Brain-Computer Interfaces

NEU/MOL 502A: **From Molecules to Systems to Behavior**

SPECIAL THANKS TO SERGEY STAVISKY

The Treatment Gap

Movement disorders are common and without treatment:

Paralysis	Stroke	Spinal Cord Injury	Multiple Sclerosis	Cerebral Palsy	Other
5.4M	1.8M	1.5M	1M	446K	646K

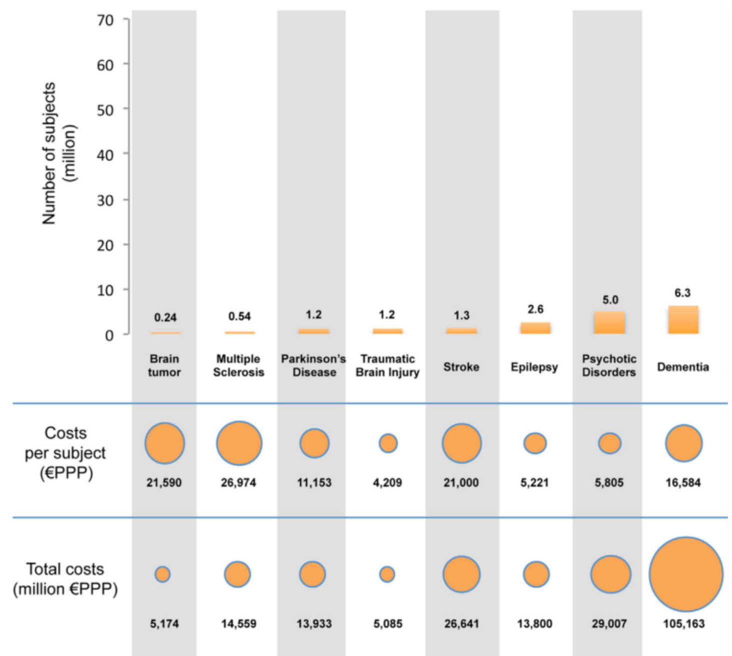
Other: traumatic brain injury, amyotrophic lateral sclerosis (ALS), neurofibromatosis, syringomyelia, post-polio syndrome, transversemyelitis, and spina bifida.

900,000 patients are living with Parkinson's in the US right now.

>**800,000** strokes in the US every year, many with motor deficits.

Treatment-resistant neuropsychiatric diseases:
~8.9 million U.S. adults have major depression. Of these, **~2.8 million** have treatment-resistant depression

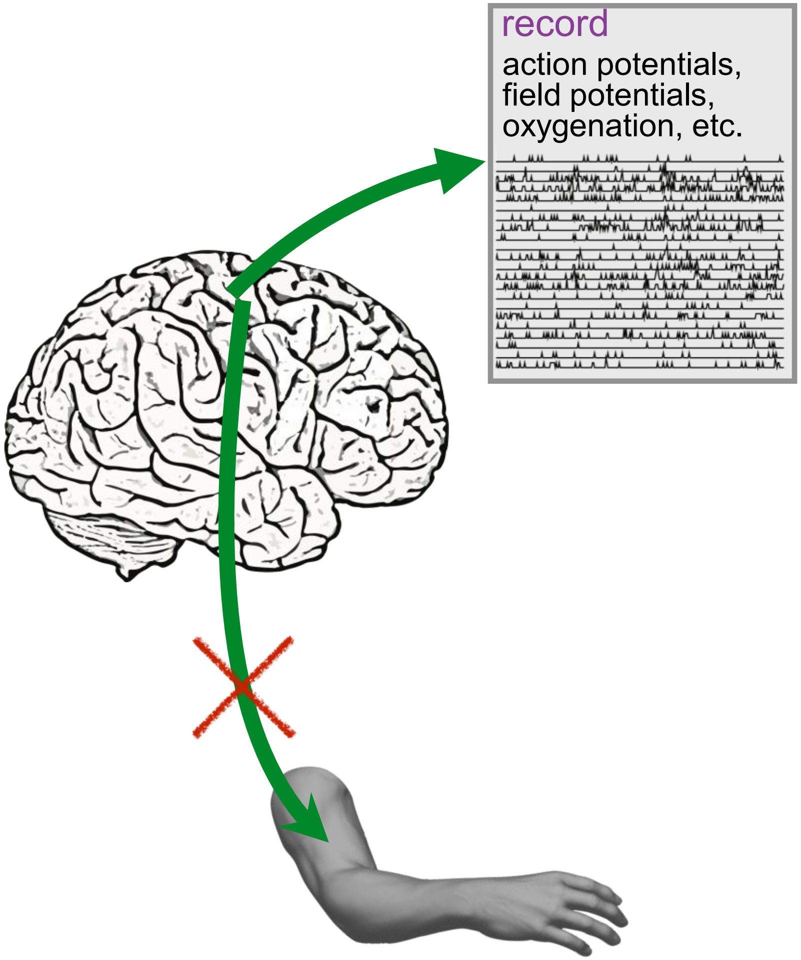
~40 million US adults suffer from some degree of anxiety disorder. Of these, ~**8–15 million** patients do not respond well to treatment.



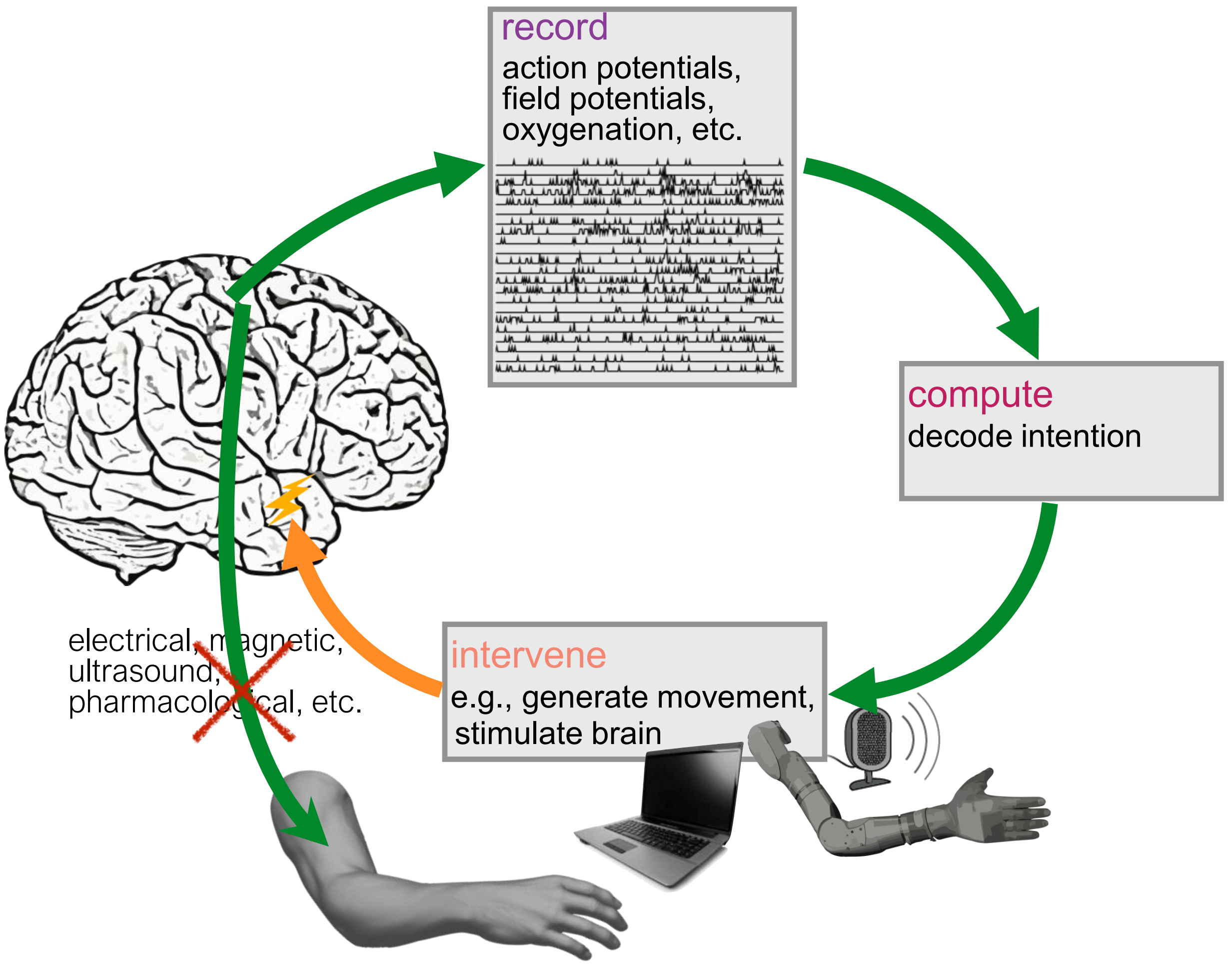
(Europe)

DiLuca & Olesen. The cost of brain diseases: A burden or a challenge? *Neuron* (2014)

Core components of a brain computer interface (BCI)



Core components of a brain computer interface (BCI)



Neural interfaces

less invasive → more invasive

Electrocorticography (EEG)

Outside body, but averages millions of neurons

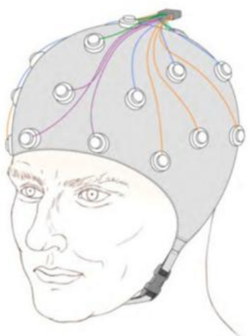


illustration from Blabe et al. (2015)

Also detects electric currents: MEG

Detects blood flow: fNIRS (light), fUS (ultrasound)

worse performance ← higher performance

Neural interfaces

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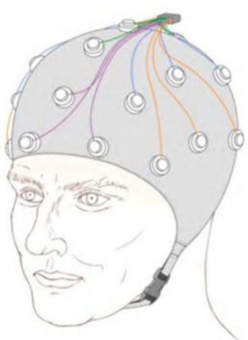

illustration from Blabe et al. (2015)

Also detects electric currents:
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Detects blood flow: fNIRS (light),
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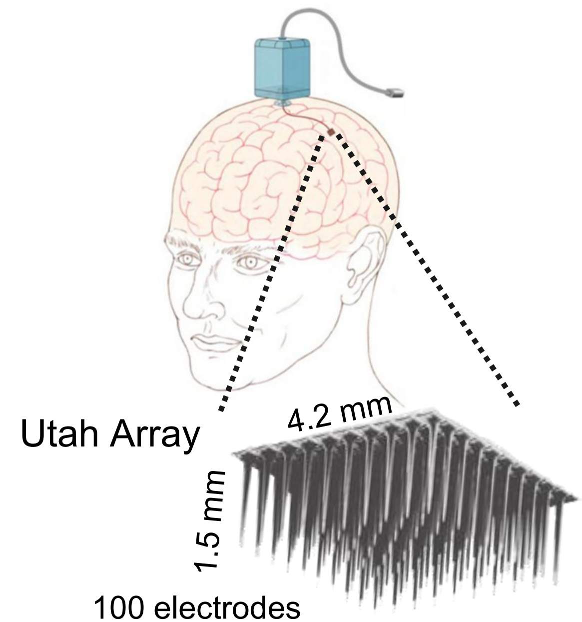
Intracortical electrodes

Narrow coverage,
single-neuron resolution



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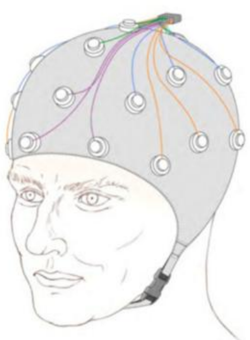


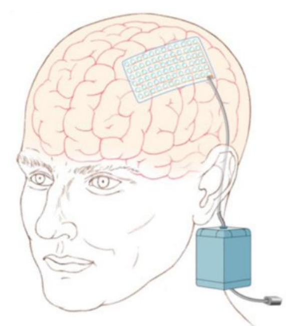
illustration from Blabe et al. (2015)

Also detects electric currents: MEG

Detects blood flow: fNIRS (light), fUS (ultrasound)

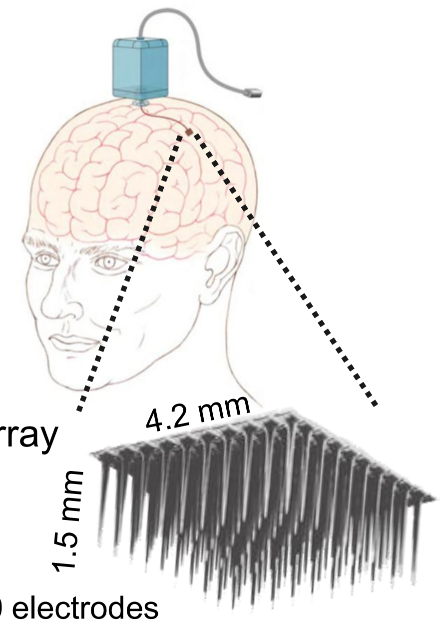
Electrocorticography (ECoG)

Wide coverage, but averages together thousands of neurons



Intracortical electrodes

Narrow coverage, single-neuron resolution



Utah Array

worse performance ← higher performance

Neural interfaces

less invasive → more invasive

Non-invasive

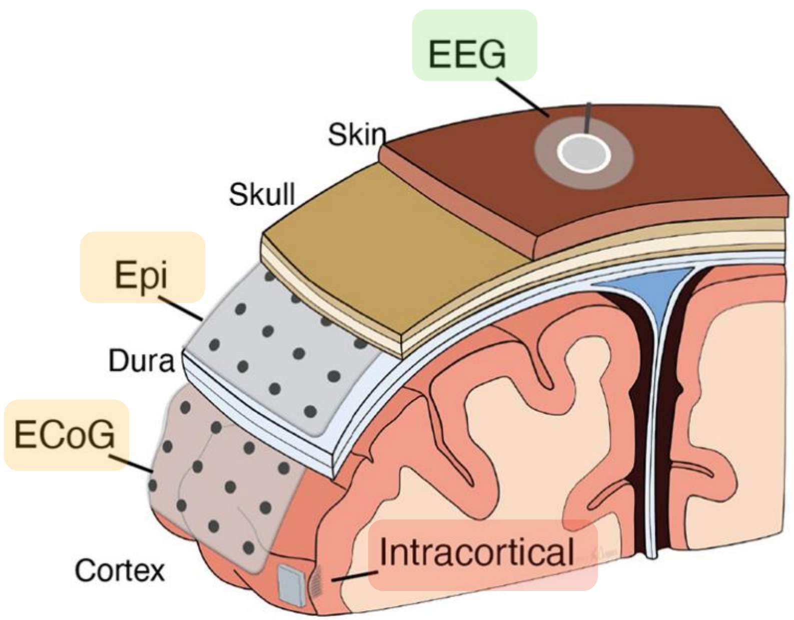
Outside body, but averages millions of neurons

Intracranial

Wide coverage, but averages together thousands of neurons

Intracortical electrodes

Narrow coverage, single-neuron resolution



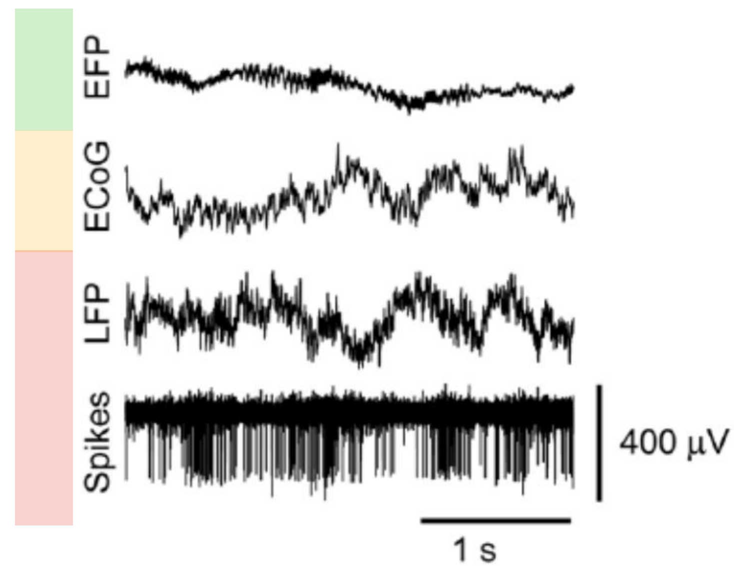


illustration from Pandarinath & Bensmaia (2021)

Slutzky & Flint (2017)

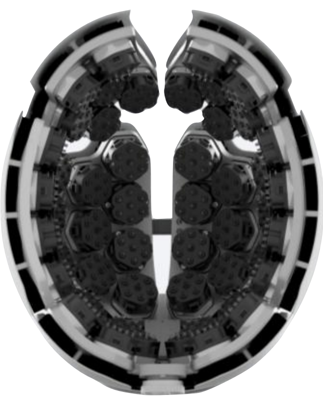
Better neural interfaces are on the horizon

less invasive → more invasive

Non-invasive

Outside body, but averages millions of neurons (or indirect measures like blood flow)

kernel



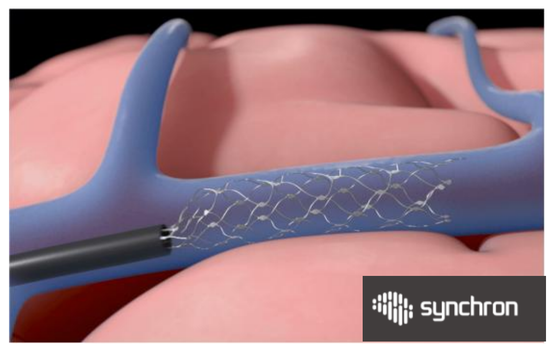
fNIRS

Sonera

MEG

Minimally invasive

Wide coverage, but averages together thousands of neurons



Inserted through veins

Intracortical electrodes

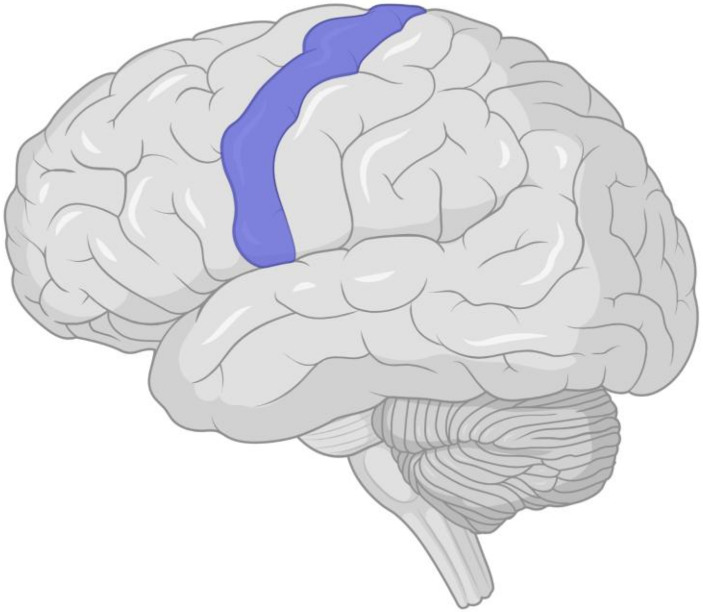
Narrow coverage, single-neuron resolution

Many tiny flexible electrodes across multiple sites

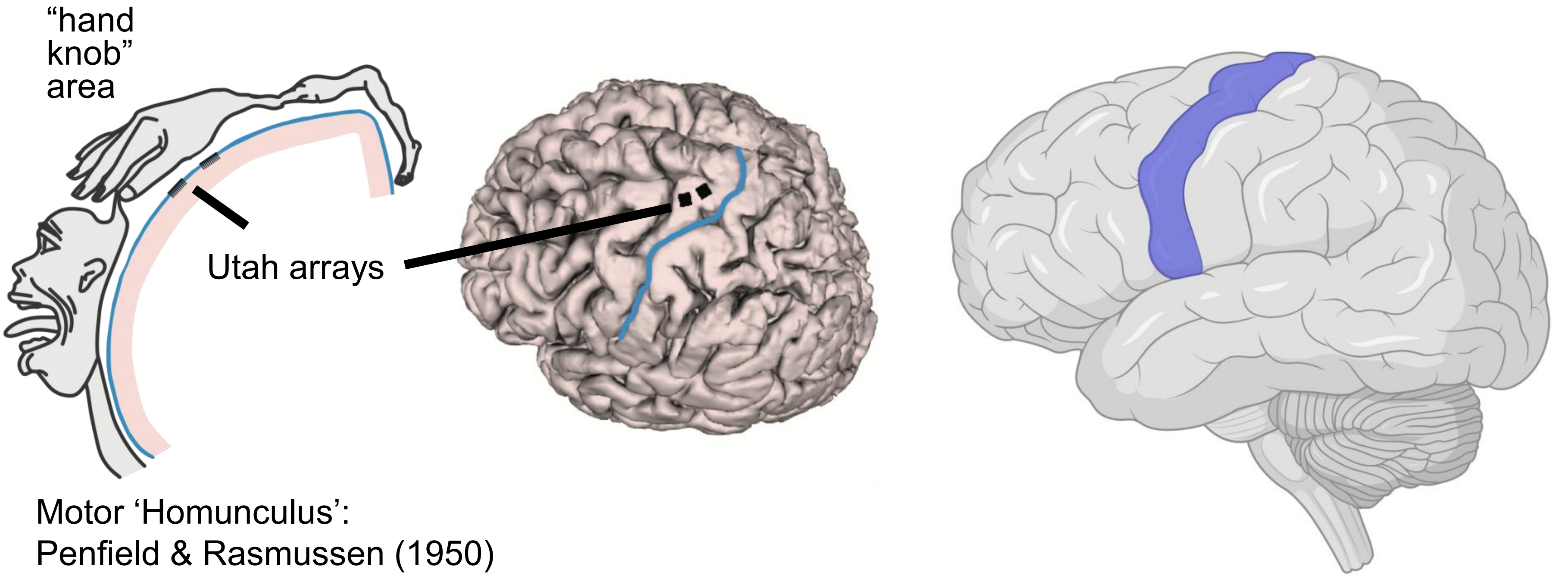
NEURALINK

Reading from the Brain

Decoding intent from motor cortex

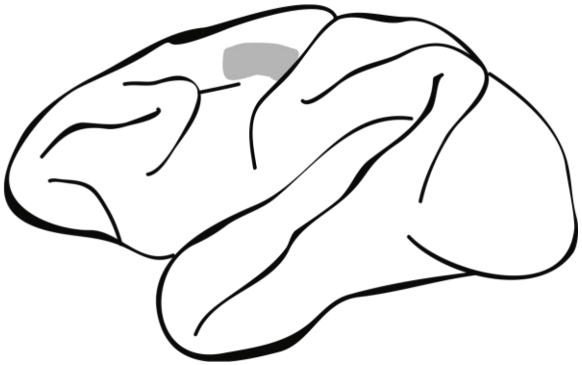


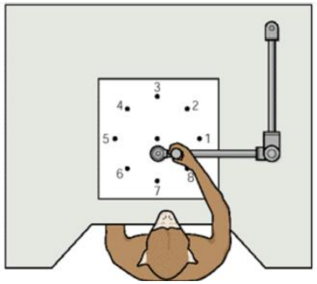
Decoding intent from motor cortex

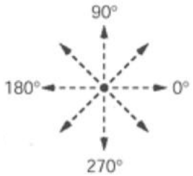


Motor ‘Homunculus’:
Penfield & Rasmussen (1950)

Velocity tuning in motor cortex

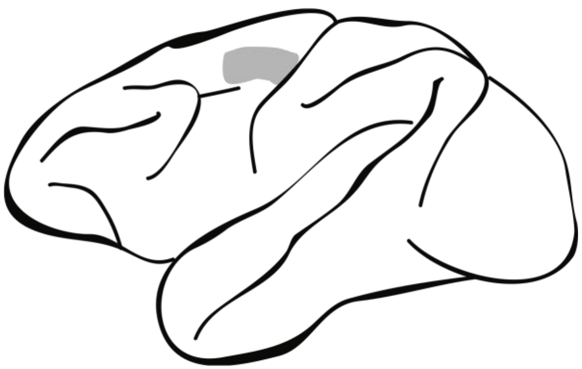


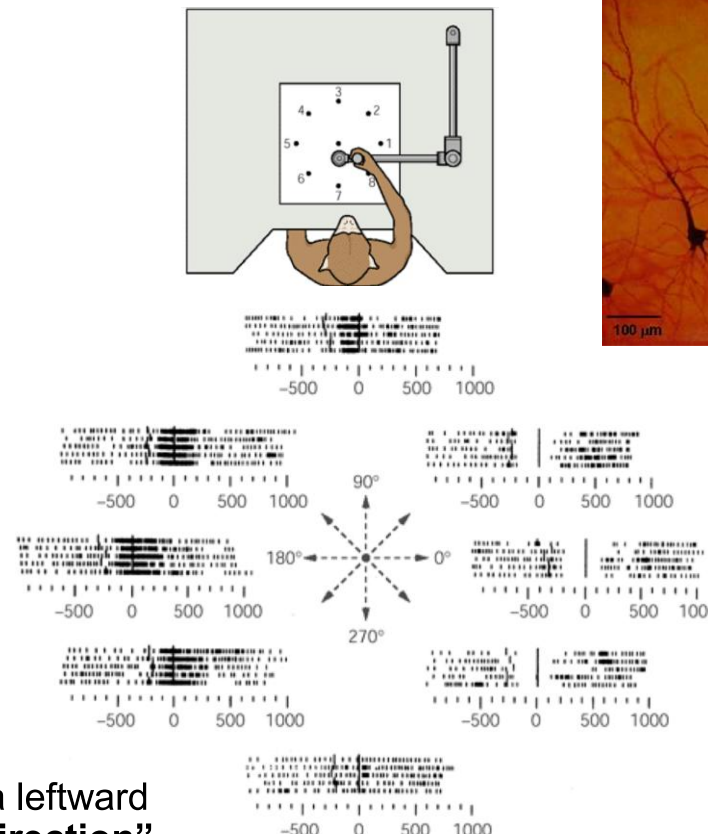




Georgopoulous et al. *Journal of Neuroscience* (1982); figure adapted from Kandel, *Principles of Neural Science*

Velocity tuning in motor cortex



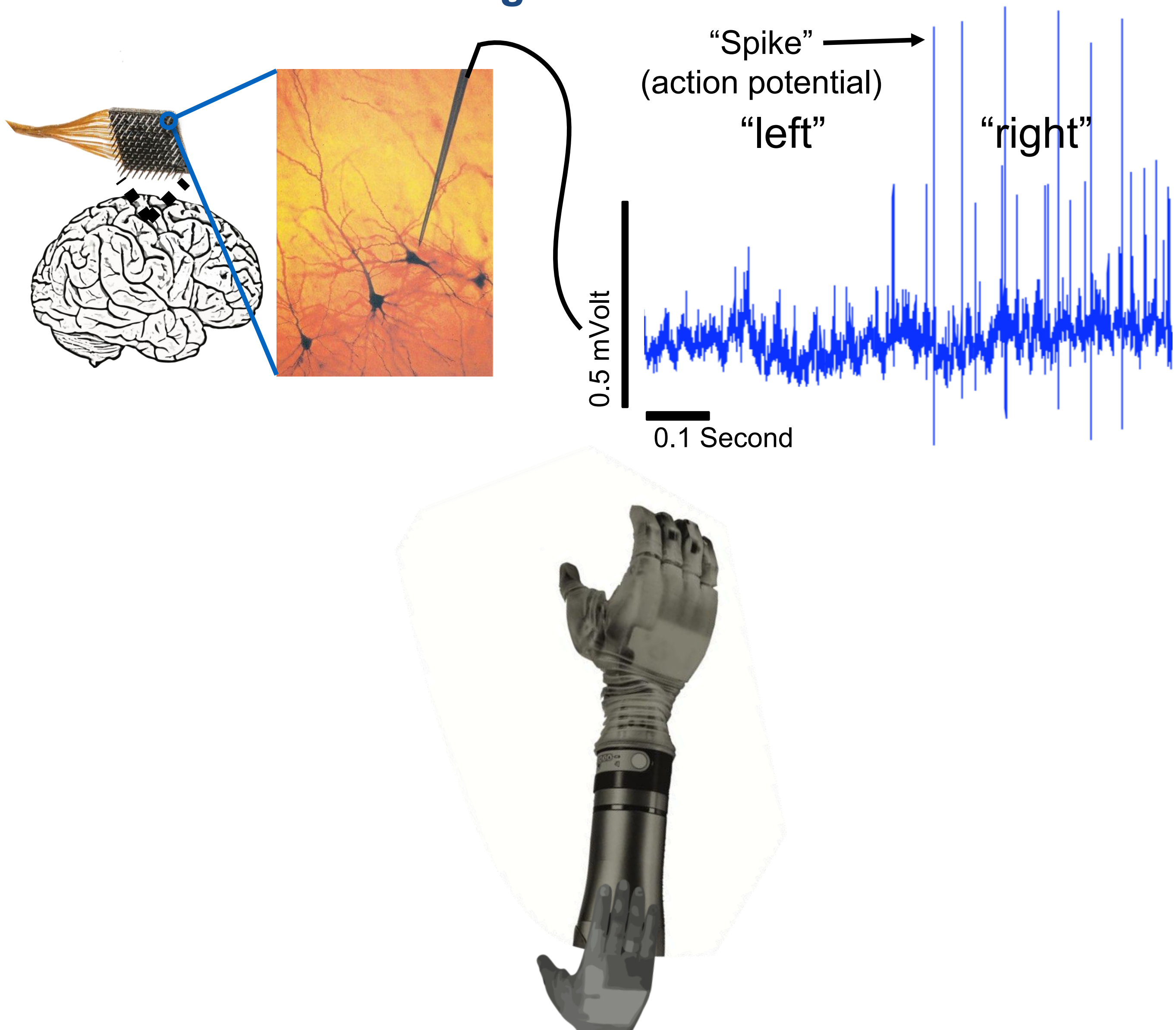


Neuron has a leftward
"preferred direction"

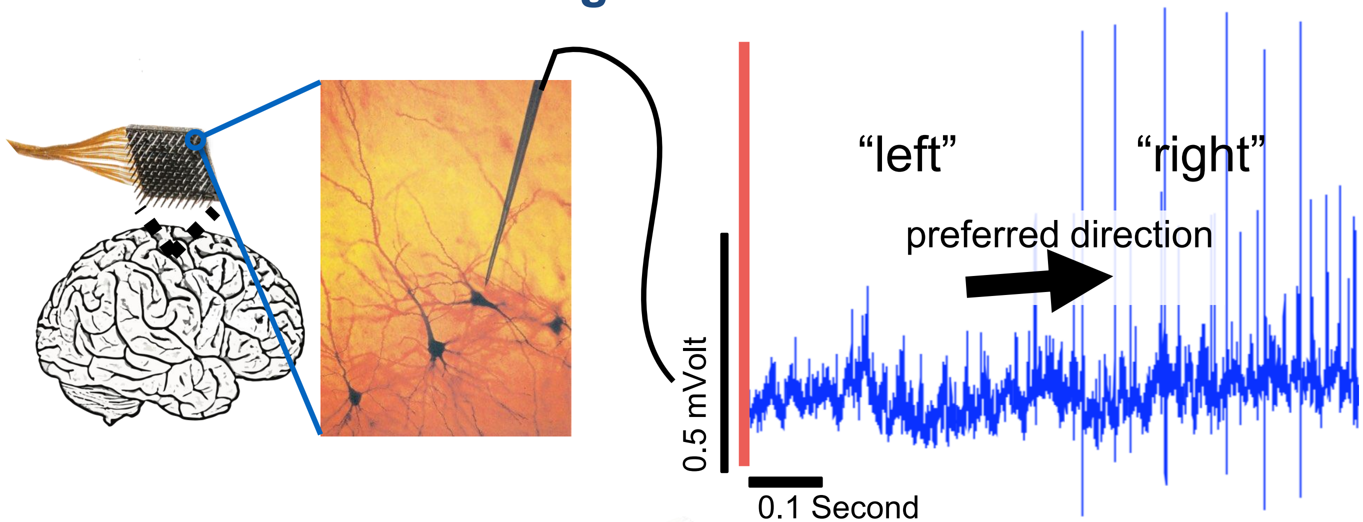
movement onset

Georgopoulous et al. *Journal of Neuroscience* (1982); figure adapted from Kandel, *Principles of Neural Science*

Decoding movement intent

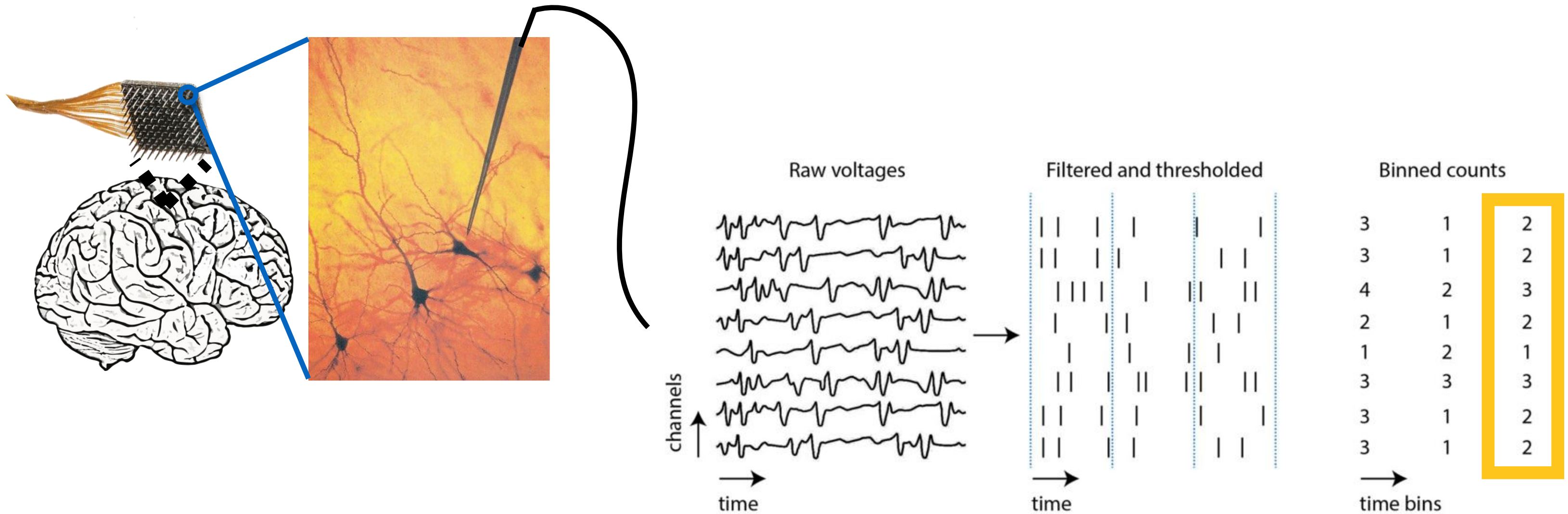


Decoding movement intent



Decoder: algorithm that maps neural activity to prosthesis movement

Decoding movement intent



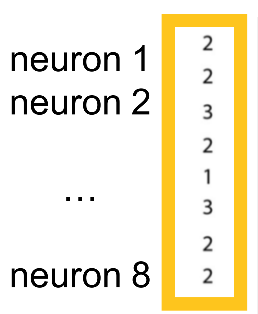
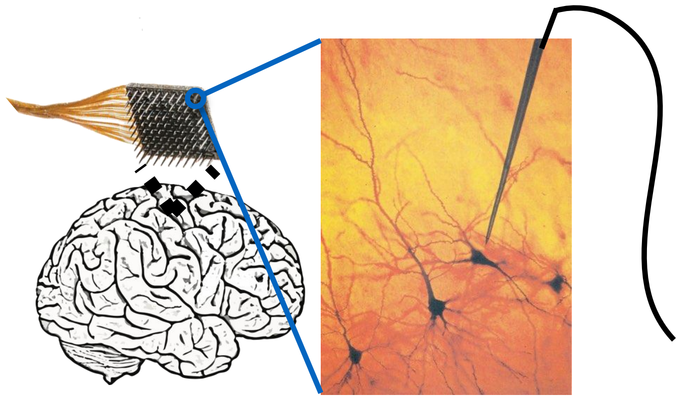
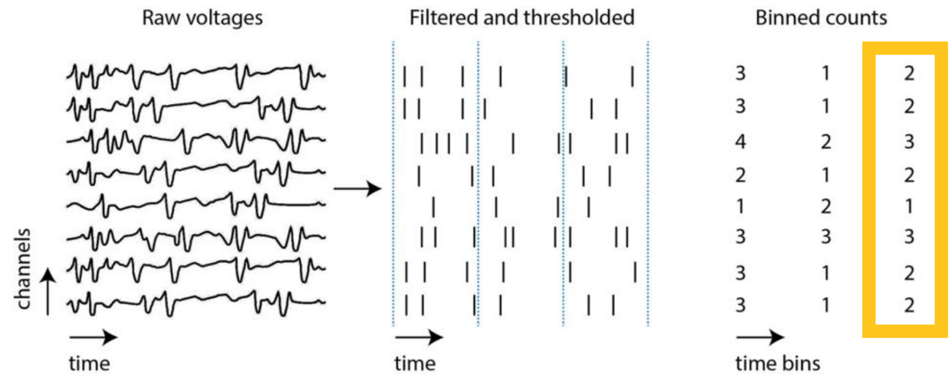
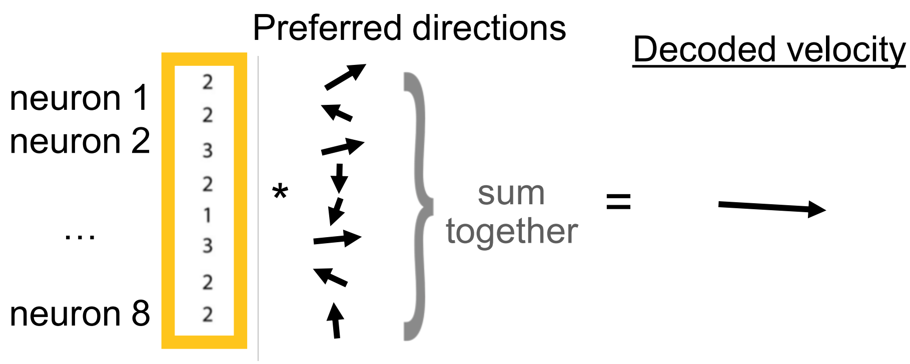


figure adapted from Pandarinath & Bensmaia (2021)

Decoding movement intent

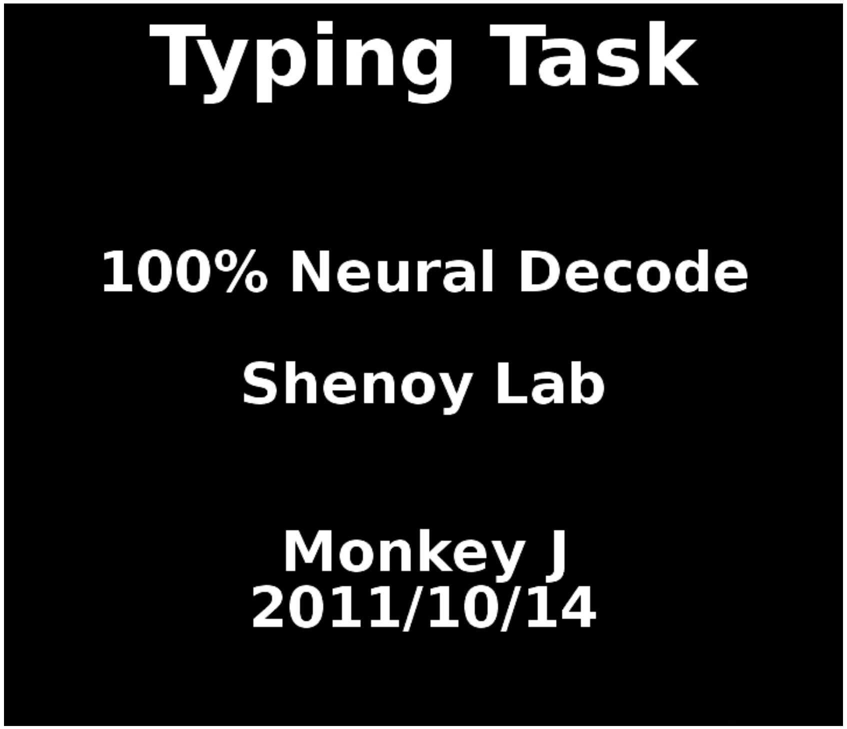


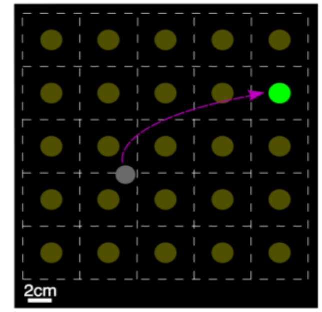




Neurons "vote" in favor of their preferred direction based on their firing rate

Quantifying performance





\# correct, # incorrect, # possible selections, seconds

$$\text{Bits per second} = \frac{(c-\ell)\log_2(N-1)}{T}$$

Nuyujukian et al. Performance sustaining intracortical neural prostheses. *Journal of Neural Engineering* (2014)

‘ReFIT’ decoder from Gilja*, Nuyujukian* et al. A high-performance neural prosthesis enabled by control algorithm design. *Nature Neuroscience* (2012)

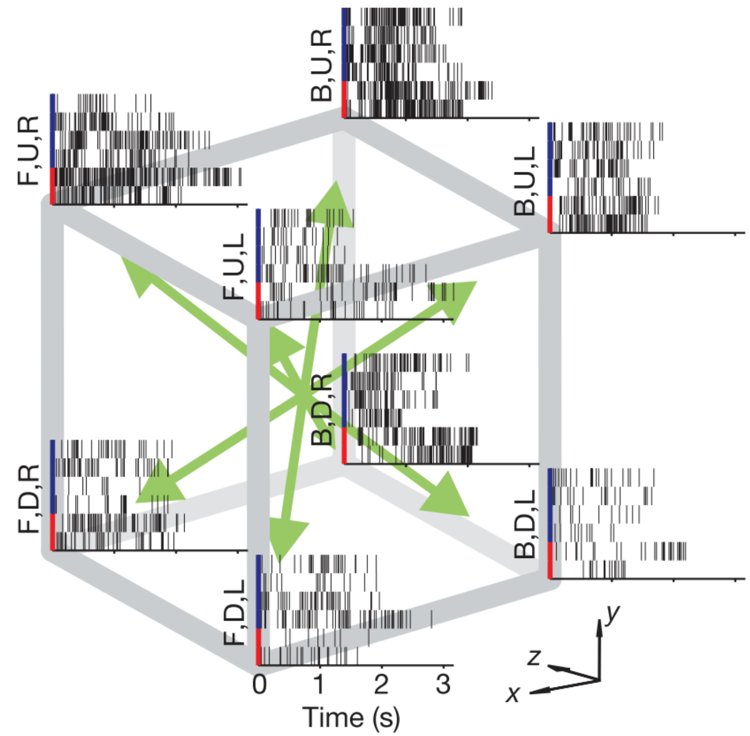
BCIs for restoring reach & grasp

Based on able-bodied NHP studies

3D + aperture decoded

Velliste et al. Cortical control of a prosthetic arm for self-feeding. *Nature* (2008)

Example neuron's 3D tuning



BCIs for restoring reach & grasp

Based on able-bodied NHP studies

Human translation

3D + aperture decoded

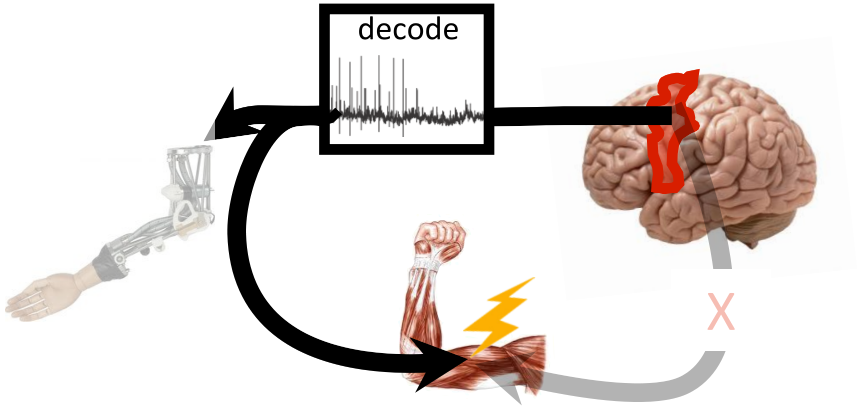
Velliste et al. Cortical control of a prosthetic arm for self-feeding. *Nature* (2008)

3D translation + 3D rotation + aperture decoded

Collinger et al. High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet* (2013)

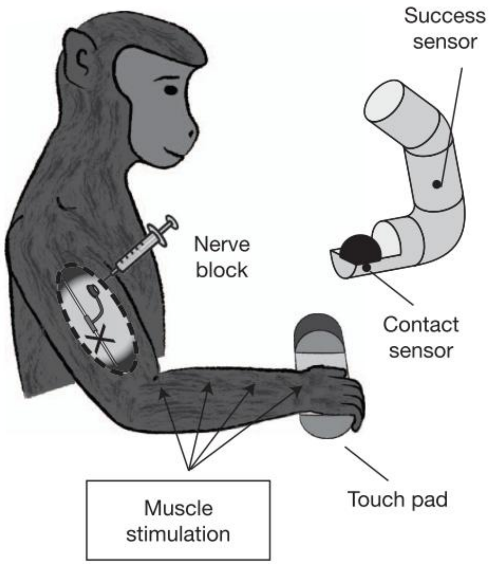
Reactivating paralyzed muscles with electrical stimulation

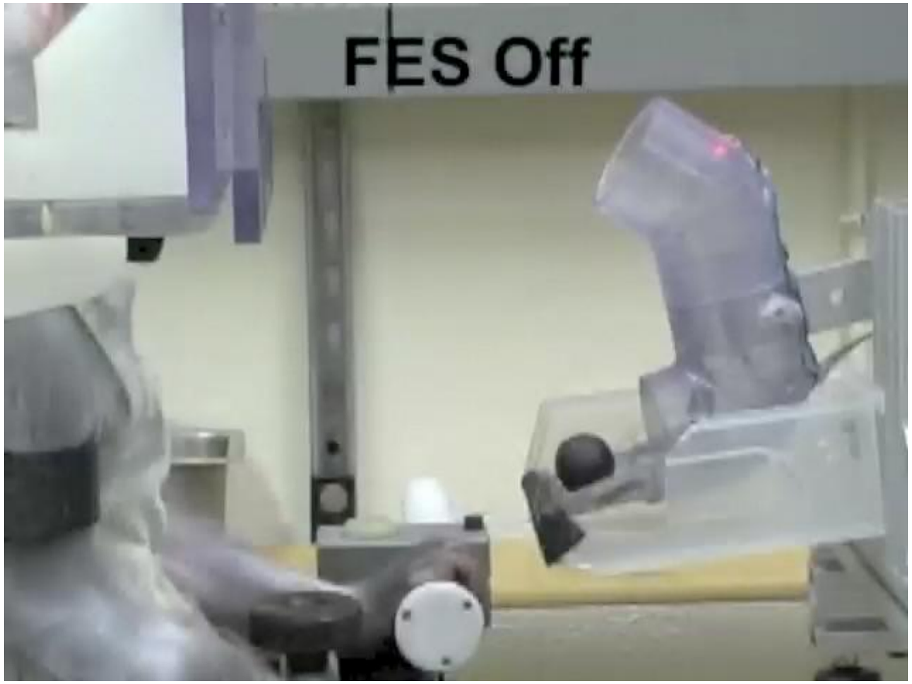
bypass injury by decoding movement intention



stimulate muscles with Functional Electrical Stimulation (FES)

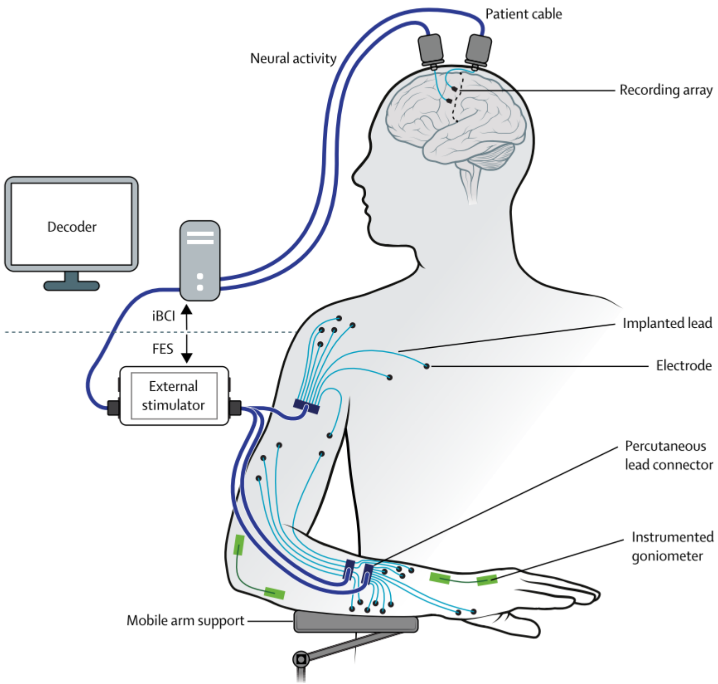
Animal model for developing FES + BCI





Ethier et al. Restoration of grasp following paralysis through brain-controlled stimulation of muscles. *Nature*, 2012

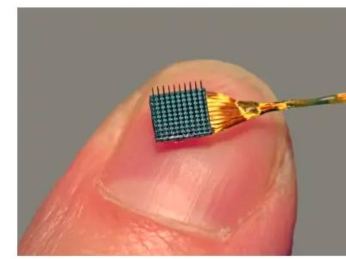
Human translation of FES to move the user's own arm



Ajiboye*, Willett* et al. Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration. *Lancet* (2017)

BCIs for communication

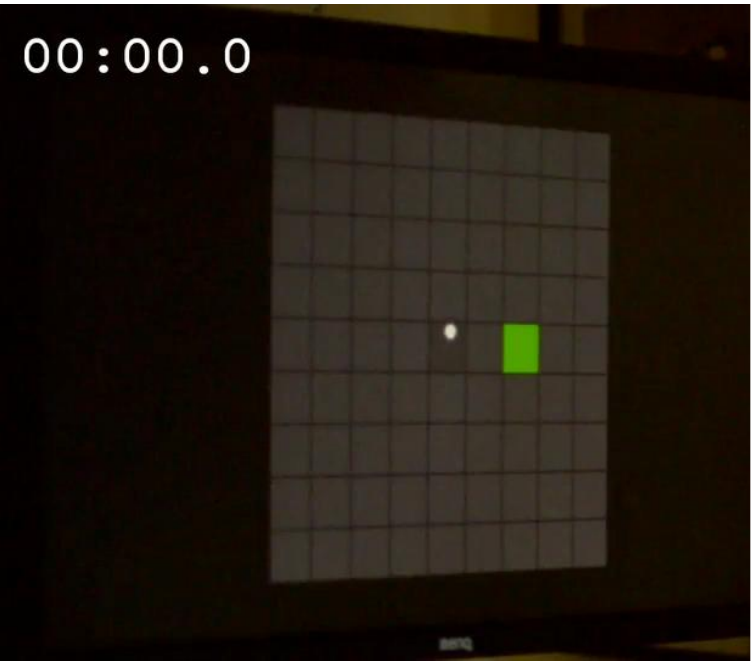
First person implanted with Utah arrays in 2004

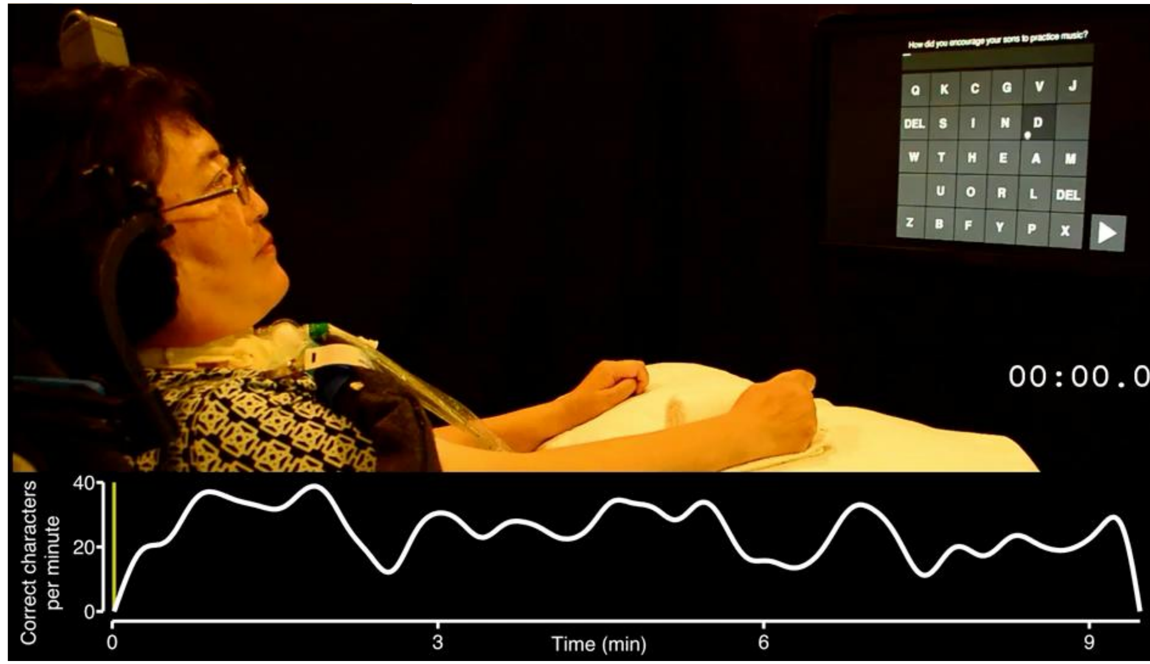


Hochberg et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature* (2006)

BCIs for communication: accurate point and click cursor control

~a decade of progress later…





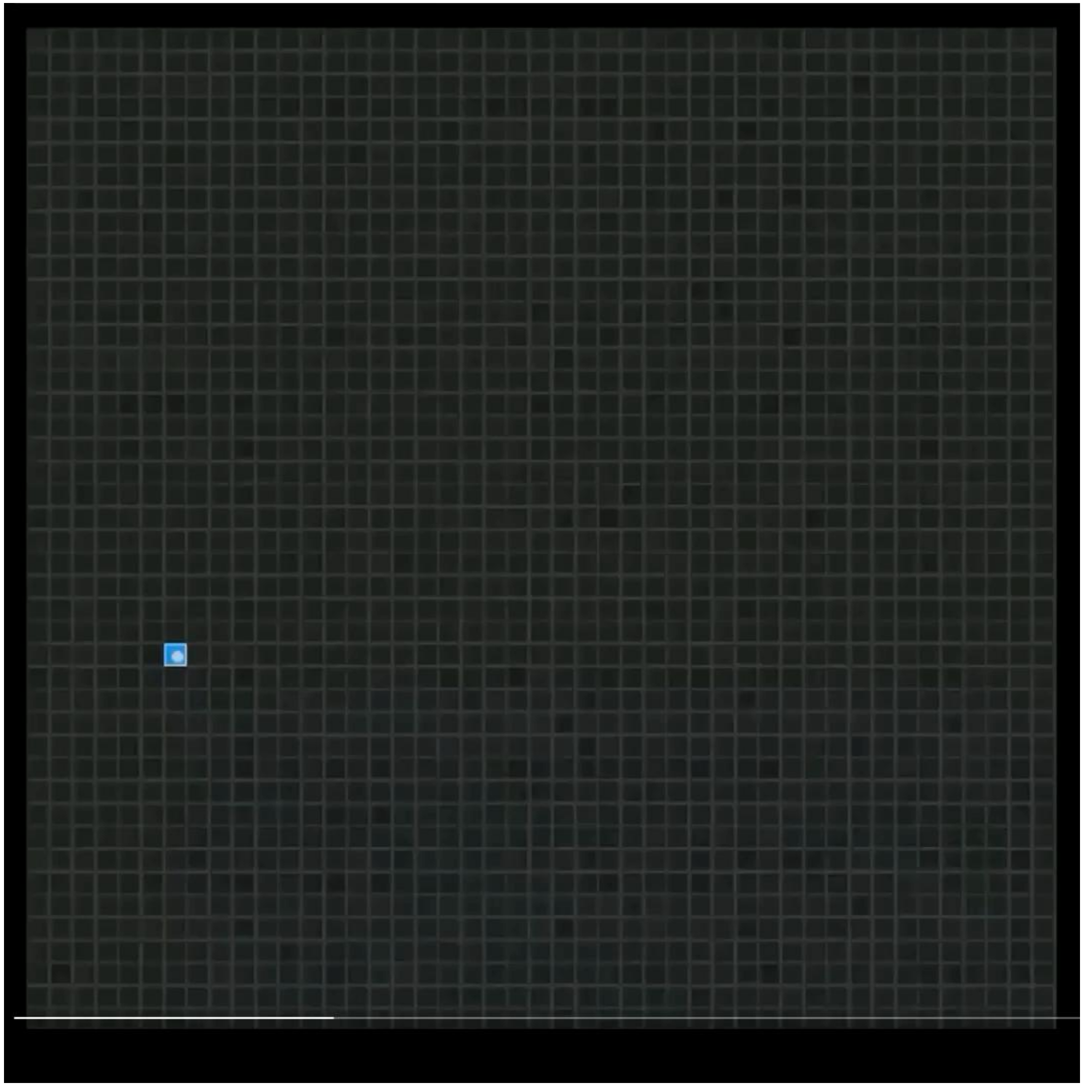
~4 bits per second or 8 words per minute

Pandarinath*, Nuyujukian* et al. High performance communication by people with paralysis using an intracortical brain-computer interface. *eLife* (2017)

Accurate point and click cursor control now in commercial trials

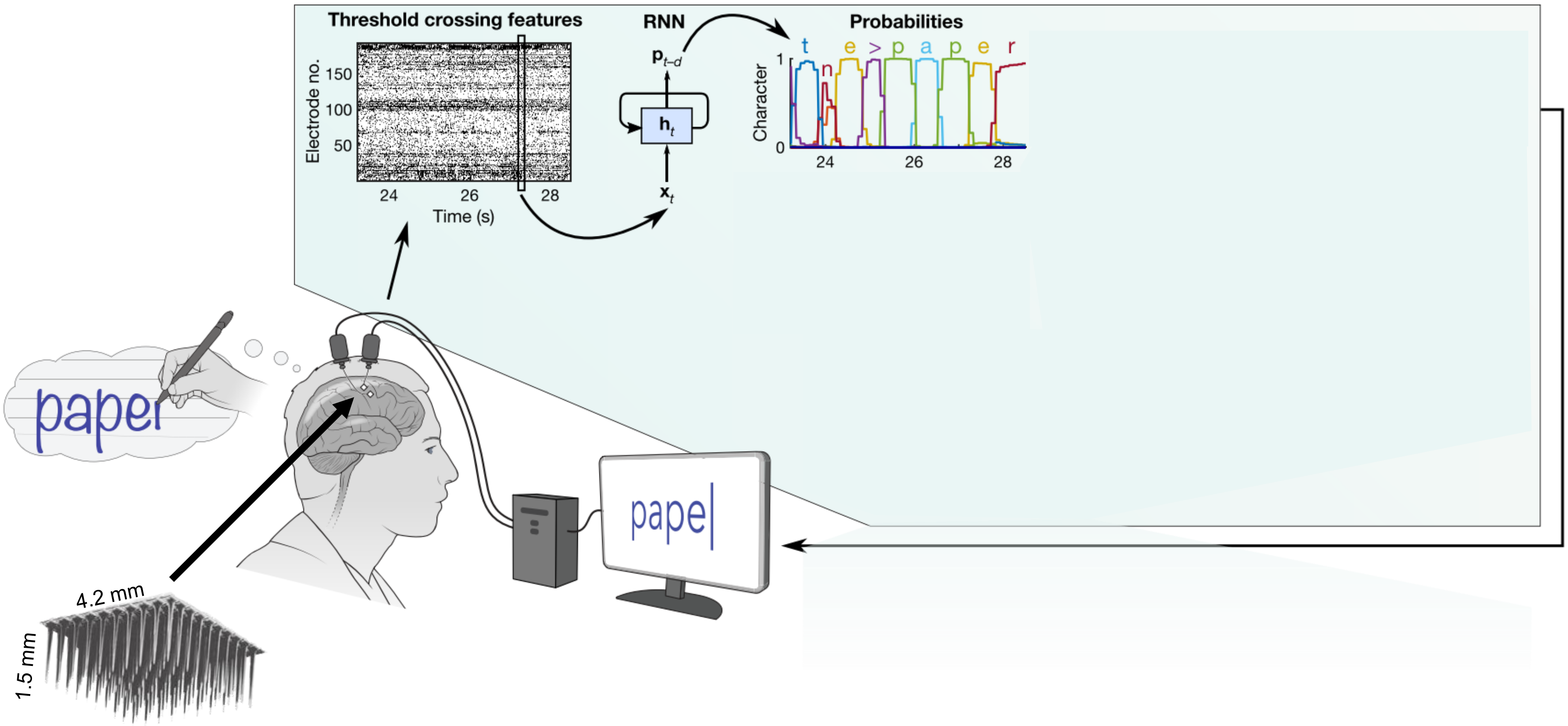
Neuralink Participant #1

Accurate point and click cursor control now in commercial trials



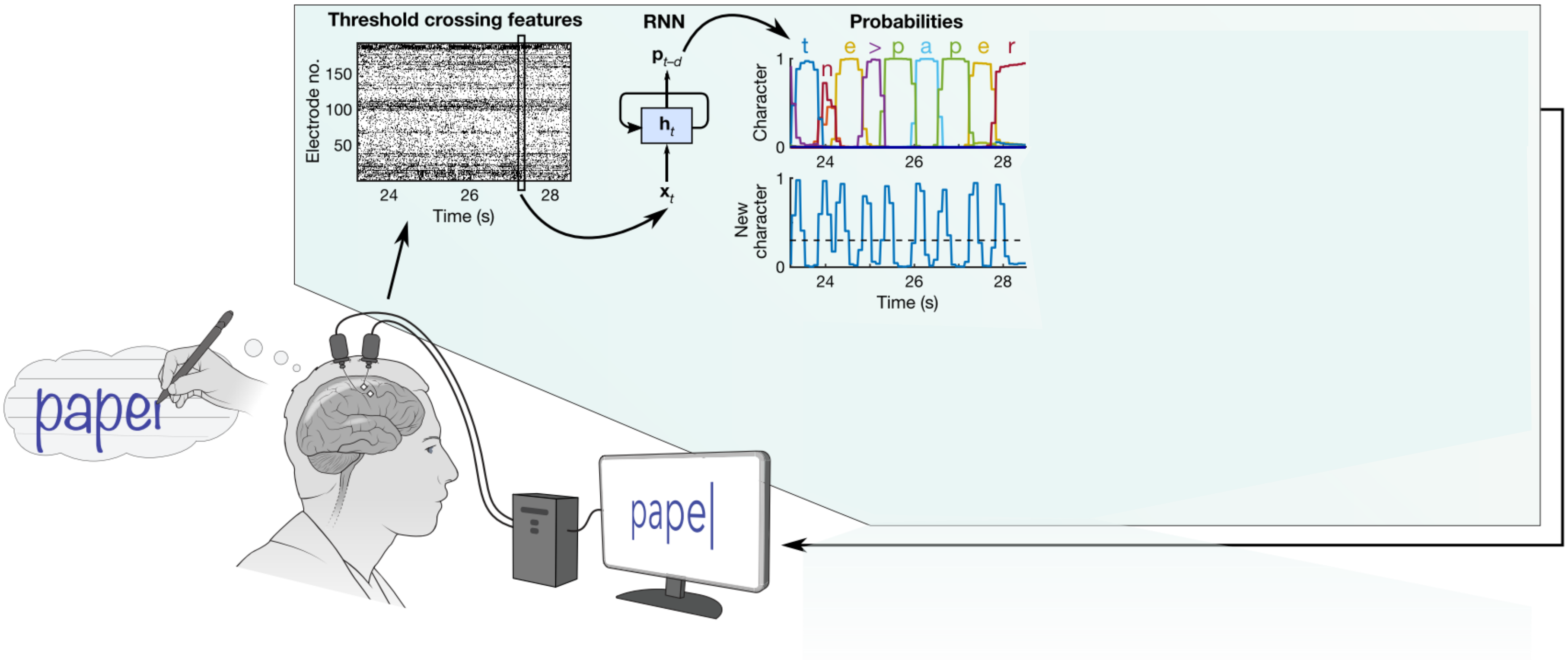
Neuralink
Participant #1:
~10 bits per second

Handwriting BCI



Willett et al. High-performance brain-to-text communication via handwriting. *Nature* (2021)

Handwriting BCI



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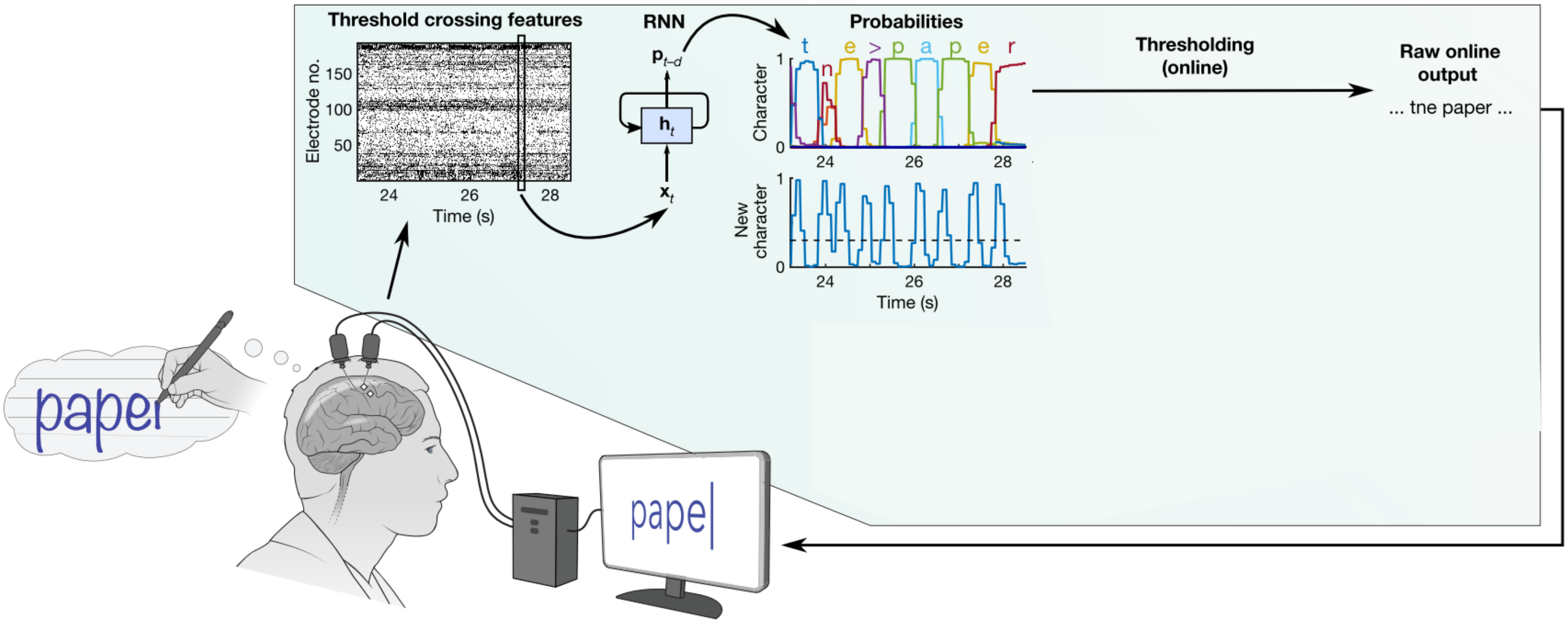

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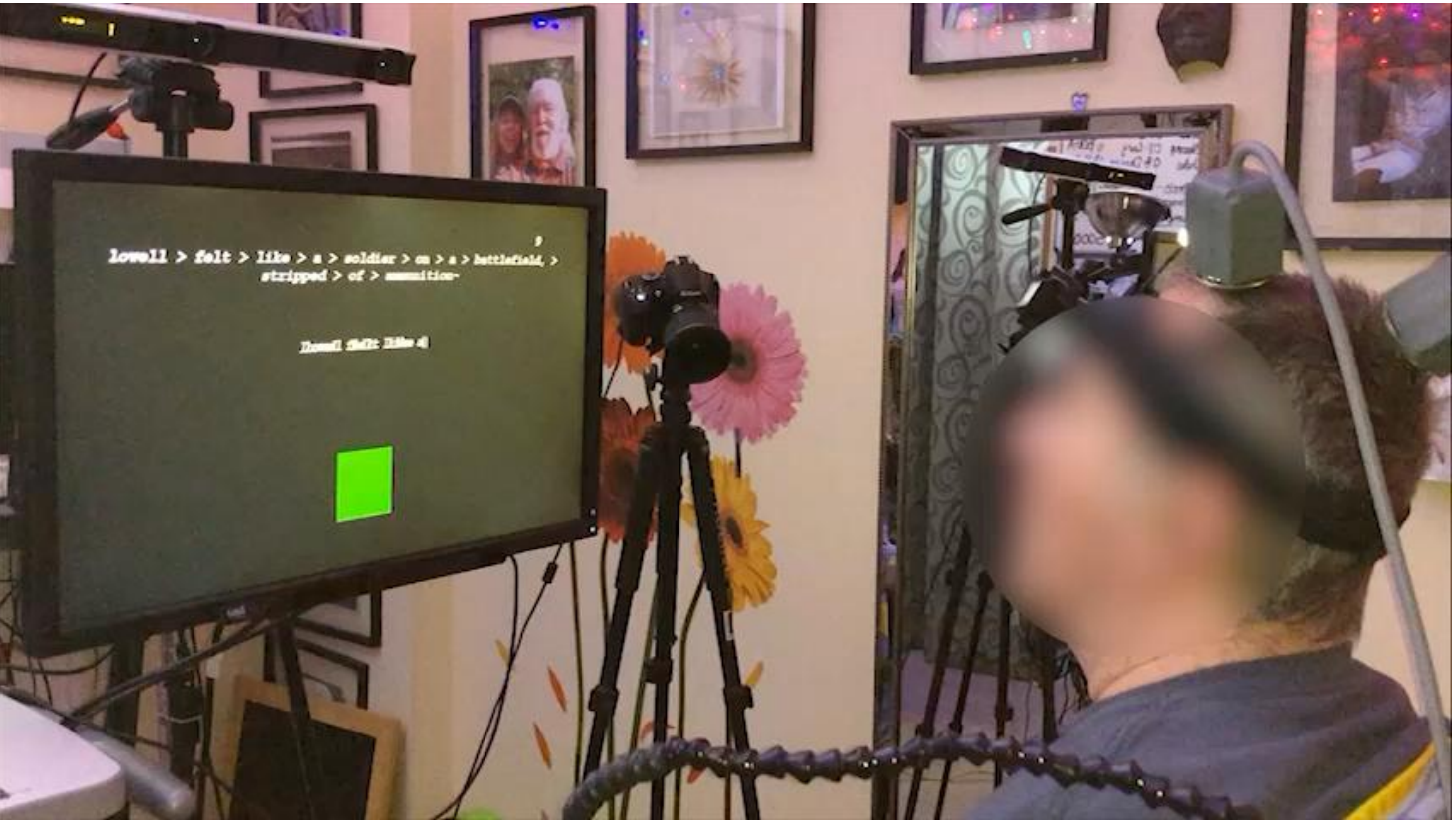
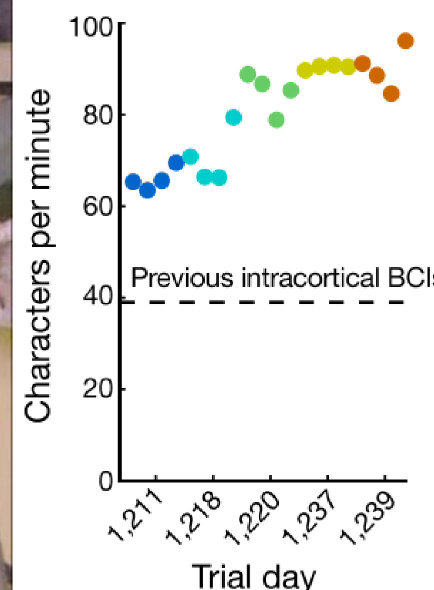
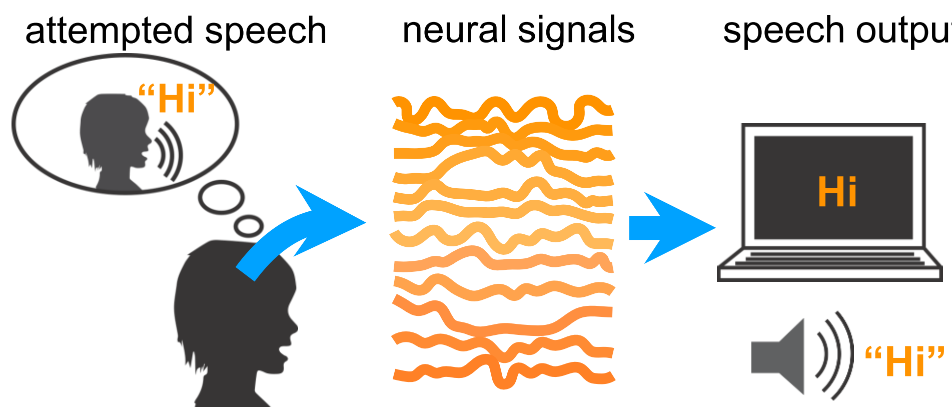


~18 words per minute



Willett et al. High-performance brain-to-text communication via handwriting. *Nature* (2021)

Next frontier: BCIs to restore lost speech

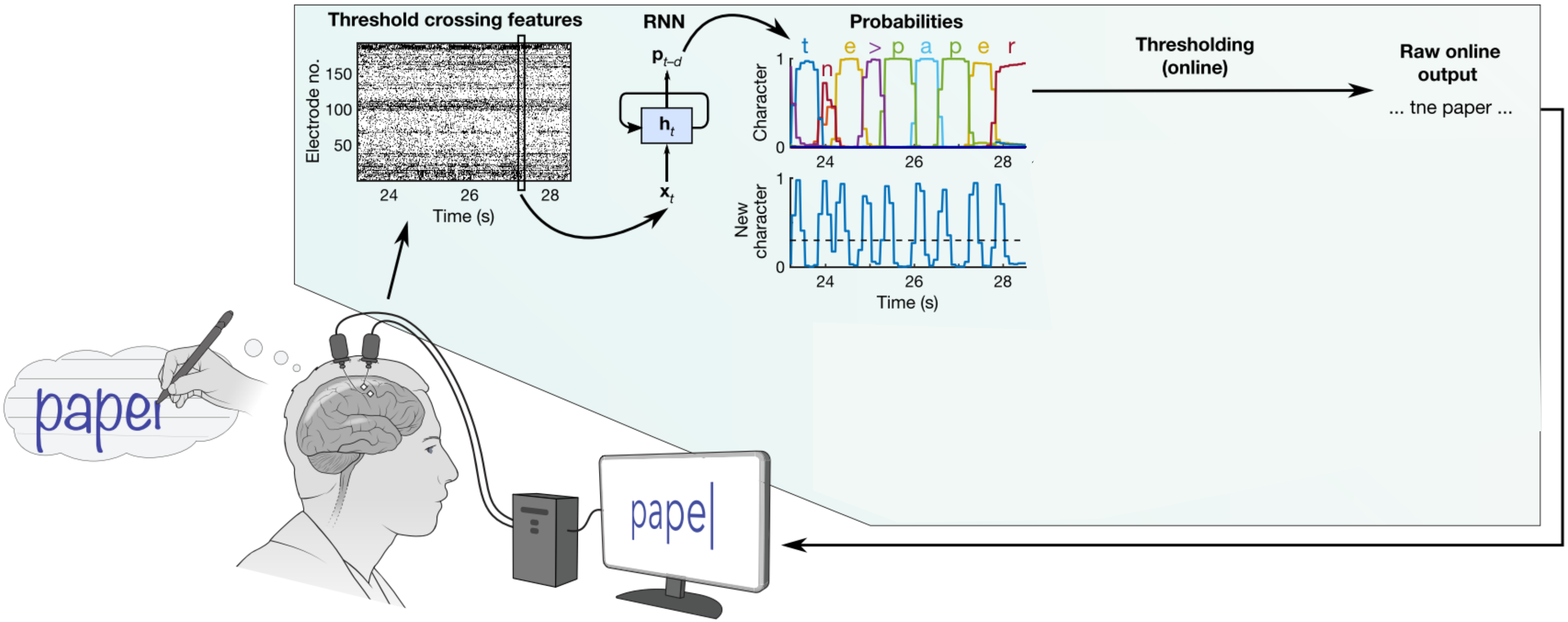


Point-and-click BCI:
Pandarinath*, Nuyujukian* et al. *eLife* (2017) ~8 words per minute

Handwriting BCI:
Willett et al. *Nature* (2021) ~18 words per minute

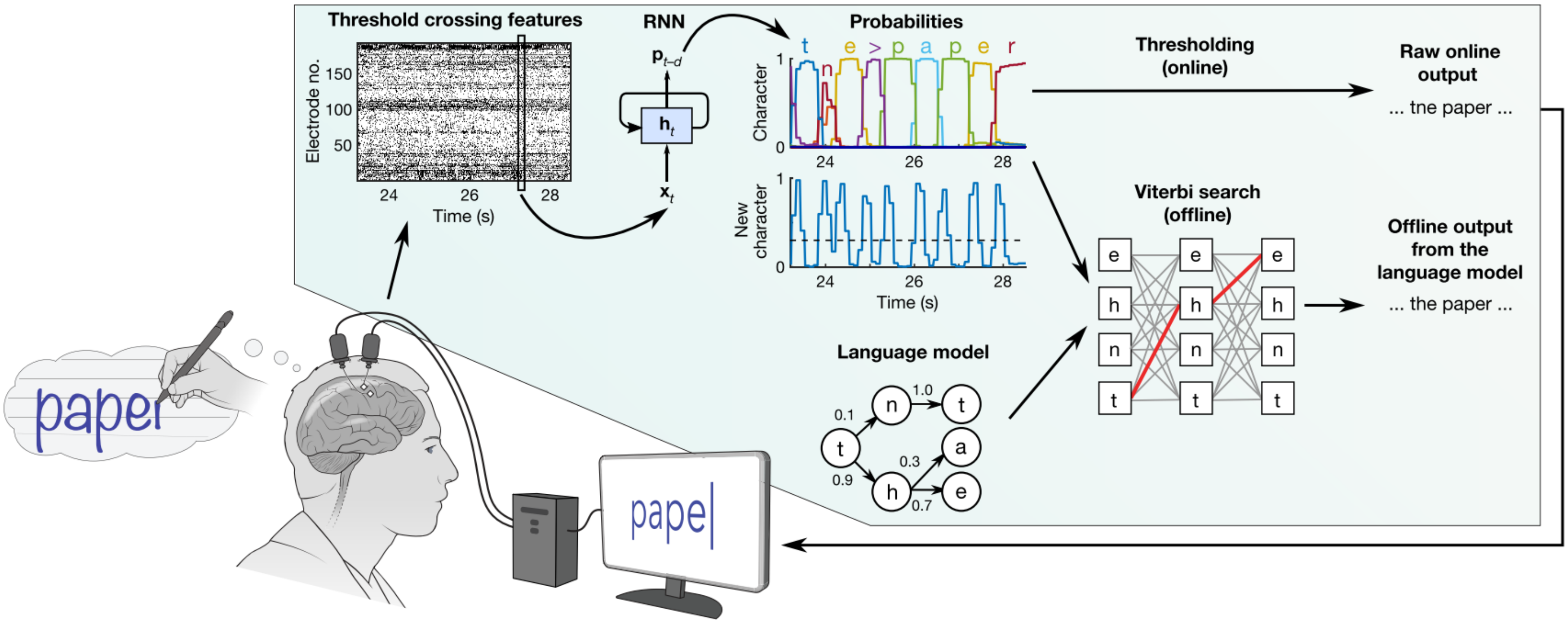
Conversational speech **~150** words per minute

Speech decoding with a similar approach to the Handwriting BCI



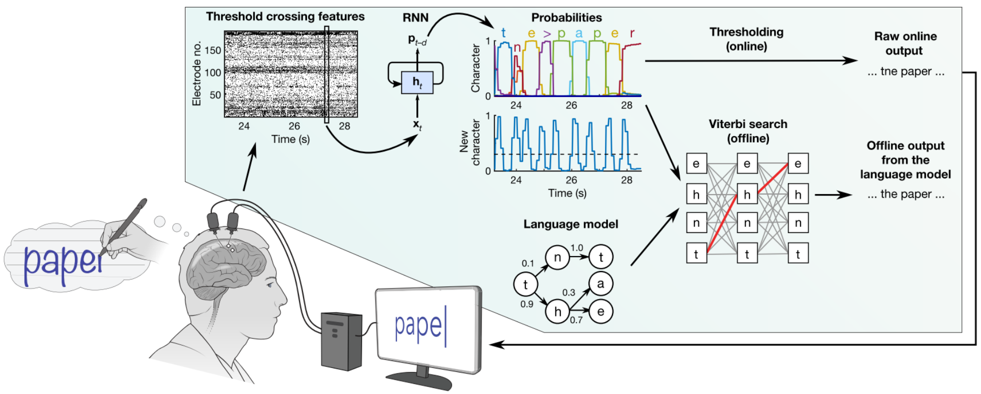
Willett et al. High-performance brain-to-text communication via handwriting. *Nature* (2021)

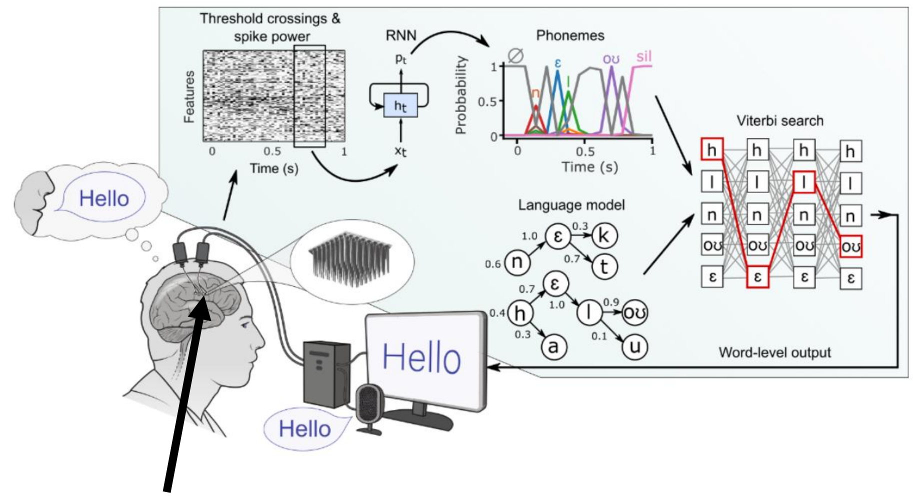
Speech decoding with a similar approach to the Handwriting BCI



Willett et al. High-performance brain-to-text communication via handwriting. *Nature* (2021)

Speech decoding with a similar approach to the Handwriting BCI





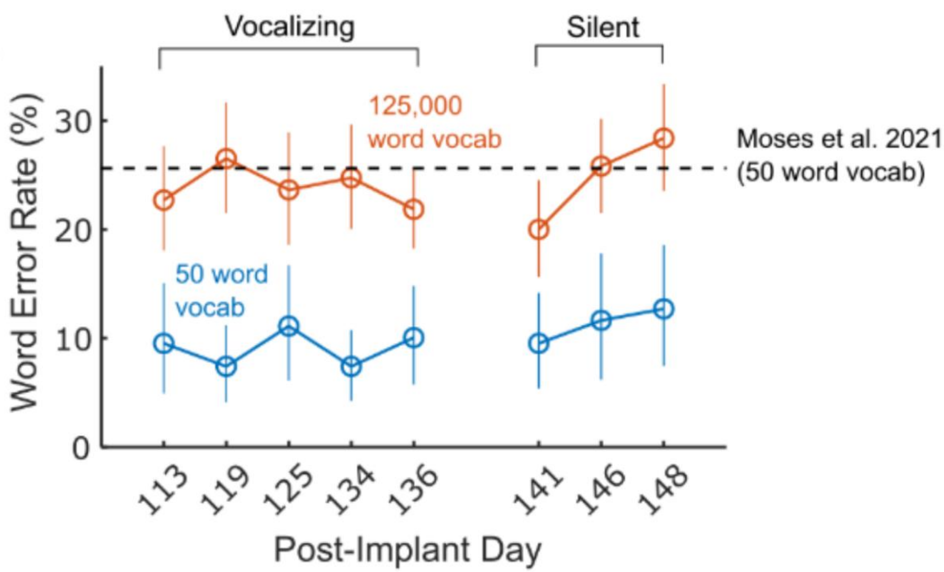
2 arrays in ventral (orofacial) motor cortex

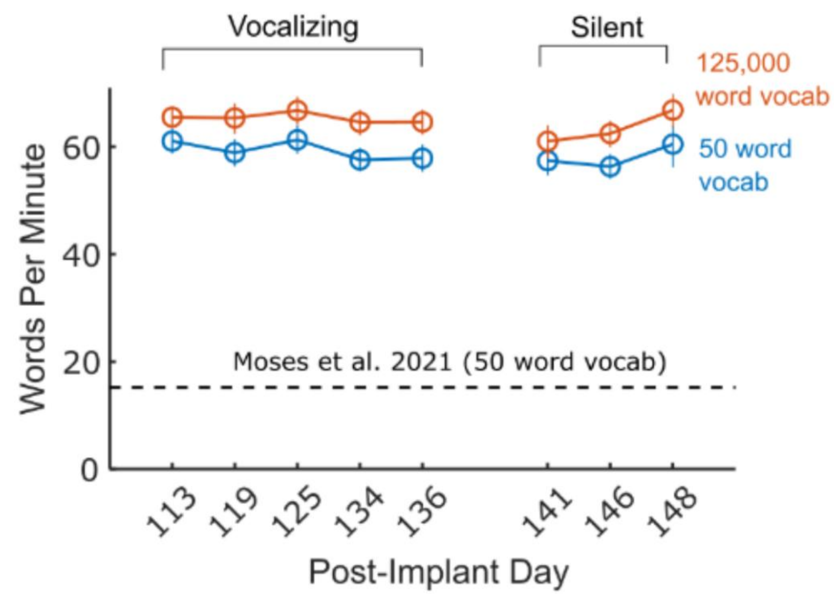
Willett*, Kunz*, Fan* et al. A high-performance speech neuroprosthesis. *Nature* (2023)

Brain-to-text speech neuroprosthesis

Willett*, Kunz*, Fan* et al. A high-performance speech neuroprosthesis. *Nature* (2023)

Brain-to-text speech neuroprosthesis





Willett*, Kunz*, Fan* et al. A high-performance speech neuroprosthesis. *Nature* (2023)

BCIs for communication

Take-away:

- Very good point-and-click computer use and handwriting decoding is possible today
- Communication rate has roughly doubled every 4 years 4 times now
- Brain-to-text speech BCI working well in n=1 participant with ALS
- Instantaneous voice BCIs represent the current frontier

Writing into the Brain

Parkinsons Diseases (PD)

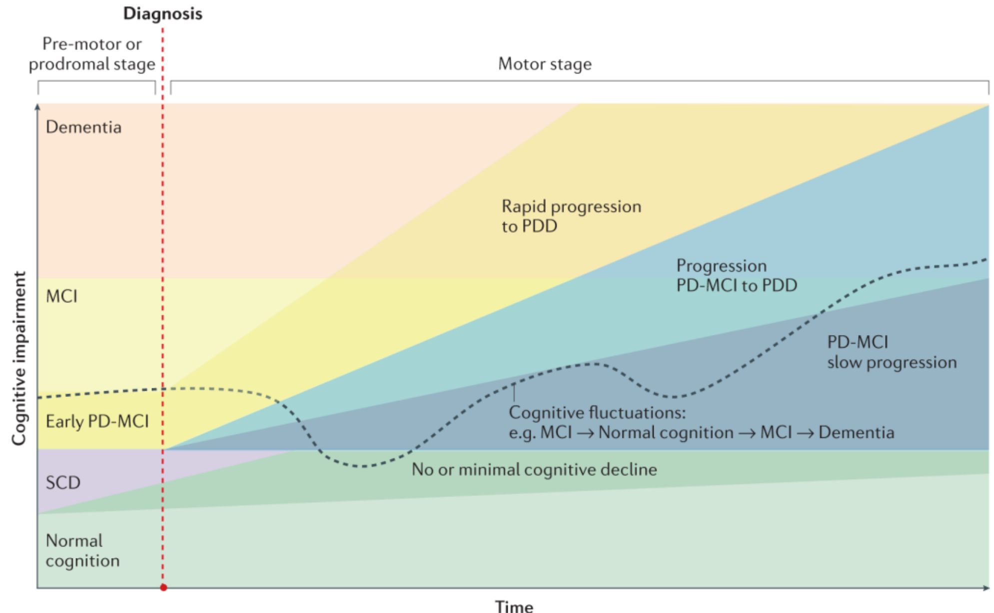
Motor Difficulties

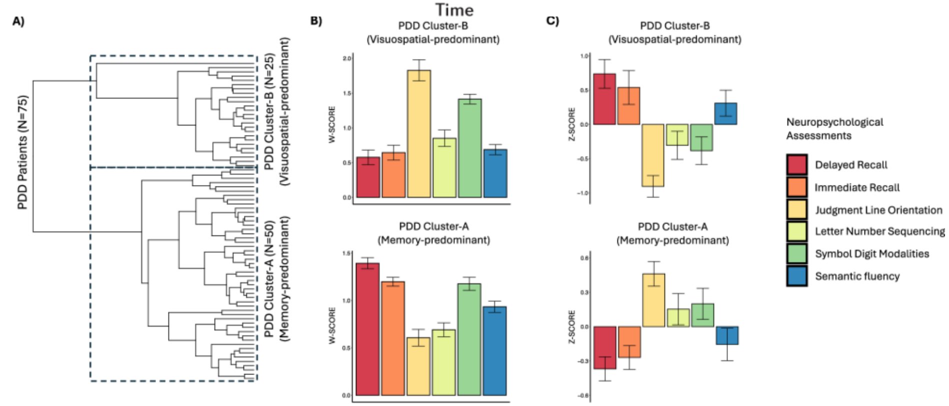
Parkinson's disease leads to tremors, muscle stiffness, and slowed movement *(bradykinesia),* making daily tasks challenging for patients.

Cognitive Challenges

Impaired executive function, slower thinking, and memory issues are cognitive symptoms that affect individuals with Parkinson's.

- Executive functions*:* Disrupted ability to plan, organize, initiate, and regulate activities with a specific goal in mind.
- Visual-spatial skills*:* Difficulty estimating distances, navigating in space, and using mental imagery.
- Attention and working memory: Difficulty focusing and hold information in working memory.
- Language: Difficulty finding the 'right' word (*anomia*) and slower/simpler speech (*fluent aphasia*).

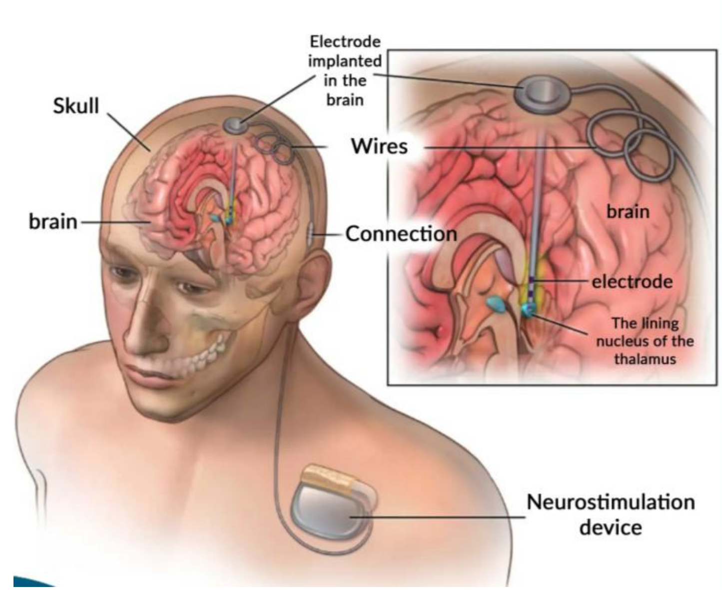




Aarsland et al, *Nat Rev Dis Primers* 2021

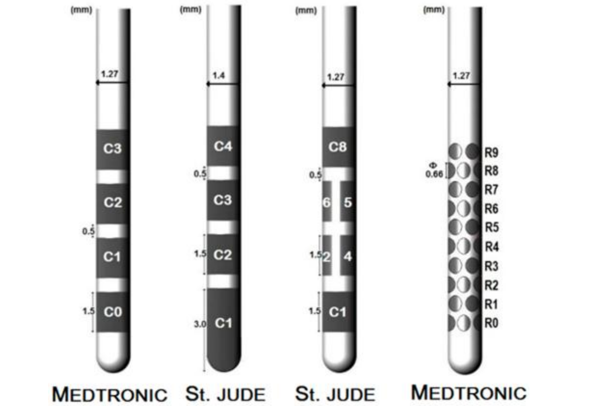
Deep-Brain Stimulation (DBS) for PD

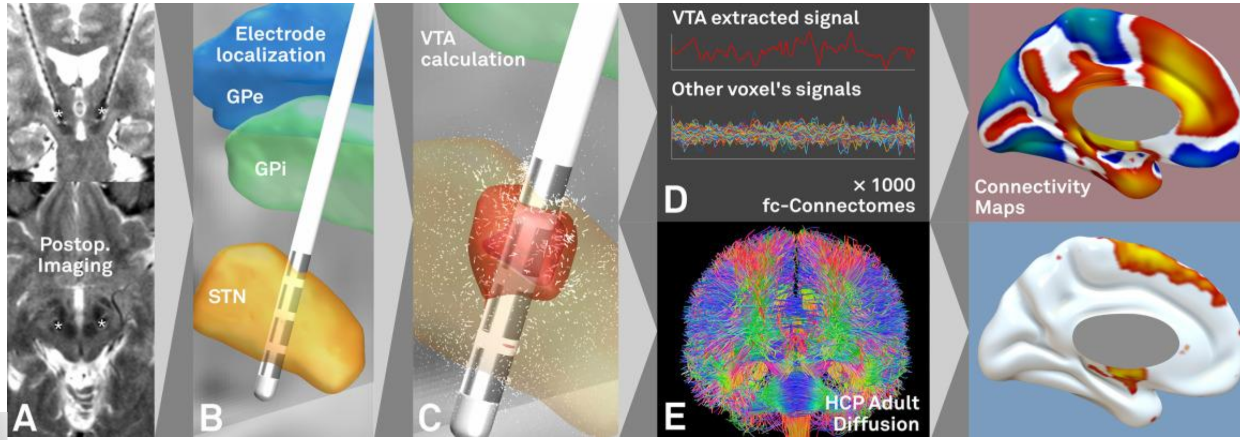
Deep-brain stimulation treats tremors and bradykinesia in PD patients:



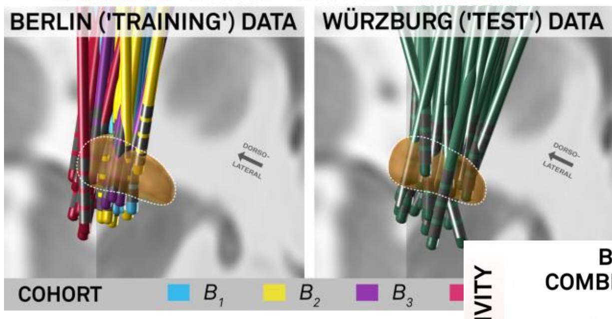
Variability in Effect of DBS

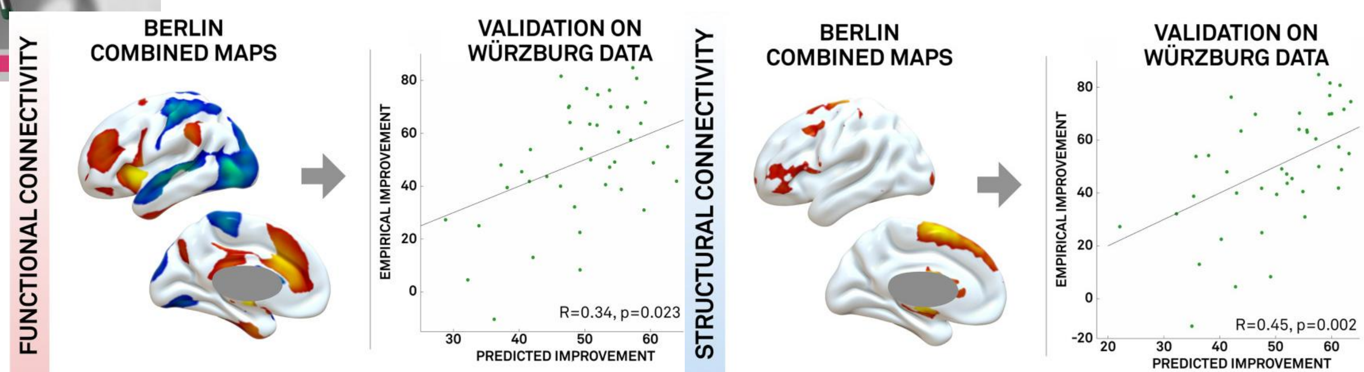
Stimulating electrodes are large, coarsely stimulating the STN or GPi:





VTA = Volume of tissue activated





Horn et al, *Annals Neurology* 2017

Side Effects of DBS

Side Effects of Deep Brain Stimulation

Deep brain stimulation has been associated with several adverse events:

	Patients [%]
Neurological (Gait disturbance, speech disturbance, Akinesia, Incontinence, etc.)	69%
Psychiatric (suicide, depression, cognitive disturbance, hallucinations, confusion)	39%
Surgery-related (intracranial hemorrhage, infection and wound healing abnormalities)	15%
Other	59%
Total	86%

~evidence for an increased risk of depression/suicide ideation in STN rather than GPi DBS.

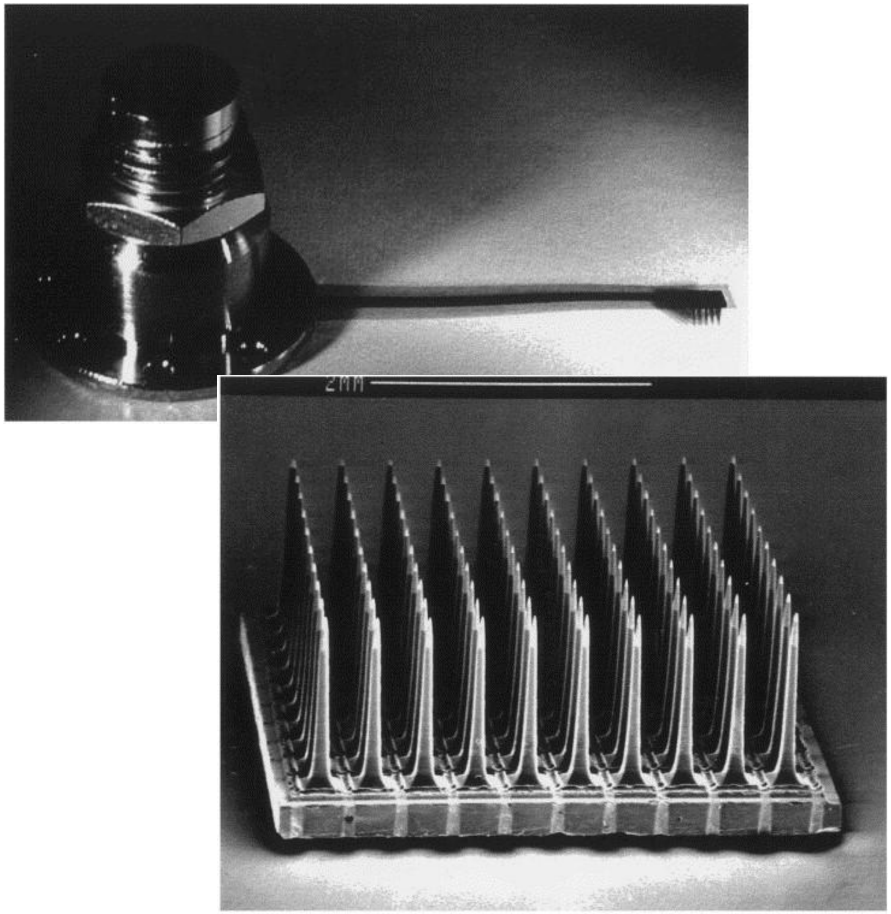
Side effects can often be mitigated by tuning of stimulation parameters.

Opens the door for improved precision!

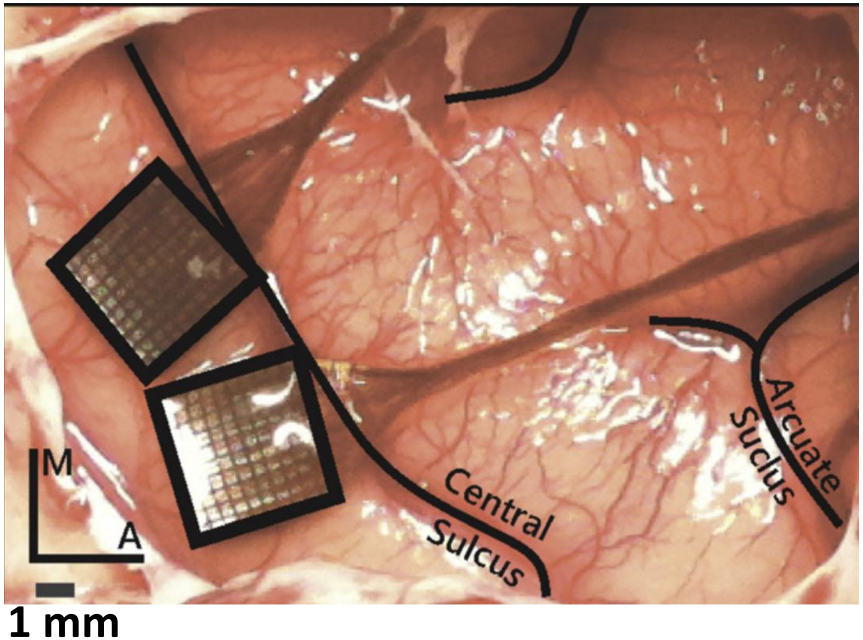
Buhmann et al, *PLoS One* 2017

Increasing the precision of stimulation

The Utah Electrode Array (UAE) was developed for precise stimulation of visual cortex:



Since then, they have been used for chronic recording and stimulating in a variety of different brain regions:

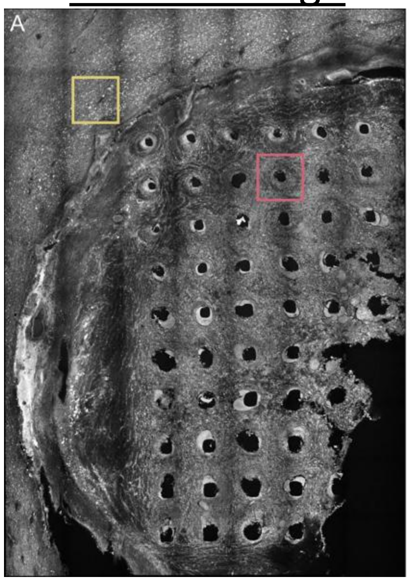


Norman et al, *Vis Research* 1998

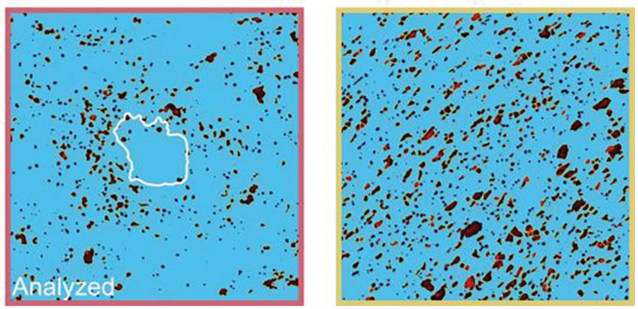
Chronically implanted Utah Arrays

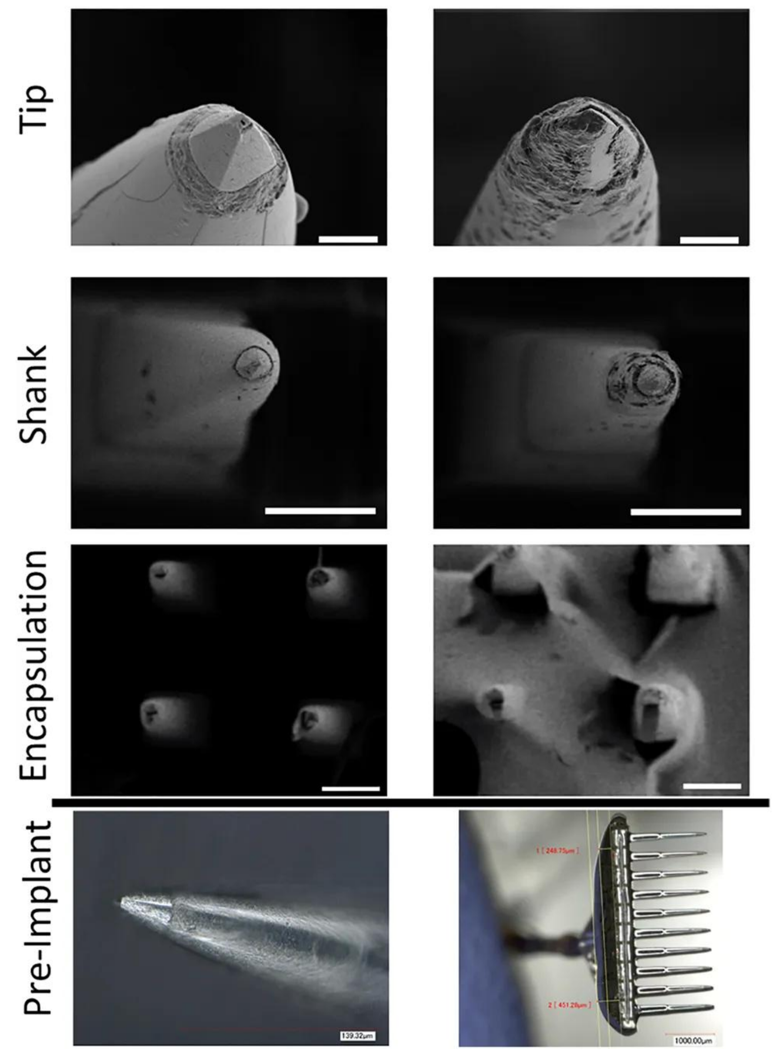
Chronic implants cause damage to neural tissue and to the electrode array itself.

Gross damage



Loss of Neurons

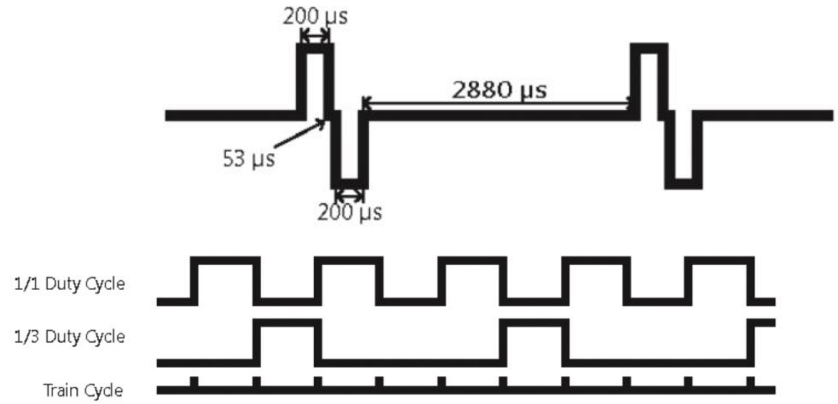


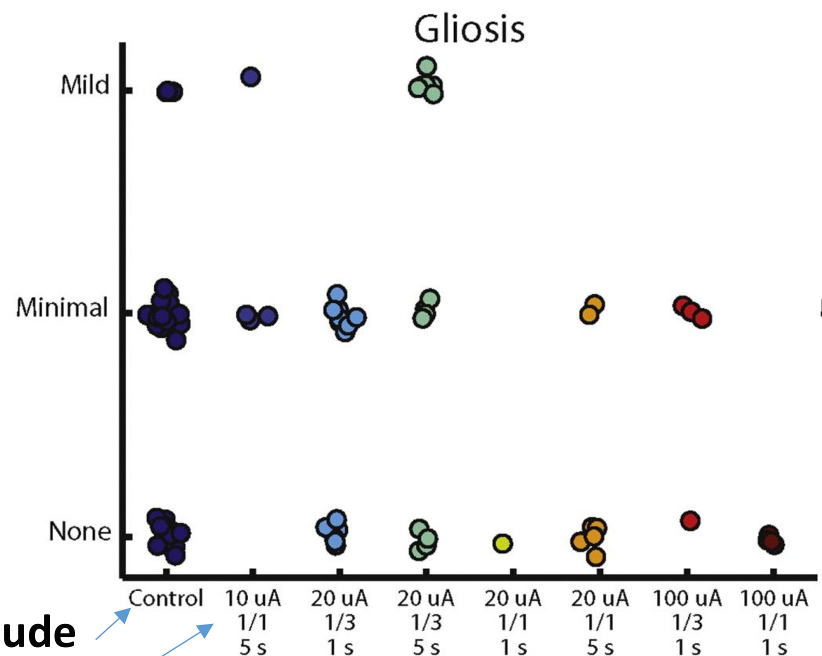


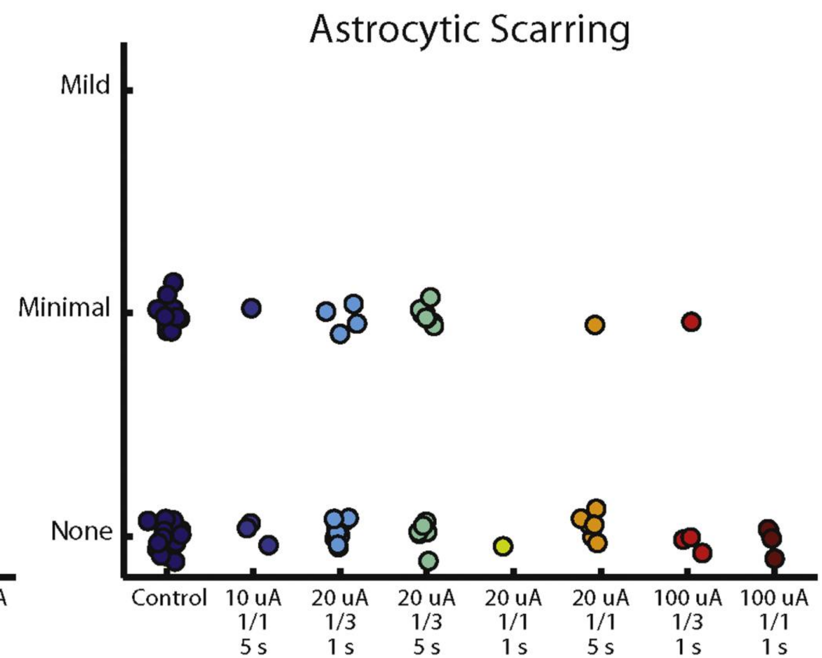
Patel et al, *J Neural Eng* 2024

Stimulation does not increase damage

Stimulation was delivered at various amplitudes and for various durations and duty cycles to measure the effect on gliosis and scarring.







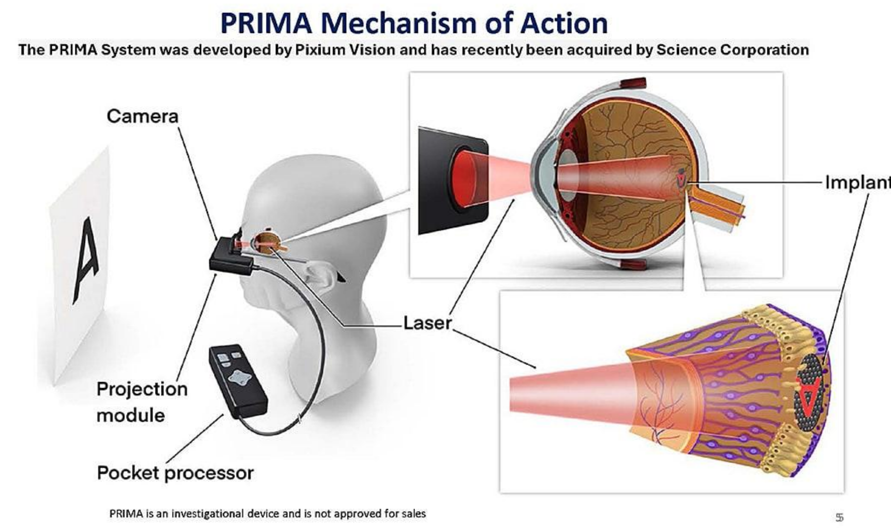
Amplitude
Duty Cycle
Duration

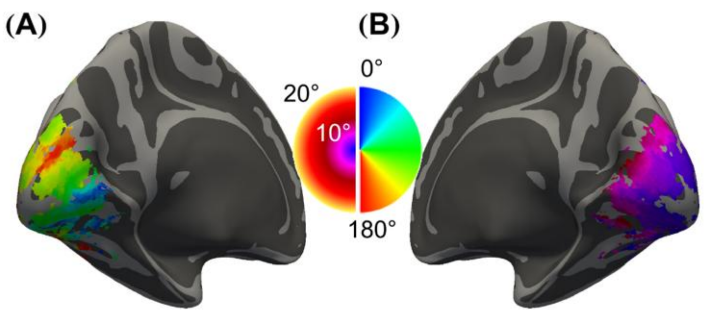
Rajan et al, *J Neural Eng* 2015

Building a Visual Prosthetic

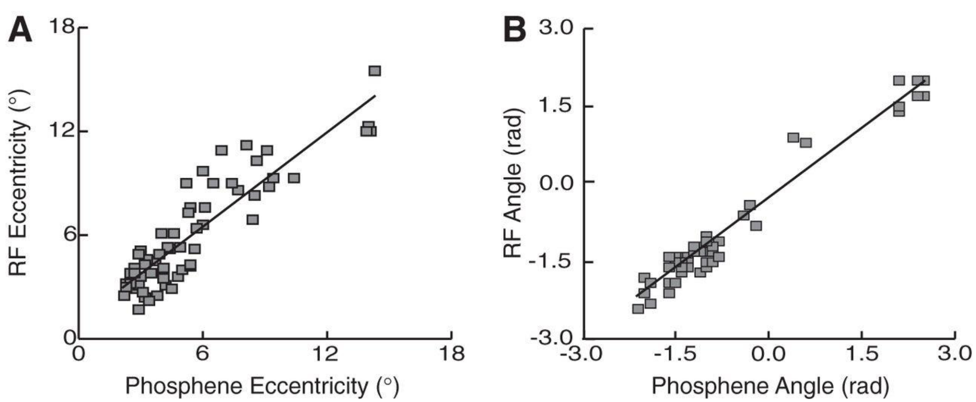
Some forms of vision loss can be treated with retina implants.

But many forms of vision loss are due to damage and/or loss in the retina and/or thalamus. This means the best target for treatment might be visual cortex.





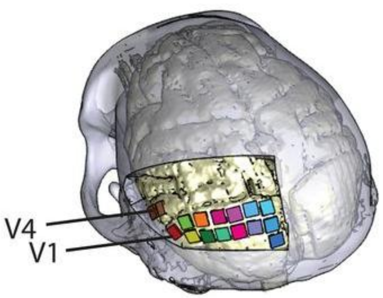
V1 is a particularly attractive target given its structured topography.

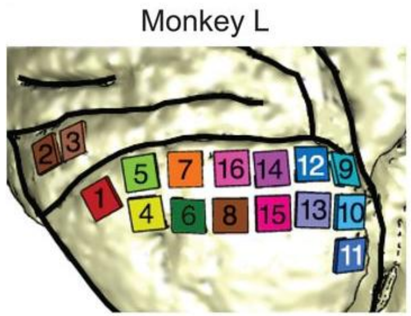


Stimulating V1 induces a ‘phosphene’. A flash of light at the stimulated location.

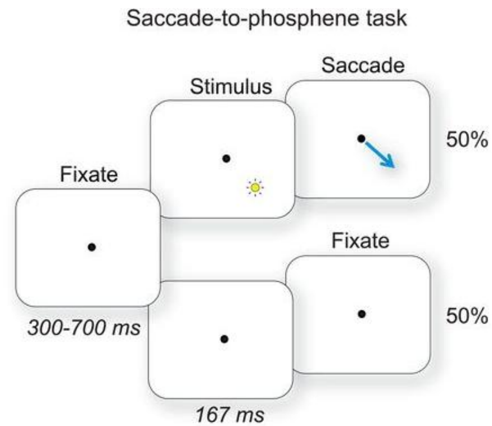
Building a Visual Prosthetic

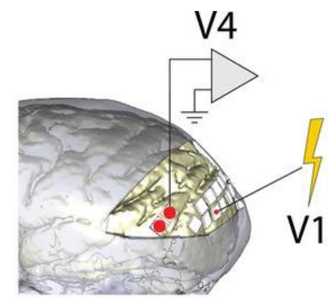
Implantation of 1024 electrodes in V1 of monkey:



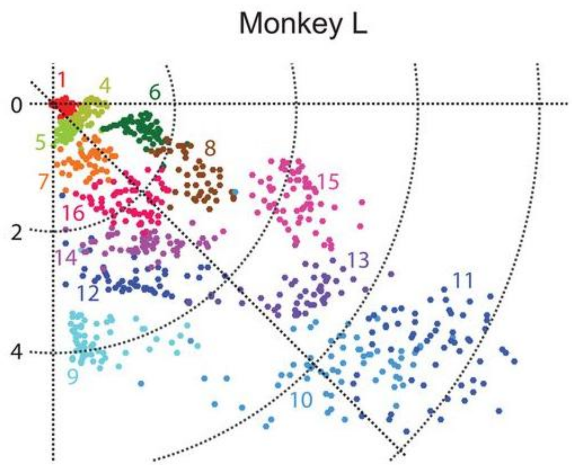


Monkeys treat electrically stimulated phosphenes similar to flashes of light:

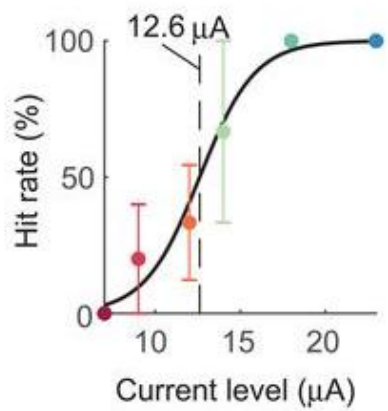




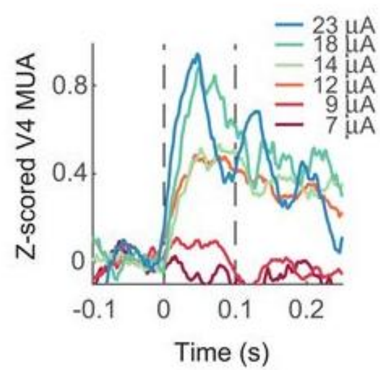
Covers a wide portion of visual field:

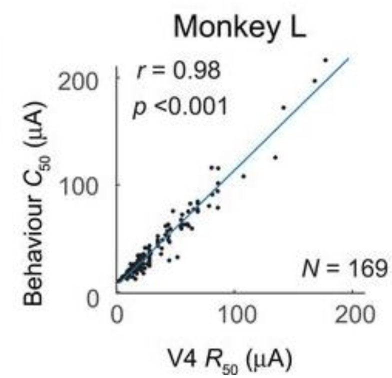


Detection rate increased with current:



As did V4 responses, which predicted behavior:

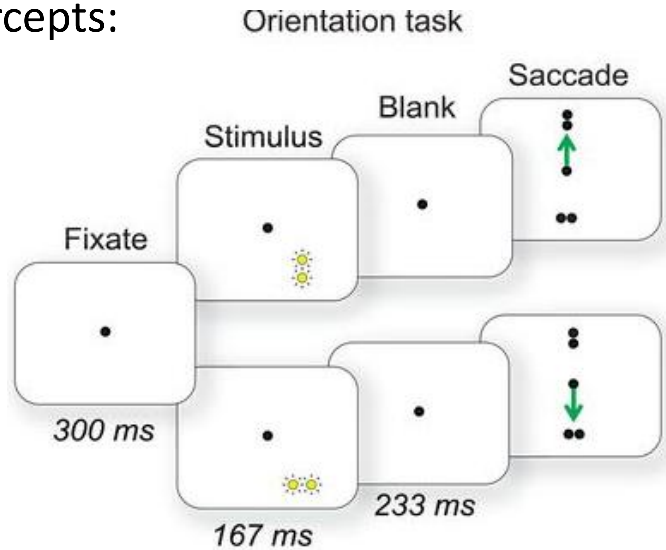




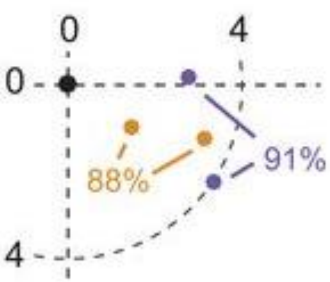
Chen et al, *Science* 2020

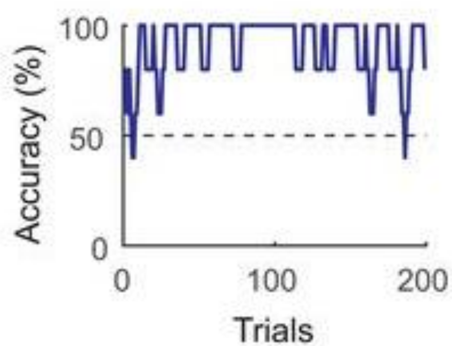
Building a Visual Prosthetic

Spatial patterning of stimuli induces percepts:

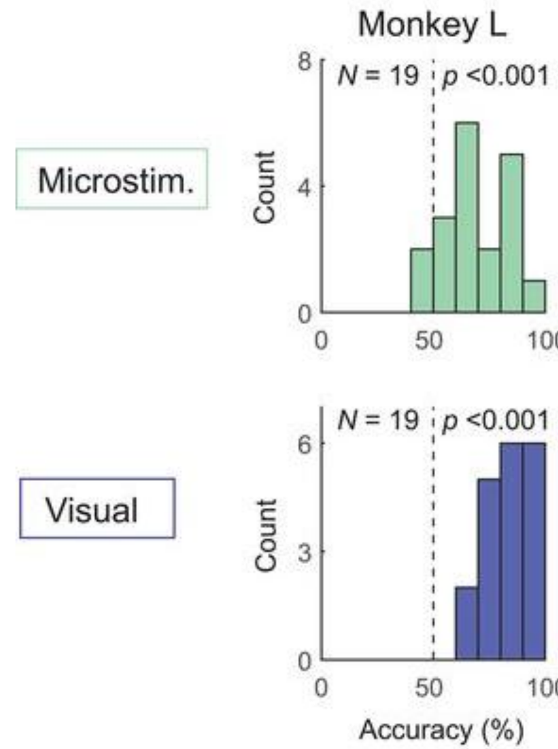


Monkeys do this task immediately:





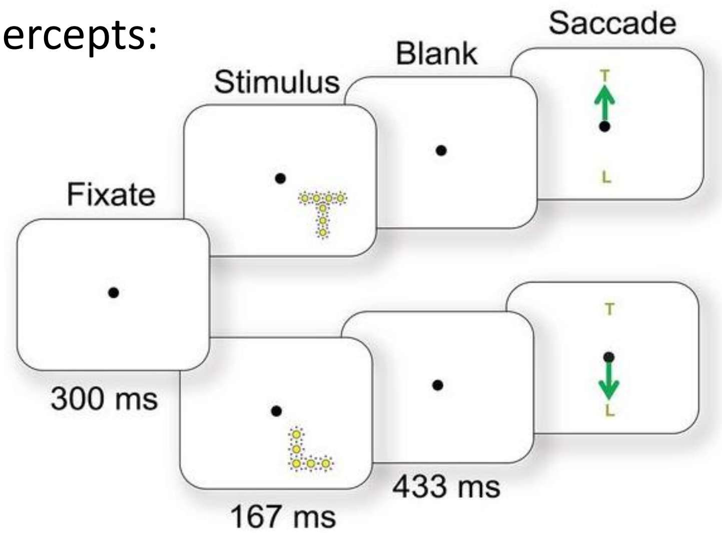
Percept of electrical microstimulation is similar to visual stimuli:



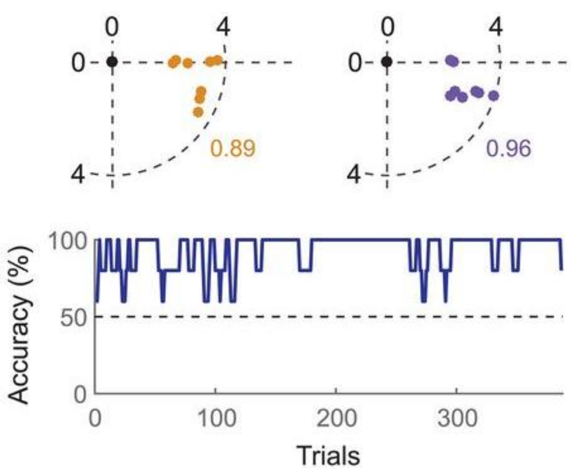
Chen et al, *Science* 2020

Building a Visual Prosthetic

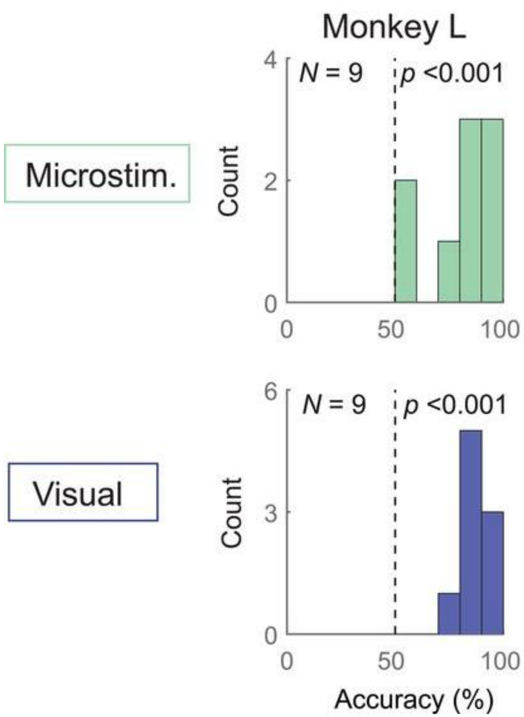
Spatial patterning of stimuli induces percepts:



Monkeys do this task immediately:



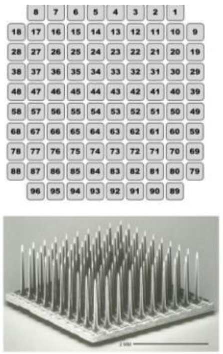
Percept of electrical microstimulation is similar to visual stimuli:

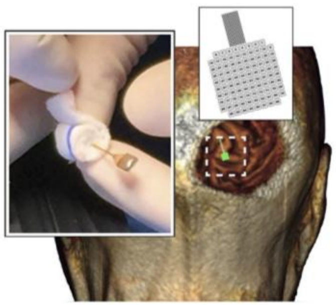


Chen et al, *Science* 2020

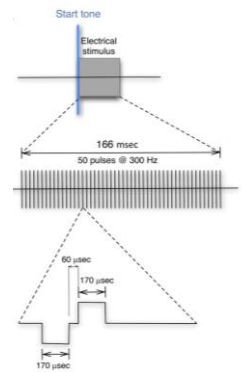
Building a Visual Prosthetic

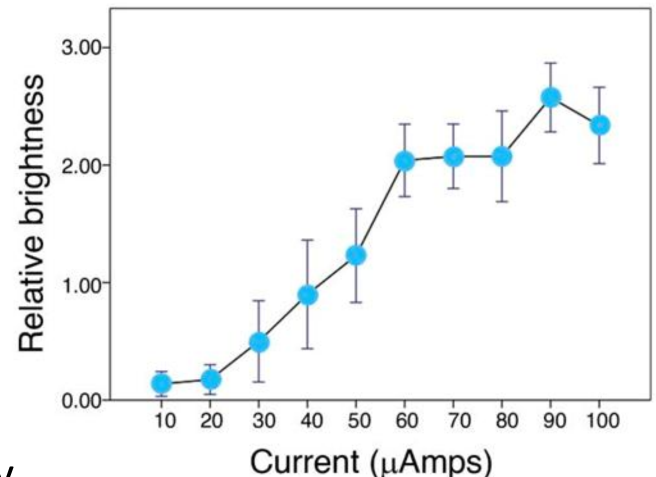
Implantation of Utah array into V1 of a human patient:



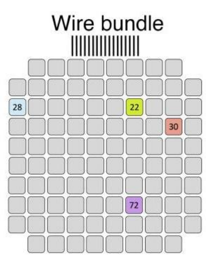


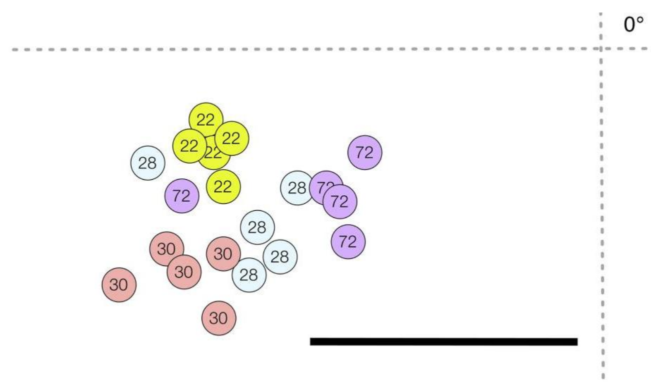
Increasing current amplitude increases perceived brightness, consistent with NHP work showing detection increases with current magnitude.





Stimulating across the array gives you the ability to spatially pattern stimulation across the array:

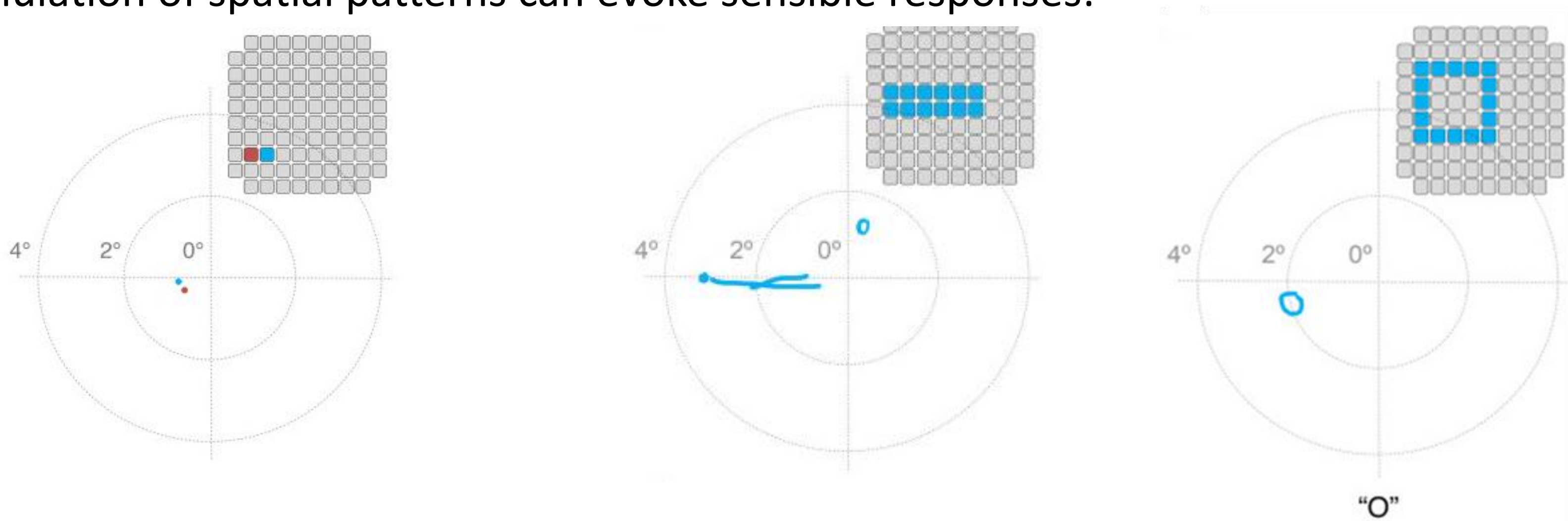




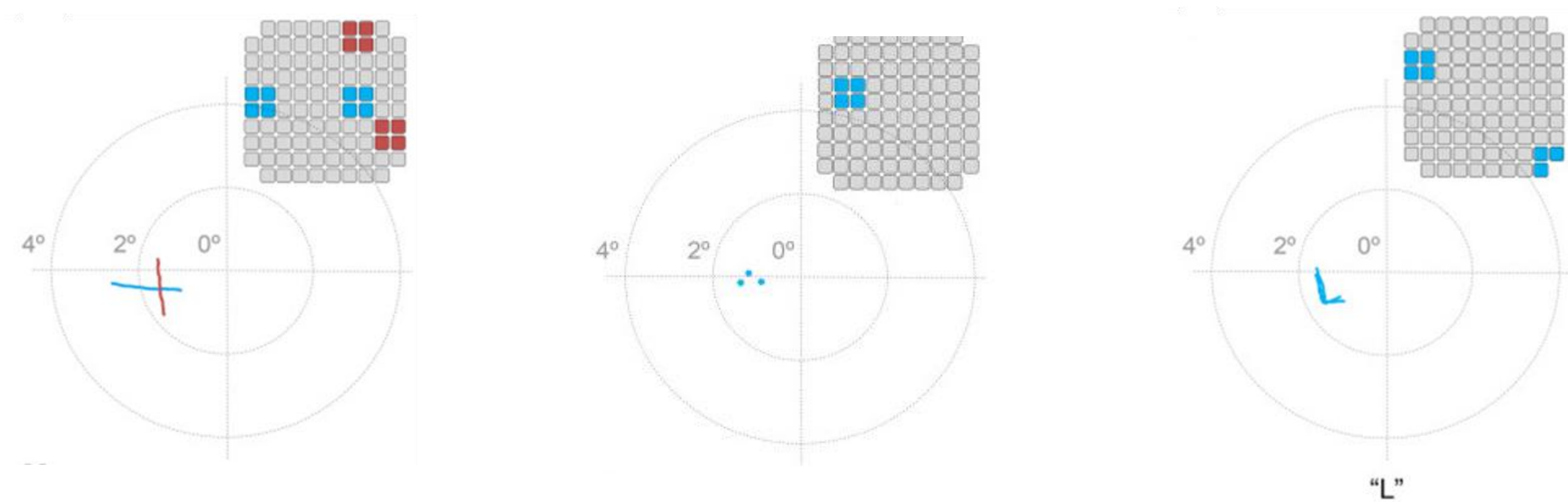
Fernandez et al, *JCI* 2021

Building a Visual Prosthetic

Stimulation of spatial patterns can evoke sensible responses:



But also can create unpredictable responses:

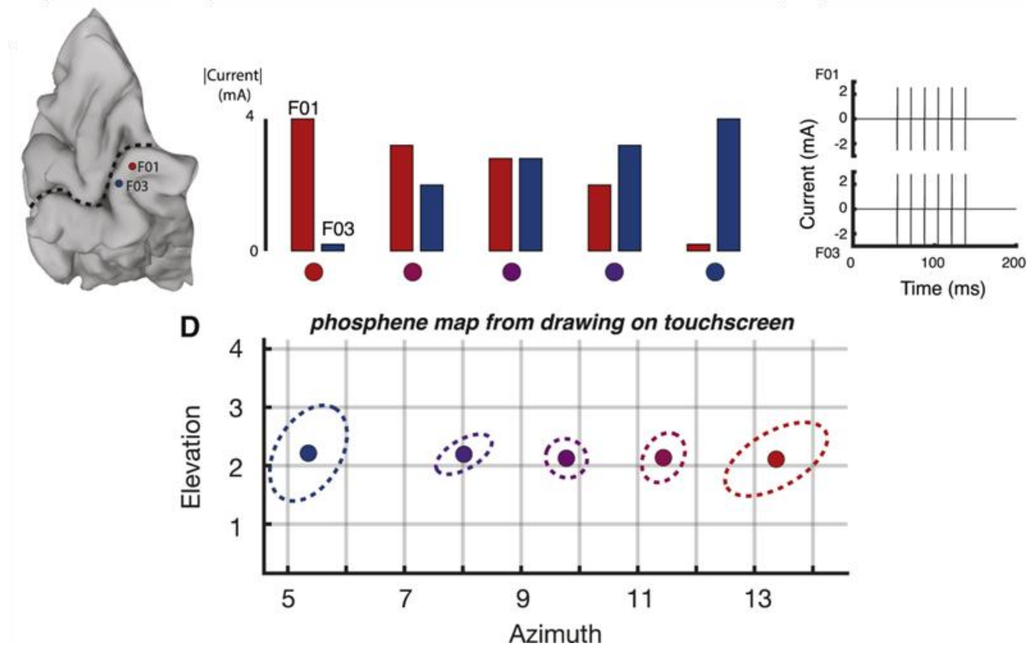


Fernandez et al, *JCI* 2021

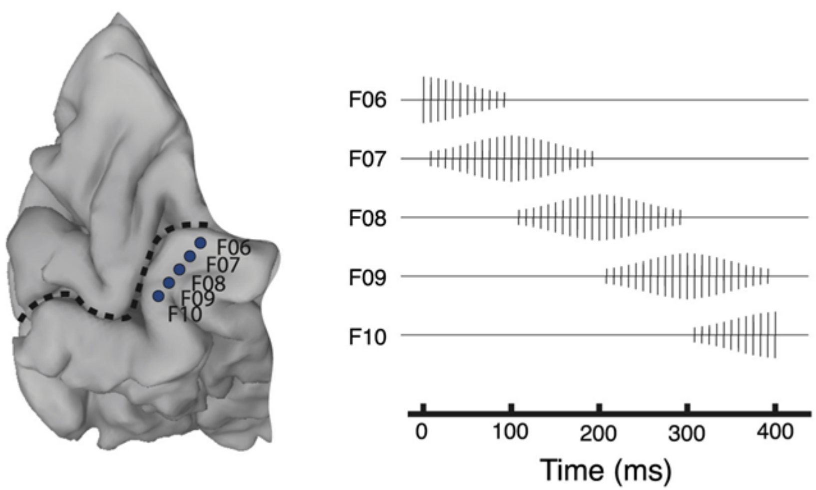
Tracing figures in a visual prosthetic

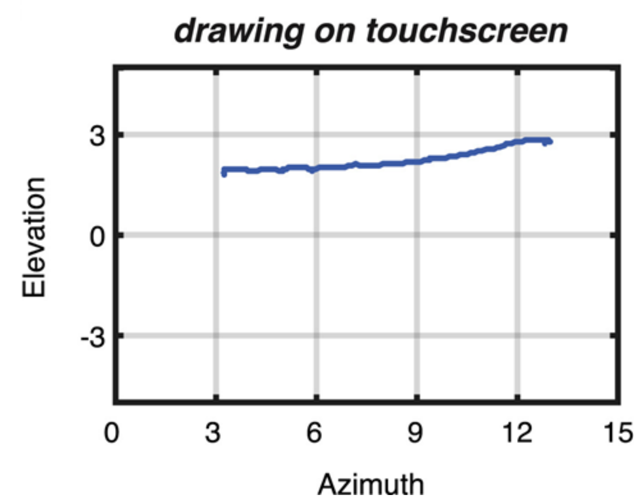
One solution to the complexity of multi-site stimulation is to only focus on a single site at a time. But this constrains the complexity of the image.

Current steering can interpolate between different electrodes:



This can then be used to trace out lines in visual space:

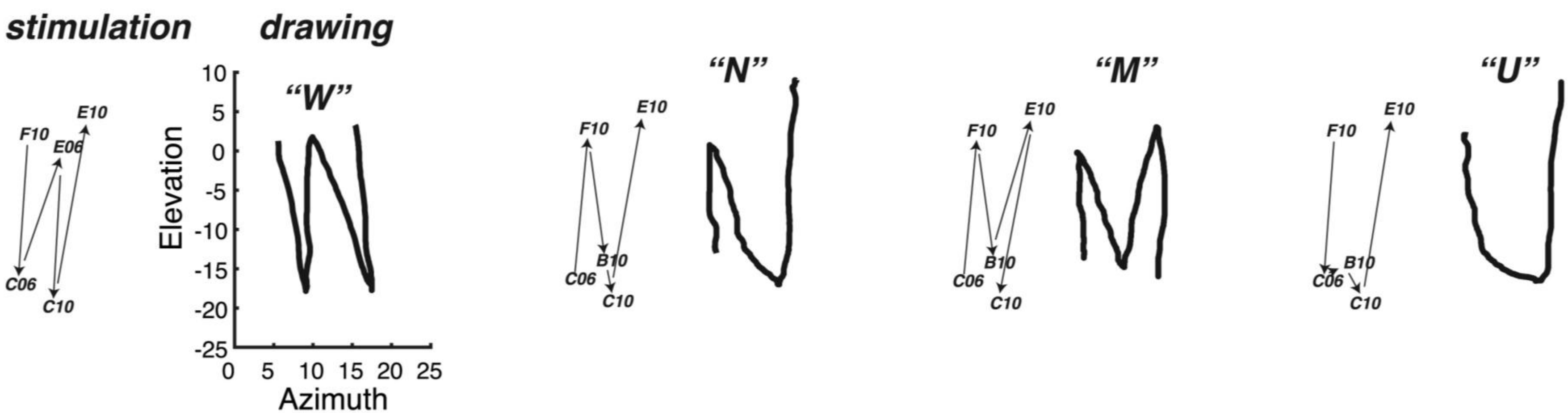




Beauchamp et al, *Cell* 2020

Tracing figures in a visual prosthetic

Once you can interpolate between points, you can start to draw out more complicated figures.

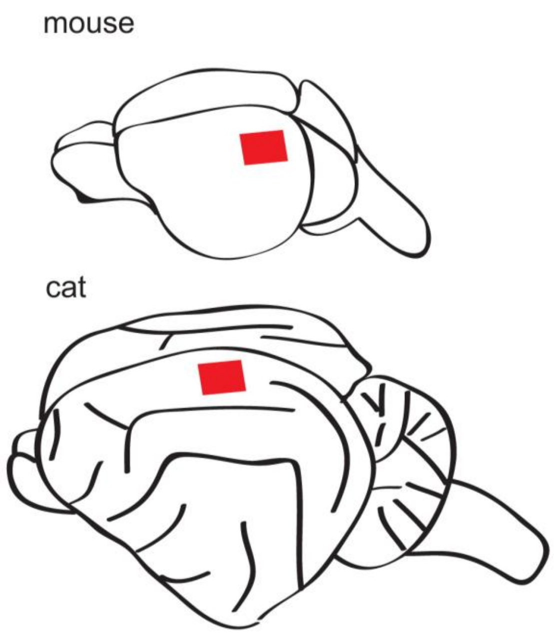


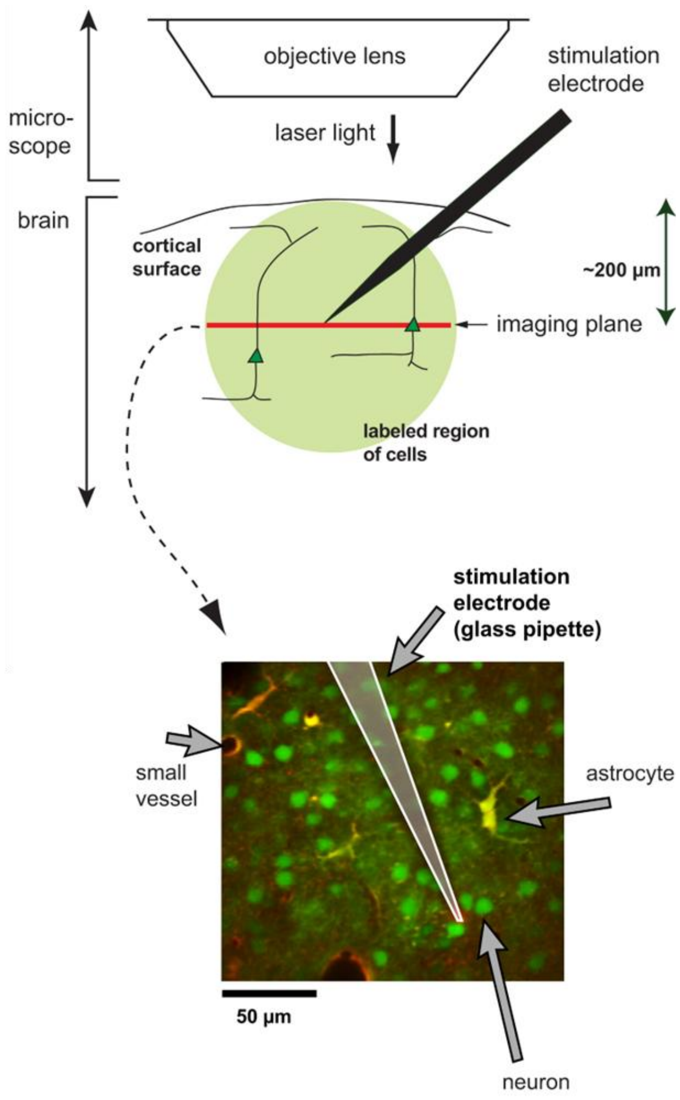
Beauchamp et al, *Cell* 2020

Effect of stimulation is hard to predict…

Mark Histed wanted to understand how electrical stimulation affects the local circuit.

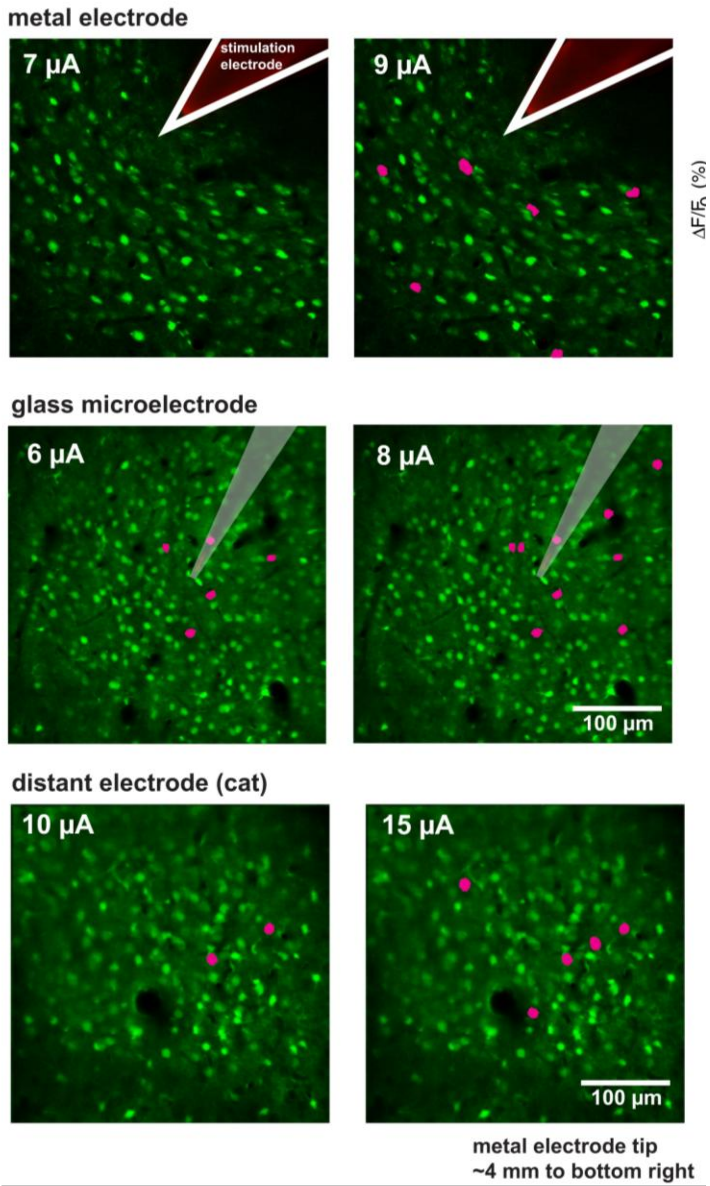
So, he used 2PT calcium imaging to record the effect of electrical microstimulation on the local population.



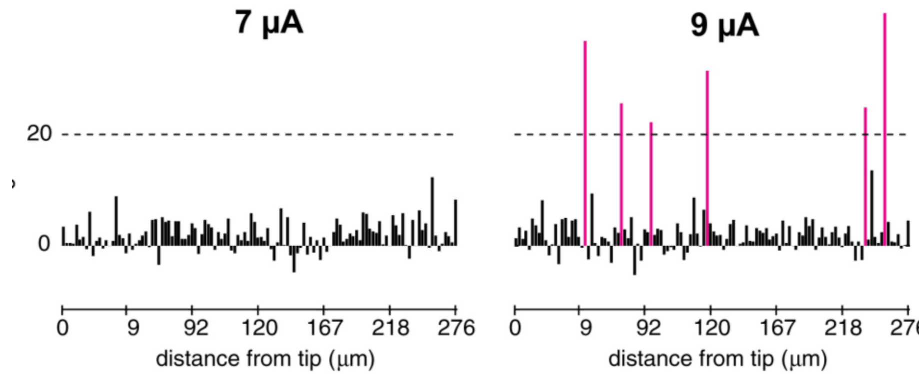


Histed et al, *Neuron* 2009

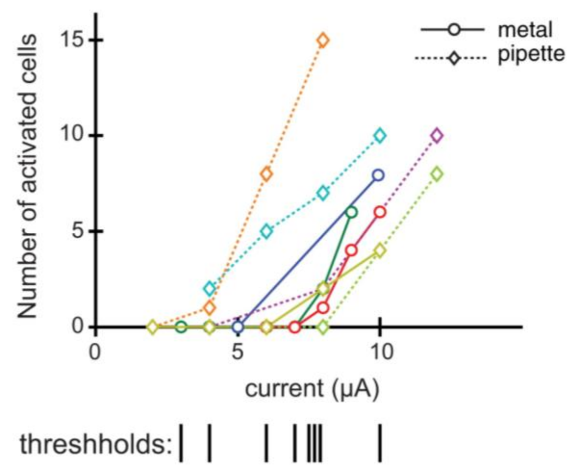
Effect of stimulation is hard to predict…



Stimulation activates a subset of neurons in the surrounding tissue.



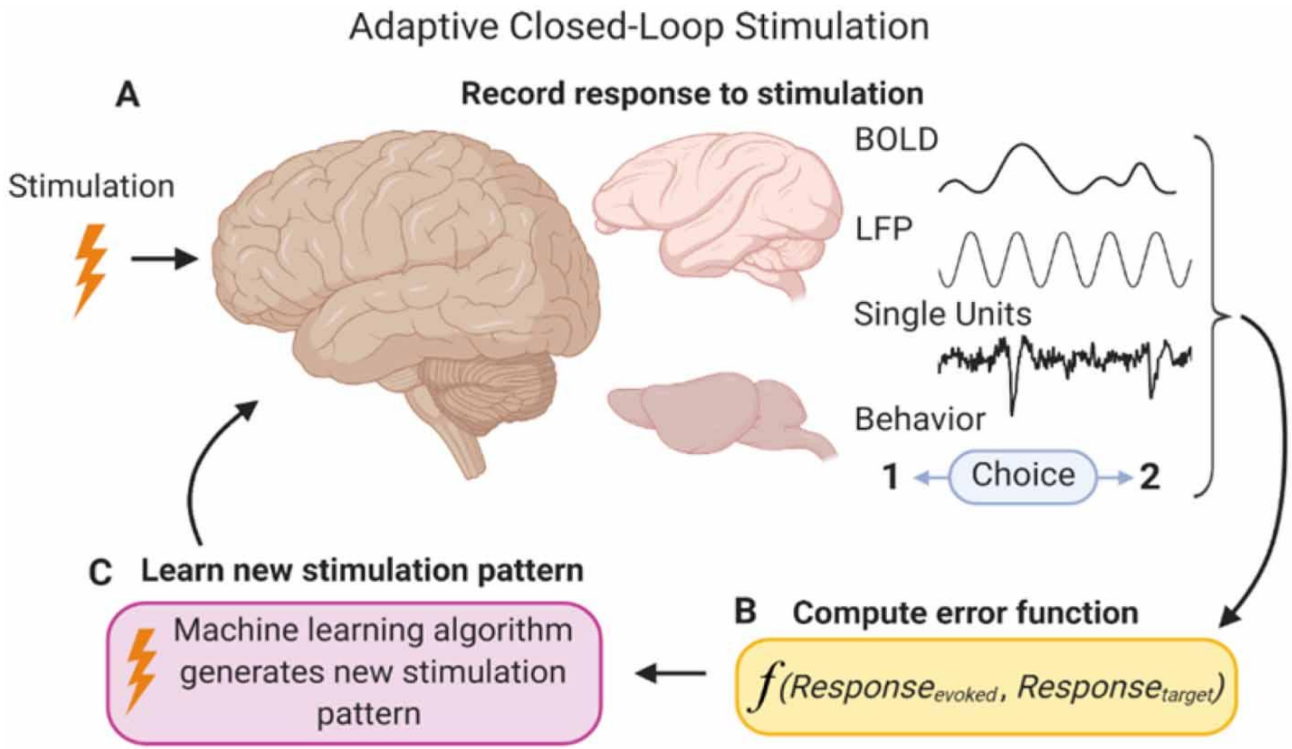
Increasing current amplitude recruits more neurons:



Histed et al, *Neuron* 2009

Learning to stimulate

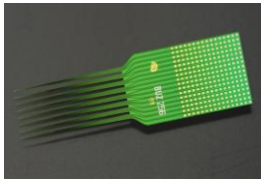
We've seen throughout the class that information is represented in the neural population. But, if we can't predict the effect of stimulation, then how could we act on the neural population?

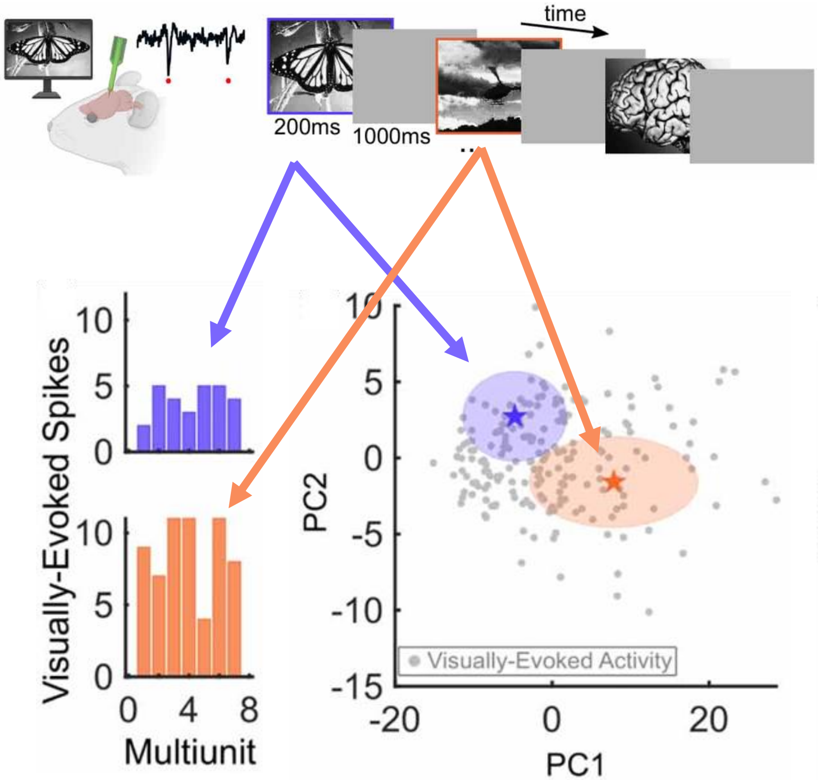


Tafazoli, MacDowell et al, *J Neural Eng* 2020

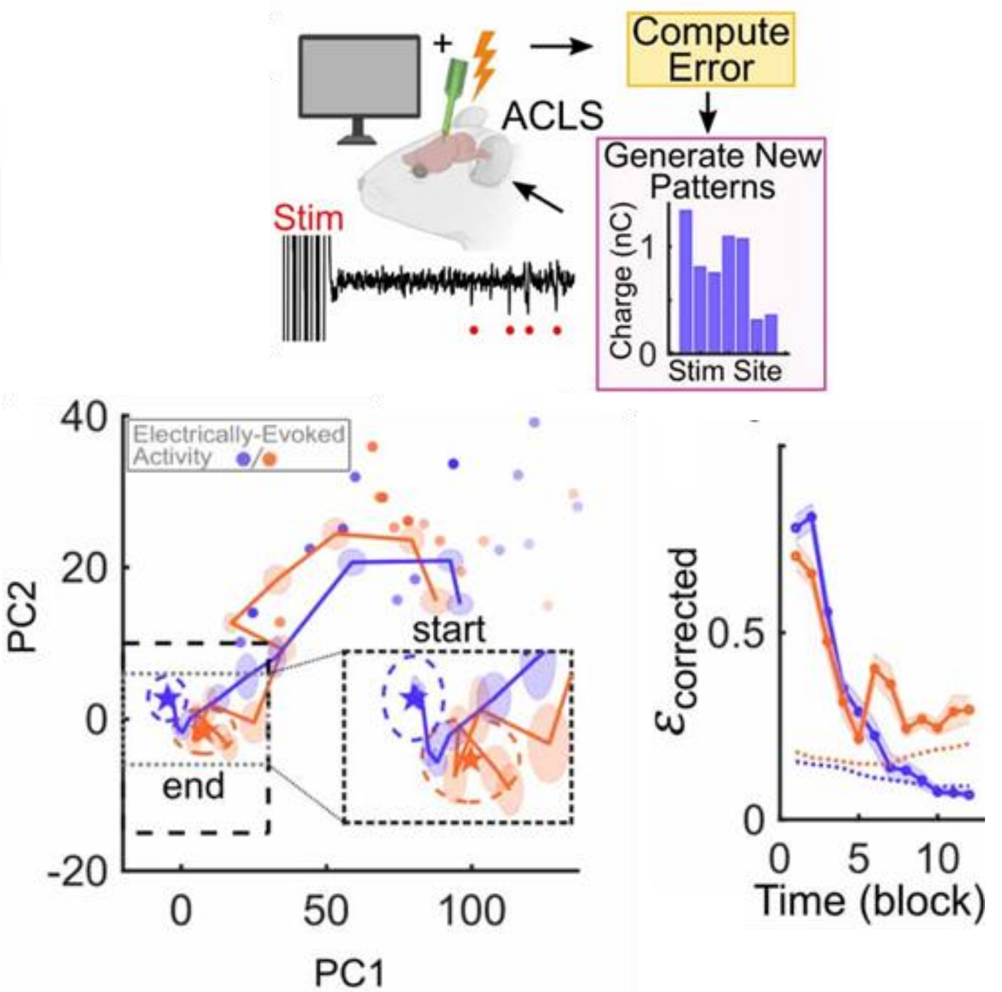
Learning to stimulate

Mapping responses using visual stimuli:





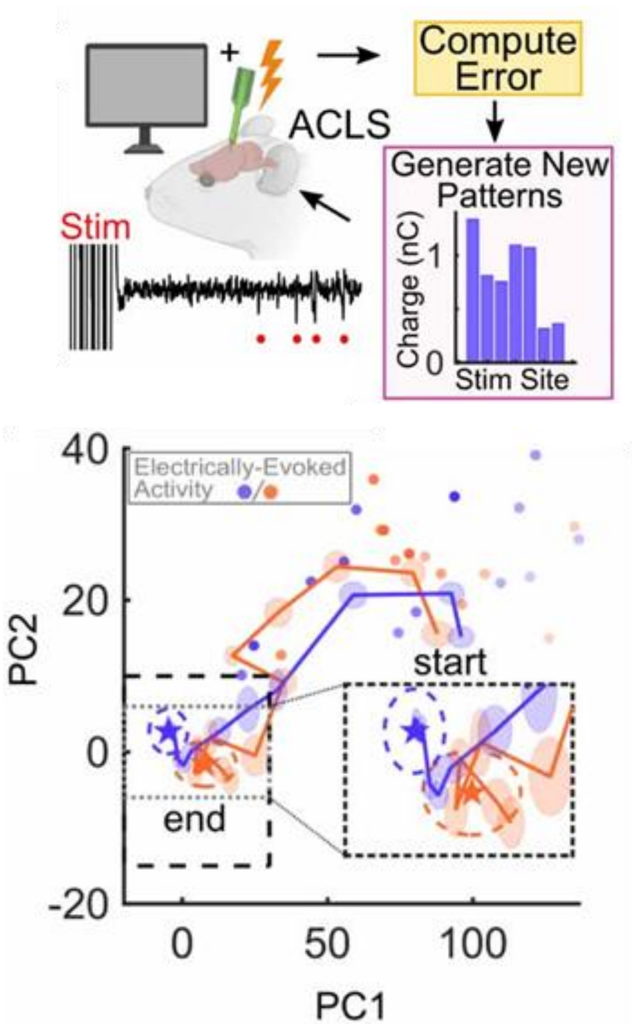
Use ACLS to find stimulation pattern that evokes patterned response.

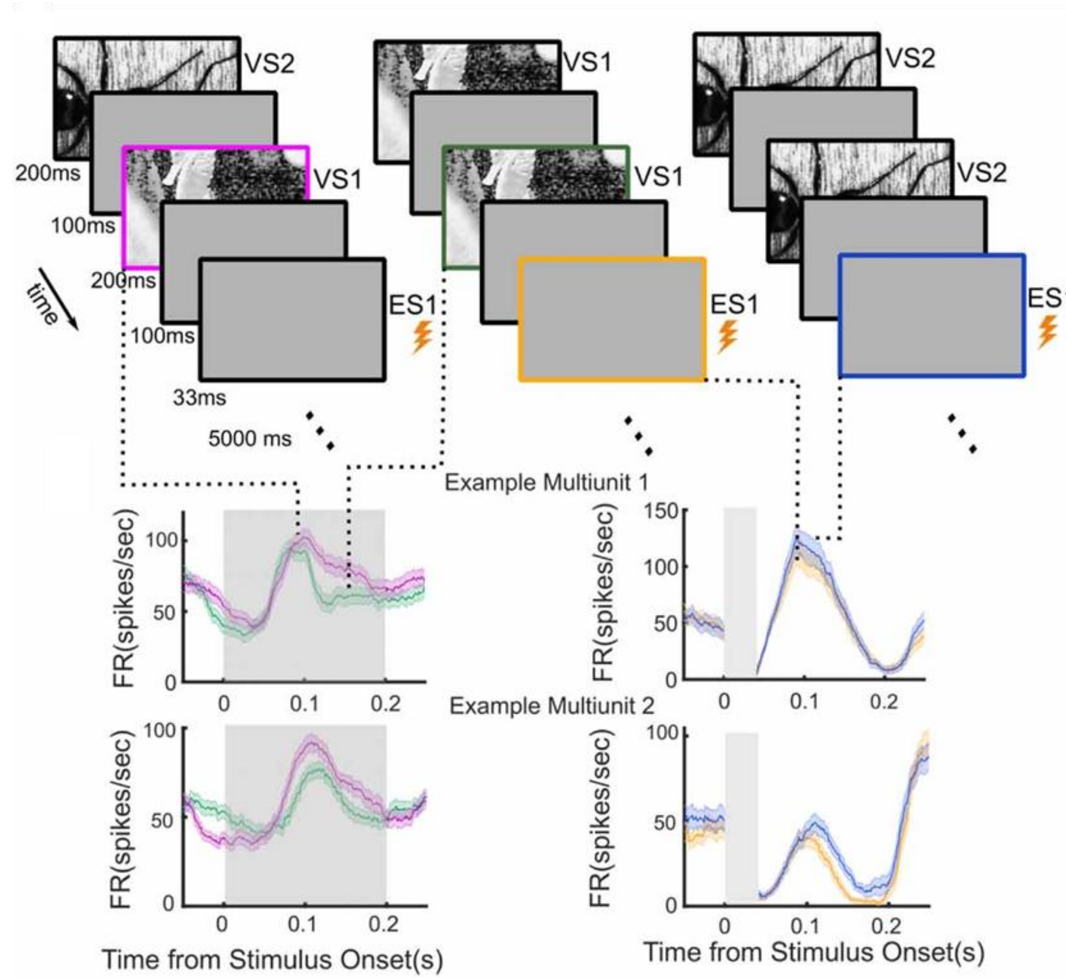


Tafazoli, MacDowell et al, *J Neural Eng* 2020

Learning to stimulate

The ACLS evokes a physiologically relevant response that is adapted in the same way as visual repetition.

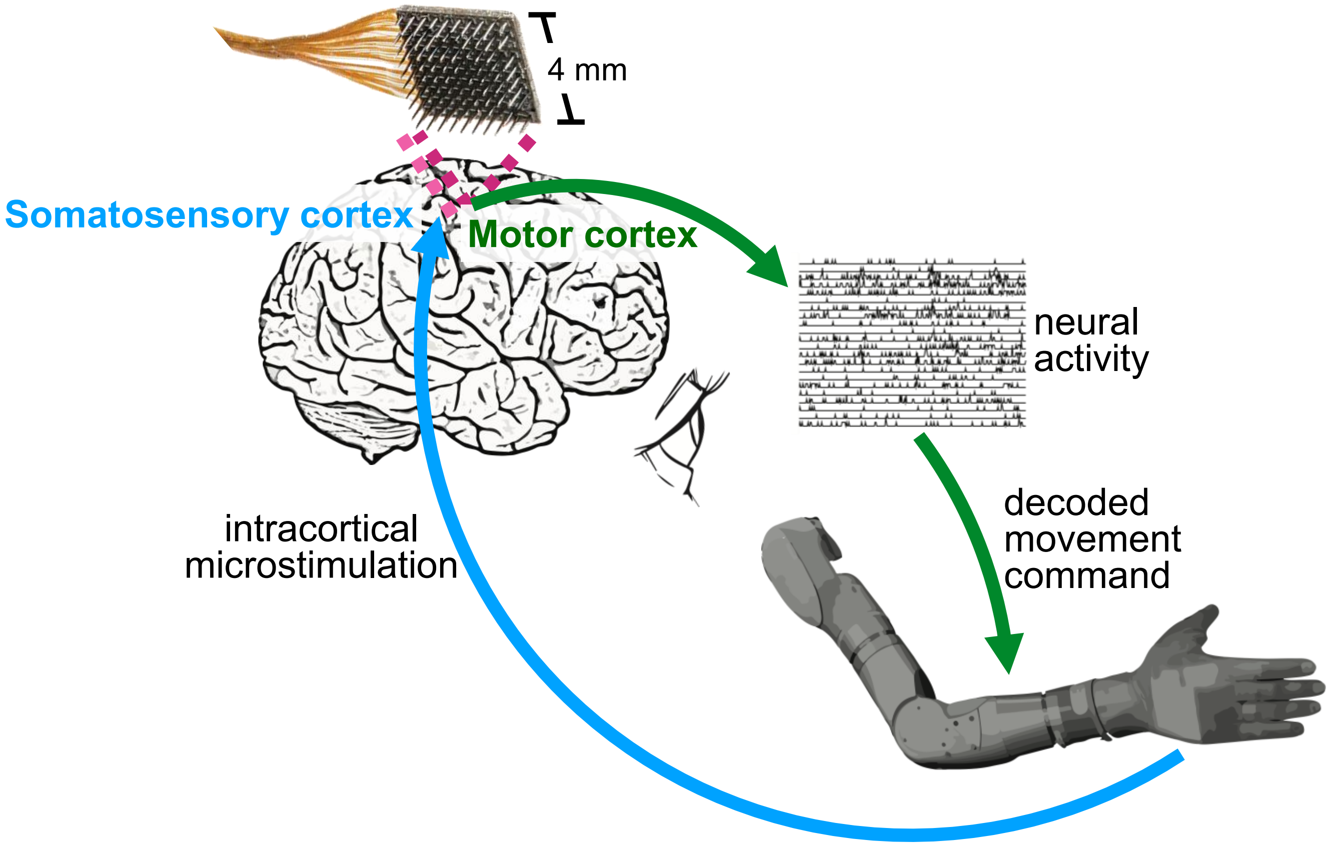




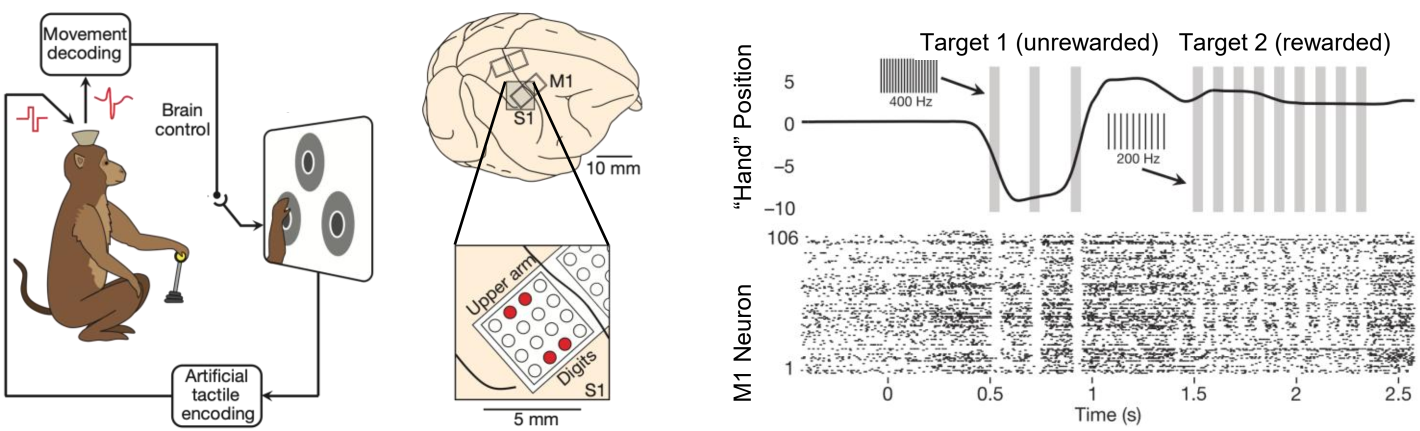
Tafazoli, MacDowell et al, *J Neural Eng* 2020

Reading from and Writing to the Brain

Restoring the sense of touch with electrical write-in

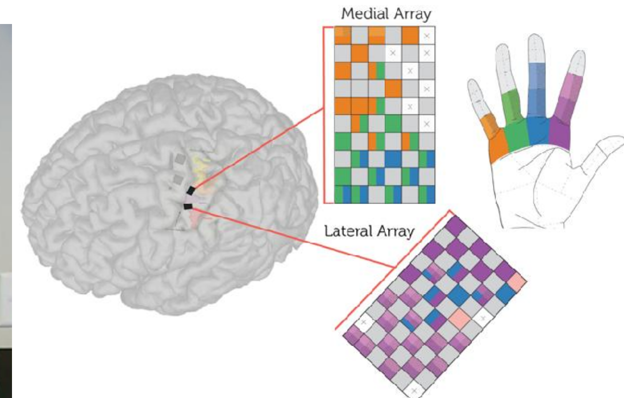


Early “bidirectional” BCI work: 2 discriminable stimulation patterns in monkeys



O’Doherty et al. Active tactile exploration using a brain–machine–brain interface. *Nature* (2011)

Electrical microsimulation of human somatosensory cortex

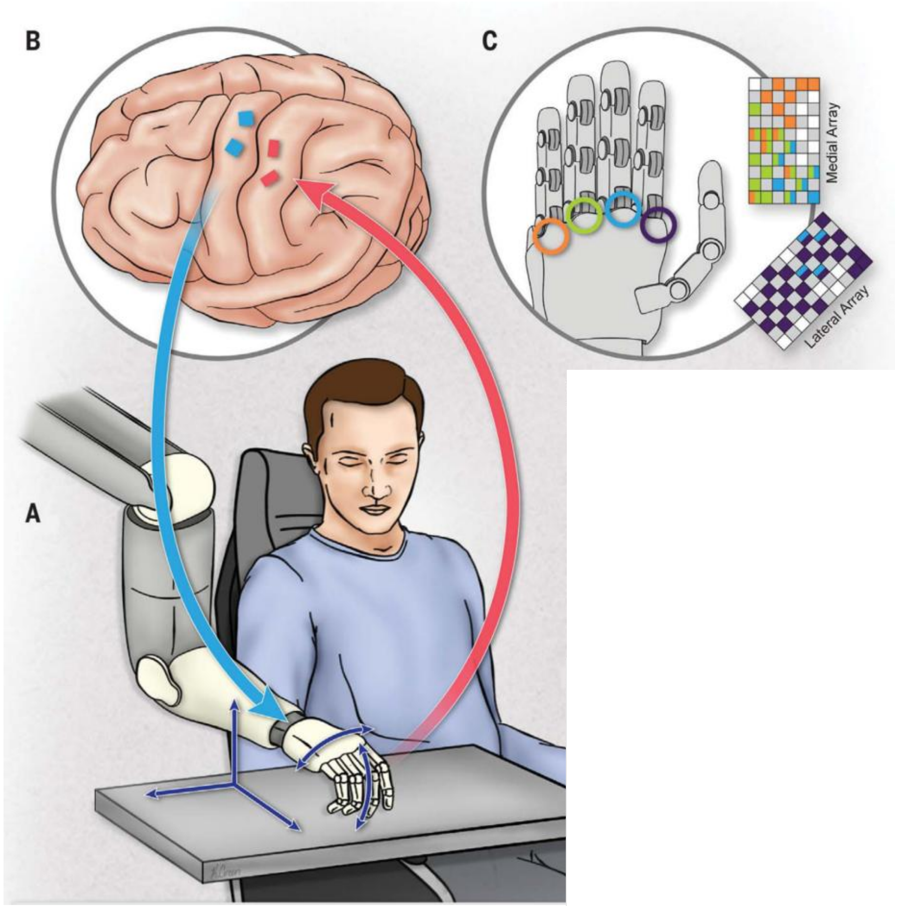


caveat 1: only 3-6 discernible amplitude ranges

caveat 2: “somewhat naturalistic”

Flesher et al. Intracortical microstimulation of human somatosensory cortex. *Science Translational Medicine* (2016)

Demonstrating functional improvement in a movement task

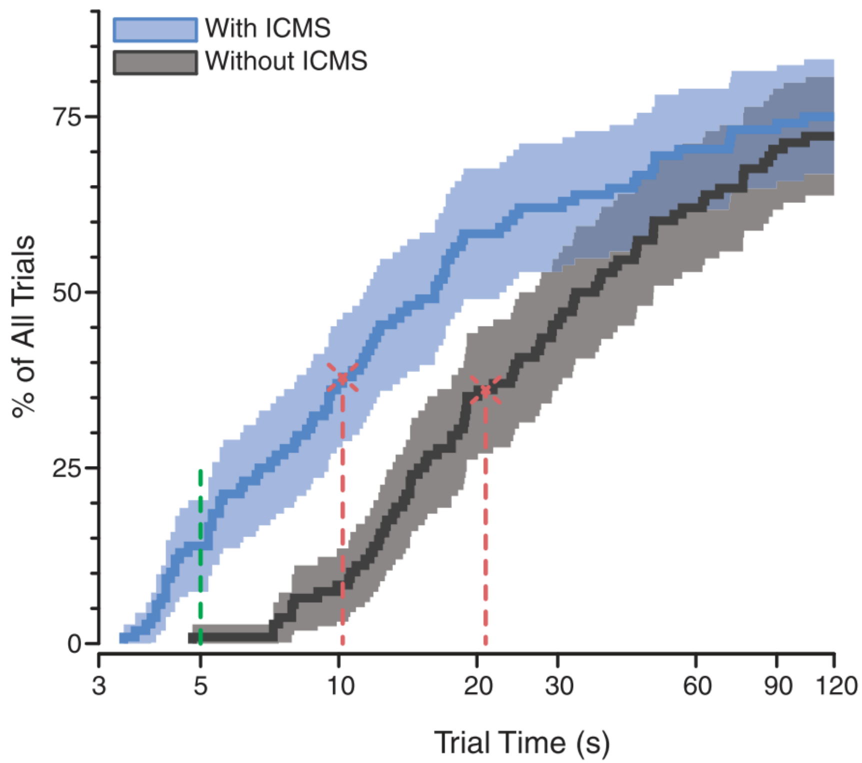


Flesher et al. Restored tactile sensation improves neuroprosthetic arm control. *Science* (2021)

Demonstrating functional improvement in a movement task

Flesher et al. Restored tactile sensation improves neuroprosthetic arm control. *Science* (2021)

Demonstrating functional improvement in a movement task



Flesher et al. Restored tactile sensation improves neuroprosthetic arm control. *Science* (2021)