# Trends in neural recording - Density

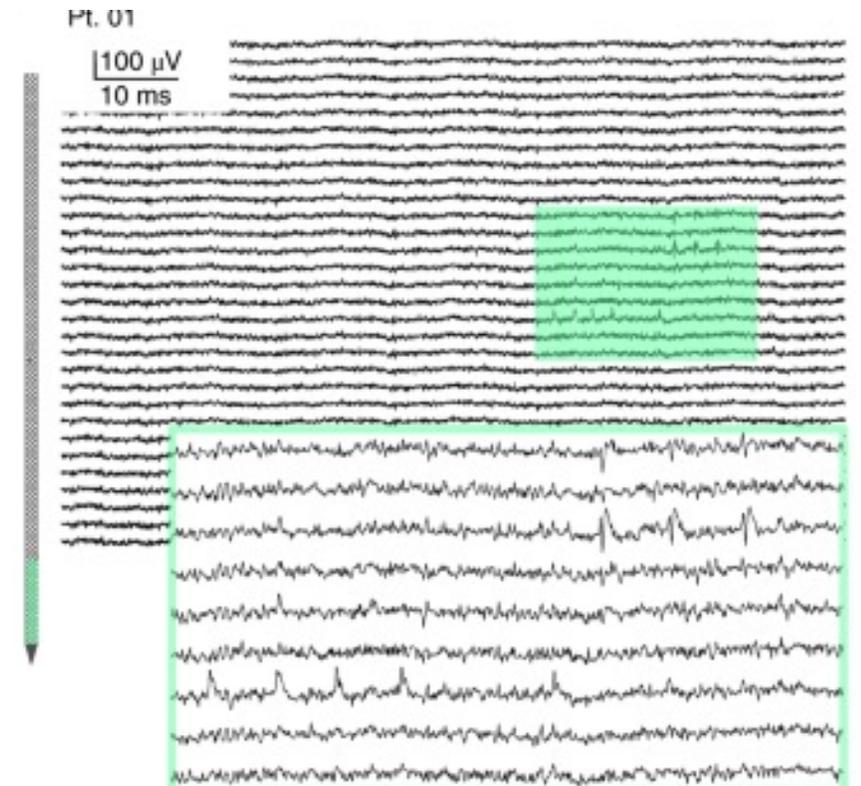
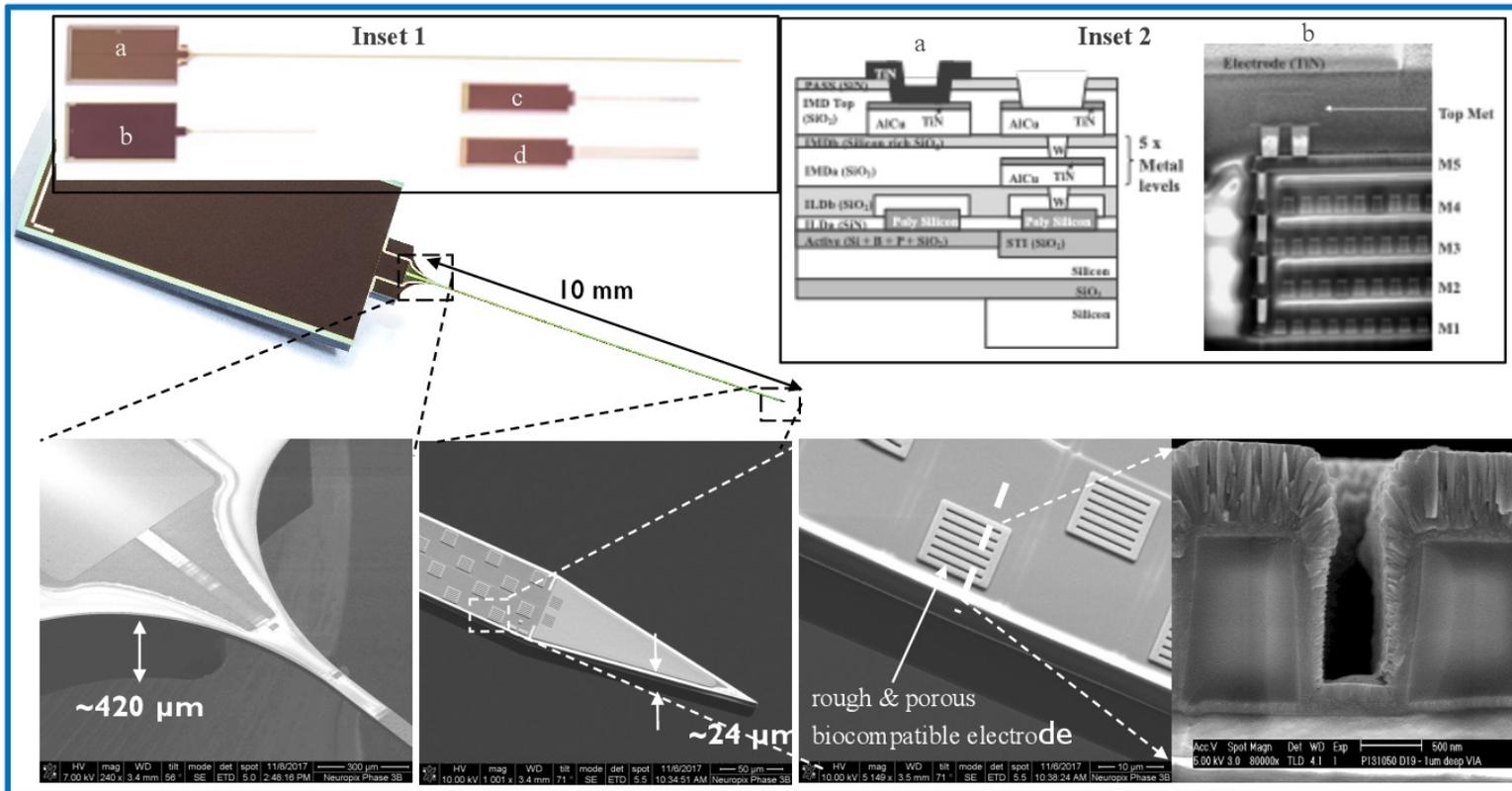


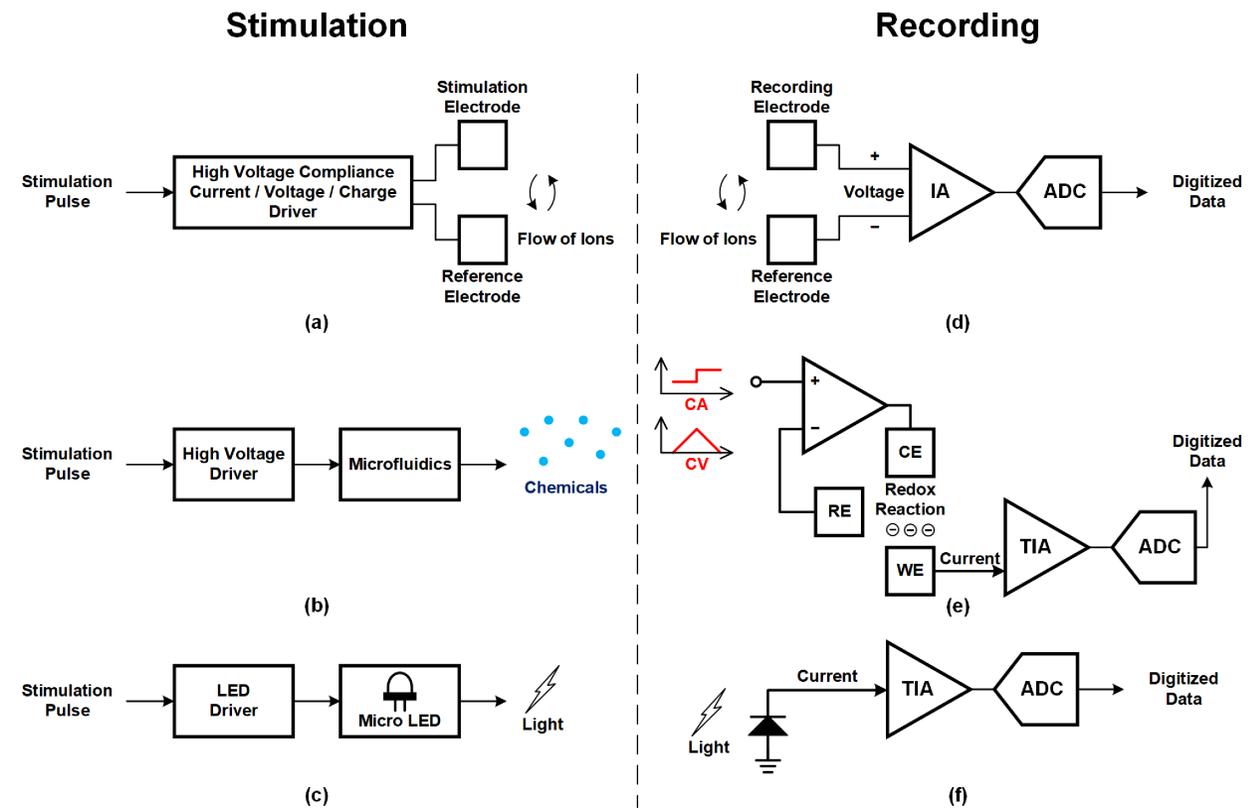
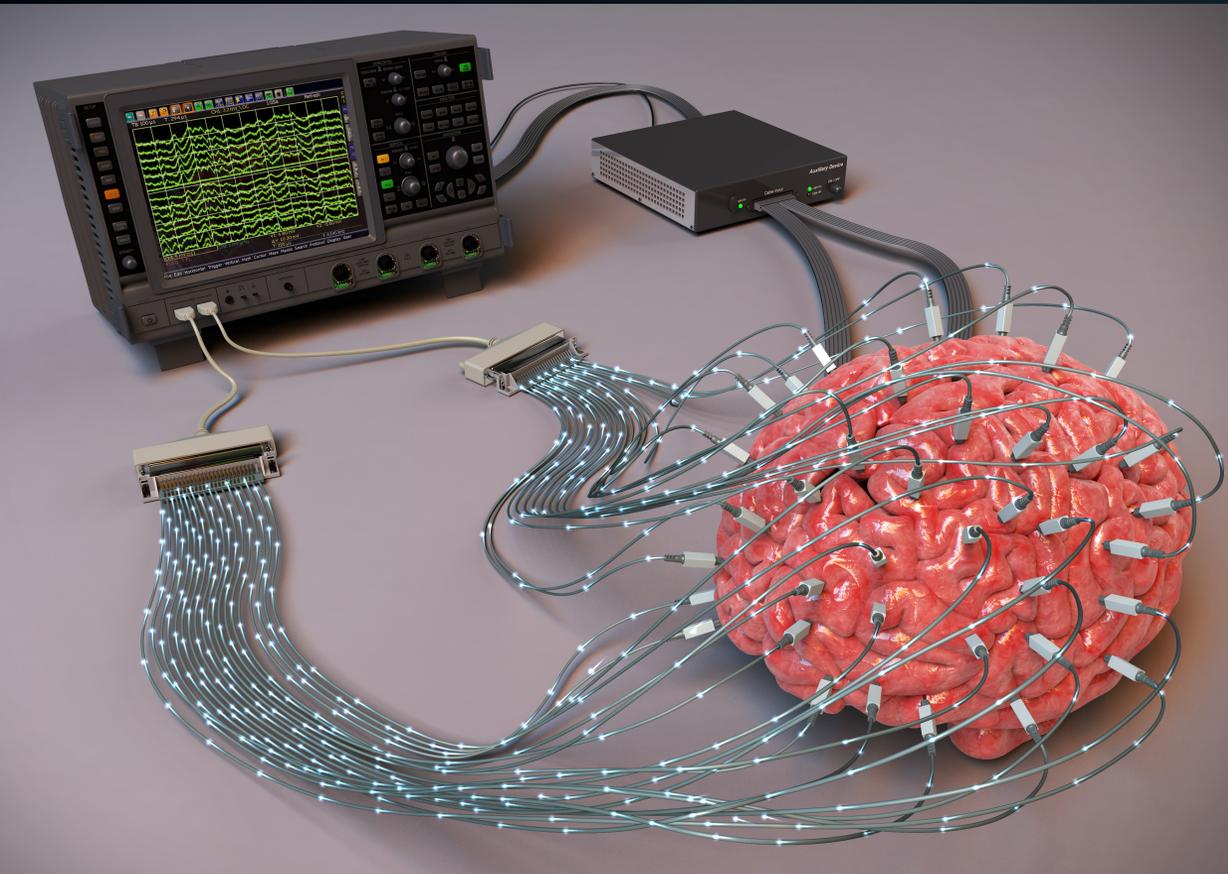
Figure 1: Schematic Cross-section and Cross-section SEM Image of Neuropixels CMOS Probe platform and custom process modules in 130nm

\*DOI:10.1109/IEDM19573.2019.8993611

# Trends in neural recording - Multimodal



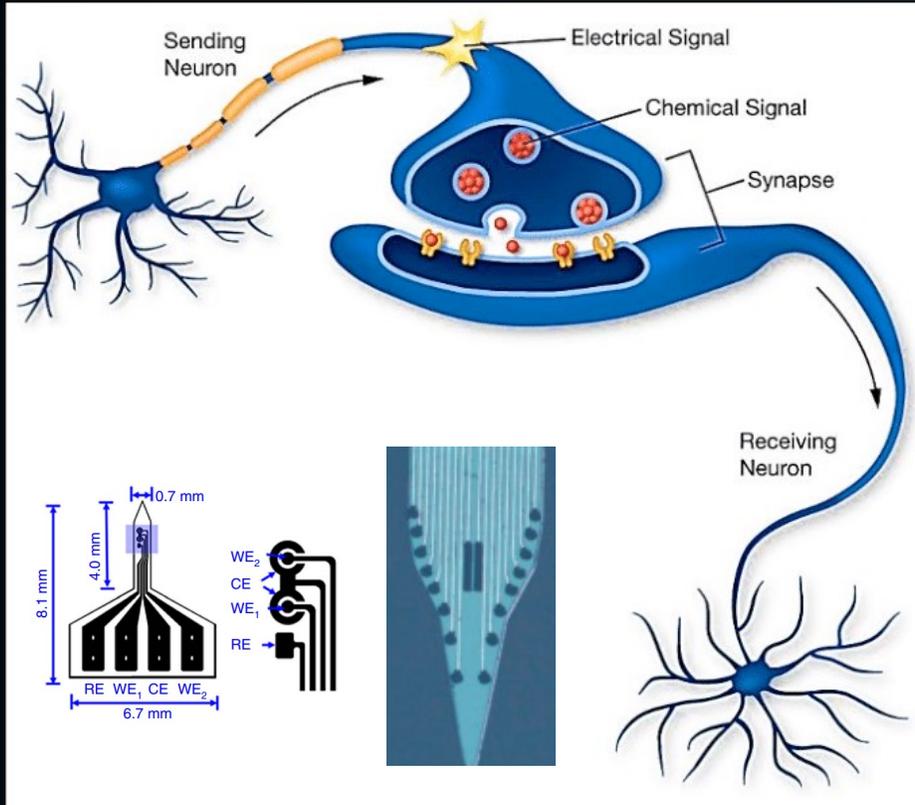
Kim, 2020 (IEEE SSC Magazine)



# Multi-modal sensing



Kim, 2022 (AMT)

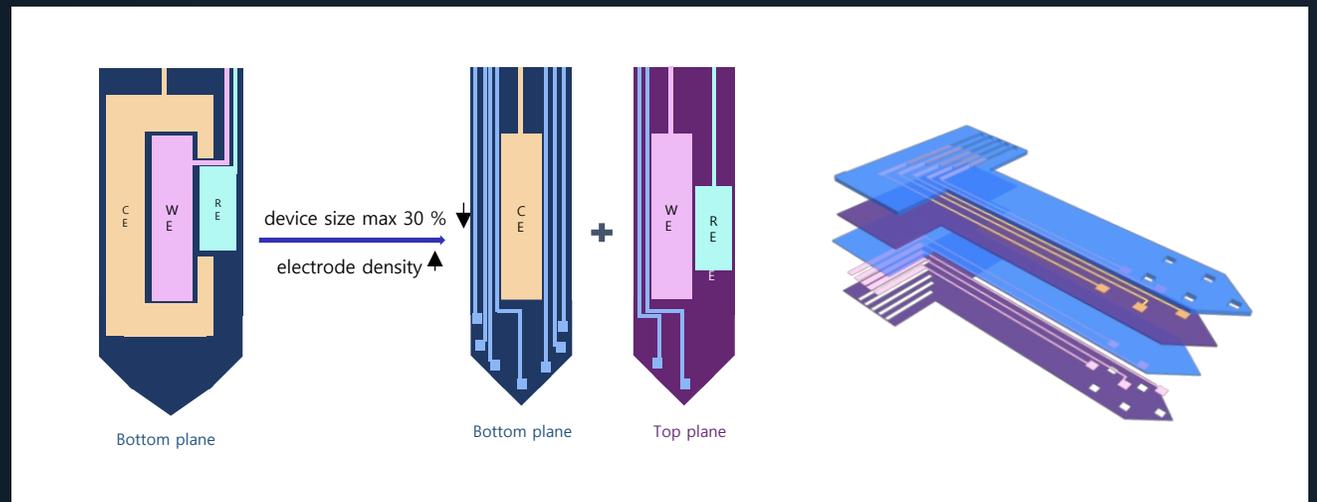


Taghizadeh-Sarabi, Mitra. (2018)  
10.1038/micronano.2017.70  
10.1038/s41378-020-0155-1

## Problem: limited probe area

- 3-electrode integration requires large area to gain high sensitivity
- Large footprint results in larger neuronal damage
- Different sensing electrodes

## Our approach: dual-side fabrication

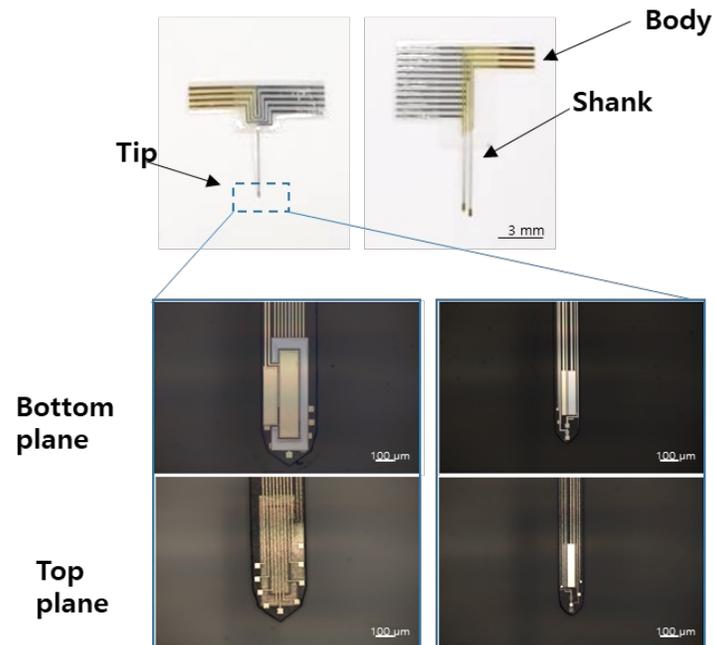


# Multi-modal sensing

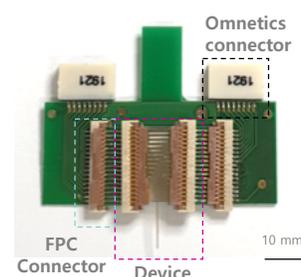
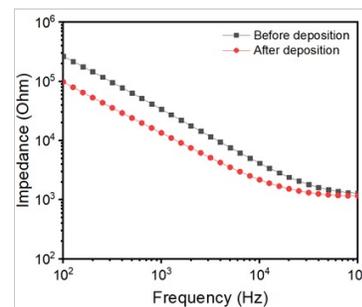
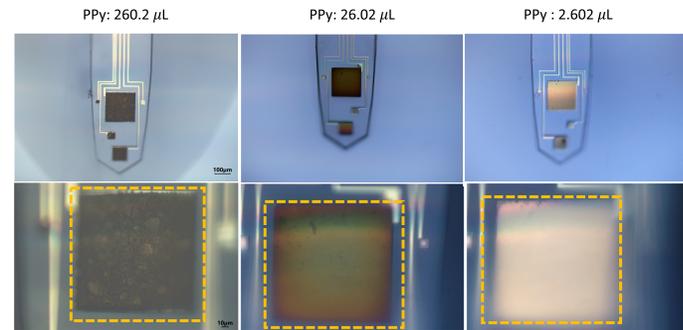


Kim, 2022 (AMT)  
Eom, 2019 (J. Electro. Chem.)

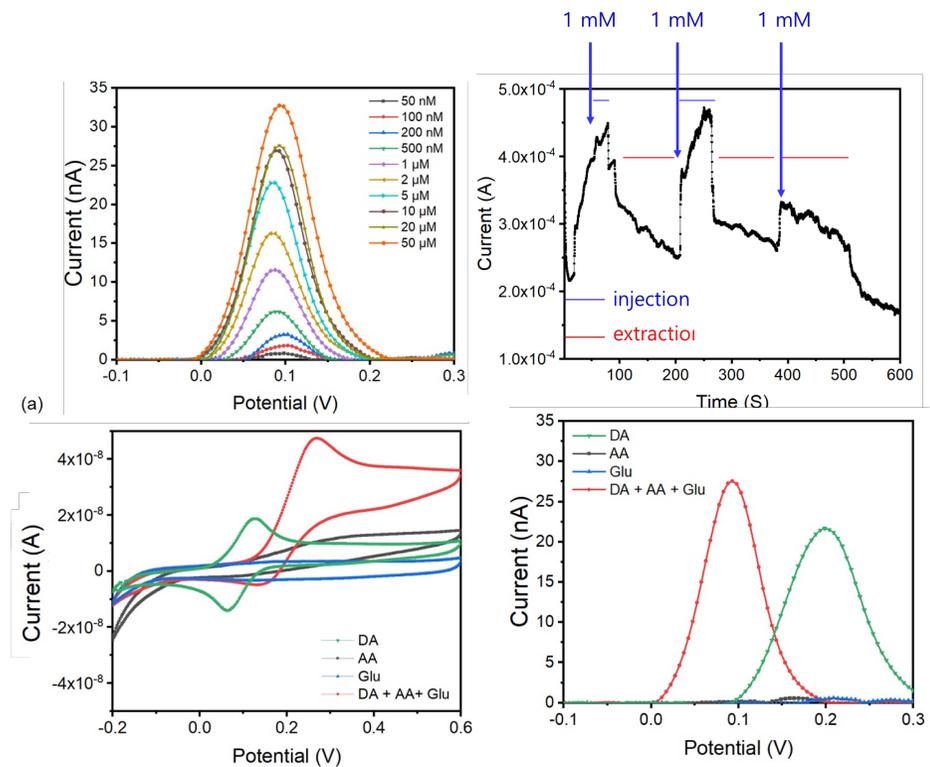
## Fabricated dual-side neural probes



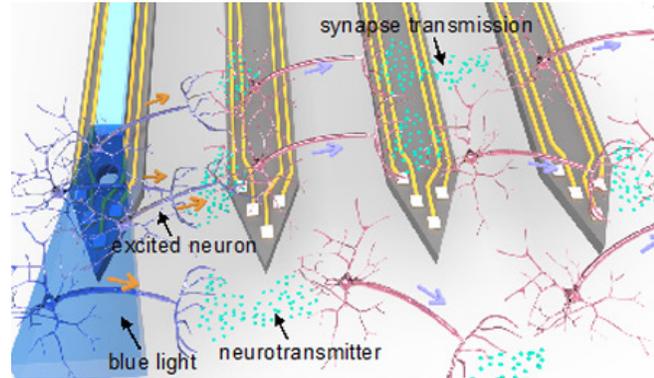
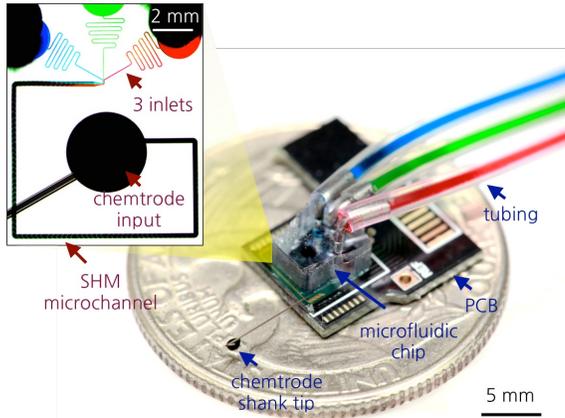
## Electrode modification & Packaging



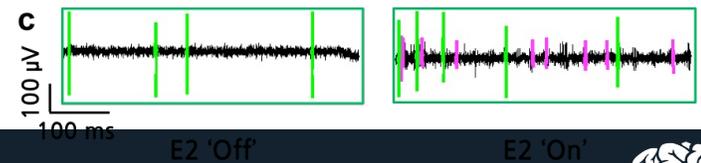
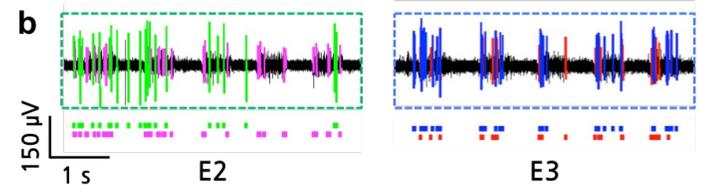
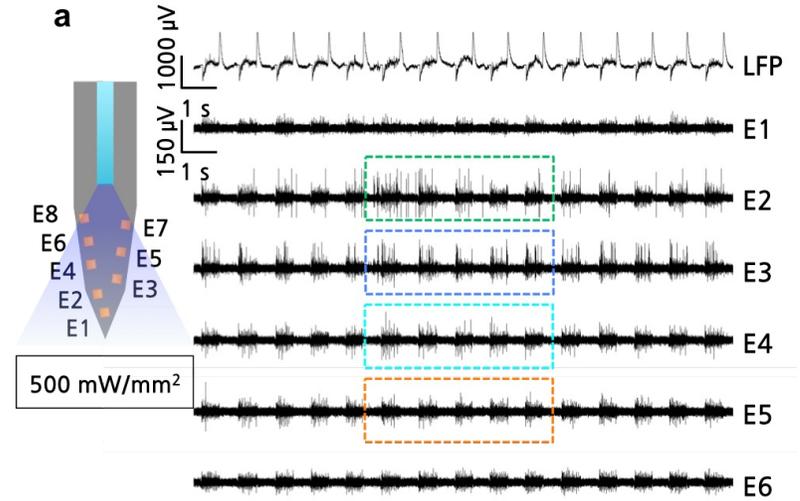
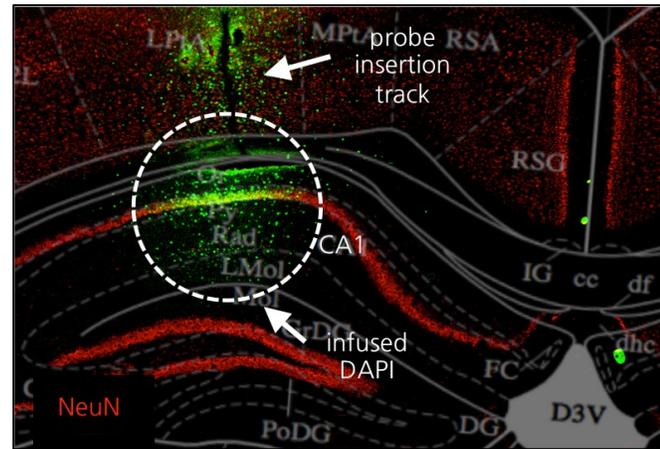
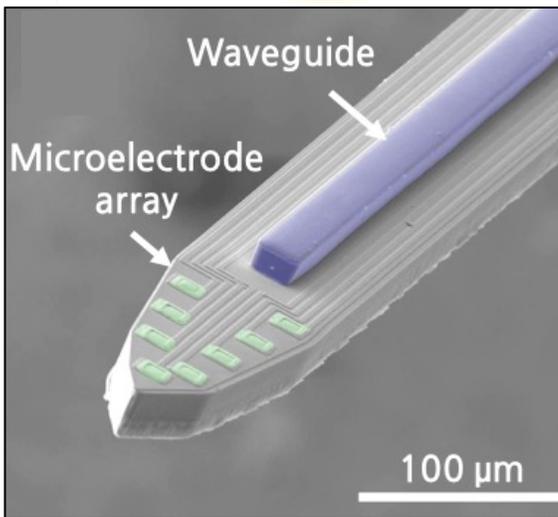
## DA detection, selectivity, in vivo experiments



# Multi-functional neural probes



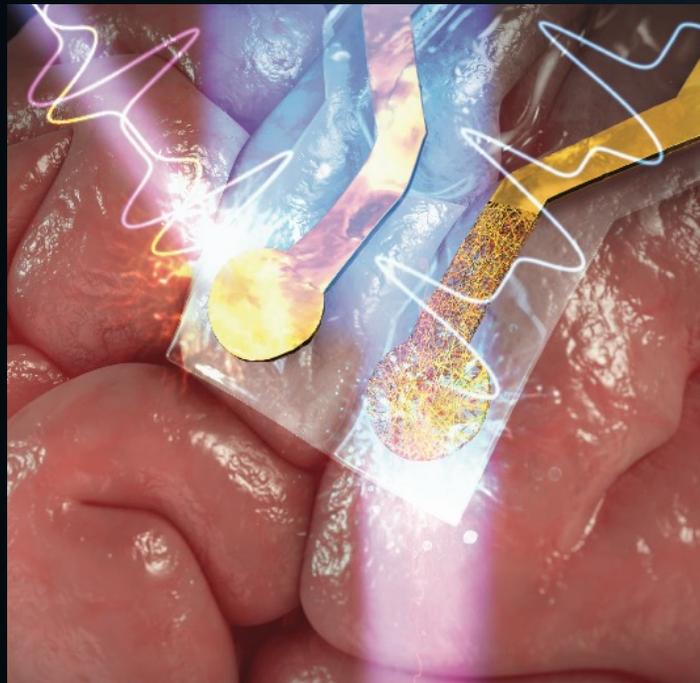
• Credit: Il-Joo Cho, Brain Science Institute, KIST, Korea



# ECoG array for optical stimulation



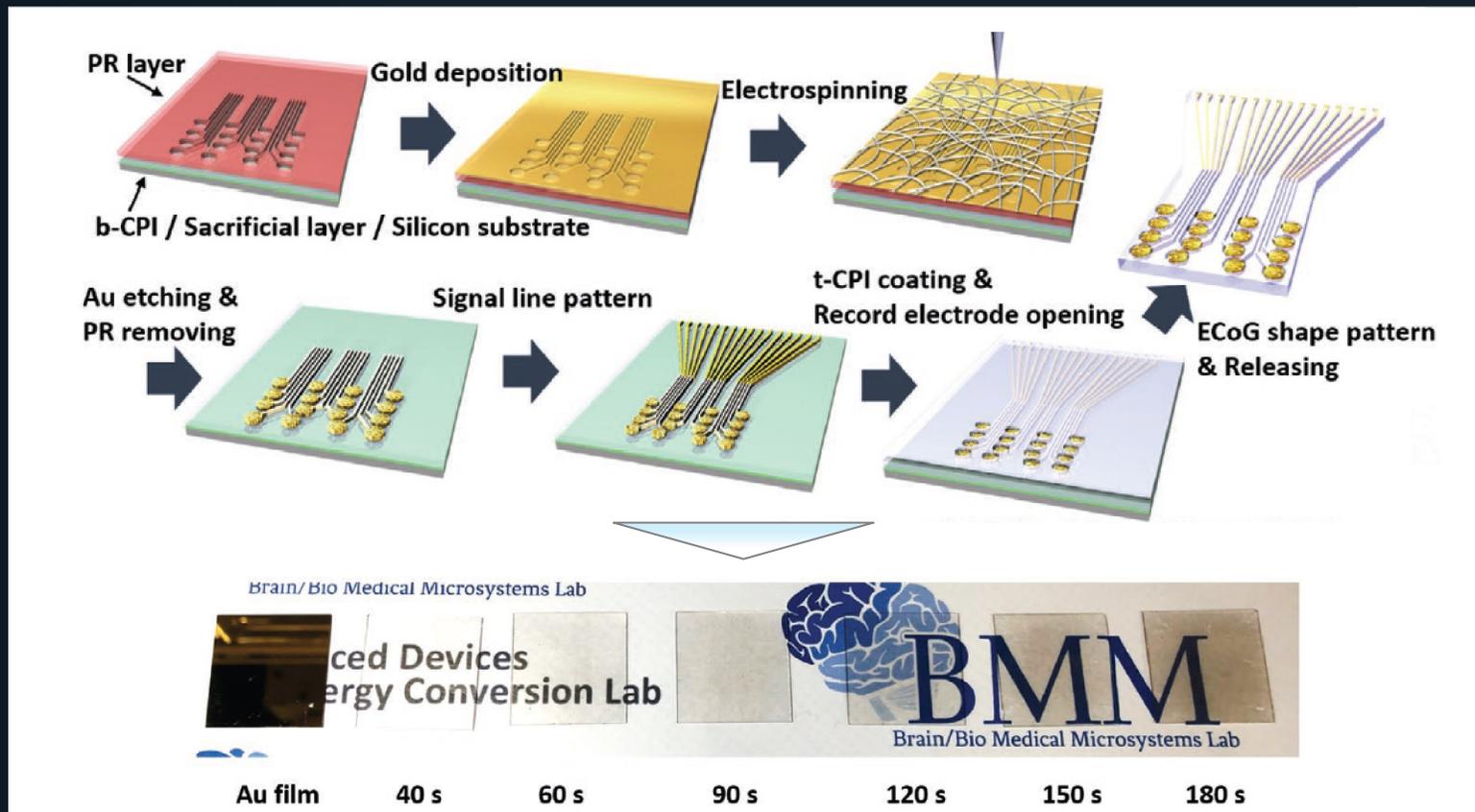
Suh & Kim, 2020 (Adv. Func. Material)



## Problem: Photoelectric artefact

- Interfere electrical recording
- Low temporal resolution

## Our approach: Use transparent electrodes



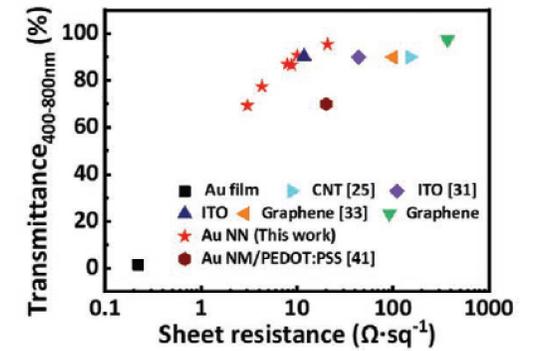
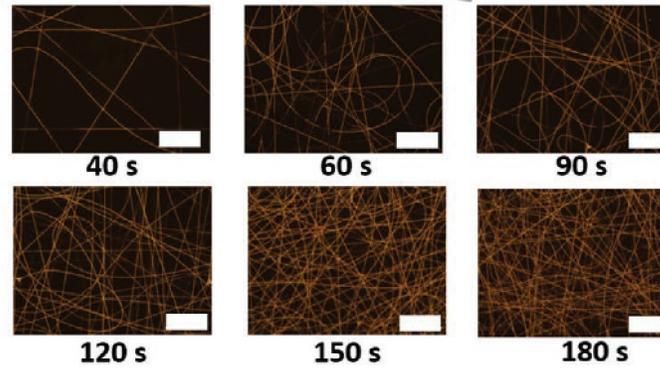
# Transparent ECoG array



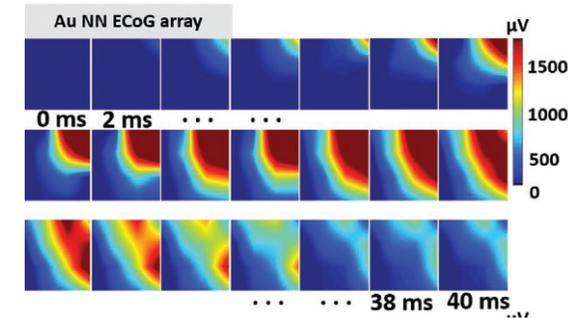
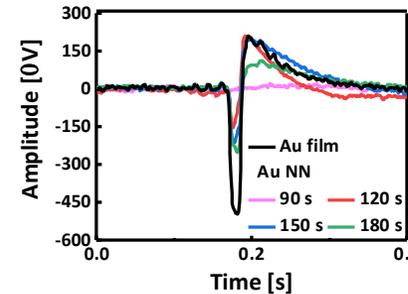
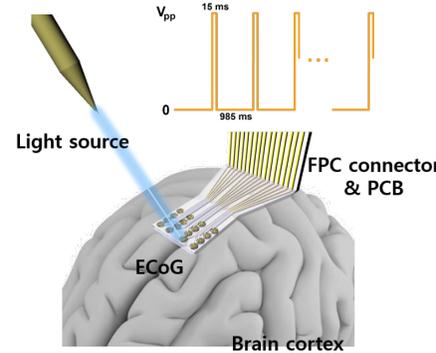
Suh & Kim, 2020 (Adv. Func. Material)



Transparent, flexible ECoG microelectrode array for optogenetics neuromodulation



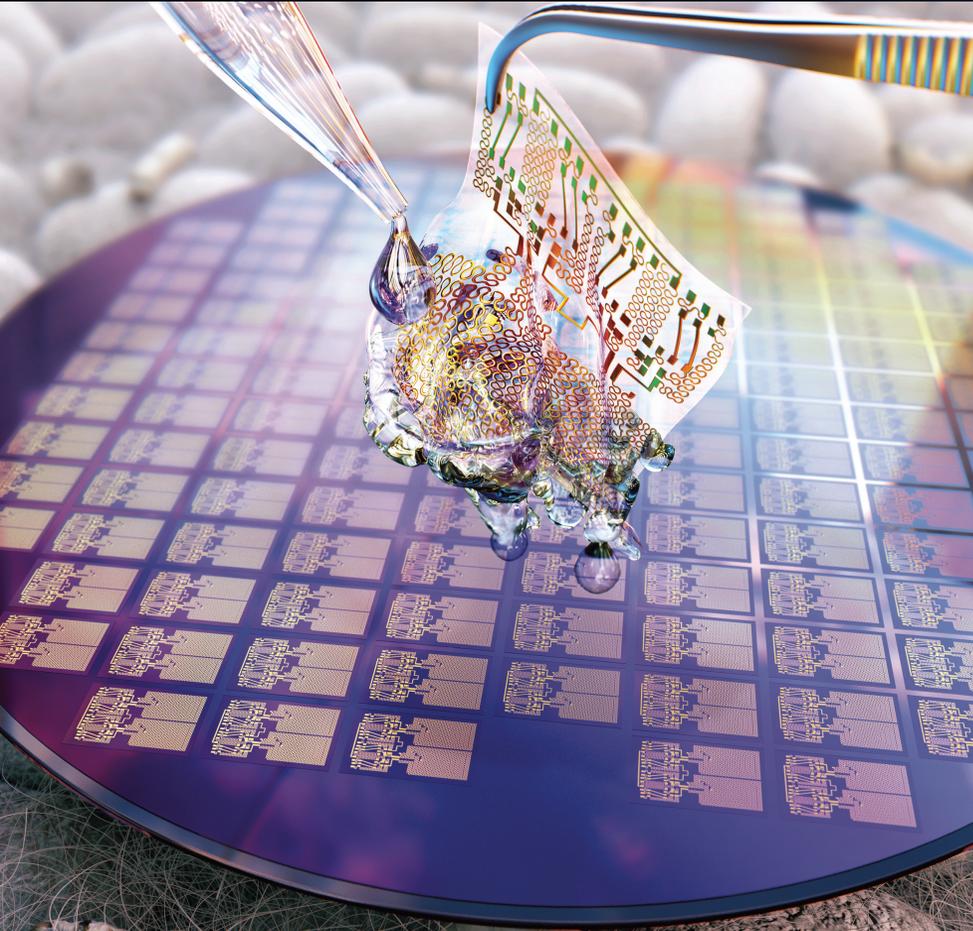
Yet, excellent electrochemical properties



# Biodegradable devices



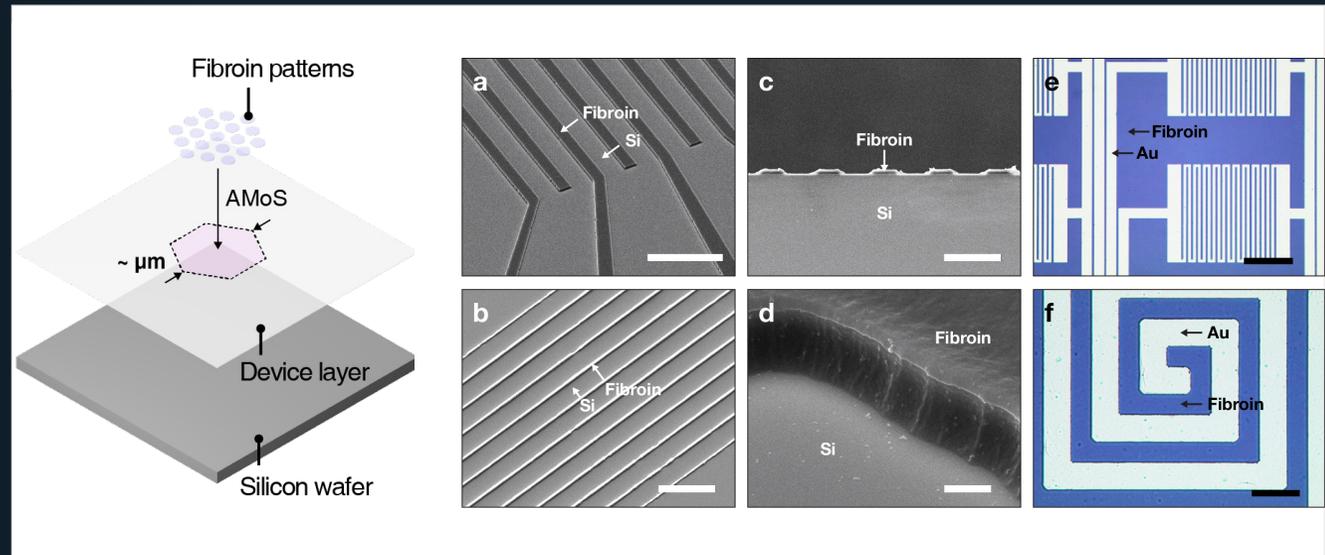
Geon, 2018 (ACS AMI)  
Geon, 2019 (AMT)



**Problem: Mass production is difficult**

Difficult to micropattern biomaterials  
Low yield (No wafer-level processing)

**Our Approach: Use hard mask to micropattern biomaterials**

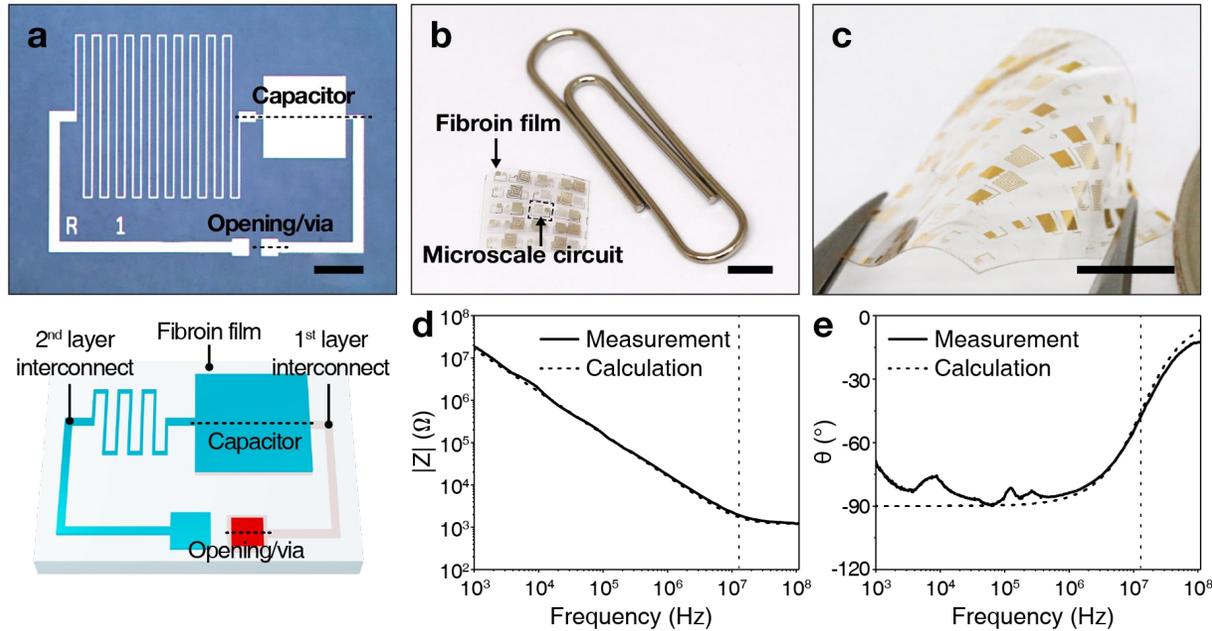


# Biodegradable devices

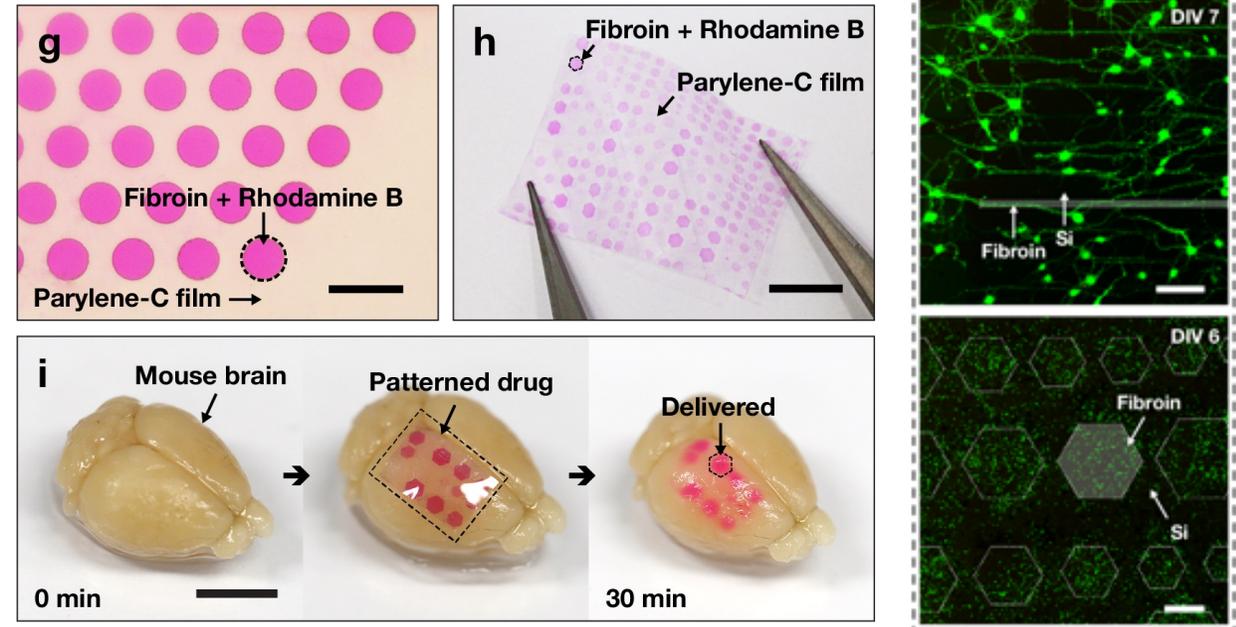


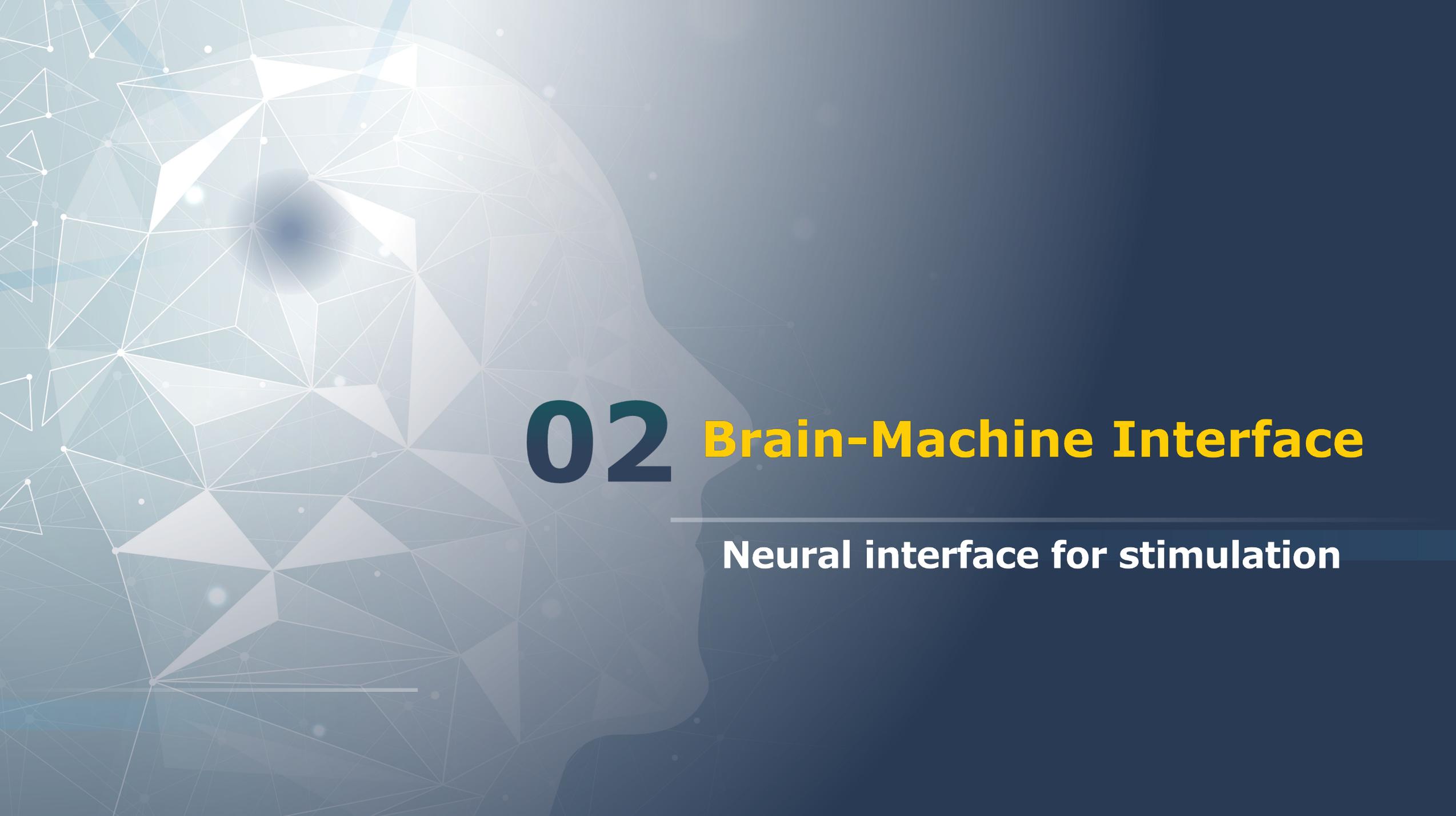
Geon, 2018 (ACS AMI)  
Geon, 2019 (AMT)

## Silk as dielectric layer



## Drug delivery application and biocompatibility



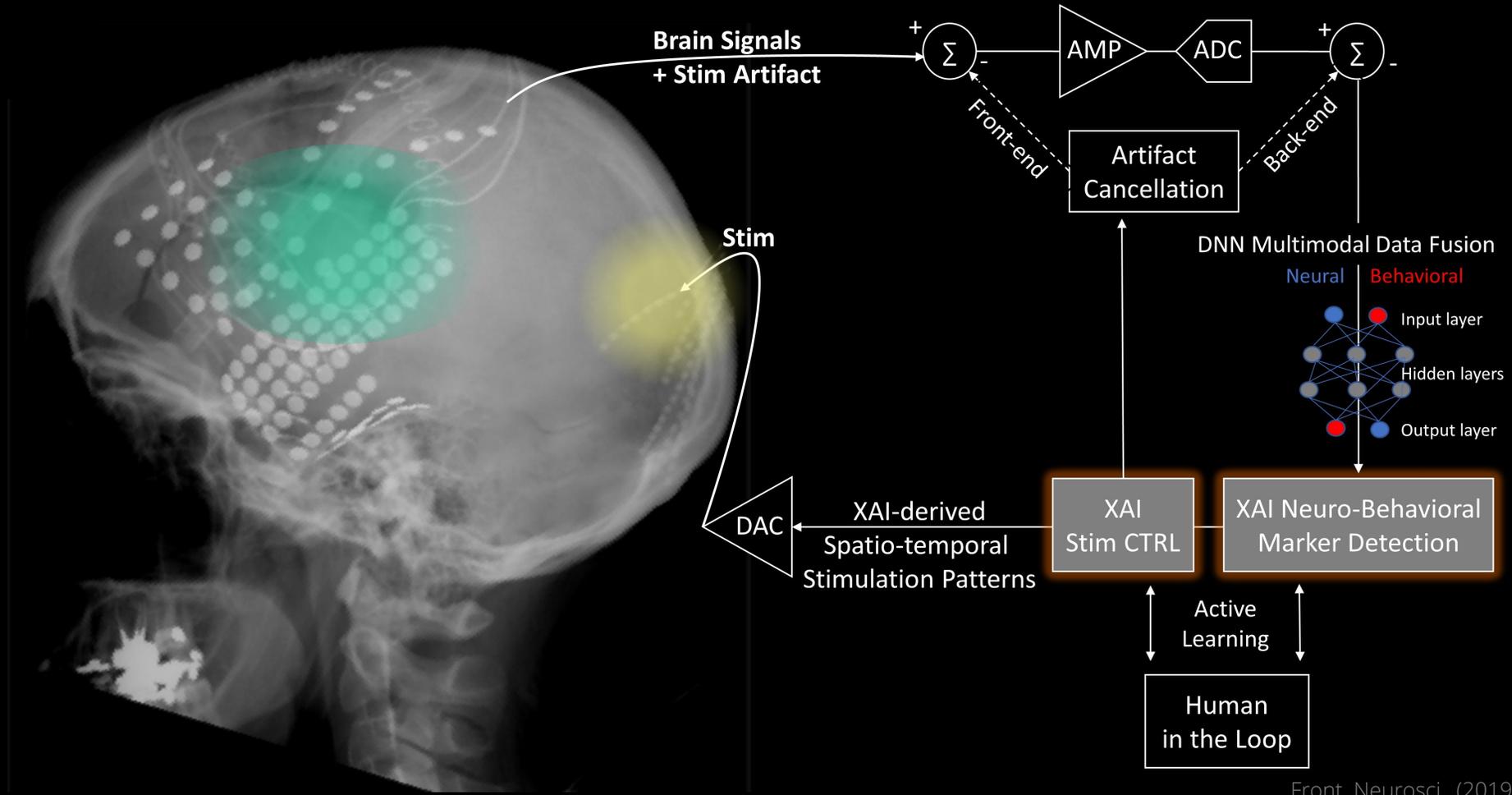


# 02 **Brain-Machine Interface**

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**Neural interface for stimulation**

# Brain as a "black box"



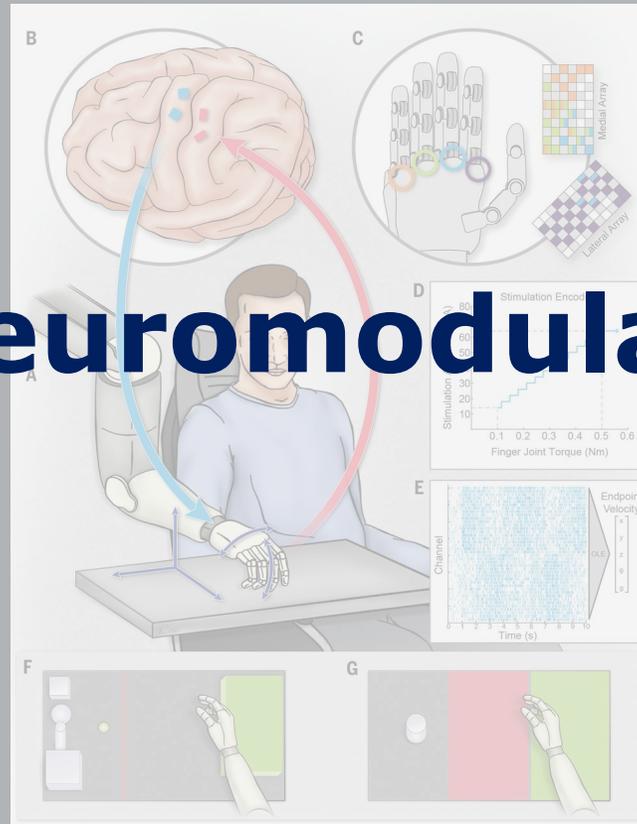
Front. Neurosci., (2019)

# Brain Machine Interface - Stimulation

## Therapeutics

**DEEP BRAIN STIMULATION**

- Addictions
- Anorexia nervosa
- Cluster headache
- Alzheimer's disease
- Refractory Aggression
- Essential Tremor
- Obsessive compulsive disorder
- Restless Leg Syndrome
- Treatment-Resistant Depression
- Dystonia
- Chronic pain
- Obesity
- Drug-resistant refractory epilepsy



# Neuromodulation

## Brain-to-X communications



### TELEPATHIC SOLDIERS

A soldier wears a headset that picks up on behavioural brain signals, this connects to a computer device in their pocket

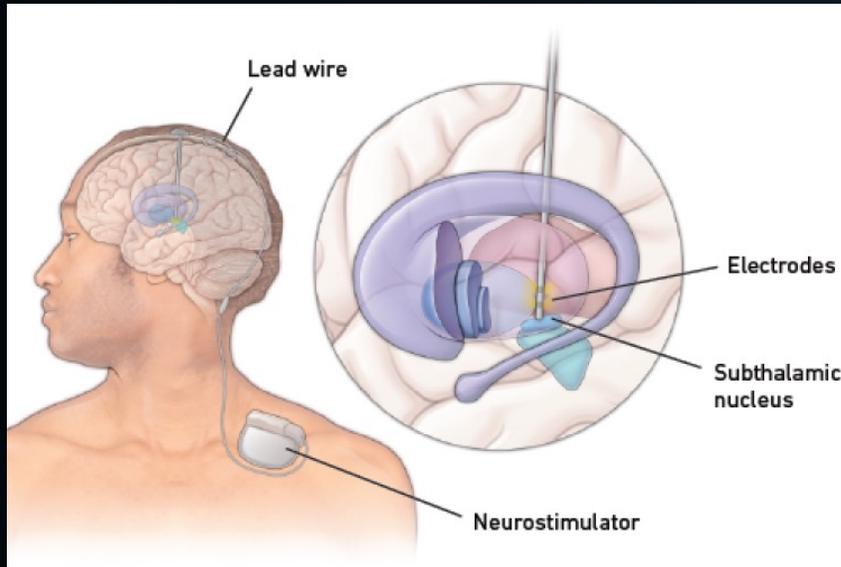
The small computer decodes the brain signals and sends an interpretation to the computer of a soldier nearby

Their computer relays the other soldier's brain signals to them via their headset and the two soldiers have communicated telepathically

\* DOI: 10.1016/j.neurop.2022.03.001

# What is **neuromodulation**?

Deep brain stimulation  
Parkinson's disease



\*templehealth.org

Transcranial magnetic stimulation  
Depression



\*primepsychiatrymd.com

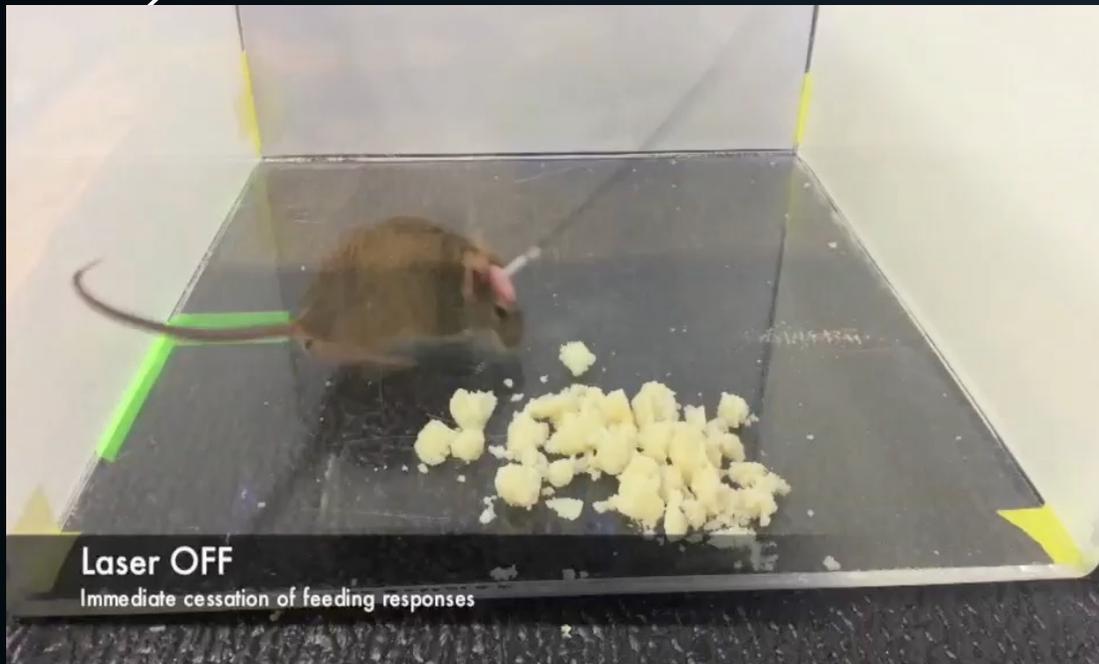
Electrical stimulation  
Migraine relief: electroceutical



\*ybrain.com

# Artificial input to neural circuits to modulate the activities

Orchestrating feeding behavior (obesity)



Science (2013) | DOI: 10.1126/science.1241812

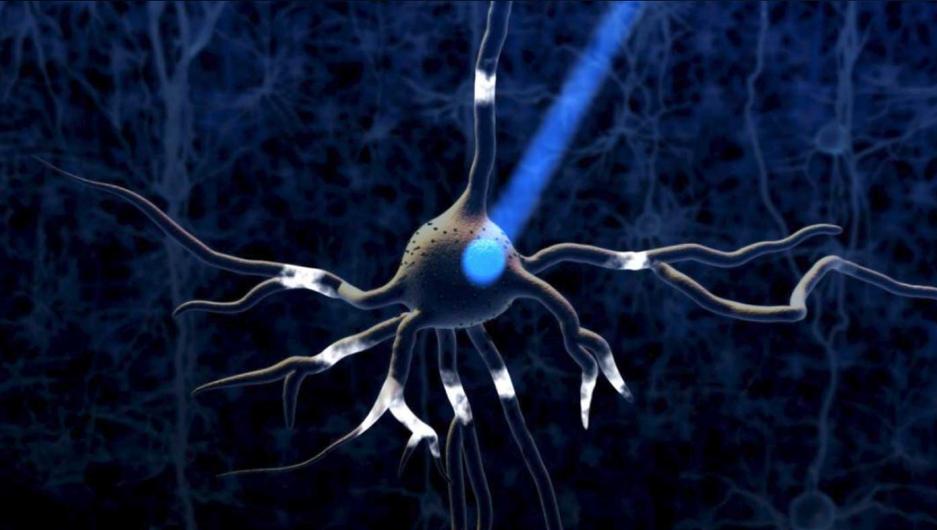
Fiberoptic Control of Locomotion in ChR2 Mouse

J. Neuroscience (2007)

Wireless control of locomotion (motor)

# Brain stimulation modalities

Optical stimulation based on optogenetics



Credit: MIT McGovern Institute

Deep brain stimulation (DBS)



<https://www.neurosciencesclinics.com/>

Transcranial magnetic stimulation (TMS)



<https://www.globalinfresearch.com>

Cell-type specific



Spatial resolution

Broad

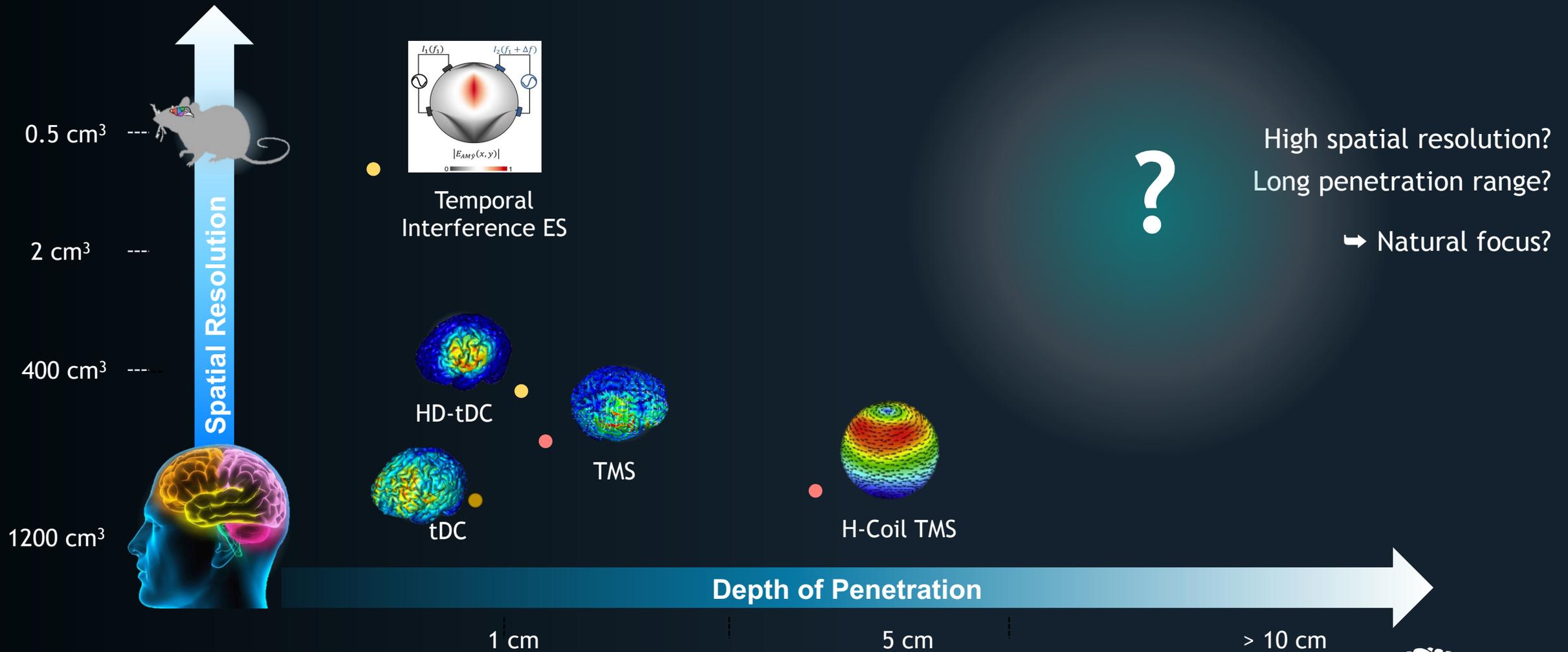
Invasive

Clinical applicability

Non-Invasive



# Non-invasive brain stimulation methods



# Ultrasound

Sound at frequency  $\geq 20\text{kHz}$

## Unique characteristics

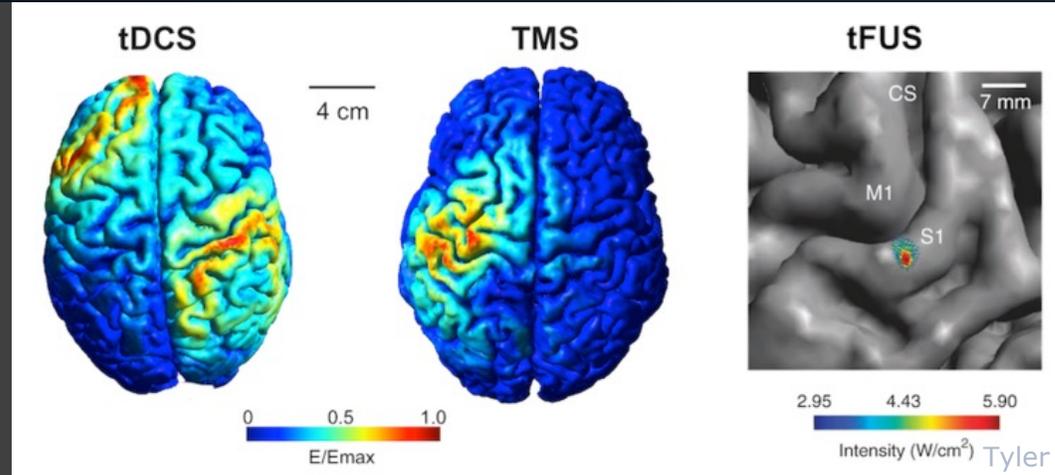
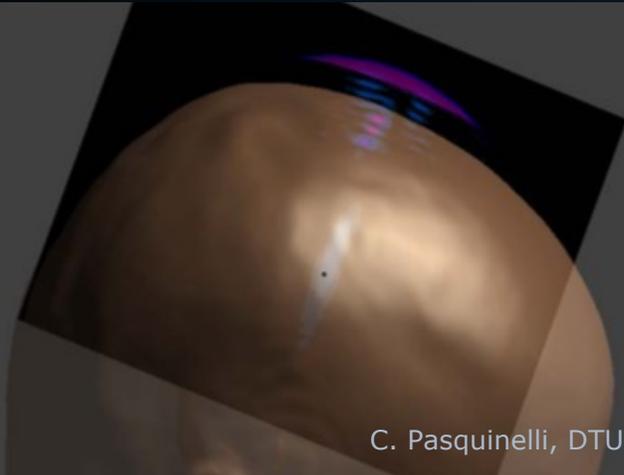
- Non-invasive
- Ability to focus and steer
- Long penetration range



## Biomedical Applications



# Ultrasound neuromodulation



## Advantages

- Deep brain stimulation
- High spatial resolution
- Non-invasiveness

## Challenges

- Unknown mechanism
- Skull barrier
- Targeting with accuracy

# Healing with sound

## Health

### How ultrasound therapy could treat everything from ageing to cancer

Ultrasound is most familiar to us as a non-invasive imaging technology used during pregnancy – now it is in clinical trials as a powerful new tool for treating all sorts of medical conditions

By Kayt Sukel

📅 14 June 2023



<https://www.newscientist.com/>

## Drug delivery



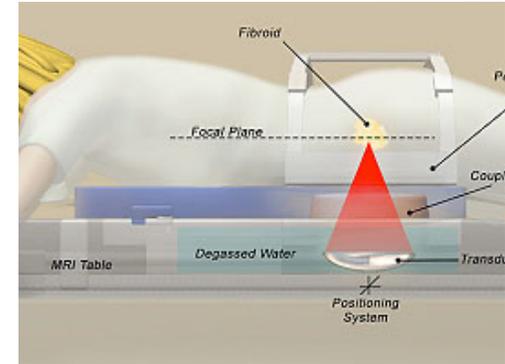
InSightec ExAblate Neuro

## Ultherapy



\*HIFU: High Intensity Focused Ultrasound

## HIFU



InSightec ExAblate Body

## Potential Applications

- Destroy body fat
- Treat back pain
- Tightening skin
- Improving immune system

# Therapeutic US for brain



Thermal effects  
Cavitation effects



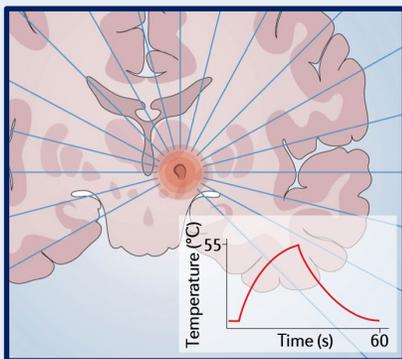
Mechanical effects  
- Acoustic radiation forces  
- Cavitation



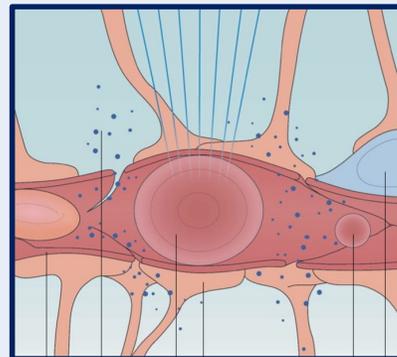
HIFU

LIFU

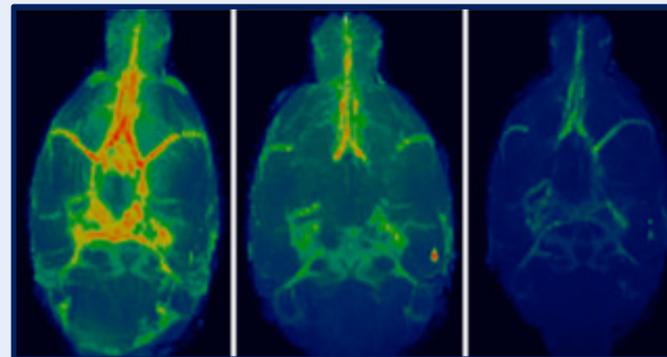
## Thermoablation Histotripsy



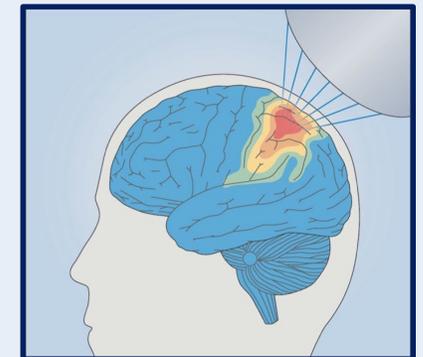
## BBB Opening Drug Delivery



## Glymphatic Clearance



## Neuromodulation / Brain Stimulation



# Brief history

## First demonstration

2010

- Tyler, Mouse (*Neuron & Nature Protocols*)
- Yoo, Rabbits, Rats, (*Neuroimage & UMB*)
- Target: Motor

## NHP

2013

- Aubry, Monkey (*Curr. Biology*)
- Badal, Human (*Brain Stimulation*)
- Target: PFC, Cognitive

## Human

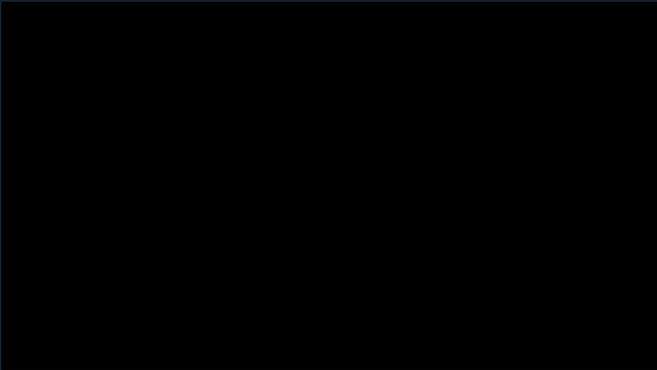
2014

- Tyler, Human (*Nat. Neuroscience*)
- Target: Somatosensory

2015

## MR Guided

- Yoo: MR Guided (*Sci. Rep.*)



KAIST BMM

## Mechanisms & Parameters

2016

- Konofagou, .9 MHz (*Med. Phys.*)
- Cui, Ion Channels (*Sci. Rep.*)
- Wu, 5 MHz (*Sci. Rep.*)
- He, EEG (*IEEE TBME*)

## + Recording & Simulation

2017

- Yoo, B-B interface (*PloS One*)
- Zheng, LFP measurement (*IUS*)
- Treeby, Simulation (*JASA*)

2018

## Freely Moving

- Lee, CMUT (*Brain Stimulations*)
- Yoo, Piezo

## Indirect Pathways

- Lim, Indirect pathways (*Neuron*)
- Tsao, Indirect pathways (*Neuron*)

2019

## Used as neural circuit verification

- Aubry: Macaque (*Nat. Neuroscience*)

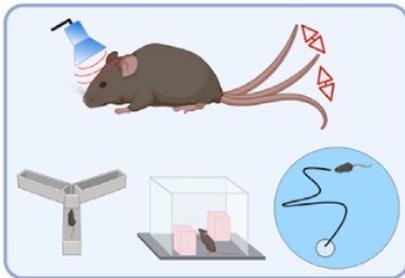
2020

## Therapeutic Effects

- Kim: Stroke

# Recent works on US neuromodulation

## Rodents

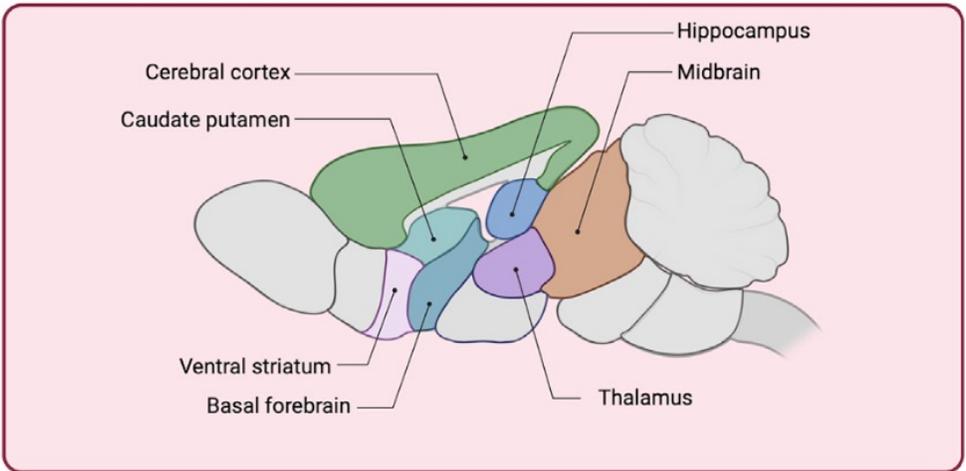


**Motor cortex**

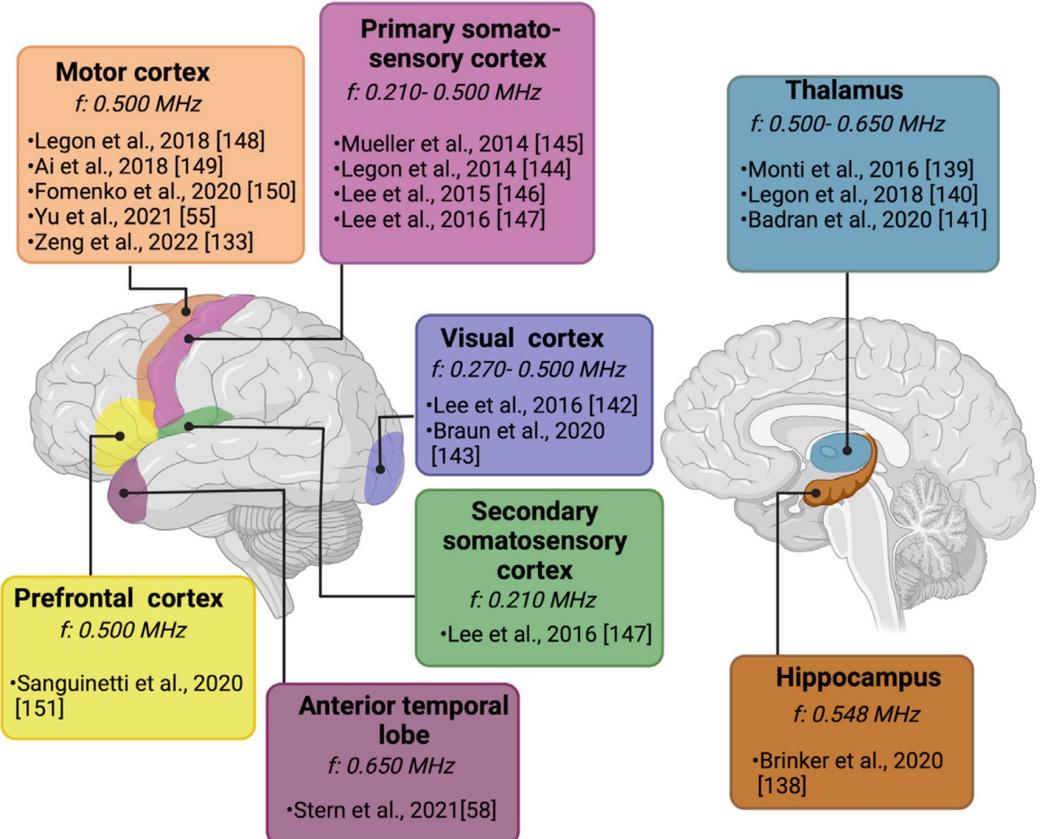
- Cui et al., 2019 [56]
- Oh et al., 2019 [20]

**Hippocampus**

- Shin et al., 2019: ↑ MWM [79]
- Shen et al., 2020: ↑ MWM, Y-maze, step-down avoidance [39]

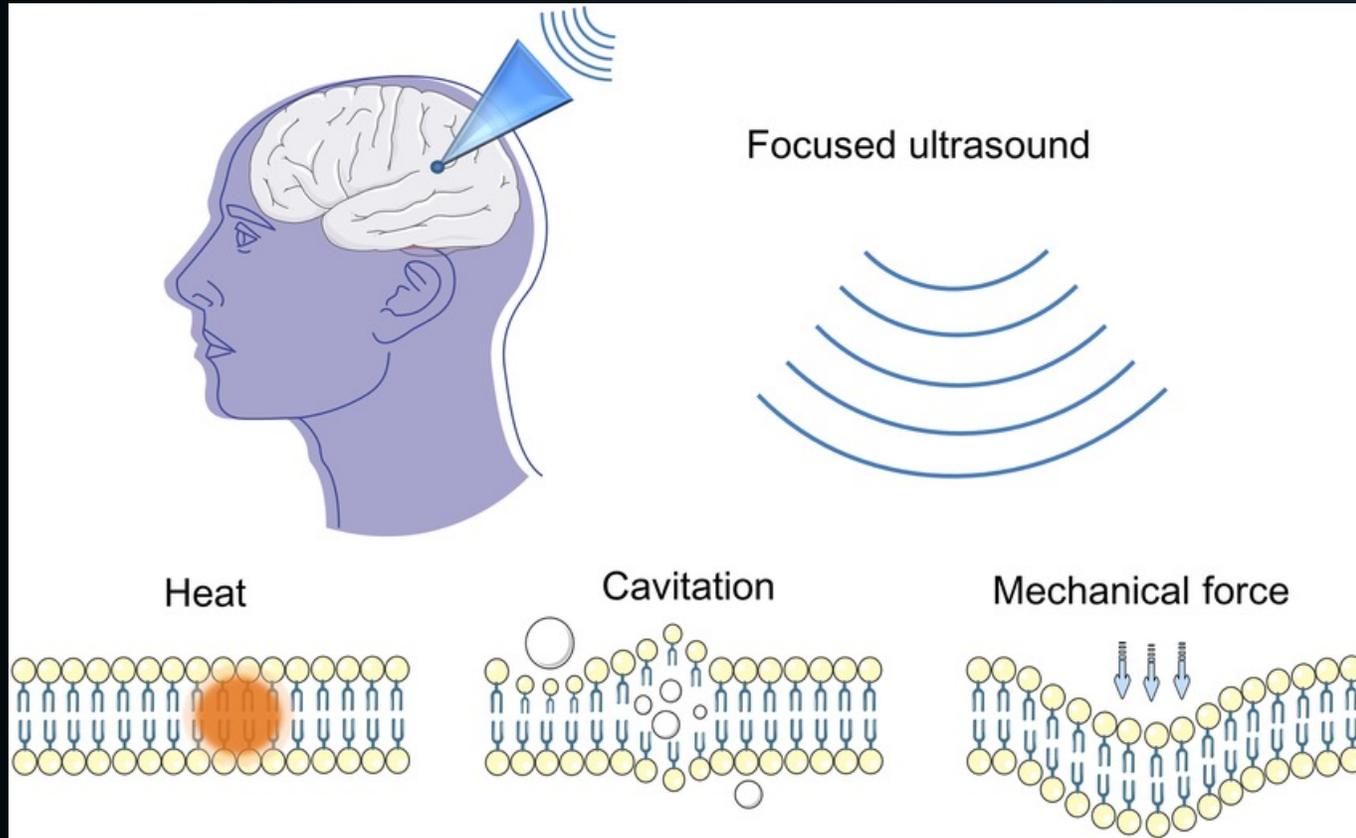


## Human

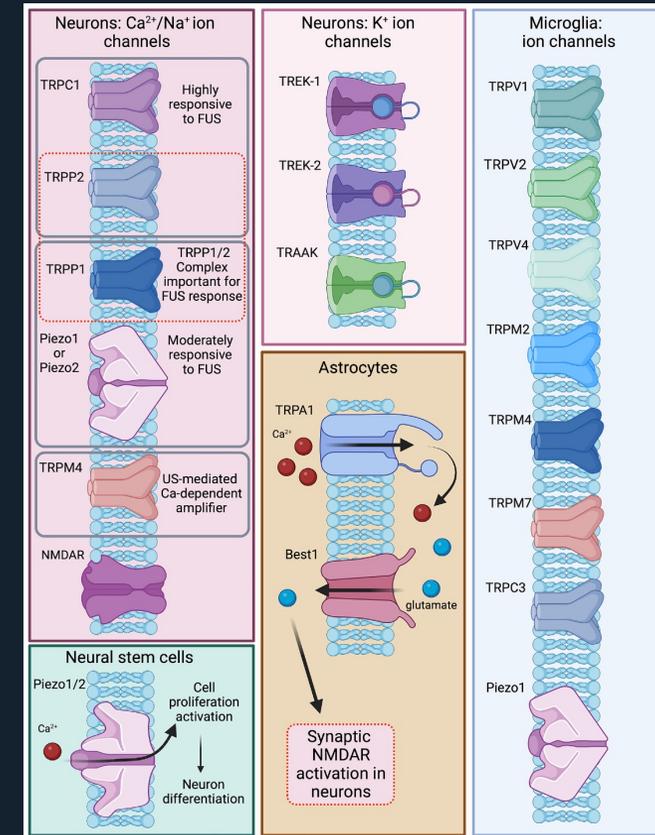


Neuron, 111, 2023

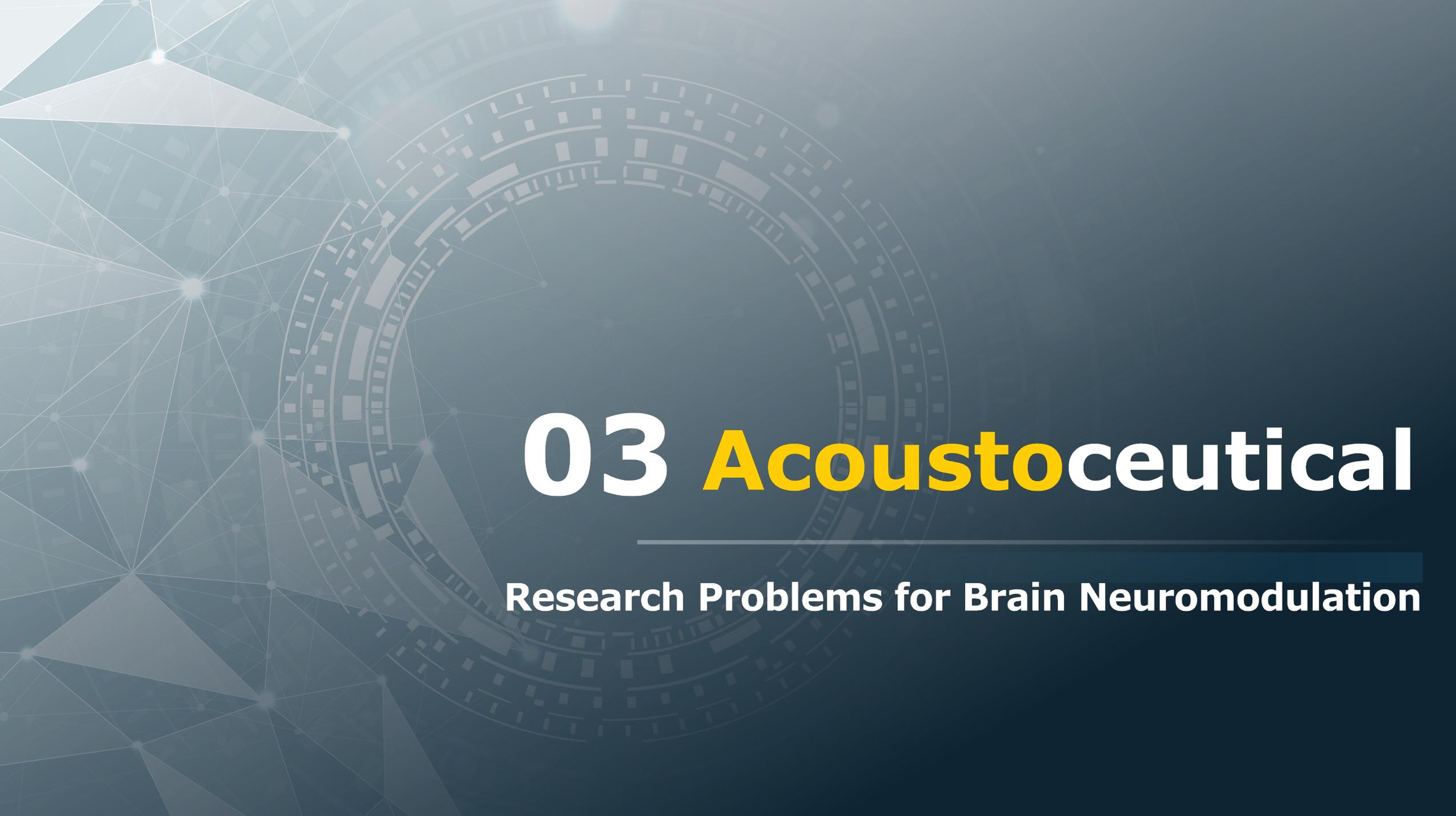
# Mechanisms for ultrasound neuromodulation



Frontiers in Behavioral Neuroscience 15, 2022a



Neuron 111, April 19, 2023

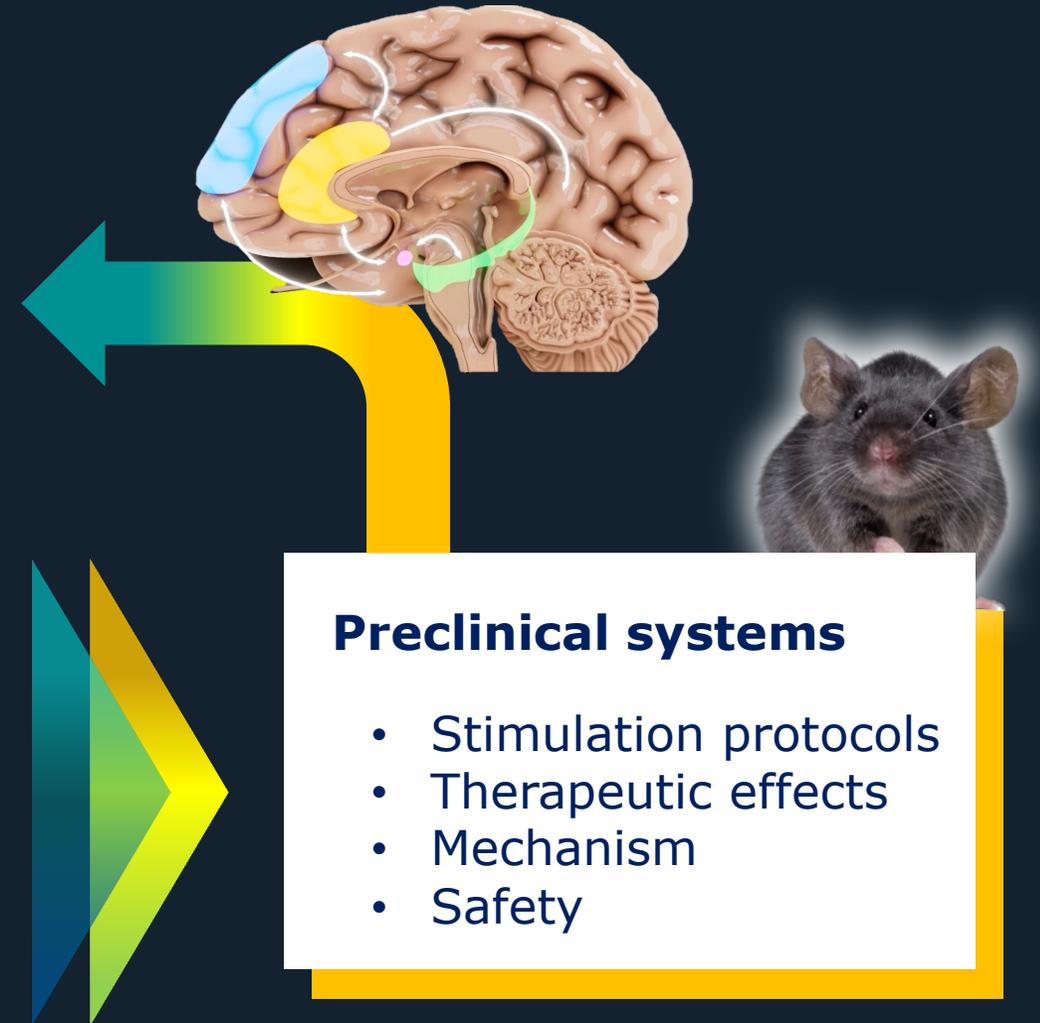
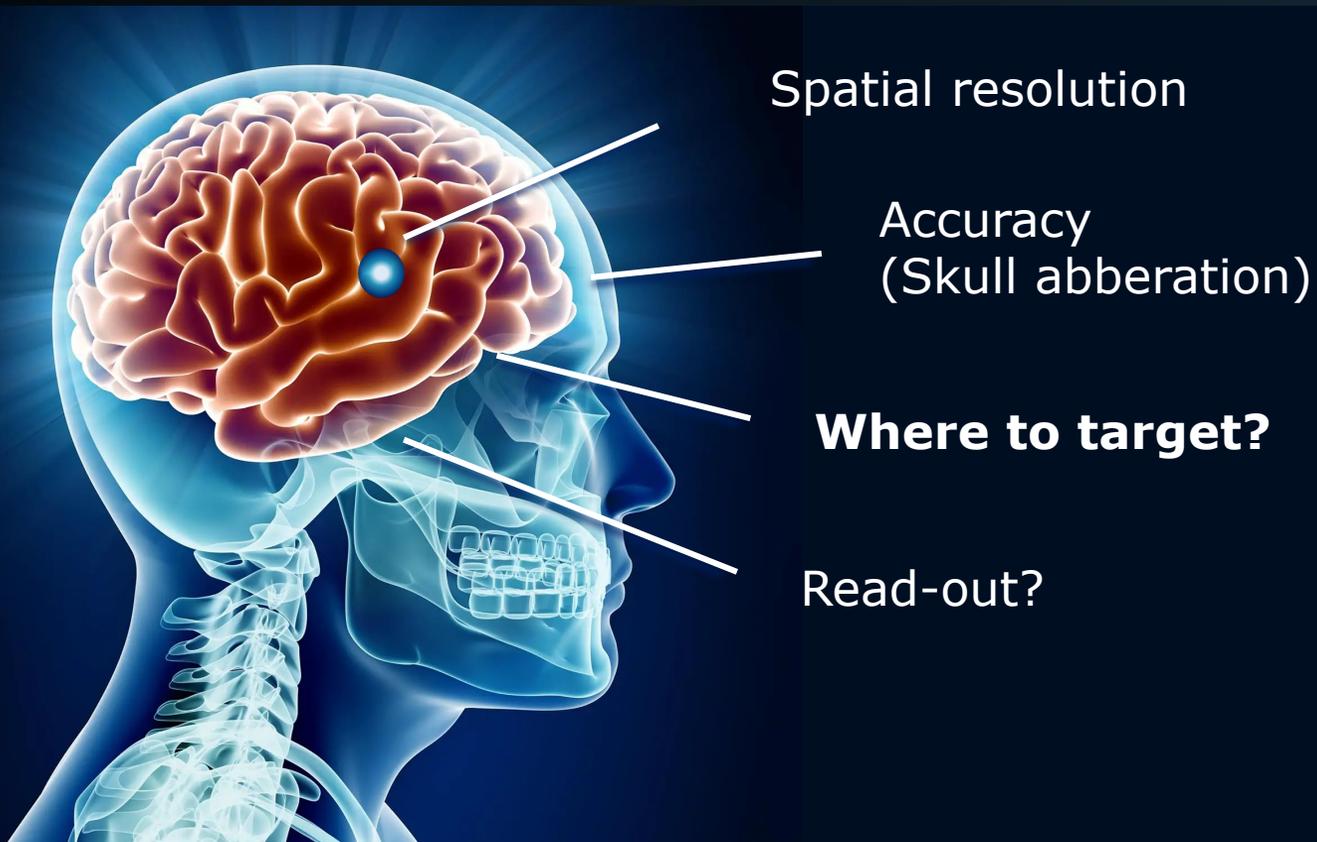
The background features a dark blue gradient with a complex geometric pattern. On the left, there is a network of white lines connecting various points, some of which are highlighted with small white circles. In the center, a large, faint circular pattern resembling a stylized eye or a target is visible, composed of concentric rings and radial lines. The overall aesthetic is technical and futuristic.

# 03 **Acousto**ceutical

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Research Problems for Brain Neuromodulation

# Research questions



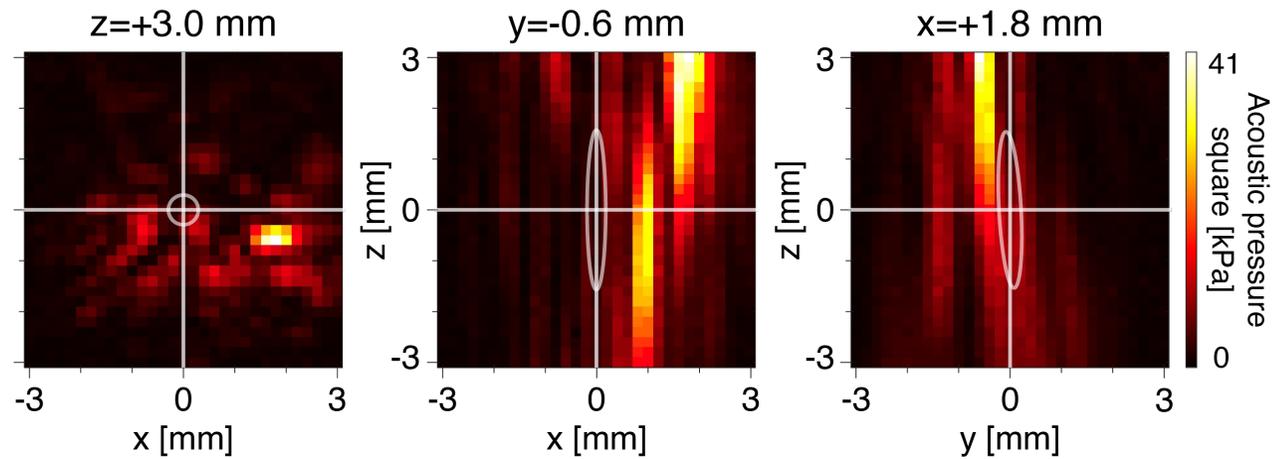
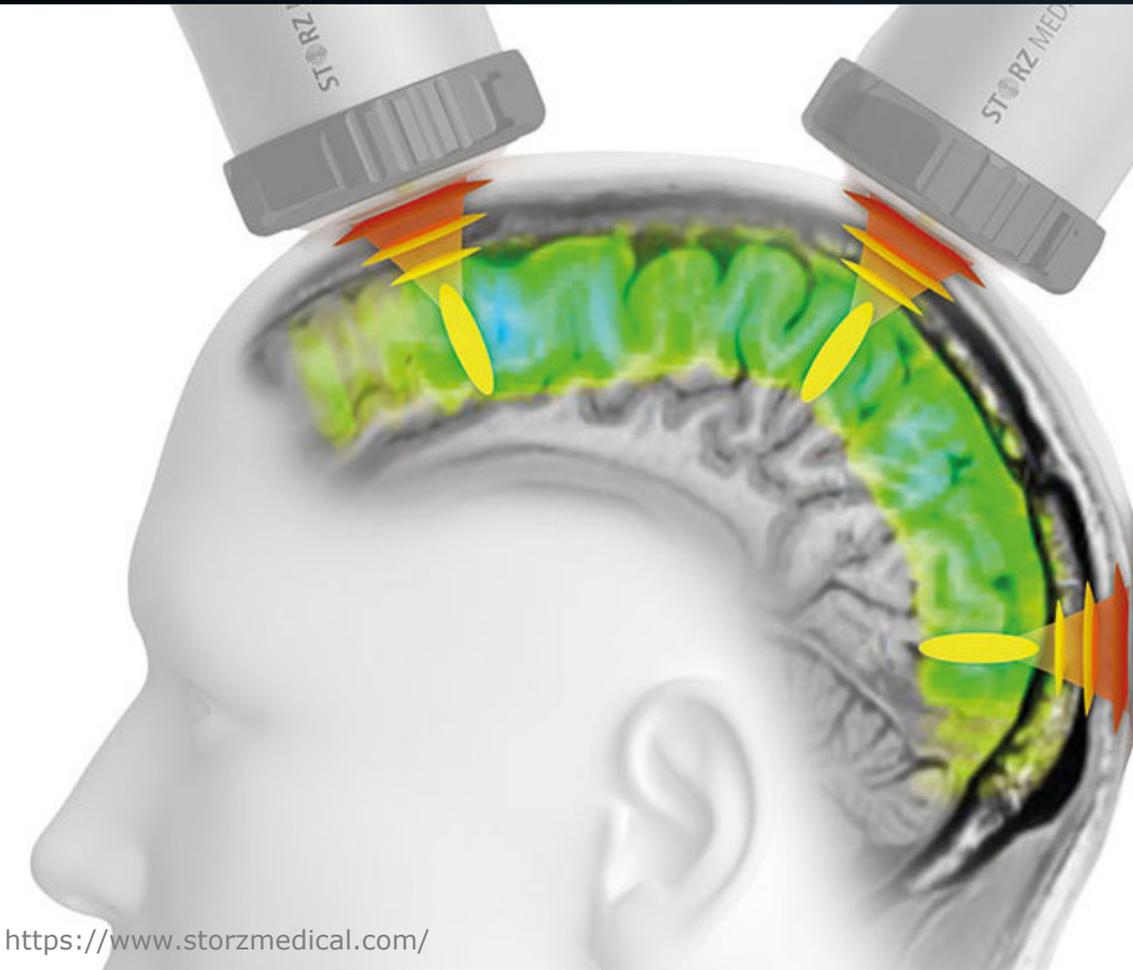
# Skull aberration problem



Geon, 2023 (M&N)

## Problem: Skull Aberration

- Skull are different in shape and composition
- Beam aberrates as it enters
- Jeopardize accurate targeting



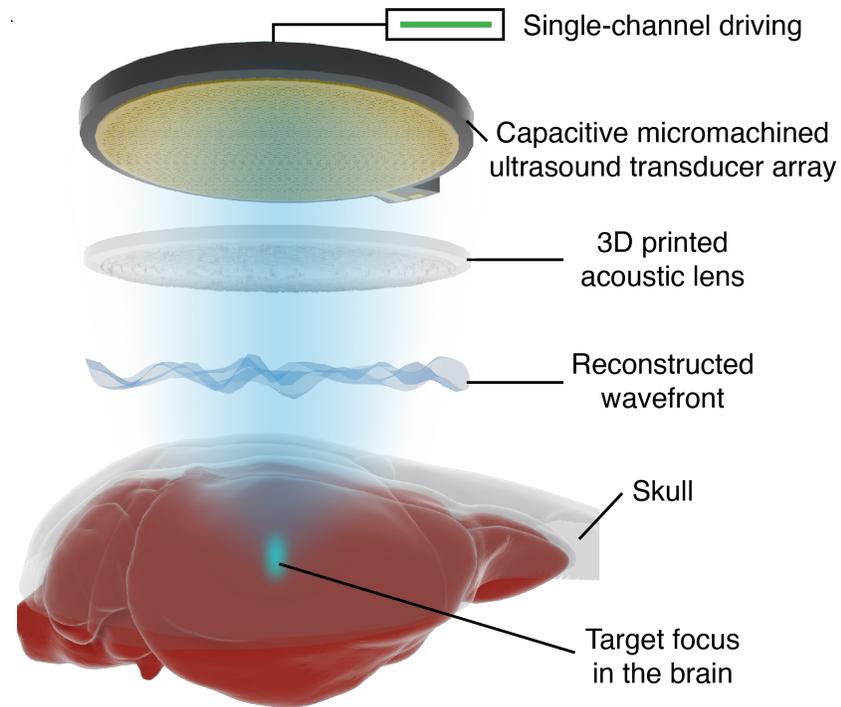
# Skull-compensated targeting



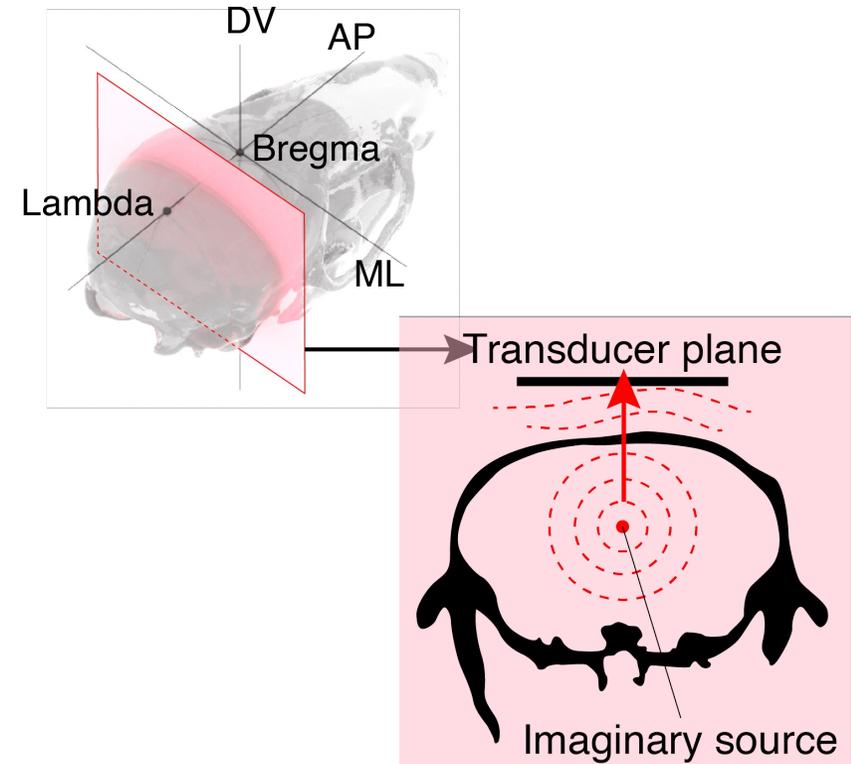
Geon, 2023 (M&N)



## Skull-compensated Acoustic Lens



## Time-reversal recording + phase conjugation mirror

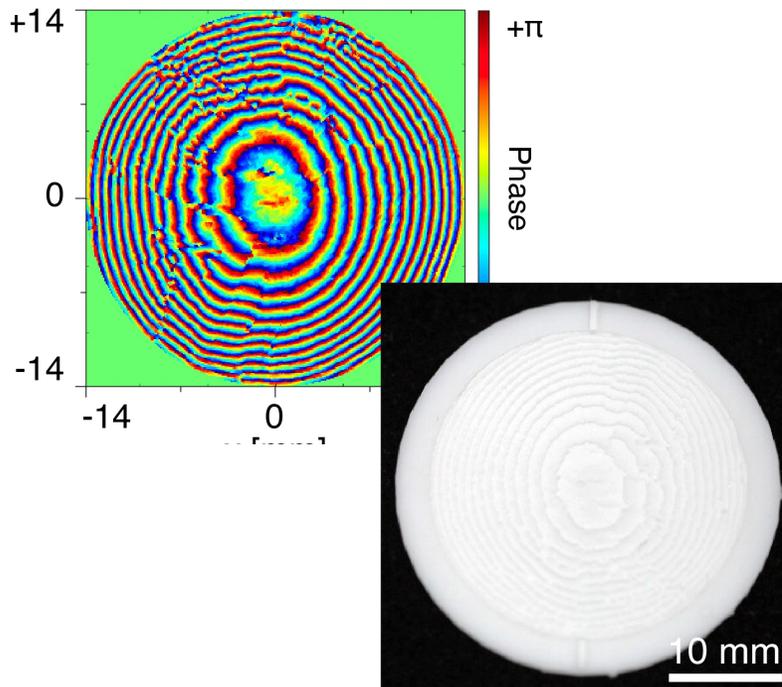


# Skull-compensated targeting

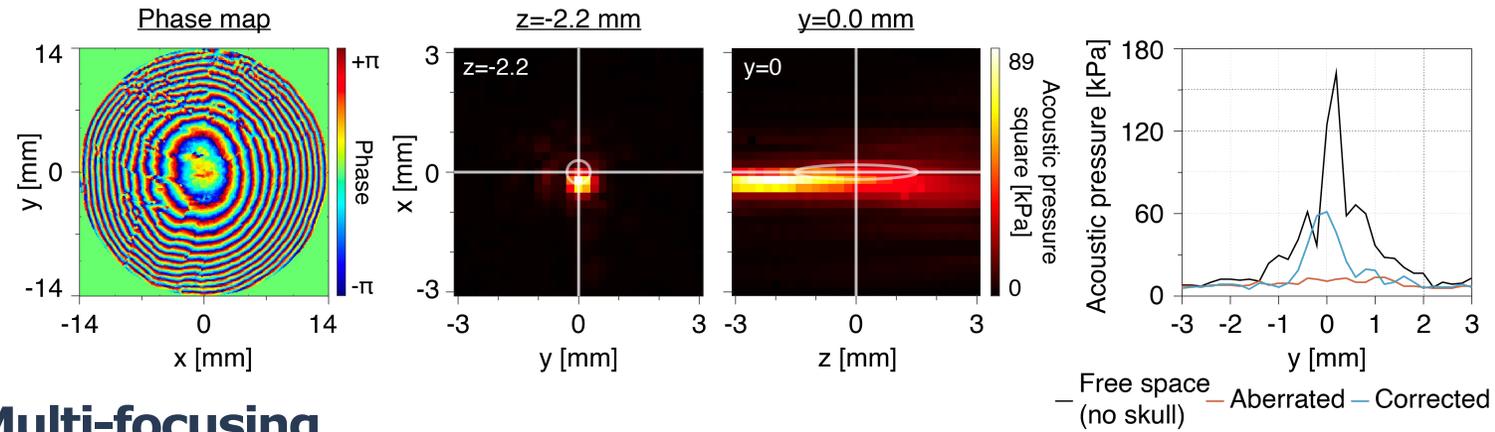


Geon, 2023 (M&N)

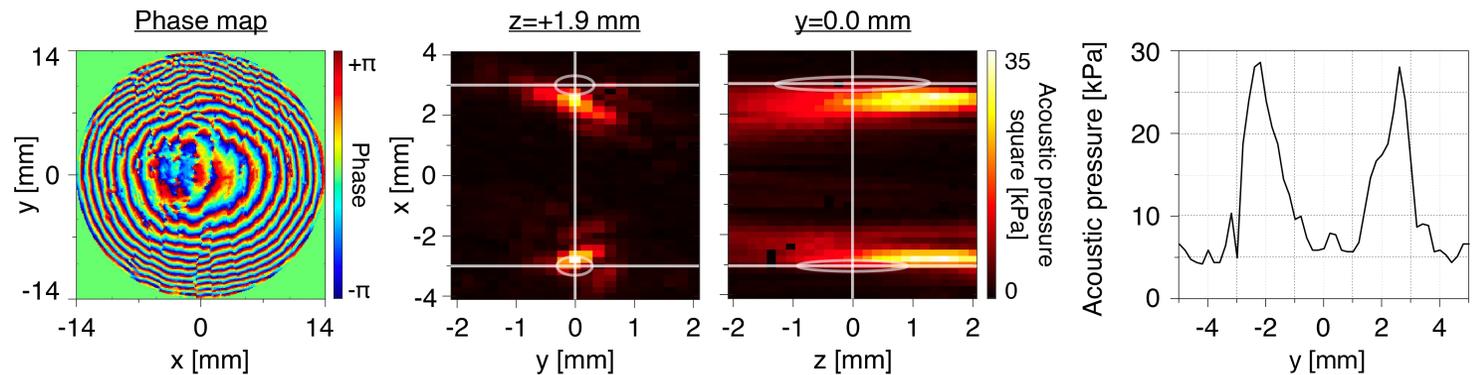
## 3D-printed Acoustic Lens



## Skull Correction



## Multi-focusing



# Therapeutic effects?



Kim, 2018  
(Brain Stimulation)

## Problem: Heavy and bulky

- Limit the range of in vivo experiments
- Fixed in stereotaxic frame
- Chronic/behavior studies are not possible

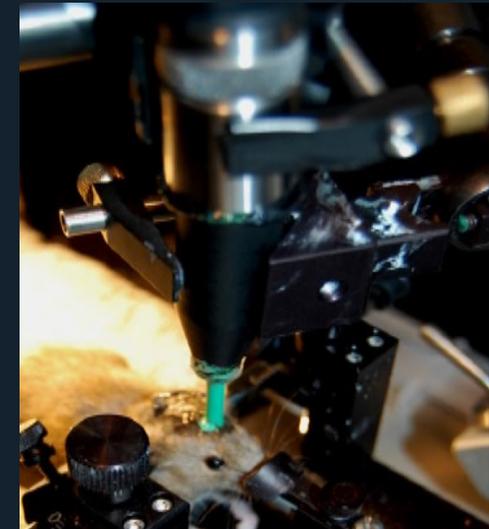


C57BL/6 Mouse  
20~30 g

Ultrasound transducer  
~100 g



Yoo et al., 2011



Tufail et al., 2010

# Freely moving preclinical system

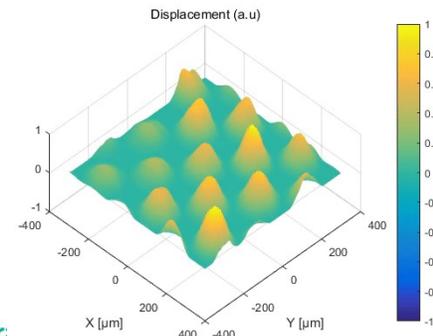
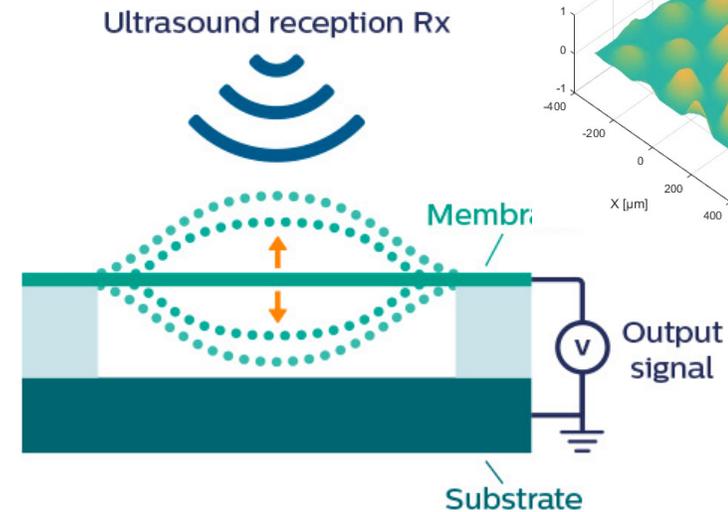
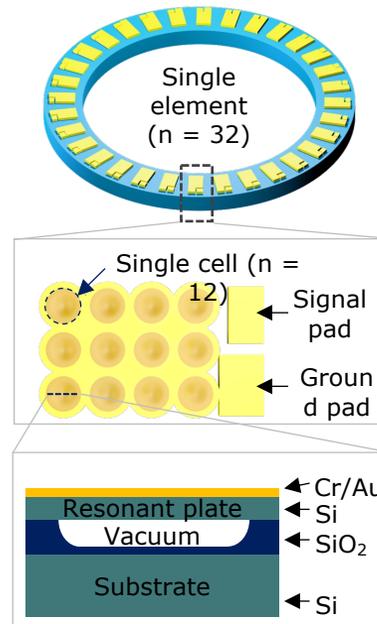


Kim, 2018  
(Brain Stimulation)



## MEMS Technology

### Capacitive Micromachined Ultrasound Transducer (CMUT)

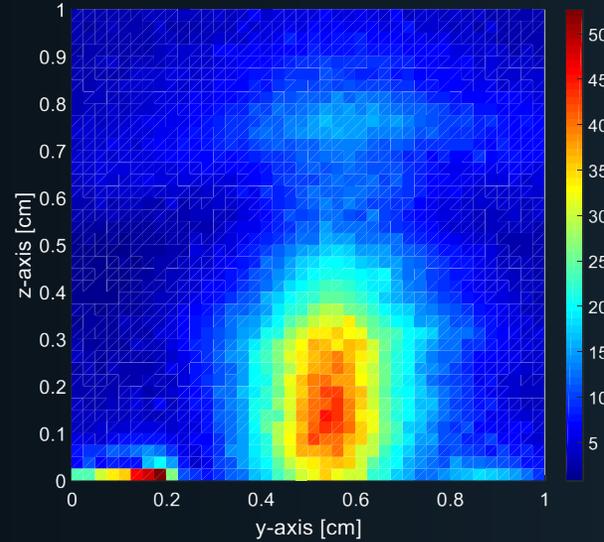
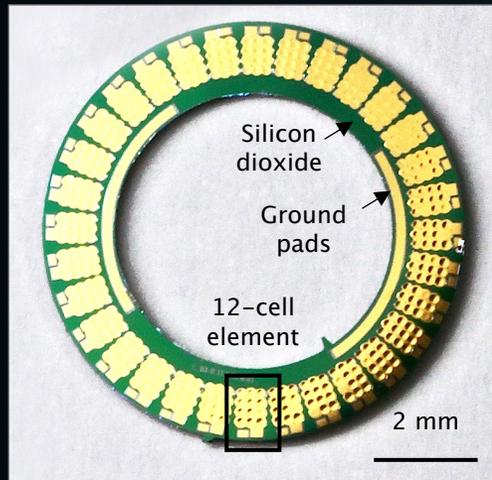


<https://www.innovationservices.philips.com/>

# Freely moving preclinical system

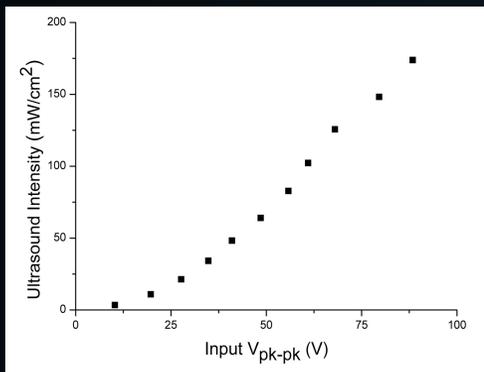


Kim, 2018  
(Brain Stimulation)



◆ Acute in vivo neuromodulation

◆ Chronic in vivo neuromodulation



Radius: 4.05 mm

Weight: 0.035 g (0.73 g w/ PCB)

Focal length: 2.25 mm

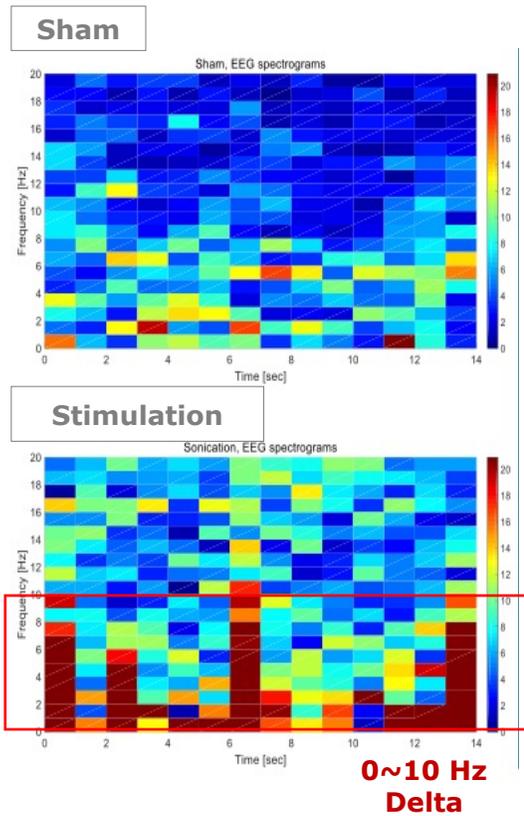
Peak intensity: 180  $mW/cm^2$

# Therapeutic effects?



Jo, 2022  
(Advanced Science)

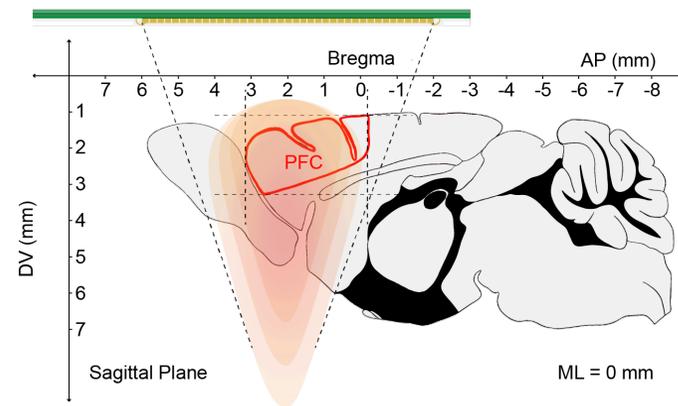
## During wake: Increase in delta wave



## In vivo protocols

- EEG implant
- 7 days Adaptation
- Wake: recording
  - Sham / Stimulation
- Day 1 • Recording
  - 10 am – 8 pm
- Day 2 • Sham / Stimulation
  - 10 am – 8 pm
  - Target: PFC
  - Stimulation at NREM
- Day 3 • Recording
  - 10 am – 8 pm
- Day 4 • Recording
  - 10 am – 8 pm

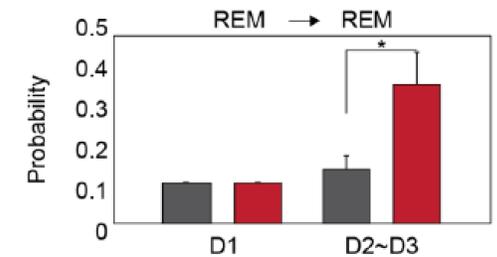
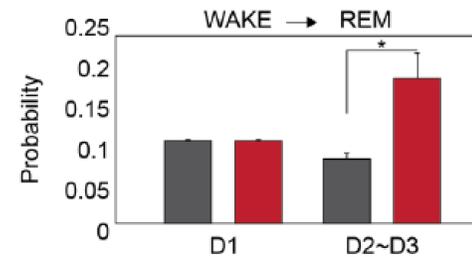
## Brain target: PFC



Rodent Prefrontal cortex (PFC):  
 -- prelimbic area (PrL)  
 -- infralimbic area (IL)  
 -- anterior cingulate area (Cg1,2)



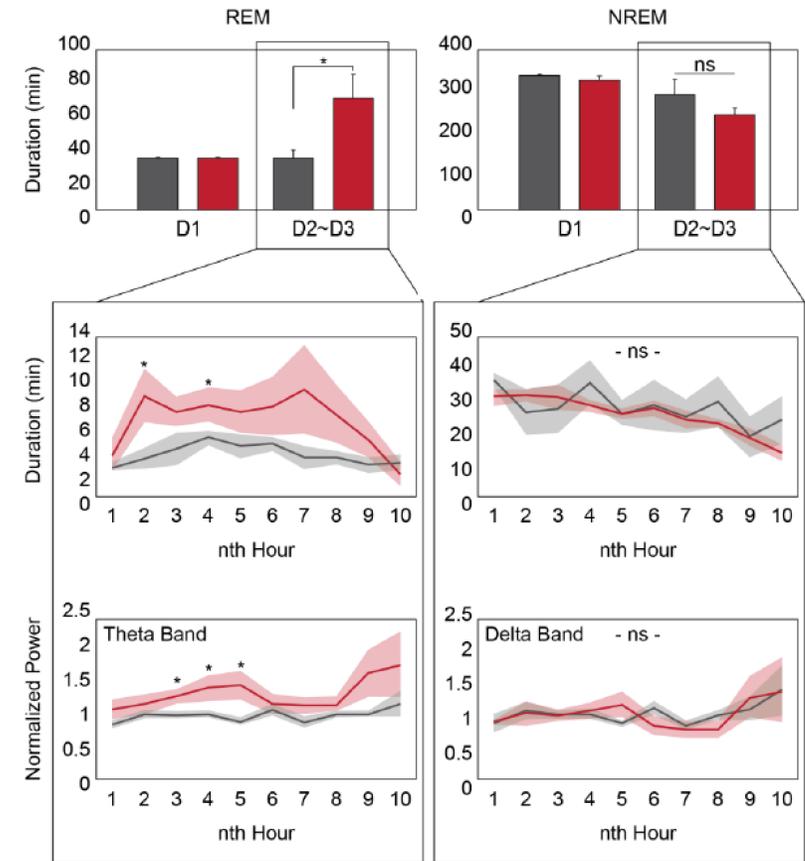
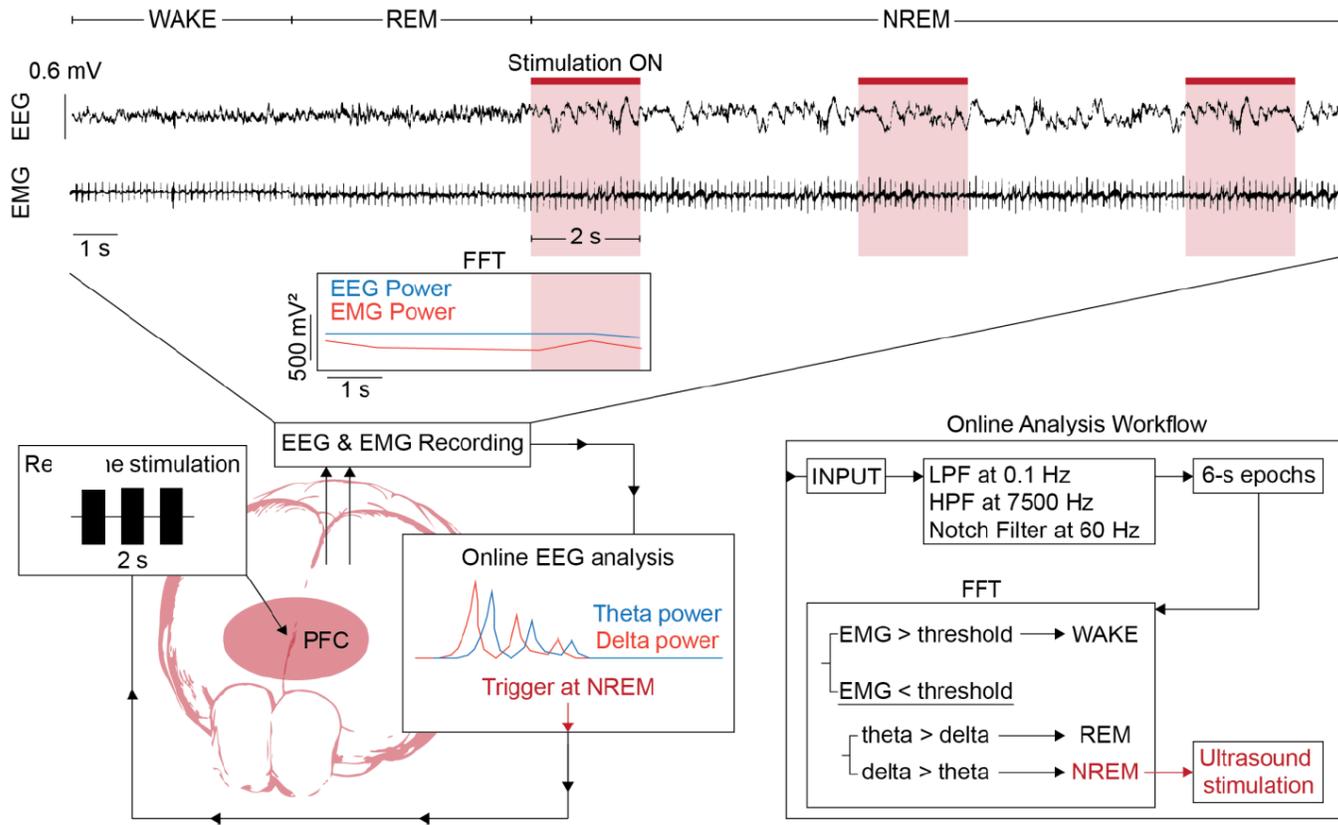
## Results



# Sleep neuromodulation



Jo, 2022  
(Advanced Science)

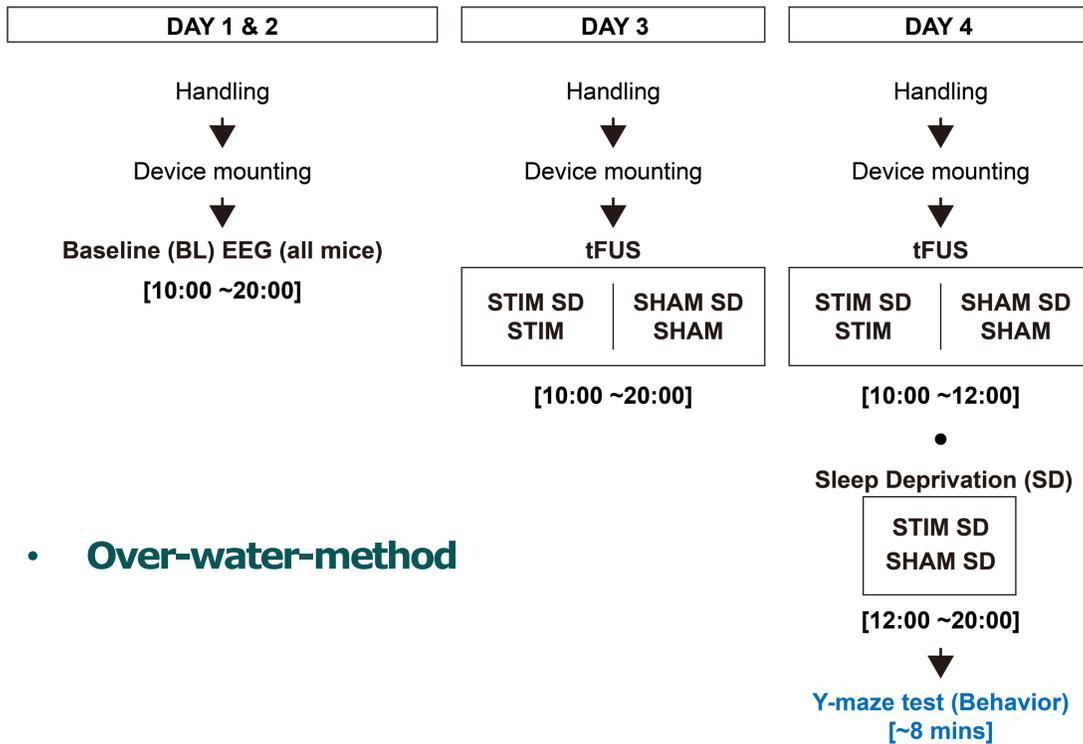


# Effects on memory consolidation

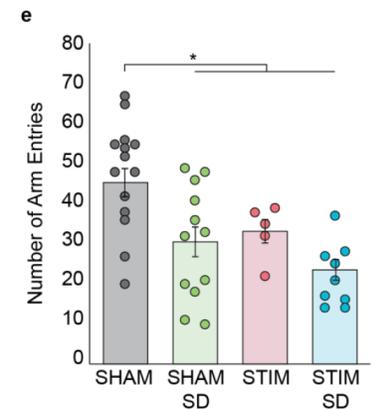
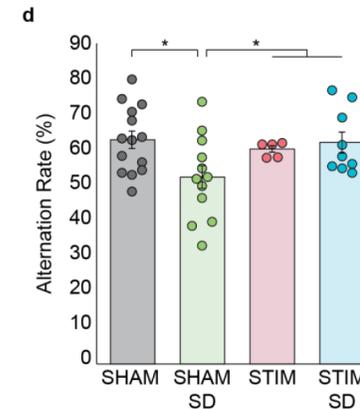
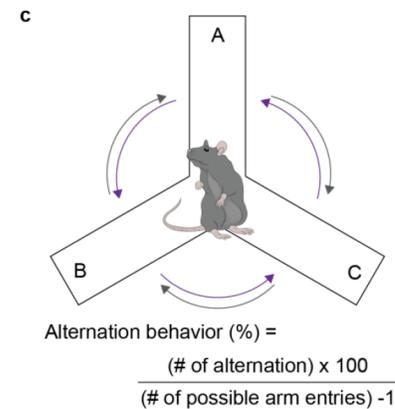
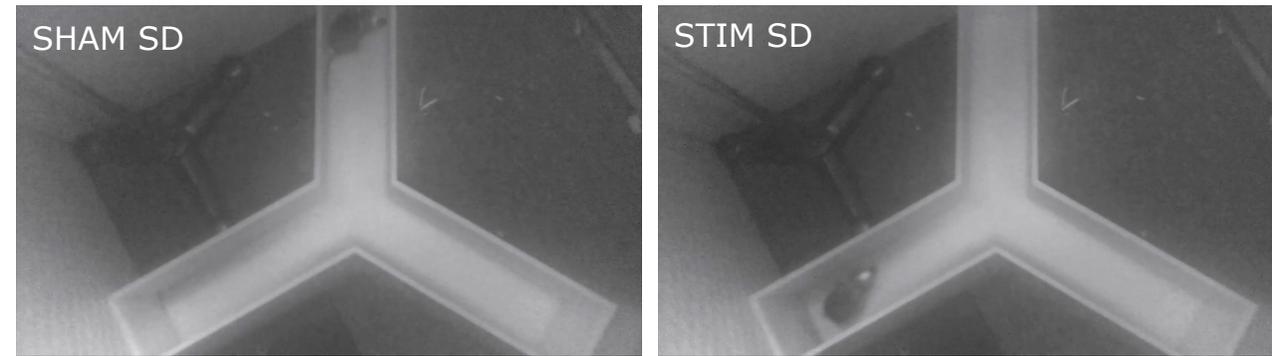


Jo, 2022  
(Advanced Science)

## Sleep deprivation (REM SD model)



## Y-maze behavioral studies





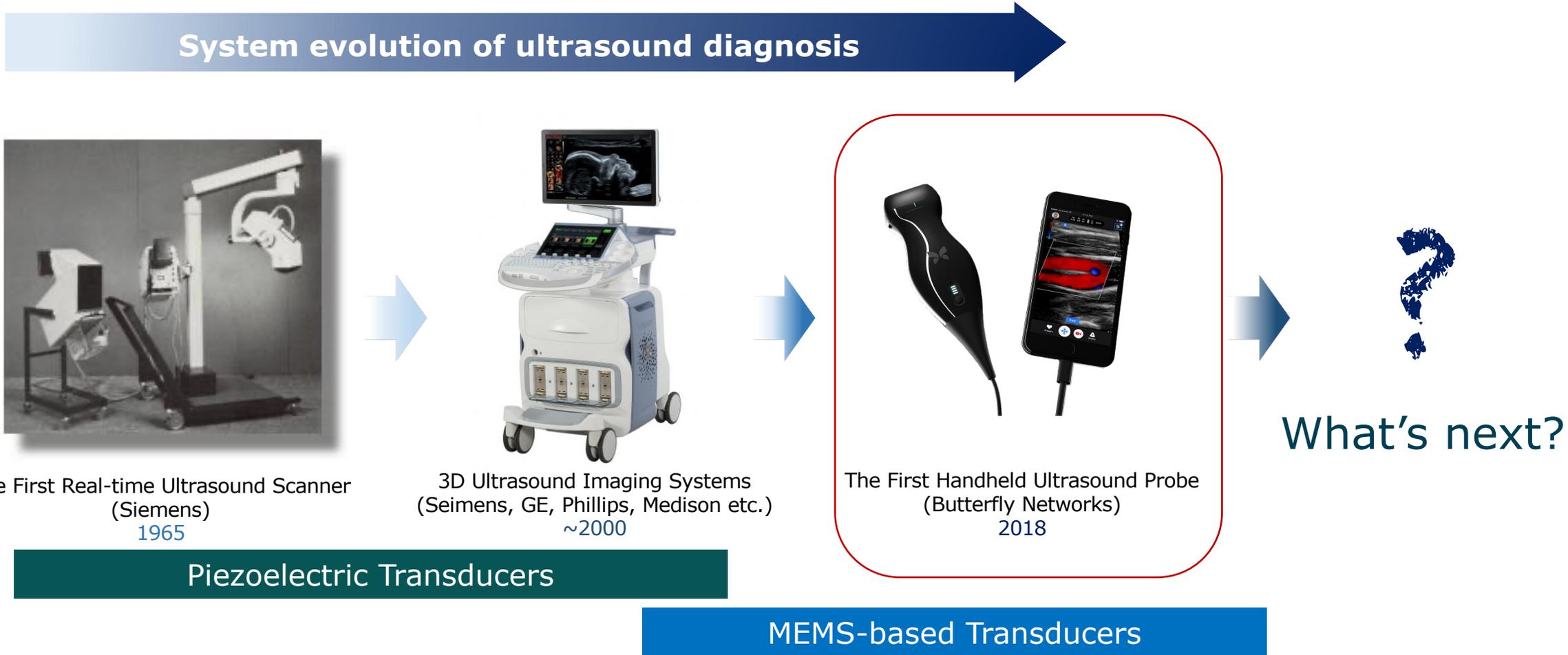
**04**

**Wearable  
Bi-directional Interface**

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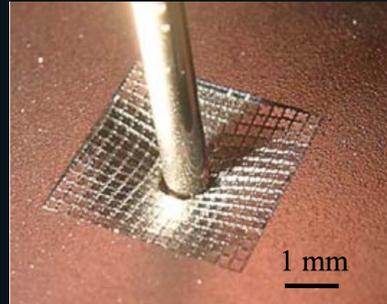
# Roadmap of Ultrasound Transducers

| Devices for acoustoceutics



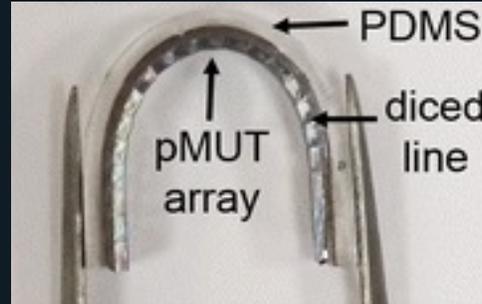
# Towards wearable ultrasound therapeutics

2D CMUT



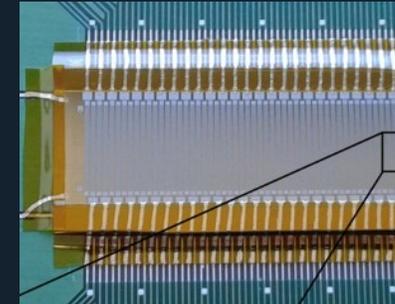
Stanford Khuri-Yakub, 2007

1D PMUT



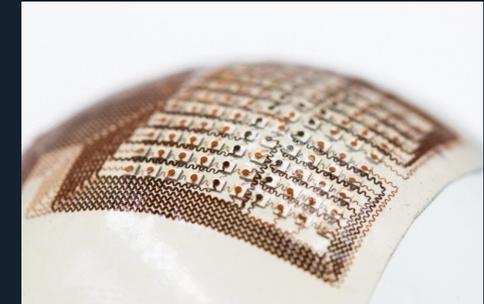
KU Jo Group, 2016

Polymer CMUT

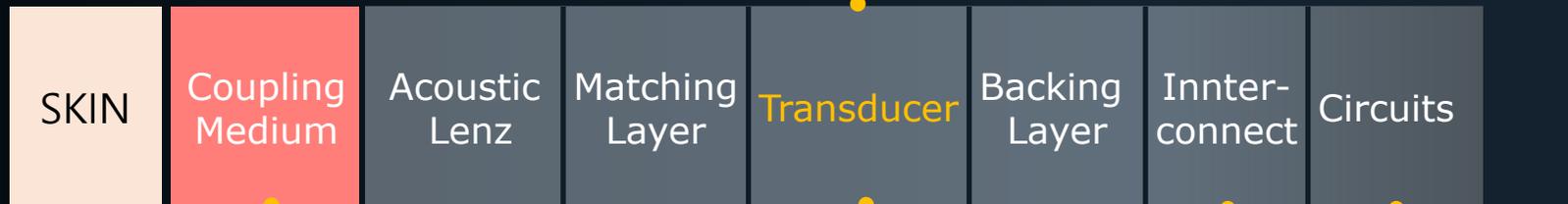


UBC Rohling, 2018

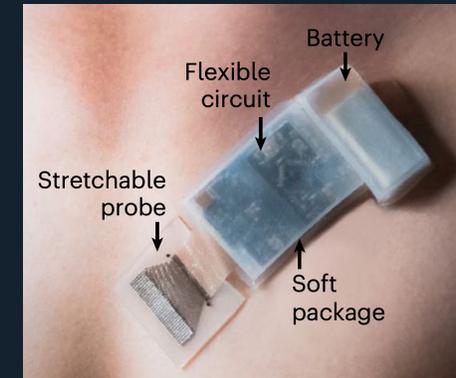
PUT



UCSD Xu, 2022



MIT Zhao, 2022



UCSD Xu, 2024

# Interface problem

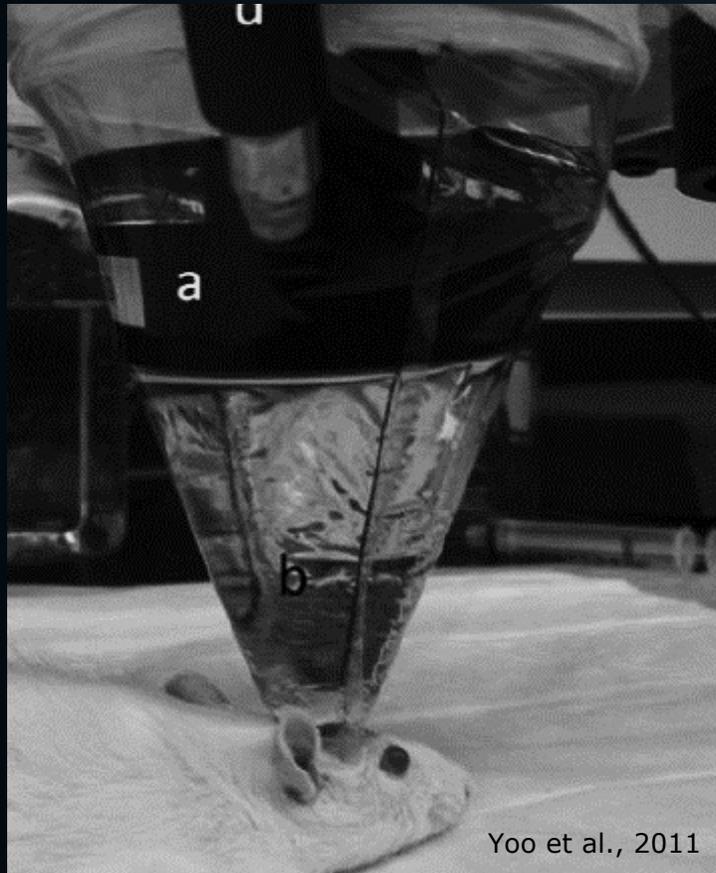


Lee & Lee (ACS AMI, 2022)

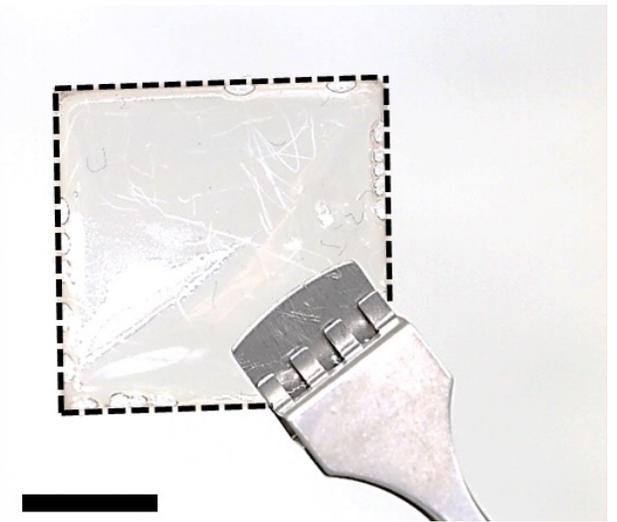
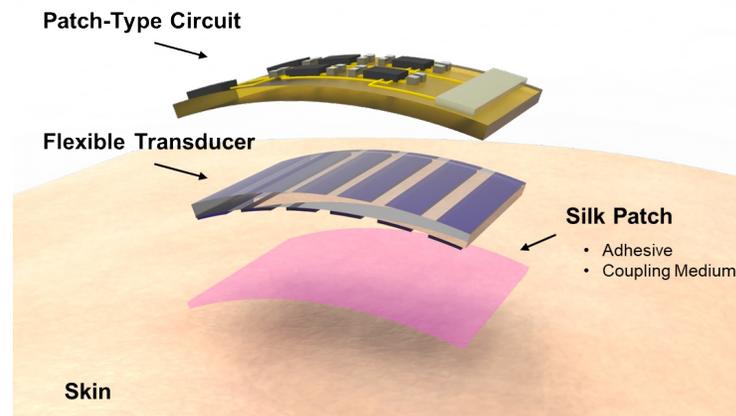
## Problem: Bulky coupling collimator

- Limit the range of in vivo experiments
- Fixed in stereotaxic frame
- Chronic/behavior studies are not possible

## Our approach: "Adhesive" ultrasound coupling thin film



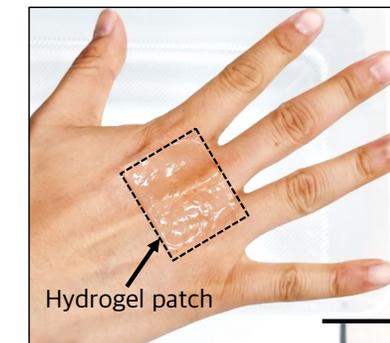
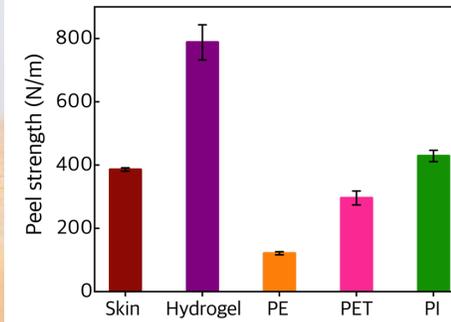
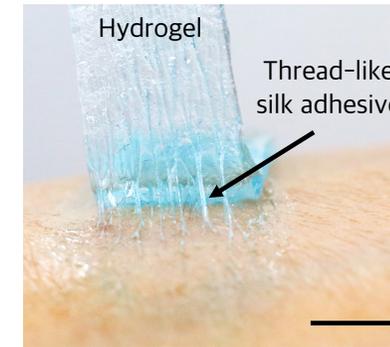
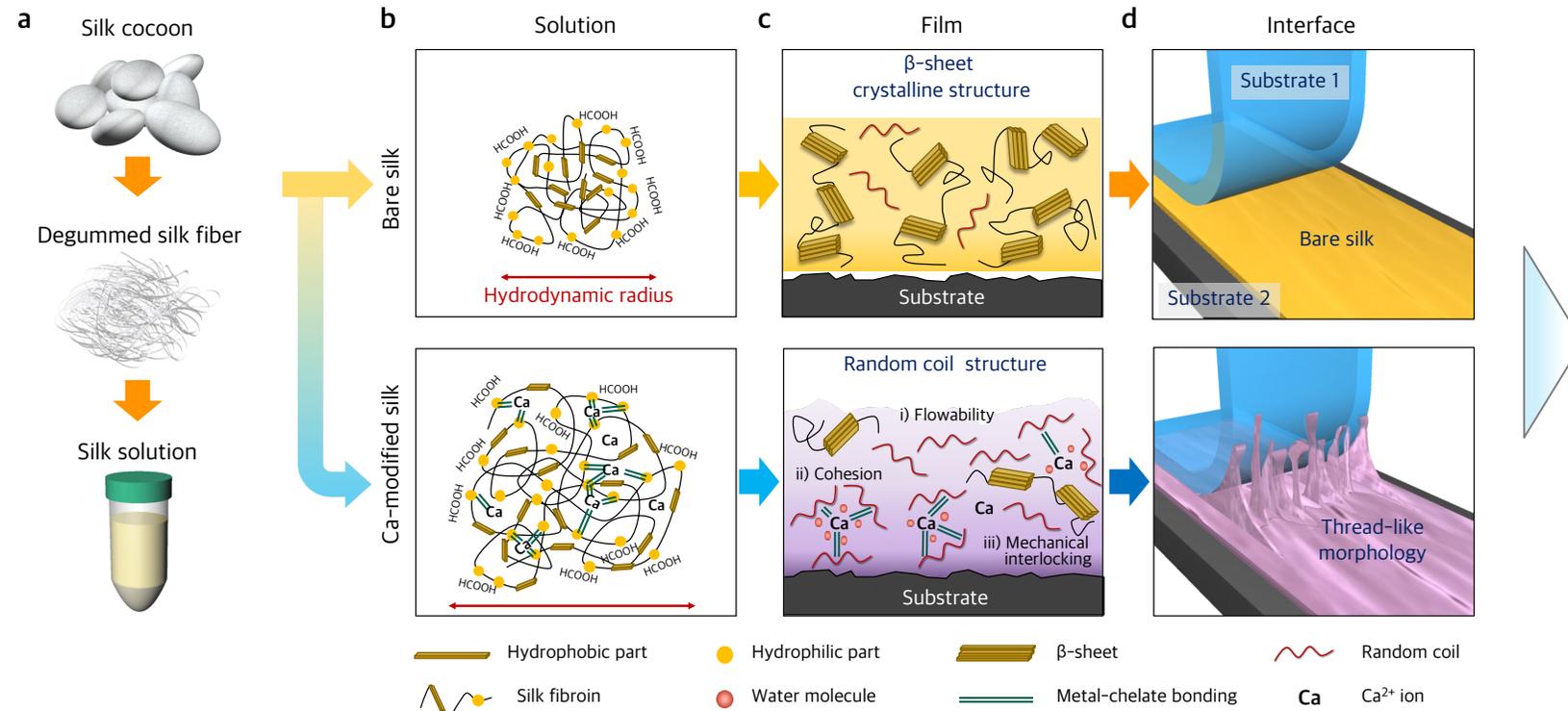
Yoo et al., 2011



# Silk adhesive



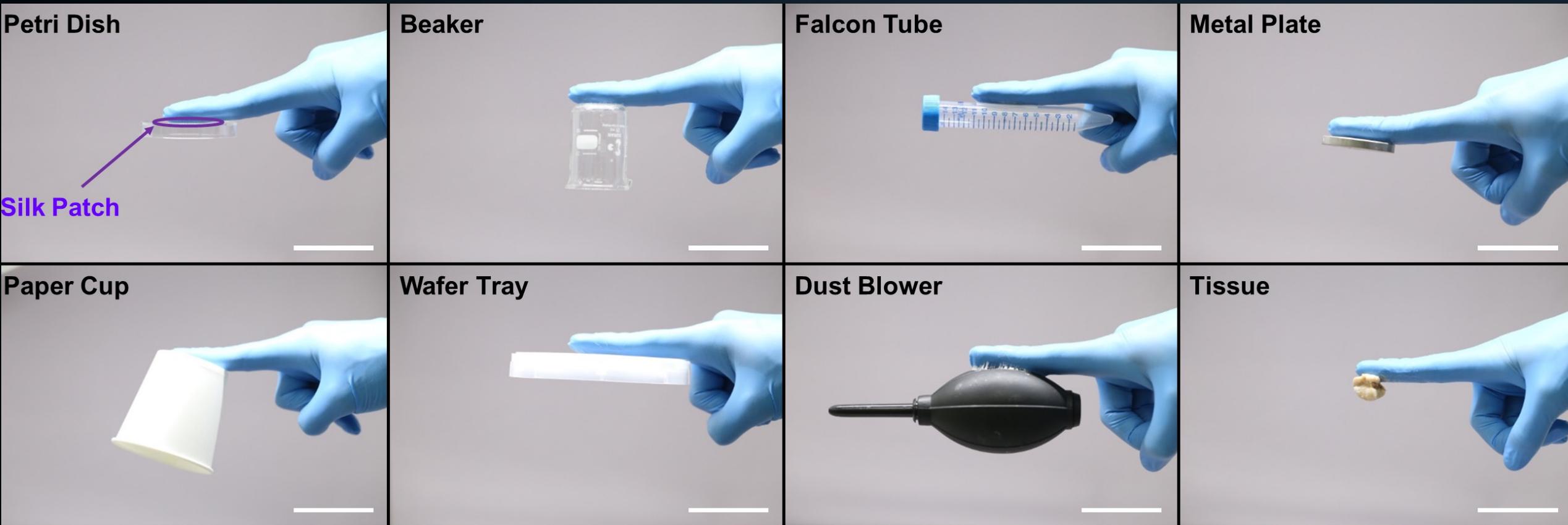
Kim & Seo (Adv. Func. Mat., 2018)



# Ultrasound coupling adhesive



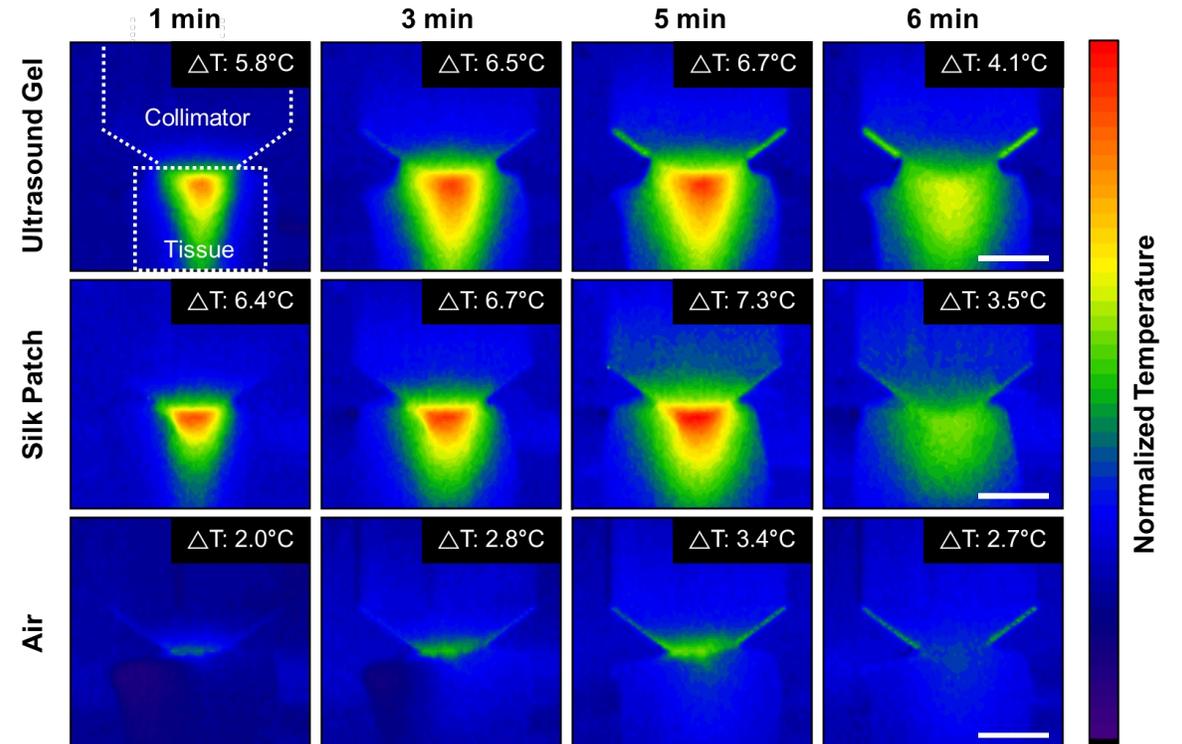
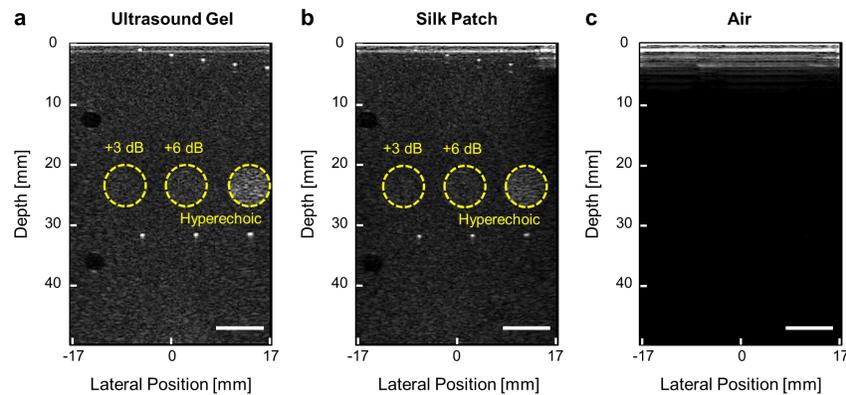
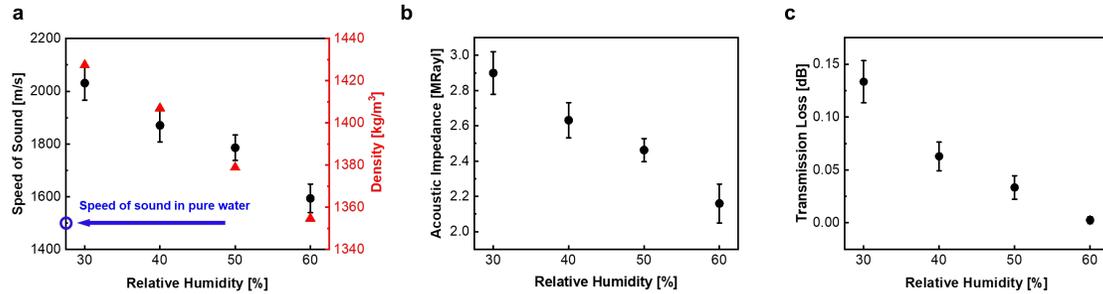
Lee & Lee (ACS AMI, 2022)



# Ultrasound coupling adhesive



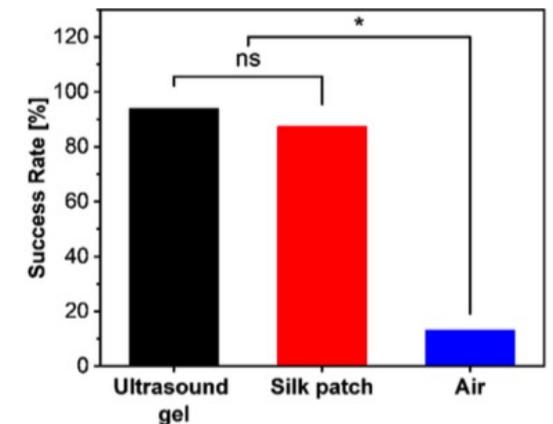
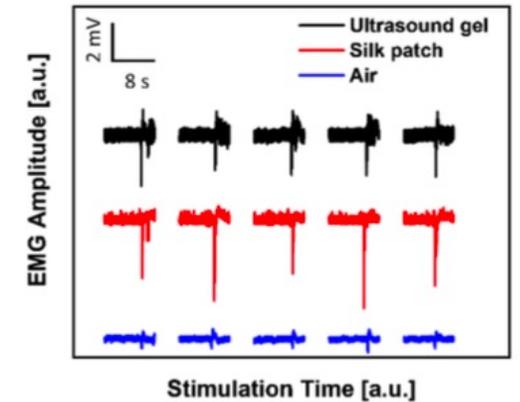
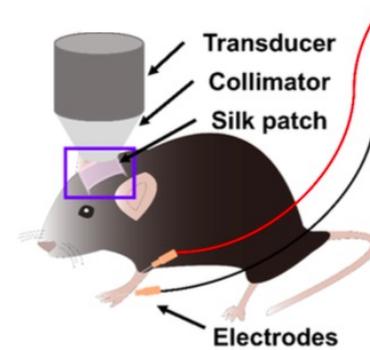
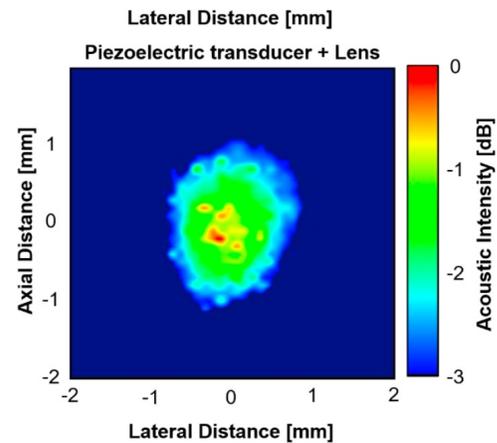
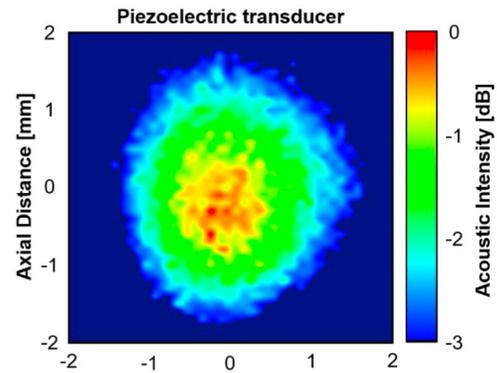
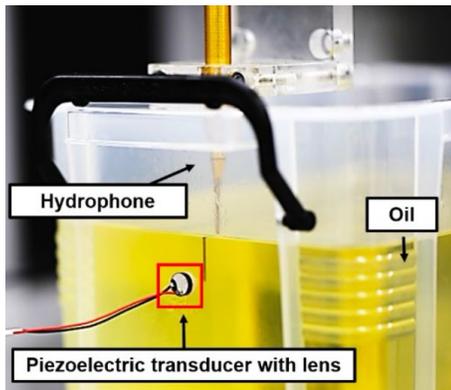
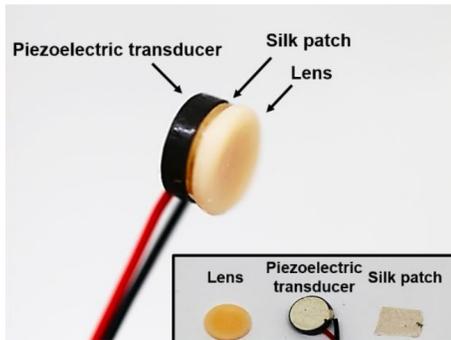
Lee & Lee (ACS AMI, 2022)



# Ultrasound coupling adhesive



Lee & Lee (ACS AMI, 2022)



# Dilemma of flexible transducers



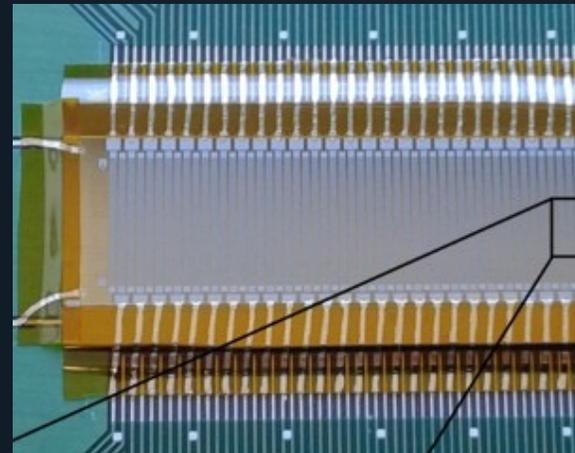
Lee, 2024 (Submitted)

## Problem: Flexibility vs. Acoustic Power

- Flexibility is required to provide a conformal contact
- Need to generate enough acoustic power
- Need for a matching layer and a thick backing layer

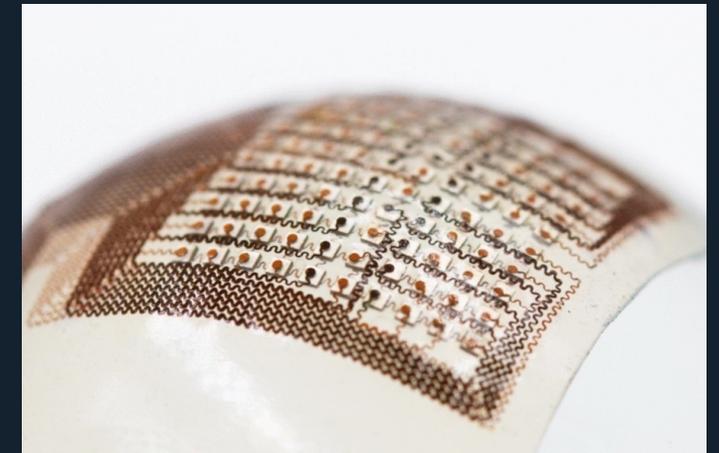


### Polymer CMUT



UBC Rohling, 2018

### PUT



UCSD Xu, 2022

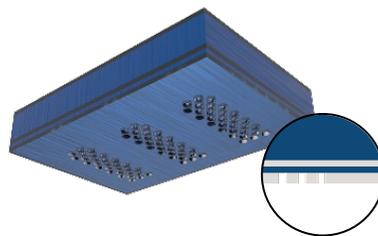
# Flex-to-Rigid (F2R) CMUT



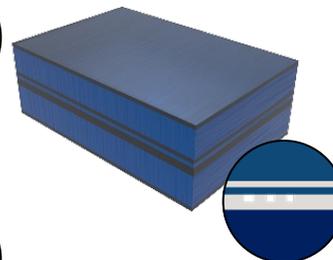
Lee, 2024 (Submitted)

## F2R Fabrication

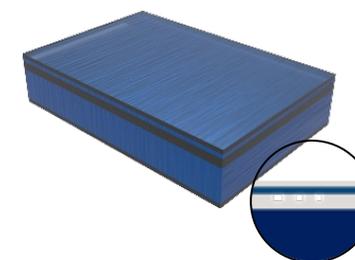
1. Wet oxidation and oxide patterning



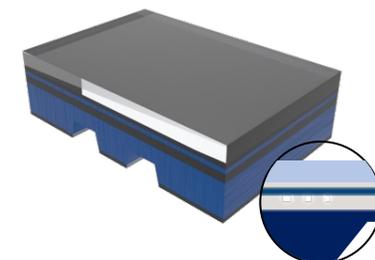
2. Oxide-oxide bonding



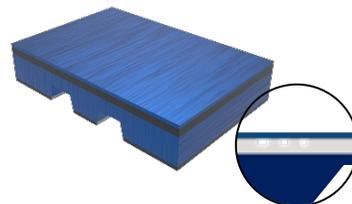
3. Handling layer removal



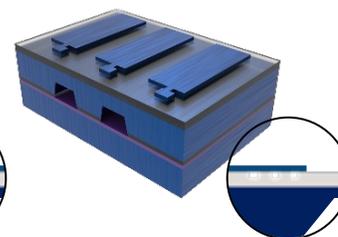
4. Backside Si patterning



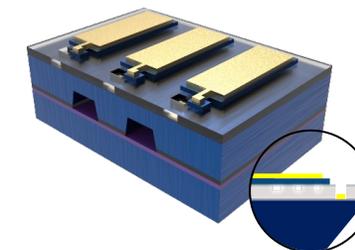
5. Box (oxide) layer etching



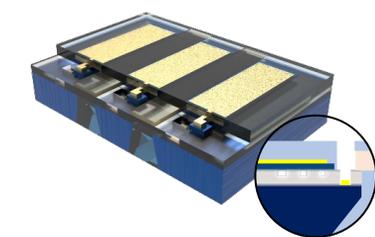
6. Membrane patterning



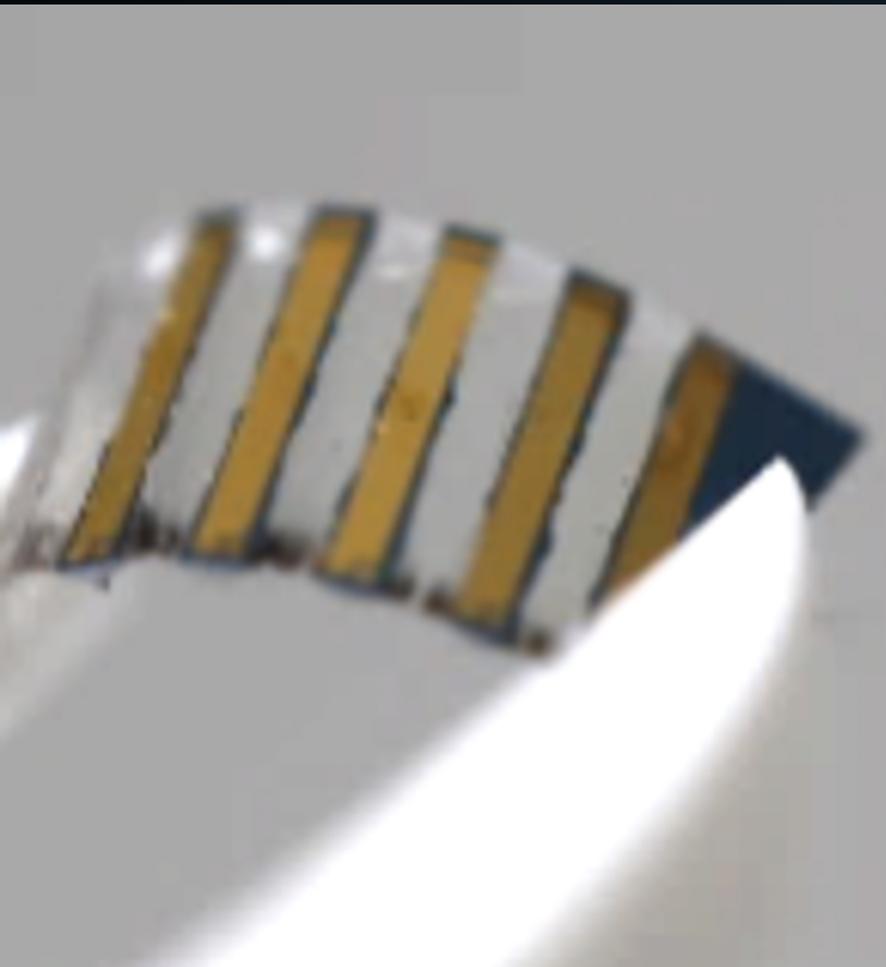
7. Ground etching & electrode patterning



8. PI patterning, Si etching & PDMS coating



Low doped Si    SiO<sub>2</sub>    PDMS  
Highly doped Si    Cr/Au    PI

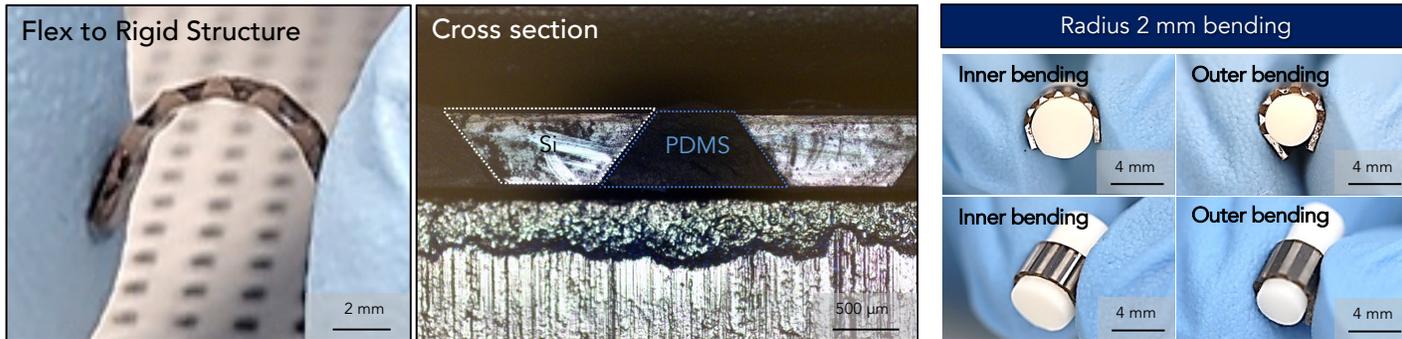


# Flex-to-Rigid (F2R) CMUT

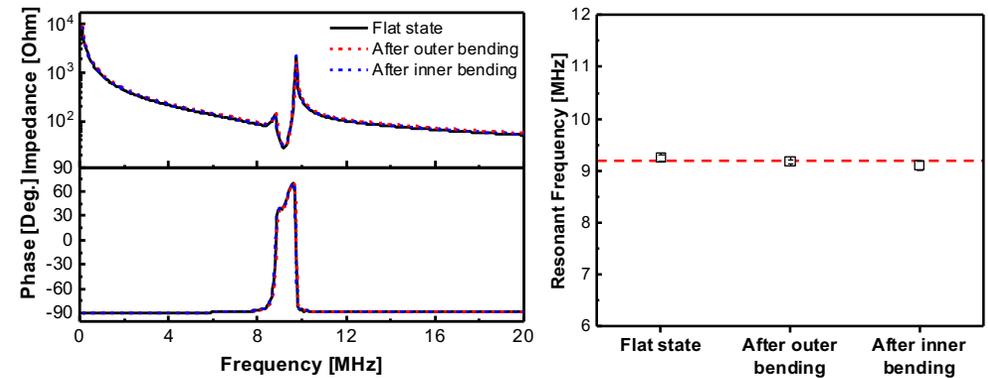
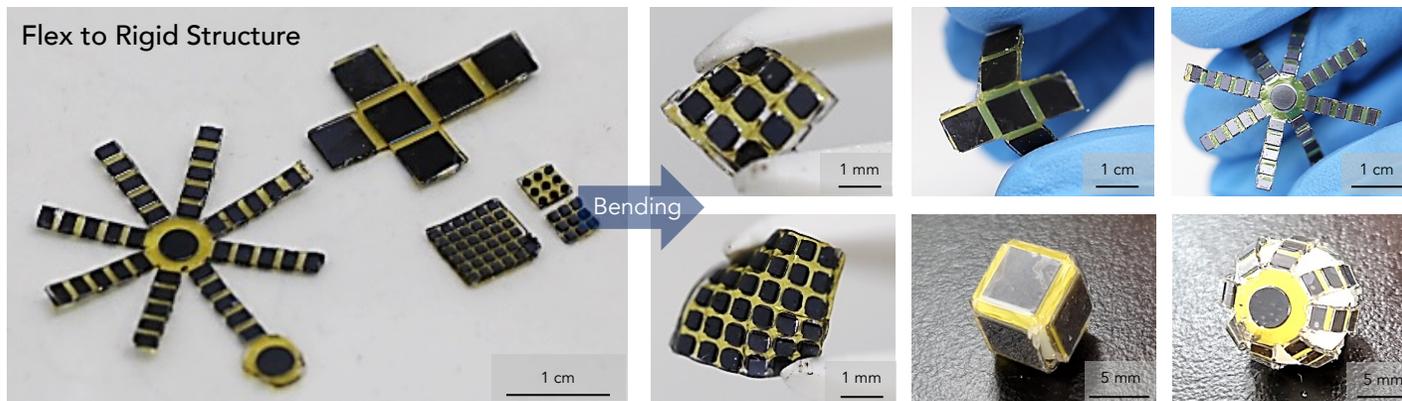
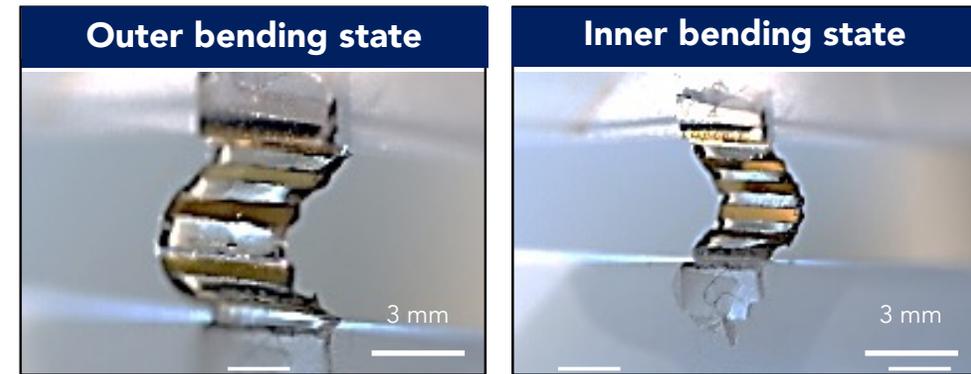


Lee, 2024 (Submitted)

## Various forms



## F2R 1D CMUT array



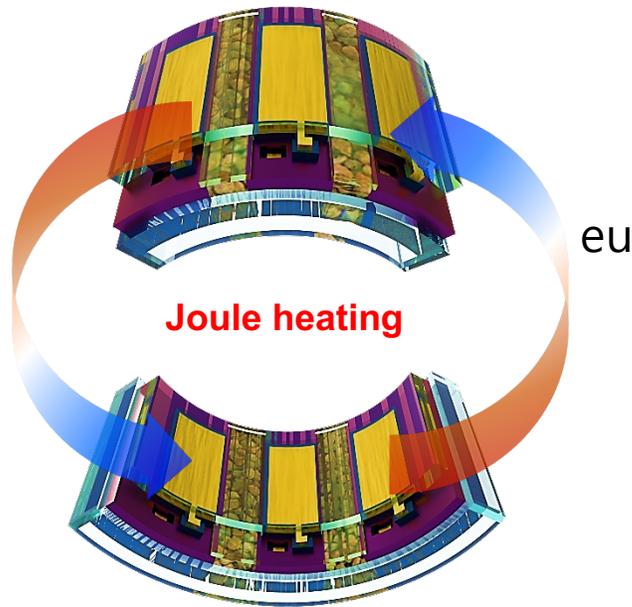
# Flex-to-Rigid (F2R) CMUT



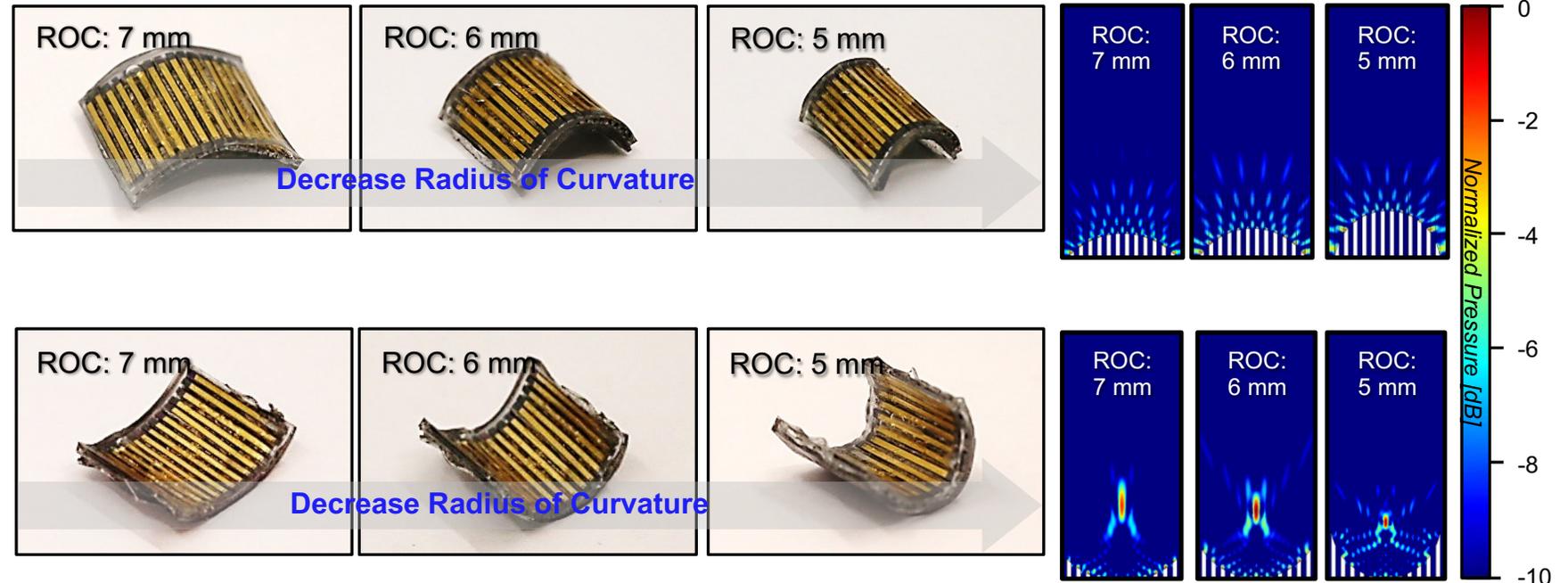
Lee, 2024 (Submitted)

## Bending modulation using using low melting point metal alloy (LMPA)

Outer bending state



Inner bending state

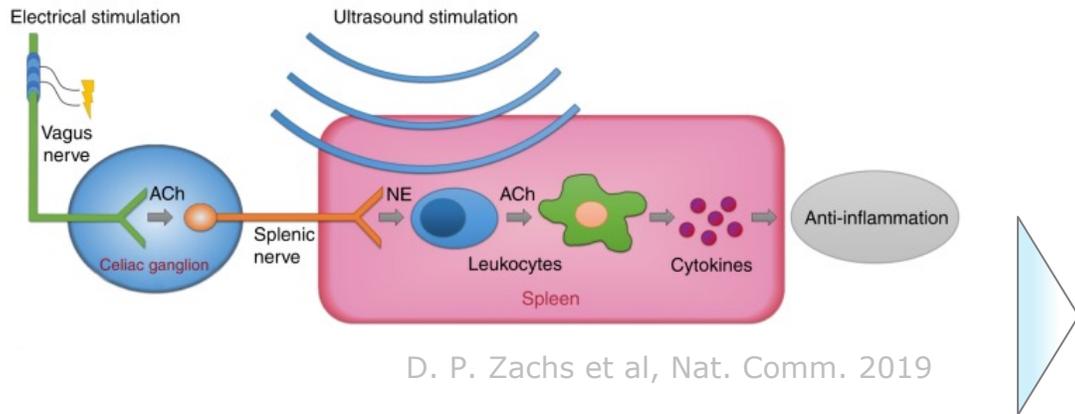


# Treatment using F2R CMUT



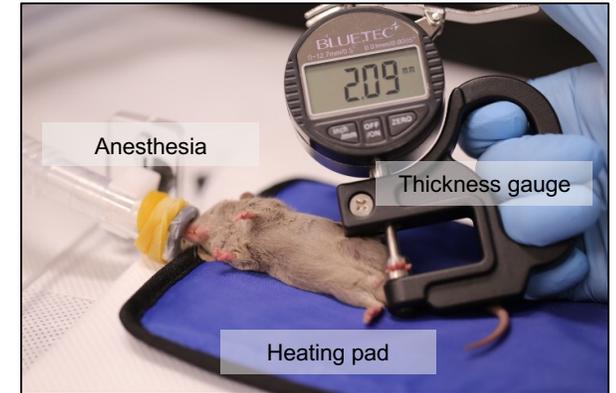
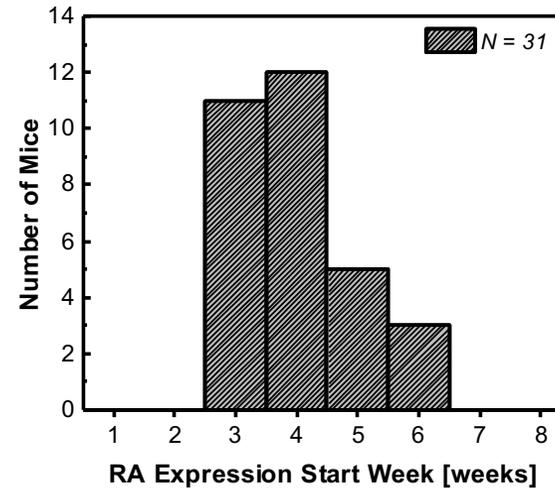
Lee, 2024 (Submitted)

## Cholinergic anti-inflammatory pathway

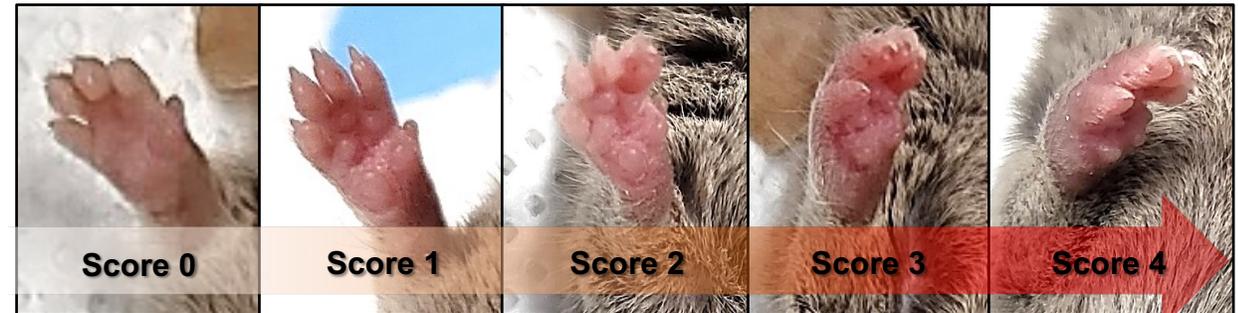


Modulate the neural communication with **T Cells and Macrophages**, **blocking the production of inflammatory cytokines** and promoting an anti-inflammatory state

## Rheumatoid arthritis model



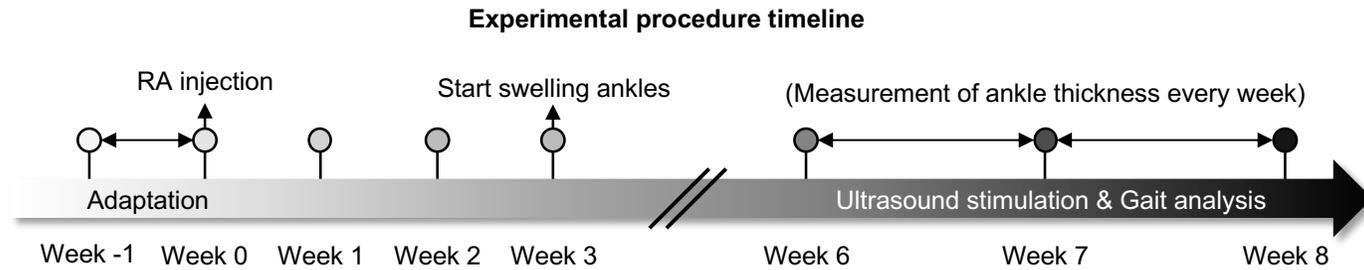
| Injection of collagen emulsion



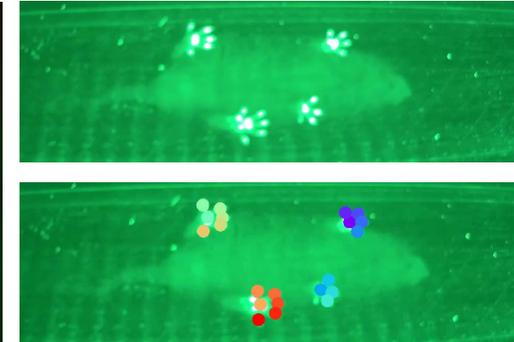
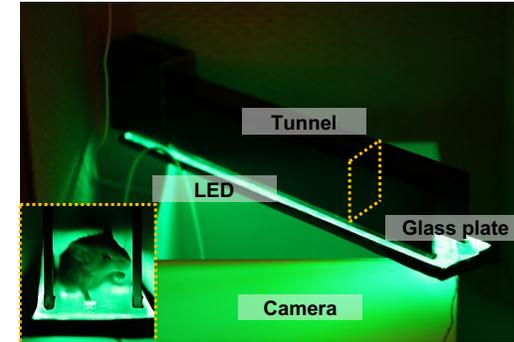
# Treatment using F2R CMUT



Lee, 2024 (Submitted)



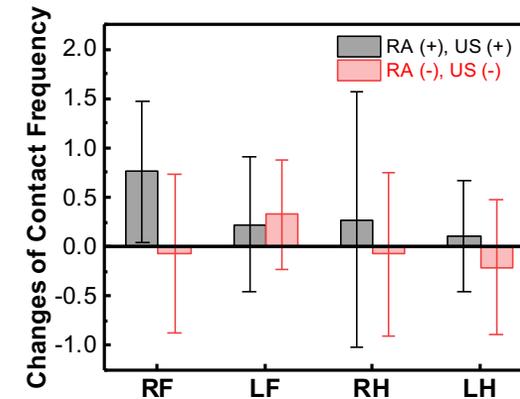
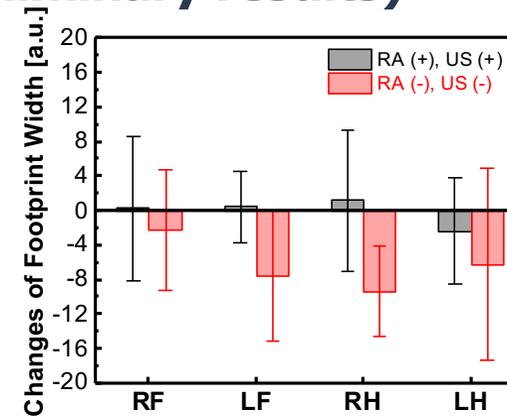
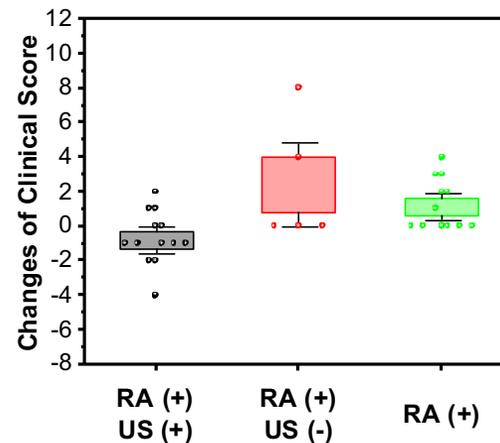
## Gait analysis



## Stimulation protocols

Frequency: 1 MHz  
 Power: 350 kPa  
 Per day: 20 min (1 s on / 5 s off) per day  
 Repetition: 3 times a week for 2 weeks

## Clinical Score (preliminary results)



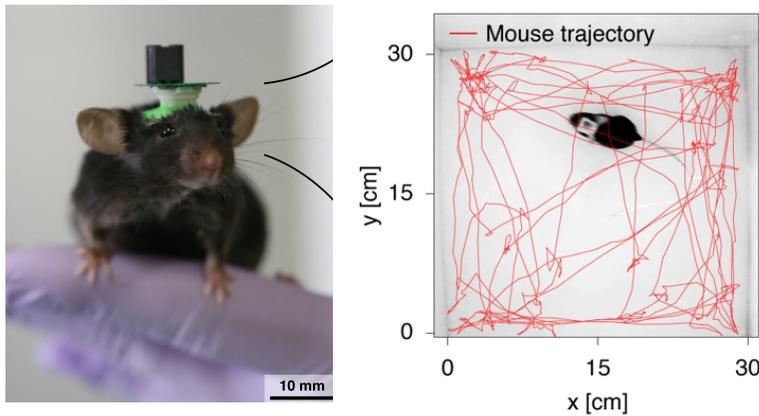


# **04** Brain-Machine Interface

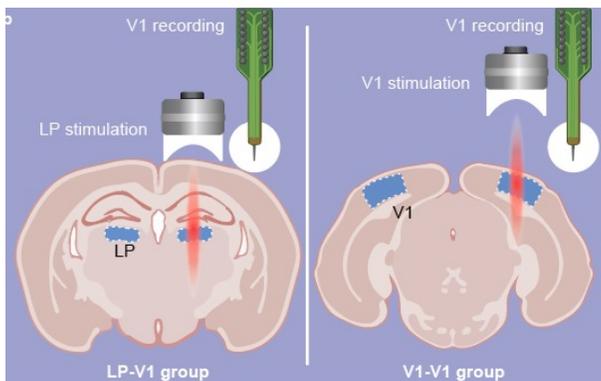
**Summary**

# Preclinical tools for ultrasound neuromodulation

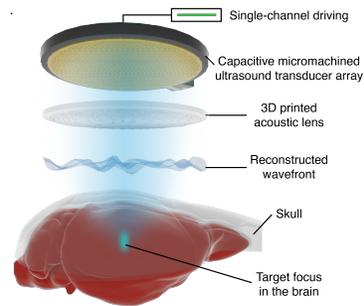
## Wireless, freely-moving system



## Functional specificity in network



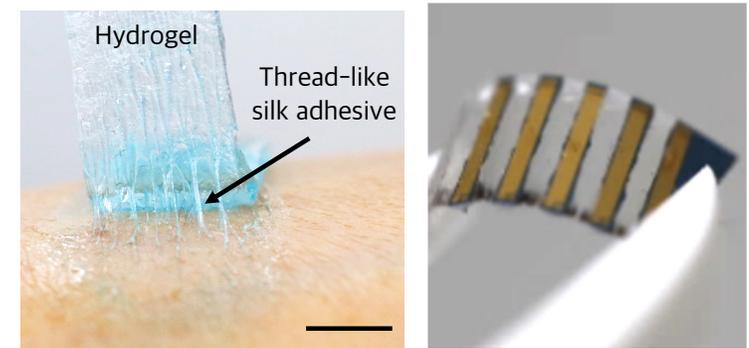
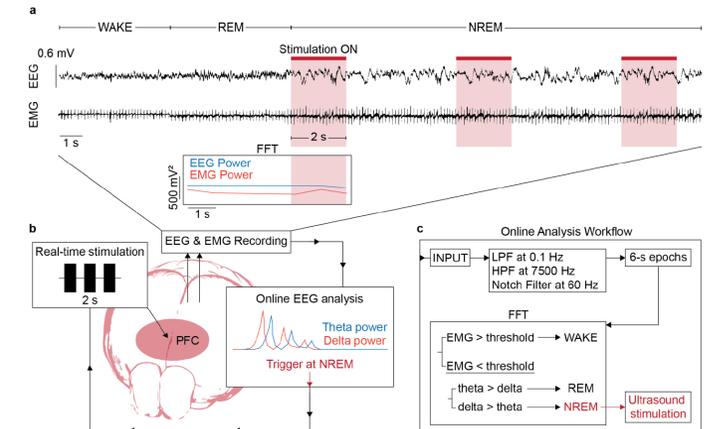
## Ultrasound holography



## Wearable system for ultrasound therapeutics



## Artifact-free closed-loop system



# Acknowledgement



# Acknowledgement



# School of Electrical Engineering

QS Ranking

23<sup>rd</sup> (2023) World  
1<sup>st</sup> in Korea

Electronic Circuits

1<sup>st</sup> in ISSCC  
for 14 consecutive years

Machine Learning  
and AI

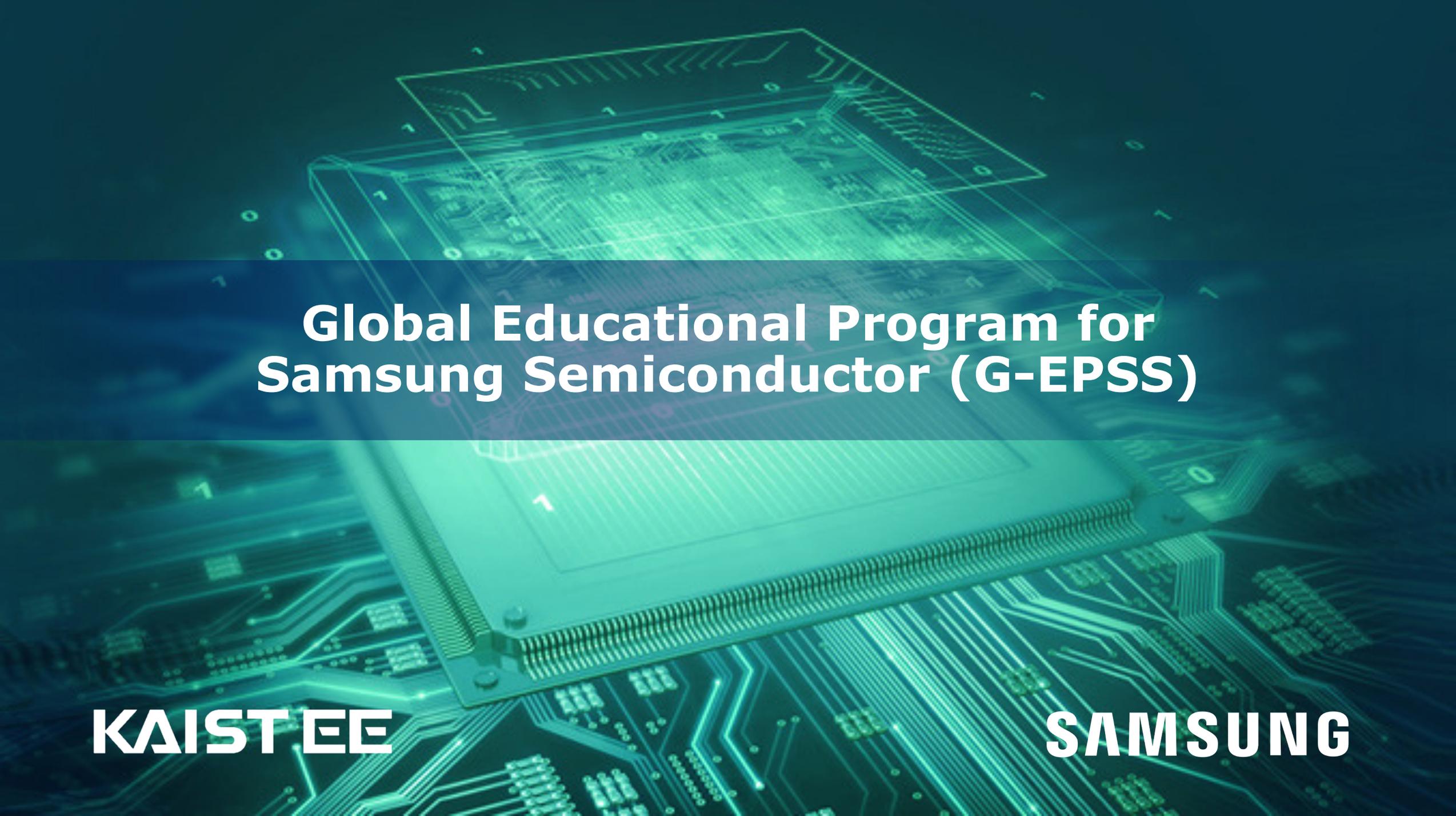
11<sup>th</sup> in the number of  
papers published in collaboration  
with the Graduate School of AI in  
ICML\*, the highest level in Asia  
in the fields of computer vision,  
AI, and deep learning

Computer Vision &  
Computer Architecture

4<sup>th</sup> in the CSRankings

Computer Systems

9<sup>th</sup> in the CSRankings

The background of the slide is a glowing green microchip on a circuit board. The chip is the central focus, with its intricate patterns and connections visible. The overall aesthetic is futuristic and technological, with a strong emphasis on the color green.

# Global Educational Program for Samsung Semiconductor (G-EPSS)

**KAIST EE**

**SAMSUNG**

# Benefits of G-EPSS

## Benefit to G-EPSS scholarship students

- KAIST Tuition: ~\$14000 USD
- Monthly Stipends: \$1000USD~\$1500 USD
- Samsung internship
- Guaranteed employment at Samsung Electronics  
(\*Mandatory employment with a minimum period that corresponds to twice the total year supported by Samsung)

