Practical Issues for Multimodal Neuroimaging
WhynHow 5/5/11

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Multimodal Imaging: Why and How

- Why do it?
- How to design the study
- How to approach data analysis
- Why don’t the datasets match up??

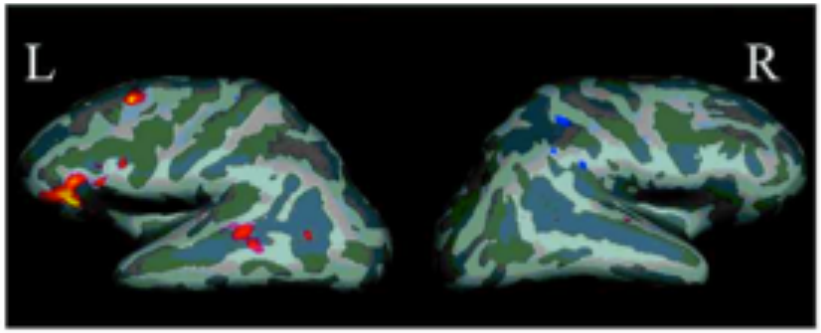
Why do it?

Why do it?

- Combine the strengths of each technique to attack a problem
  - E.g. the holy grail: space+time

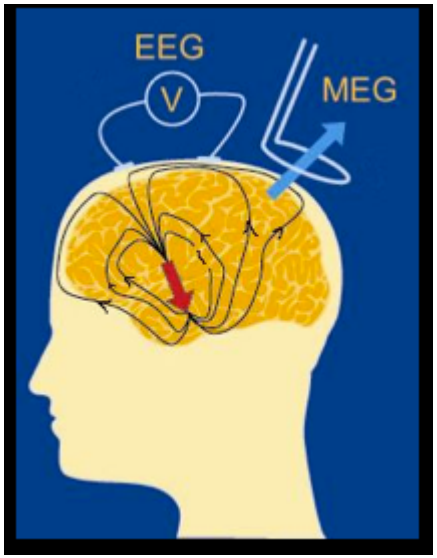
fMRI

- Measure differences in BOLD associated with different stimulus or task evoked processes
- Slow, non-temporally specific
- Fairly spatially accurate

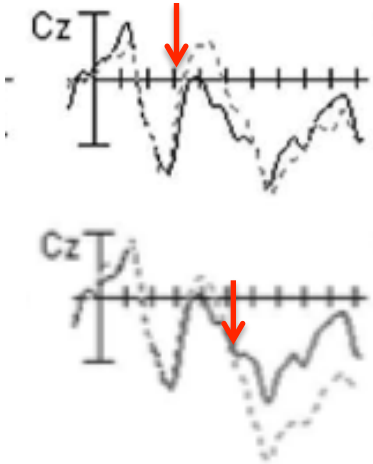


EEG

- Measure differences in voltage measured at scalp, probably arising from summed post-synaptic potentials
- Temporally precise
- Spatially imprecise
- Cheap, so very well-established literature

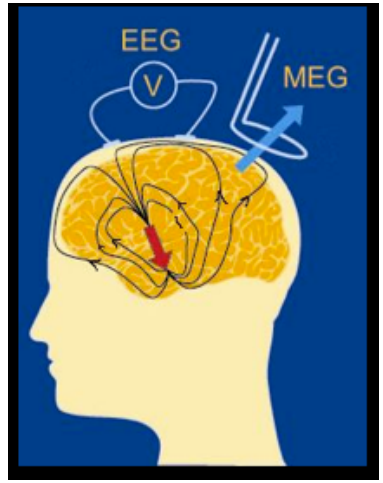


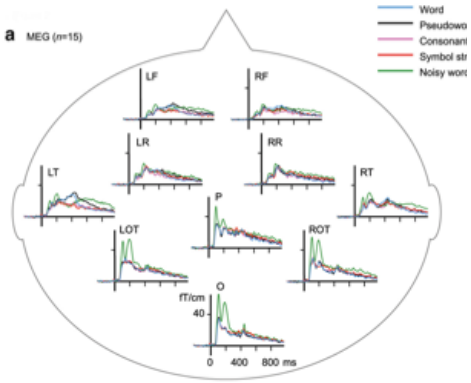
Matti Hamalainen

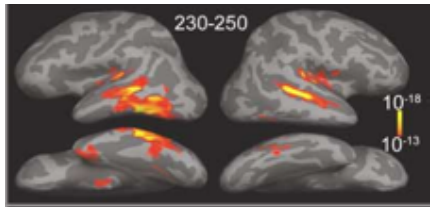


MEG

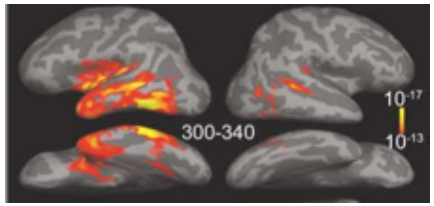
- Measure differences in magnetic field in sensors surrounding head, probably arising from post-synaptic potentials
- Temporally precise
- Some reliable spatial estimates possible







230-250 ms



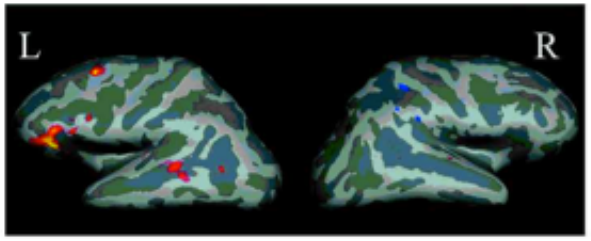
300-340 ms

Marinkovic et al.

Why do it?

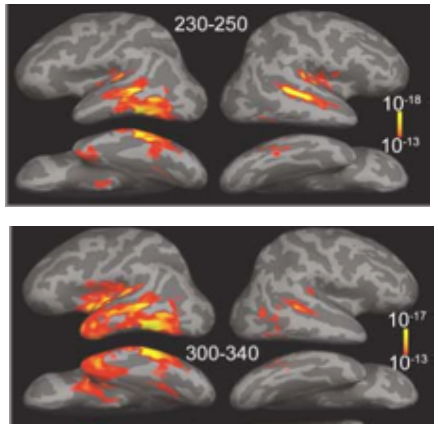
- Combine the strengths of each technique to attack a problem
  - the holy grail: space+time

fMRI



• Precise in space, not time

MEG

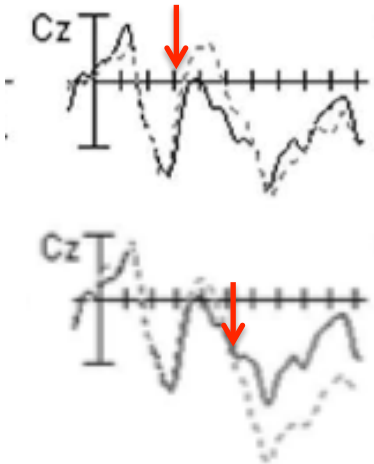


230-250 ms

300-340 ms

• Precise in time
• Some spatial information

EEG

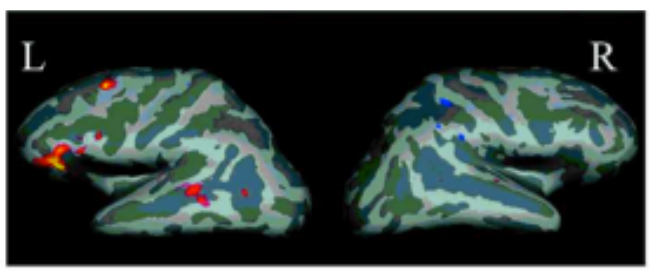


• Precise in time, not space

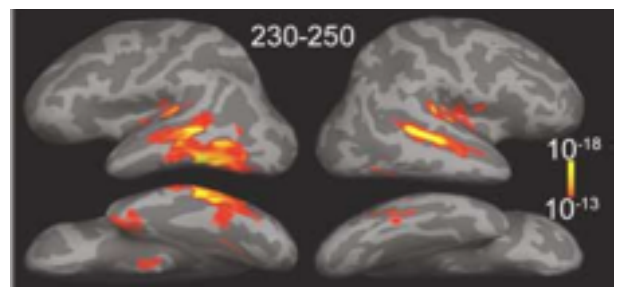
Why do it?

- Converging evidence
  - E.g. compare spatial estimates from two techniques

fMRI



MEG



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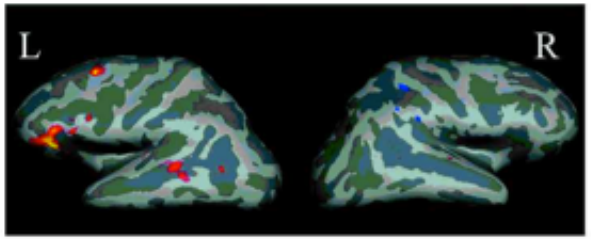
Why do it?

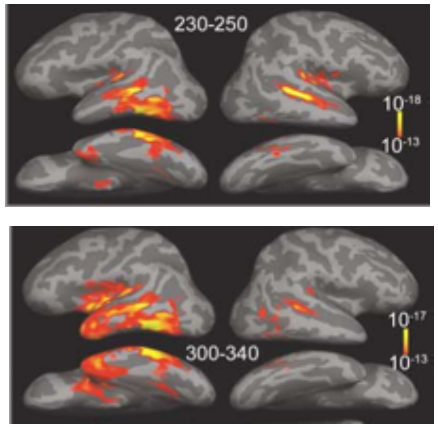
- Get a better understanding of the properties of different recording techniques

fMRI



• Precise in space, not time

MEG

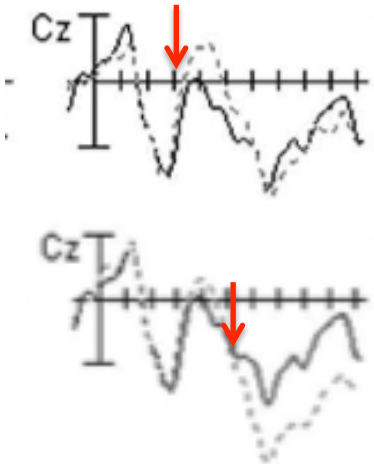


230-250 ms

300-340 ms

• Precise in time
• Some spatial information

EEG



• Precise in time, not space

How to design the study

Design

- Separate recording sessions with different subjects

fMRI

MEG

Design

- Separate recording sessions with same subjects

Session 1

fMRI

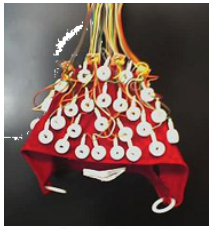
Session 2

MEG

Design

- Simultaneous recording

EEG



MEG

Design

- Mixed separate and simultaneous

Session 1

fMRI

Session 2

EEG

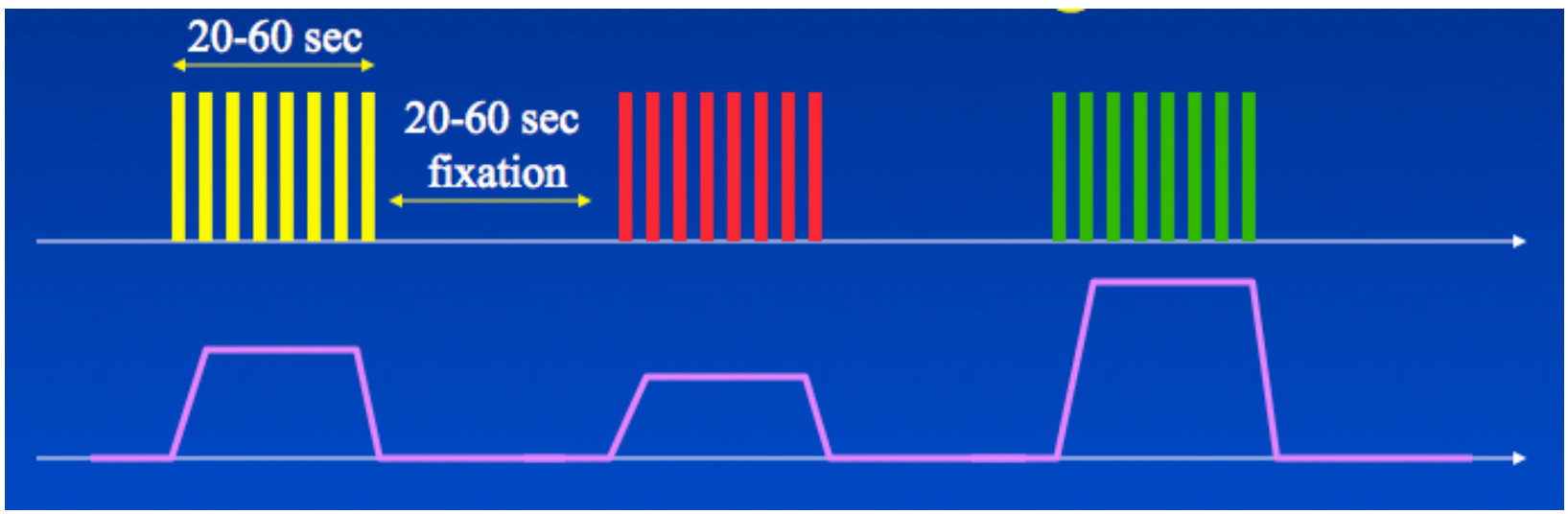
MEG

Design

- In deciding which to pursue, must consider
  - Facilities available
  - **Goal** of multimodal component
  - Analysis resources available
  - Constraints of your paradigm
  - Constraints of your subject population
  - How much effort you want to devote to the project!

Design: General

- Stimulus presentation must be reasonably well-matched across techniques
  - Block designs



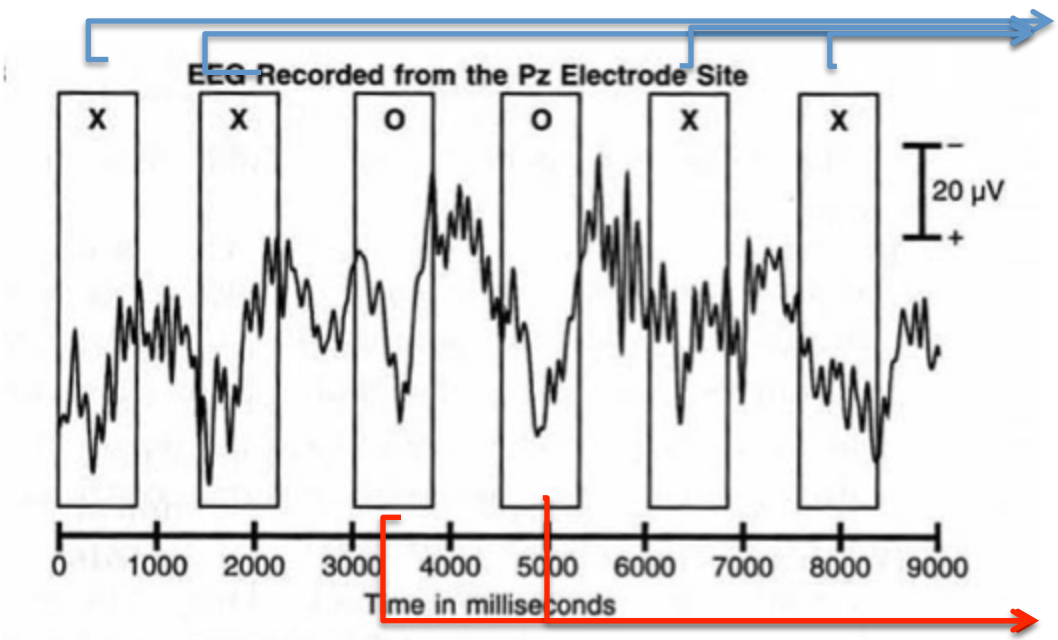
Doug Greve

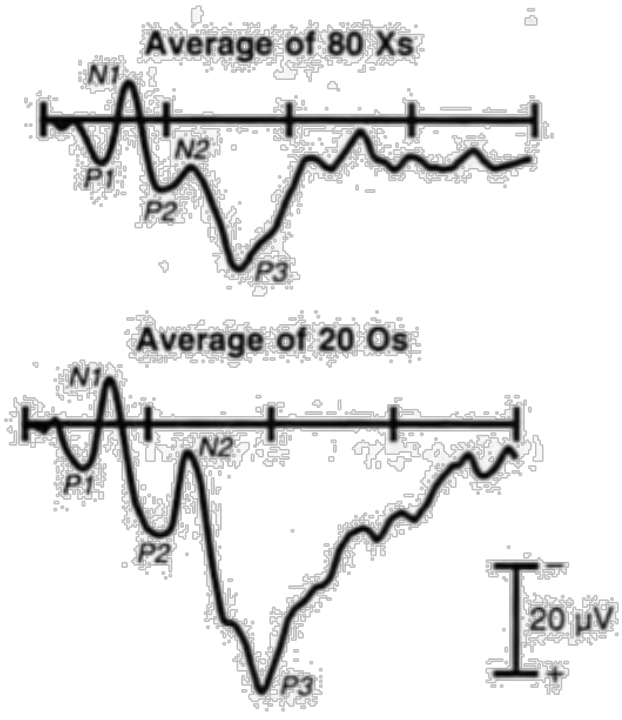
Design: General

- Stimulus presentation must be reasonably well-matched across techniques
  - Block designs
    - Could work for EEG/MEG if you are looking at steady-state responses, i.e. whether power in a certain frequency band is different for A blocks and B blocks
    - Won't work if you are looking at stimulus evoked responses in EEG/MEG

Design: General

- Stimulus presentation must be reasonably well-matched across techniques
  - Event-related designs: EEG/MEG

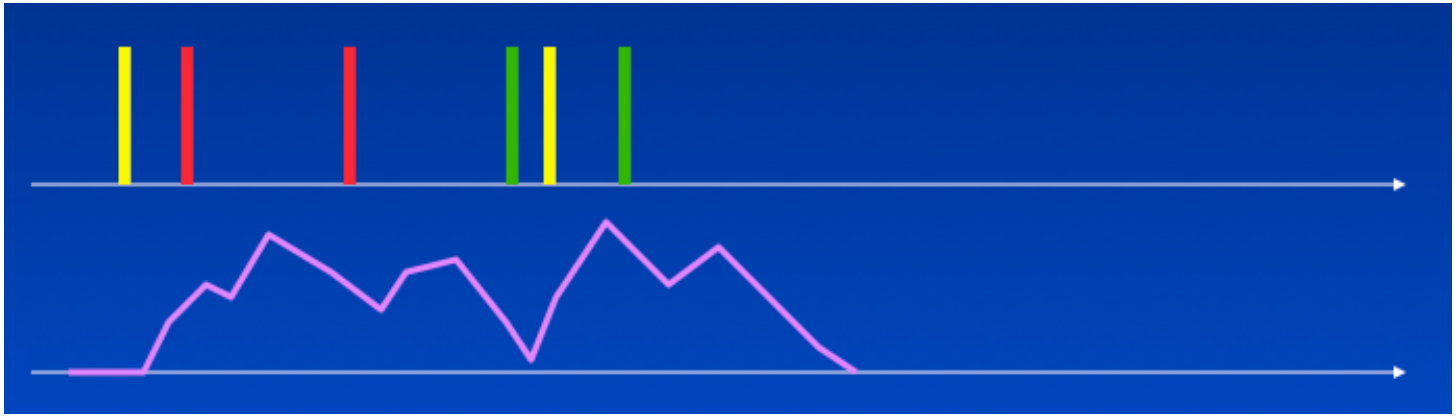




Luck 2005

Design: General

- Stimulus presentation must be reasonably well-matched across techniques
  - Event-related designs: fMRI



Doug Greve

Design: General

- Stimulus presentation must be reasonably well-matched across techniques
  - Special requirements for stimuli in event-related fMRI
    - To get the most robust estimates, need to optimize order of stimulus presentation such that sequence is not completely random (e.g. 'optseq' software)
    - Need to add 'null' periods of fixation for fMRI deconvolution

Design: General

- Stimulus presentation must be reasonably well-matched across techniques
  - Special requirements for event-related stimuli in MEG/EEG
    - Regular rest intervals for people to blink
    - May need a larger number of trials to estimate source solutions

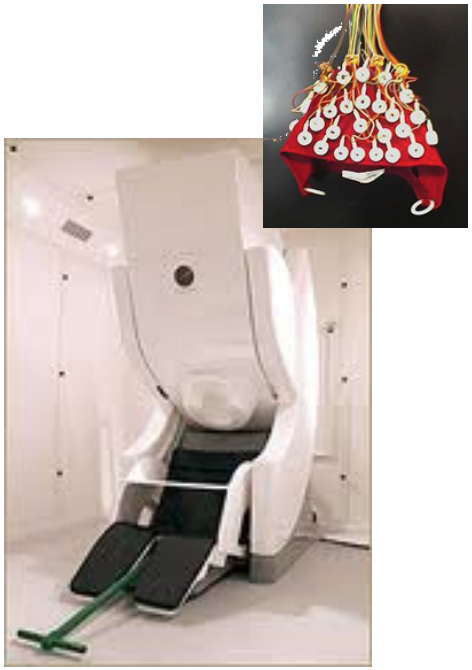
Design: General

- Stimulus presentation must be reasonably well-matched across techniques
  - Matching visual angle, resolution, and other low-level properties across very different projection setups
  - And so on…

Design

- Run two separate experiments yourself
- Do a post-hoc comparison of previous results

MRI



MEG or EEG

Between-Subjects Design

- Need to have enough subjects for it to be reasonable to generalize to (sub)population
  - For MEG, EEG, and fMRI, personal rule of thumb is about 16 good subjects drawn from approximately same age-range and educational level
  - Should be recruited in the same way

Design

- Separate recording sessions with same subject

Session 1

MRI

Session 2

MEG

Within Subjects

- Effects of repeating paradigm
  - Practice effects on task performance
  - Memory effects (for higher-level cognitive paradigms)
  - Psychological effects (arousal, fear, attention)
- Effects of repeating stimuli
  - If you repeat, memory effects
  - If you don't repeat, not exactly same experience
  - If not repeating, need twice as many!

Within Subjects

- Counterbalancing, counterbalancing…
  - Order of measures (fMRI-MEG, MEG-fMRI) most important
  - Order of stimuli lists (if different)
  - List x measure interaction?
  - Can be difficult because of limited sample size
- Controlling delay between Session 1 and Session 2?
  - Can be difficult because of logistics!

Within Subjects

- Participants
  - Double the possible exclusion factors
    - E.g. metal fillings for MEG, vertigo/claustrophobia/body size for fMRI
  - Participant scheduling
    - 'Need someone who can make it to our lab's Thursday 2-4 MRI slot and our Monday 10-1 MEG slot'
  - Participant drop-out
    - Spend 1k on the fMRI and they don't return for MEG!
  - Uneven data quality
    - Subject keeps still in the MRI but moves a lot in MEG

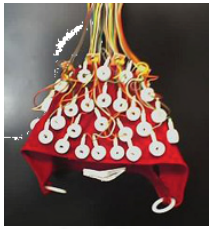
Within Subjects

- Participants
  - Inevitably, you will end up with participants that have one good dataset but not the other, so try to design experiment in such a way that data from each technique by itself is still valuable

Design

- Simultaneous recording

EEG



MEG

Simultaneous Recording

- Recording is more difficult and more prone to error
  - More steps to remember, more pieces of equipment, more chances something will go wrong on a given day
    - Extreme organization is absolutely necessary!
  - Participants may become more anxious or bored during a long setup

Simultaneous Recording

- One measure may cause artifact in the other
  - E.g. simultaneous fMRI-EEG
- Or pain
  - E.g. electrodes pressing into the back of subject's head

How to approach the analysis

Summary

- In deciding which design to pursue, must consider
  - Facilities available
  - **Goal** of multimodal component
  - Analysis resources available
  - Constraints of your paradigm
  - Constraints of your subject population
  - How much effort you want to devote to the project!

Analysis

- Now you have two (or more) datasets: how do you integrate them?
  - Often uncharted territory!
  - Could just try to do an automatic combination in some fancy software package
    - E.g. Combine MEG+EEG data to do source localization and use fMRI as a constraint in MNE package
  - However, this kind of sight-unseen analysis is risky and unlikely to work
    - Think about *matching* your datasets before you integrate them

Cond B – Cond A

	fMRI		MEG/EEG
154	Ventrolateral prefrontal cortex	——	200-220 ms centroparietal

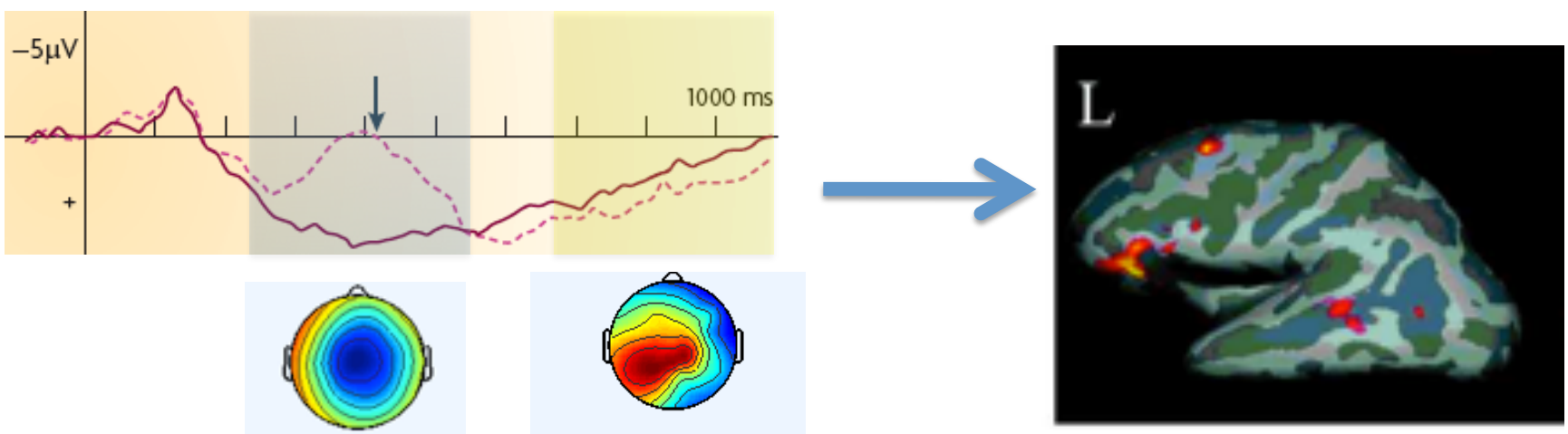
Cond B – Cond A

fMRI		EEG
154	L Ventrolateral prefrontal cortex	200-220 ms centroparietal negativity
103	Anterior cingulate	340-500 ms frontal positivity
91	R supramarginal gyrus	600-900 ms widespread negativity
24	L cerebellum	

?

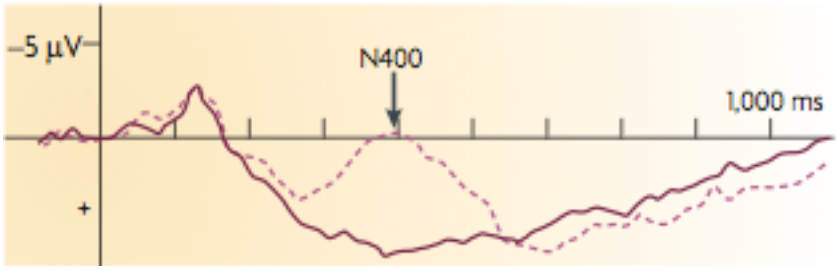
Analysis

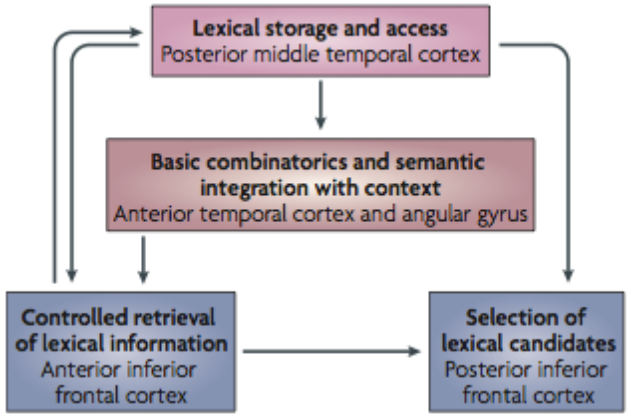
- Matching up datsets
  - Event-related analyses in EEG/MEG usually interpreted in windows of 10-300 ms duration
  - fMRI: one picture summing all effects in >2 s window

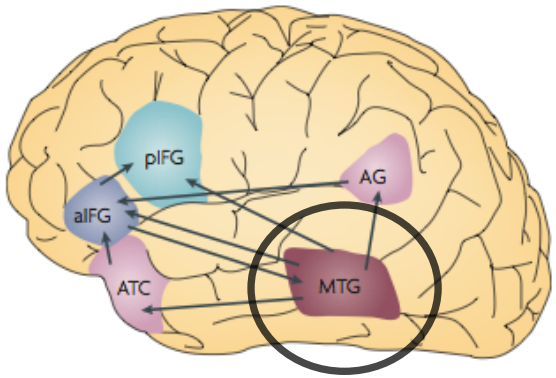


Analysis

- Matching up datasets
  - Start with prior knowledge







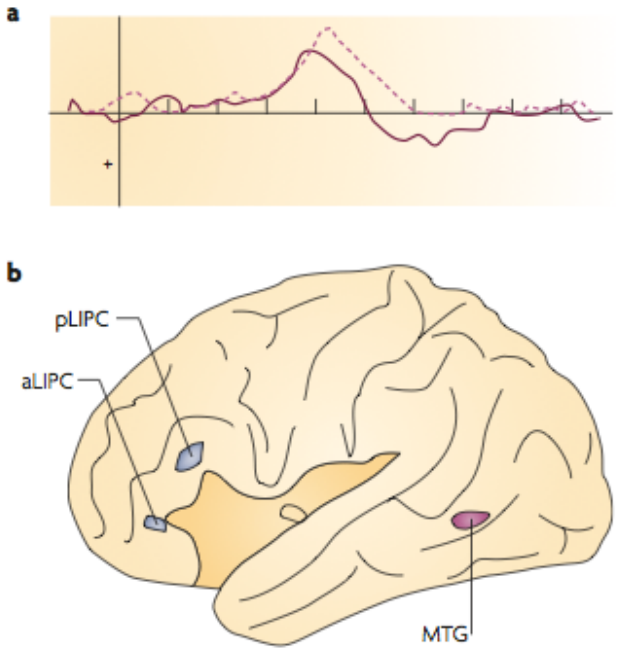
Lau et al 2008

Analysis

- Matching up datasets
  - Covariation across multiple manipulations

- <u>Long</u> prime-target asynchronies
  - Reduced N400 amplitude in ERP
  - Reduced BOLD in IFG **and** MTG

- <u>Short</u> prime-target asynchronies
  - Reduced N400 amplitude in ERP
  - Reduced BOLD **in MTG only**



Analysis

- Matching up datasets: within-subjects designs
  - Can take advantage of within-subjects nature of the design with individual subject analyses, e.g.
    - Lateralization index in each measure
    - Location of activity in the individual relative to the group average, in each measure
    - Correlations in effect size in each measure across individuals

Analysis

- Matching up datasets: within-subjects designs
  - If you can figure out a reliable means of matching up the two datasets, you can now use one measure to aid in source localization for the other measure on an individual basis (i.e., fMRI as a constraint on MEG/EEG source localization)

Analysis

- Matching up datasets: simultaneous recording
  - Can take advantage of the fact that you have simultaneous data from individual trials—but how?

Analysis

- Matching up datasets: simultaneous recording
  - Correlation analyses over individual trials
    - Note that many software programs may not be specialized to access individual trial information
    - Also have to decide what correlations to look for, and what will count as a meaningful correlation

Summary

- Plan analysis ahead!

A few references to get started…

- Sharon et al. (2007) *Neuroimage* – fMRI + MEG/ EEG within subjects
- Ahveninen et al. (2006) *PNAS* – fMRI + MEG within subjects
- Vartiainen et al. (2011) *J. Neurosci* – fMRI + MEG/ EEG within subjects
- Kveraga et al. (2011) *PNAS* – fMRI + MEG in frequency domain, partly within subjects
- Ahveninen et al. (2011) *PNAS* – fMRI + MEG/EEG

Why might measures differ?

Accounting for Differences

- Different spatial sensitivity profiles
  - MEG not very sensitive to deep sources, best for sulci
  - EEG may suffer from increased source cancellation
  - fMRI areas of significant artifact such as anterior medial temporal cortex

Accounting for Differences

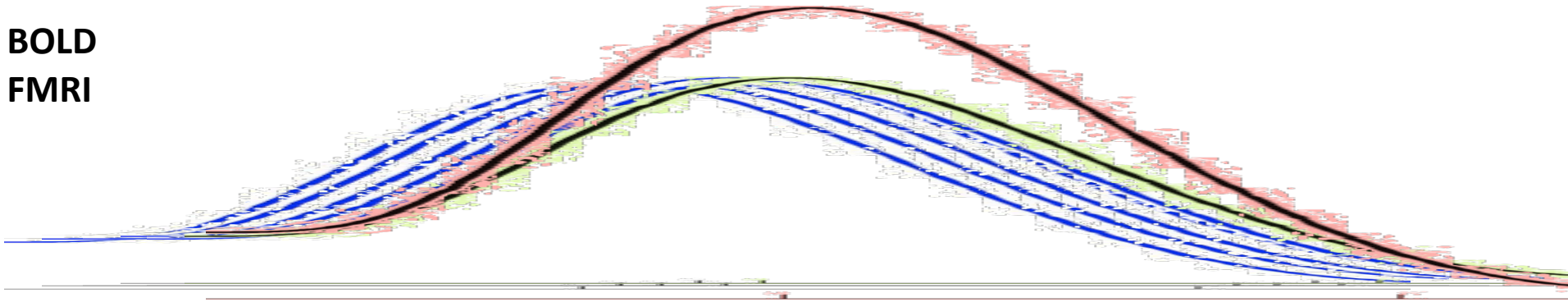
- Different temporal sensitivity profiles
  - fMRI sums across time, so better at picking up small effects with a long duration, or effects with less precise onsets relative to stimulus presentation
  - Event-related MEG/EEG in the time domain does not sum across time, so good at picking up short-lasting effects with a precise onset relative to stimulus presentation
  - Frequency analysis of MEG/EEG across larger time windows may be closer to fMRI in temporal sensitivity

Accounting for Differences

- Matching up datasets
  - Different levels of background variability
    - E.g., in sentence comprehension in fMRI, pulling out brain area involved in fixing violations versus area involved in lexical access

Example

BOLD FMRI

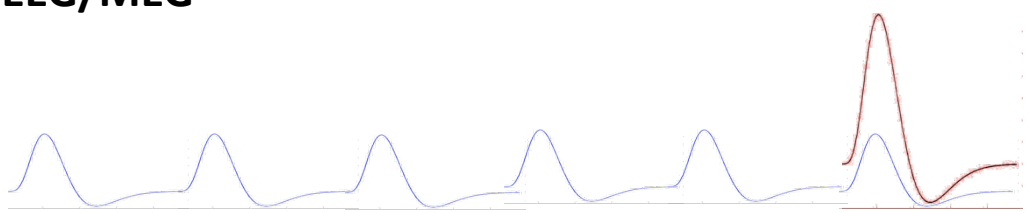


The boy was flying a kite

pickle

'Fixing-Violations' Brain Area

EEG/MEG



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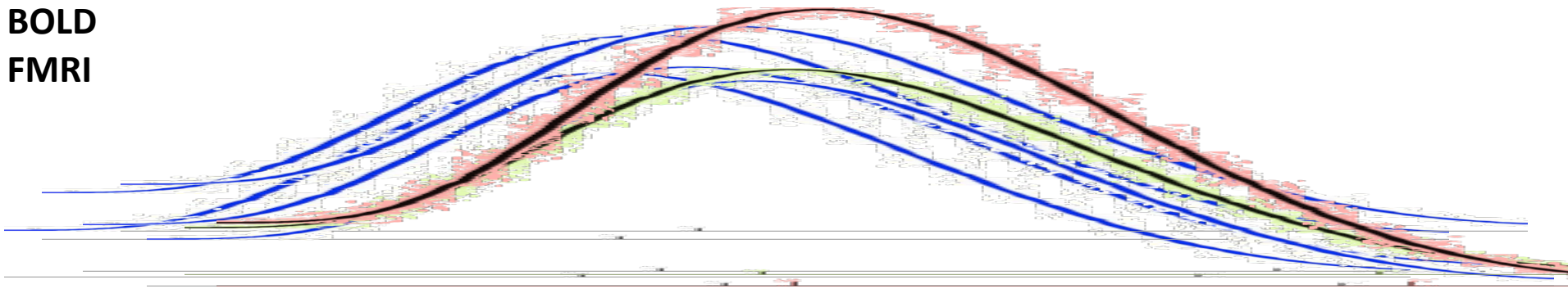
pickle

Example

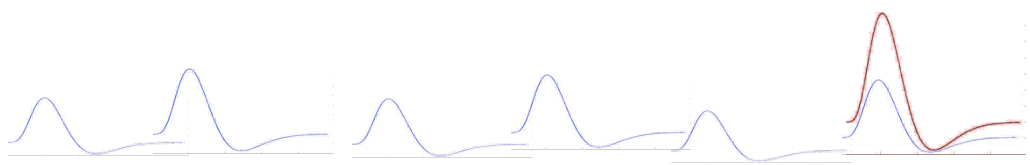
BOLD FMRI



The boy was flying a kite
glider

Lexical Access Brain Area

EEG/MEG



The boy was flying a kite
glider

A few ‘mismatch’ references

- Vartiainen et al., 2011, *J. Neurosci.*
- Yigal Agam (submitted)
- Brem et al., 2009, *Hum. Brain Mapp.*
- Lau et al., 2008, *Nat. Rev. Neurosci.*

Multimodal Neuroimaging is difficult…

- Don't need to be an expert in each modality
  - But good to have an expert *consultant* for each
- Do need a lot of foresight, organization, and planning
  - Not a 'tack-on'
- Few cookie-cutter analysis routines available, so analysis needs to be planned ahead

…but rewarding!

- Can have great payoffs in better understanding both system of interest and the measures themselves