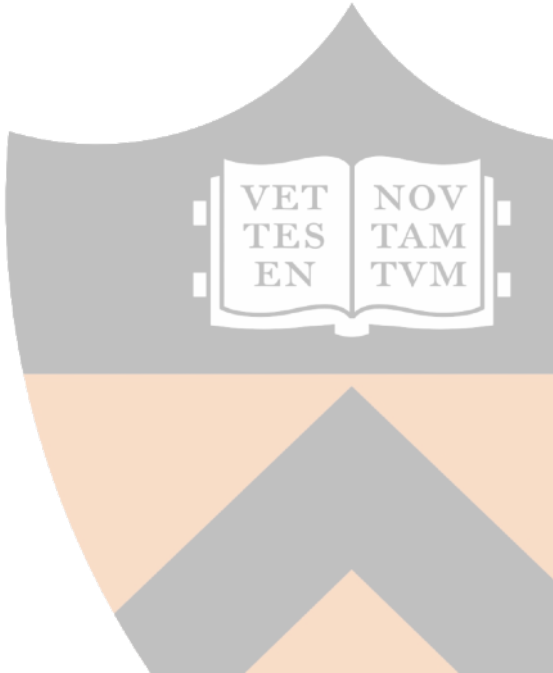
From Molecules to Systems to Behavior

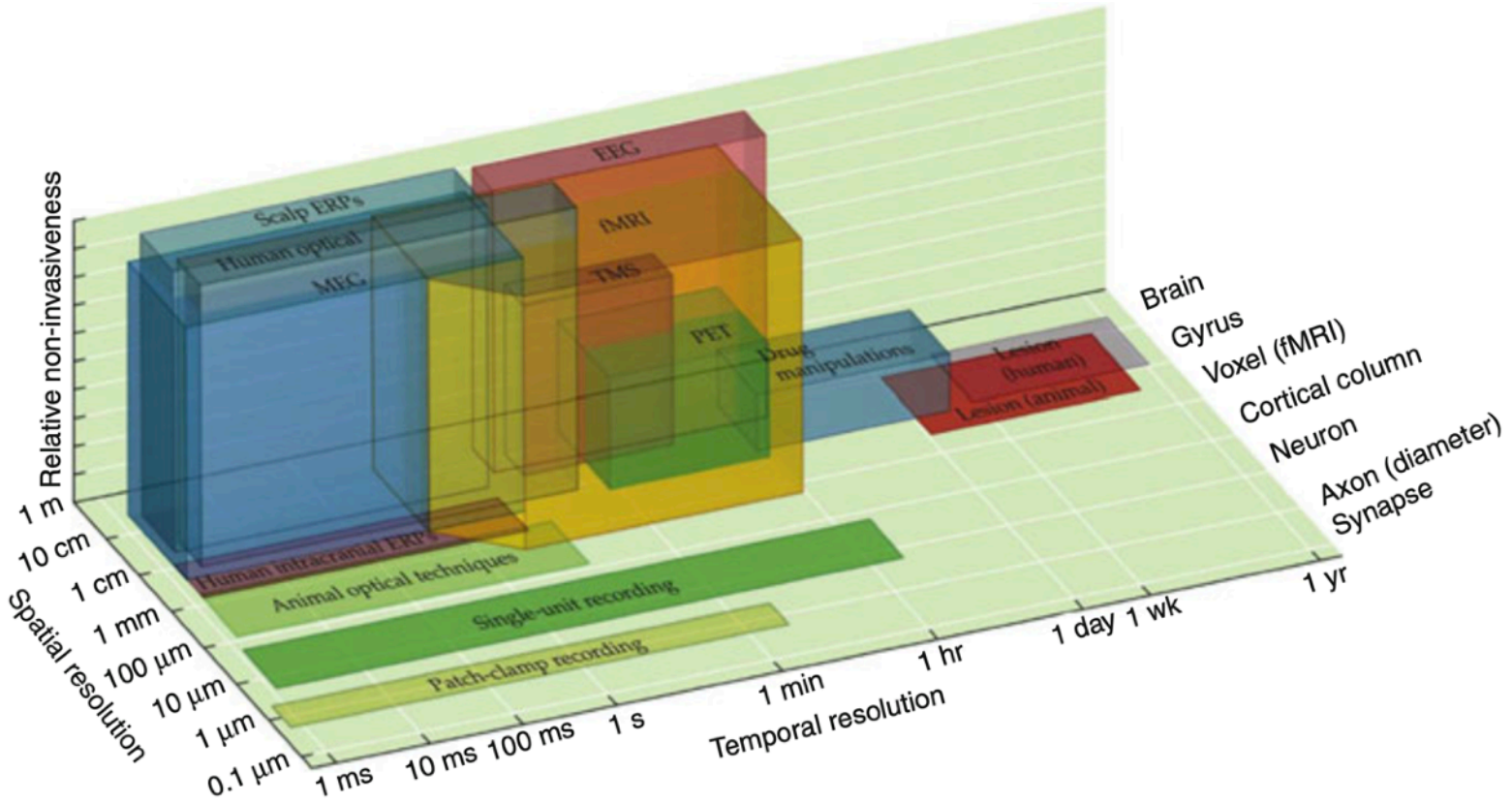
NEU502B: From Molecules to Systems to Behavior
Lecture 7(?): April 1, 2025
Guest Instructor: Leigh Nystrom
Princeton Neuroscience Institute



M/EEG methods

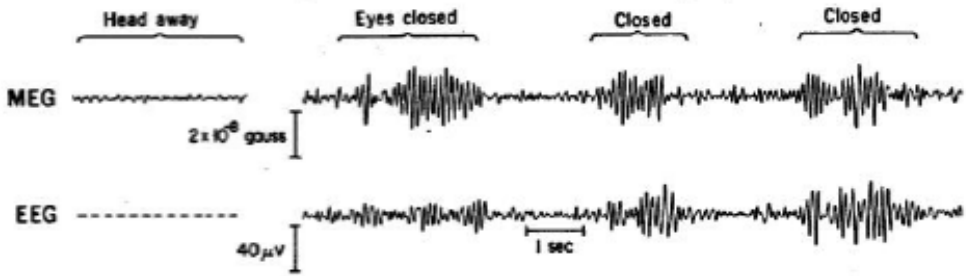
Neuroscience methods overview:

Temporal vs. spatial resolution — but also non-invasiveness



EEG and MEG

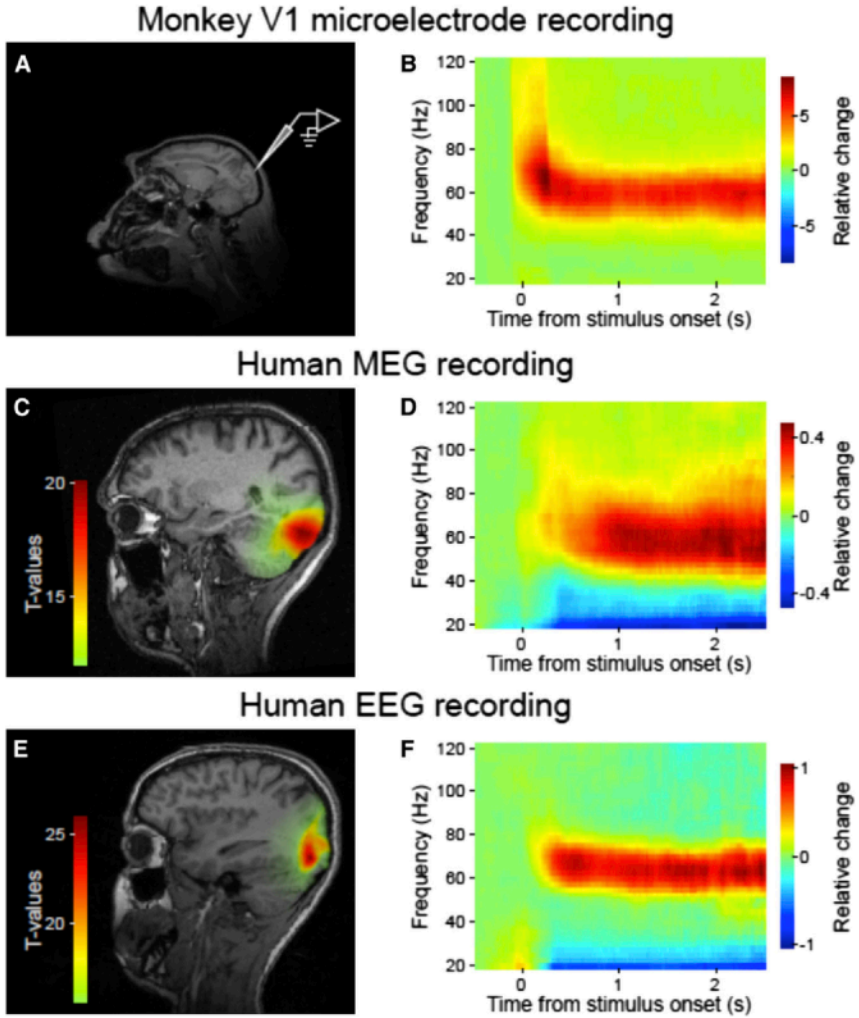
Electroencephalography (EEG) and magnetoencephalography (MEG) are non-invasive methods that measure the same underlying neural currents.



EEG: Measures differences in electric potentials on the scalp

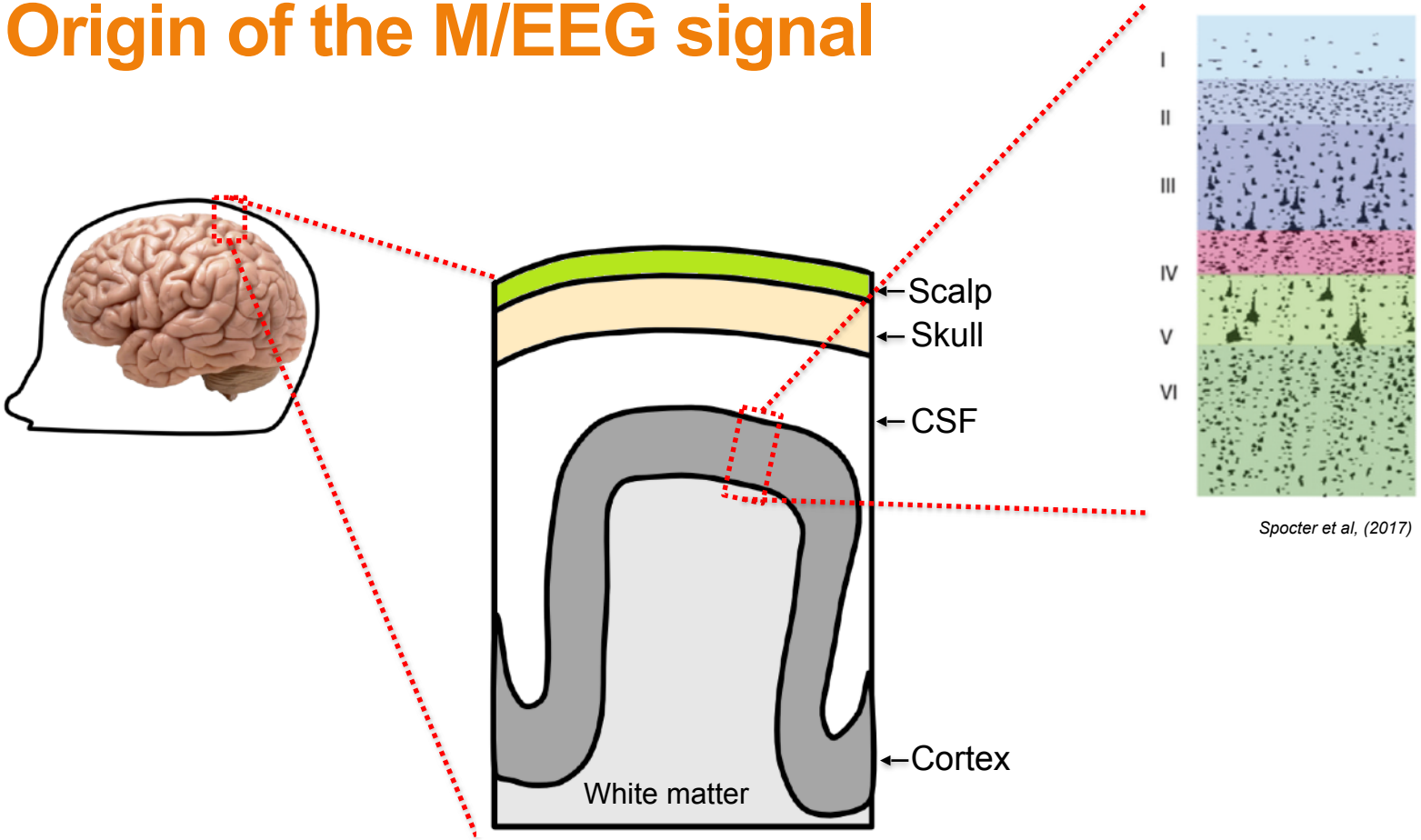
MEG: Measures changes in magnetic flux density outside of the head

M/EEG comparability



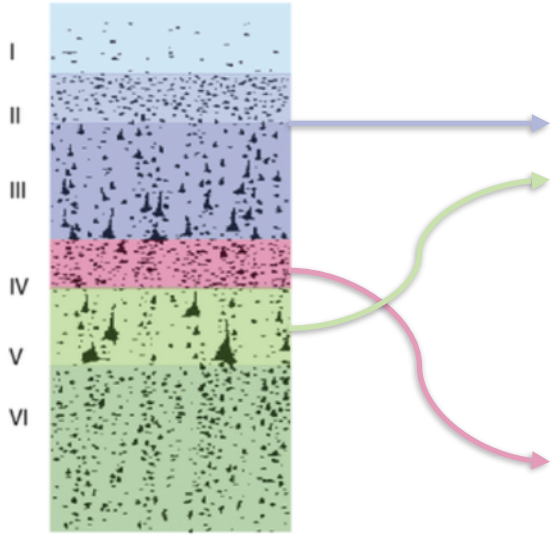
Fries, 2008

Origin of the M/EEG signal



Spocter et al, (2017)

Origin of the M/EEG signal



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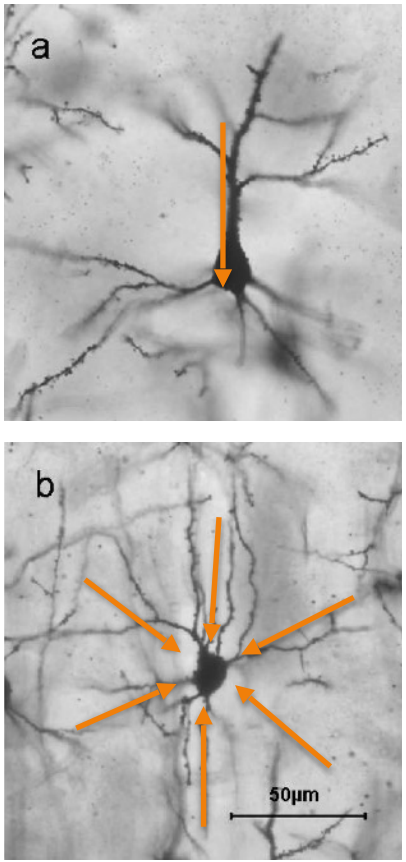


Pyramidal cells

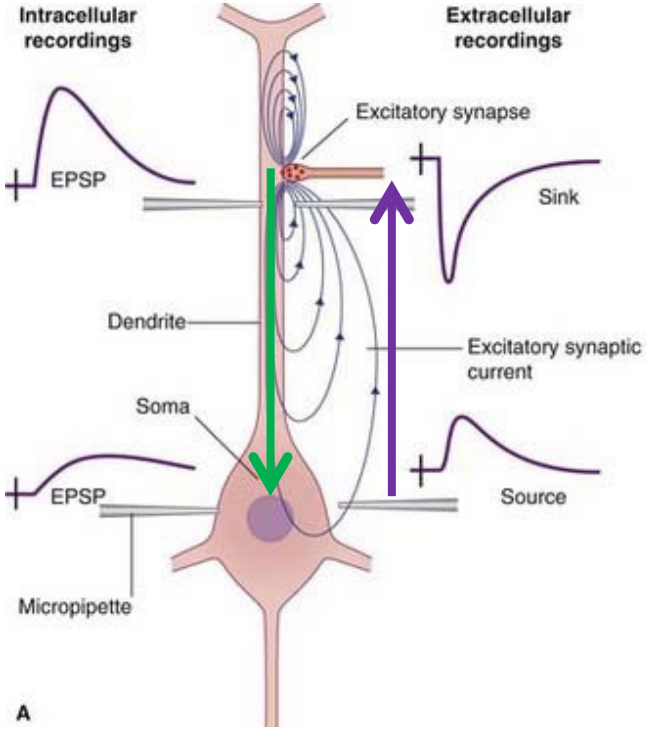
- Found in layers II/III and V
- Organized so primary axis is perpendicular to the cortical surface
- *Open field layout makes this detectable with M/EEG*

Stellate cells

- This example from layer IV
- Closed fields cancel out, so *not seen by M/EEG*

Post Synaptic Potentials

Synaptic input leads to ionic currents across the postsynaptic membrane



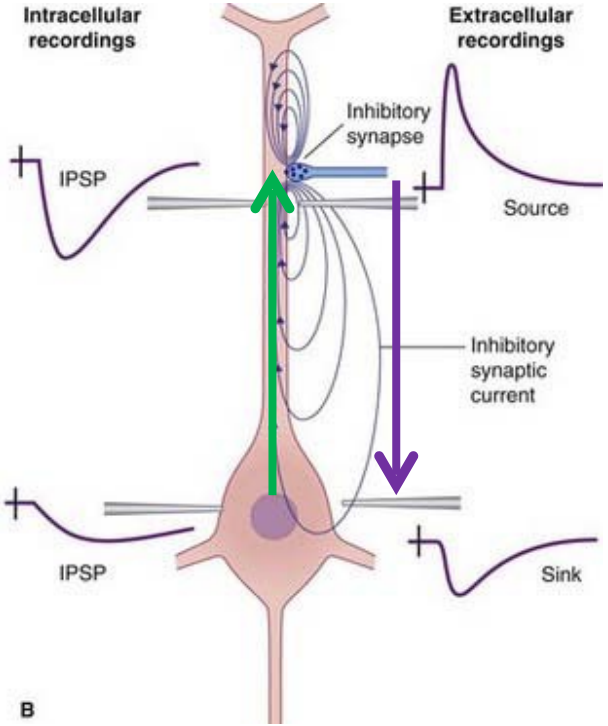
Excitatory Post-Synaptic Potential (EPSP): influx of positive Na+ ions at apical dendrites causes depolarization of the postsynaptic cell

Extracellular volume currents complete the loop of ionic flow so that there is no build-up of charge

MEG is more sensitive to intracellular currents, EEG to extracellular

Post Synaptic Potentials

Synaptic input leads to ionic currents across the postsynaptic membrane

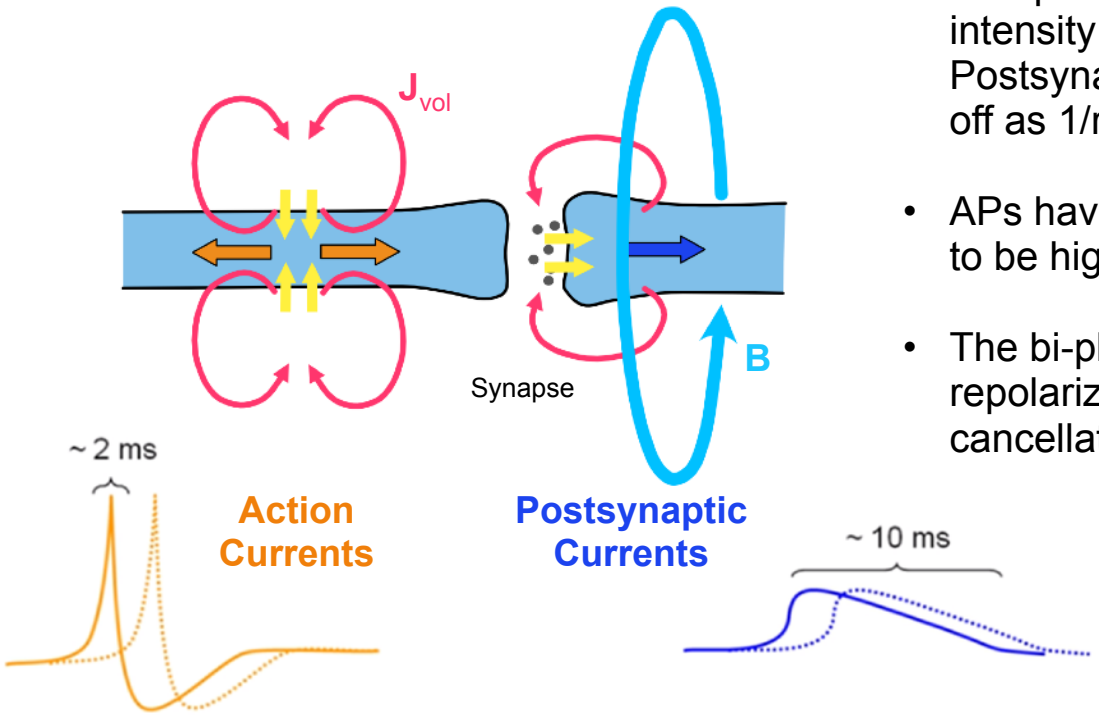


Inhibitory Post-Synaptic Potential (IPSP): influx of negative Cl- ions causes hyperpolarization of the postsynaptic cell

So reversing the direction of the detectable current, relative to EPSPs

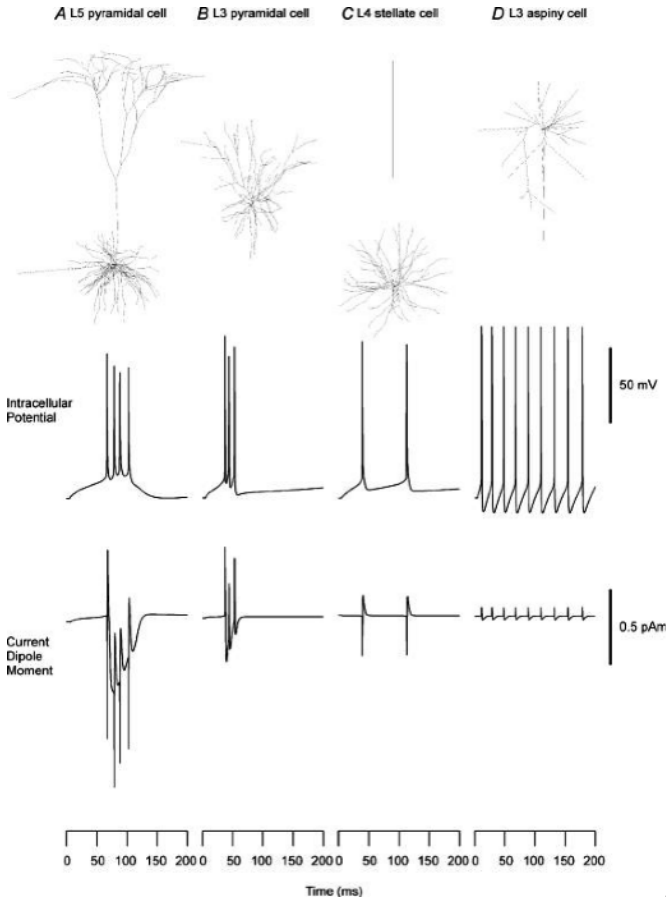
What about action potentials?

Action potentials (APs) are unlikely to contribute to the M/EEG signal.



- APs produce electric quadropoles, with their intensity declining steeply with distance ($1/r^3$). Postsynaptic currents are dipolar, which drop off as $1/r^2$.
- APs have a very short duration. Would need to be highly synchronized to be measurable.
- The bi-phasic nature of the depolarizing and repolarizing currents might result in mean field cancellation.

How many neurons needed to detect?

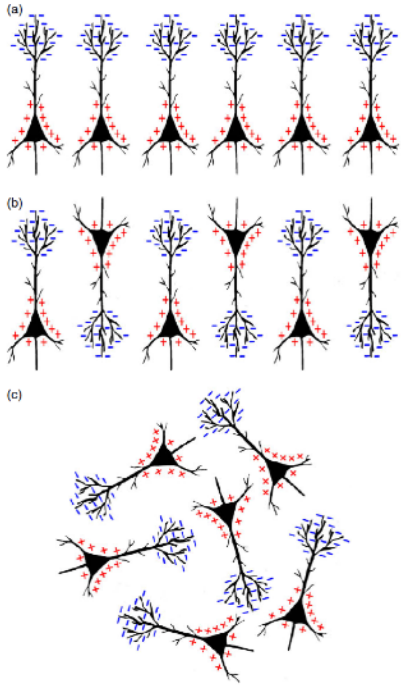


A single neuron is not detectable.

- Neuronal models of detailed morphology were simulated, excited by virtually injecting current.
- Equivalent current dipole (ECD) moment was estimated by summing across dipoles in an area.
- ~50,000 cells is sufficient to generate a dipole source of 10 nAm

Murakami et al (2006)

How many neurons needed to detect?



Jackson & Bolger (2014)

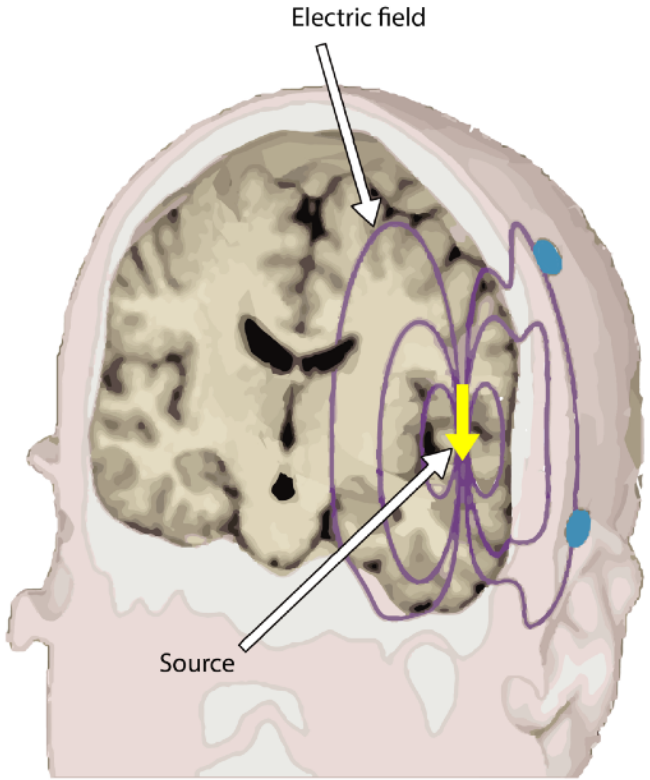
These tens of thousands of neurons need to be well-aligned in space and polarity

- (a) nice! cumulative sum >> individual neuron
- (b) ugh! the dipole +/- signs cancel out = 0
- (c) chaos reigns supreme! probably also = 0

Another rough estimate for spatial resolution:

- ~ 1 Million synapses needed
- with ~10K cells / mm^2, ~1K synapses / cell,
  - then a few mm^2 can potentially produce a measurable signal

EEG: Conduction of the electric field



EEG: Measures differences in electric potential at the scalp

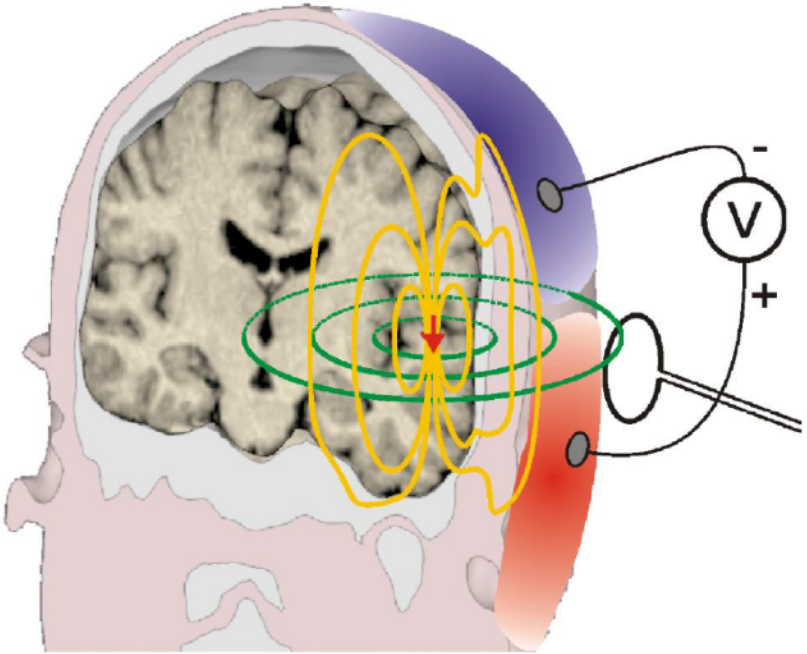
Volume conduction – primary currents along dendrites of neurons give rise to secondary currents.

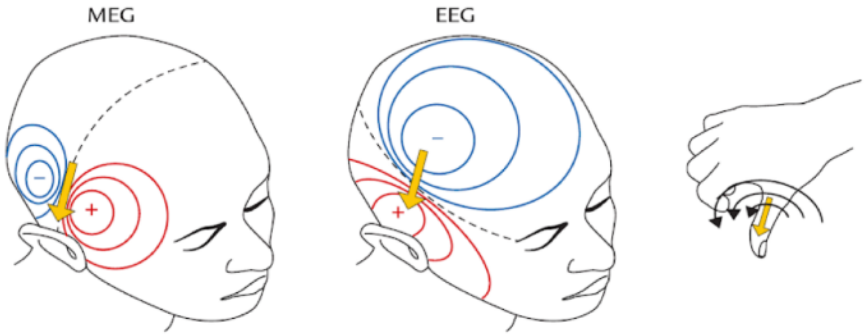
These propagate to be detectable at multiple sites on the scalp.

In a uniformly conducting medium, electrical field strength is related to the inverse square of the distance.

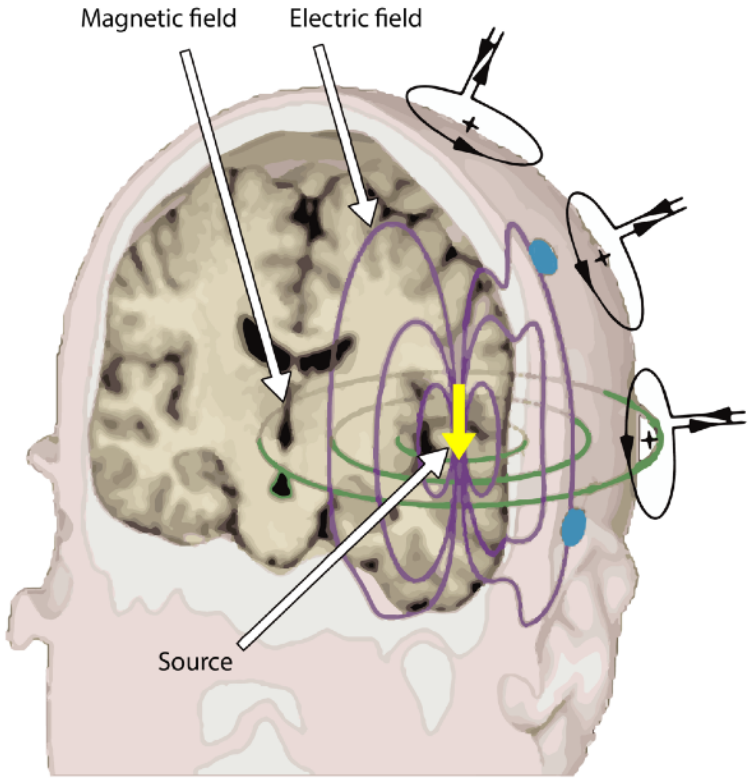
But conductivity actually varies across different tissue types in the head (e.g. grey matter, CSF, skull, scalp…)

EEG and MEG: complementary data, “right hand rule”





MEG: Conduction of the magnetic field



MEG: Measures changes in magnetic flux density outside of the head

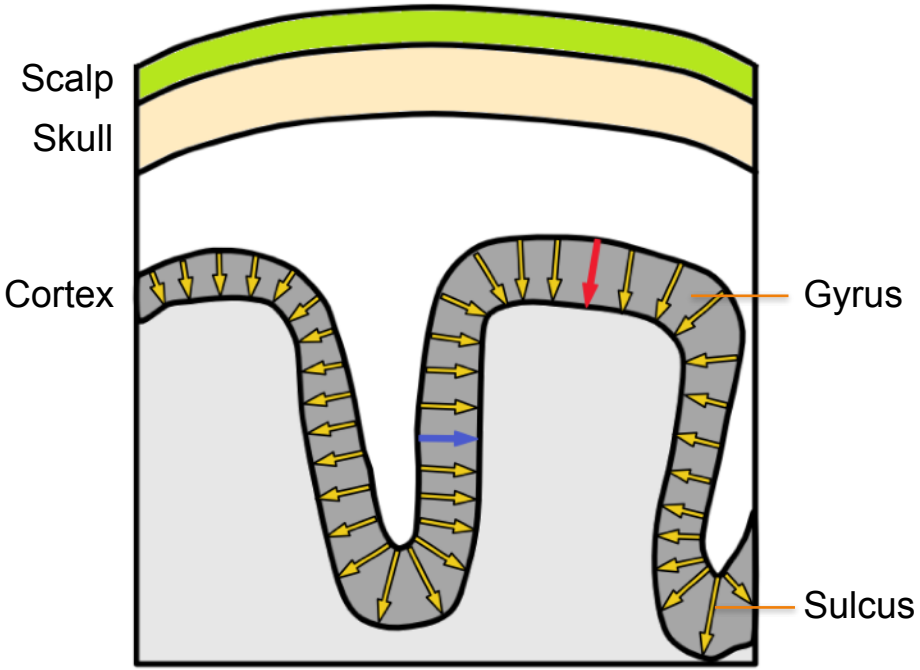
Magnetic fields are mainly induced by primary currents whereas electric fields are mainly sensitive to secondary (volume) currents

Magnetic fields are generated perpendicular to electric fields, from both the primary and secondary currents

Magnetic fields are <u>not</u> affected by differences in conductivity with different tissue types.

M/EEG source orientation

Bulk current flow from EPSPs is oriented perpendicular to the cortical ribbon.

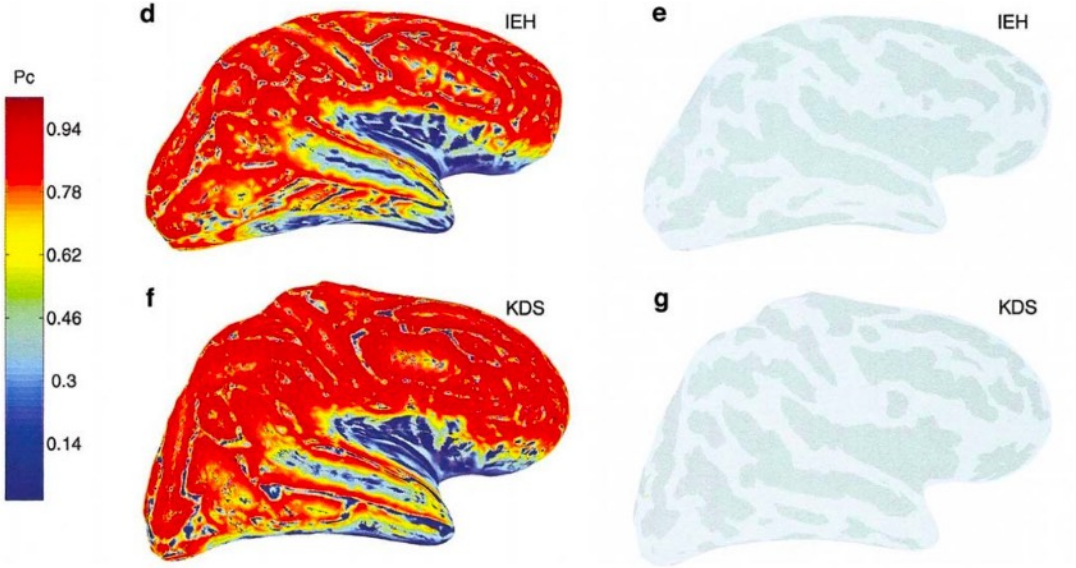


Orientation of source is important….

- EEG can detect both tangential and radial oriented dipoles
- MEG can see tangential, but struggles to sense radial dipoles
    - If you assume a symmetric sphere for the head, radial dipoles are ***impossible*** to detect

M/EEG source orientation

So what's the point if MEG can't see any sources in the gyri/sulci?



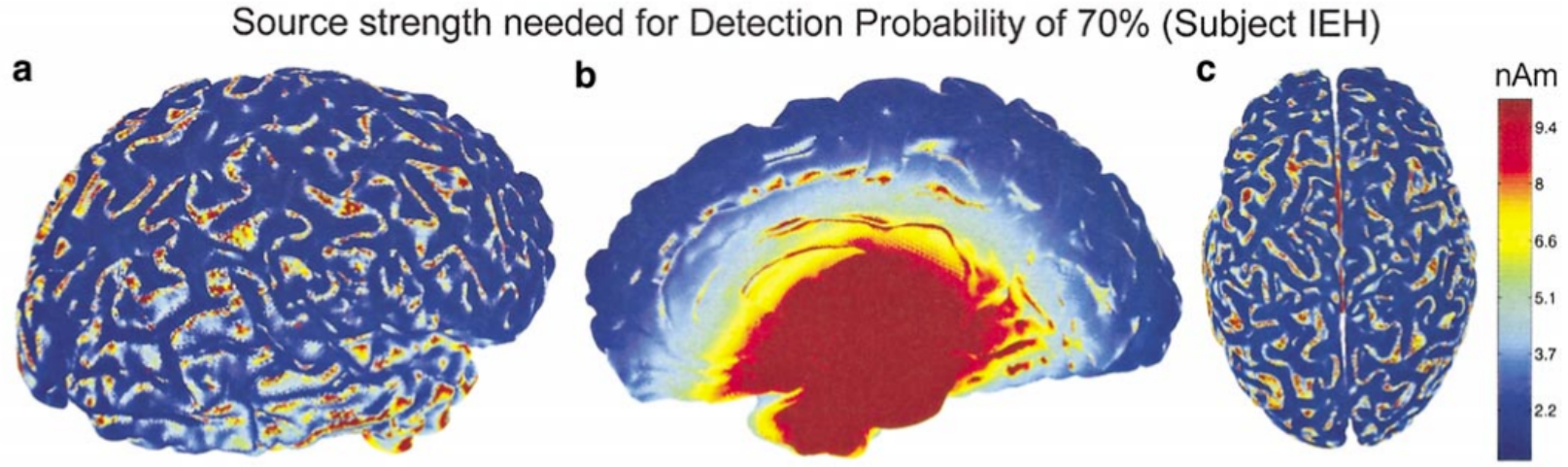
Hillebrand and Barnes (2002)

- The head isn't a perfect sphere.
- Even if you assume it is very few sources are truly radial
- Most sources are not point sources, so will likely contain a tangential component.

tl;dr - it's not a massive concern.

M/EEG source depth

Depth is a limiting factor in MEG measurements.



Hillebrand and Barnes (2002)

- Sensor-level amplitude decreases with distance from source ($1/r^2$)
- Deeper sources appear more radial, which MEG is less sensitive to

History of EEG

1924: Hans Berger coined the term “electroencephalography” (EEG)

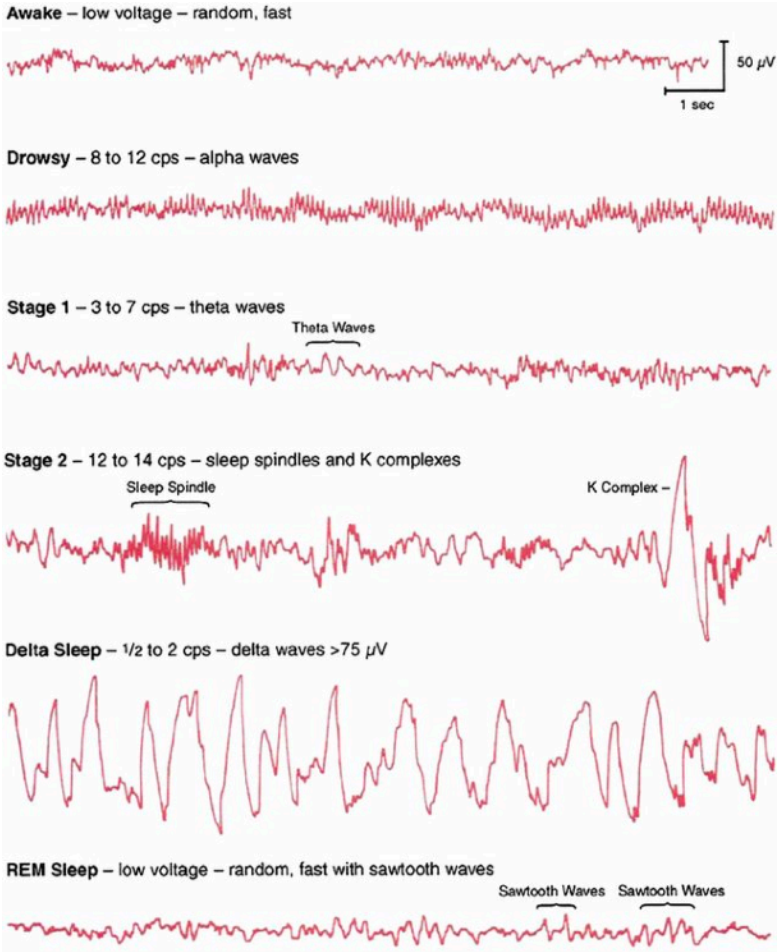
- his initial attempts in humans were *uncomfortable*…
  - he stuck thin sliver wires under his own scalp, 1 each in front & back
  - studied his own son for years, refined less invasive on-scalp electrodes
- sat on his results for 5 years before publishing his discoveries
  - he called it the “alpha wave”
    - roughly 10Hz, grows larger when subject closes their eyes
    - (also discovered a “beta wave” around 12-30 Hz)

sadly, nobody believed him! (._.`)

1930: William Grey Walter localized alpha rhythm to occipital cortex using multi-electrode EEG, and also discovered *delta* waves associated with deep sleep and epilepsy

Oscillations

Scalp EEG can detect ***oscillations*** associated with characteristic frequency bands, cortical distributions, and brain states (e.g. alertness)



Oscillations

These oscillations reflect the ***synchronized activity*** of large-scale ***networks of neurons*** (e.g. thalamocortical loops drive sleep spindles)

Band	Frequency (Hz)	Location	Normally	Pathologically
Delta	< 4 Hz	Front regions in adults, posterior regions in children	Slow-wave sleep	Subcortical and diffuse lesions
Theta	4–7 Hz	Regions not engaged by a given task	Drowsiness, idling, inhibition	Focal subcortical lesions
Alpha	8–12 Hz	Bilateral posterior and central regions	Relaxing, closed eyes, inhibition	Coma
Beta	13–30 Hz	Symmetric bilaterally, particularly frontal regions	Active thinking, alertness, stress	Benzodiazapines
Gamma	> 32 Hz	Somatosensory cortex	Multimodal sensory processing, memory tasks	Decreases with cognitive decline

Event-related potentials

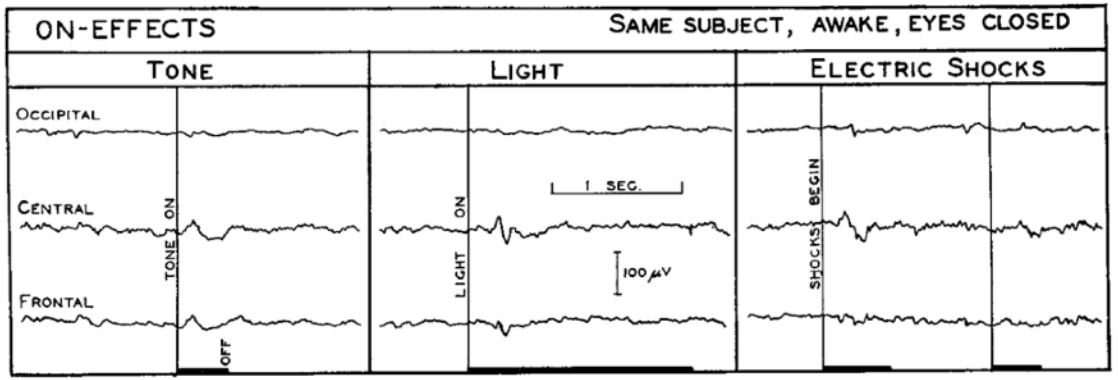
1939: Pauline and Hallowell Davis observed the first ***event-related potentials*** (ERPs) — brief electrical potentials in response to certain stimuli (instead of oscillations)

ELECTRICAL REACTIONS OF THE HUMAN BRAIN TO AUDITORY STIMULATION DURING SLEEP

H. DAVIS, P. A. DAVIS, A. L. LOOMIS, E. N. HARVEY, AND G. HOBART
From the Department of Physiology, Harvard Medical School, Boston, Mass., and The Loomis Laboratory, Tuxedo, N. Y.

Evoked potentials (EPs): early, stereotyped responses to stimulus

Event-related potentials (ERPs): later, stereotyped responses linked to higher cognitive processes



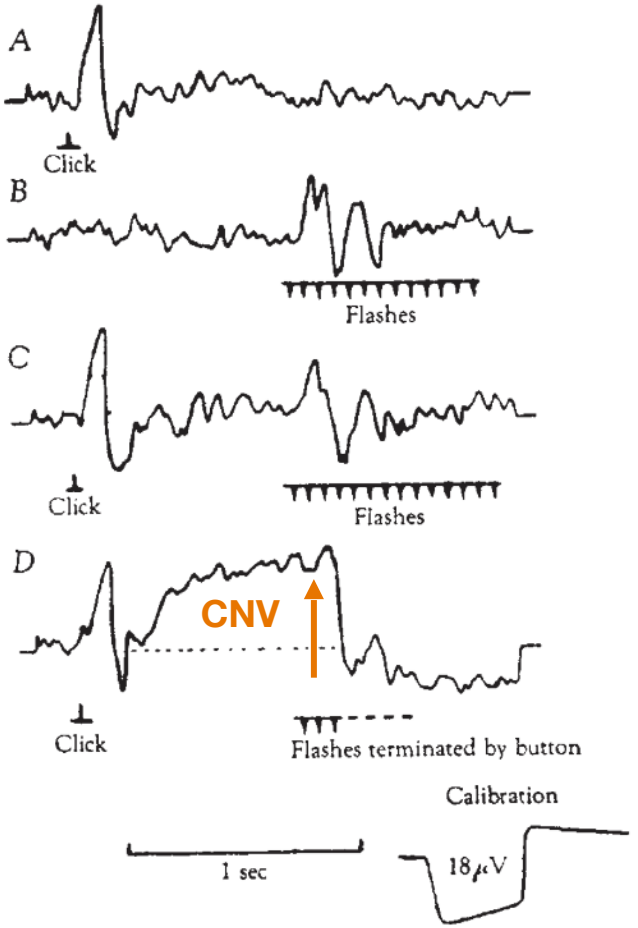
Event-related potentials

1964: William Grey Walter discovers first “cognitive” ERP — “contingent negative variation” is a negative potential indexing *expectation* between a “warning” (cue) stimulus and a “imperative” stimulus the subject intends to suppress or terminate

CONTINGENT NEGATIVE VARIATION: AN ELECTRIC SIGN OF SENSORI-MOTOR ASSOCIATION AND EXPECTANCY IN THE HUMAN BRAIN

By Dr. W. GREY WALTER, Dr. R. COOPER, V. J. ALDRIDGE, W. C. McCALLUM and A. L. WINTER

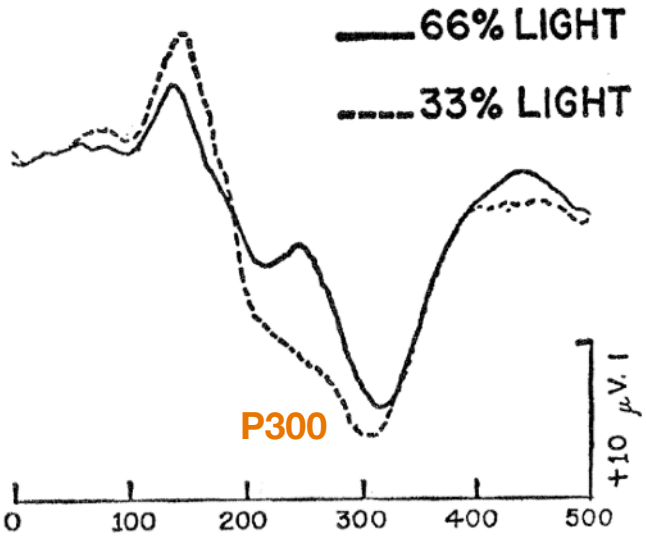
Burden Neurological Institute, Stapleton, Bristol



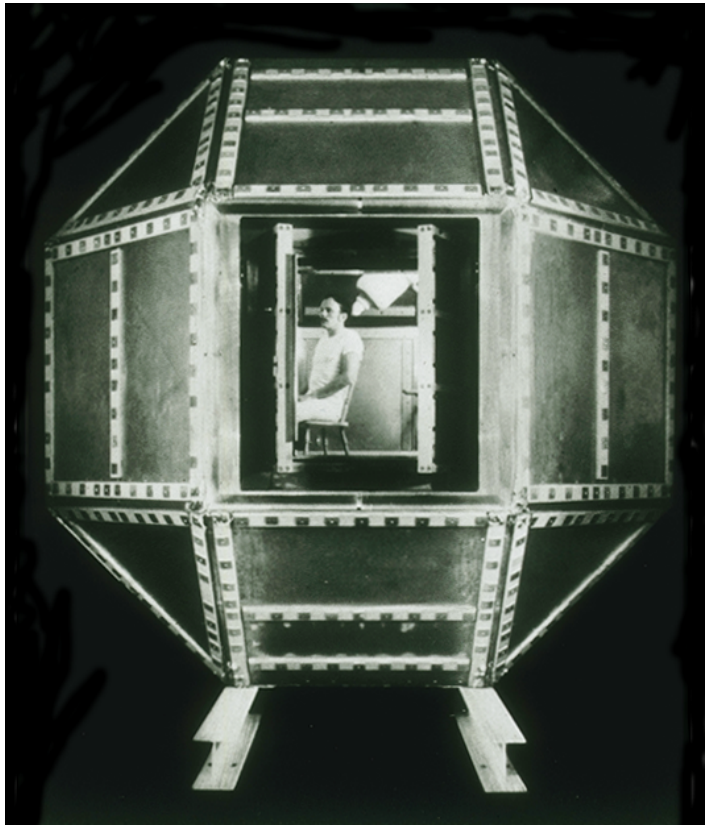
Event-related potentials

1964: William Grey Walter discovers first “cognitive” ERP — “contingent negative variation” is a negative potential indexing *expectation* between a “warning” (cue) stimulus and a “imperative” stimulus the subject intends to suppress or terminate

1965: Samuel Sutton discovers P300—a positive deflection corresponding to more uncertain/informative stimuli (e.g. oddballs)



Invention of MEG 1968



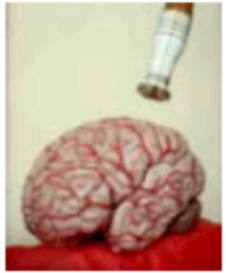
First pioneered by David Cohen & James Zimmerman at MIT in 1968

Single SQUID sensor inside shielded booth

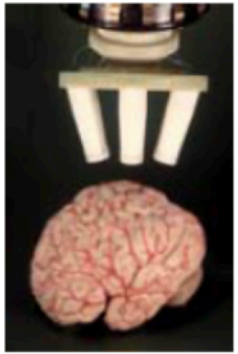
Only began to get popular** in the early 1990s after introduction of high-density sensor arrays

***(Still rare though, due to cost — millions of $$)*

Refinement of MEG



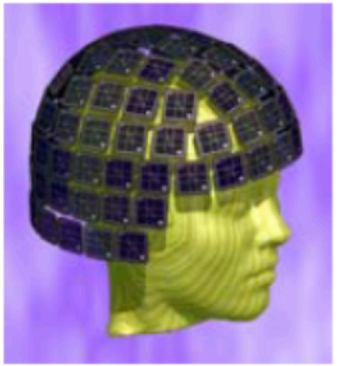
1983
by HUT
4 channels
30 mm in diameter
(coverage: 7 cm^2)
Axial



1986
by HUT
7 channels
93 mm in diameter
(coverage: 68 cm^2)
Axial

1989
by HUT
24 channels
125 mm in diameter
(coverage: 123 cm^2)
Planar

1991
by Neuromag
122 channels
whole head
(coverage: 1100 cm^2)
Planar
12 Deliveries



1997
by Neuromag
306 channels
whole head
(coverage: 1220 cm^2)
Planar & Magnetometers

Refinement of MEG

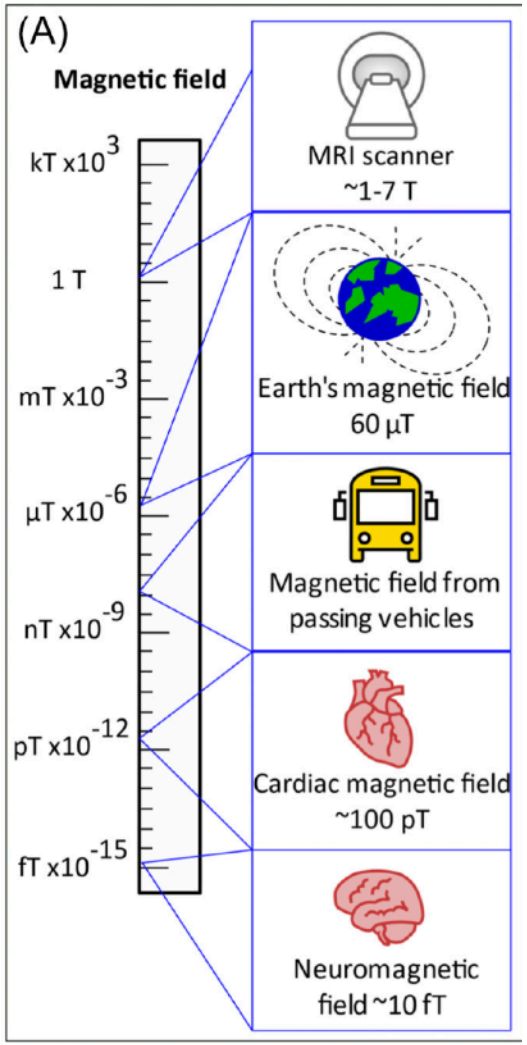
mid 2000s - present: Development and standardization of a radically different type of MEG sensor, the Optically Pumped Magnetometer (OPM)

not cryogenic SQUID-based, but rather room-temperature
not huge room-sized, but tiny, portable, wearable (a lot like EEG)

MEG Signal Challenges

The MEG signal is tiny!

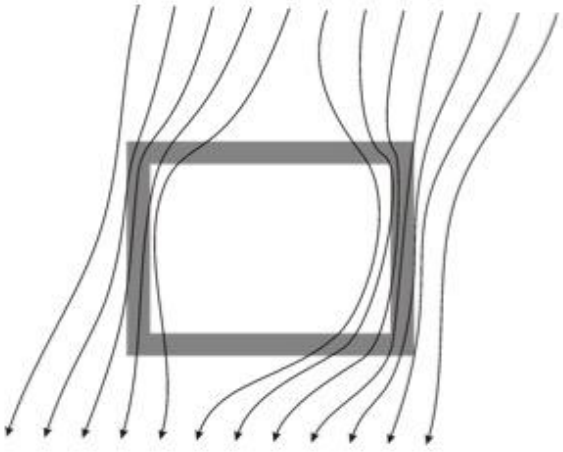
We need approaches to shield our sensors from this noise to be able to measure anything useful.

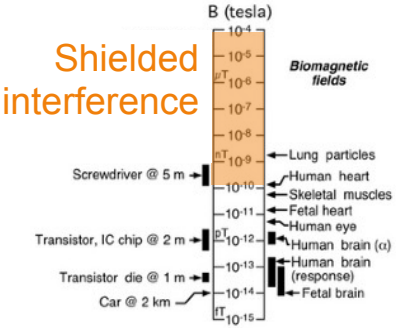


Magnetically shielded rooms

MEG systems are currently housed within Magnetically Shielded Rooms (MSRs),
which give passive shielding against noise from the environment, on the order of tens of nT.

Degaussing coils can reduce this further to ~ 5nT (still too high for MEG though).



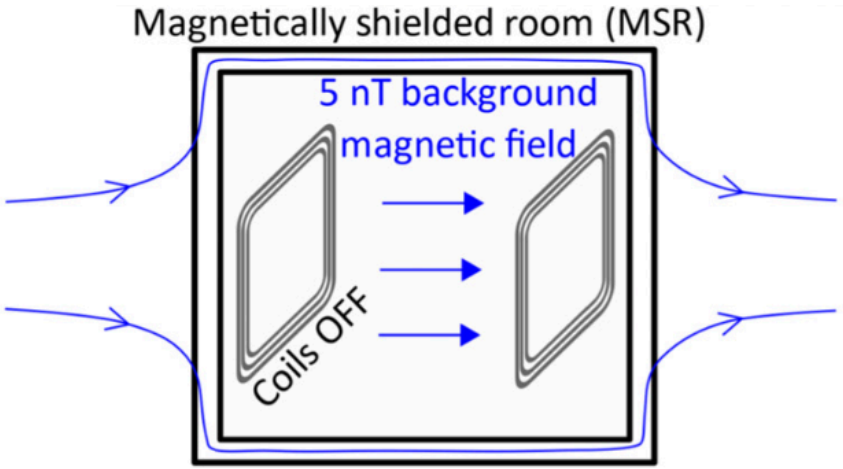


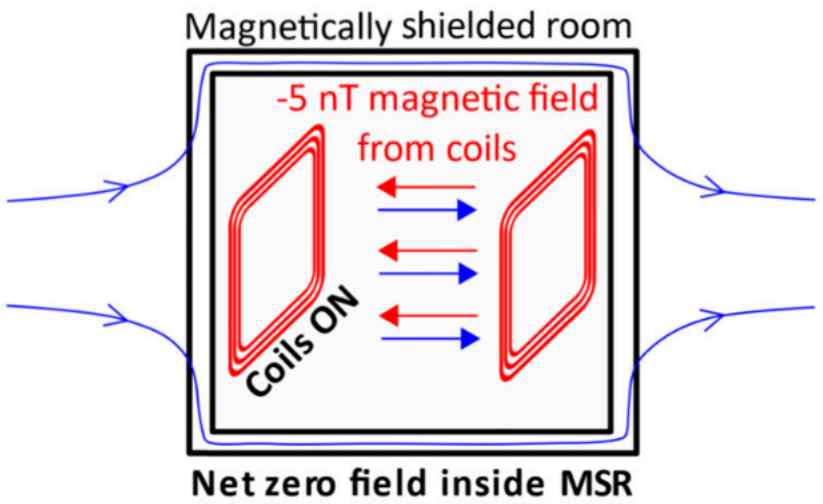
Concentric shells of mu metal, copper and aluminum bend external fields around the MSR

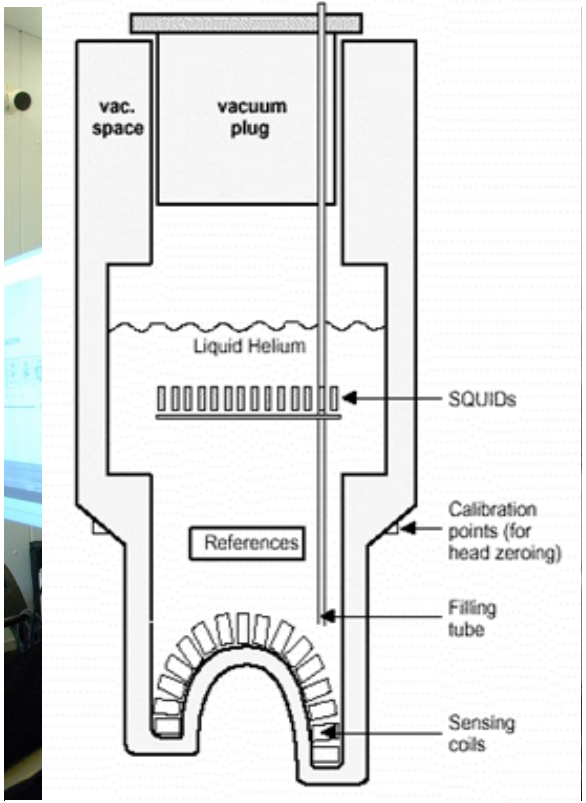
Magnetically shielded rooms

Adding active shielding coils (like MRI coils) can lower the remnant background fields to near zero.

Some systems even drive these coils dynamically, to counteract field changes from subject motion.





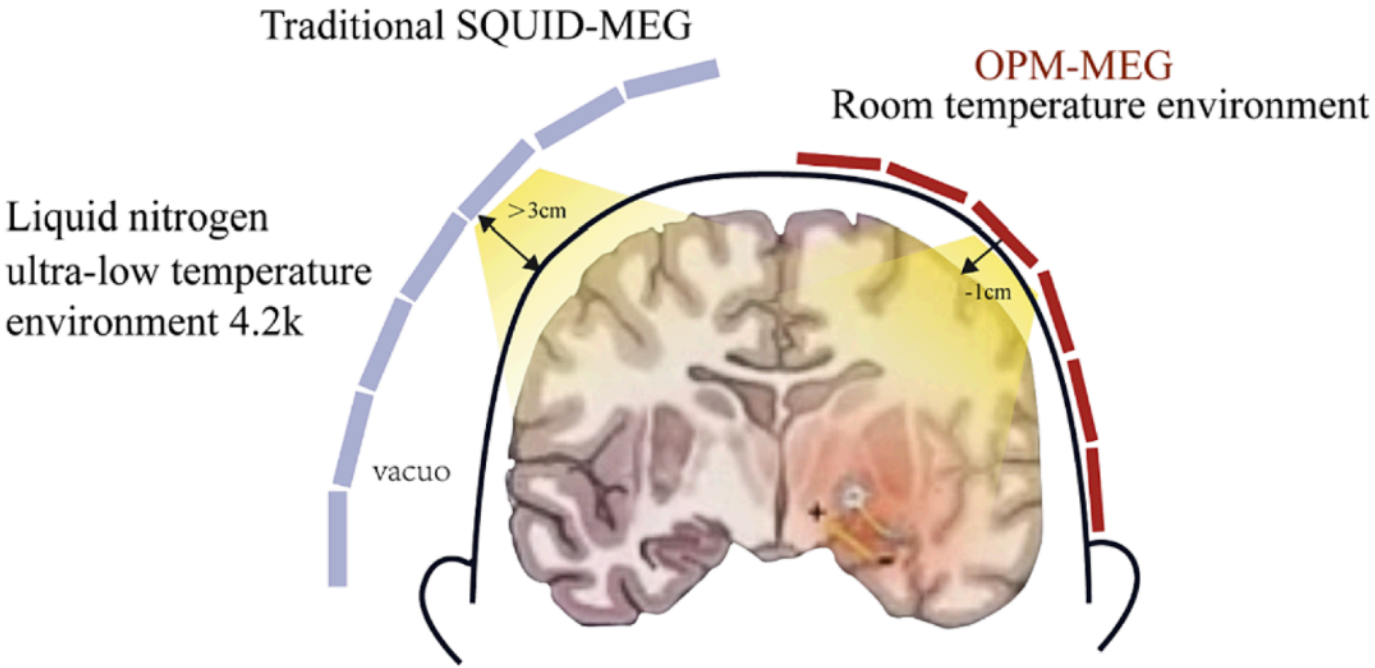


National Institute of Mental Health, NIH

QuSpin

Why Use OPMs?

Wearability 1 – Higher Signal



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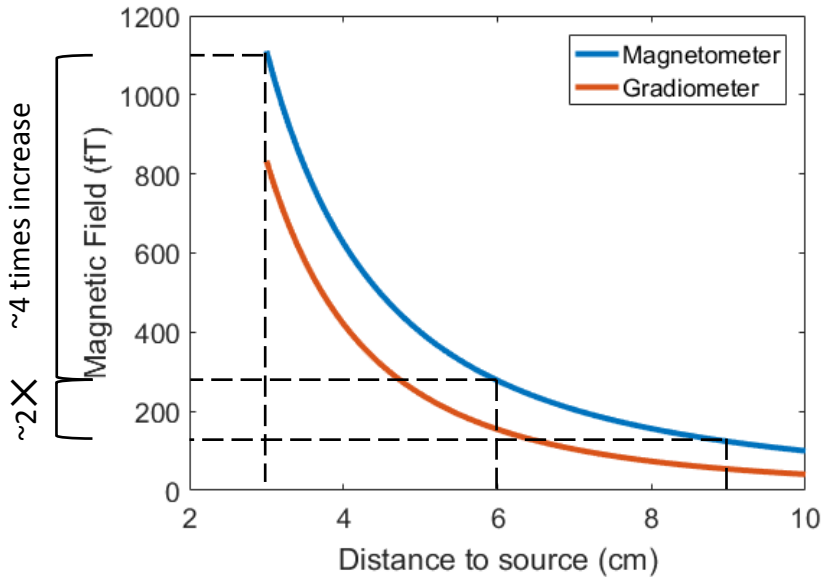
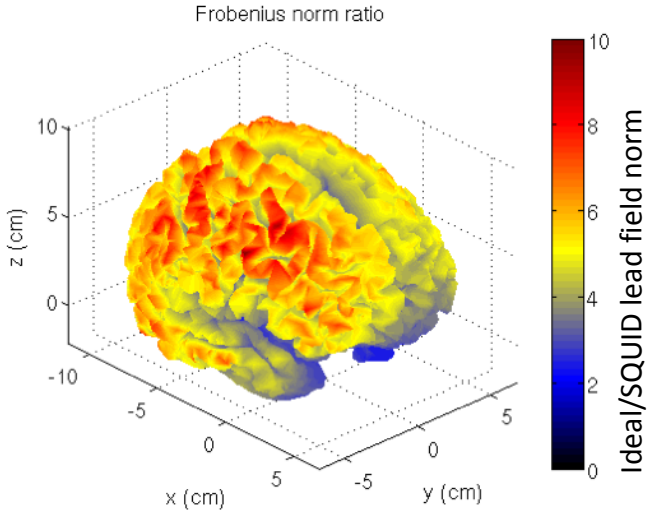
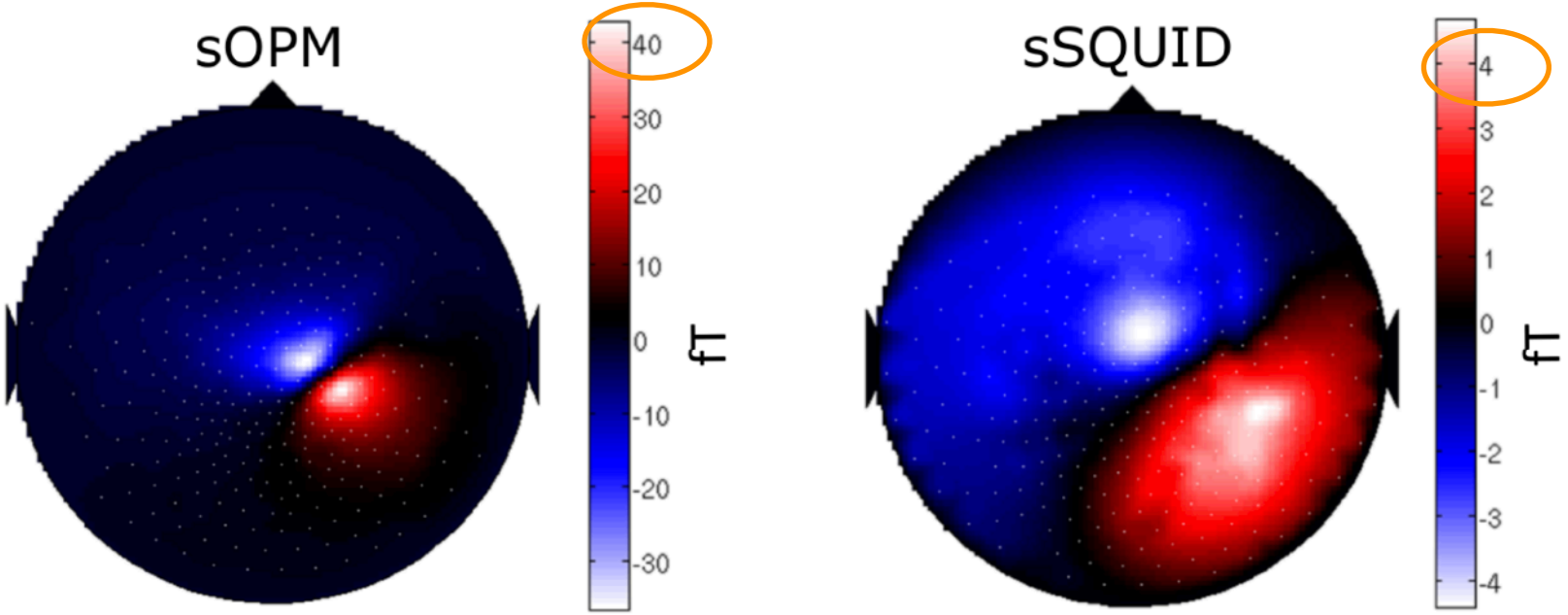




Boto et al. 2016

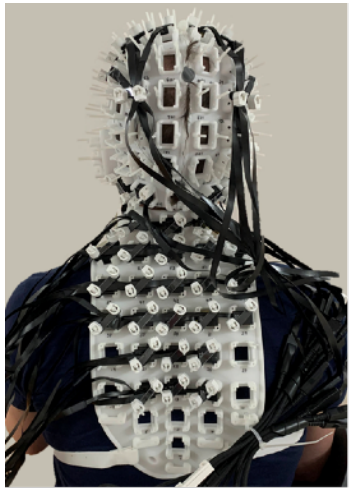
Why Use OPMs?

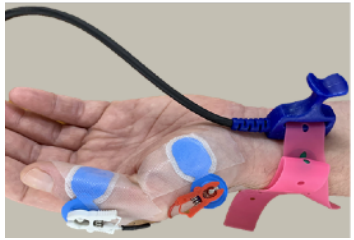
Wearability 2 – Spatial Information

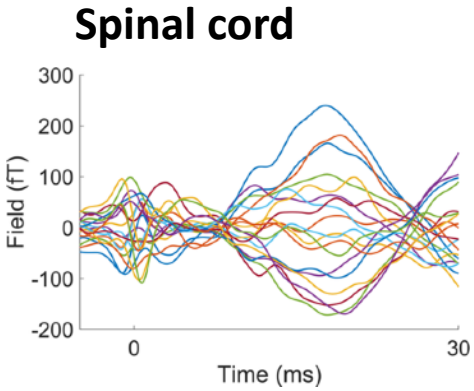


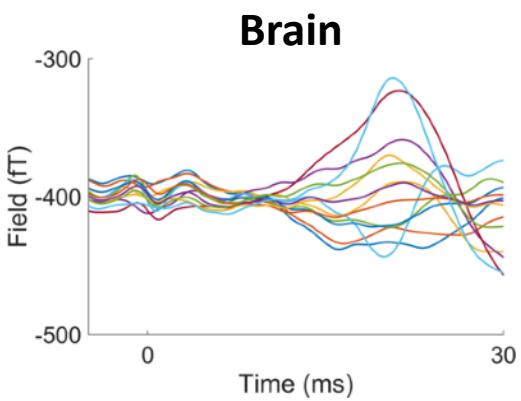
Why Use OPMs?

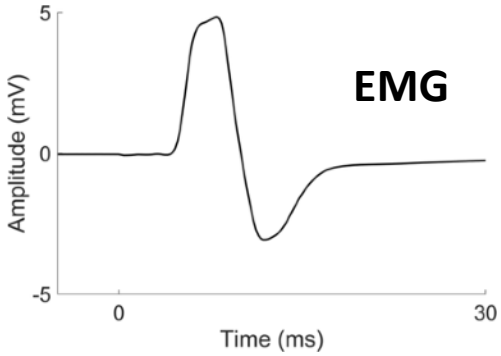
Flexible Sensor Placement







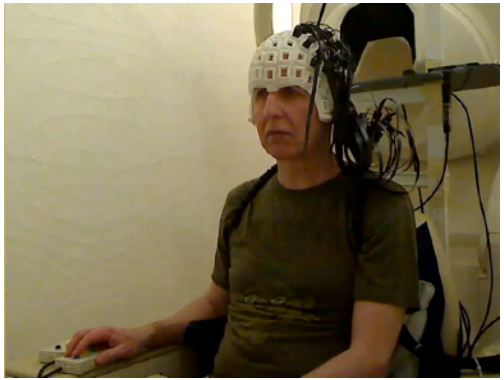


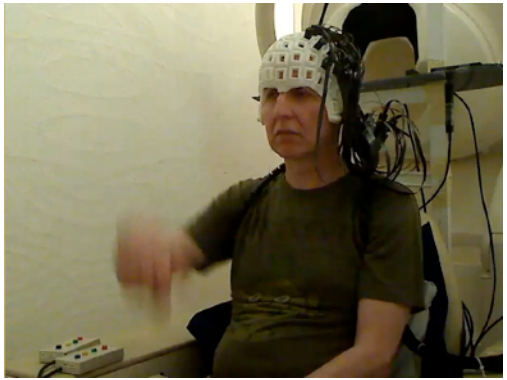


Mardell et al., submitted
Mardell et al., 2022 BioRxiv

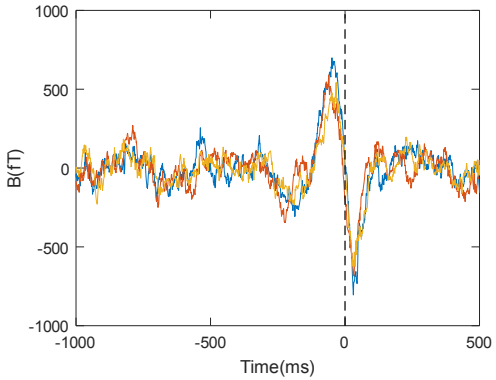
Why Use OPMs?

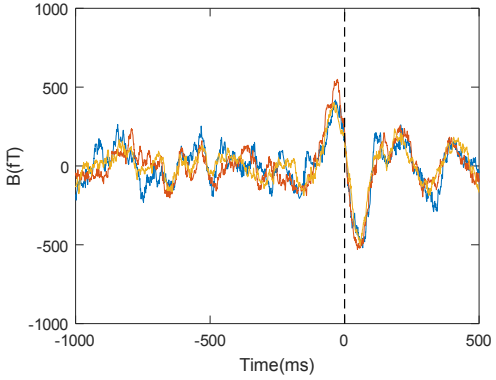
Movement





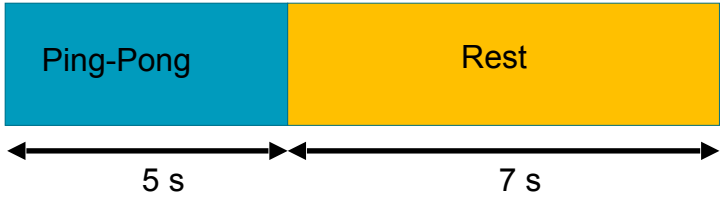
Evoked response to button press



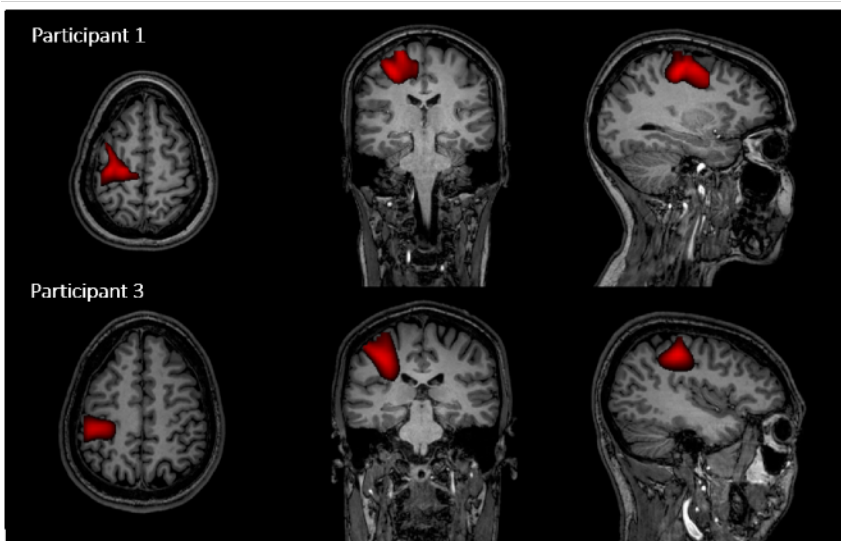


Two person MEG demonstration

Holmes et al., BioRxiv 2021



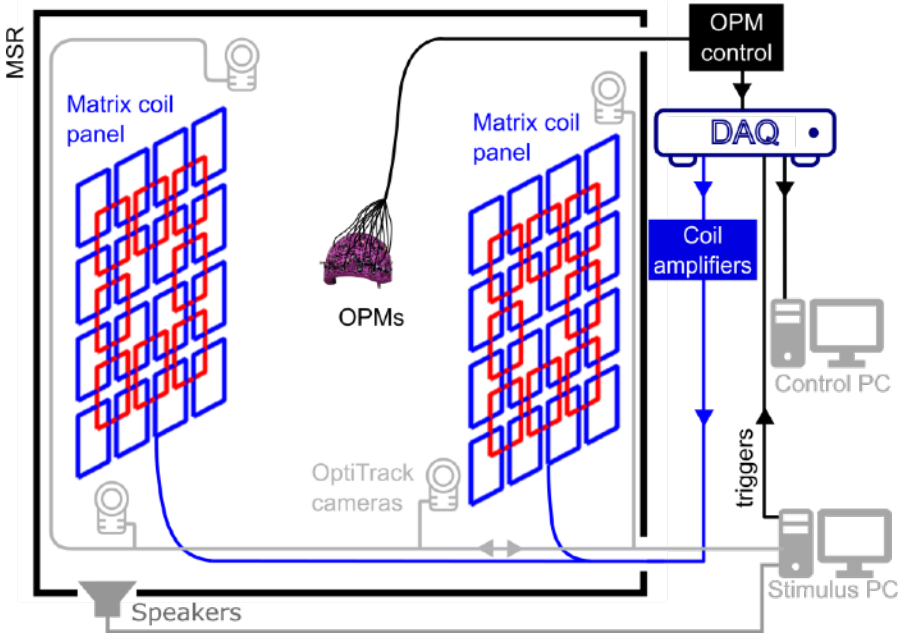
Rally ping pong ball for 5 seconds then rest
25 trials
Requires more unpredictable, rapid head movements!

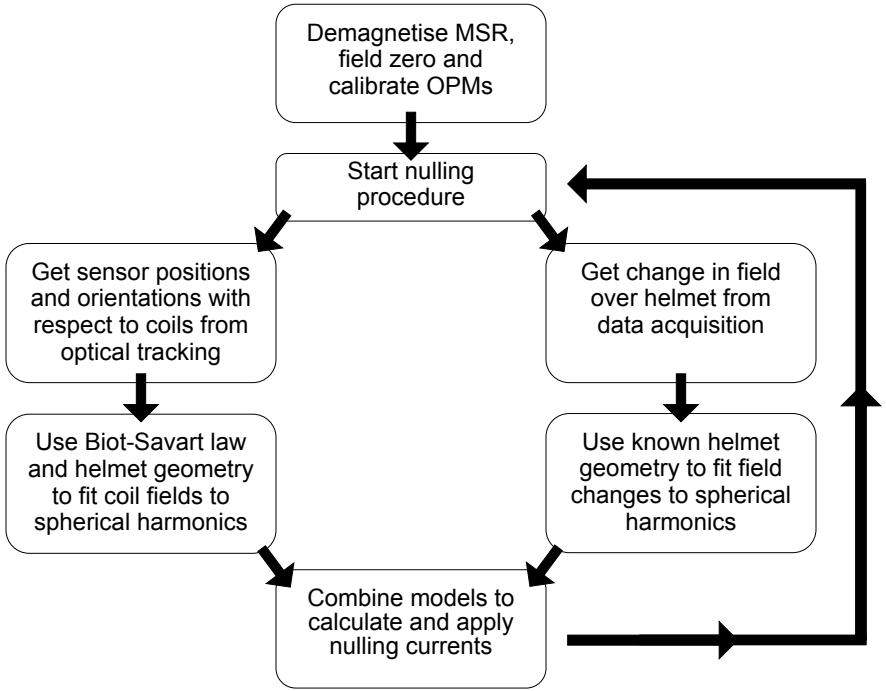


BUT…
Shielded region is still fixed, participants can't move away from initial positions

Real-time active shielding

Holmes et al., in preparation 2022





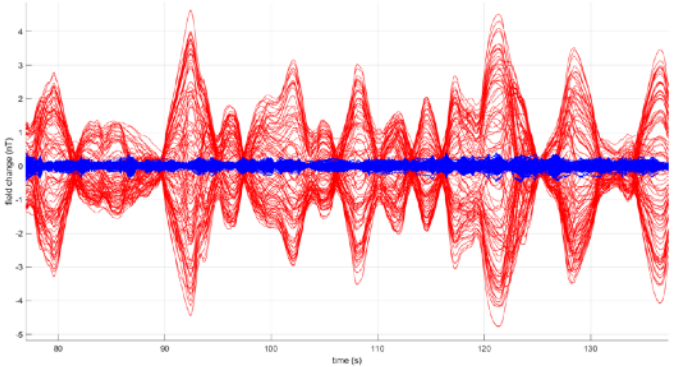
Ambulatory movement in MEG

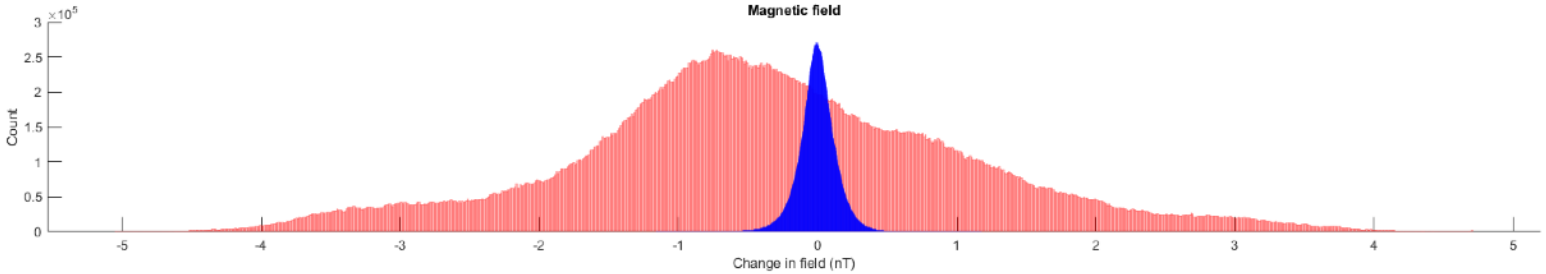
Holmes et al., in preparation

Active shielding at UoN

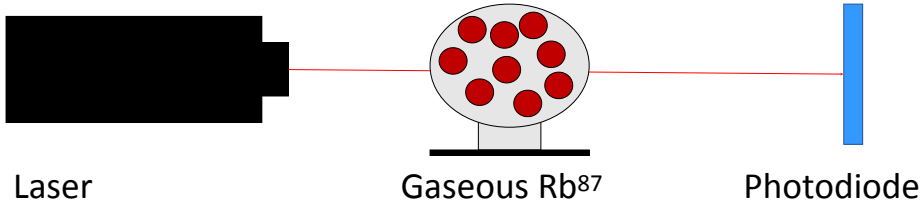
Field distribution

Holmes et al., in preparation

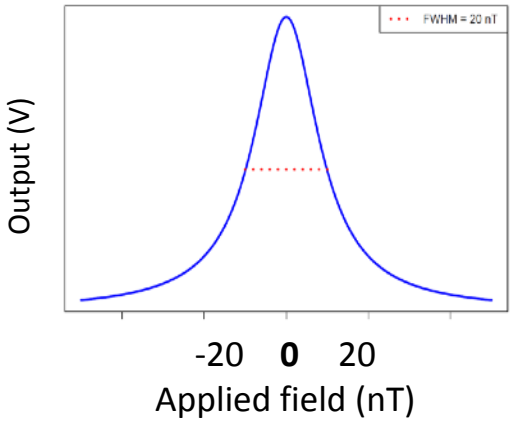




How does an OPM work?



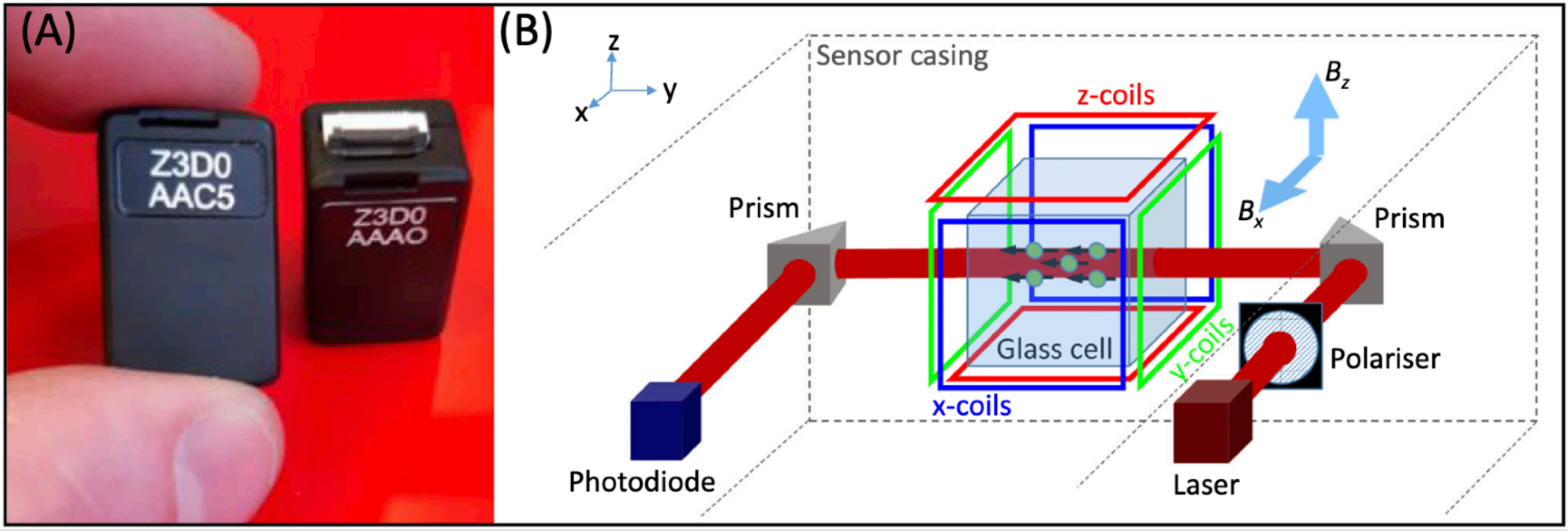
- The laser pumps the Rubidium into a higher energy state, where the spin of each atom is aligned
- Once aligned, the gas is transparent to laser light
- A magnetic field transverse to the laser beam will knock atoms out of this energy state
- The laser can then do work to bring the vapor back to this higher energy state. This uses energy and means less laser light arrives at the photodiode.



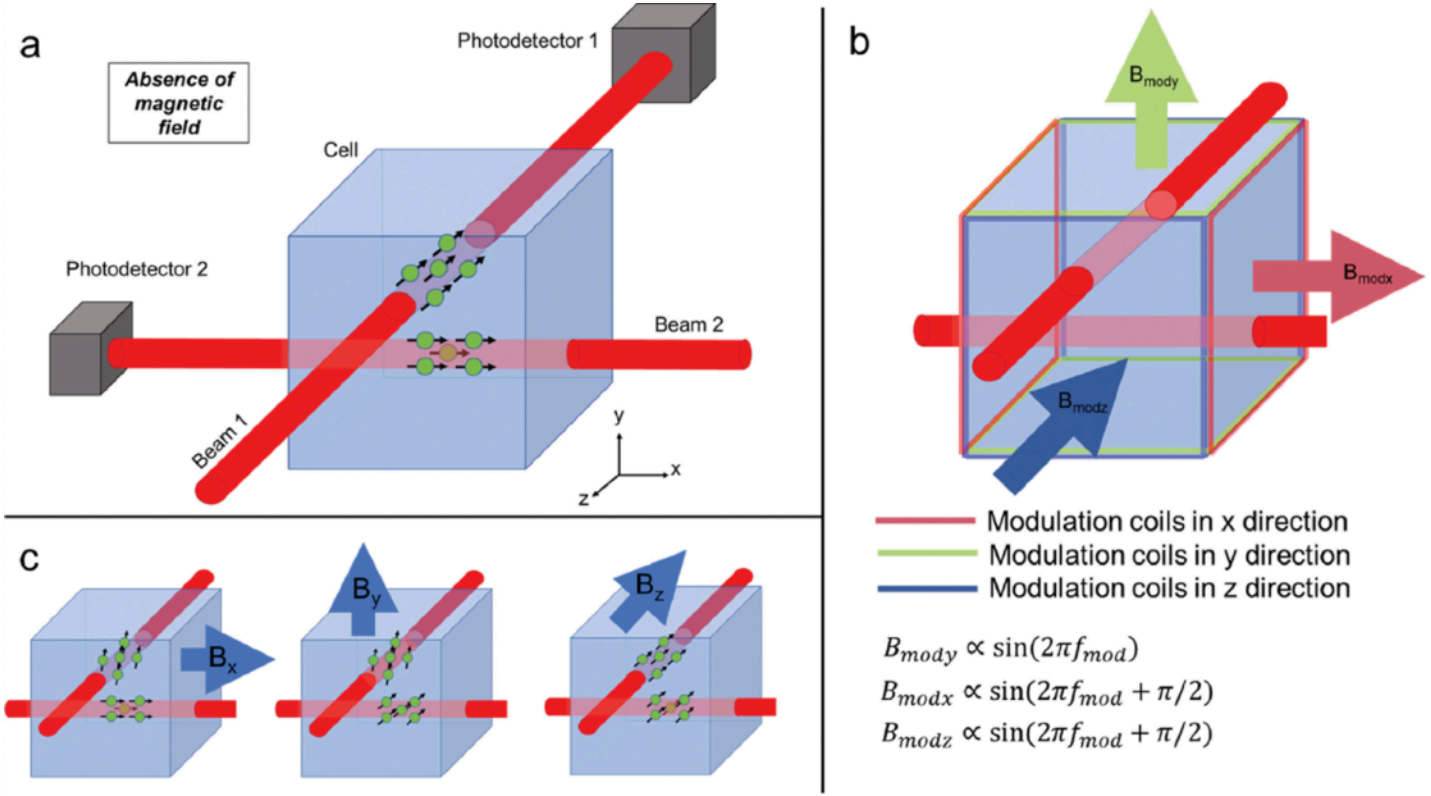
Physics: Spin Exchange – a loose metaphor

(via Tim Tierney, UCL)

Actual design of a QuSpin OPM sensor (Gen 2)



Design of a QuSpin OPM sensor (Gen 3 - triaxial)

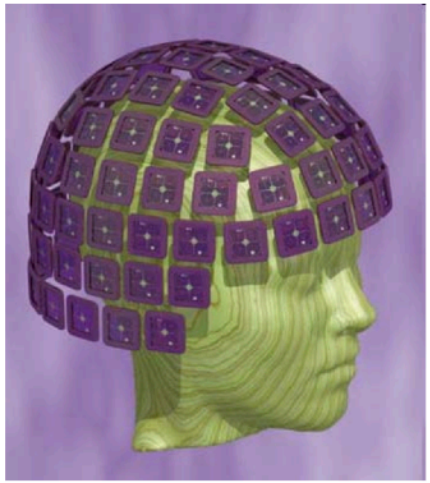


EEG vs. MEG

	ADVANTAGES	DISADVANTAGES
EEG	- Cheap ($30-100K) - Can be done anywhere - Sensitive to all dipole orientations - Some movement allowed	- Slow setup - Signal propagation distorted by tissue types - High frequencies lost
MEG	- Faster setup (cryogenic MEG) - Movement compatible (OPM MEG) - Signal propagation undistorted - Higher frequencies can be measured (cryogenic MEG)	- Very expensive ($2 Mil) - Movement incompatible (cryogenic MEG) - Requires extensive shielding - High frequencies lost (OPM MEG) - Sensitive to orientations of the dipole


WHY NOT BOTH?

e.g. MEGIN Triux System
306 MEG sensors (102 magnetometers, 204 gradiometers)
64 EEG electrodes



M/EEG Analysis

Preprocessing: Denoising

M/EEG preprocessing

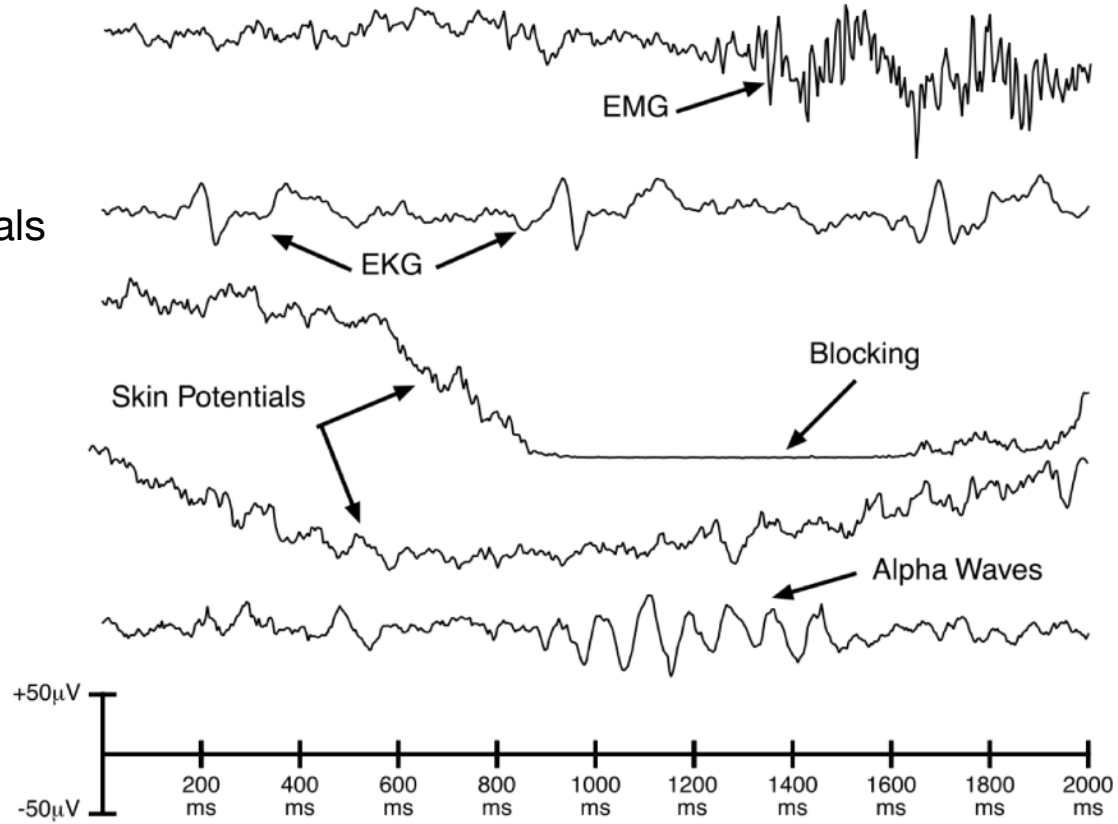
Filtering can be used to mitigate certain common M/EEG artifacts:

—low-pass: filter out EMG

—high-pass: filter out skin potentials

—band-reject 60 Hz AC line noise

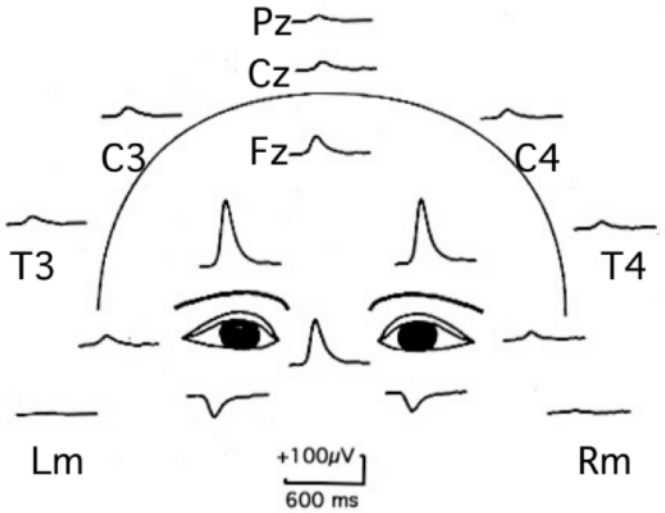
Filters should be used sparingly: ERP/Fs are not really a sum of infinite-duration sine waves, despite what Fourier analysis assumes.

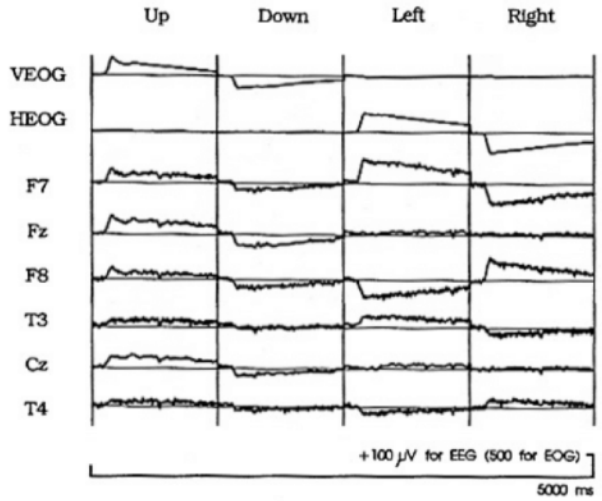


M/EEG preprocessing

Artifact rejection procedures simply discard trials with artifacts (e.g. eye blinks)

Artifact correction procedures aim to estimate artifacts and then subtract them out of the signal (instead of simply discarding corrupted trials entirely)

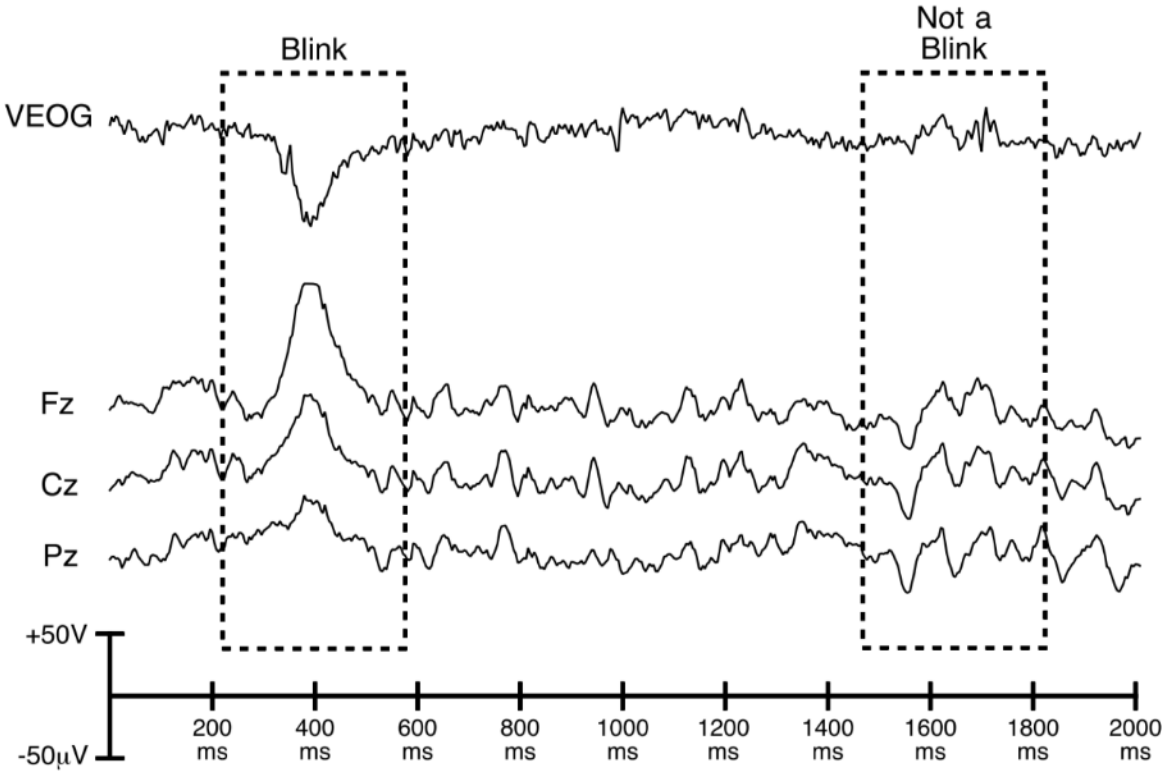




M/EEG preprocessing

Artifact rejection procedures simply discard trials with artifacts (e.g. eye blinks)

The “best” criterion or threshold to discard trials (e.g. voltage threshold) will depend on the cost of misses versus false alarms



M/EEG preprocessing

Artifact correction procedures aim to estimate artifacts and then subtract them out of the signal (instead of discarding corrupted trials entirely)

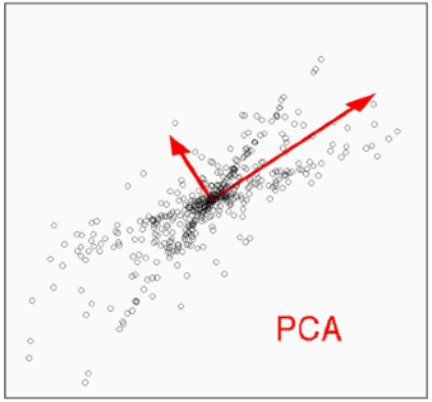
Independent component analysis (ICA) can be used to “unmix” mixed signals by maximizing non-Gaussianity of marginal distributions; effective for identifying:
—eye-blinks and saccades (EOG)
—cardiac artifacts (ECG)

M/EEG preprocessing

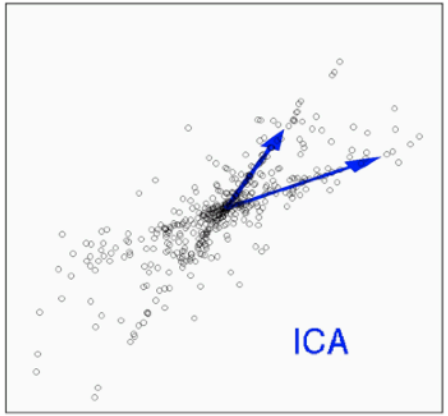
Artifact correction procedures aim to estimate artifacts and then subtract them out of the signal (instead of discarding corrupted trials entirely)

Independent component analysis (ICA) can be used to "unmix" mixed signals by maximizing non-Gaussianity of marginal distributions; effective for identifying:
—eye-blinks and saccades (EOG)
—cardiac artifacts (ECG)

These artifacts tend to have a consistent scalp distribution



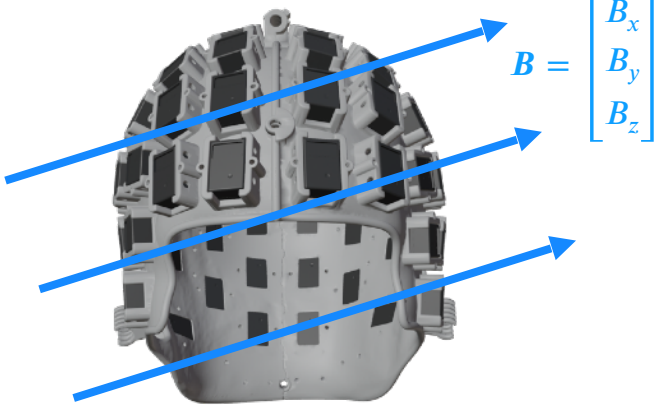
Works with variance, orthogonality



Works with kurtosis, independence

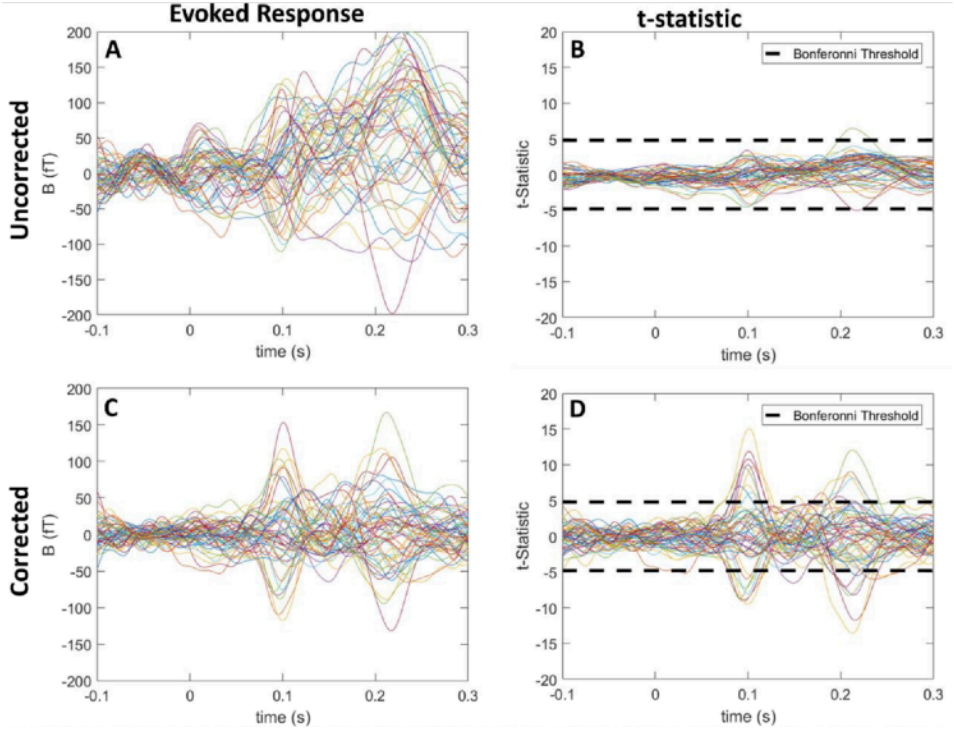
Homogeneous Field Correction for OPM-MEG

- Find/remove magnetic fields components that hit all the sensors in parallel
  - they couldn't possibly come from a source from within the spherical sensor array
  - must come from a more distant (noise) source



$$\boldsymbol{B} = \begin{bmatrix} B_x \\ B_y \\ B_z \end{bmatrix}$$

Tierney *et al.*, 2021

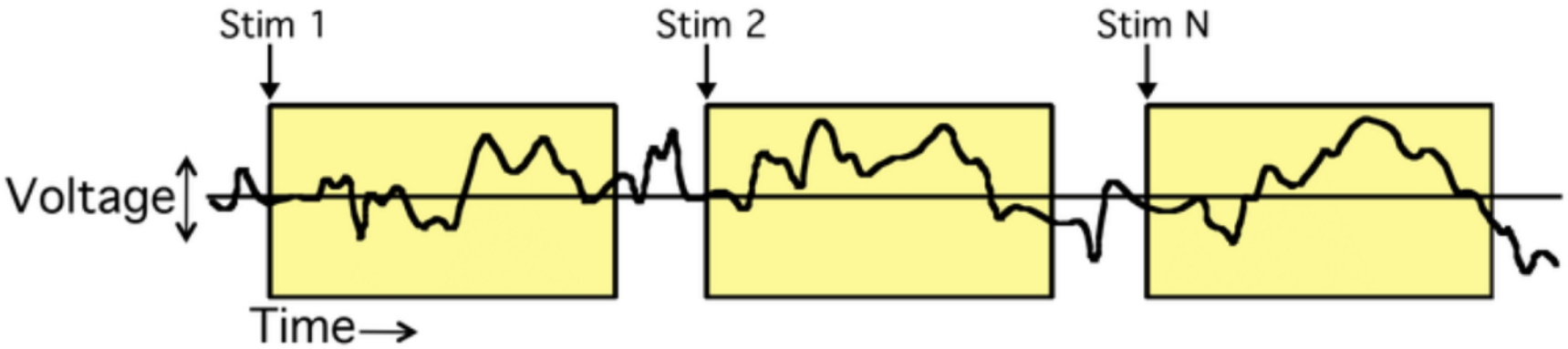


M/EEG Analysis

Preprocessing: Time Segmentation, Baselining

Event-related analysis

In event-related potential (**ERP**) or field (**ERF**) **analysis**, we extract and average ***epochs*** surrounding each event of interest



Event-related potentials

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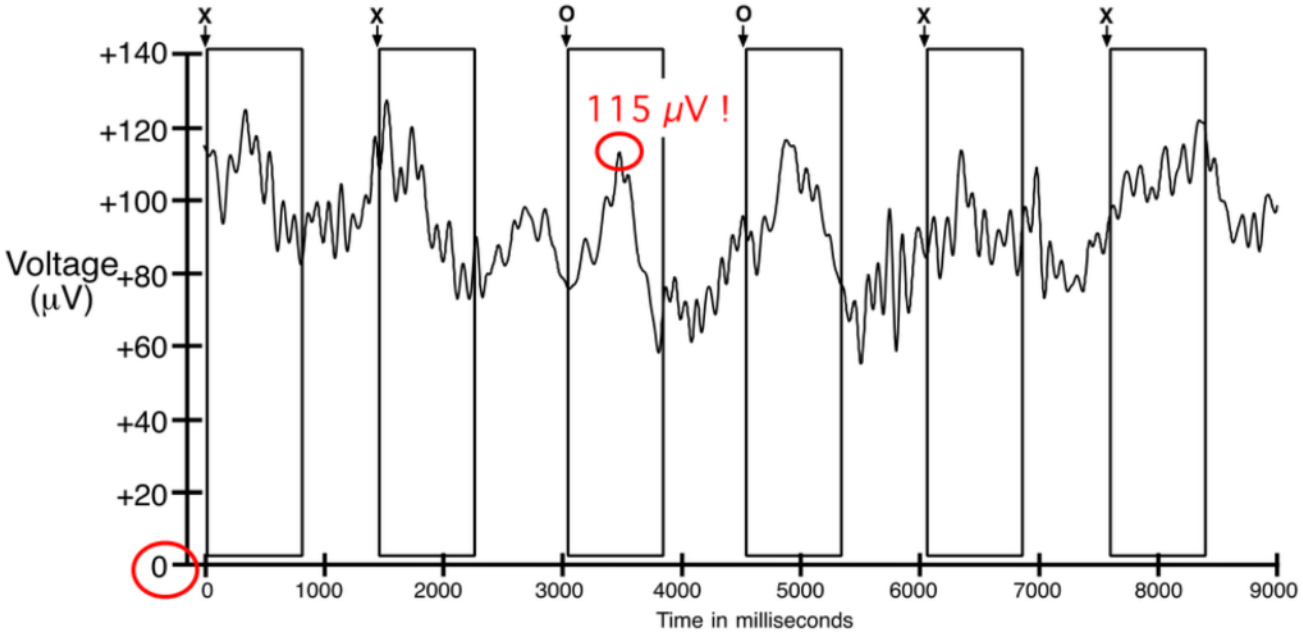
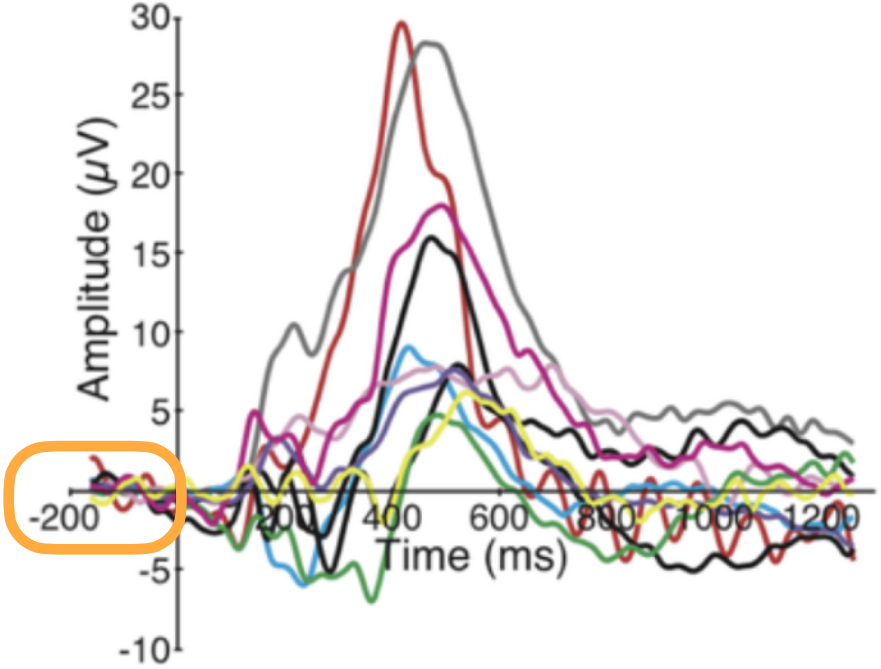


Normalize by baseline prior to each epoch

Event-related potentials

A commonly-used baseline period would be the 100 or 200 ms prior to each event



Event-related potentials

Let’s take a look at some classic ERPs studied over many decades now…

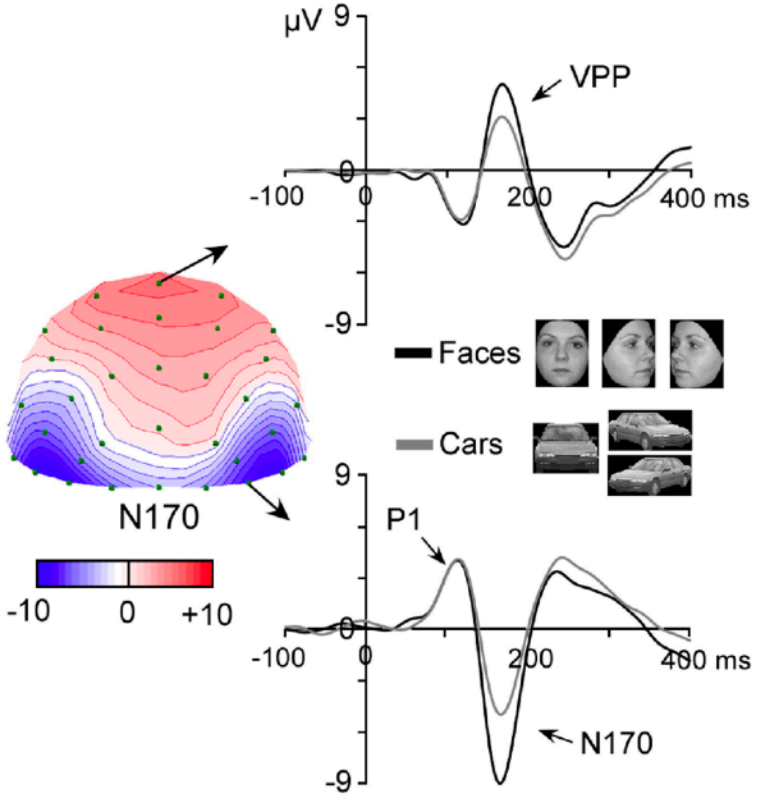
(Most of these have analogous ERFs as well, using MEG)

Event-related potentials

The **N170** is sensitive to face stimuli (relative to non-face objects) and is strongest at posterior lateral electrodes

Does physical interstimulus variance account for early electrophysiological face sensitive responses in the human brain? Ten lessons on the N170

Bruno Rossion* and Corentin Jacques

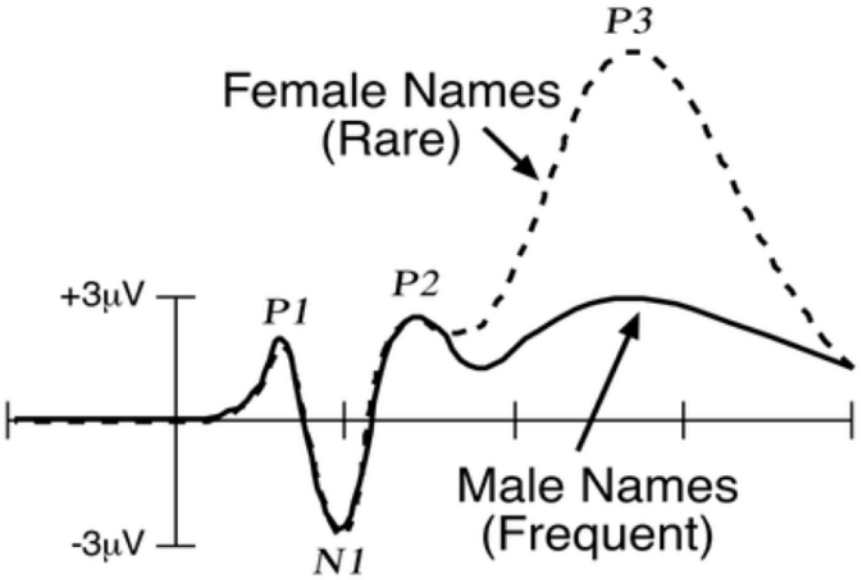


Event-related potentials

The **P300** is an endogenous potential in parietal electrodes linked to the probability of a *task-defined* stimulus category (not low-level stimulus properties)

—peaks at 250–500 ms

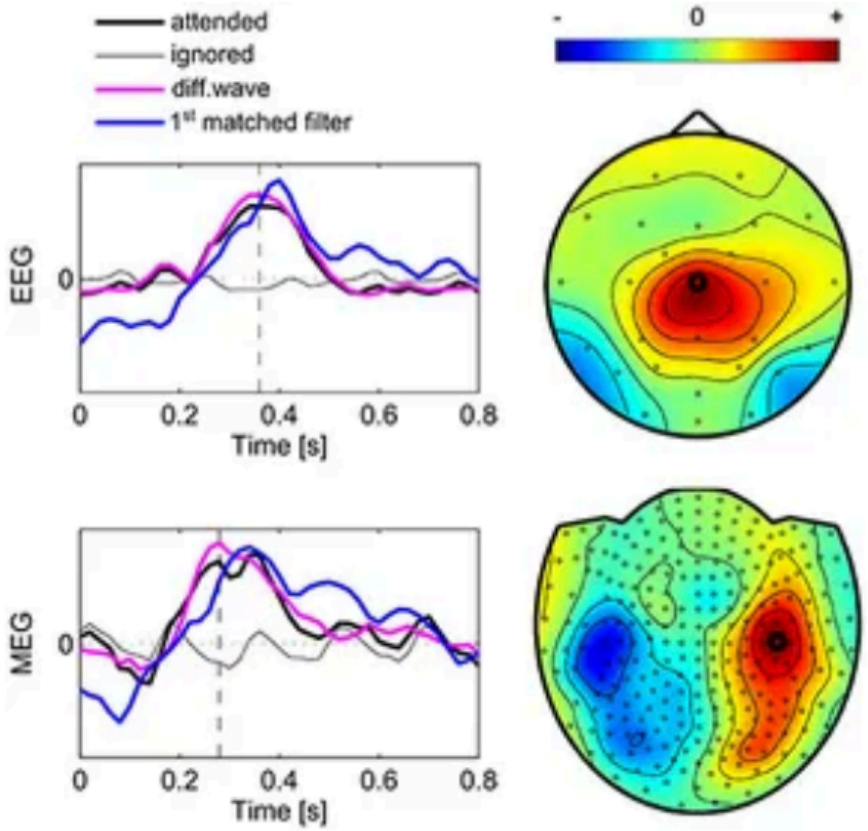
—P300 latency indexes stimulus evaluation



Event-related potentials

As mentioned before, there is (usually) a magnetic event-related field (ERF) to correspond with ERPs.

Here's a comparison between the EEG and MEG versions of the "P300"



(Reichert et al., 2017)

Event-related potentials

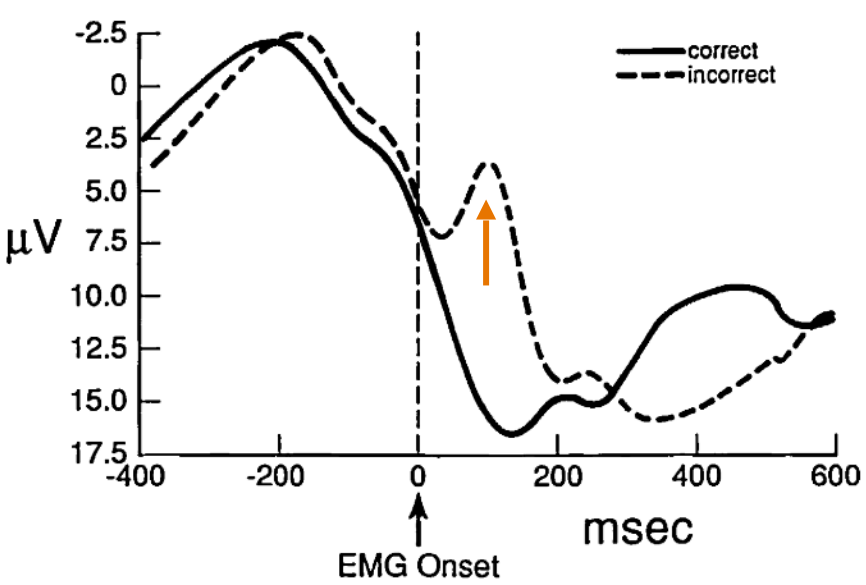
The **error-related negativity** (ERN) emerges shortly after a mistaken action is initiative in frontro-central electrodes

—peaks 80–150 ms after response begins

—originates in dorsal ACC or pre-SMA

A NEURAL SYSTEM FOR ERROR DETECTION AND COMPENSATION

William J. Gehring,[1] Brian Goss,[1] Michael G.H. Coles,[1] David E. Meyer,[2] and Emanuel Donchin[1]



The Neural Basis of Error Detection: Conflict Monitoring and the Error-Related Negativity

Nick Yeung
Princeton University

Matthew M. Botvinick
University of Pennsylvania

Jonathan D. Cohen
Princeton University and University of Pittsburgh

Time-frequency analysis

Time-domain analysis: ERP analysis treats waveform peaks and troughs as *events* localized in time—"***when*** do differences in amplitudes occur relative to stimulus?"

Frequency-domain analysis: spectral (Fourier) analysis collapses across time—"which ***frequencies*** have different power (or phase)?"

Time-frequency analysis: wavelet analysis provides a compromise, allowing us to examine "***when*** and ***how much*** do different frequencies occur?"

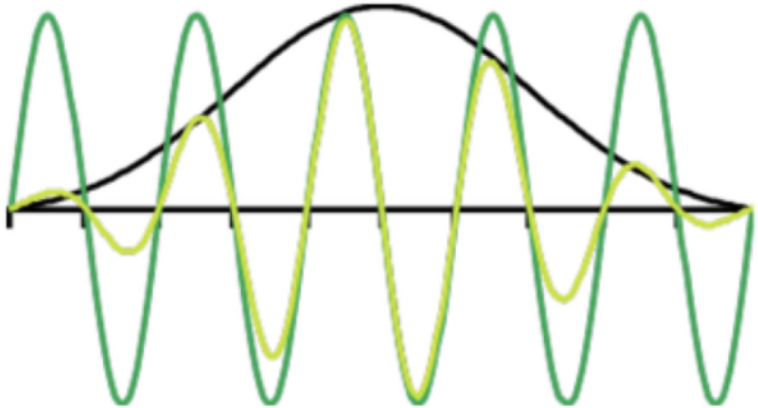
A major assumption of ERP analysis is that the timing of the ERP signal is the same on each trial; i.e. oscillations must be ***in phase*** or they'll get averaged out

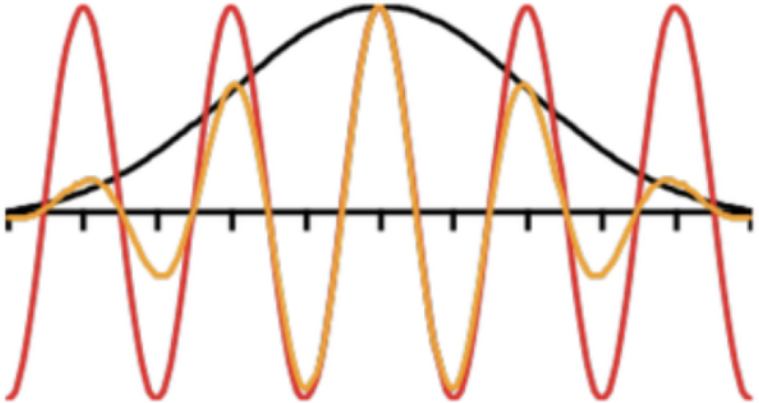
Fourier analysis assumes that the signal is ***stationary***; i.e. statistics don't change over time

Time-frequency analysis

Wavelet analysis aims for an optimal tradeoff between time and frequency by combining a waveform (e.g. sine/cosine) and a smooth window (e.g. Gaussian)
—analyze high frequencies in a narrow time window for better temporal resolution
—analyze low frequencies in a wider time window for better spectral resolution

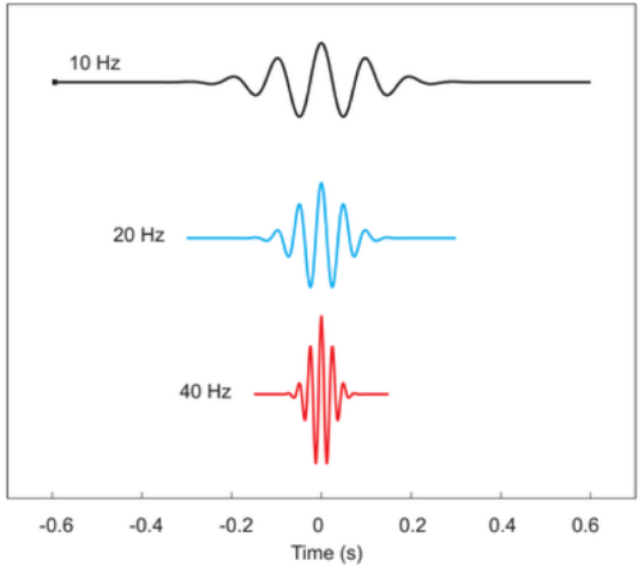
Morlet wavelet

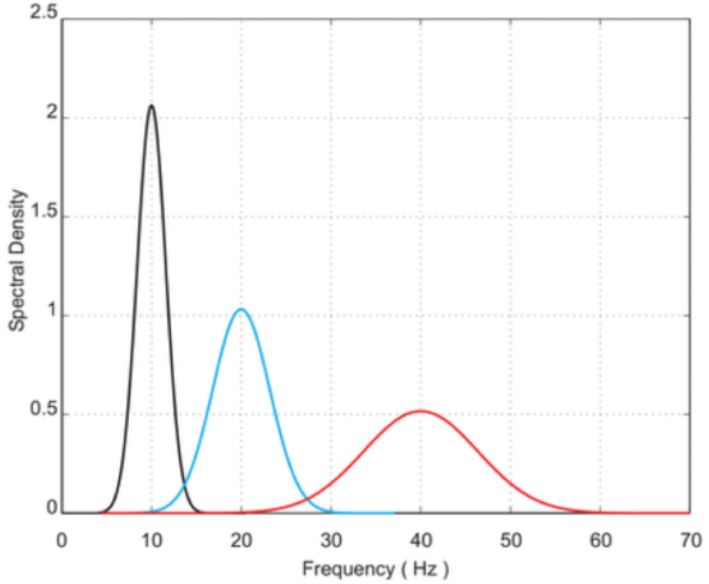




Time-frequency analysis

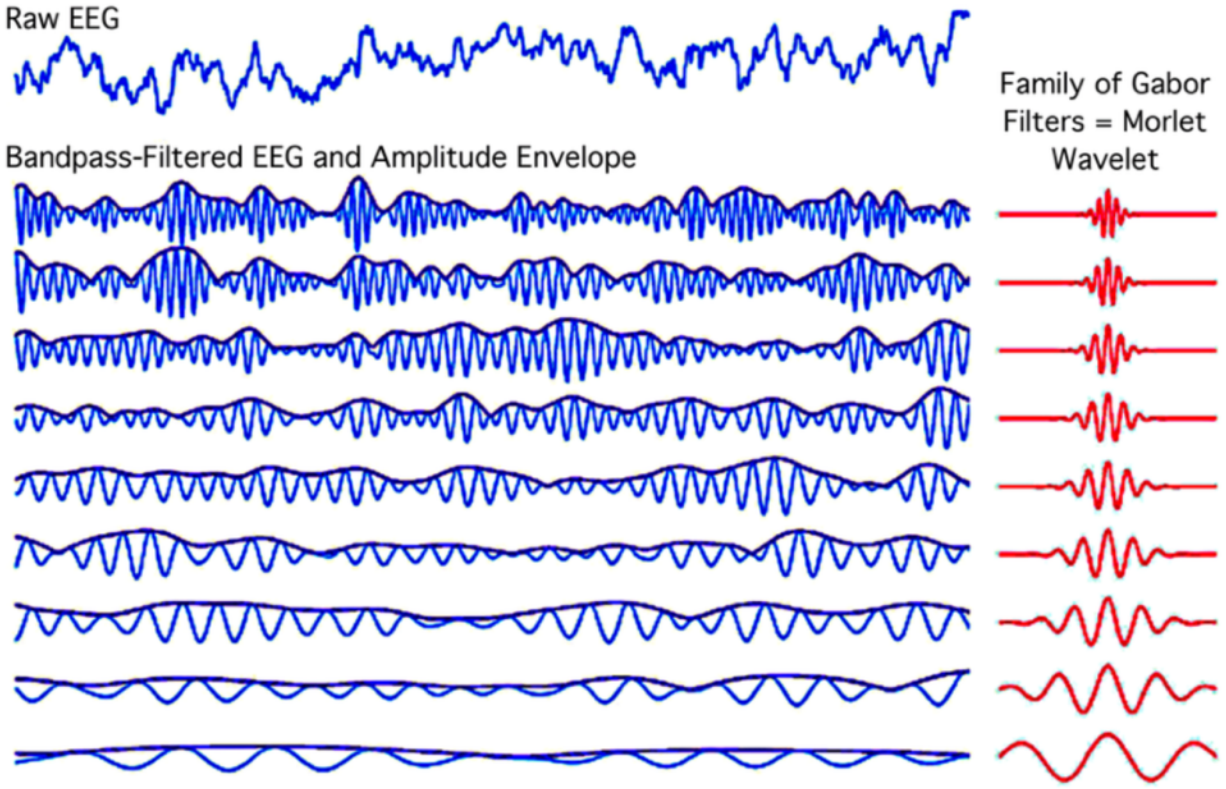
The ***mother wavelet*** is a function for deriving wavelets for any frequency
—zero mean amplitude and finite duration
—can be scaled (compressed) and translated





Time-frequency analysis

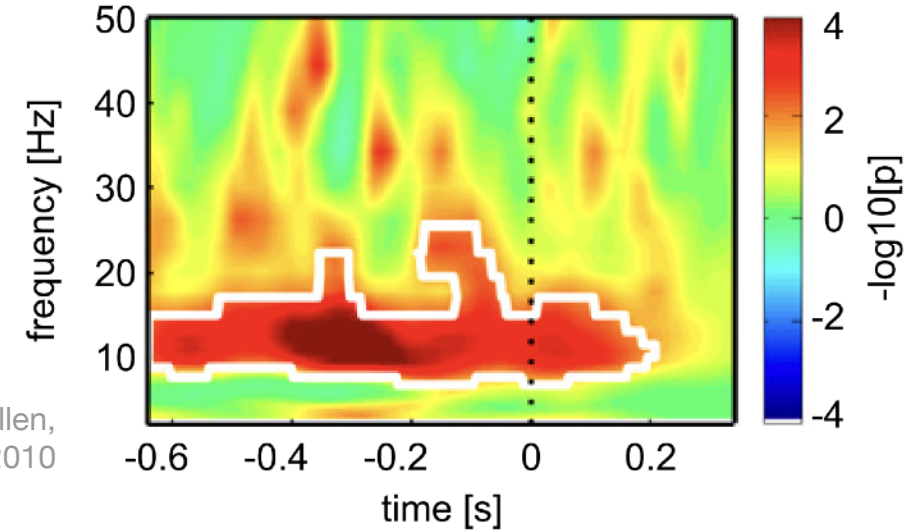
Toy wavelet analysis of a raw EEG signal

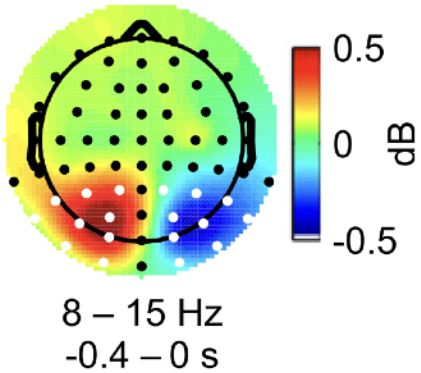


Time-frequency analysis

Time-frequency spectrogram display power at particular ***frequency bands*** at particular ***times*** (e.g. relative to stimulus onset)

Spatial attention to left or right hemifield yields increased alpha oscillation in ipsilateral hemisphere





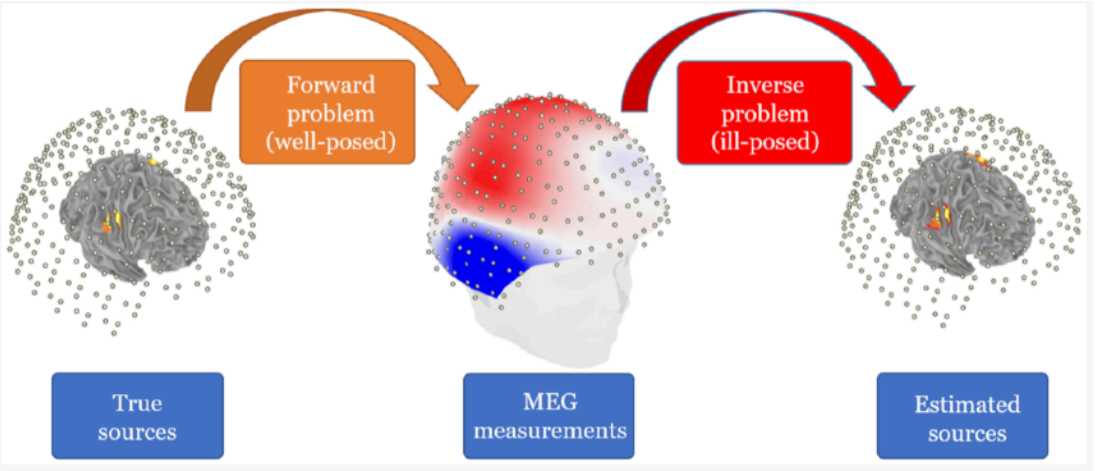
Busch & VanRullen, *PNAS*, 2010

M/EEG Analysis

Preprocessing: for Source Localization

M/EEG preprocessing

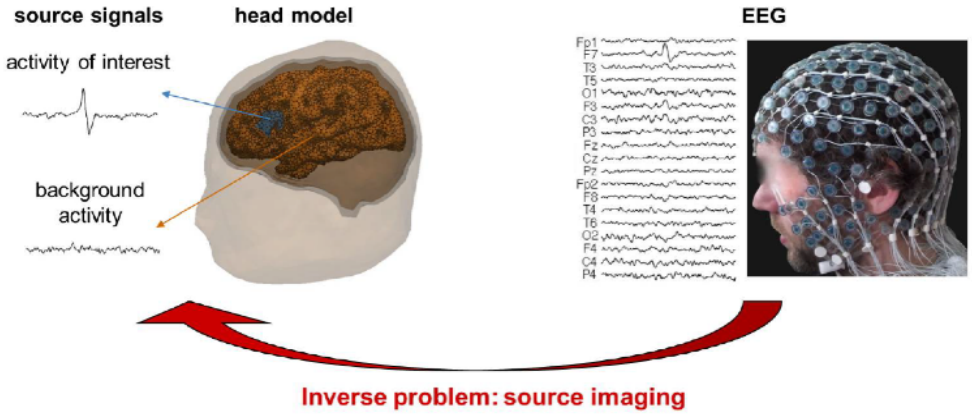
- Up to now, all preprocessing has involved time series from sensors
  - mostly ignoring their positioning relative to the brain dipole signal generators
    - although we might still plot our data on a 2D circle “surface” layout
- What if we used our knowledge of the structure of a brain to try to determine the origins of the scalp signals from multiple deeper dipole sources?
  - AKA “***Source localization***”



M/EEG preprocessing

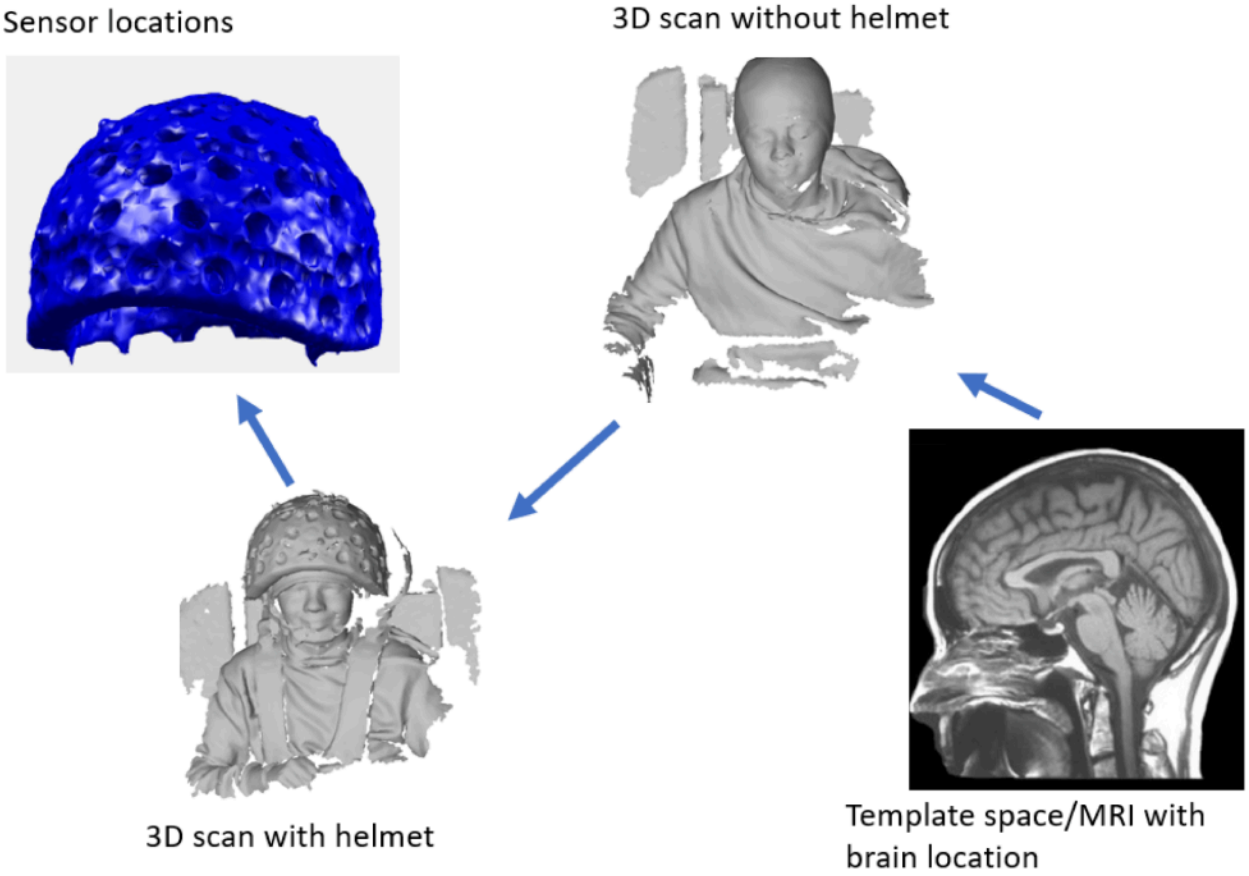
Source localization preprocessing:

- Unless we want to assume that everyone's brain is shaped alike, we'll need to collect a structural MRI from our M/EEG participant
    - and need to segment the image into scalp vs. skull vs. different brain tissues
- We'll also need to digitize the locations of all our sensors on that person's scalp
- Finally, we'll need to coregister all of this disparate info into a common 3D space



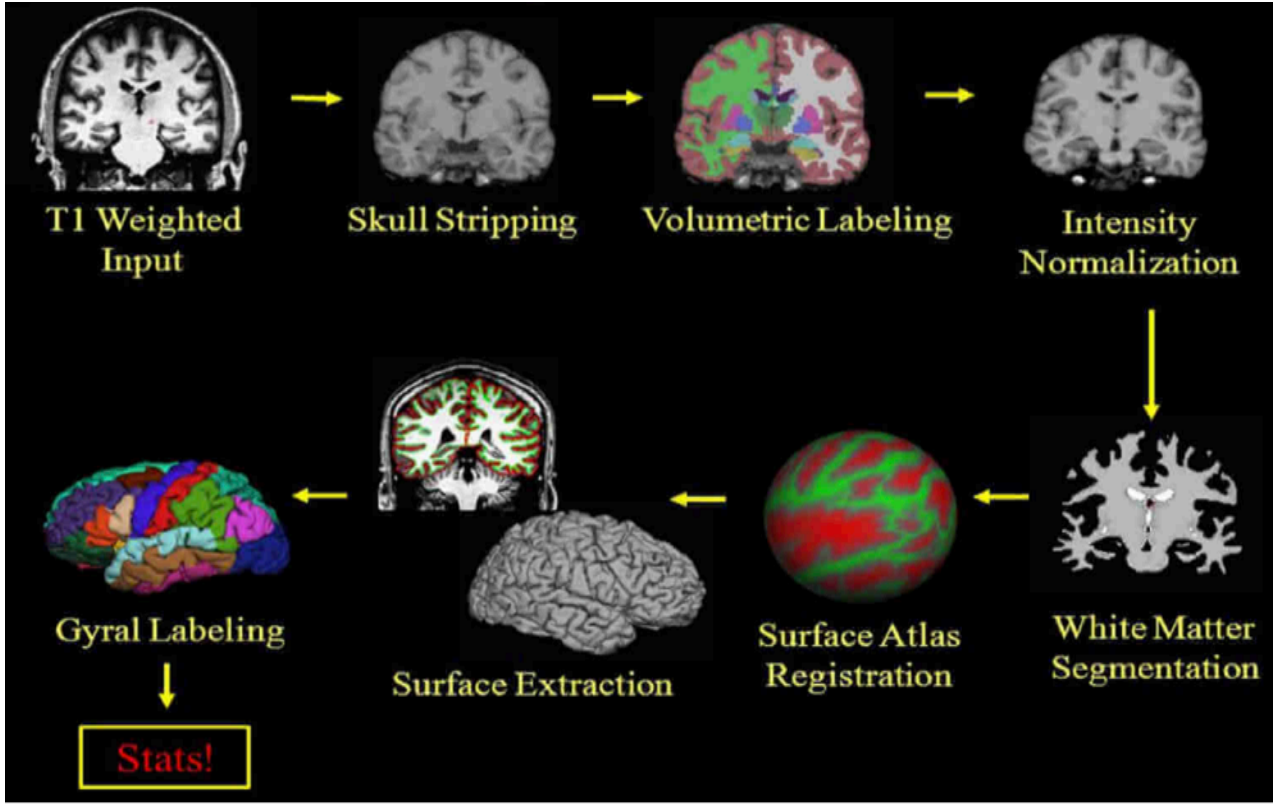
M/EEG preprocessing

Four step coregistration procedure from MRI to sensor locations



M/EEG preprocessing

Use FreeSurfer to parcellate the structural MRI



A generative model of sources

Starting from our sensor-level M/EEG data, $\boldsymbol{y}$, for a given time, t, that we can assume is generated by k sources in the brain:

$$\boldsymbol{y}(t) = \sum_{k=1}^{n} \boldsymbol{l}_k \boldsymbol{j}_k(t) + \epsilon(t),$$

Lead fields: How a source is represented at sensors

Source strength at time *t*

Everything unexplained (noise)

Encapsulate all time and we can turn this into a set of matrices.

All data across all time $\boldsymbol{Y} = \boldsymbol{L}\boldsymbol{J} + \boldsymbol{\epsilon}$ *'noise' across all time*

All lead fields

All source activity across all time

Lead fields: the forward problem

$$Y = LJ + \epsilon$$

Lead fields

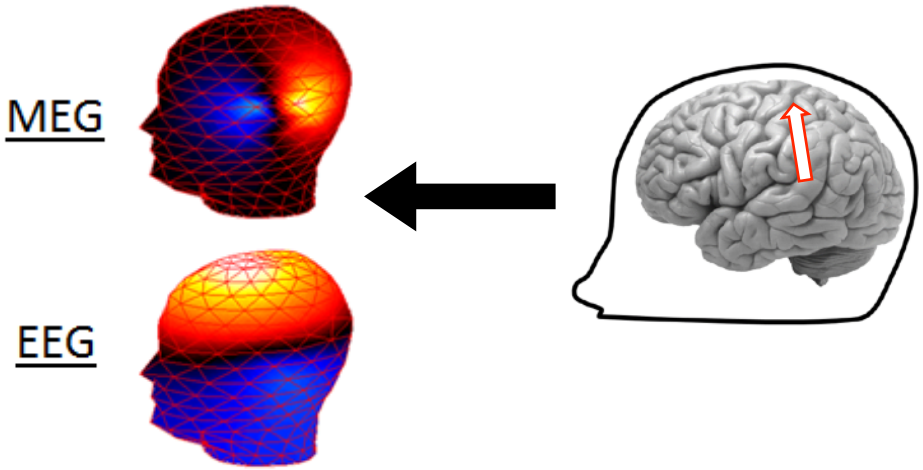
The forward problem

If we know the precise position/orientation/amplitude of a dipole in the brain, can we estimate what the associated sensor-level pattern should be?

YES!

For a given dipole, there exists one unique solution. This makes it straightforward to solve!

BTW, for MEG data, the solutions are typically a lot simpler than for EEG data, because they're not distorted by different tissue types like with EEG



Forward models

Various approximations to the problem are available:

EEG requires more complex models which are able to predict electric potential differences better than the simple spherical models (typically a 3-shell BEM or better).

This does require more knowledge about the anatomy.

Workflow of MNE