CENTER FOR MIND AND BRAIN

UNIVERSITY OF CALIFORNIA, DAVIS

ERPs in Translational Research: Opportunities & Challenges

Steve Luck

University of California, Davis

The Big Picture

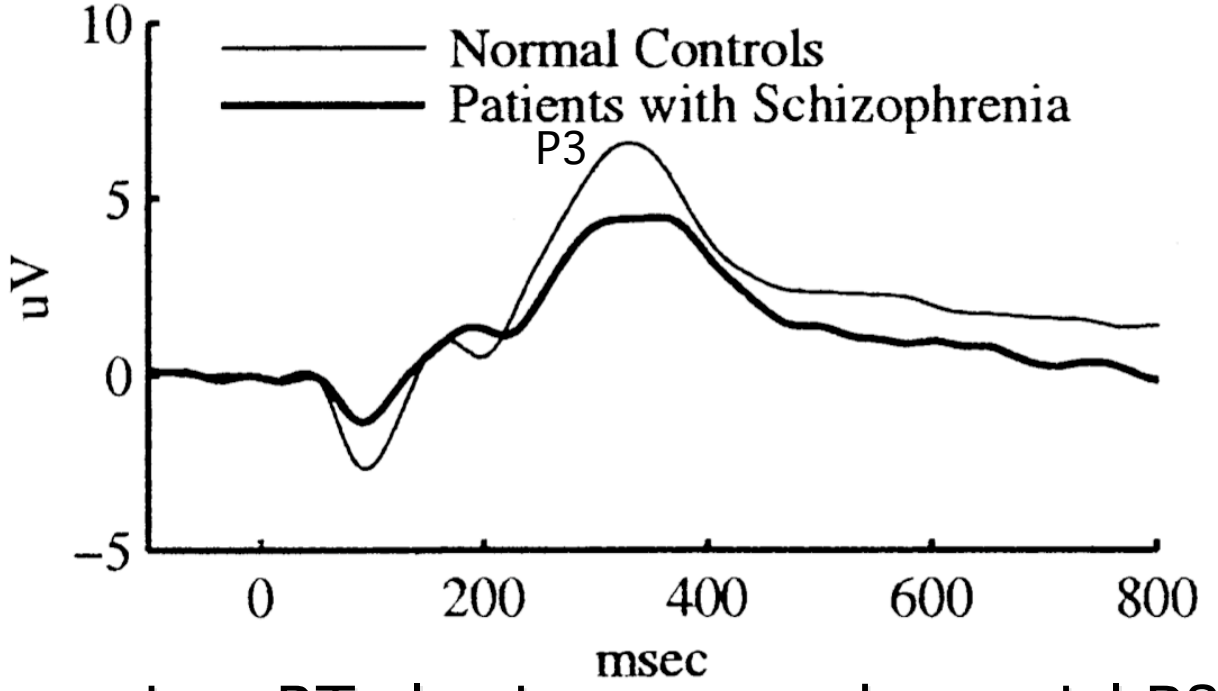
- General goal: Identify and measure dysfunctional neural systems in schizophrenia
  - Identify endophenotypes to study etiology
  - Define treatment targets
  - Rapidly test likely efficacy of new compounds
  - Assess treatment outcomes
- Must be better than simple behavioral neuropsych measures
  - Not enough to have sensitivity, reliability, large effect size
  - Must also have link to specific cognitive functions, neural circuits, and/or pharmacology
- Why might ERPs be useful in achieving this goal?
- What obstacles must be overcome?

Why Might ERPs be Valuable?

- High temporal resolution
  - Explicit: Are specific components slowed in patients?

P3 Latency in Schizophrenia

- RTs are typically 50-150 ms greater in SC patients
- P3 amplitude substantially reduced (d = 0.89)
  - But not clear what this really means
- P3 latency only slightly increased



- Interesting: RT slowing + no substantial P3 slowing

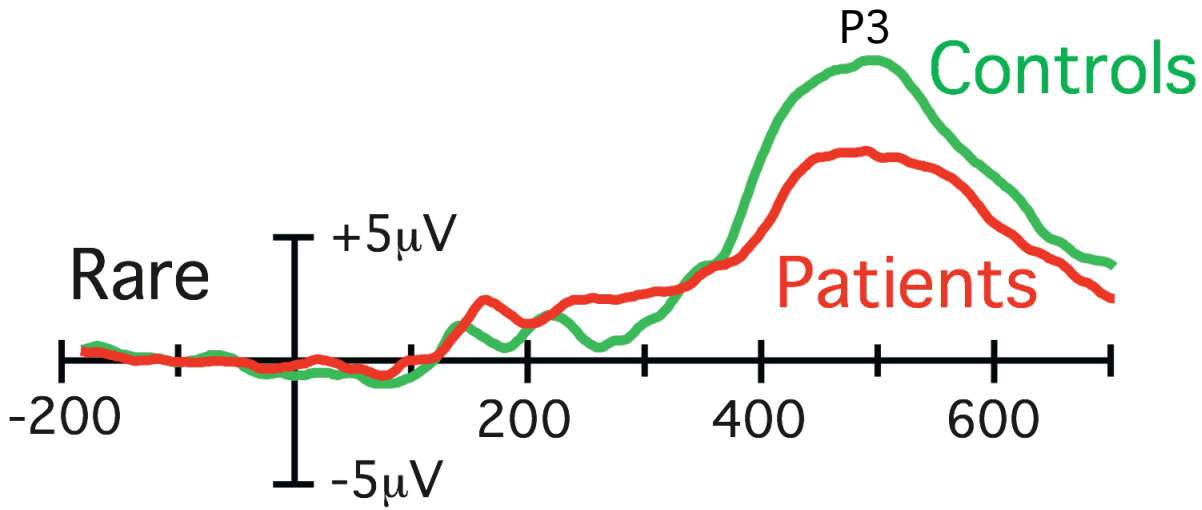
Mathalon et al., 2000

P3 Latency in Schizophrenia

Digit (p = .80) -> Left Hand
Letter (p = .20) -> Right Hand

Luck et al., 2009

P3 Latency in Schizophrenia



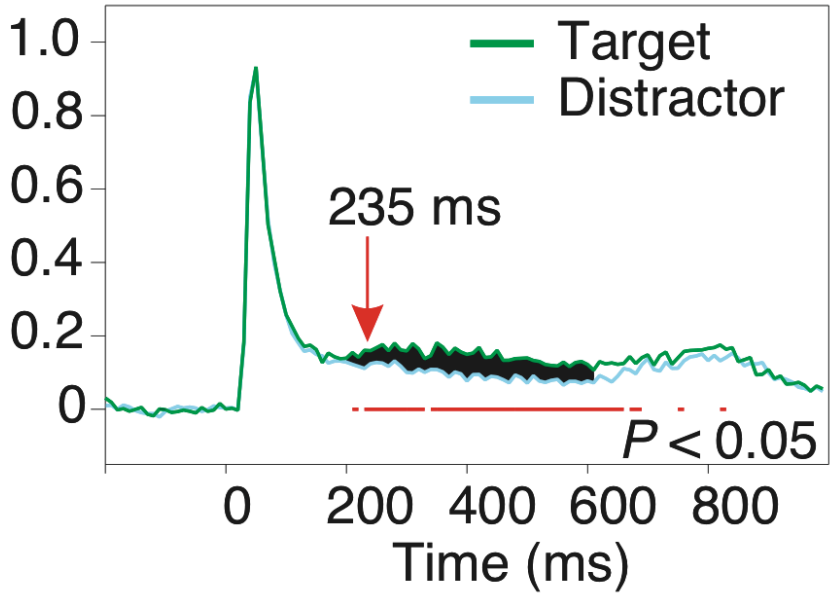
RT slowed by 70 ms in patients
No slowing of P3 latency in patients
Conclusion: RT slowing arises at a late stage

Luck et al., 2009

Why Might ERPs be Valuable?

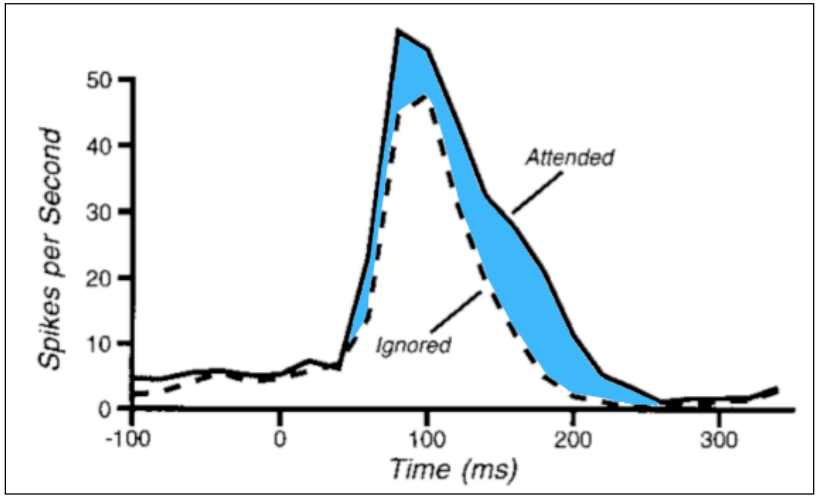
- High temporal resolution
  - Explicit: Are specific components slowed in patients?
  - Implicit: Isolating feedforward sensory processes from recurrent feedback, multiplexed memory processes, etc.

V1: Attention does not influence feedforward wave



Roelfsema et al., 1998

V4: Attention does influence feedforward wave



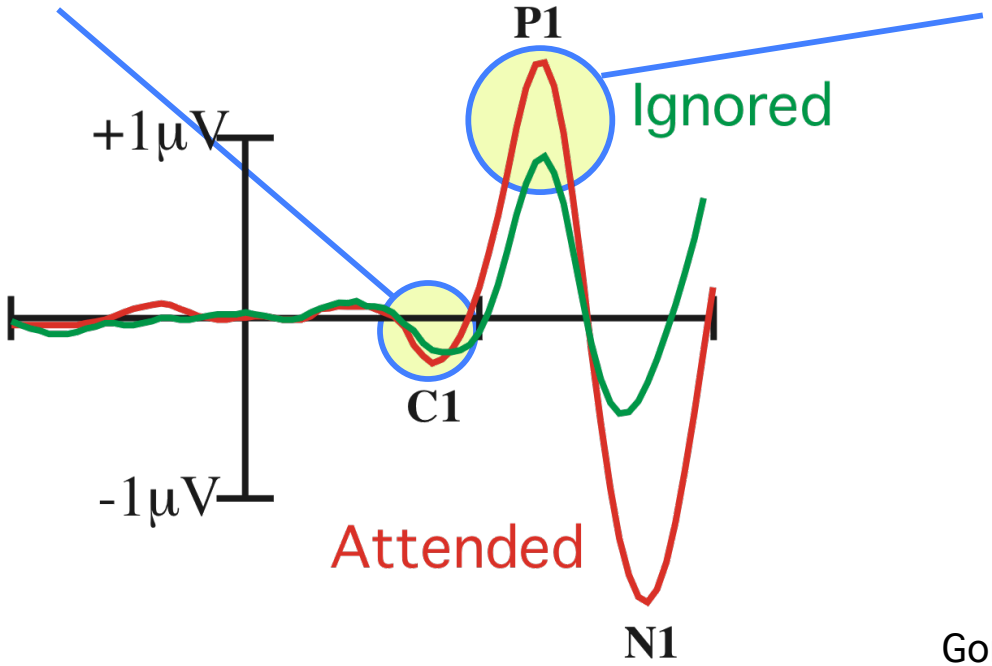
Luck et al., 1997

Why Might ERPs be Valuable?

- High temporal resolution
  - Explicit: Are specific components slowed in patients?
  - Implicit: Isolating feedforward sensory processes from recurrent feedback, multiplexed memory processes, etc.

V1: Attention does not influence feedforward wave

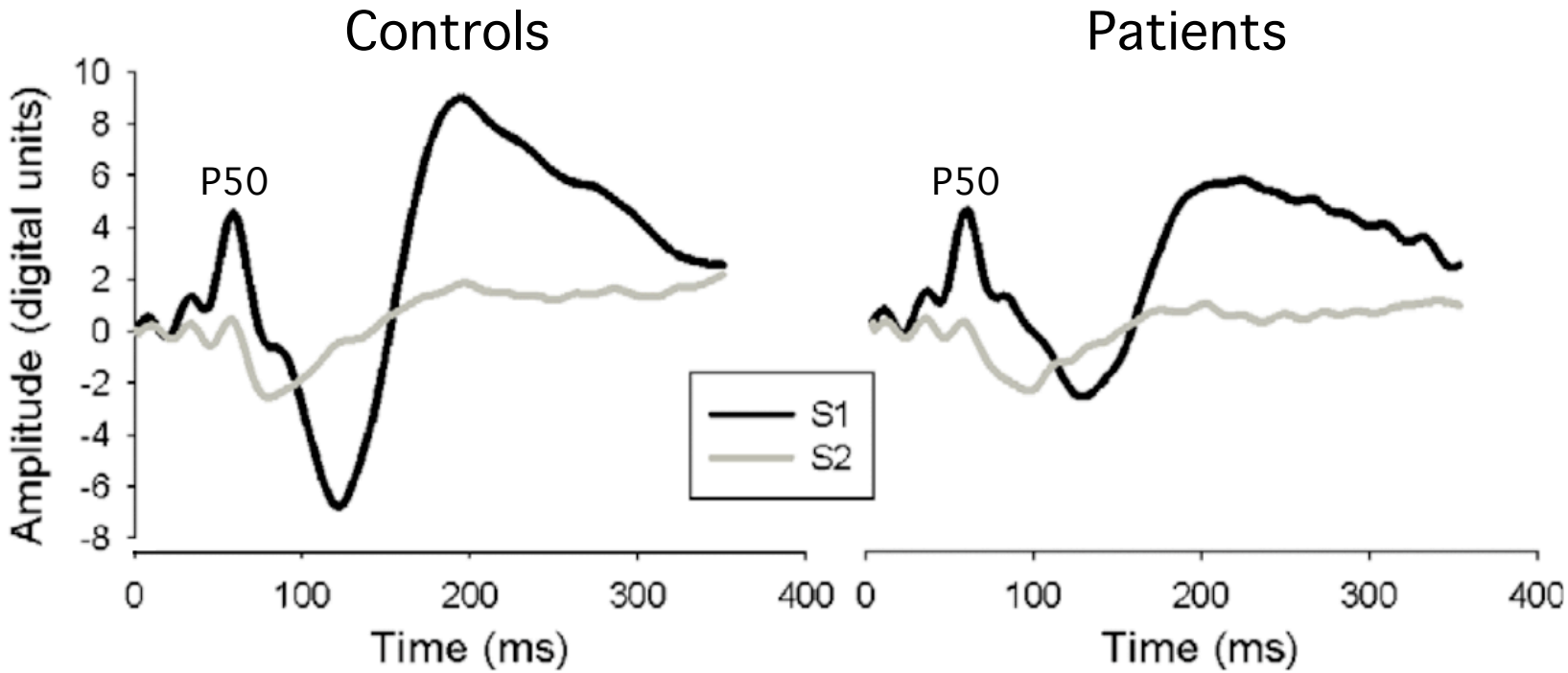
V4: Attention does influence feedforward wave



Gomez Gonzales et al., 1996

Why Might ERPs be Valuable?

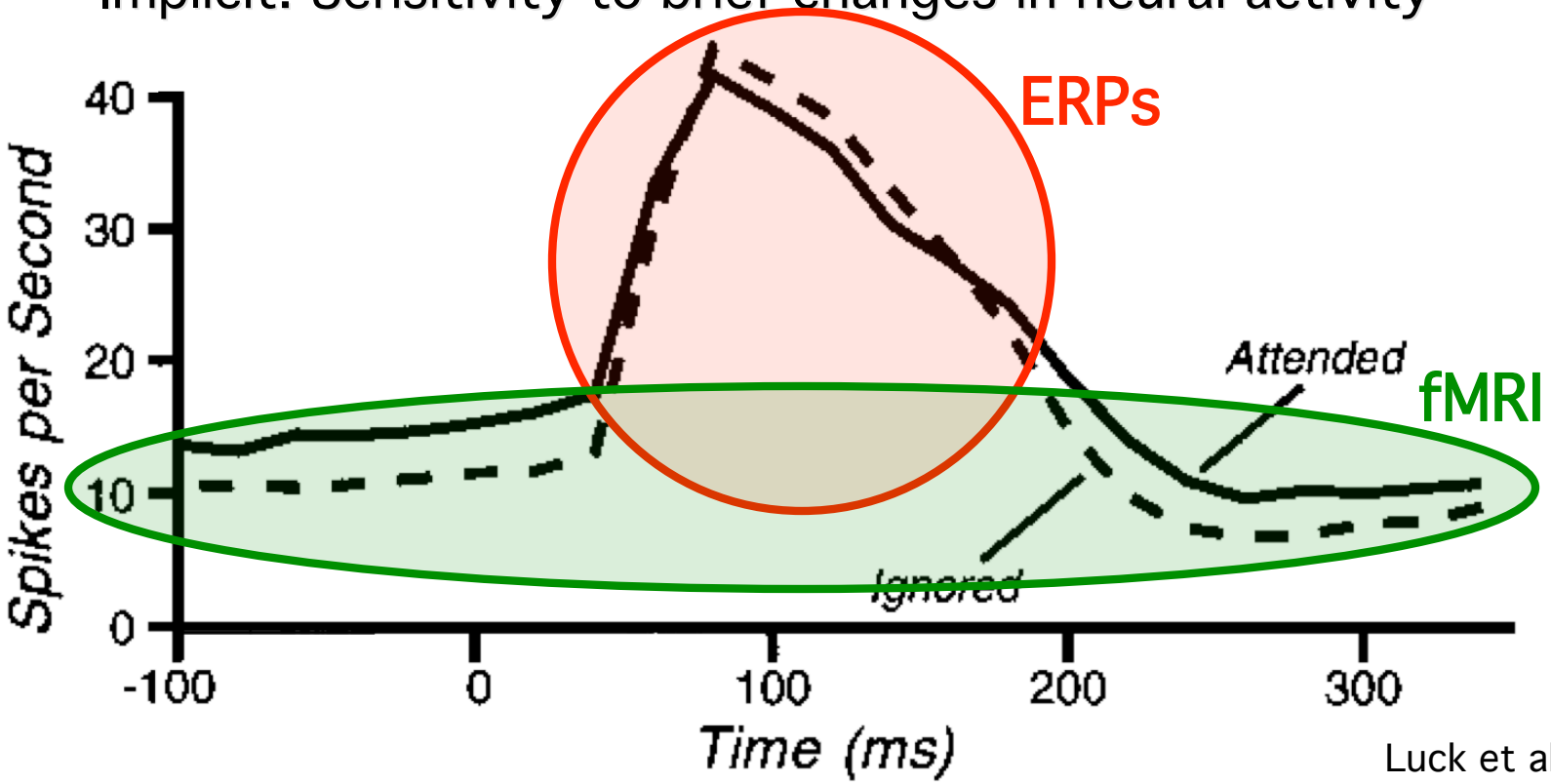
- High temporal resolution
  - Explicit: Are specific components slowed in patients?
  - Implicit: Isolating feedforward sensory processes from recurrent feedback, multiplexed memory processes, etc.



Johannesen et al., 2005

Why Might ERPs be Valuable?

- High temporal resolution
  - Explicit: Are specific components slowed in patients?
  - Implicit: Isolating feedforward sensory processes from recurrent feedback, multiplexed memory processes, etc.
  - Implicit: Sensitivity to brief changes in neural activity



Luck et al., 1997

Why Might ERPs be Valuable?

- Direct measure of neural activity
  - PSPs conducted to scalp at nearly speed of light
  - May be strongly linked to specific receptor subtypes (e.g., MMN and NMDA; P50 and nicotinic AChR)
  - Not secondary change in blood flow that might be influenced by changes in vasculature
- Relatively easy to record in rodents/primates
  - Many ERP paradigms are largely task-free (e.g., MMN, P50)
  - No restraint is necessary to prevent movement artifacts during task performance
  - Need to overcome microelectrode snobbery!

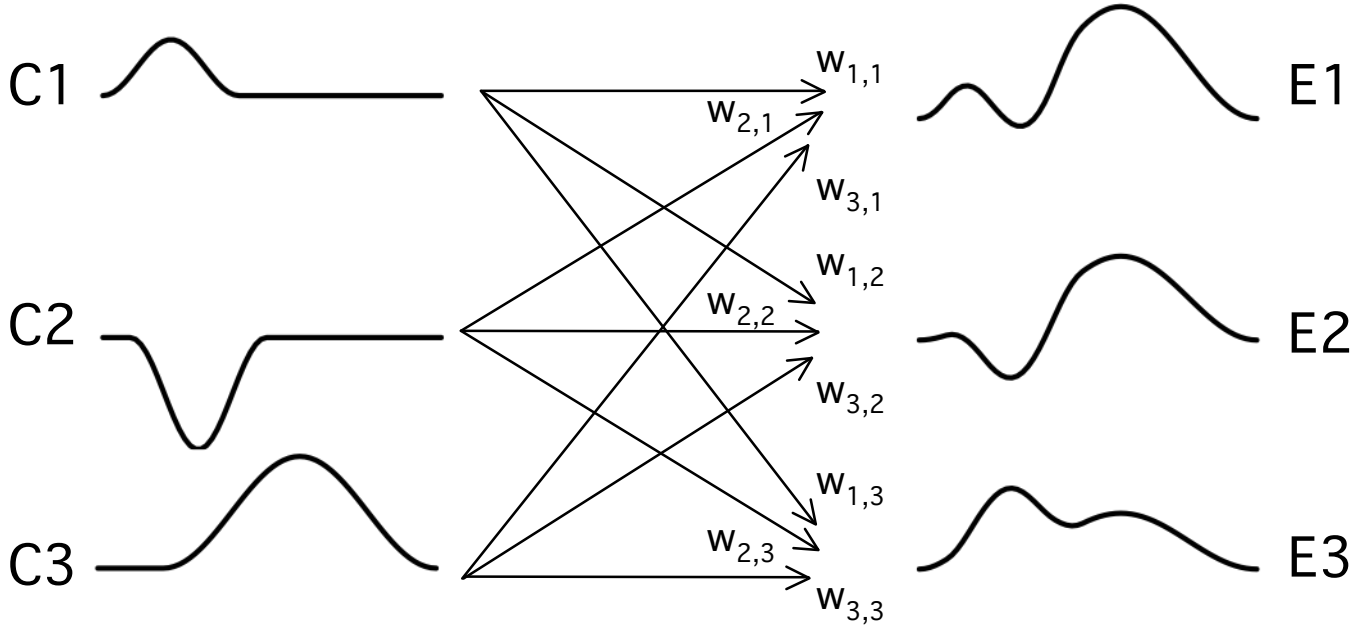
Why Might ERPs be Valuable?

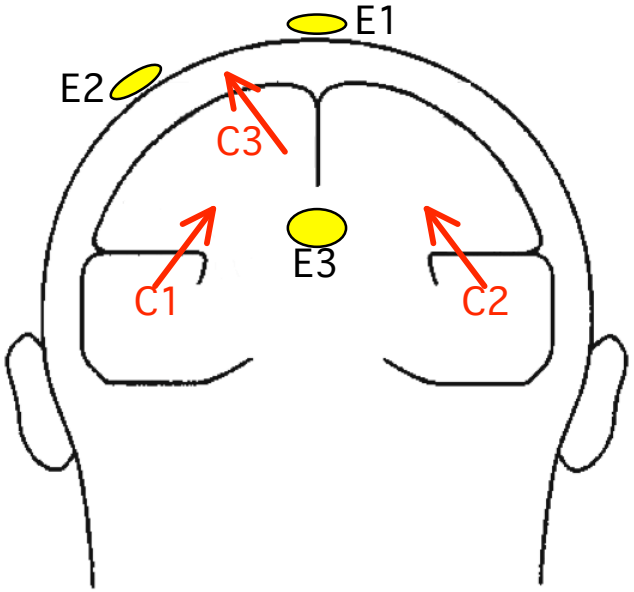
- Practical
  - Can be fast, easy, and cheap (but not always)
  - 8 electrodes and 15 minutes for many paradigms
  - <$20K for a simple ERP recording system
  - Easily tolerated by most patients; obesity not an issue
  - Relatively insensitive to small movements
  - Feasible in large-N clinical trials / genetic studies

Challenges

- Superposition problem
  - Waveform is sum of multiple overlapping components
  - Difficult to isolate a specific component from the sum

The Superposition Problem

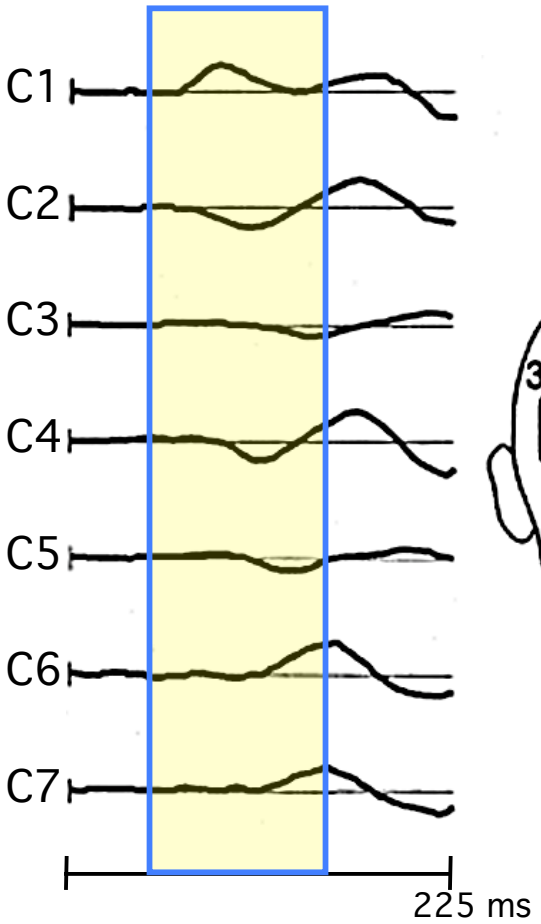




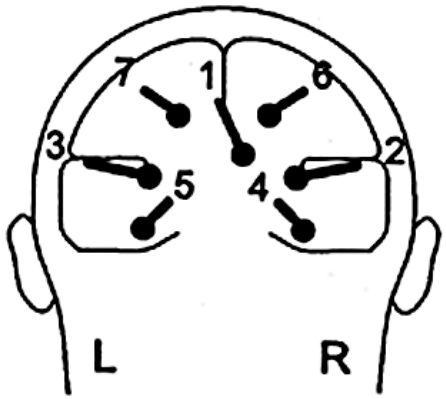
Voltage at an electrode at time *t* is a weighted sum of all components that are active at time *t*

There is no foolproof way to recover the underlying components from the observed waveforms

The Superposition Problem

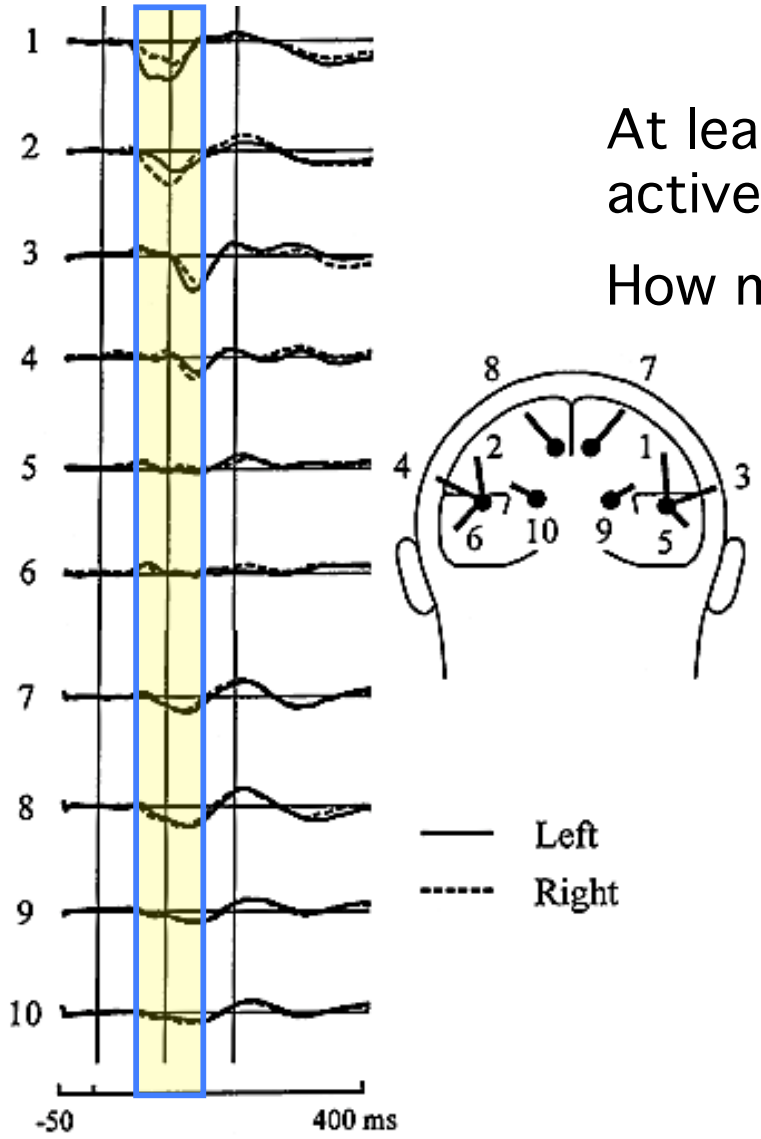


At least 7 components simultaneously active from 50-150 ms for visual stimuli



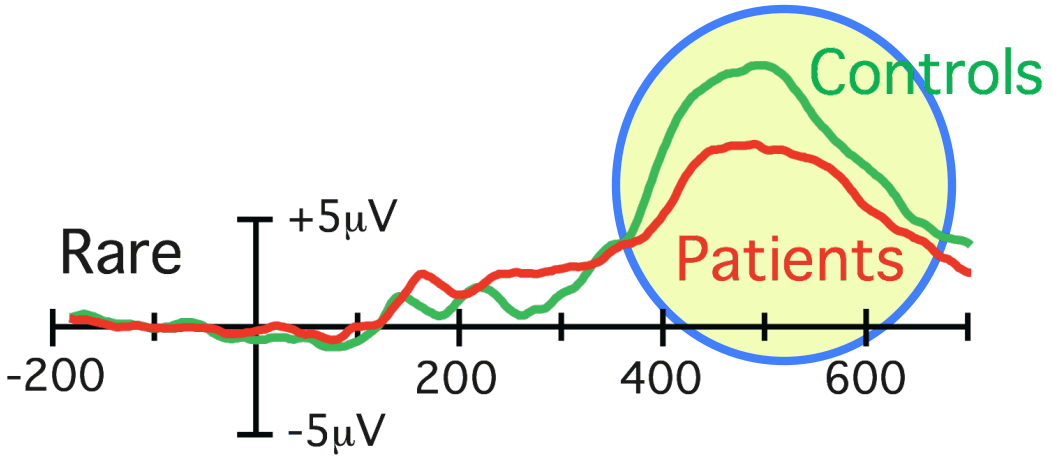
Di Russo et al., 2002

The Superposition Problem



At least 10 components simultaneously active from 50-150 ms for auditory stimuli

How many are active in the P300 period?

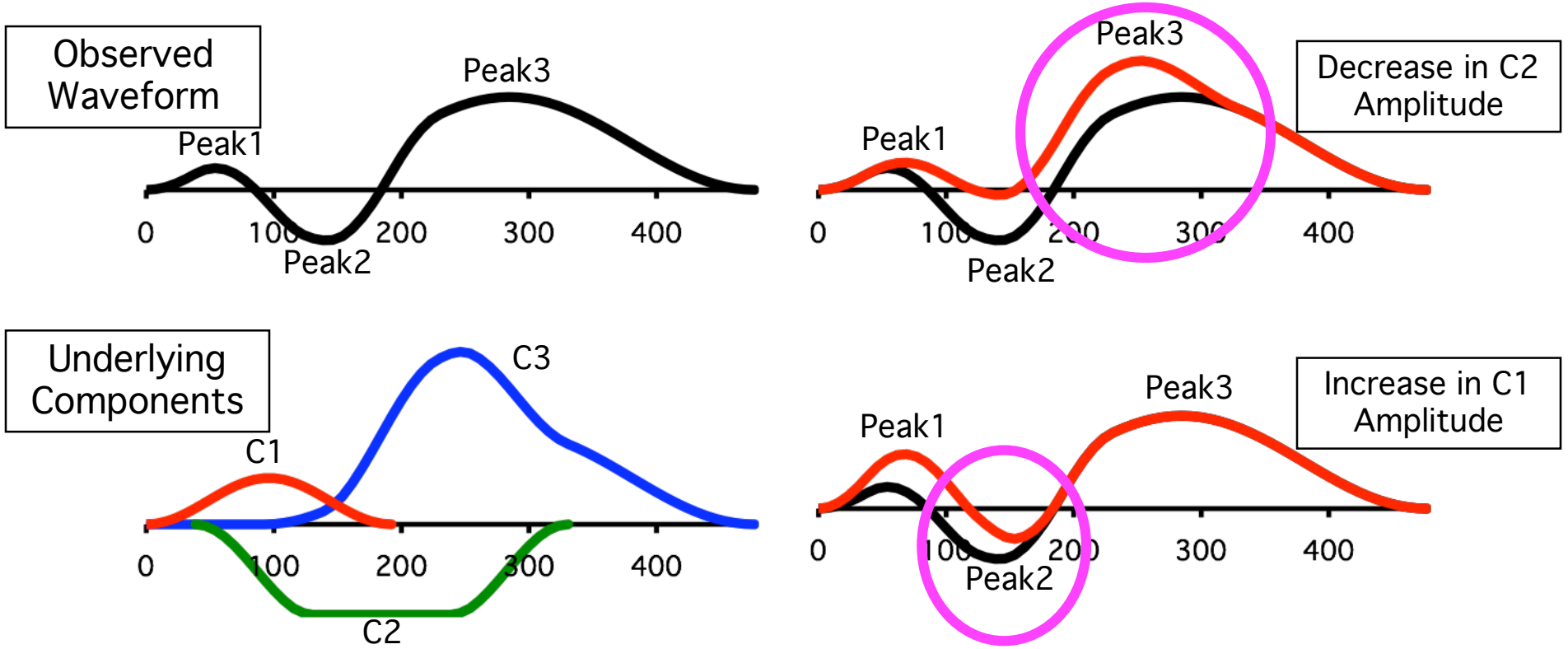


Is this really a change in <u>the</u> P300?

Picton et al., 1999

Luck et al., 2009

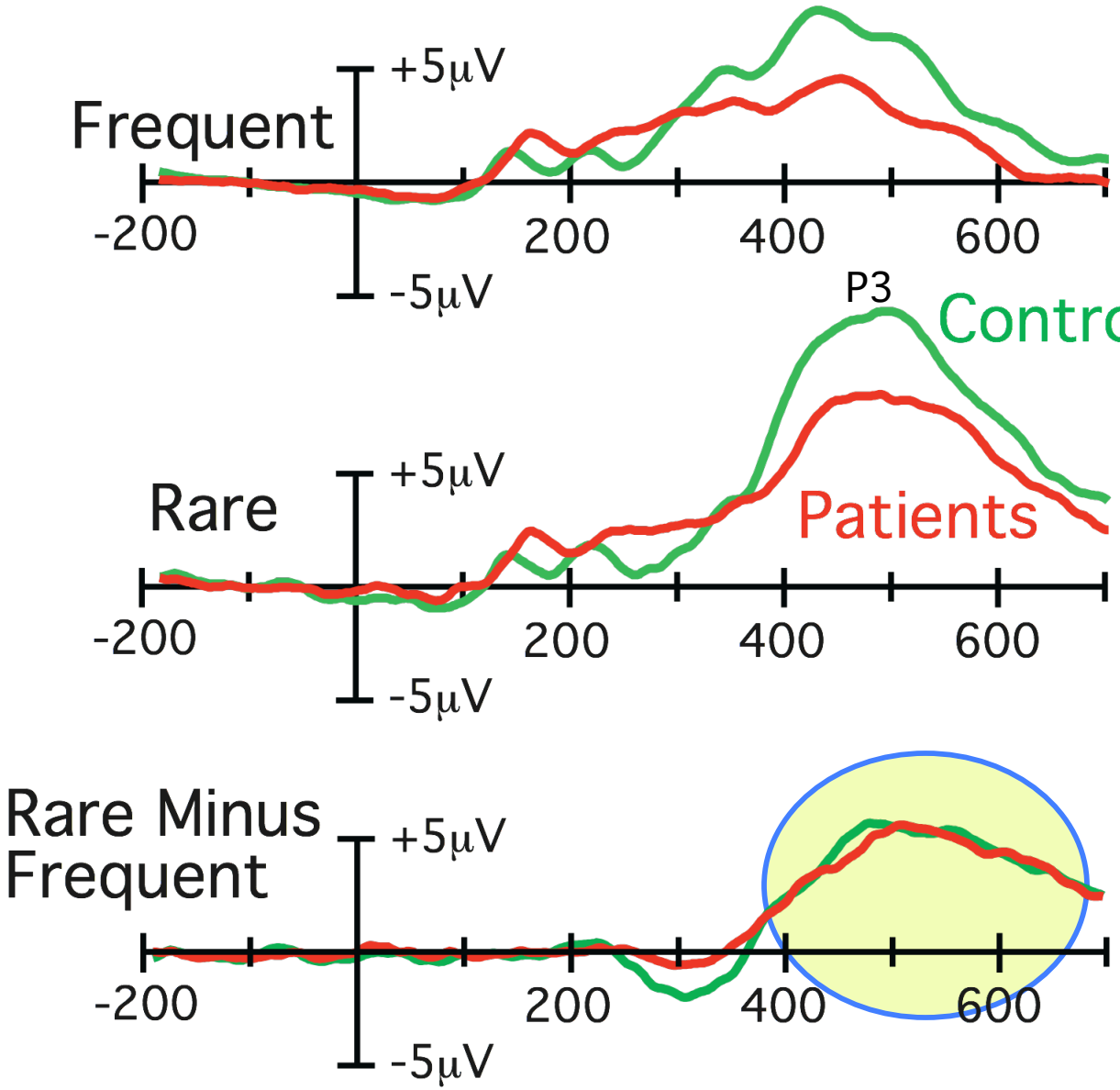
Component Identification



It is often difficult to determine which underlying component is affected by a given experimental manipulation

Focusing on difference waves can help by reducing the number of simultaneously active components

Using Difference Waves: P300



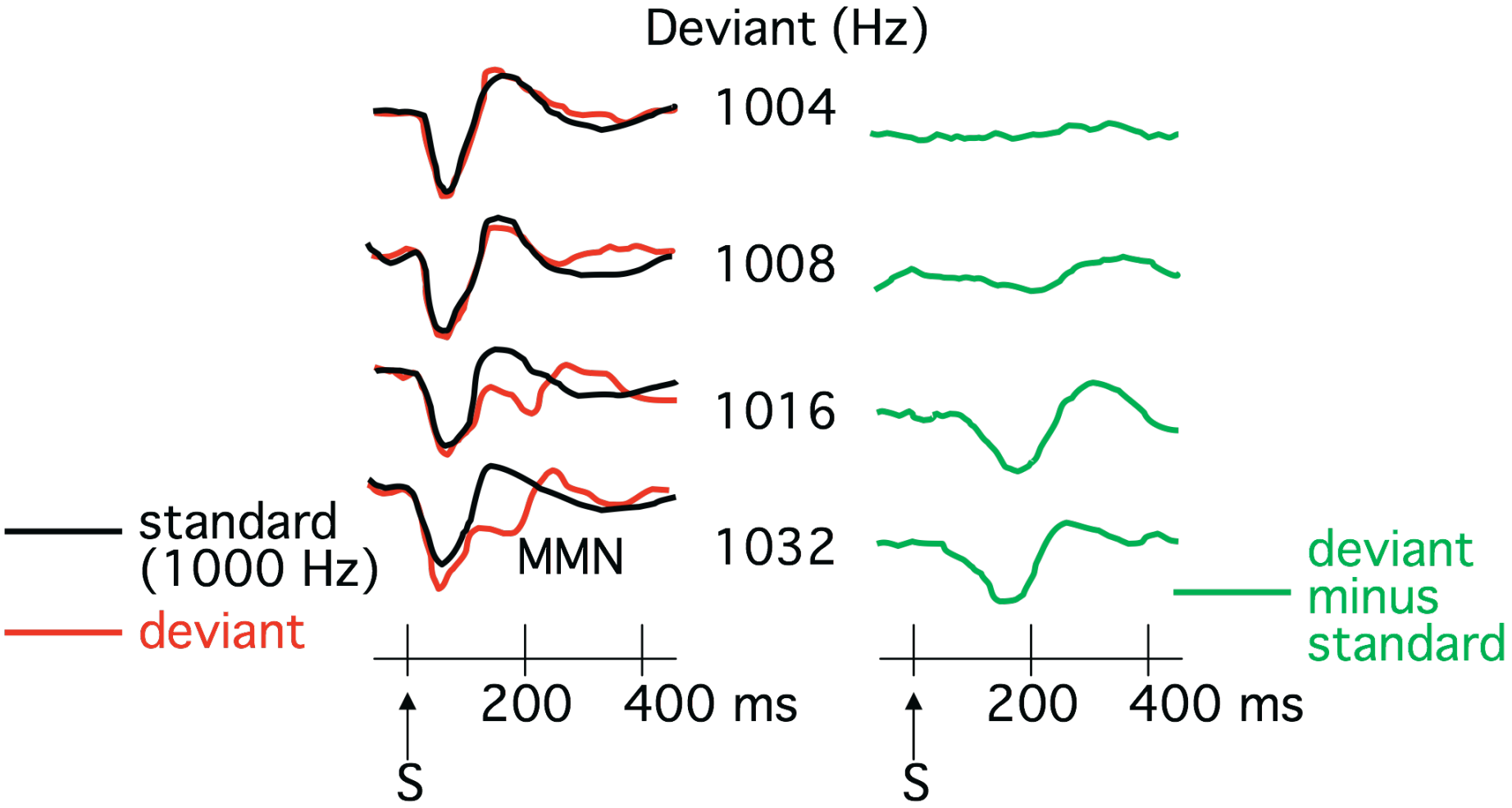
The difference wave reflects the brain's differential processing of rare and frequent stimulus categories

This is a small subset of the activity present in the individual Rare and Frequent ERPs

Is the P300 reduced in schizophrenia?

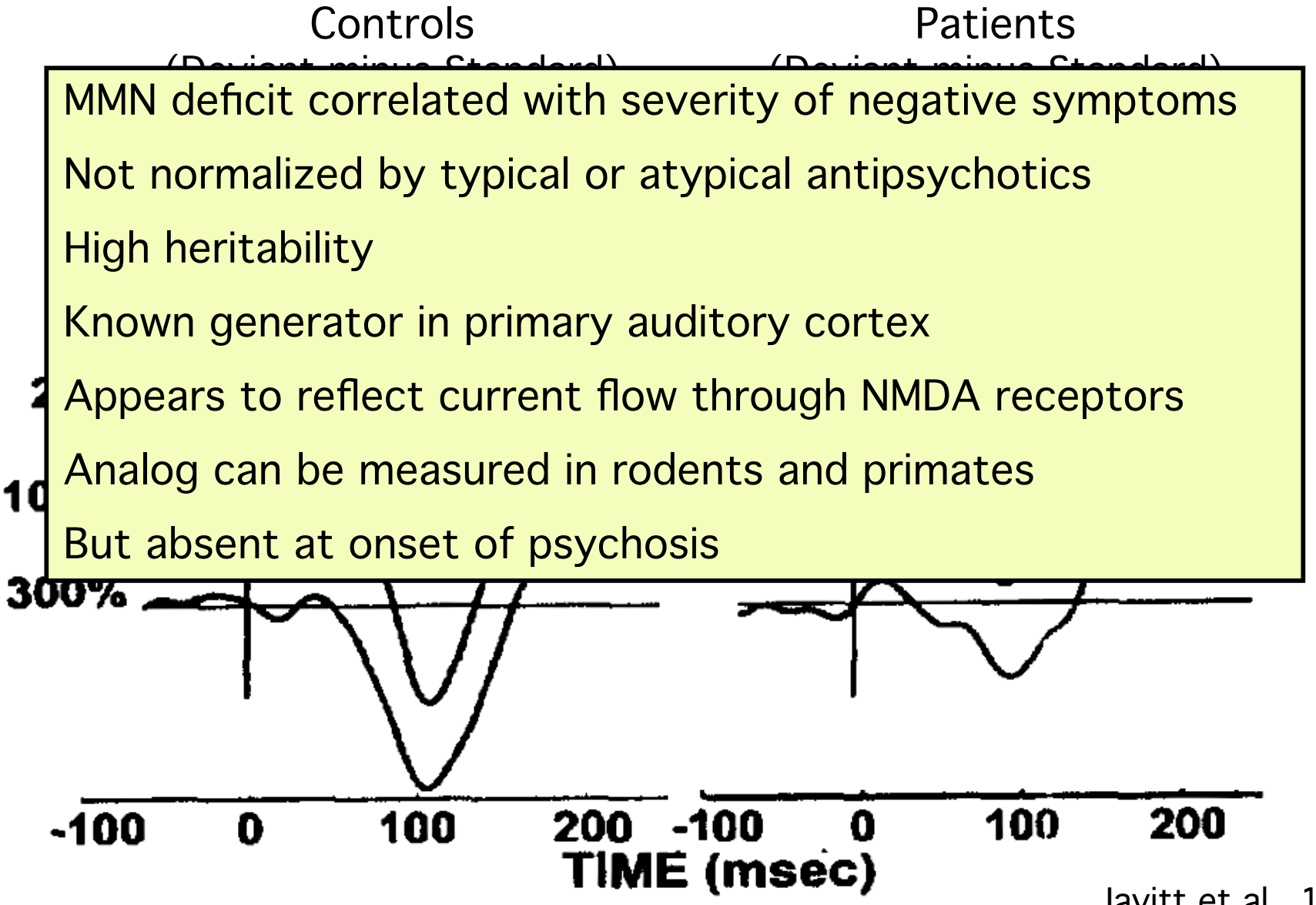
Luck et al., 2009

Using Difference Waves: MMN



Näätänen and Kreegipuu (in press)

Using Difference Waves: MMN



MMN deficit correlated with severity of negative symptoms

Not normalized by typical or atypical antipsychotics

High heritability

Known generator in primary auditory cortex

Appears to reflect current flow through NMDA receptors

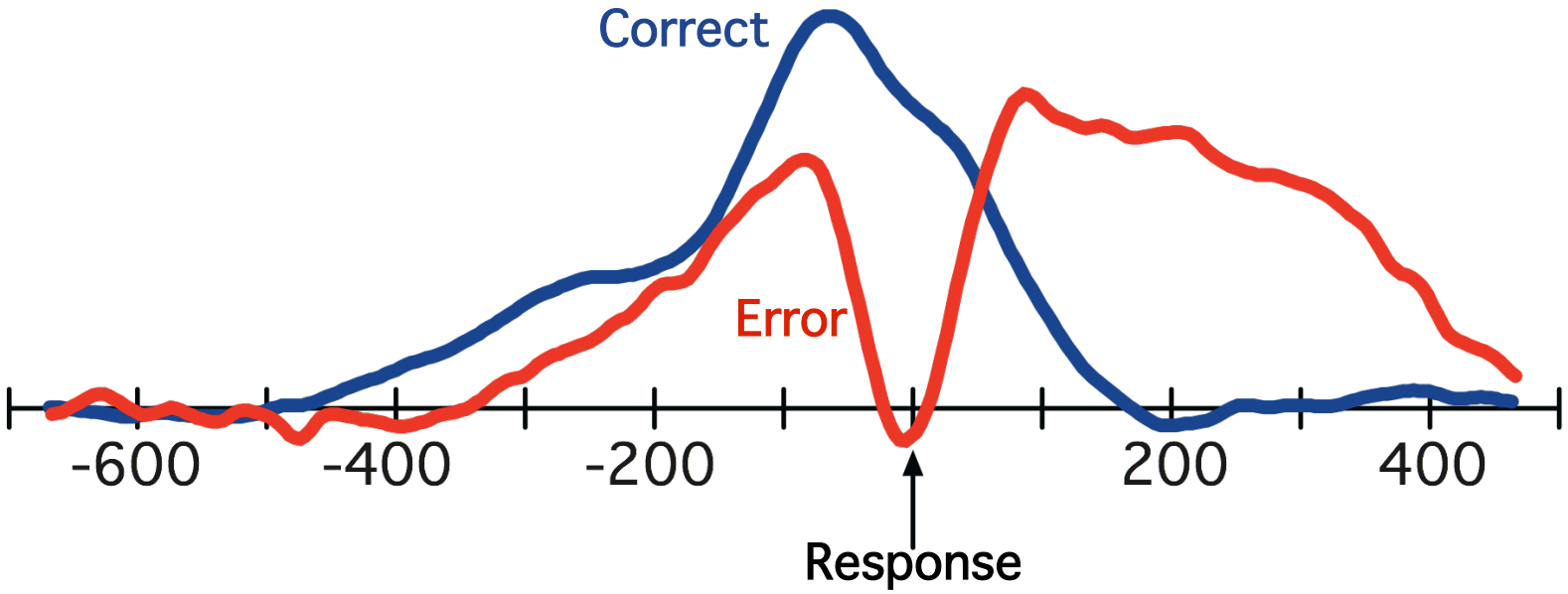
Analog can be measured in rodents and primates

But absent at onset of psychosis

Javitt et al., 1998

Using Difference Waves: ERN?

How much of this difference is the result of a latency shift in the late positive component?



How can we measure the magnitude of the ERN separately on correct trials and error trials?

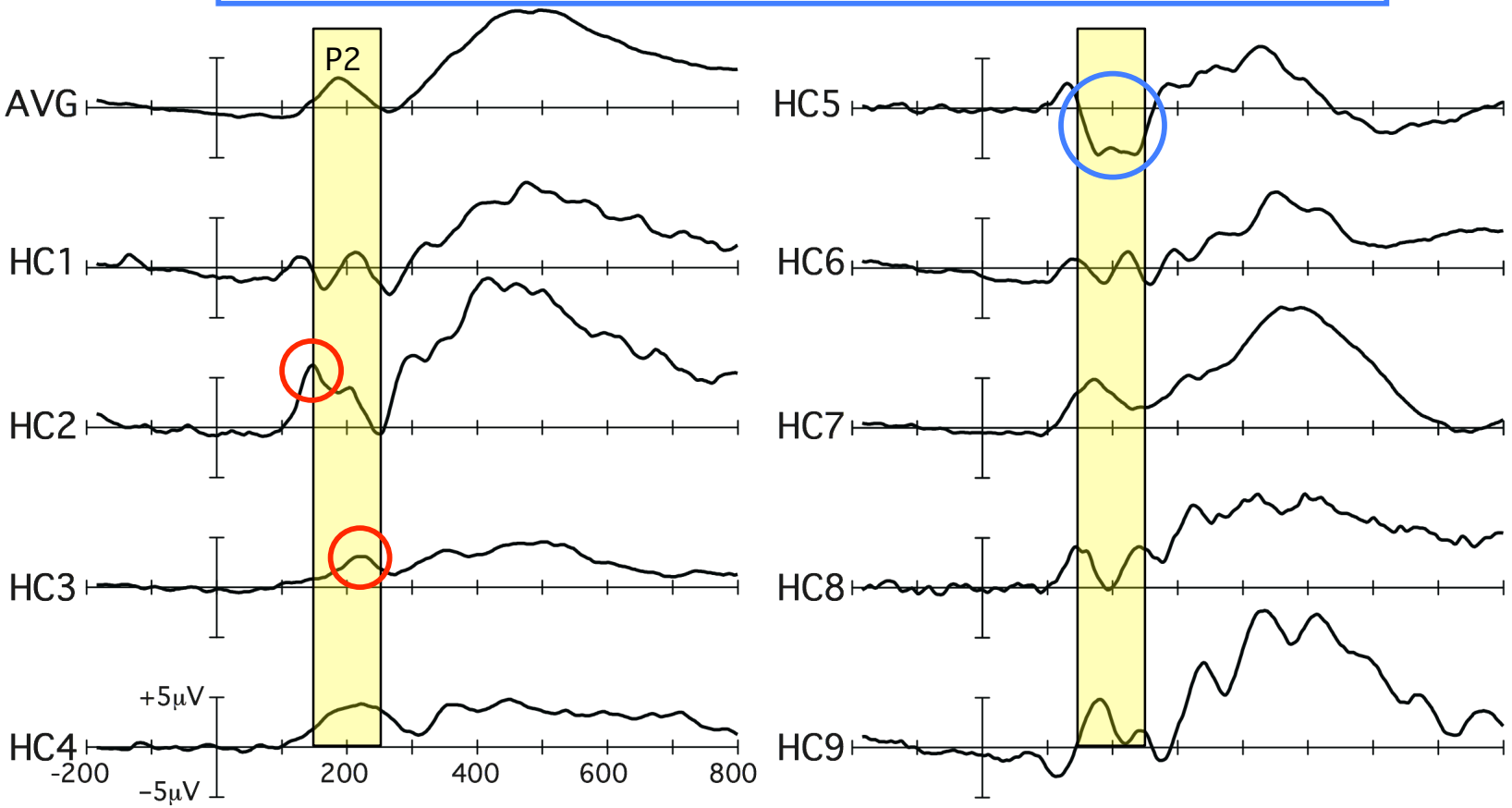
Even a difference wave doesn't solve this problem

Challenges

- Measurement issues
  - Large individual differences in waveform morphology: Difficult to identify a given component in many subjects

Individual Differences

Could this be a normal P2 overlapped by a large idiosyncratic negative wave?



Unlikely that the same neural process occurs at 150 ms in HC2 and at 225 ms in HC3

What Causes Individual Diffs?

- Possibility 1: Measurement error
  - No: test-retest usually shows same basic morphology
- Possibility 2: Nonfunctional differences
  - Idiosyncratic cortical folding patterns lead to large differences in generator orientation and/or cancellation
- Possibility 3: Stable, functional differences
  - May be useful in defining subgroups or differences in treatment response
- New analytical strategies need to be developed to capitalize on individual differences

Challenges

- Flexibility/Scope
  - Only a small fraction of brain processes have an ERP signature
  - A few dozen widely studied ERP components
  - Reliability, neural correlates, patient diffs for only a handful
  - Many processes occur too slowly to track well with ERPs
- Link to underlying neural circuitry
  - ERP localization based on topography alone is difficult
  - But ERP components can often be localized by means of strong converging evidence (e.g., lesion data)
  - Don't need to do localization in every study!
  - Great potential for links to specific transmitter systems and receptor subtypes, but only a few have been worked out
  - Need more primate/rodent work to aid in localization & pharmacology

Summary & Future Directions

- ERPs have the potential to be extremely useful in future clinical/translational research
  - Explicit and implicit temporal resolution
  - Direct measure of neural activity; linked to specific receptors
  - Relatively easy to record in rodents/primates
  - Practical for large-scale studies (genes, clinical trials)
- But must deal with superposition problem and individual differences
- More work is needed to:
  - Develop analytical approaches to individual differences
  - Link more components to specific neural systems, especially in rodents and nonhuman primates
  - Determine which ERP measures provide the most specific and sensitive measures of impaired neural/cognitive processes in schizophrenia

Acknowledgments

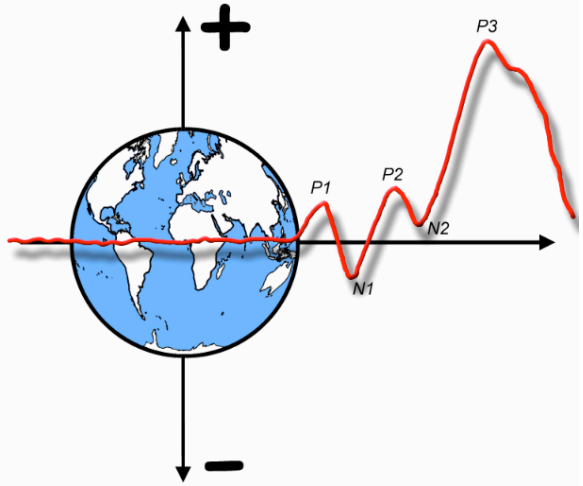
Collaborators

Jim Gold, Maryland Psychiatric Research Center
Becky Fuller, Catholic University of America
Ben Robinson, Maryland Psychiatric Research Center
Britta Hahn, Maryland Psychiatric Research Center
Ann Summerfelt, Maryland Psychiatric Research Center
Emily Kappenman, University of California, Davis
Carly Leonard, University of California, Davis
Valerie Beck, University of California, Davis
Javier Lopez-Calderon, University of California, Davis

Funding

R01MH65034, R01MH06850, R01MH076226, R01MH63001

Training & Software



The ERP Boot Camp

10-day intensive workshop in fundamental ERP methods every summer at UC Davis

erplab

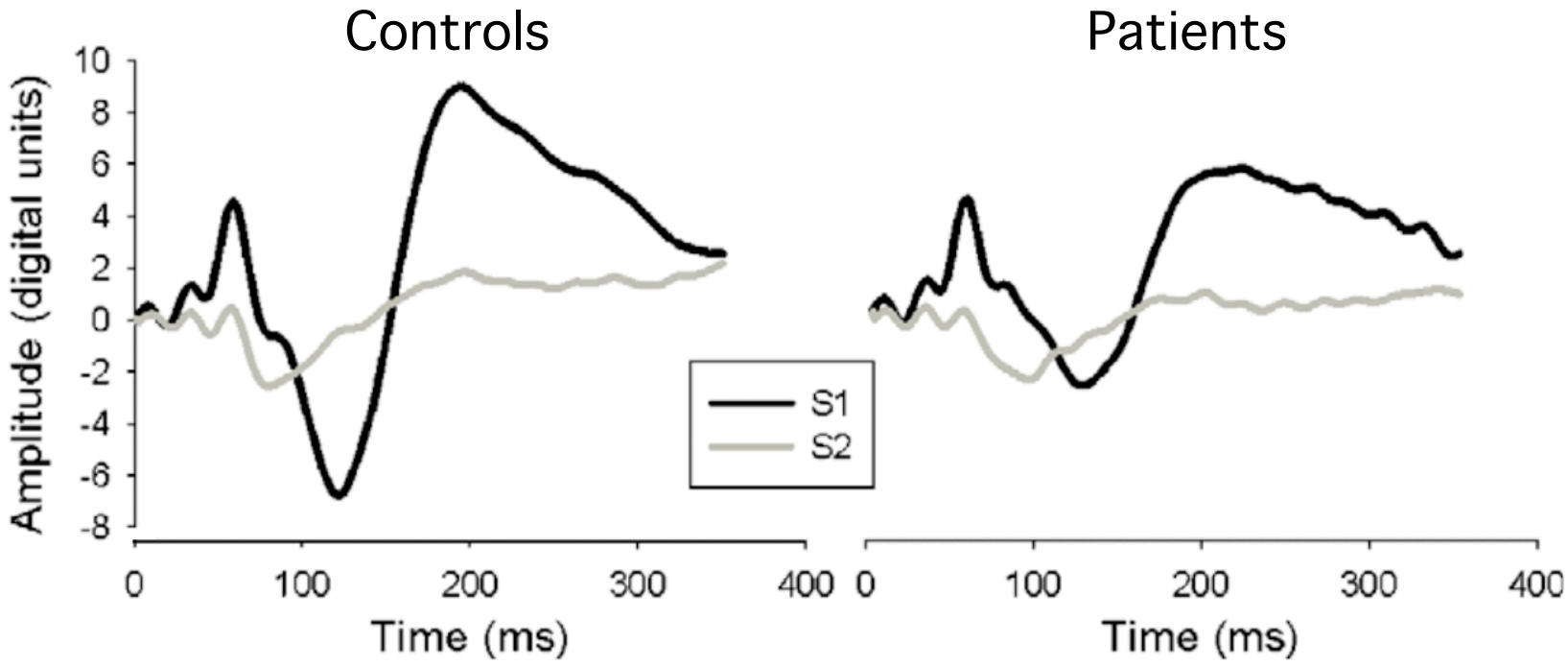
ERPLAB Toolbox

Free, open-source Matlab toolbox for ERP data analysis (coming soon!)

For details, go to http://erpinfo.org

Using Difference Waves: P50

- Virtually every component will differ for S1 vs S2
  - Making a difference wave (or using a ratio) doesn't really help
- But this may not matter if the goal is to measure early sensory inhibition, broadly construed

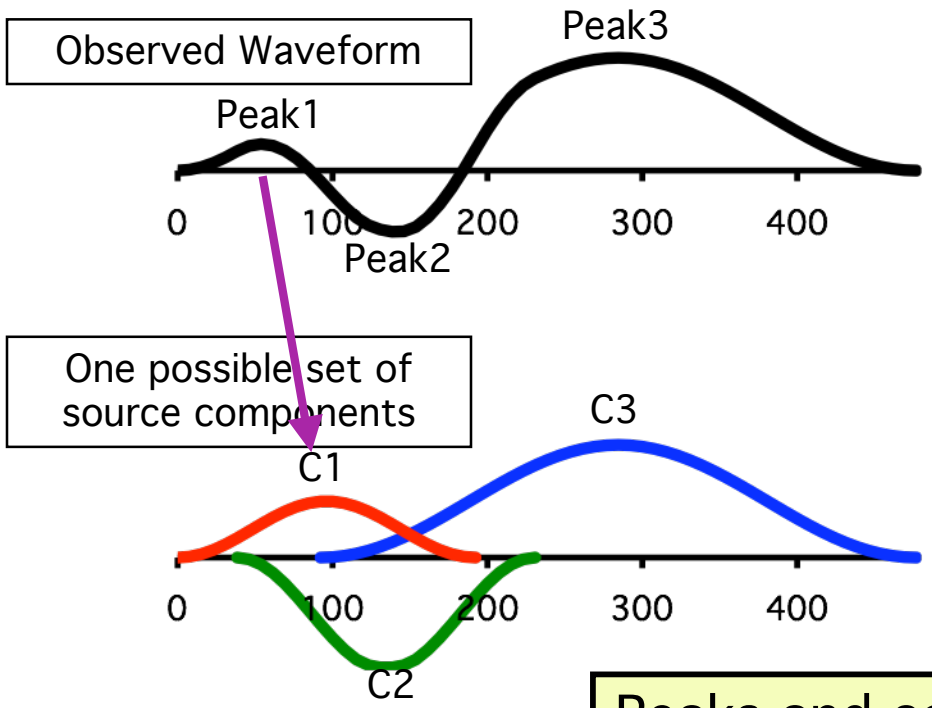


Johannesen et al., 2005

Solutions

- How to isolate the underlying components?
- Source localization
  - ERP localization based on topography alone is difficult
  - But precise localization may not be necessary to separate the components
- PCA/ICA
  - Assumptions often unjustified
  - But can still be helpful in certain cases
- Experimental design & difference waves
  - Difference waves reduce the number of simultaneously active components
  - Can be used in combination with source localization and PCA/ICA

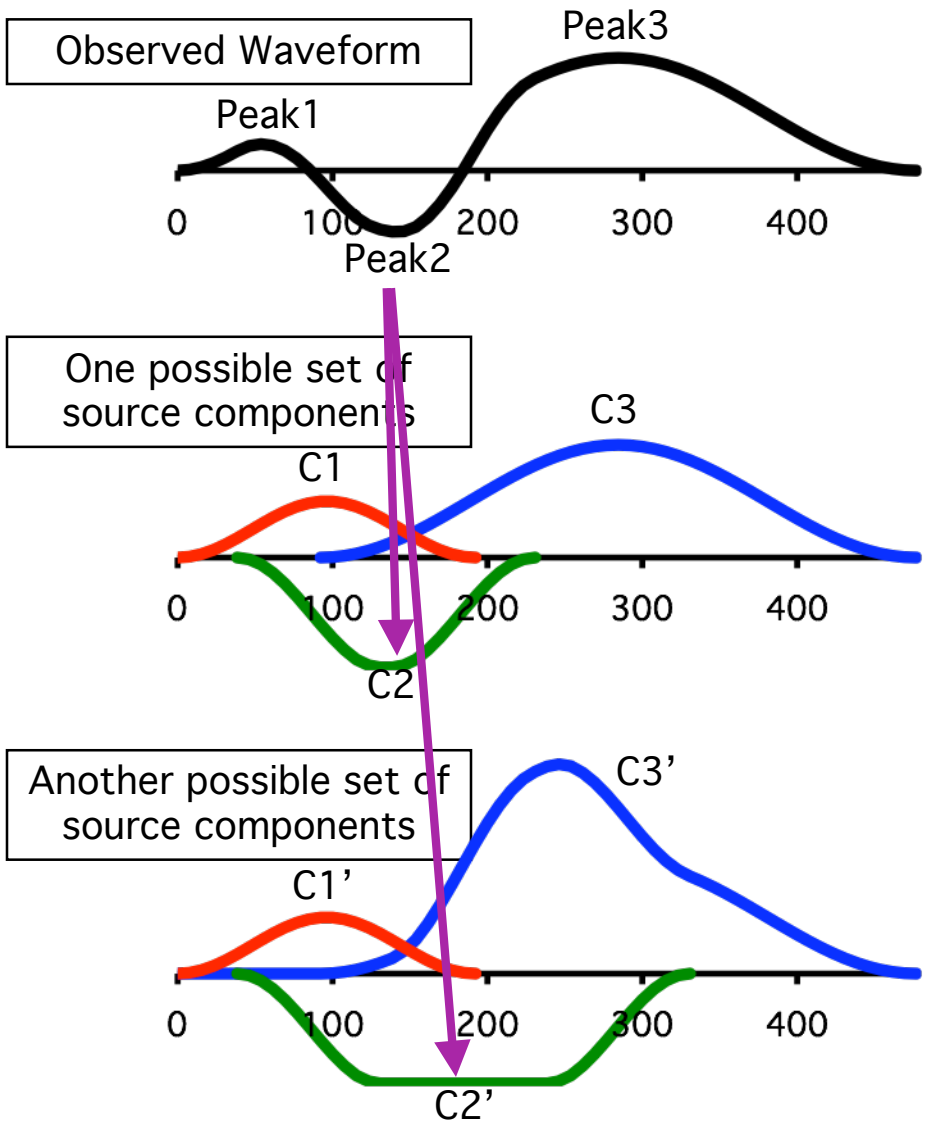
Peaks and Components



Peaks and components are not the same thing

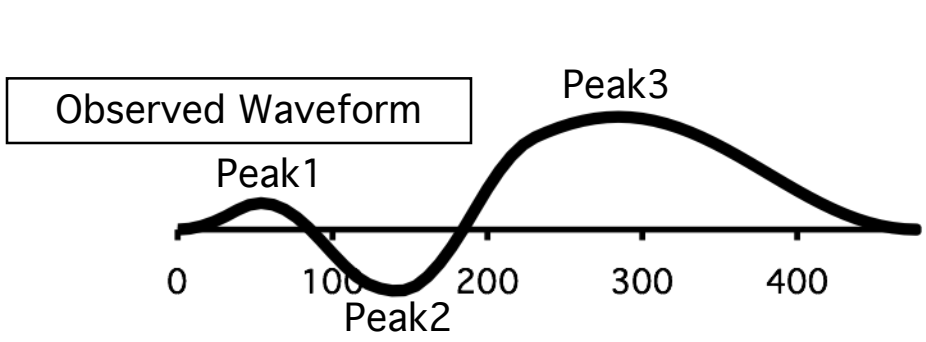
There is nothing special about the point at which the observed waveform reaches a local maximum

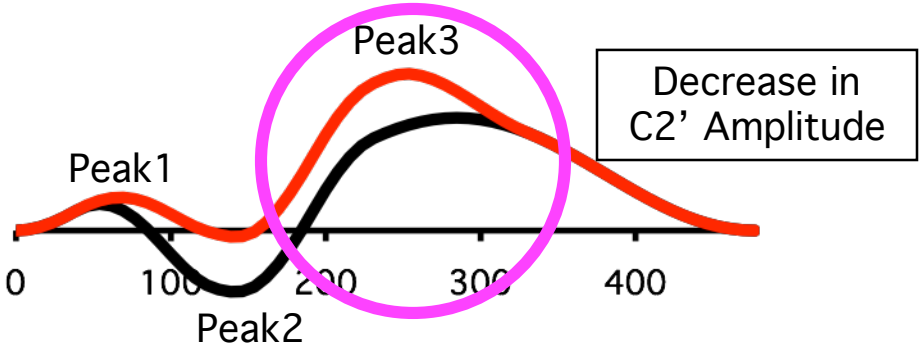
Peaks and Components

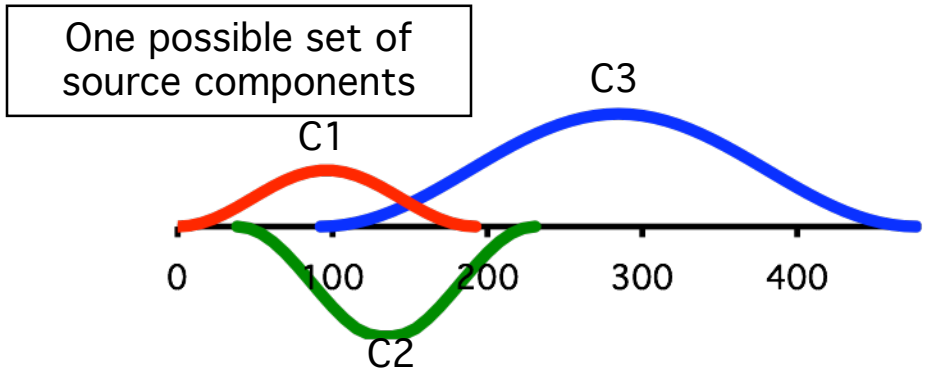


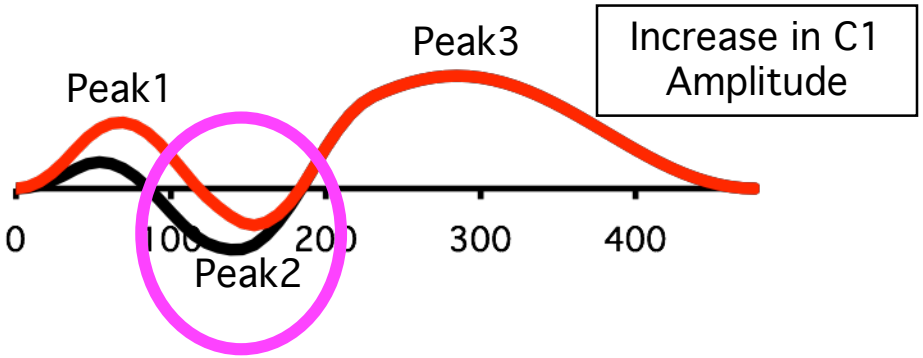
There may be no obvious relationship between the shape of the peaks and the underlying components

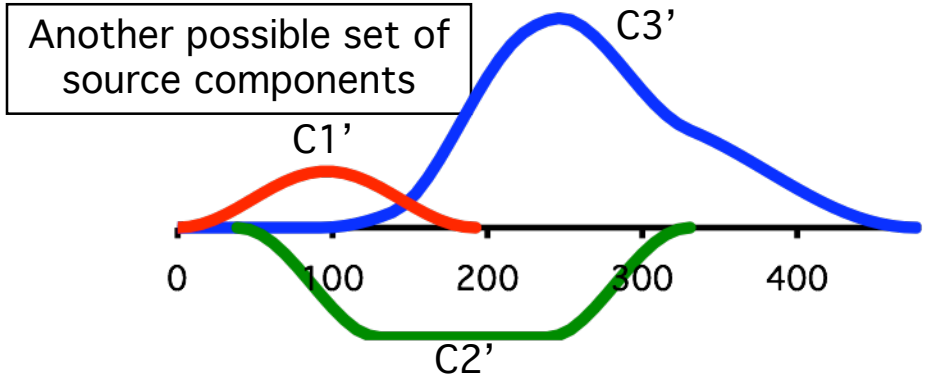
Peaks and Components











An effect during the time period of a particular peak may not reflect a modulation of the underlying component