Methodological challenges (and value) of intracranial electrophysiological recordings in humans

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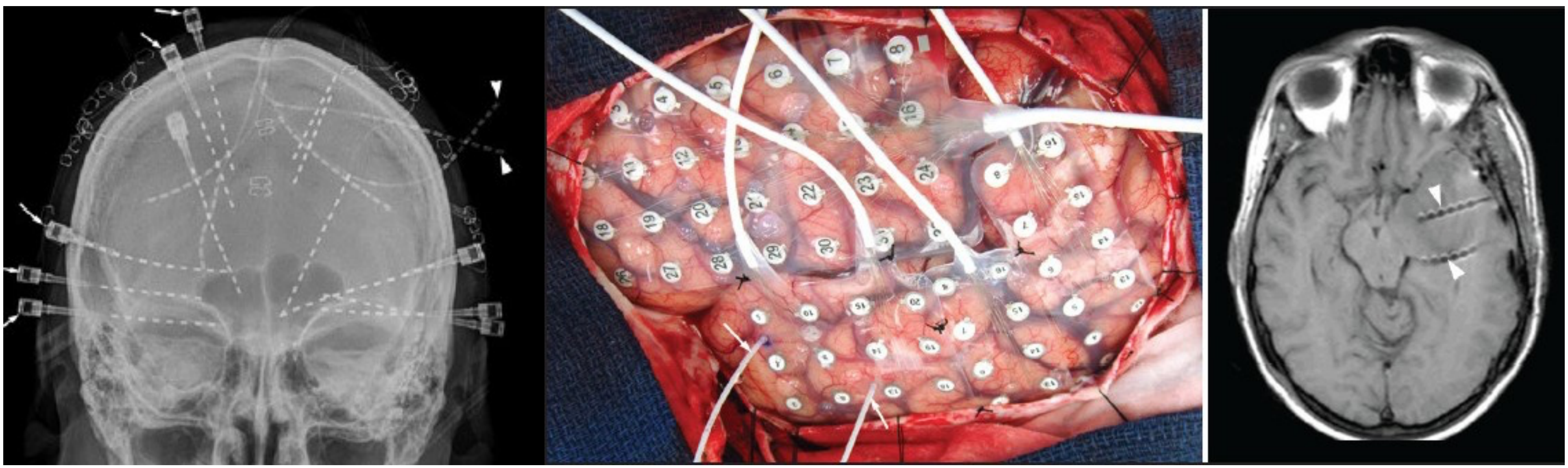
Intracranial Recordings in Humans

- Acute Intracranial Recordings
  - Depth Electrode recordings
  - Grid Electrode recordings
- Chronic Intracranial recordings
  - Depth Electrode recordings
  - Strip electrode recordings

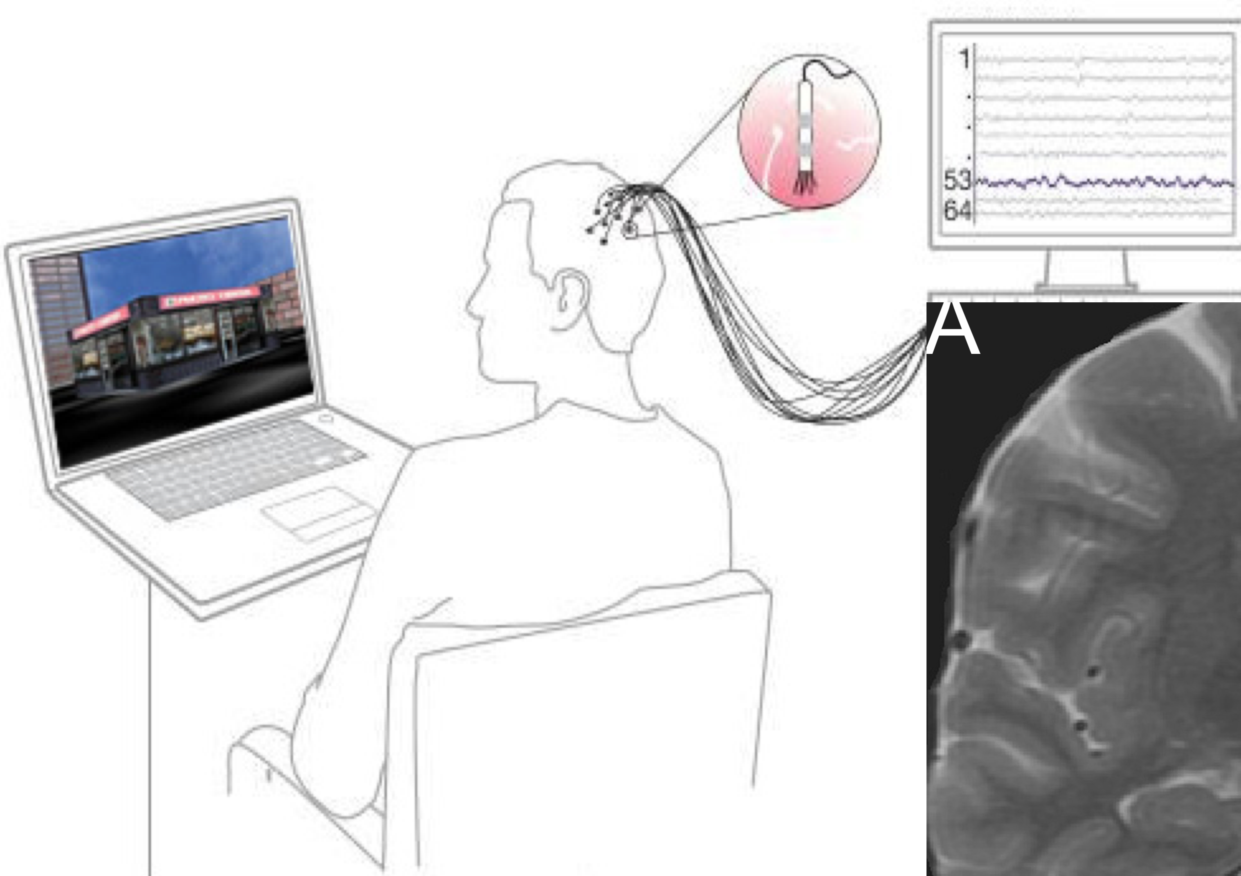
ECoG, stereo EEG, iEEG

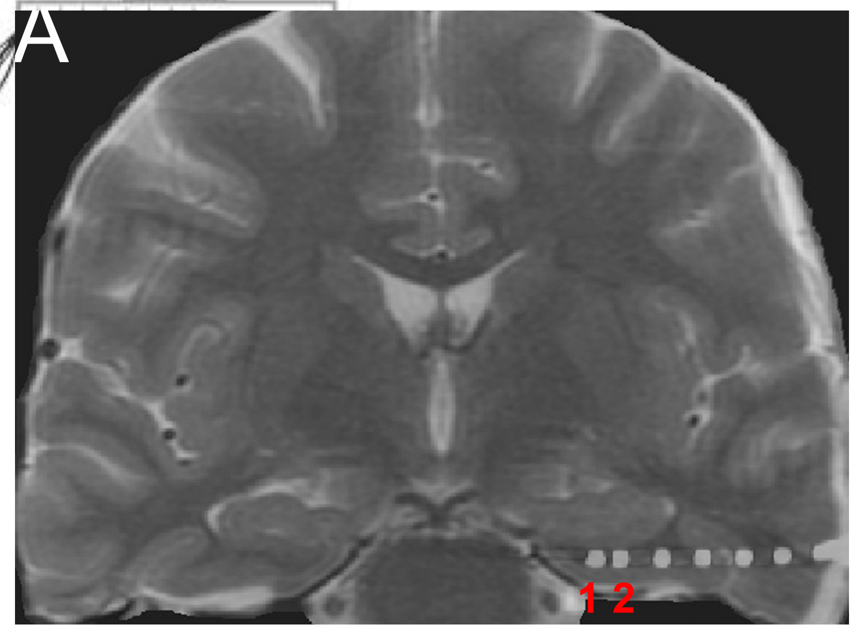
- Intraoperative vs. extraoperative

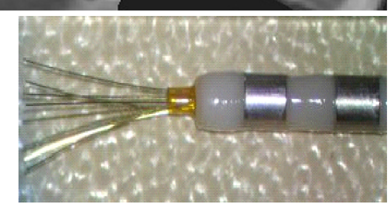


Type of electrode	Subdural grid/strip	Depth electrodes
Location	Subdural over the surface of the brain	In brain tissue
How inserted	Usually require craniotomy for grids but strips can be inserted via burr holes	Burr holes or small holes percutaneously
Available arrays	Many different choices commonly used are 1×4–1×10 strips and 2×4–8×8 grids	4–10 contacts depth electrodes
Advantages	Many different sizes and configurations	Less invasive than subdural grids
	Provides excellent coverage of the cortical surface to define seizure onset	Can reach deeper structures
	Can be used for mapping of eloquent cortex	Can be placed bilaterally simultaneously
Disadvantages	Requires more invasive means to place	Limited cortical coverage so difficult to localize neocortical seizure onset
	Can be placed only on the surface	Requires more experienced surgeon and neuronavigation
	Higher rate of morbidity/complications	Blind procedure, hemorrhage can occur without knowledge

Acute Depth Electrode Recordings







Suthana et al., TICS, 2012

Risks

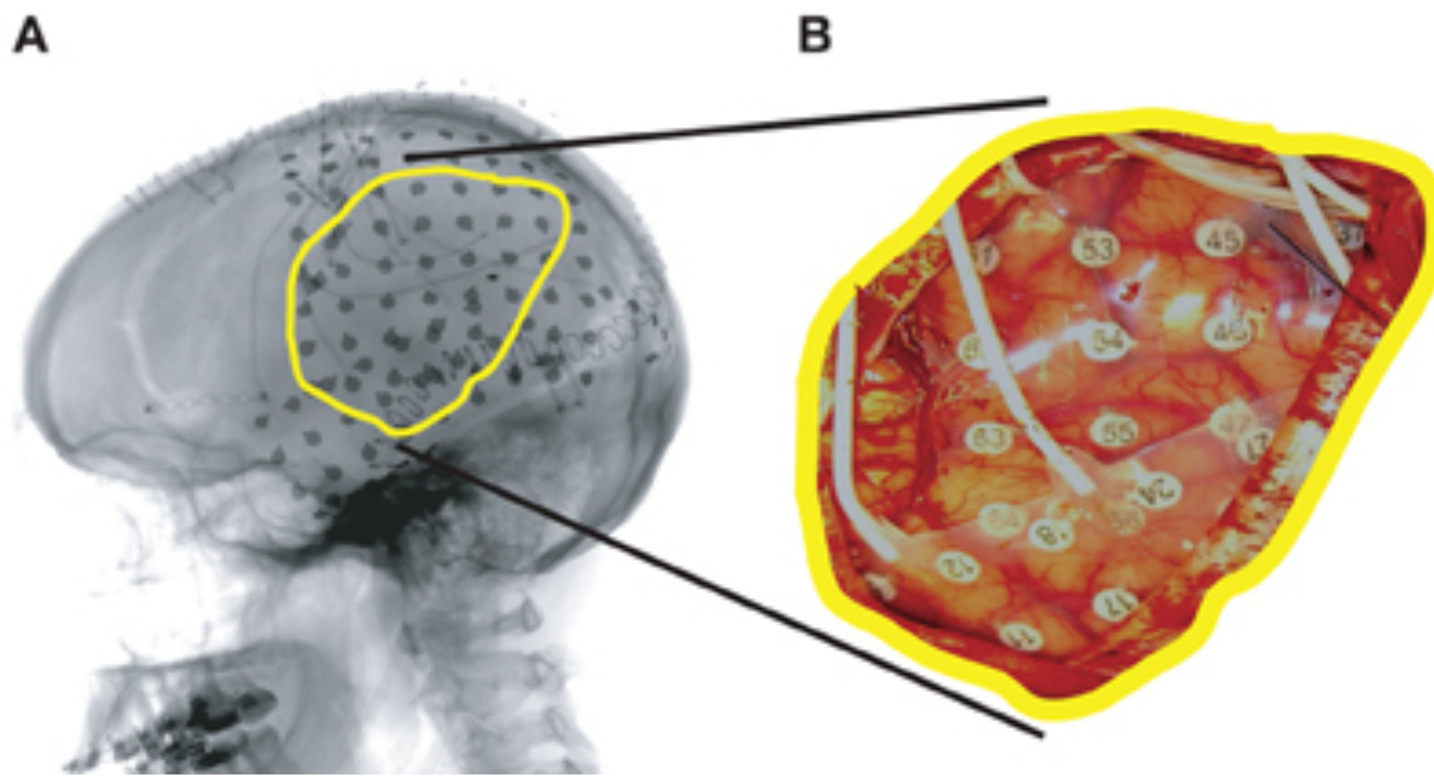
- The most common adverse events reported include intracranial hemorrhage, superficial infection, elevated intracranial pressure and cerebral infections.

- Rates extremely low (less than 1%)

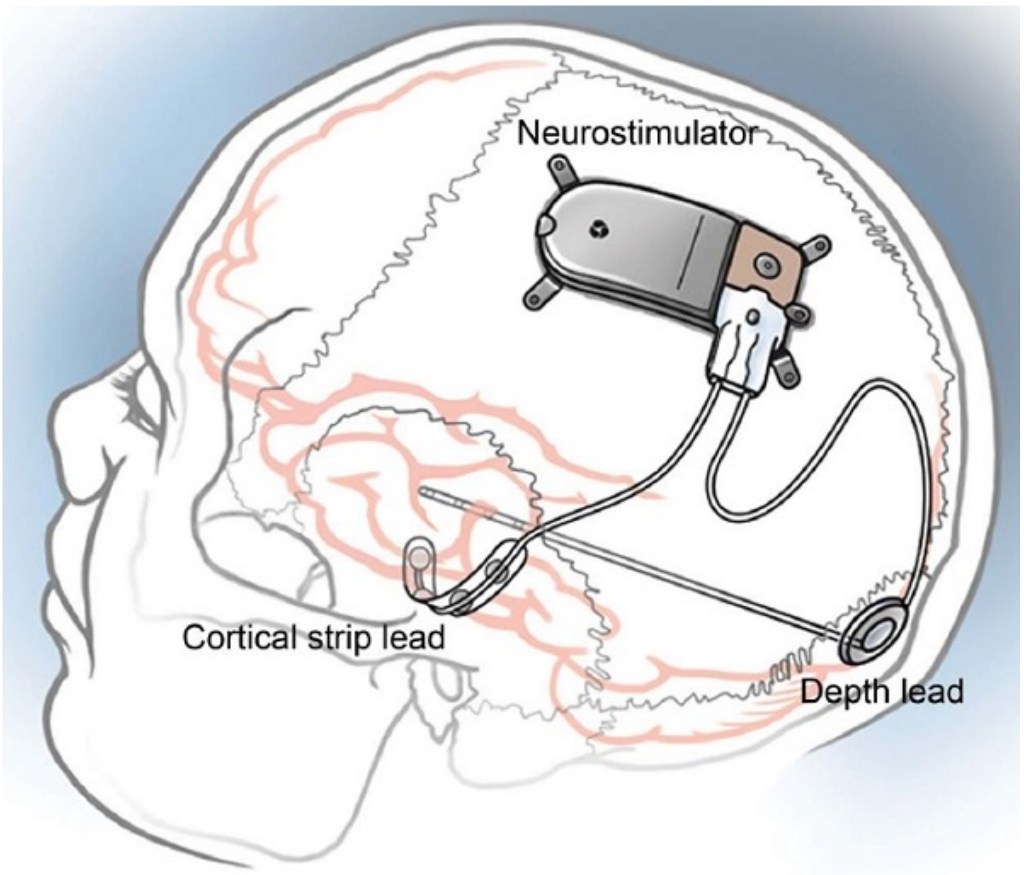
Ethical Challenges

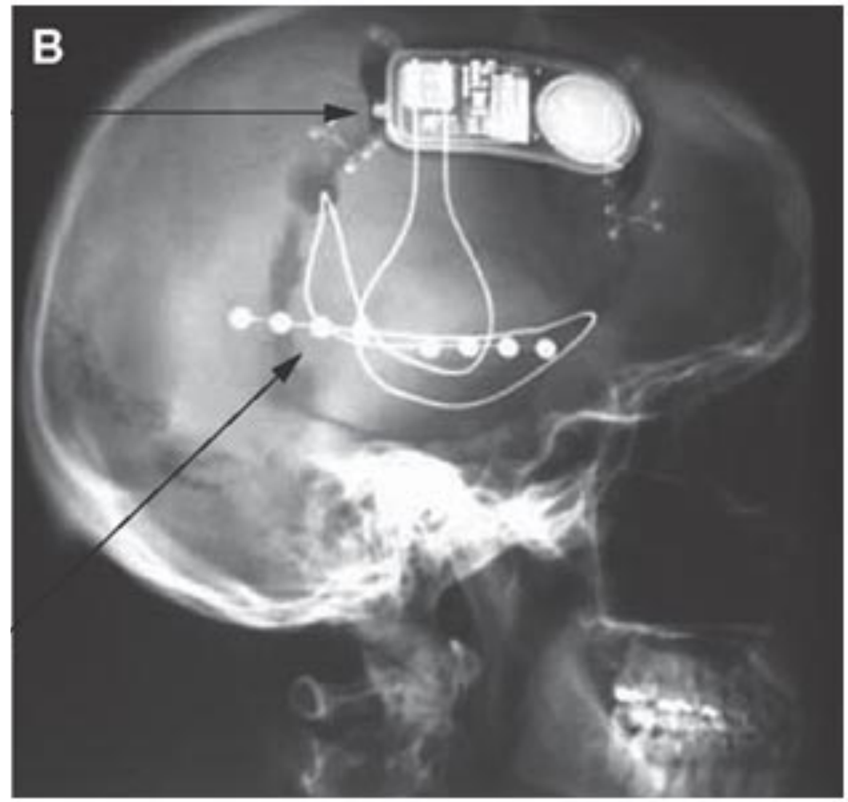
- Epilepsy, Parkinson’s disease, dystonia
- Simple and short tasks
- Be prepared to abandon tasks
- Clinician conflict
- Have repertoire of tasks available
- Be prepared to work and troubleshoot quickly

Acute Grid Electrode Recordings



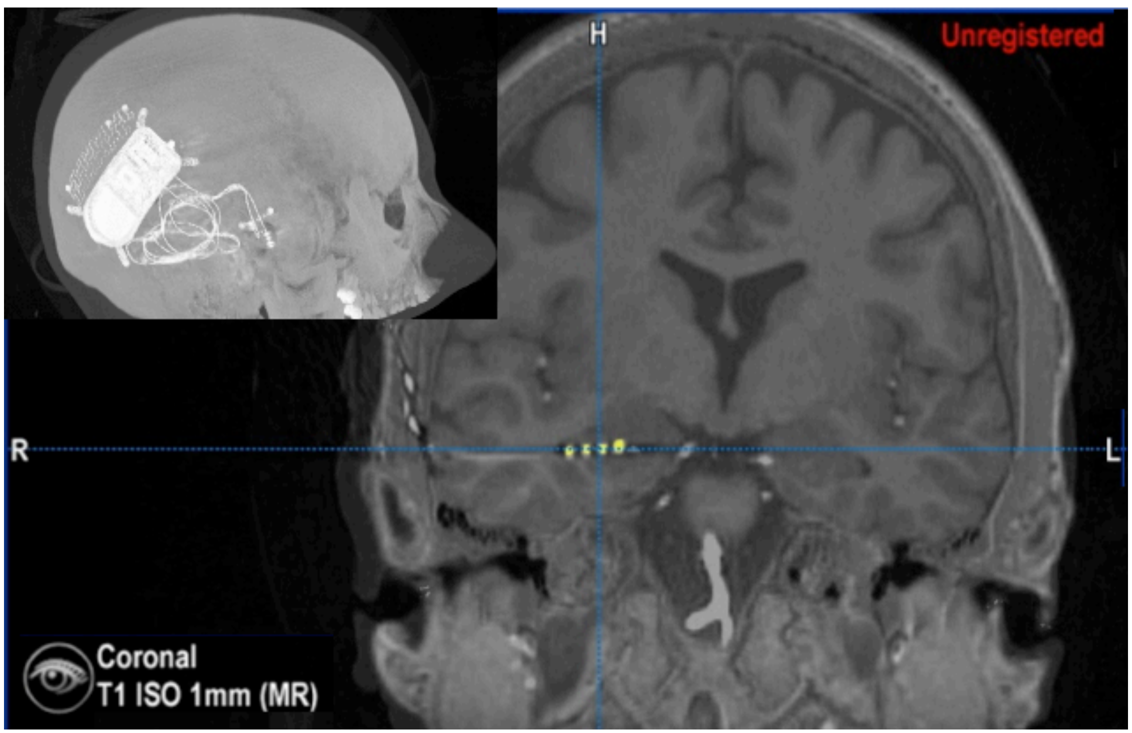
Chronic Strip Electrode Recordings
FDA approved 2013

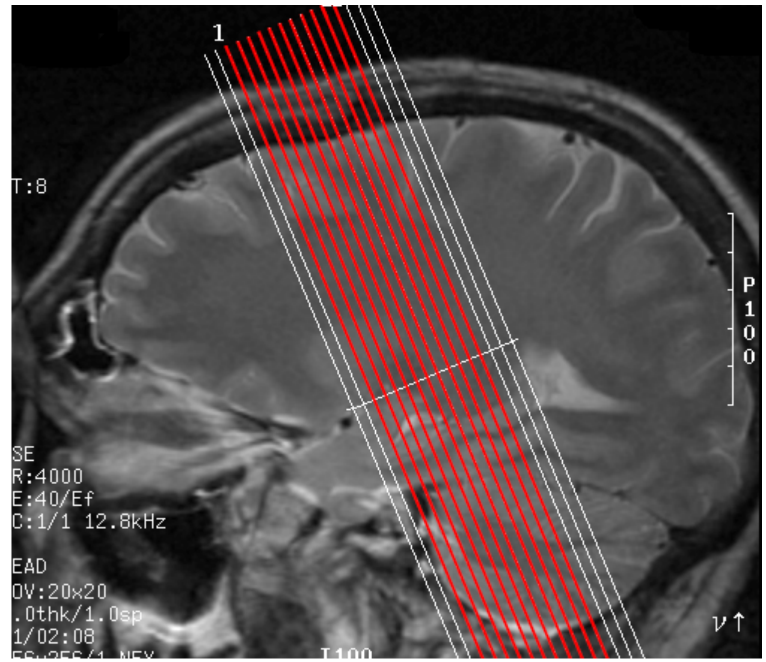




Neuropace RNS System

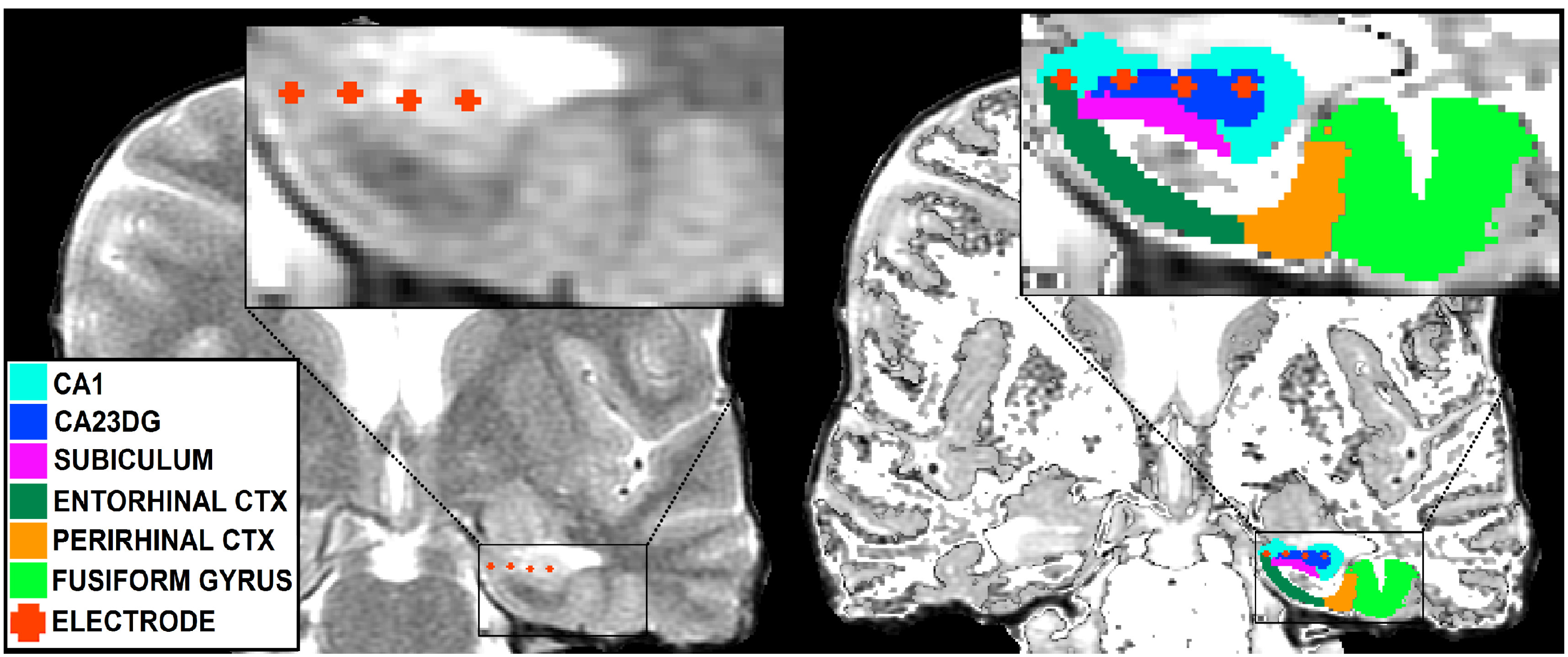
Chronic Depth Electrode Recordings
FDA approved 2013



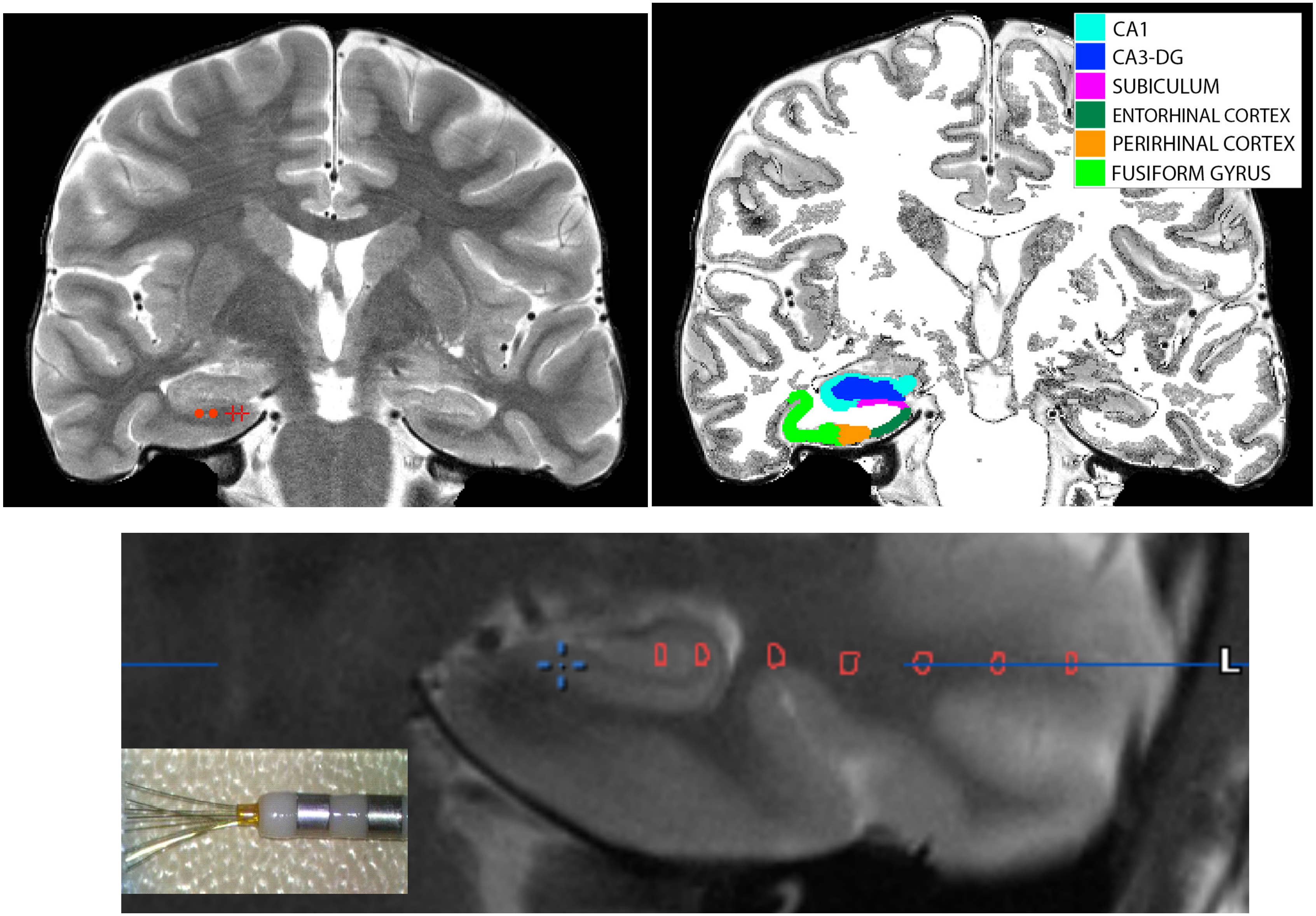


Spatial resolution

- Use of high-resolution MRI and high-resolution CT



Localization of intracranial electrodes using high-resolution CT and MRI

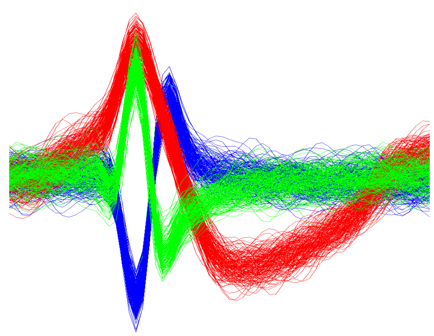


Spatial resolution

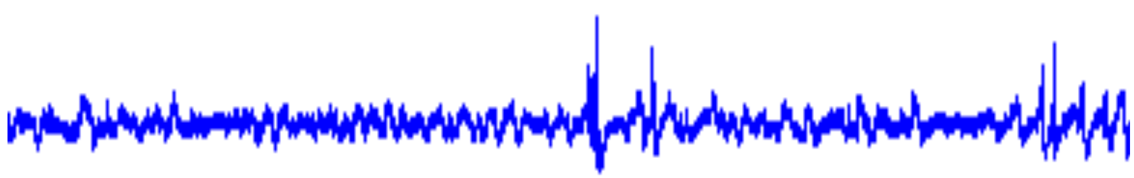
- iEEG spatial resolution depends on:
  - Impedance
  - Size of contacts
  - Volume conduction of tissue around electrode

Temporal Resolution
Signals recorded

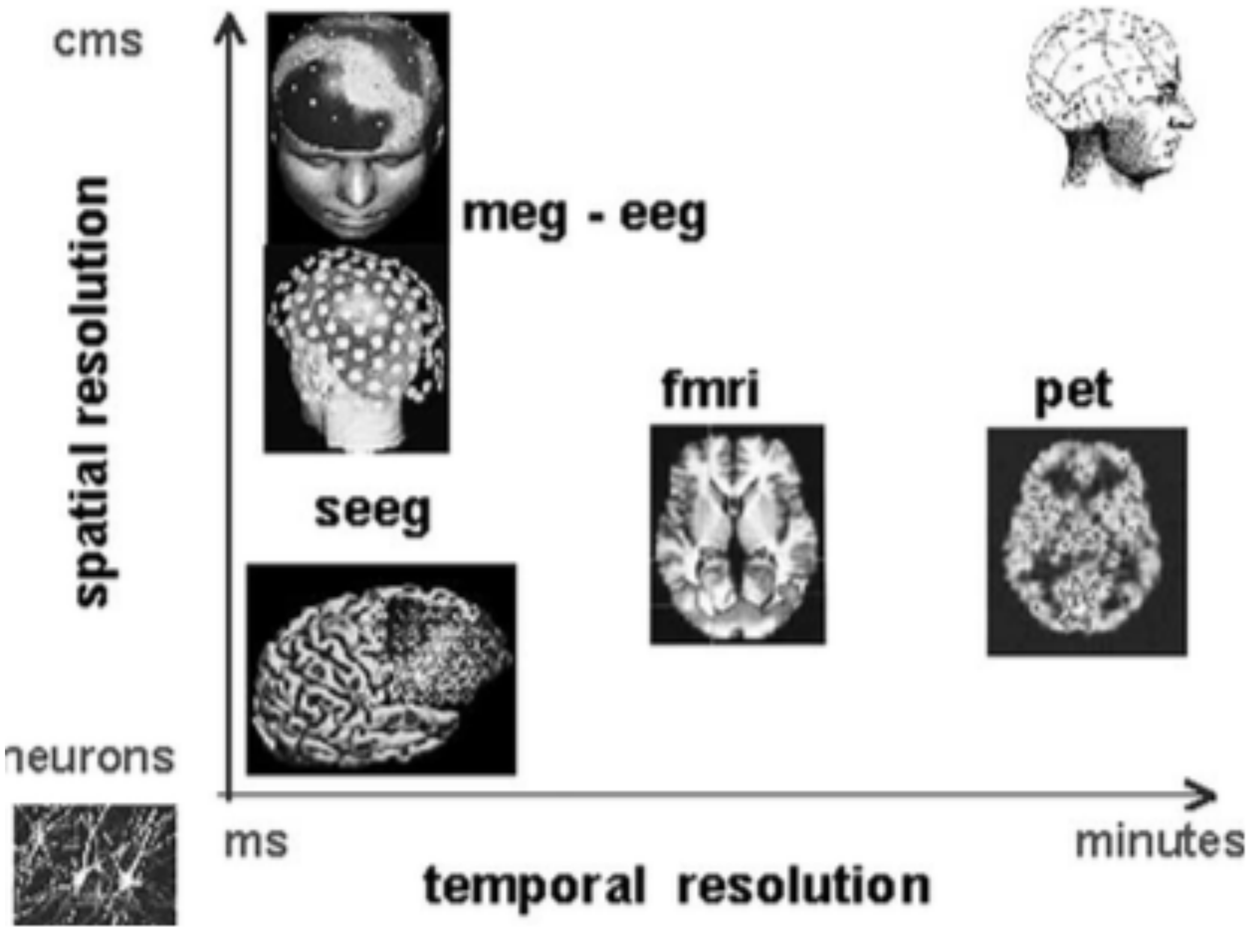
- Single-units / Multi-units (30 KHz sampling rate)
  - Depth microelectrode recordings only



- Local field potentials (e.g., 512 Hz)



Resolution of iEEG



(Lachaux et al., 2003)

Single-unit recordings

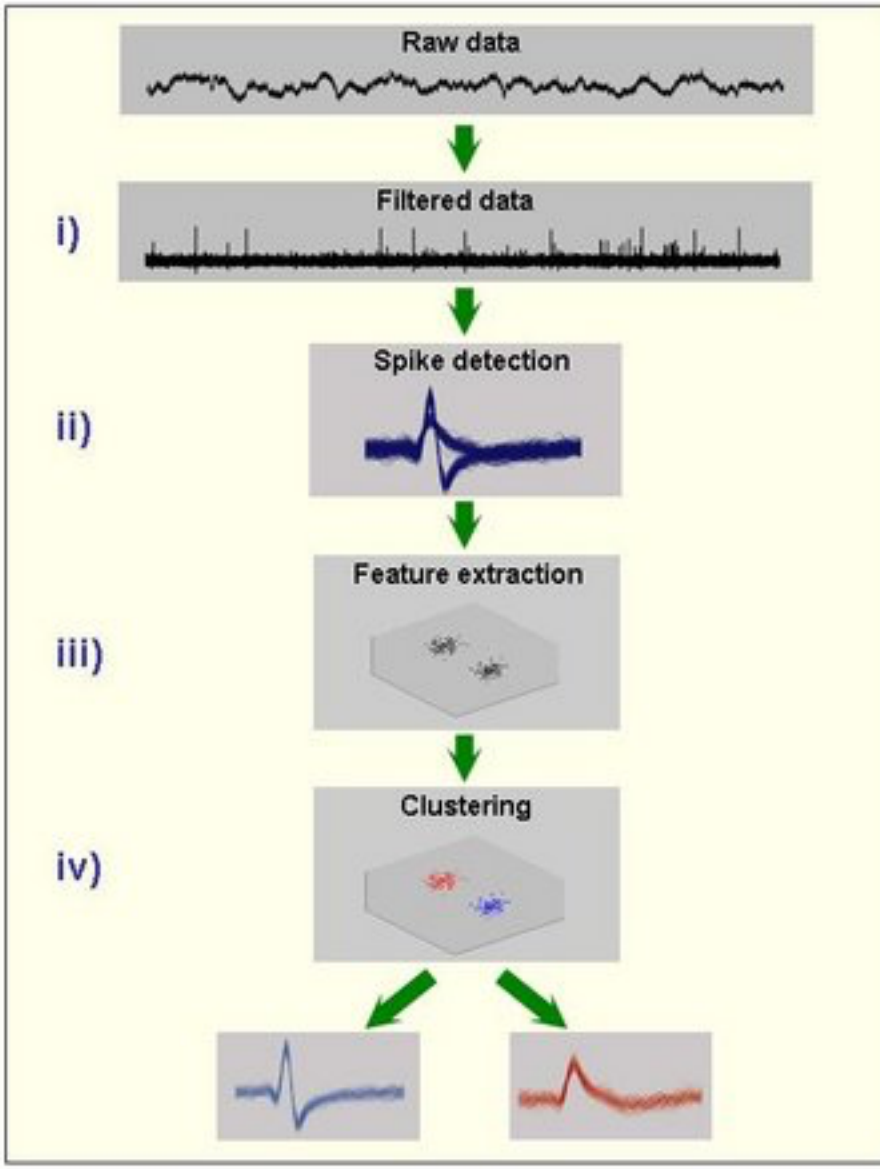
- Parkinson's (OR), tumor patients (in OR), Epilepsy patients (acute)
- Use of an electrode to record the electrophysiological activity (action potentials) from a single neuron.
- Extra-cellular signal: voltages generated in the extra cellular matrix by the current fields outside the cell when it generates an action potential. (usually tens of microns away)
- Action potentials look very much like the action potentials that are recorded intracellularly, but the signals are much smaller (typically about 0.1 mV).
- Sampling rates usually 20-30 kHz; action potential waveforms on order of 1-2 msec

Quality of single-unit recordings

- Depends on amplitudes of spikes relative to background noise
  - Thermal
  - Firing of neurons far from recording electrode

Challenges

- Spike Sorting
- Electrode Design
- Electrode and Waveform Drift
- Bias
  - Sampling
  - Operator

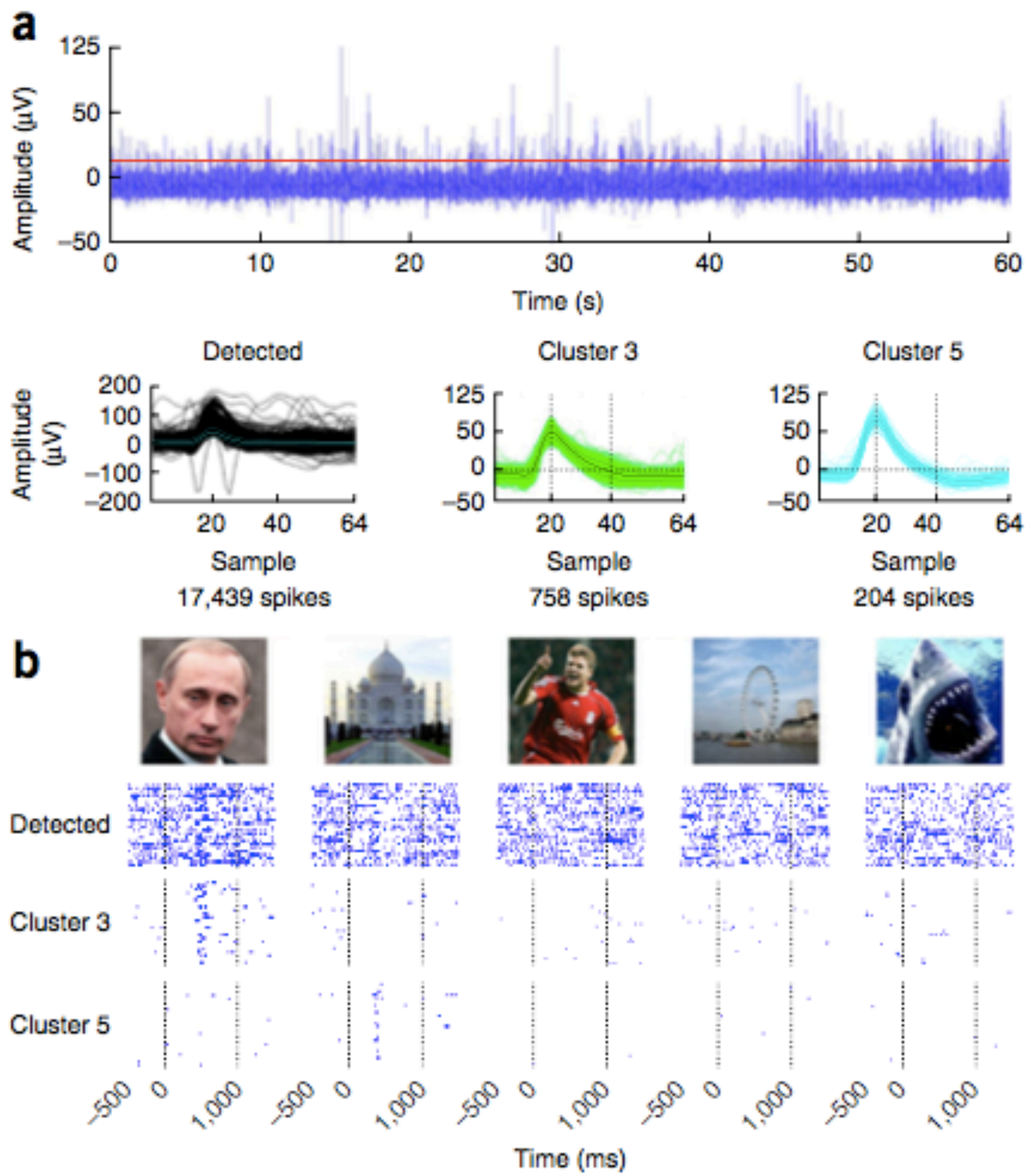


Spike sorting methods

- Semi-automatic
  - Advantages: time, few errors
  - Disadvantage: still subject to bias and subjectivity

Spike Sorting

Why necessary?



(Harris et al., 2016)

Types of Cognitive studies

- Learning and memory
- Perception
- Sleep
- Emotion
- Decision making
- Reward processing
- Language

Challenge: Types of neurons

- Pyramidal vs. interneuron
  - Spike width, peak amplitude, firing rates etc (Viskontas et al., 2007)
- Single- vs. multi-unit
  - % of ISI under 3 msec, spike shape, high SNR

Electrode Design

- Very fine wires made from tungsten or platinum-iridium alloys that are insulated except at their extreme tip
- Limiting damage to tissue vs. number of channels
- Enough stiffness and strength to survive handling but flexible enough for patient safety
- Limit long-term accumulation of scar tissue
- MRI safe
- Size versus unit isolation

UCLA: 80% platinum, 20% iridium, covered by polyimide insulation, 40 μM diameter with 2mm of insulation removed

Electrode and Waveform Drift

- Physical movement of the electrode relative to brain
- Spike amplitude variability
  - Largest for high-amplitude spikes
- More severe for acute recordings compared to chronic

Sampling Bias

- Selection bias
  - High firing rate neurons e.g., in PD
  - Stimuli or condition specific neurons

- Ameliorated by
    - Long-term recordings (~chronic)
    - Fixed electrodes

Operator Bias

- Spike sorting manual step
- Single-user who is blinded
- Compute inter-operator reliability

Local Field Potential or iEEG

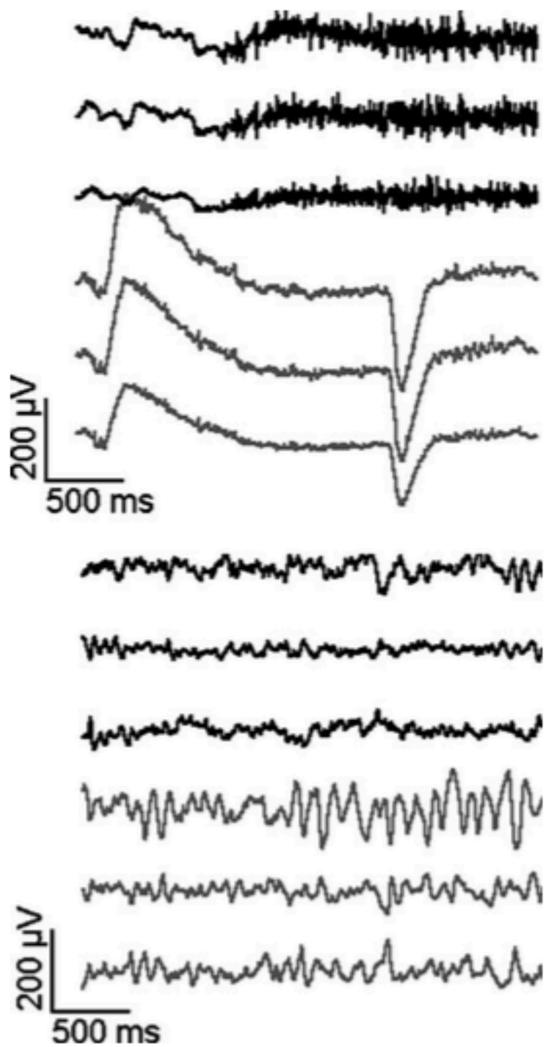
- Separated from single-units by filtering
- Represents the sum of synaptic activity across cells
- Indirect measure of ongoing global activity patterns

Single-units versus LFPs

- Direct relationship in some areas
  - Auditory cortex (Mukamel et al., 2005)
  - If neurons receive majority local input

- Not so simple in other areas
  - Sparse coding areas (e.g., hippocampus, Ekstrom et al., 2009)
  - Also depends on frequency band (e.g., theta and single-unit activity in hippocampus

Intracranial EEG less vulnerable to muscle and eye movement artifacts than scalp EEG



(Lachaux et al., 2003)

Other challenges

- Reference Issue
  - Single-units
  - LFPs
- Data storage issues

Other challenges

- Generalization beyond patients
  - Epileptic tissue
  - Epileptic spikes / discharges
  - Medications

Summary

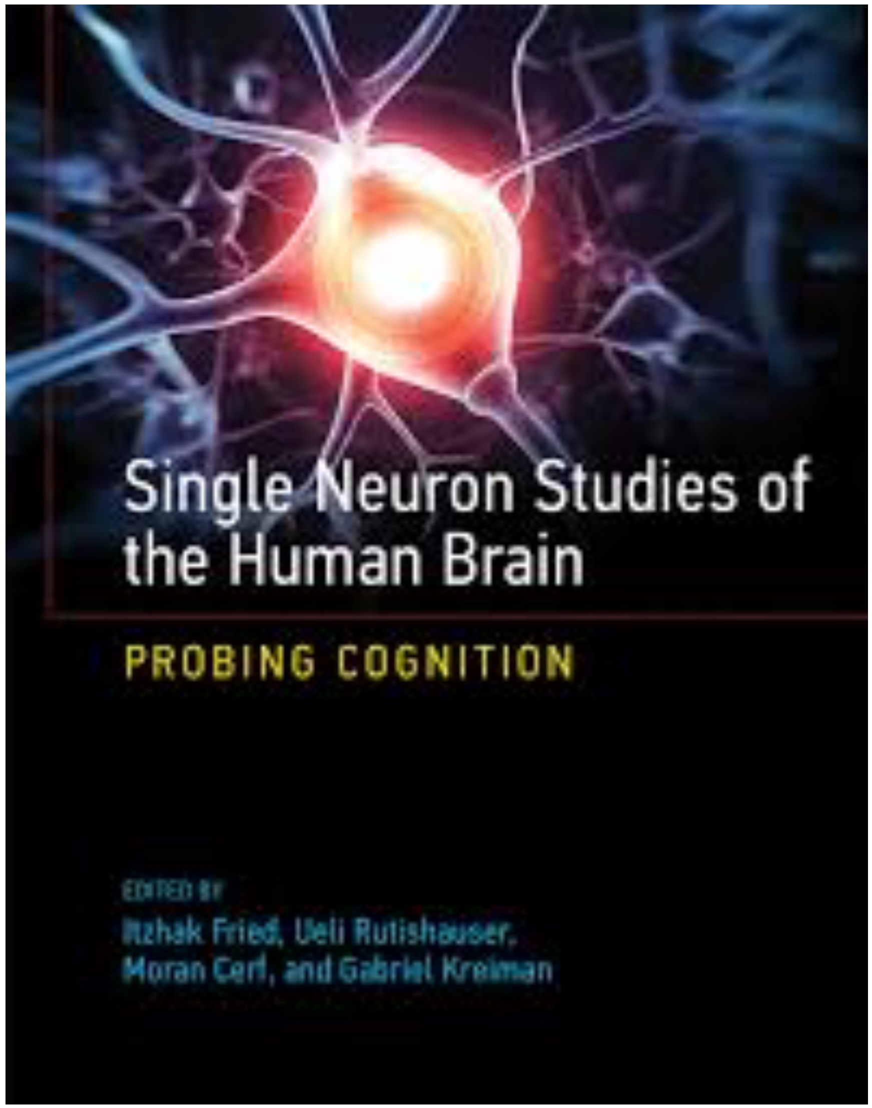
- Challenges
  - Risks and ethical issues
  - Patient brains
  - Spike sorting, electrode types, operator and sampling bias
- Value
  - Rare window into human brain
  - Less vulnerable to movement artifacts
  - High level of temporal and spatial resolution

Future Directions

- Combining with other Neuroimaging technologies
  - EEG, fMRI, DBS

- Combining across research sites (Brain Initiative)

Value of iEEG and Single-unit Recordings in Humans

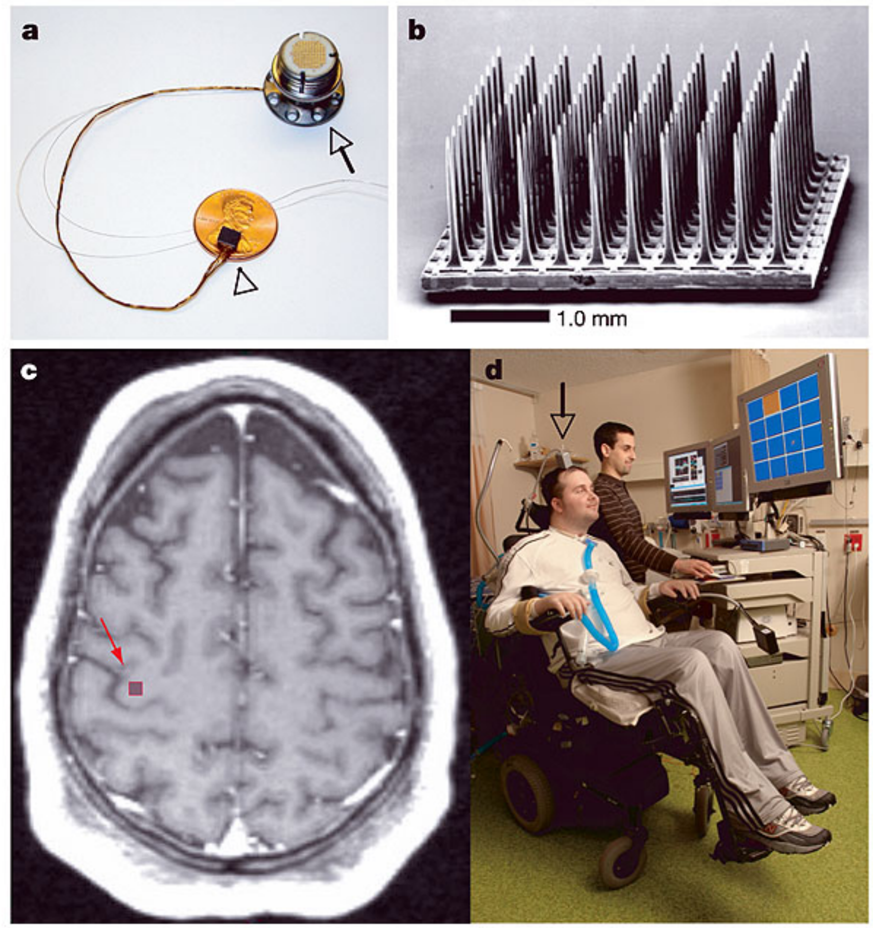


Value of iEEG and Single-unit Recordings in Humans

- Brain oscillations control timing of single-neuron activity in humans (Jacobs et al., 2007, J of Neuroscience)
- Correlation between BOLD fMRI and theta-band local field potentials in the human hippocampal area (Ekstrom et al., 2009, J Neurophys)
- Observational learning computations in neurons of the human anterior cingulate cortex (Hill et al., 2016, Nature Commun)
- Single-neuron activity and eye movements during human REM sleep and awake vision (Andrillon et al., 2015, Nature Commun)
- Rapid Encoding of New Memories by Individual Neurons in the Human Brain (Ison et al., 2015, Neuron)
- Single-cell responses to face adaptation in the human medial temporal lobe (Quian Quiroga et al., 2014, Neuron)

Future Directions

- Brain-Machine Interfaces (BMI)
  - Utah arrays



- Advancements in neuroprosthetic technology