Frequency-domain EEG applications and methodological considerations

Applications

- Emotion Asymmetries
  - Lesion findings
    - Catastrophic reaction (LH)
    - RH damage show a belle indifference
  - EEG studies
    - Trait (100+ studies)
    - State (oodles more studies)

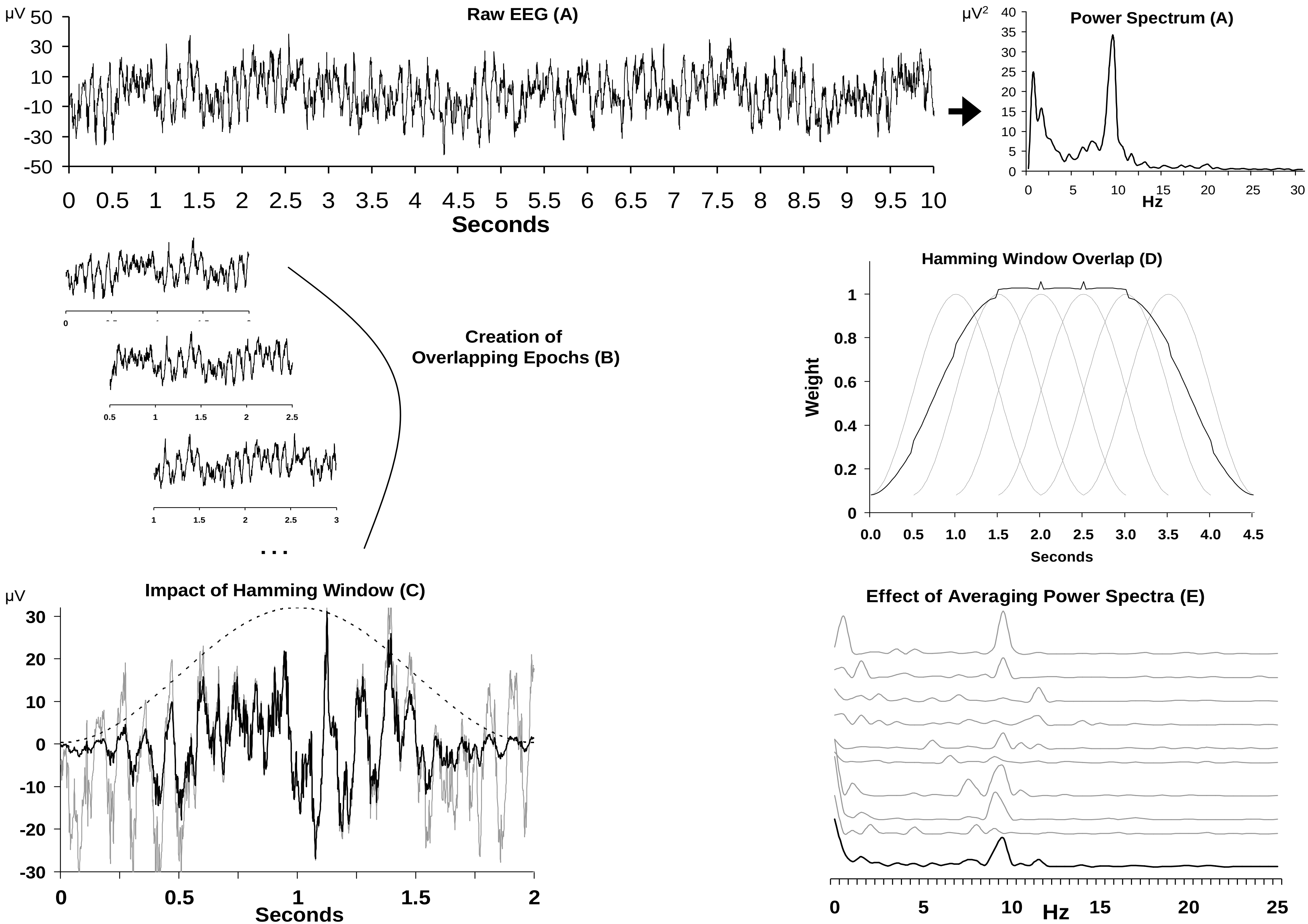
Types of Studies

- Trait
  - Resting EEG asymmetry related to other traits (e.g. BAS)
  - Resting EEG asymmetry related to psychopathology (e.g. depression)
  - Resting EEG asymmetry predicts subsequent emotional responses (e.g. infant/mom separation)
- State
  - State EEG asymmetry covaries with current emotional state (e.g., self report, spontaneous emotional expressions)

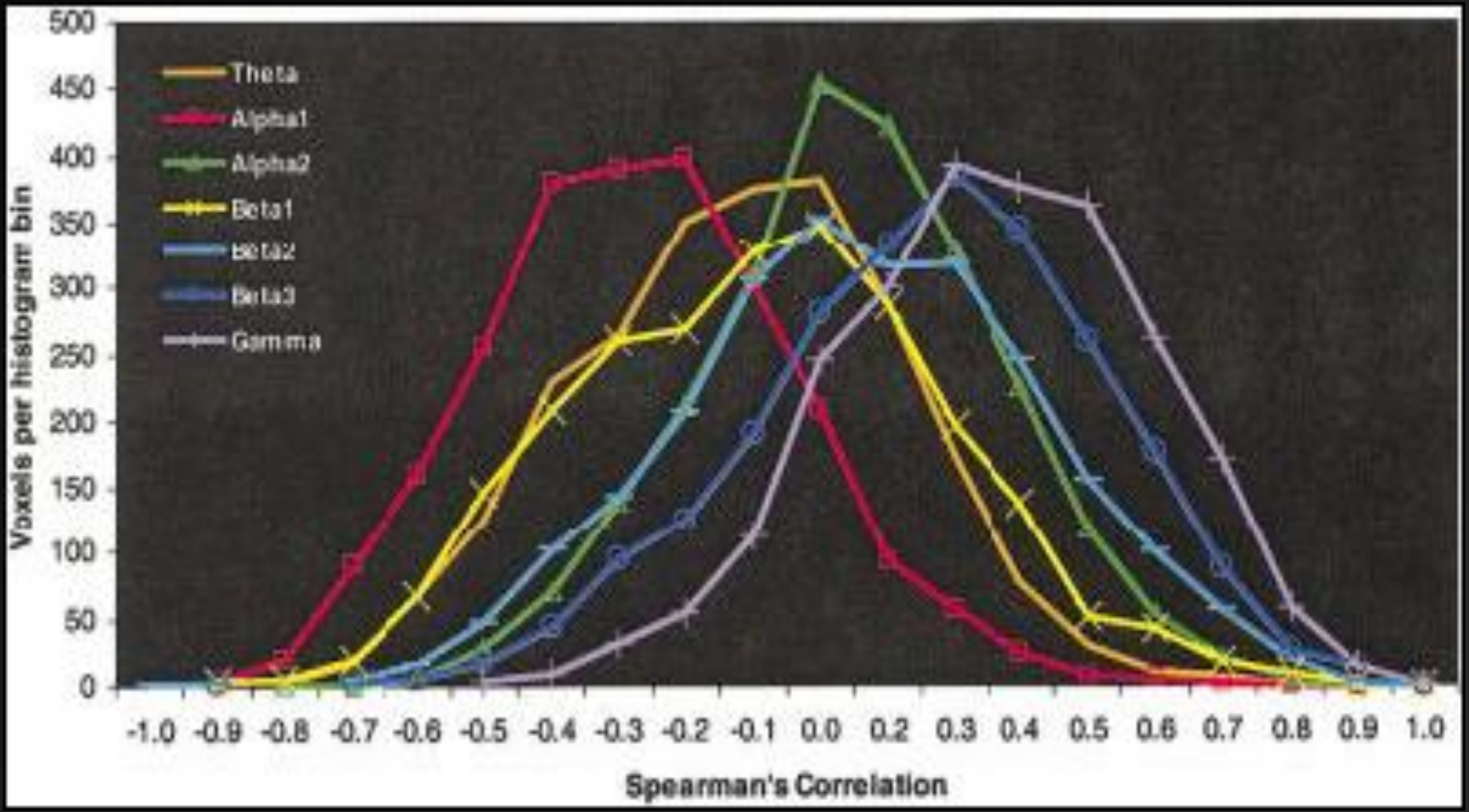
Trait, Occasion, and State variance

- Three sources of reliable variance for EEG Asymmetry
  - *Stable trait consistency* across multiple assessments
  - *Occasion-specific* variance
    - reliable variations in frontal asymmetry across multiple sessions of measurement
    - may reflect systematic but unmeasured sources such as current mood, recent life events and/or factors in the testing situation.
  - *State-specific* variance
    - changes within a single assessment that characterize
      - the difference between two experimental conditions
      - the difference between baseline resting levels and an experimental condition.
      - conceptualized as proximal effects in response to specific experimental manipulations
      - should be reversible and of relatively short duration
- Unreliability of Measurement (small)

Allen, Coan, & Nazarian 2004


Raw EEG (A)
μV
Seconds
Power Spectrum (A)
μV2
Hz
Creation of
Overlapping Epochs (B)
Hamming Window Overlap (D)
Weight
Seconds
Impact of Hamming Window (C)
μV
Seconds
Effect of Averaging Power Spectra (E)
Hz

Alpha Vs Activity Assumption (AAA)



Oakes et al, 2004, *Human Brain Mapping*

Alpha and Activity

- May be more apt to think of alpha as regulating network activity
- High alpha has inhibitory function on network activity (more in advanced topics)

EEG Asymmetry, Emotion, and Psychopathology

PAPER SESSION II

"During positive affect, the frontal leads display greater relative left hemisphere activation compared with negative affect and vice versa"

202 SPR ABSTRACTS, 1978 *Vol. 16, No. 2*

PAPER SESSION II

1\. **Silverstein, L. D., & Graham, F. K.** (University of Wisconsin - Madison) **Selective attention effects on reflex activity.** Bohlin and Graham (1977) found that reflex blinking, unlike spontaneous blinking, was facilitated in association with cardiac deceleration when subjects were required to attend to the reflex-eliciting stimulus. The enhancement of sensory processing on the attended channel was proposed as an explanation for the facilitation. If so, directing attention to a different channel should remove the facilitation. This hypothesis was tested in two experiments analogous to the Bohlin and Graham (1977) studies. The critical change was requiring subjects to attend to a stimulus in a modality orthogonal to that of the reflex-eliciting stimulus.

In each experiment, 15 college students received 60- or 120-msec, low-intensity, electrotactile stimuli concurrently with a 50-msec auditory startle pulse. A warning tone preceded electrotactile and startle stimuli by 2 sec in the experimental conditions, while in the control conditions the two stimuli were presented without warning. Subjects' task was to discriminate electrotactile stimulus duration.

As in earlier intramodal studies, the warning tone elicited significant cardiac deceleration during the warning intervals of both experiments. Significantly better discrimination occurred on warned than unwarned control trials (Exp. 1—73.7% vs 60.3%; Exp. 2—73.2% vs 49.5%). Reflex blink latency was also significantly facilitated in both experiments. However, unlike the intramodal studies, blink magnitude was reduced. A small reduction in Experiment 1 was not a reliable effect, but increased startle pulse intensity in Experiment 2 resulted in a larger and significant reduction.

The hypothesis that reflexive motor activity is influenced by selective sensory enhancement was clearly supported. The results are interpreted with respect to a general theory of orienting and reflex control.

(Supported by the Grant Foundation, by an NSF grant BMS75-17075, and by a Research Scientist Award K3-MH21762 and a Fellowship Award MH07198-01 from NIMH)

2\. **Washton, A. M.** (New York Medical College) **Autonomic and stimulus control of conditional cardiac rate responses in rhesus monkeys.** Conditional cardiac rate responses (cardiac CRs) of 6 rhesus monkeys were examined under systematic and broad manipulation of the temporal variable of CS-US interval length. A Pavlovian delay conditioning procedure was employed in which the duration of a visual conditional stimulus (CS) preceding an aversive electric-shock unconditional stimulus (US) was increased progressively from 2 to 120 sec for each animal. At each of 8 differing CS-US interval conditions, selective autonomic blocking agents were administered to assess the relative roles of the sympathetic and parasympathetic branches of the autonomic nervous system in the elaboration of observed cardiac rate CRs. Each subject was tested both in the absence of any drugs and under: 1) sympathetic blockade with propranolol, 2) parasympathetic blockade with atropine, 3) double blockade with a combination of propranolol and atropine, and 4) ganglionic blockade with chlorisondamine.

The within-CS waveform of the cardiac rate CR was least consistent at the first 3 CS-US intervals of 2–6 sec, where instances of accelerative, decelerative, and biphasic HR patterns were observed during CS both within and among subjects, with the direction of response varying with the level of HR just prior to CS onset. By contrast, at CS-US intervals from 10 to 120 sec, a stable and consistent biphasic HR pattern of initial acceleration followed by deceleration was uniformly observed during CS despite continued wide fluctuations in pre-CS HR.

Both accelerative and decelerative HR changes within the CS-US interval were eliminated almost entirely by parasympathetic blockade alone, combined sympathetic and parasympathetic blockade, and ganglionic blockade. Sympathetic blockade alone left large HR changes within the CS-US interval, with CR deceleration often facilitated relative to pre-drug. These effects were similar across the full range of CS-US intervals employed, and whether the pre-drug form of the cardiac CR was monophasic or biphasic. The unconditional HR response (UCR) to shock was similar in form to the CR, consisting of an initial accelerative and subsequent decelerative component, and was similarly affected by the pharmacological agents, although the UCR was less suppressed by the drugs.

3\. **Davidson, R. J.** (State University of New York at Purchase), **Schwartz, G. E.** (Yale University), **Saron, C., Bennett, J.** (State University of New York at Purchase), **& Goleman, D. J. Frontal versus parietal EEG asymmetry during positive and negative affect.** A variety of data suggest that positive and negative affect may be differentially lateralized in the human brain. This report describes an experiment which explored the differential effect of positive versus negative affect on parietal and frontal brain regions. Seventeen right-handed subjects were exposed to portions of a television show judged to vary in emotional content. Subjects were asked to press down on a pressure-sensitive knob according to how much they disliked and to let up according to how much they liked the program, with hand use counterbalanced across subjects. These pressure changes, along with EEG filtered for 8–13 Hz recorded from F_4, F_3, P_4 and P_3 referenced to C_z were digitized and printed every 30 sec. Two epochs representing the most positively and most negatively judged segments were chosen for analysis on the basis of each subject's ratings and were compared on parietal and frontal asymmetry as reflected in the ratio R−L/R+L alpha. The results revealed a significant Region (Frontal vs Parietal) × Affective Valence (positive vs negative) interaction. During positive affect, the frontal leads display greater relative left hemisphere activation compared with negative affect and vice versa. Parietal asymmetry does not discriminate between these conditions, but does show right hemisphere activation during both.

A second experiment was conducted (Schwartz, Davidson, & Saron) during which self-generated positive and negative affective imagery served as the main inde-

3. **Davidson, R. J.** (State University of New York at Purchase), **Schwartz, G. E.** (Yale University), **Saron, C., Bennett, J.** (State University of New York at Purchase), **& Goleman, D. J. Frontal versus parietal EEG asymmetry during positive and negative affect.** A variety of data suggest that positive and negative affect may be differentially lateralized in the human brain. This report describes an experiment which explored the differential effect of positive versus negative affect on parietal and frontal brain regions. Seventeen right-handed subjects were exposed to portions of a television show judged to vary in emotional content. Subjects were asked to press down on a pressure-sensitive knob according to how much they disliked and to let up according to how much they liked the program, with hand use counterbalanced across subjects. These pressure changes, along with EEG filtered for 8–13 Hz recorded from F_4, F_3, P_4 and P_3 referenced to C_z were digitized and printed every 30 sec. Two epochs representing the most positively and

Left Hypofrontality in Depression

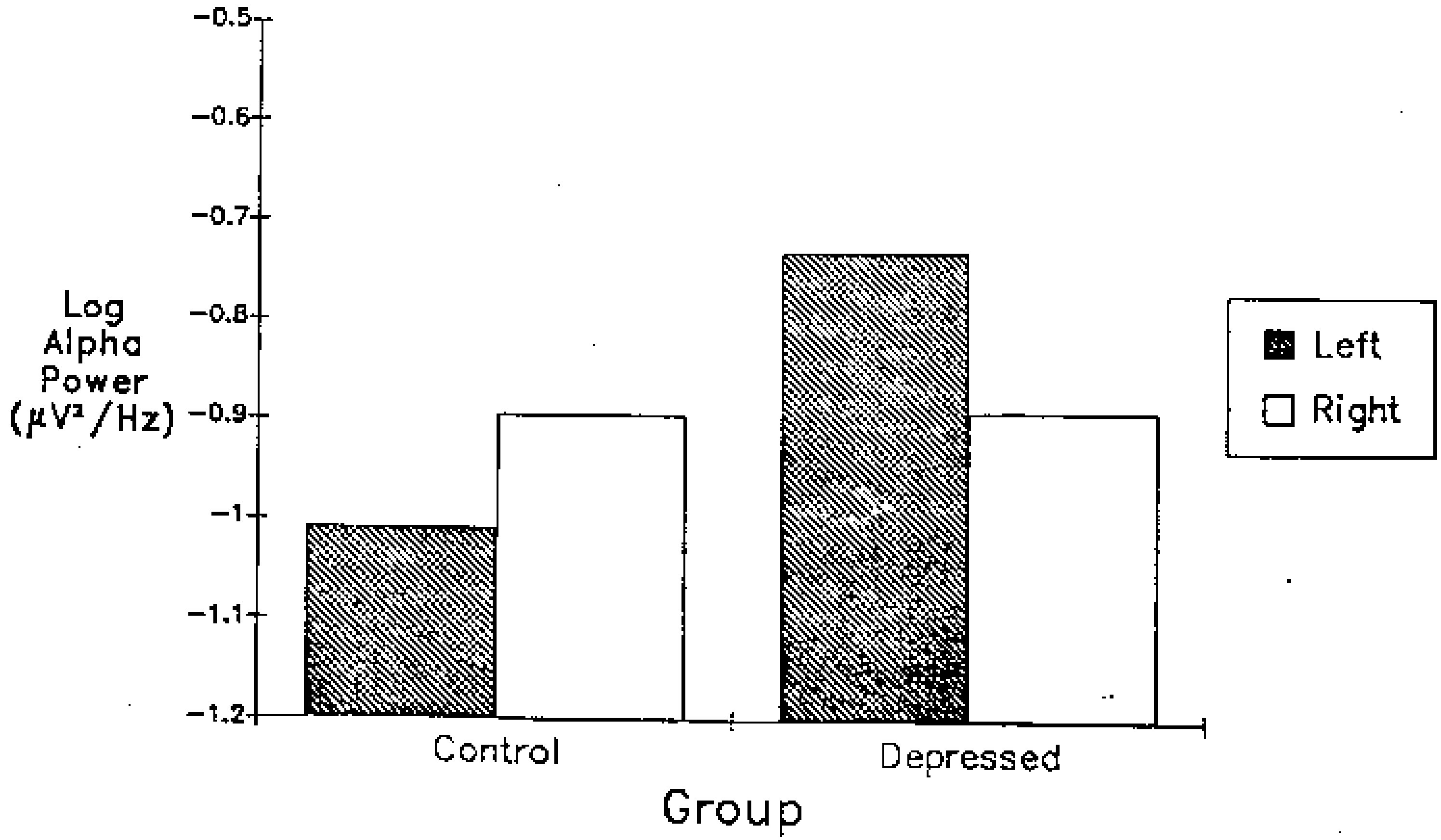
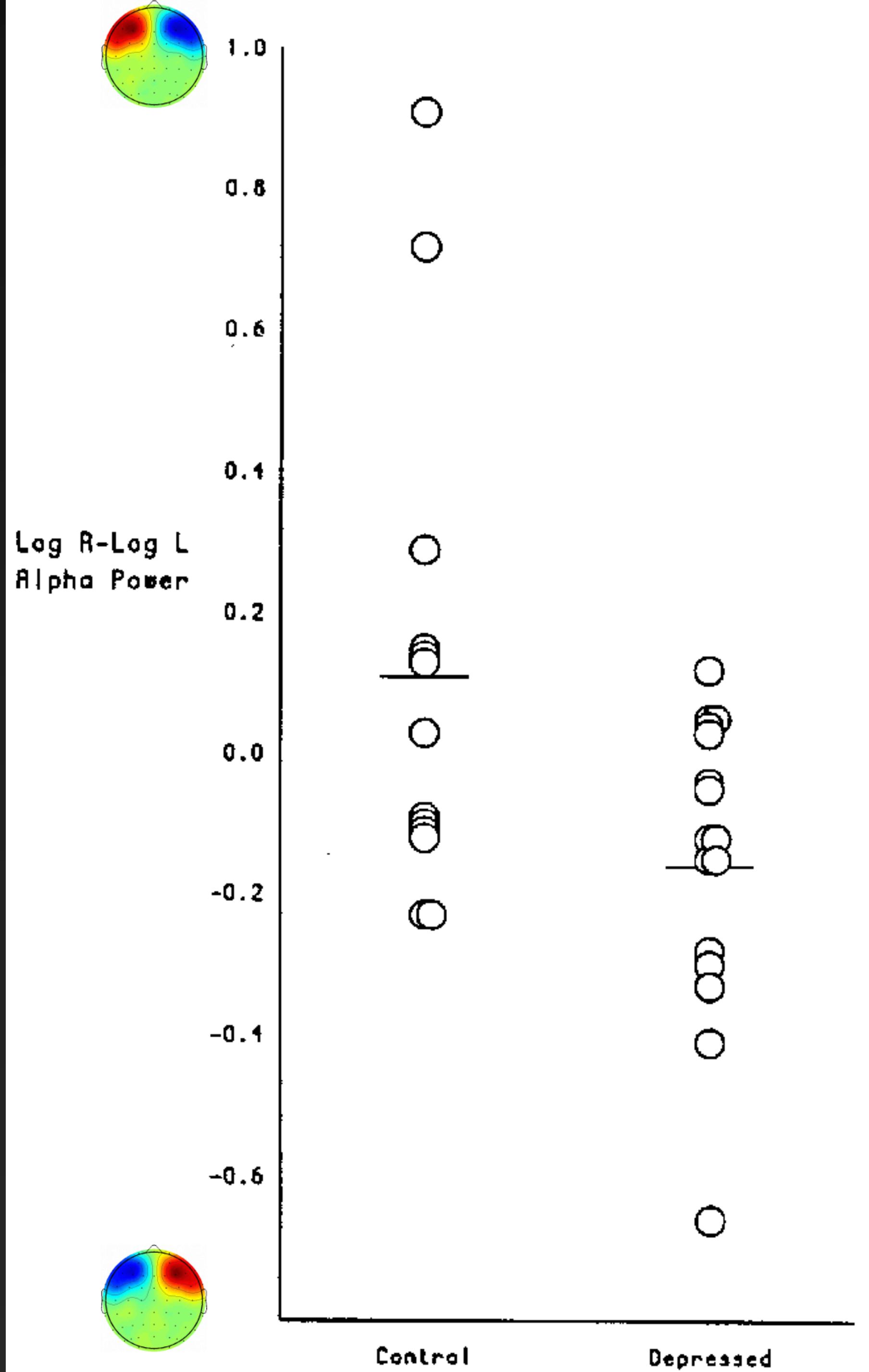


Figure 1. Mean log-transformed alpha (8–13 Hz) power (in $\mu V^2/Hz$) for Cz-referenced electroencephalograms (averaged across eyes-open and eyes-closed baselines), split by group and hemisphere, for the mid-frontal region. (Decreases in alpha power are indicative of increased activation.)

Henriques & Davidson (1991); see also, Allen et al. (1993), Gotlib et al. (1998); Henriques & Davidson (1990); Reid Duke and Allen (1998); Shaffer et al (1983)

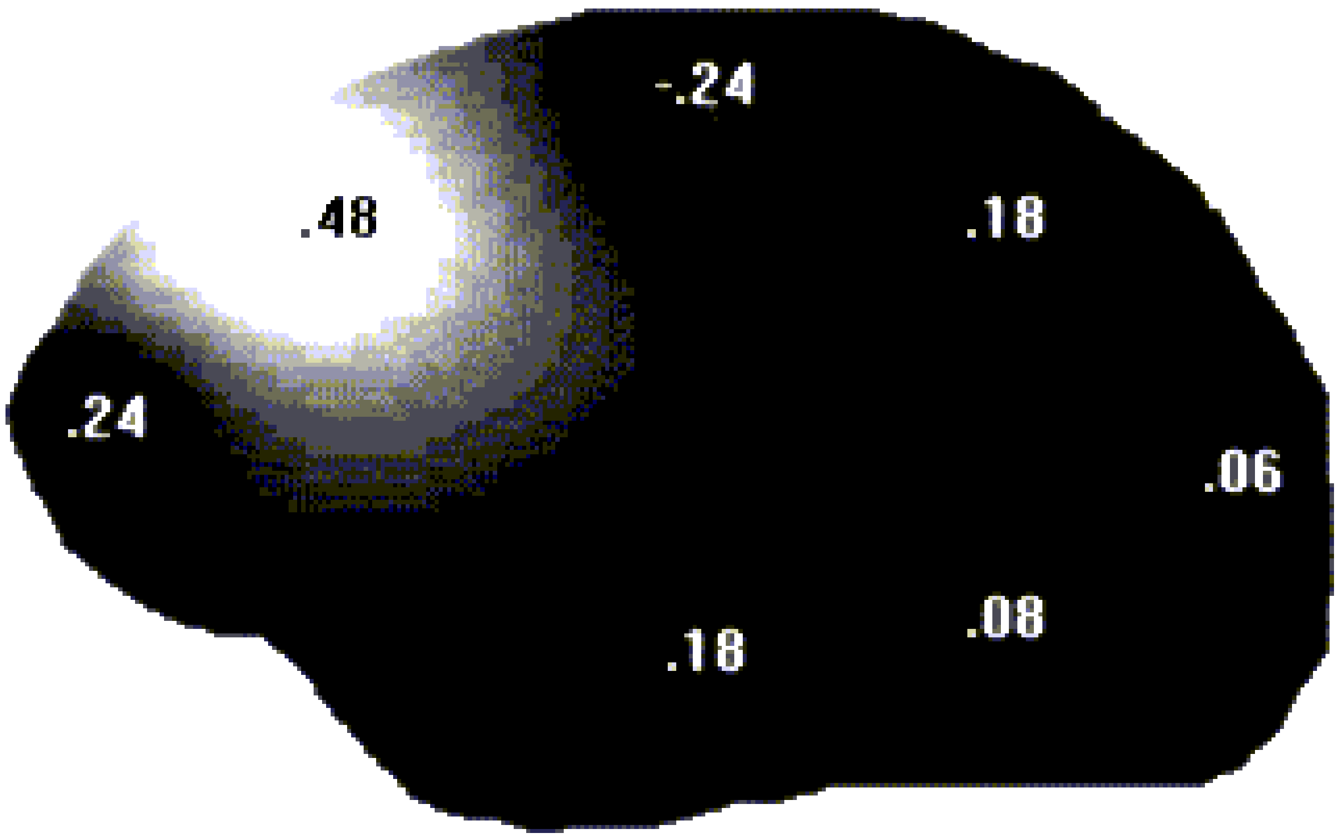
Individual Subjects' Data



Henriques & Davidson (1991)

Valence Vs Motivation

- Valence hypothesis
  - Left frontal is positive
  - Right frontal is negative
- Motivation hypothesis
  - Left frontal is Approach
  - Right frontal is Withdrawal
- Hypotheses are confounded
  - With possible exception of Anger



Correlation with alpha asymmetry (ln[right]-ln[left]) and trait anger. Positive correlations reflect greater left activity (less left alpha) is related to greater anger.

After Harmon-Jones and Allen (1998).

State Anger and Frontal Asymmetry

- Would situationally-induced anger relate to relative left frontal activity?

Harmon-Jones & Sigelman, *JPSP*, 2001

Method

- Cover story: two perception tasks – person perception & taste perception
- Person perception task – participant writes essay on important social issue; another ostensible participant gives written feedback on essay
- Feedback is neutral or insulting
  - negative ratings + "I can't believe an educated person would think like this. I hope this person learns something while at UW."

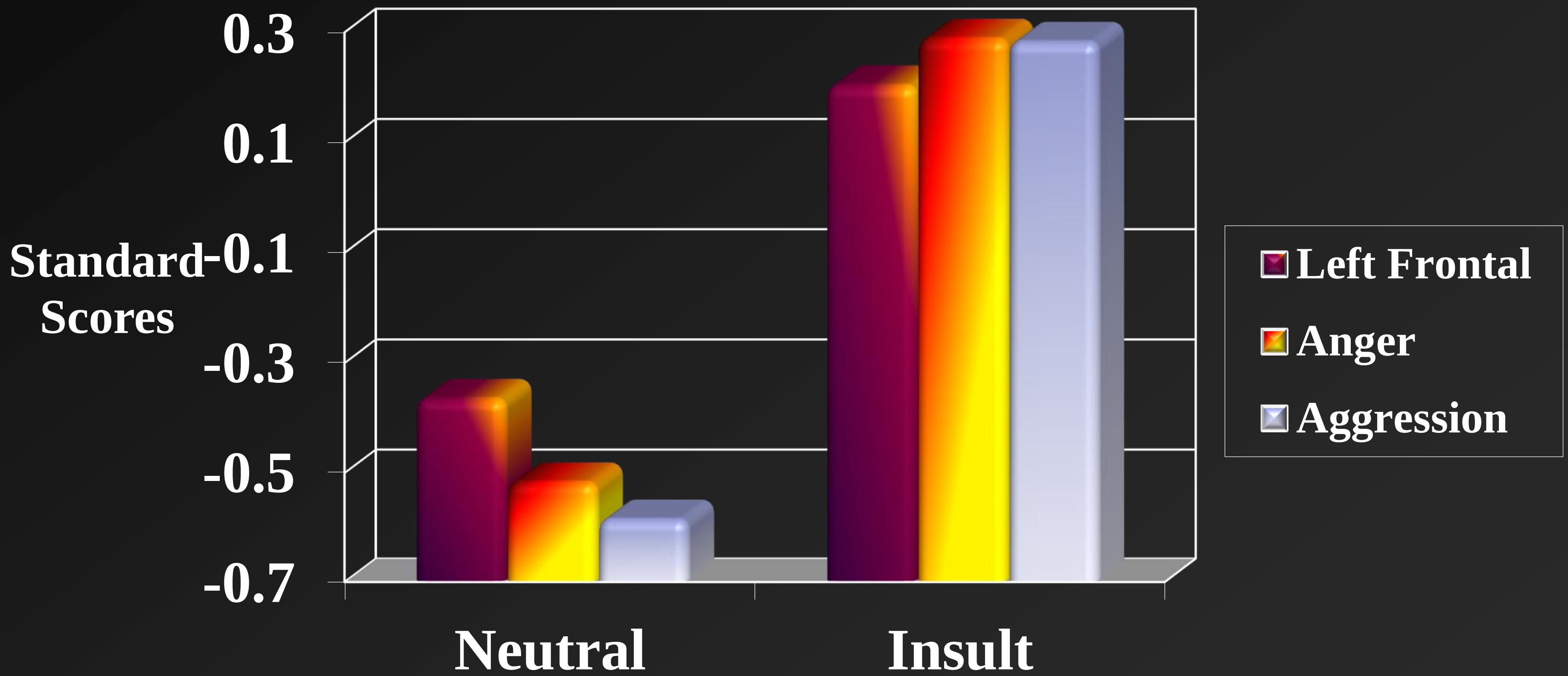
Harmon-Jones & Sigelman, *JPSP*, 2001

- Record EEG immediately after feedback
- Then, taste perception task, where participant selects beverage for other participant, "so that experimenter can remain blind to type of beverage."
- 6 beverages; range from pleasant-tasting (sweetened water) to unpleasant-tasting (water with hot sauce)
  - Aggression measure

Harmon-Jones & Sigelman, *JPSP*, 2001

Harmon-Jones & Sigelman, *JPSP*, 2001

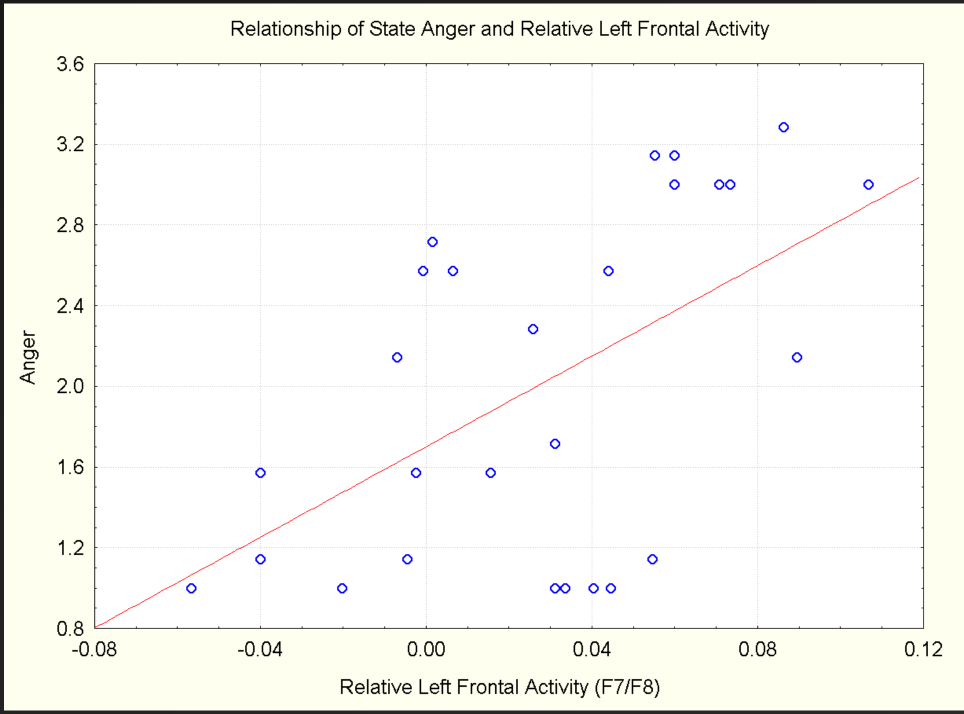
Relative Left Frontal, Anger, & Aggression as a Function of Condition



Harmon-Jones & Sigelman, *JPSP*, 2001

Frontal EEG asymmetry predicts Anger and Agression

- Not in Neutral condition … no relationship
- Strongly in Insult condition
  - r = .57 for anger
  - r = .60 for aggression
  - Note: partial r adjusting for baseline indiv diffs in asymmetry and affect



Harmon-Jones & Sigelman, *JPSP*, 2001

Manipulation of EEG
Peterson, Shackman, Harmon-Jones (2008)

- Hand contractions to activate contralateral premotor cortex
- Insult about essay (similar to Harmon-Jones & Sigelman, *JPSP*, 2001) followed by chance to give aversive noise blasts to the person who insulted them
- Hand contractions:
  - altered frontal asymmetry as predicted
  - Altered subsequent aggression (noise blasts)
- Asymmetry duruing hand contractions predicted aggression

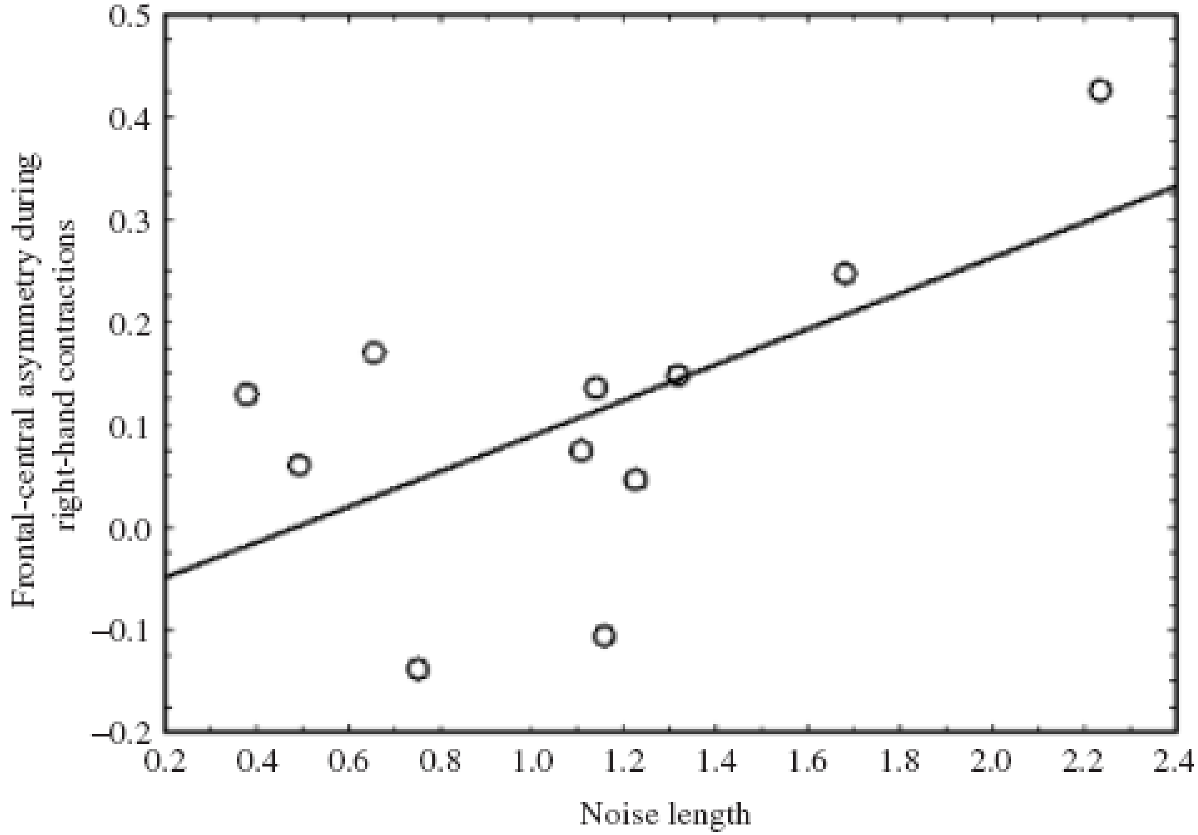


Figure 1. Relation between noise length and frontal-central asymmetry during right-hand contractions. Higher asymmetry scores indicate greater relative left than right activation.

Peterson, Shackman, Harmon-Jones (2008)

The BAS/BFS/Approach System

- **sensitive to signals of**
  - **conditioned reward**
  - **nonpunishment**
  - **escape from punishment**
- **Results in:**
  - **driven pursuit of appetitive stimuli**
  - **appetitive or incentive motivation**
  - **Decreased propensity for depression (Depue & Iacono, 1989; Fowles 1988)**

Motivational Styles and Depression

Behavioral Activation Scale

- Reward Responsiveness

  When I see an opportunity for something I like, I get excited right away.

- Drive

  I go out of my way to get things I want.

- Fun Seeking

  I'm always willing to try something new if think it will be fun.

Carver & White, 1994

Motivational Styles and Depression

$r = .45$

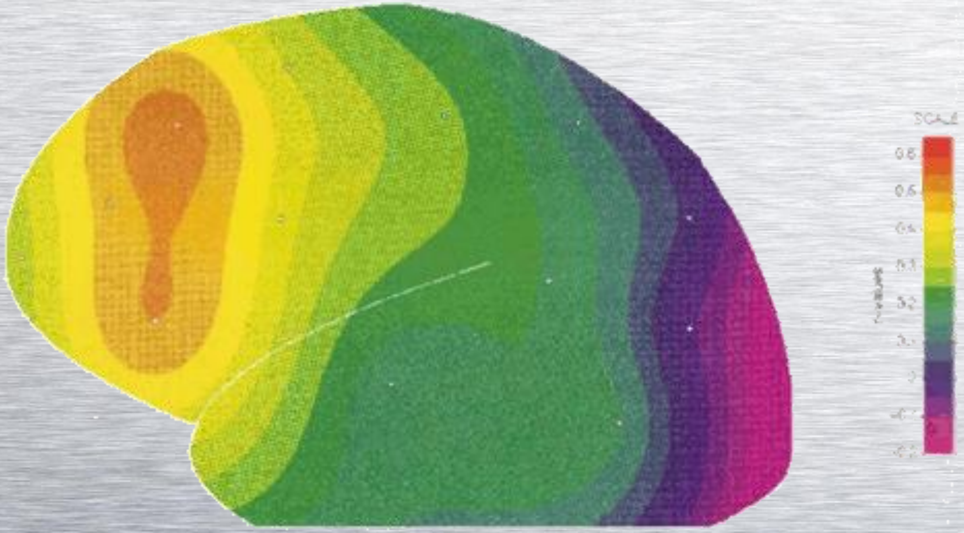
Mid-Frontal Asymmetry and BAS Scores

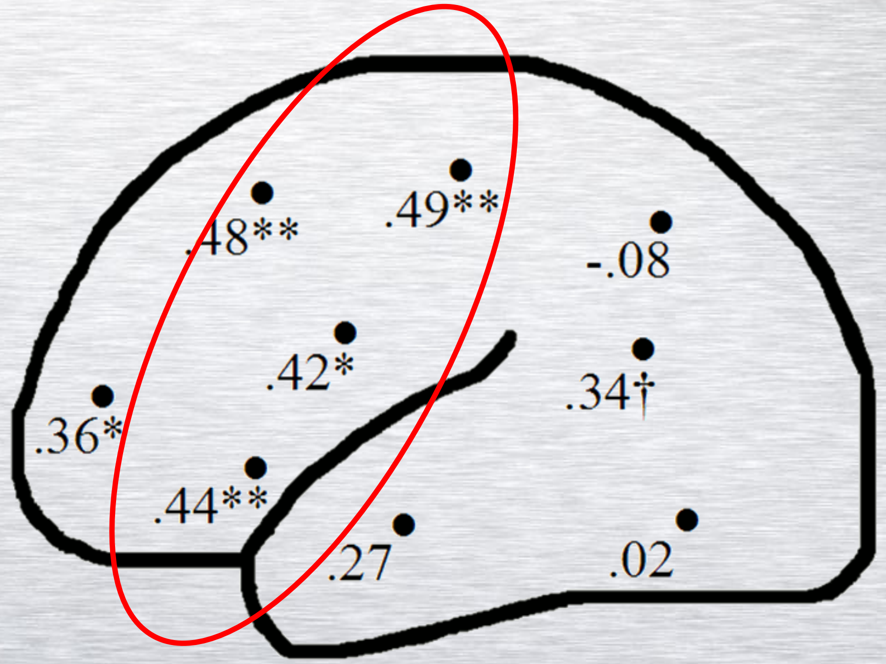
Mid-Frontal Asymmetry and PA Scores

$r = .00$

Harmon-Jones & Allen, 1997

Motivational Styles and Depression Replications





Sutton & Davidson, 1997

Coan & Allen, 2003

Correlations with alpha asymmetry (ln[right]-ln[left]) and self-reported BAS scores (right) or BAS-BIS (left).

Positive correlations reflect greater left activity (less left alpha) is related to greater BAS scores or greater BAS-BIS difference

L>R Activity (R>L Alpha) characterizes:

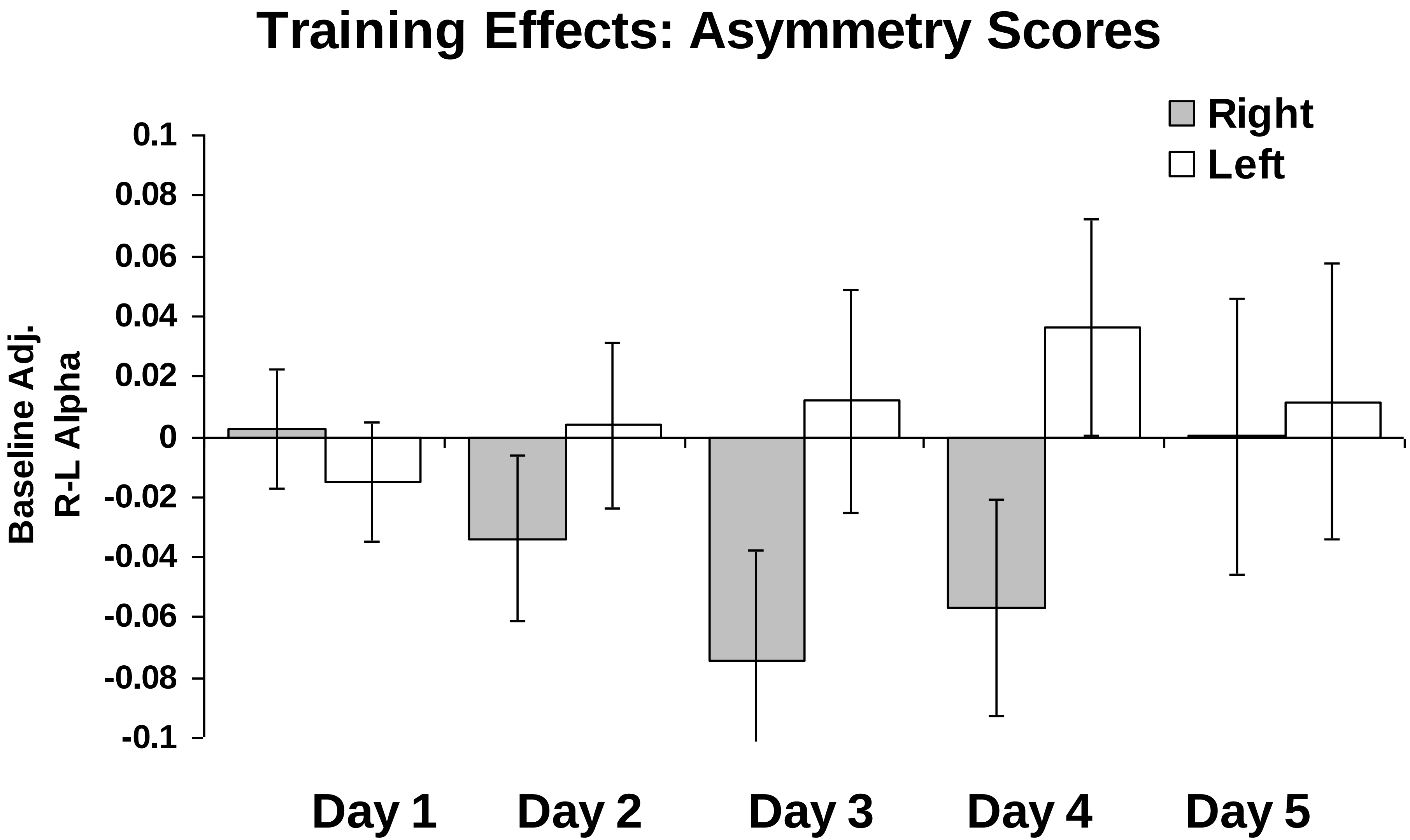
- an approach-related motivational style (e.g. Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997)
- higher positive affect (e.g. Tomarken, Davidson, Wheeler, & Doss, 1992)
- higher trait anger (e.g. Harmon-Jones & Allen, 1998)
- lower shyness and greater sociability (e.g. Schmidt & Fox, 1994; Schmidt, Fox, Schulkin, & Gold, 1999)

R>L Activity (L>R Alpha) characterizes:

- depressive disorders and risk for depression (e.g. Allen, Iacono, Depue, & Arbisi, 1993; Gotlib, Ranganath, & Rosenfeld, 1998; Henriques & Davidson, 1990; Henriques & Davidson, 1991 but see also Reid, Duke, & Allen, 1998
- certain anxiety disorders (e.g. Davidson, Marshall, Tomarken, & Henriques, 2000; Wiedemann et al., 1999)

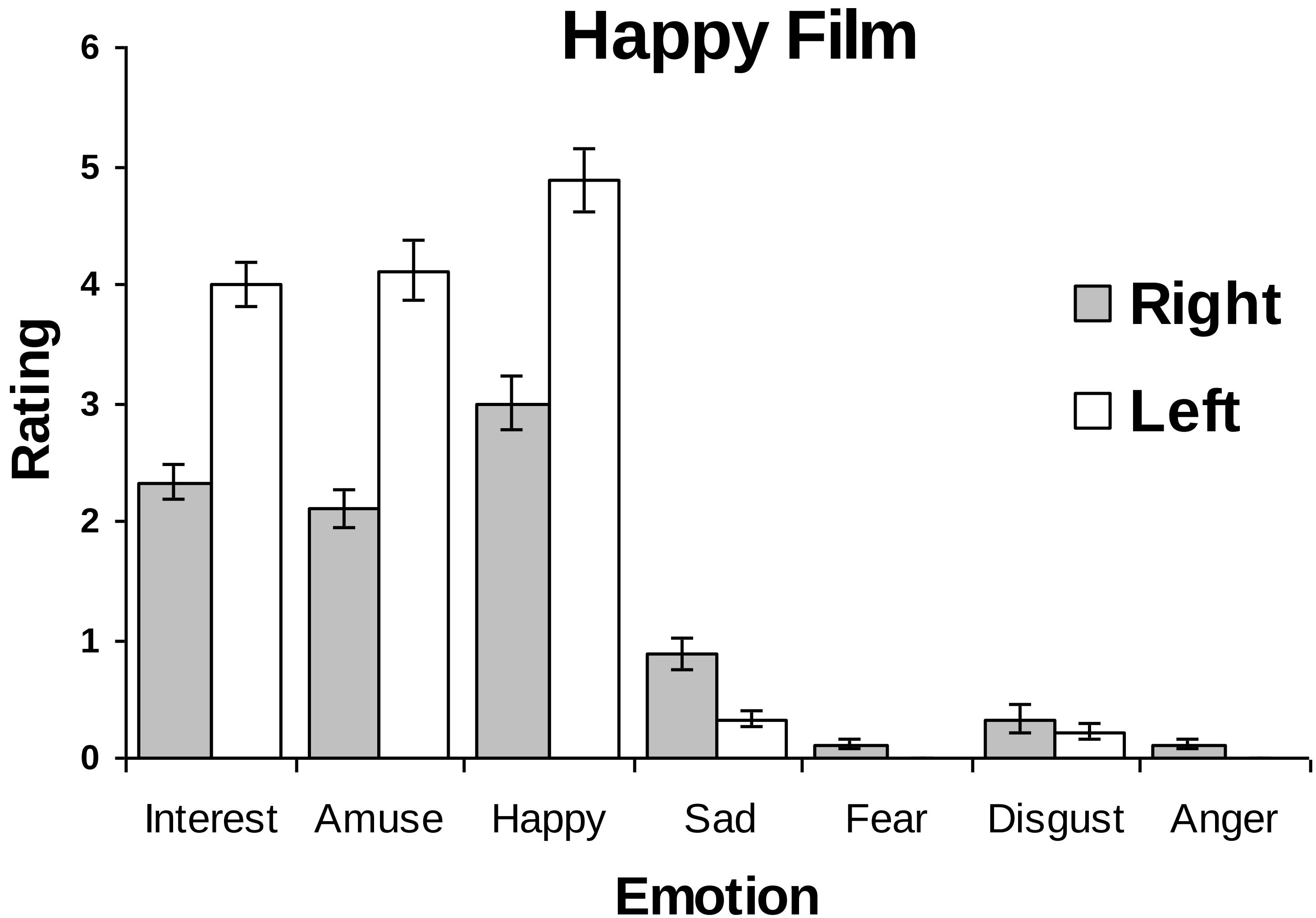
Correlations ≠ Causality

- Study to manipulate EEG Asymmetry
- Five consecutive days of biofeedback training (R vs L)
  - Nine subjects trained “Left”; Nine “Right”
  - Criterion titrated to keep reinforcement equal
- Tones presented when asymmetry exceeds a threshold, adjusted for recent performance
- Films before first training and after last training



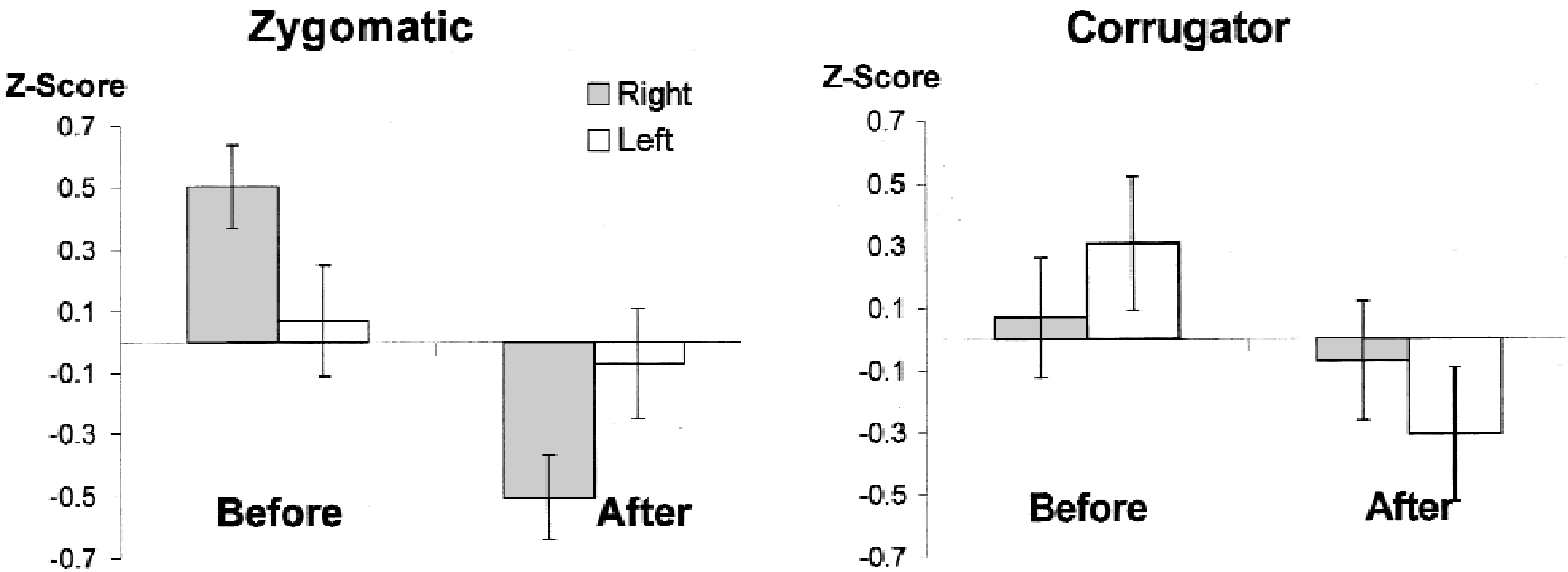
Manipulation of EEG asymmetry with biofeedback produced differential change across 5 days of training; Regression on Day 5

From Allen, Harmon-Jones, and Cavender (2001)



Despite no differences prior to training, following manipulation of EEG asymmetry with biofeedback subjects trained to increase left frontal activity report greater positive affect.

From Allen, Harmon-Jones, and Cavender (2001)

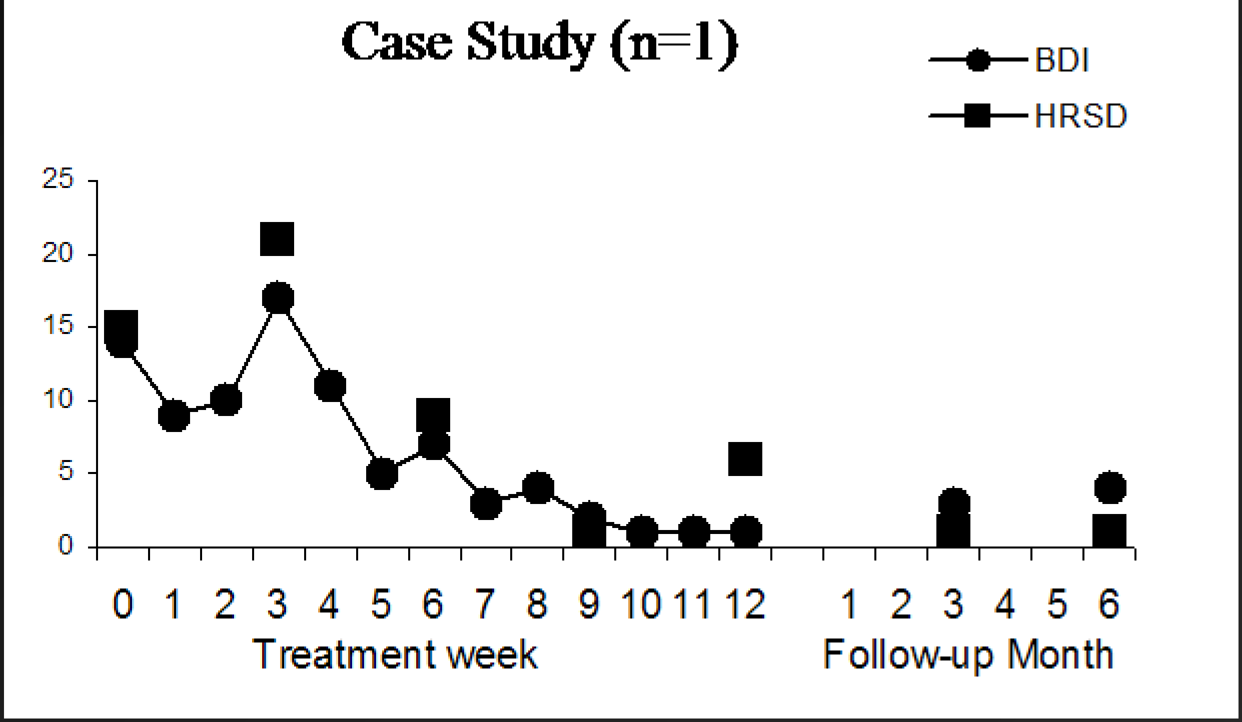


From Allen, Harmon-Jones, and Cavender (2001)

Manipulation of Asymmetry using Biofeedback

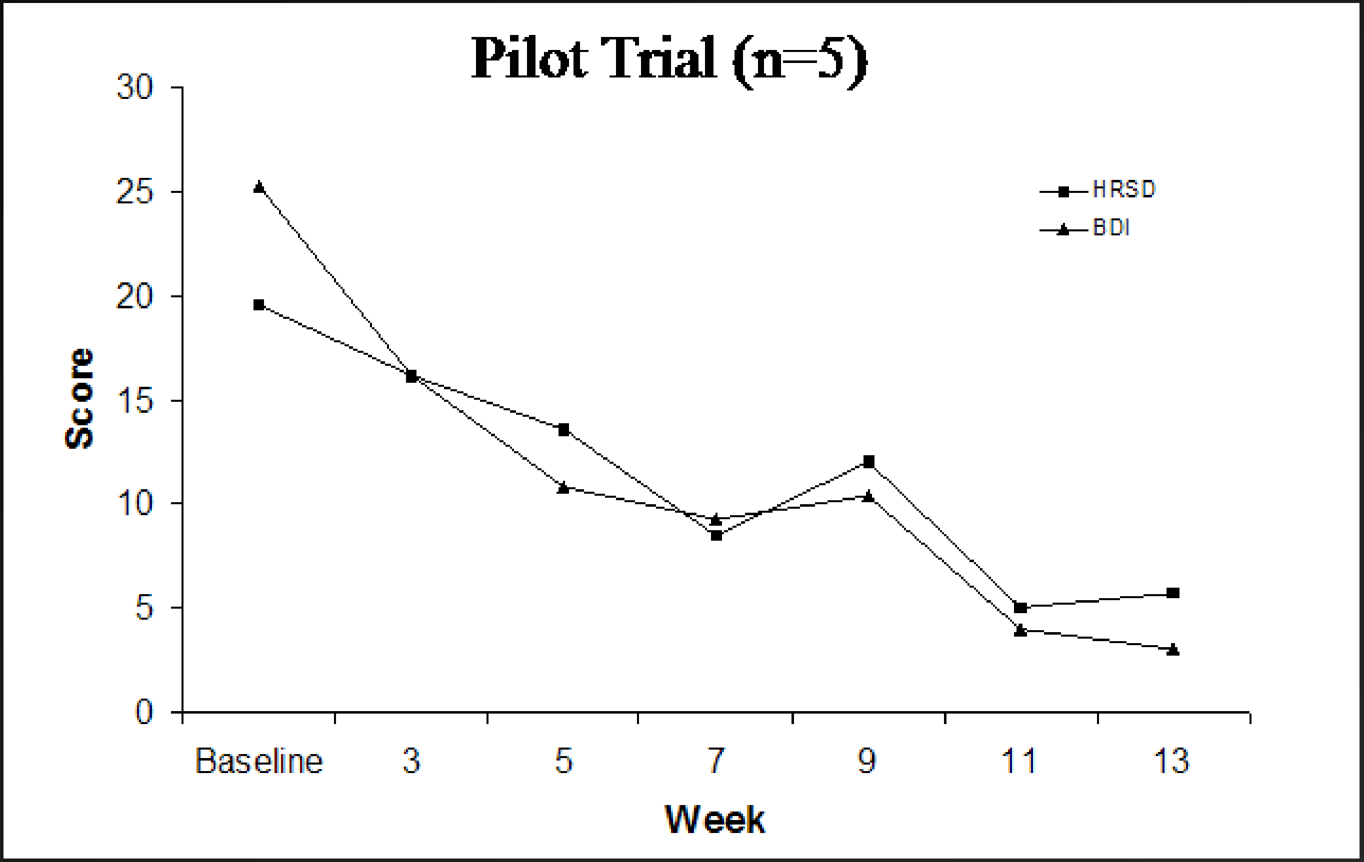
- Phase 1: Demonstrate that manipulation of EEG asymmetry is possible
- Phase 2: Determine whether EEG manipulation has emotion-relevant consequences
- Phase 3: Examine whether EEG manipulation produces clinically meaningful effects
- Phase 4: Conduct efficacy trial

Phase 3a



Biofeedback provided 3 times per week for 12 weeks

Phase 3b



"Open Label" pilot trial, with biofeedback provided 3 times per week for 12 weeks

Phase 4: Randomized Control Trial

- Depressed subjects ages 18-60 to be recruited through newspaper ads
- Ad offers treatment for depression but does not mention biofeedback
- Participants meet DSM-IV criteria for Major Depressive Episode (nonchronic)

Design

- Contingent-noncontingent yoked partial crossover design
- Participants randomly assigned to:
    - *Contingent Biofeedback*: tones presented in response to subject's EEG alpha asymmetry
    - *Noncontingent Yoked*: tones presented that another subject had heard, but tones not contingent upon subject's EEG alpha asymmetry
- Treatments 3 times per week for 6 weeks
- After 6 weeks, all subjects receive contingent biofeedback 3 times per week for another 6 weeks

Results

State Changes

- Infants
  - Stanger/Mother paradigm (Fox & Davidson, 1986)
  - Sucrose Vs water (Fox & Davidson, 1988)
  - Films of facial expressions (Jones & Fox, 1992; Davidson & Fox, 1982)
- Primates
  - Benzodiazepines increases LF (Davidson et al., 1992)

State Changes

- Adults
  - Spontaneous facial expressions (Ekman & Davidson, 1993; Ekman et al., 1990; Davidson et al., 1990)
  - Directed facial actions (Coan, Allen, & Harmon-Jones, 2001)

EEG responds to directed facial actions

From Coan, Allen, and Harmon-Jones (2001)

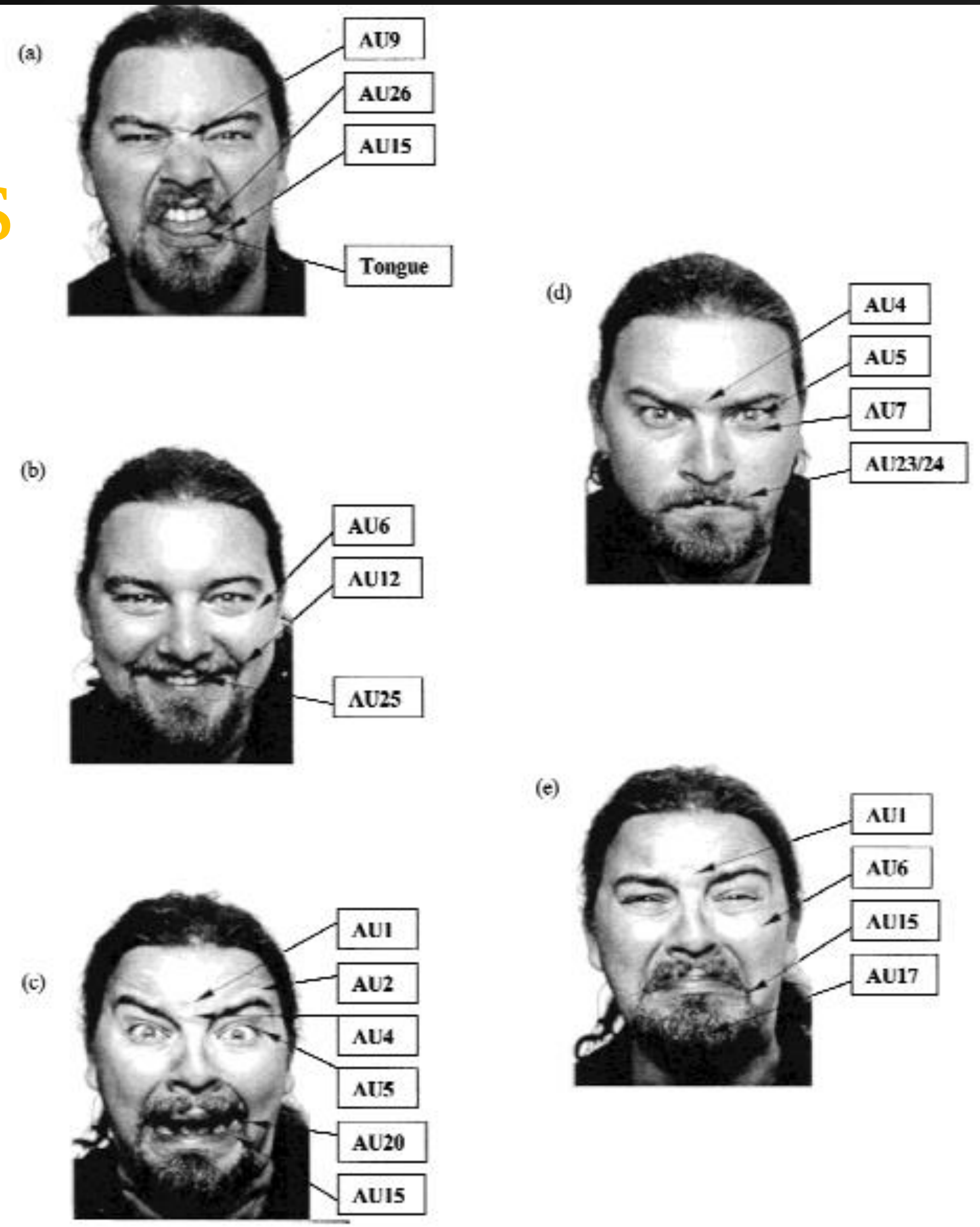
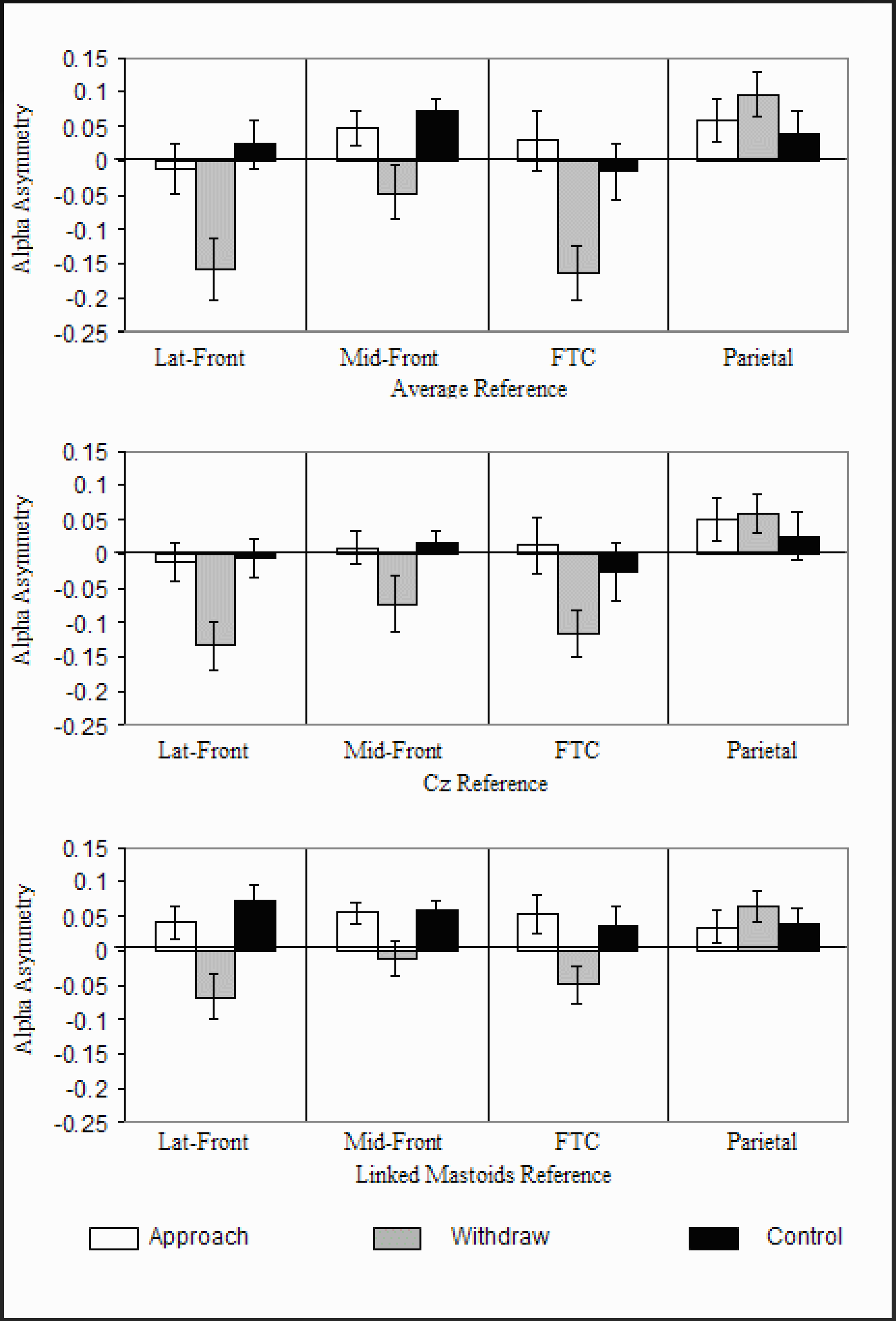


Figure 1. Muscle movements in the full face conditions: (a) disgust, activating AUs 9 (nose wrinkler), 15 (lip corner depressor), 26 (jaw drop), and the "tongue show;" (b) joy, activating AUs 6 (cheek raiser), 12 (lip corner puller), and 25 (lips part); (c) fear, activating AUs 1 (inner brow raiser), 2 (outer brow raiser), 4 (brow lowerer), 5 (upper lid raiser), 15 (lip corner depressor), and 20 (lip stretch); (d) anger, activating AUs 4 (brow lowerer), 5 (upper lid raiser), 7 (lid tightener), 23 (lip tightener), and/or 24 (lip pressor); (e) sadness, activating AUs 1 (inner brow raiser), 6 (cheek raiser), 15 (lip corner depressor), and 17 (chin raiser).

EEG responds to directed facial actions



From Coan, Allen, and Harmon-Jones (2001)

States – how short can they be?

Psychophysiology, *46* (2009), 132–142. Wiley Periodicals, Inc. Printed in the USA.

DOI: 10.1111/j.1469-8986.2008.00759.x

A better estimate of the internal consistency reliability of frontal EEG asymmetry scores

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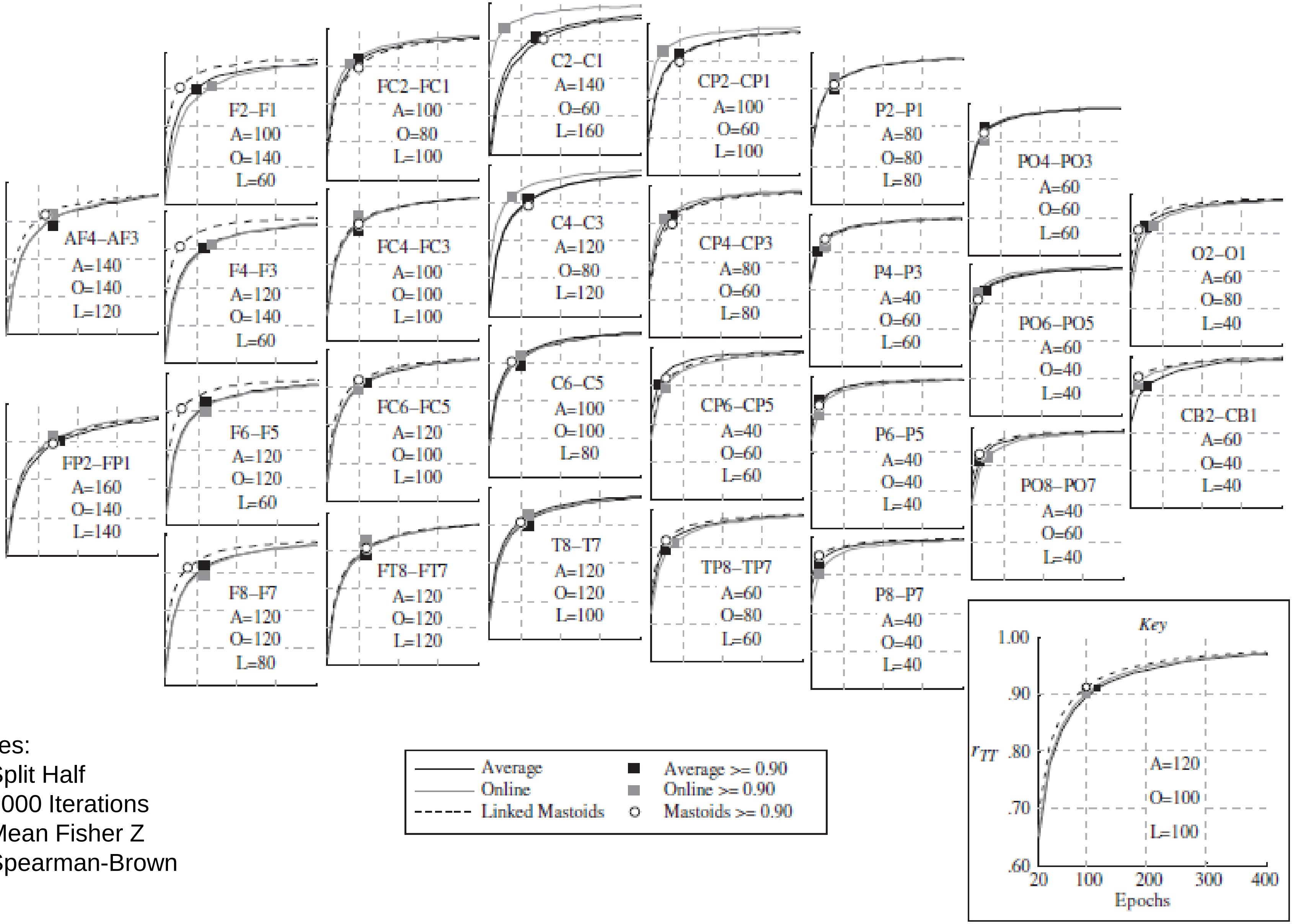
Abstract

Frontal alpha asymmetry is typically computed using alpha power averaged across many overlapping epochs. Previous reports have estimated the internal consistency reliability of asymmetry by dividing resting EEG sessions into segments of equal duration (e.g., 1 min) and treating asymmetry scores for each segment as "items" to estimate internal consistency reliability using Cronbach's alpha. Cronbach's alpha partly depends on the number of items, such that this approach may underestimate reliability by using less than the number of distinct items available. Reliability estimates for resting EEG data in the present study (204 subjects, 8 sessions) were obtained using mean split-half correlations with epoch alpha power as treated as separate items. Estimates at all scalp sites and reference schemes approached .90 with as few as 100 epochs, suggesting the internal consistency of frontal asymmetry is greater than that previously reported.



Notes:

- Split Half
- 1000 Iterations
- Mean Fisher Z
- Spearman-Brown

Figure 1. Estimated internal consistency reliability (r_{TT}) of asymmetry scores for epoch set sizes n ranging from 20 to 400, across average (black), online (gray), and linked-mastoids (dashed) reference derivations and all homologous electrode pairs. Graph markers and table insets indicate the epoch set size n at which the estimated internal consistency reliability coefficient for each reference derivation was greater than or equal to .90.

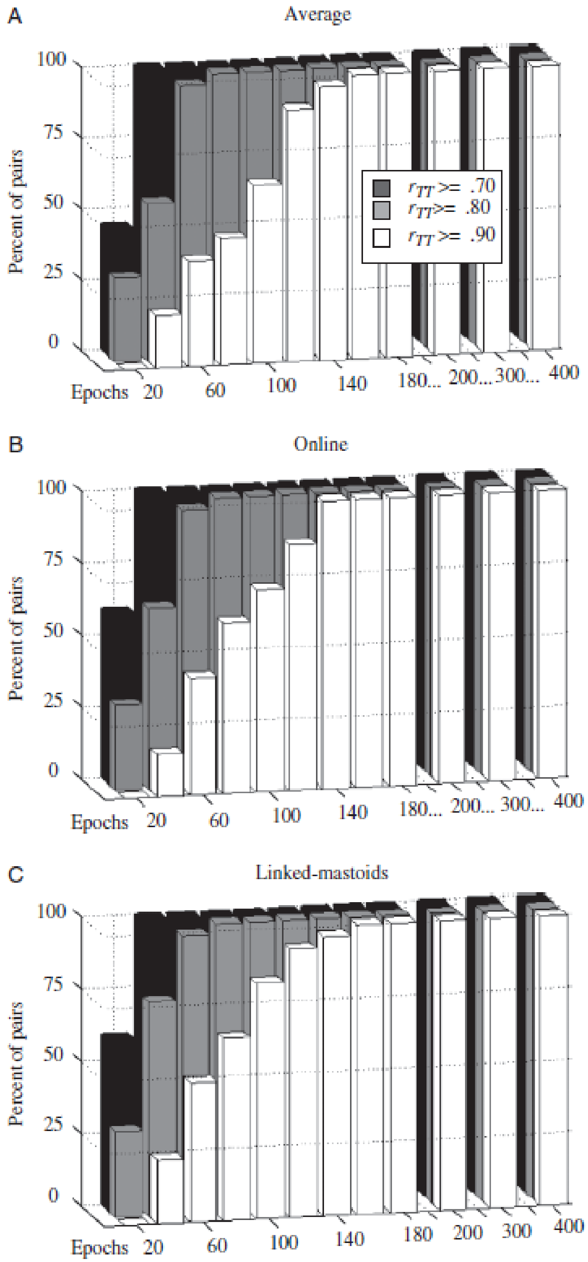


Figure 2. Percentage of homologous electrode pairs in which estimates of internal consistency reliability (r_{TT}) of asymmetry scores were greater than or equal to .70 (white), .80 (light gray), and .90 (dark gray) as a function of epoch set size n and reference derivation.

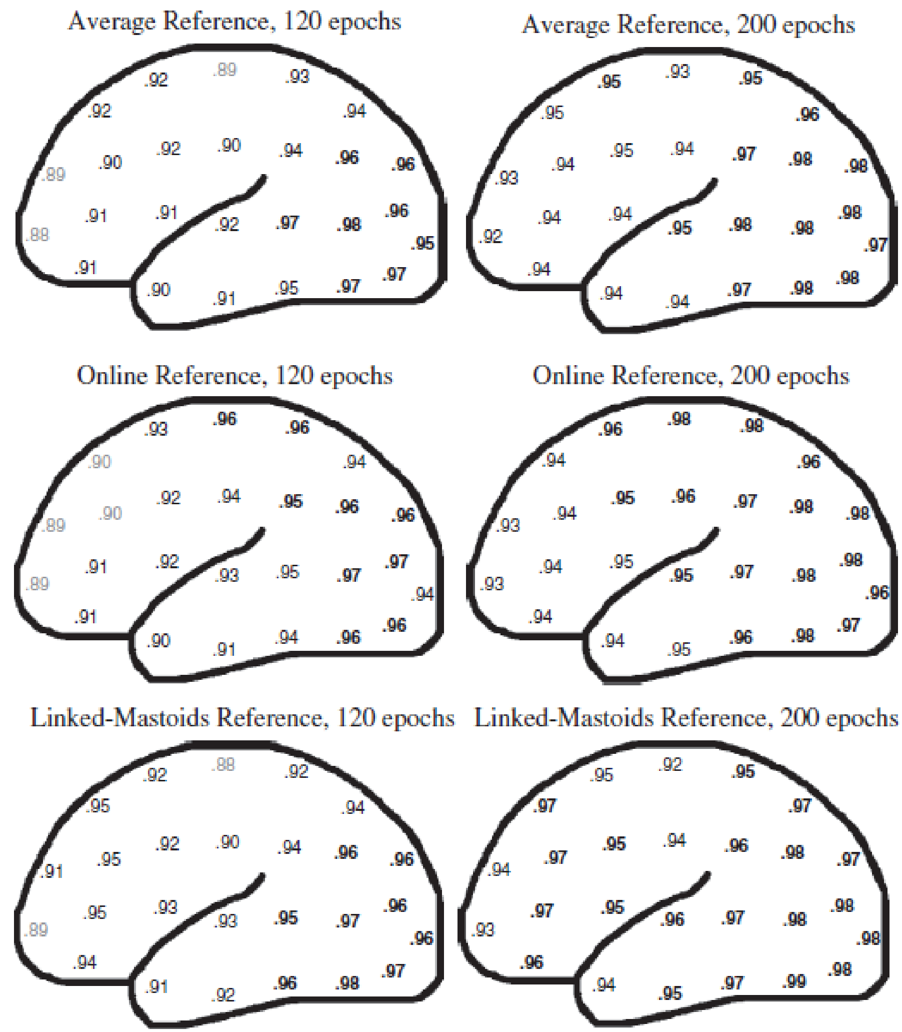


Figure 3. Estimated internal consistency reliability (r_{TT}) of asymmetry scores for epoch set sizes of 120 and 200, with light gray numbers indicating $.85 \leq r_{TT} < .90$ and bold numbers indicating $r_{TT} \geq .95$ (the pair CB2–CB1 was omitted).

State EEG in CIT!

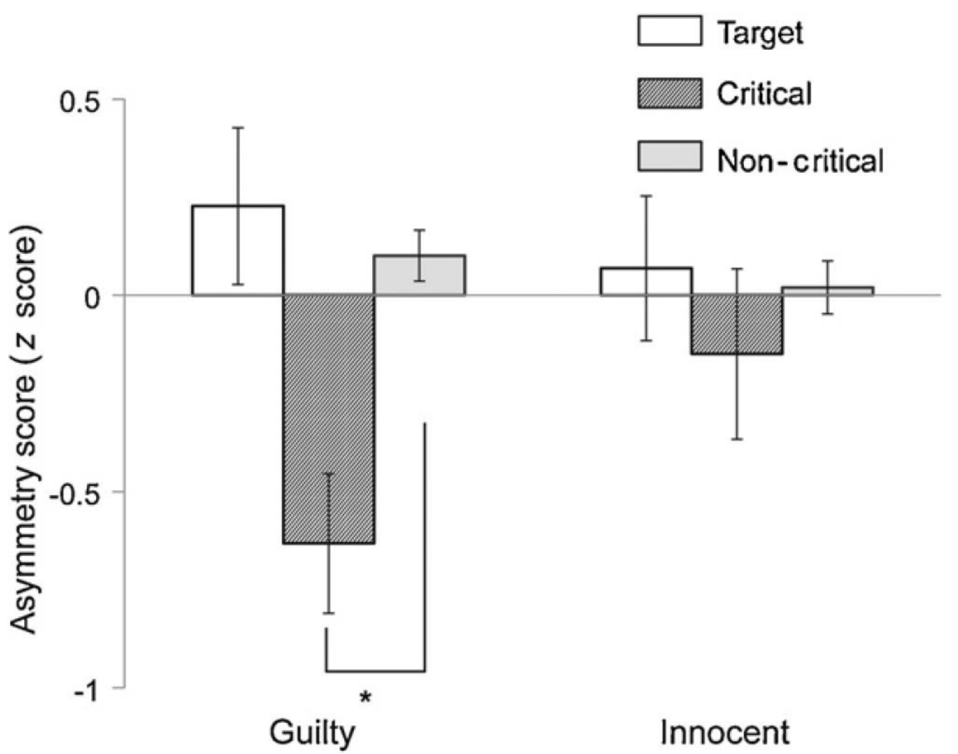


Fig. 2. Grand average frontal EEG asymmetry scores for target, critical, and non-critical items in the guilty and innocent condition. Asymmetry score = ln[F4 alpha power] – ln[F3 alpha power]. Bars depict standard errors. $^{*}p < .05$.

Matsuda, Nittono, & Allen, *Neurosci Letters,* 2013

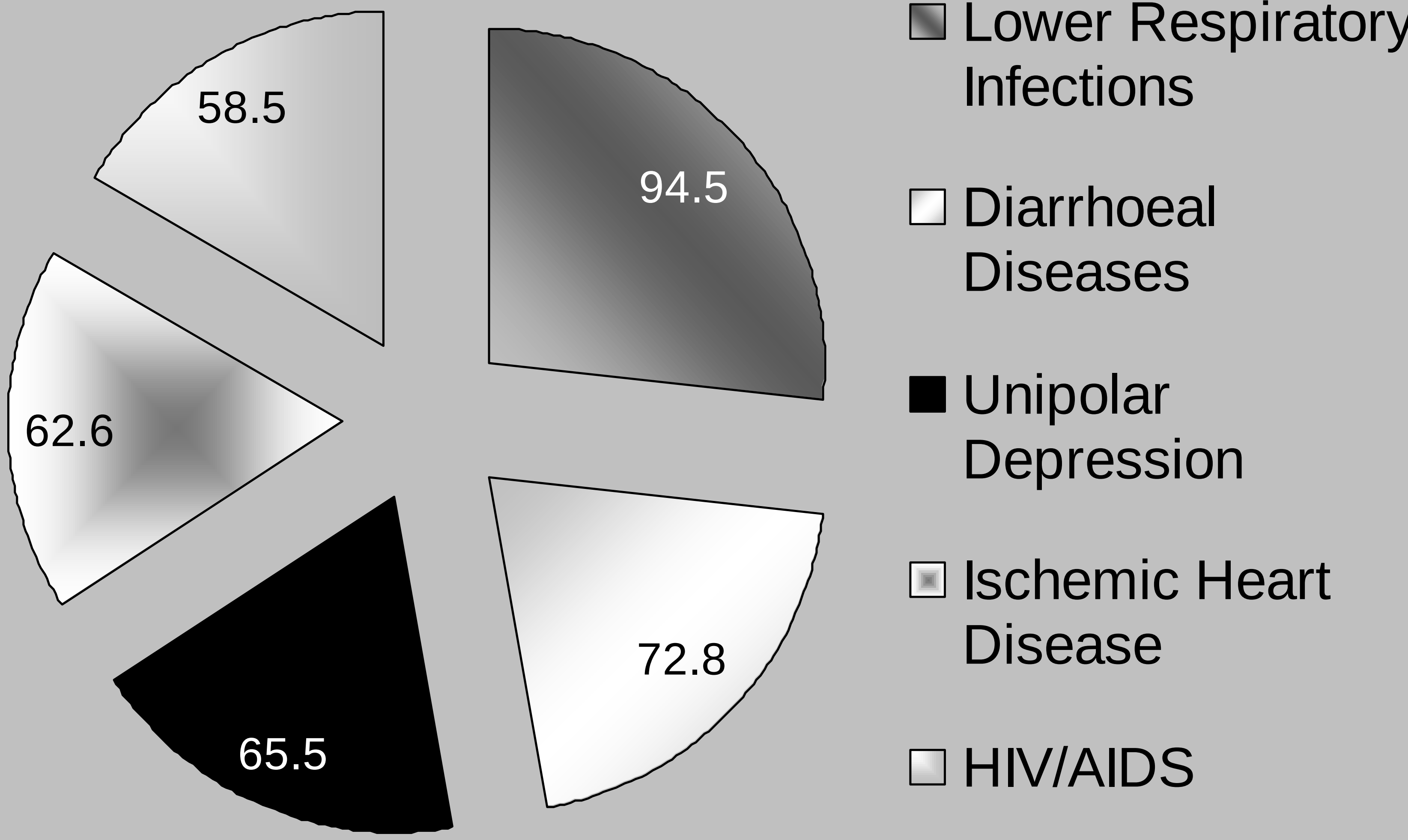
Resting brain asymmetry as an endophenotype for depression

Endophenotypes

- Intermediate-level measure of characteristics related to risk for disorder
- Less complex phenotype for genetic association
- Can include, biochemical and imaging measures, among others
- Desiderata
  - Specificity
  - Heritability
  - State-independence
  - Familial Association
  - Co-segregation within families
  - Predicts development of disorder

Gottesman & Shields, 1972; Gottesman & Gould, 2003; Iacono, 1998

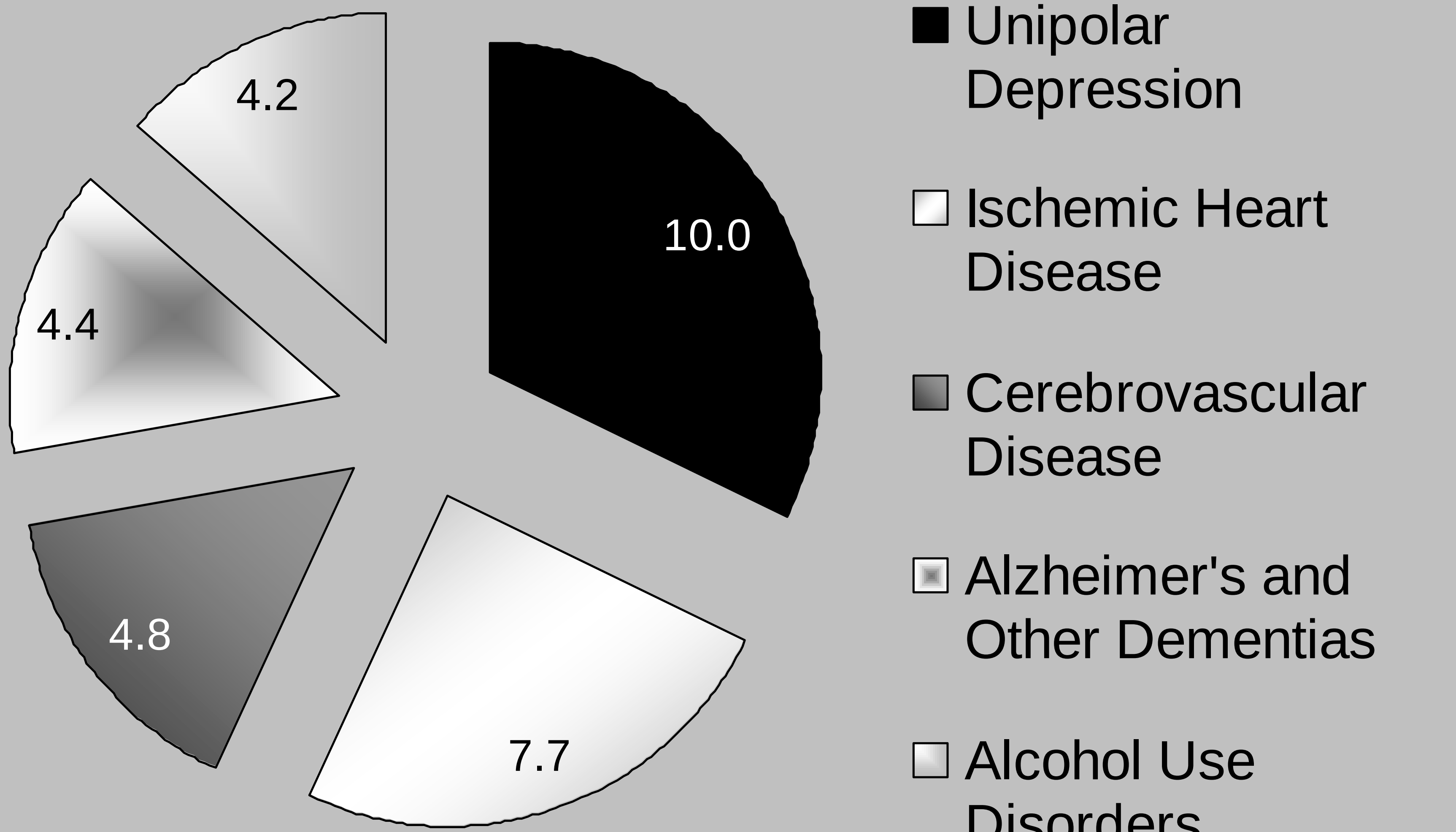
World Disability Adjusted Life Years (Millions)



World Health Organization, 2008

Upper Income Countries

World Disability Adjusted Life Years (Millions)

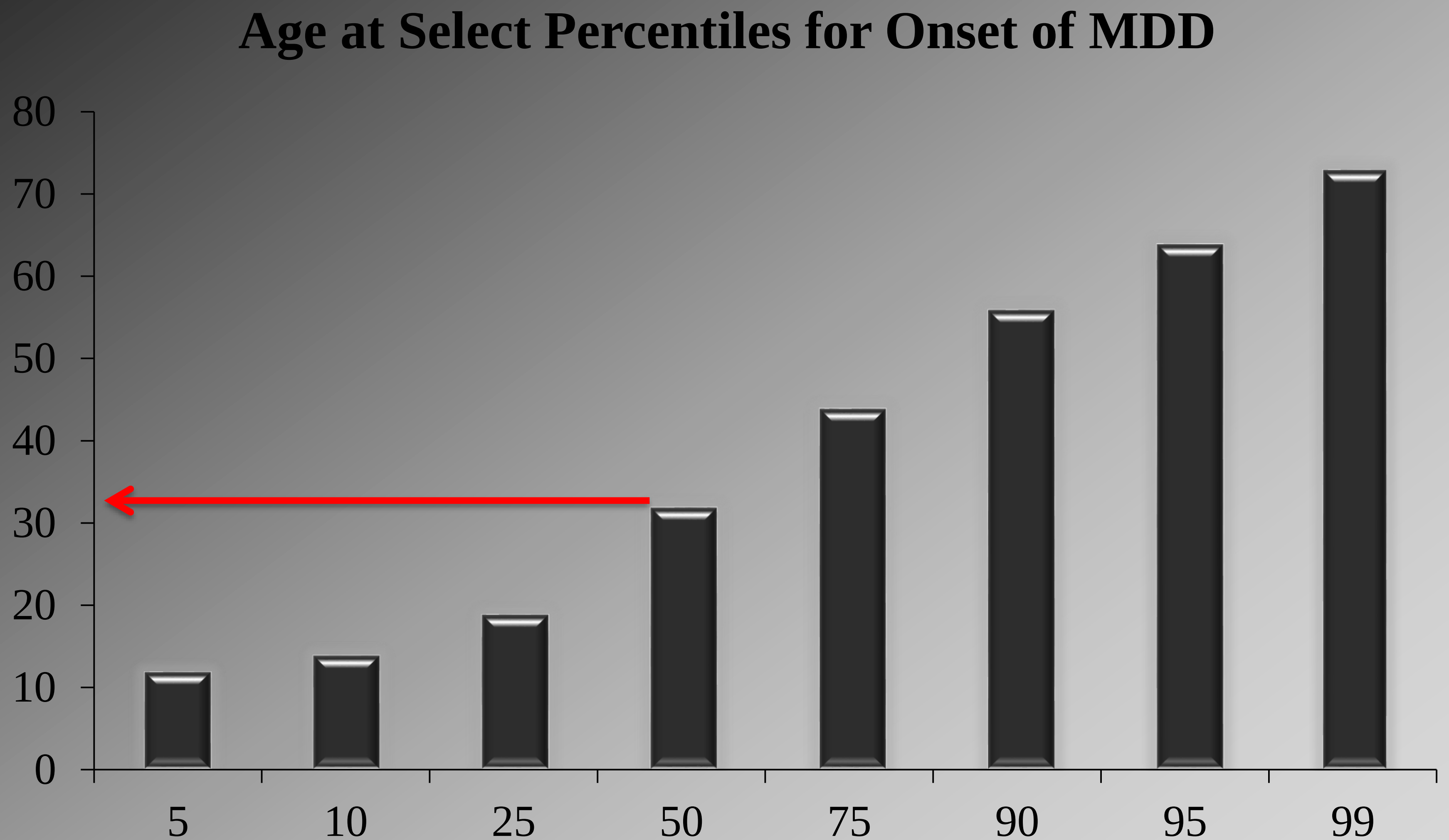


World Health Organization, 2008

Depression as a Heterogeneous Phenotype

- Variable Age of Onset
- Variable Symptom Presentation
- Variable Course
- Variable Response to Treatment

Depression: Variable Age Onset



Data from Kessler et al., Arch Gen Psychiatry, 2005, 62:593-602

Depression: Variable Age Onset

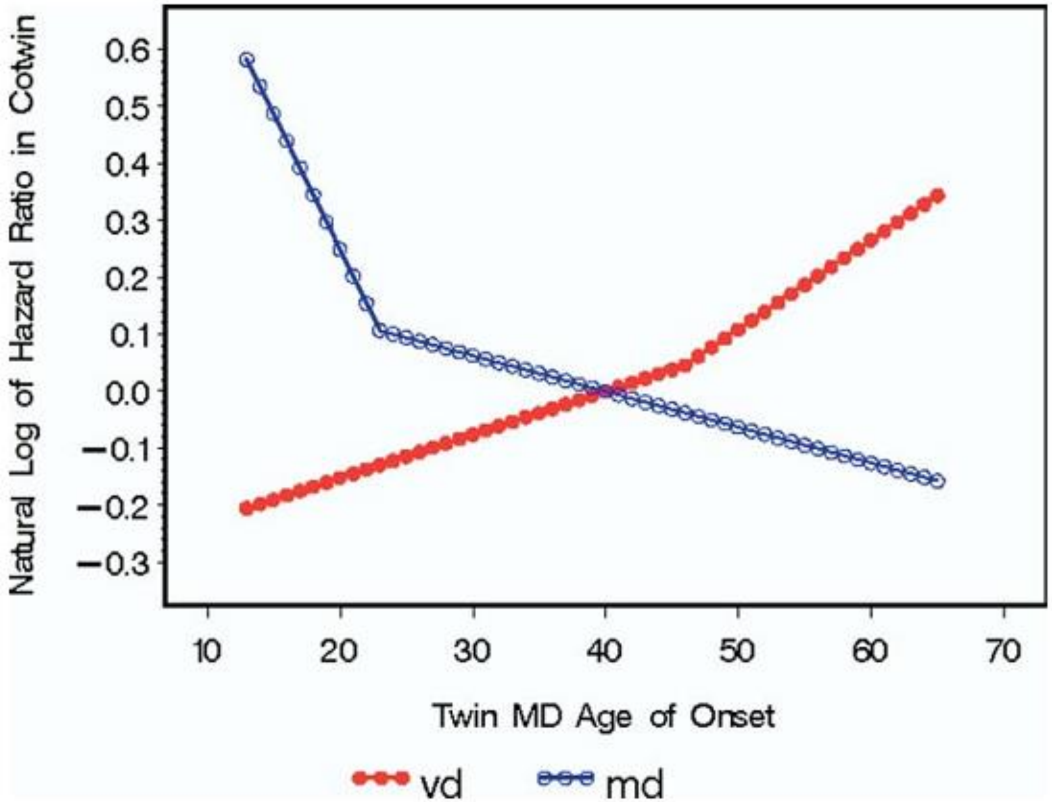
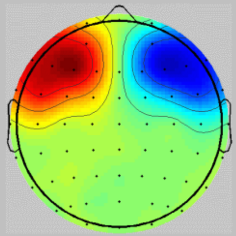


Figure 1. The relationship between the age at onset of major depression (MD) in an affected twin and the natural logarithm of the hazard ratio in the cotwin for MD (in open circles) and vascular disease (VD) (in filled-in circles). These results are obtained from a Cox proportional hazard model controlling for age, sex, and birth cohort. We fitted to these results piecewise models with a single inflection point using a grid search to find the single inflection point that maximized the model's −2 log likelihood.

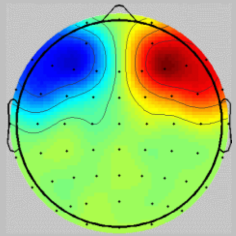
Kendler, Fiske, Gardner, & Gatz, 2009, *Biological Psychiatry*

Treating and Preventing Depression

- Identify those at risk
- Identify factors that place folks at risk
- Develop interventions to address those factors

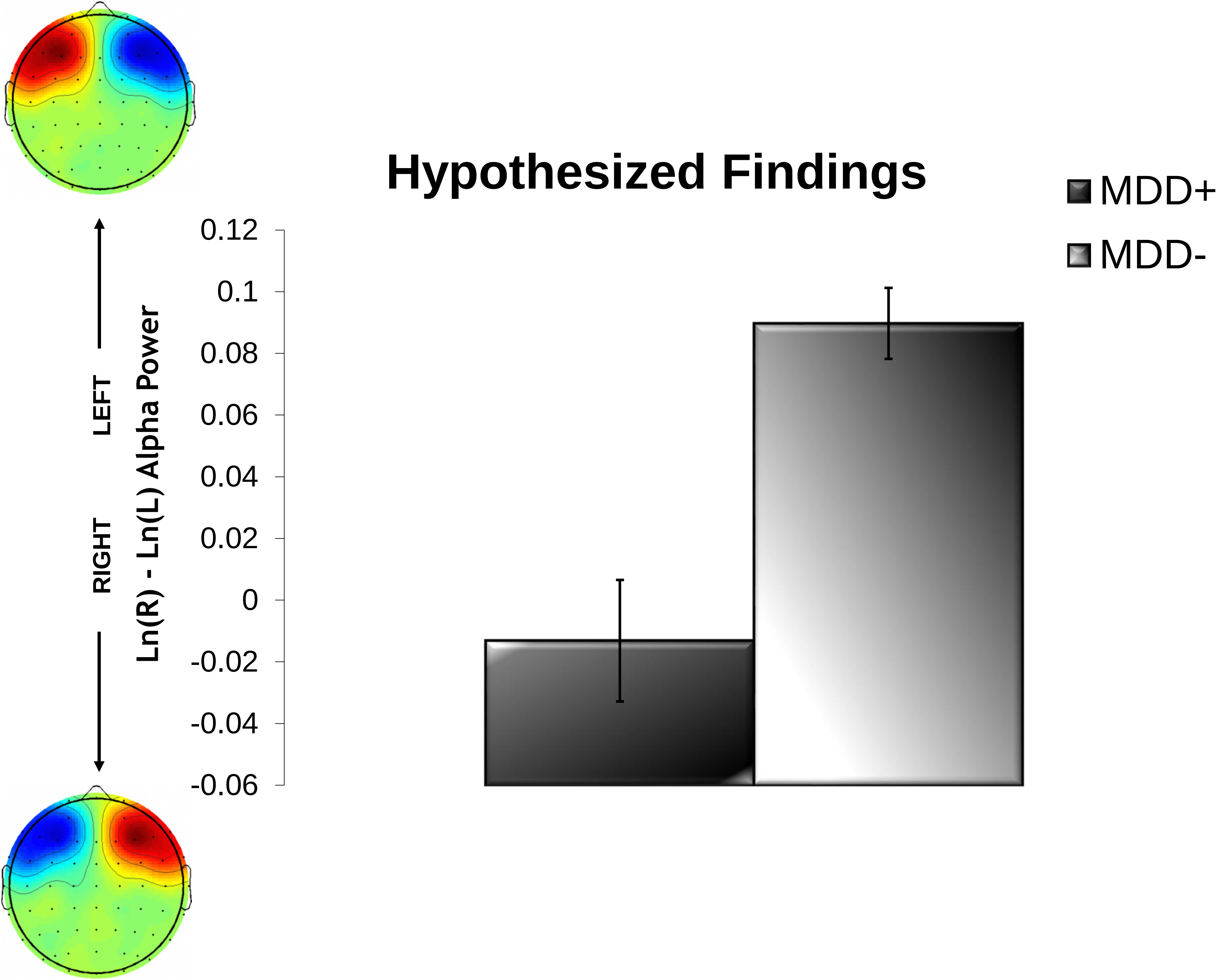


Ln(R)-Ln(L) Alpha



- Positive Affect and Mood
- Behavioral Engagement
- Approach Motivation (including Anger)
- High Behavioral Activation

- Negative Affect and Mood
- Behavioral Disengagement
- Withdrawal Motivation
- Low Behavioral Activation



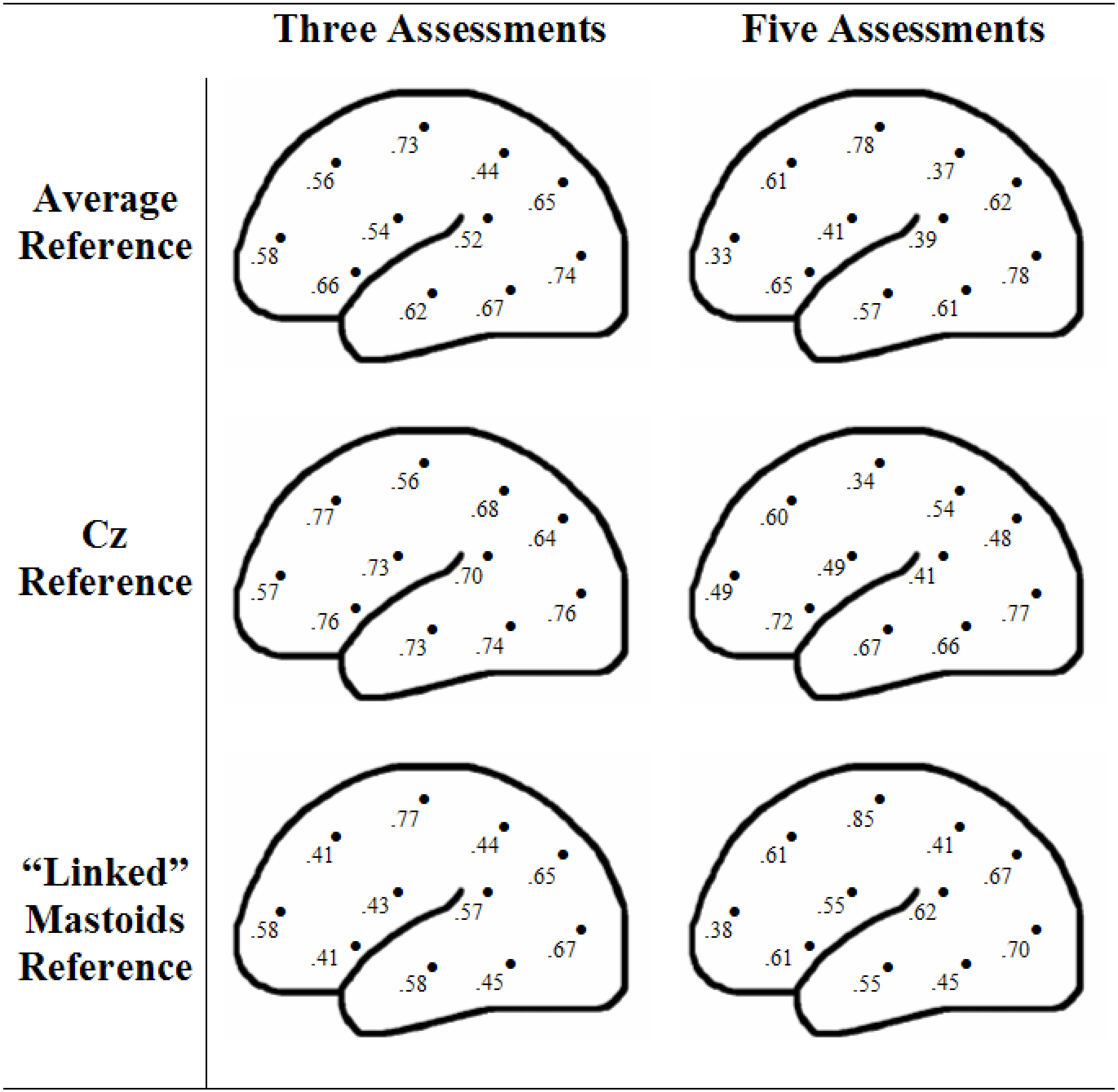
Hypothesized Findings
MDD+
MDD-
Ln(R) - Ln(L) Alpha Power
LEFT
RIGHT
0.12
0.1
0.08
0.06
0.04
0.02
0
-0.02
-0.04
-0.06

Frontal EEG asymmetry as risk marker for MDD

Several Desiderata…

Frontal EEG asymmetry as risk marker for MDD

- Resting EEG asymmetry is a stable trait
  - in clinical populations
    (Allen, Urry, et al., 2004; Jetha, Schmidt, & Goldberg, in press; Niemic & Lithgow, 2005; Vuga, et al., 2006)
  - and nonclinical populations
    (Hagemann, Naumann, Thayer, & Bartussek, 2002; Jones, Field, Davalos, & Pickens, 1997; Papousek & Schulter, 1998, 2002; Tomarken, Davidson, Wheeler, & Doss, 1992; Tomarken, Davidson, Wheeler, & Kinney, 1992)



Allen, Urry, Hitt, & Coan (2004), *Psychophysiology*

Frontal EEG asymmetry as risk marker for MDD

- Changes in clinical status are not associated with changes in resting EEG asymmetry
  (Allen, Urry, et al., 2004; Debener, et al., 2000; Vuga, et al., 2006).

Frontal EEG asymmetry as risk marker for MDD

- Resting EEG asymmetry is:
  - modestly heritable
    (Anokhin, Heath, & Myers, 2006; J. A. Coan, Allen, Malone, & Iacono, 2009; Smit, Posthuma, Boomsma, & De Geus, 2007)
  - related to serotonergic candidate genes such as HTR1A allele variations (Bismark, et al., 2010)

Frontal EEG asymmetry as risk marker for MDD

- Resting EEG asymmetry relates to internalizing disorders:
  - MDD and depressive symptoms (Allen, Urry, et al., 2004; Bruder, et al., 2005; Debener, et al., 2000; Diego, Field, & Hernandex-Reif, 2001; Diego, Field, & Hernandez-Reif, 2001; Fingelkurts, et al., 2006; Ian H. Gotlib, Ranganath, & Rosenfeld, 1998; J. B. Henriques & Davidson, 1990; Jeffrey B. Henriques & Davidson, 1991; Mathersul, Williams, Hopkinson, & Kemp, 2008; Miller, et al., 2002; Pössel, Lo, Fritz, & Seeman, 2008; Schaffer, Davidson, & Saron, 1983; Vuga, et al., 2006);

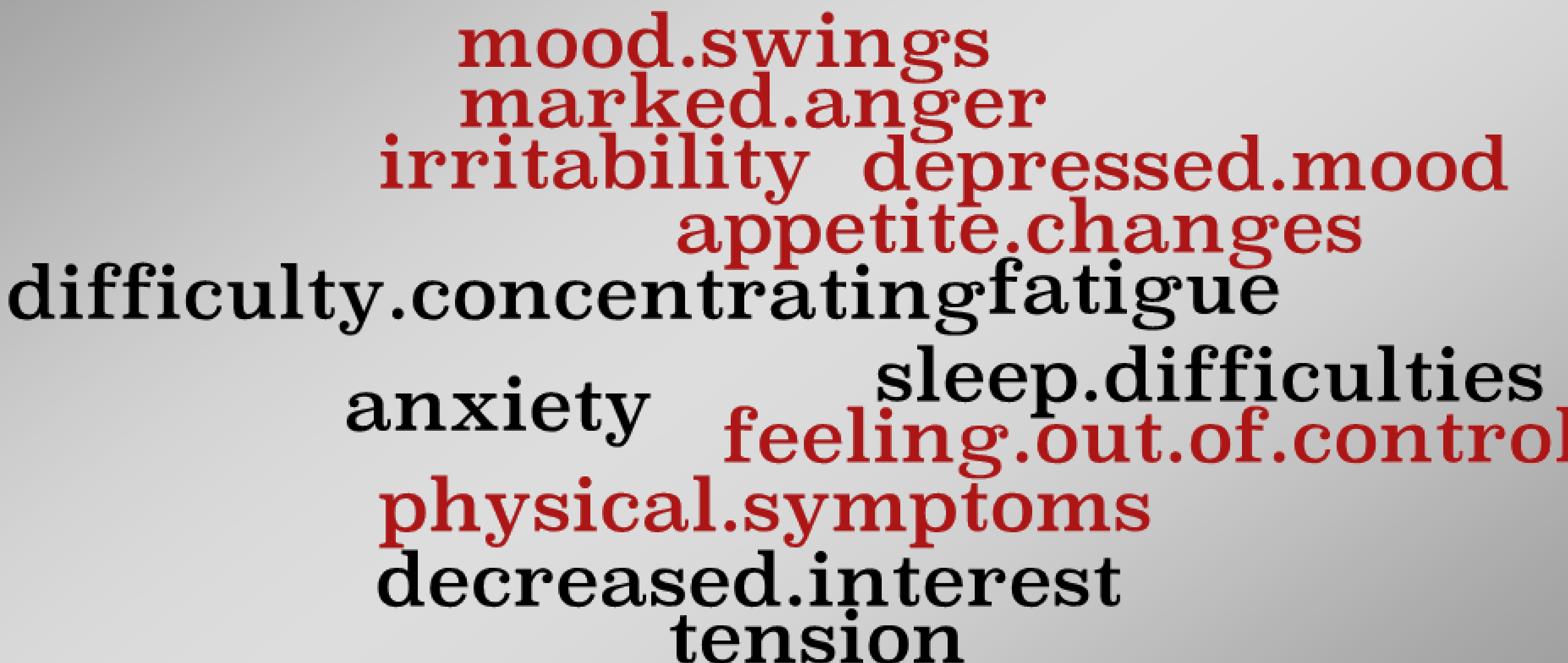
Frontal EEG asymmetry as risk marker for MDD

- Resting EEG asymmetry relates to internalizing disorders:
  - Anxious arousal/somatic anxiety (Mathersul, et al., 2008; Nitschke, Heller, Palmieri, & Miller, 1999; J.L. Stewart, Levin-Silton, Sass, Heller, & Miller, 2008);
  - Panic disorder (Wiedemann, et al., 1999);
  - Comorbid anxiety/depression (Bruder, et al., 1997);
  - Social phobia (R. J. Davidson, Marshall, Tomarken, & Henriques, 2000);

Frontal EEG asymmetry as risk marker for MDD

- Resting EEG asymmetry relates to internalizing disorders:
  - Premenstrual dysphoria (Accortt & Allen, 2006; Accortt, Stewart, Coan, Manber, & Allen, 2010);

PMDD



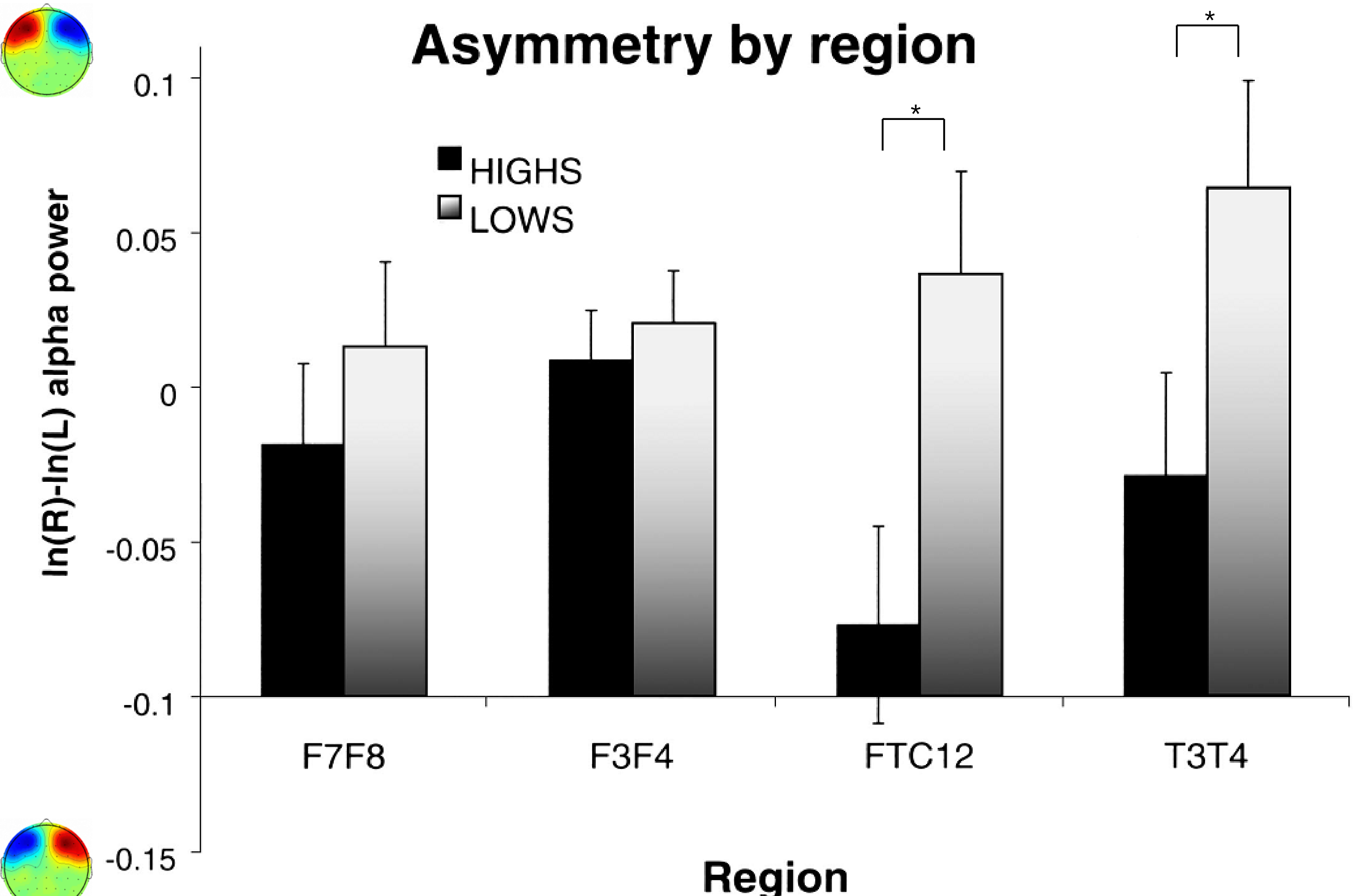
Accortt & Allen, 2006

PMDD

- Assessed at
  - Late-Luteal
  - Follicular

Accortt & Allen, 2006

Specificity or Spectrum: PMDD



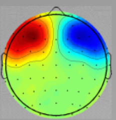
Accortt & Allen, 2006

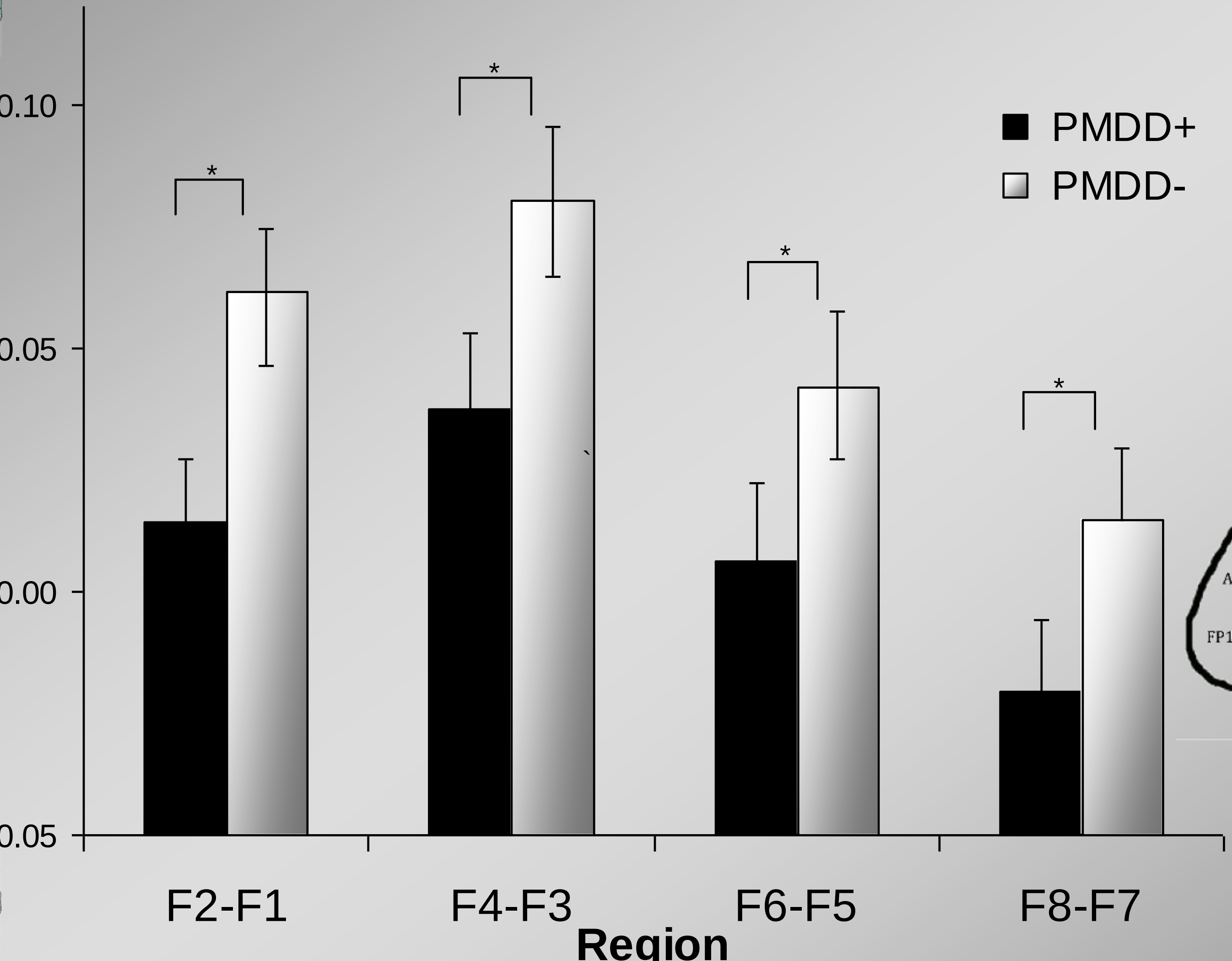
PMDD

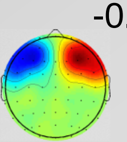
- Larger Sample
- Diagnostic Interviews
- Matched for MDD

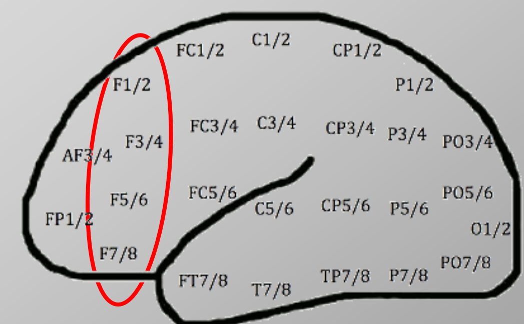
Accortt, Stewart, Coan, & Allen, 2010

PMDD









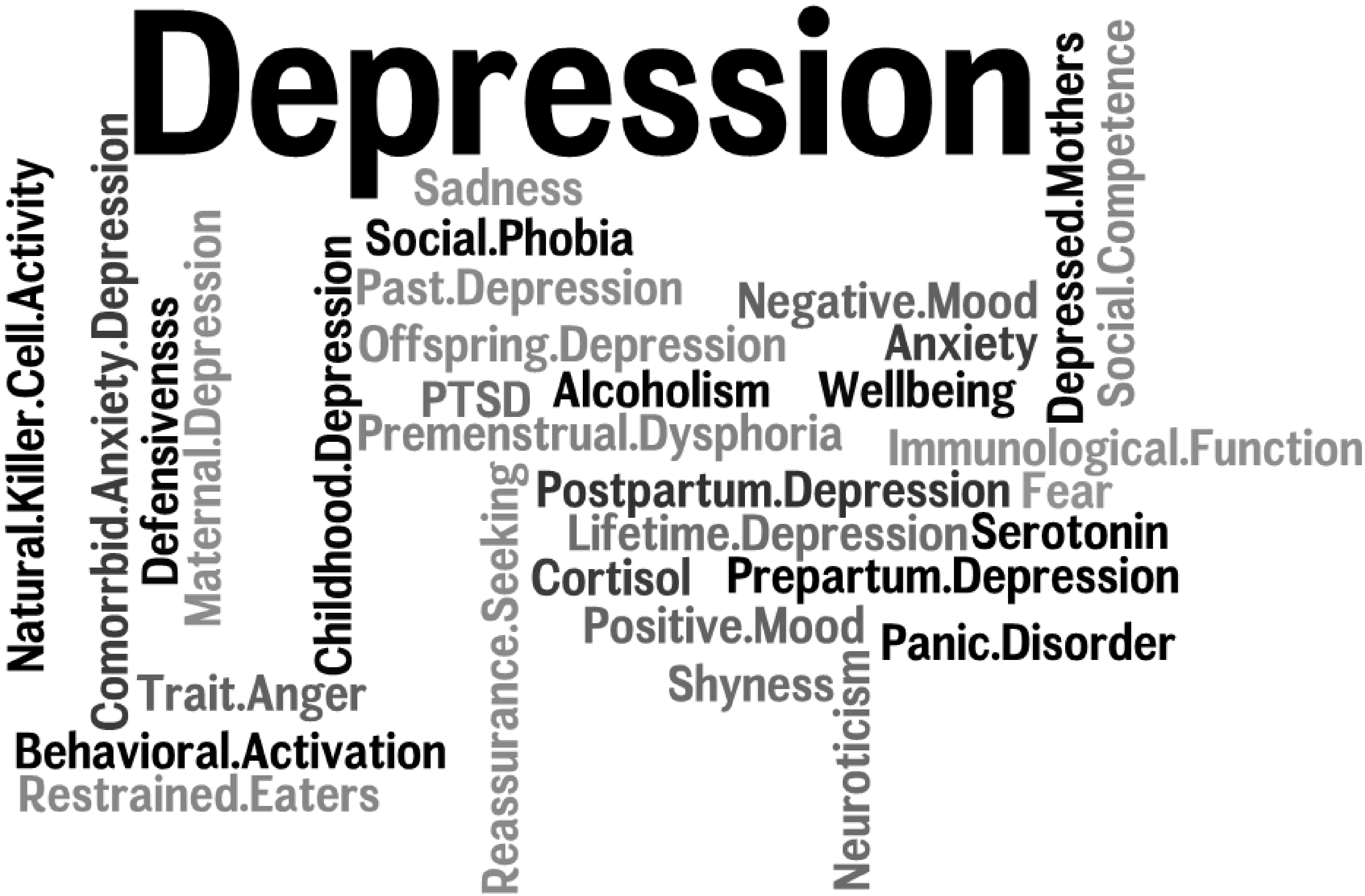
Accortt, Stewart, Coan, & Allen, 2010

Frontal EEG asymmetry as risk marker for MDD

- Resting EEG asymmetry relates to internalizing disorders:
  - Childhood/adolescent internalizing psychopathology (anxiety, sadness, disappointment, low empathy and sociability, higher stress cortisol, and avoidant-withdrawn behavior
    (Baving, Laucht, & Schmidt, 2002; Buss, et al., 2003; R.J. Davidson, 1991; Forbes, Fox, Cohn, Galles, & Kovacs, 2005; N.A. Fox, Henderson, Rubin, Calkins, & Schmidt, 2001; Henderson, Marshall, Fox, & K.H., 2004; Schmidt, Fox, Schulkin, & Gold, 1999).

Frontal EEG asymmetry as risk marker for MDD

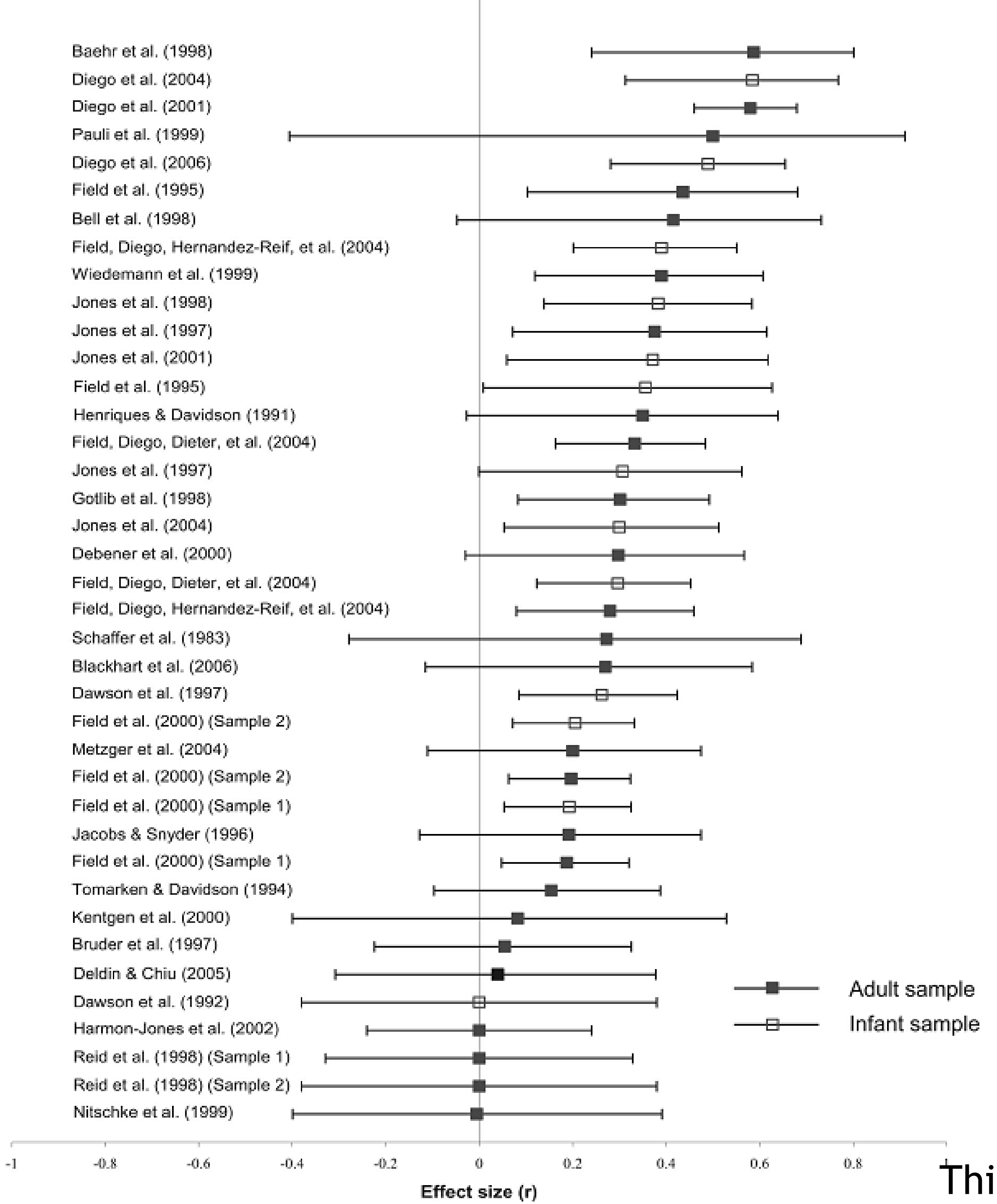
- Resting EEG asymmetry identifies *family members* of those with internalizing disorders
  - MDD (Dawson, Frey, Panagiotides, Osterling, & Hessl, 1997; Dawson, Frey, Panagiotides, et al., 1999; Dawson, Frey, Self, et al., 1999; Field, Diego, Hernandez-Reif, Schanberg, & Kuhn, 2002; Forbes, et al., 2007; Jones, Field, & Davalos, 2000; Jones, et al., 1997; Miller, et al., 2002; Tomarken, Dichter, Garber, & Simien, 2004).


Depression
Sadness
Social.Phobia
Past.Depression
Negative.Mood
Offspring.Depression
Anxiety
PTSD
Alcoholism
Wellbeing
Premenstrual.Dysphoria
Immunological.Function
Postpartum.Depression
Fear
Lifetime.Depression
Serotonin
Cortisol
Prepartum.Depression
Positive.Mood
Panic.Disorder
Shyness
Trait.Anger
Behavioral.Activation
Restrained.Eaters
Natural.Killer.Cell.Activity
Comorrbid.Anxiety.Depression
Defensivensss
Maternal.Depression
Childhood.Depression
Reassurance.Seeking
Neuroticism
Depressed.Mothers
Social.Competence

Meta-Analysis: Depression, Anxiety

- Studies of resting frontal alpha asymmetry
- Measures of depression or anxiety
- Both adult and infant samples
- Literature Sample:
  - 31 papers
  - 59 tests (studies, sites, reference)
  - Adult samples predominantly female

Thibodeau, Jorgensen, & Kim, 2006



Mean Effect Sizes

- Adults d=0.54
- Infants d=0.61

Moderators

- Reference
- Recording length
- Co-morbidity

Publication Bias

- ↑ Effect Size
- Can’t account for full effects

Thibodeau, Jorgensen, & Kim, 2006

A “Definitive” Study

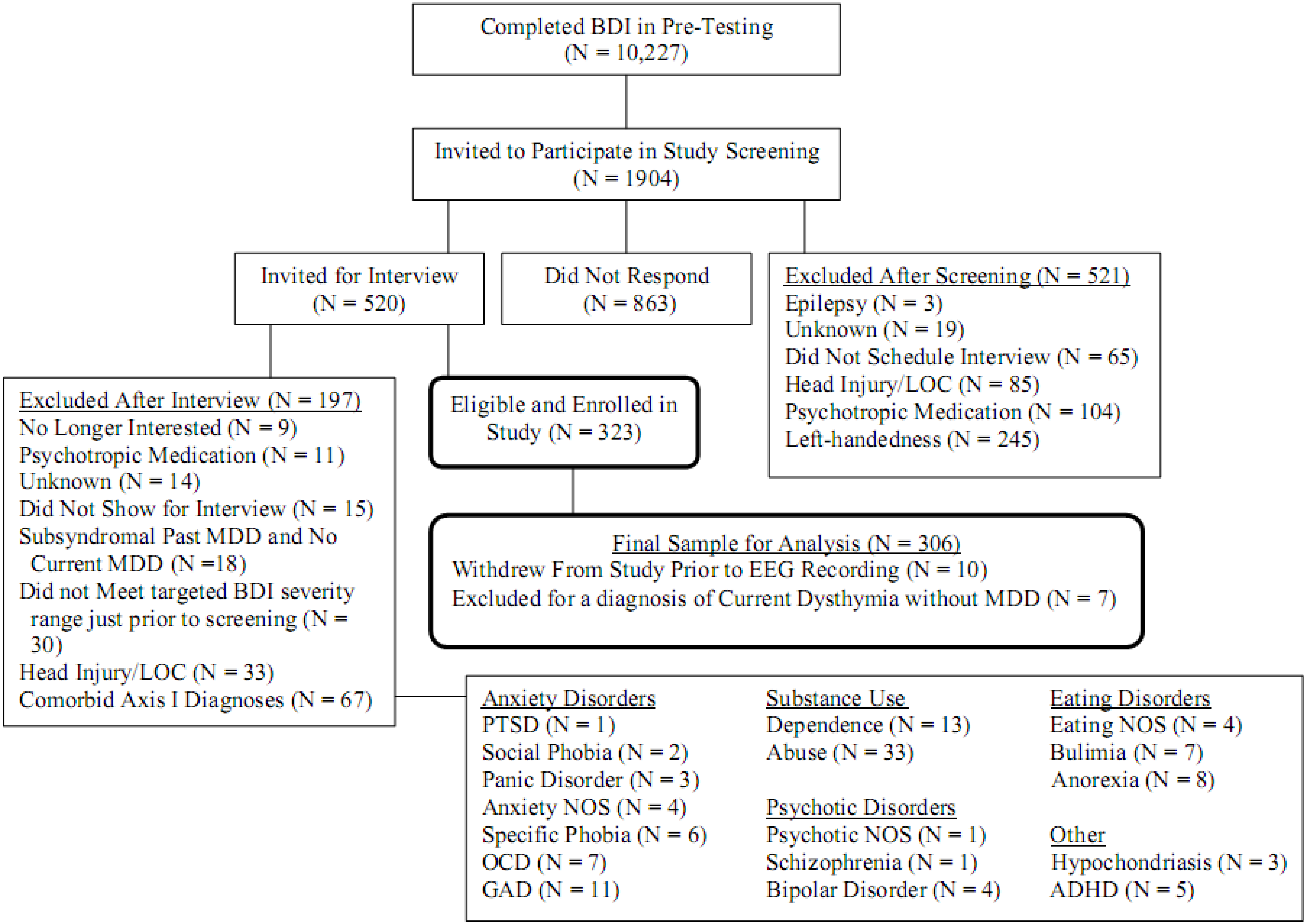
- Large (n=306), medication-free
  - Both men (n=95) and women (n=211)
  - Lifetime Depressed (n=143)
  - Never Depressed (n=163)
- Assessed for Family History
- No co-morbidity, medically healthy

Stewart, Bismark, Towers, Coan, & Allen, 2010

A “Definitive” Study

- Large (n=306), medication-free
- Assessed for Family History
- No co-morbidity, medically healthy
- Resting EEG
  - Two sessions per day
  - Four days
- Four Reference Montages
- Mixed Linear Models

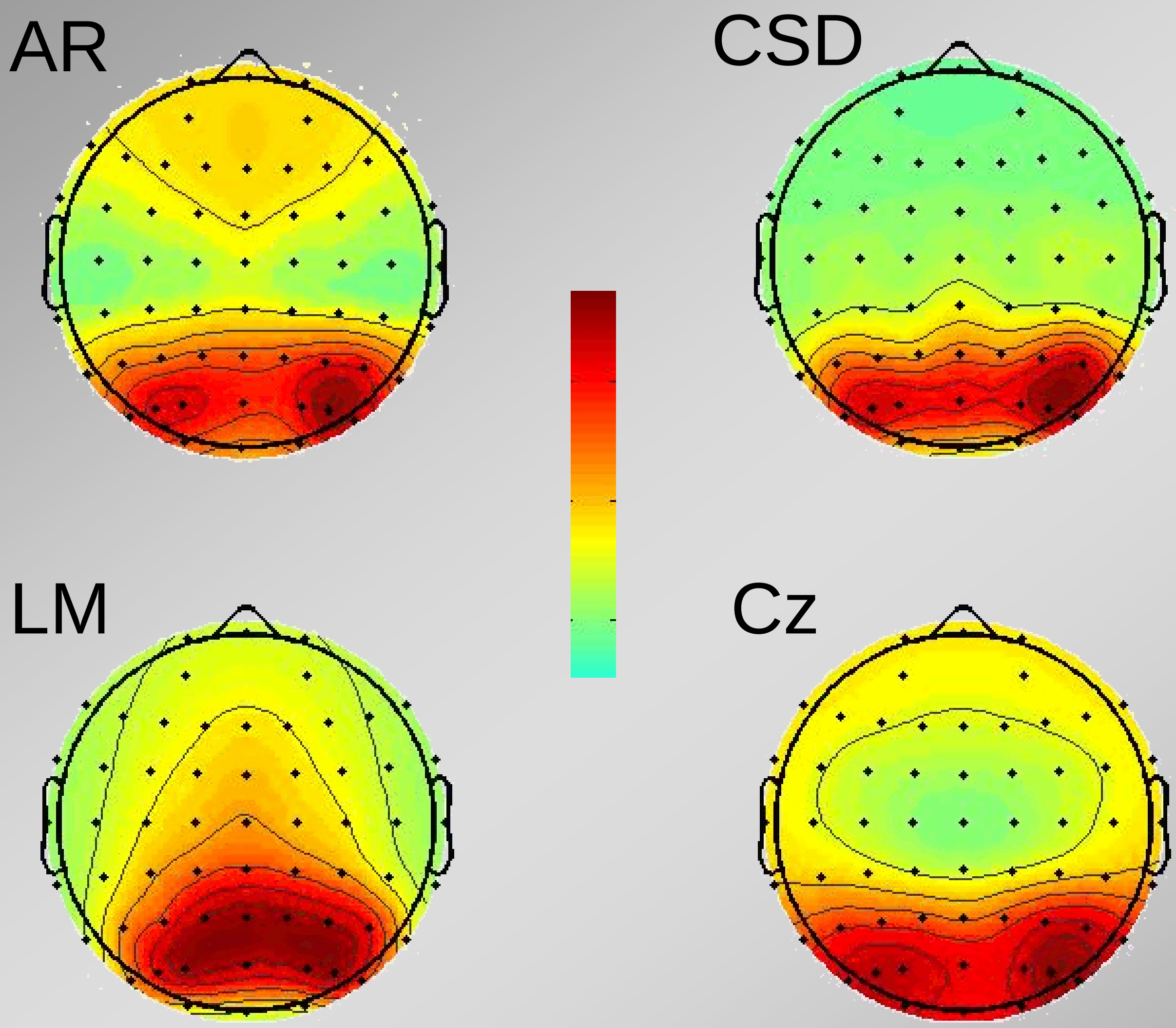
Stewart, Bismark, Towers, Coan, & Allen, 2010



Stewart, Bismark, Towers, Coan, & Allen 2010, *J Abnormal Psychology*

Reference Effects

Resting
Eyes Closed
Alpha Power



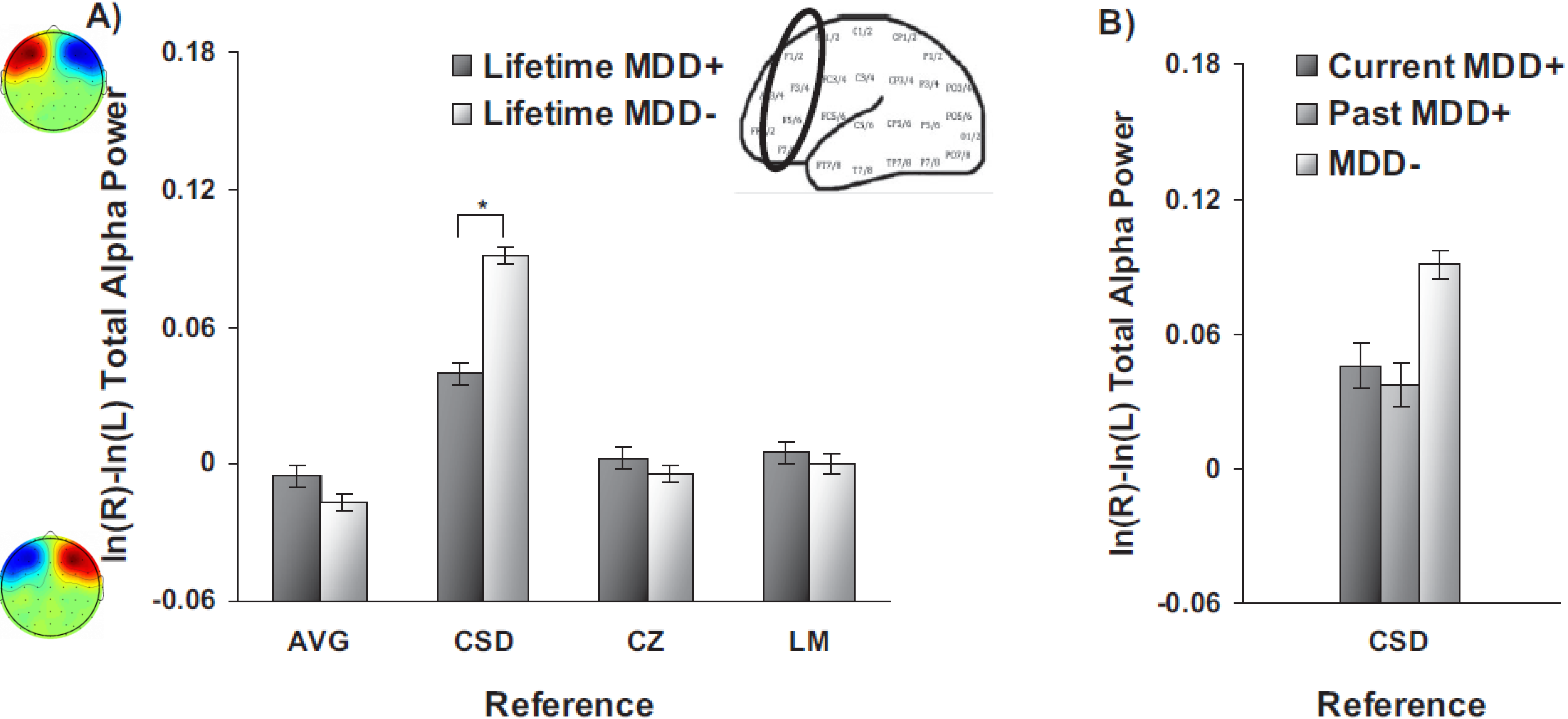


Figure 2. Panel A shows frontal alpha asymmetry scores (8–13 Hz at F2–F1, F4–F3, F6–F5, F8–F7) by lifetime MDD status for each reference montage across all four frontal regions depicted on the head insert. Error bars reflect standard error. Panel B shows results of a follow-up assessment indicating that the relationship of lifetime MDD status to CSD-referenced asymmetry is not solely accounted for by current MDD status. The *y*-axis is ln μV^2 for AVG, Cz, and LM references, and ln $\mu V^2/cm^2$ for CSD referenced data. MDD = major depressive disorder; AVG = average; CSD = current source density; CZ = Cz; LM = linked mastoid.

Stewart, Bismark, Towers, Coan, & Allen, 2010

STICK WITH CSD…

Interim Synopsis: Endophenotype Desiderata

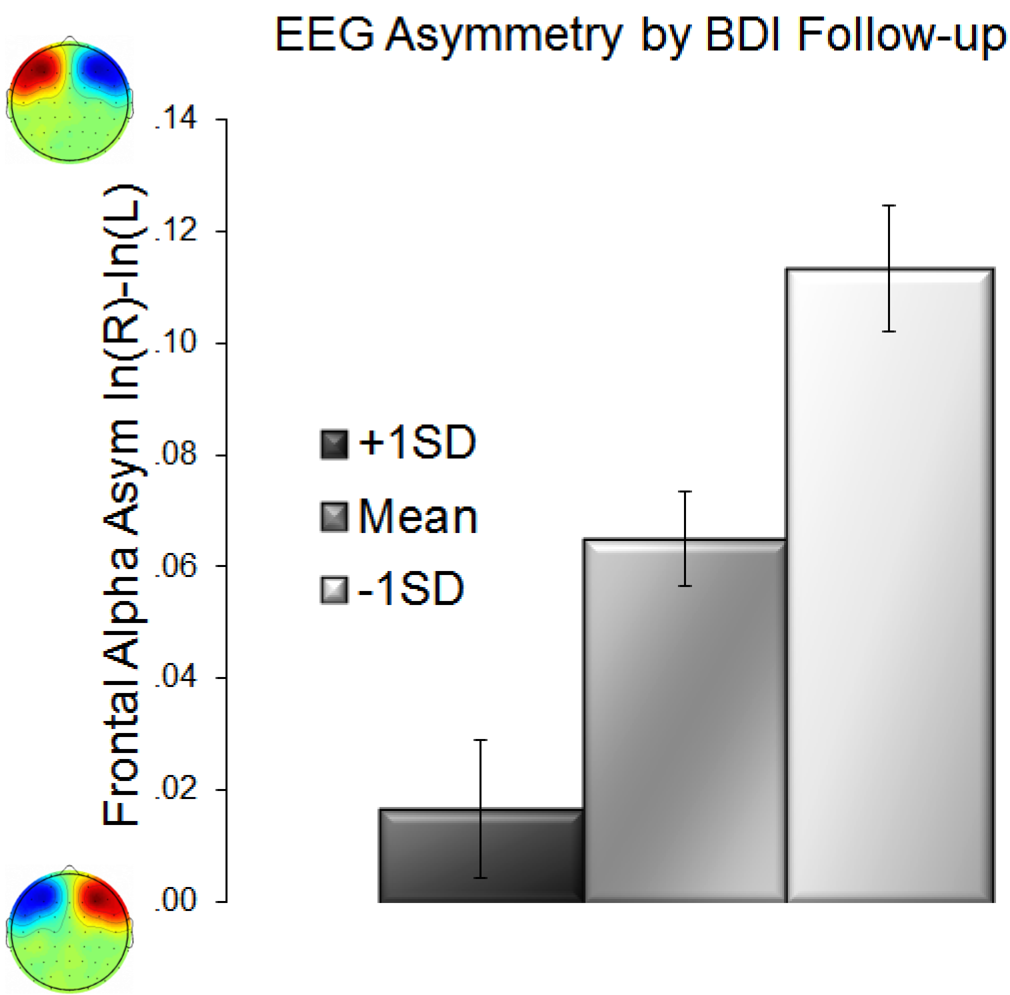
Gottesman & Shields, 1972; Gottesman & Gould, 2003; Iacono, 1998

- Specificity: Associated with disorder
- Heritability
- State-independence: Primarily trait
- Familial Association: Seen in unaffected family members at rates higher than general population
- Predictive Power: predicts future disorder in unaffected individuals

Prospective Pilot Data

- Assessed never depressed (MDD-) individuals ~1 year after EEG
- Obtained 53 of 163 (representative)
- Completed BDI based on “worst month”
- BDI worst month residualized on BDI at EEG assessment
- Can EEG predict this worst month BDI score?

Prospective Pilot Data



See also Nusslock et al., *J Abnormal Psychology*, 2011

Stewart & Allen, *In preparation*

Thus

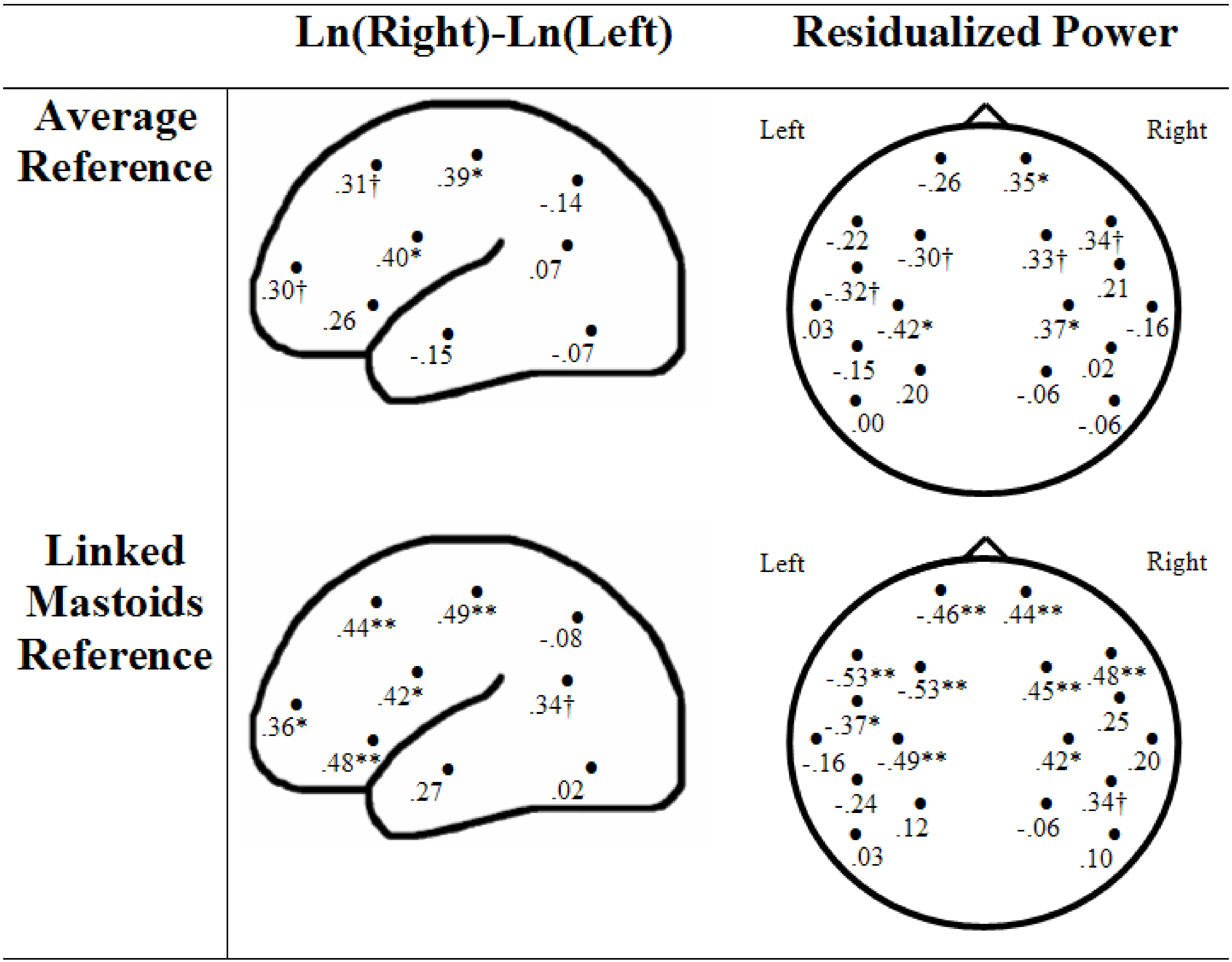
- Frontal EEG asymmetry has promise as a risk indicator for MDD and other internalizing disorders
- Need:
  - Large-scale prospective study
  - Links to underlying neural systems

Asymmetry Metric Vs Individual Sites

- Is it left or is it right?
- Can assess using ANOVA with hemisphere as a factor
  - Removes overall power before testing for interaction of emotion/temperament/psychopathology with hemisphere
  - But not easily amenable for assessing relationship of EEG at given site to continuous variables

Asymmetry Metric Vs Individual Sites

- The Problem:
  - Power at an individual site reflects:
    - Underlying neural activity
    - Scalp thickness
- An early (nonoptimal) solution
  - Residualize power at each lead based on
    - Whole head power (reasonable)
    - Homologous lead power (troublesome)


Ln(Right)-Ln(Left)
Residualized Power
Average Reference
.31†
.39*
-.14
.40*
.07
.30†
.26
-.15
-.07
Left
Right
-.26
.35*
-.22
-.30†
.33†
.34†
-.32†
.21
.03
-.42*
.37*
-.16
-.15
.02
.20
-.06
.00
-.06
Linked Mastoids Reference
.44**
.49**
-.08
.42*
.34†
.36*
.48**
.27
.02
Left
Right
-.46**
.44**
-.53**
-.53**
.45**
.48**
-.37*
.25
-.16
-.49**
.42*
.20
-.24
.34†
.12
-.06
.03
.10

†p < .10; *p < .05; ** p < .01

Why does it do *that?!*

- This double residualization results in correlations with the outcome variable similar in magnitude to the difference score, but with opposite signs for the two hemispheres.
- This is actually to be expected when the predictor and criterion variable are highly correlated

Allen, Coan, & Nazarian (2004)

Alpha Power at Homologous Sites is *Highly* Correlated

Sites	Reference	
	AR	LM
FP1 .. FP2	.997	.998
F7 .. F8	.983	.971
F3 .. F4	.990	.992
FTC1 .. FTC2	.975	.943
C3 .. C4	.977	.981
T3 .. T4	.918	.891
TCP1 .. TCP2	.944	.948
P3 .. P4	.965	.982
T5 .. T6	.907	.932

Allen, Coan, & Nazarian (2004)

Consider residualized left lead power when L ≈ R

$$L_{resid} = L - \hat{L}$$

$$\hat{L} = a + b(R)$$

In limiting case where $r_{lr} \to 1.0$

$$\hat{L} = 0 + 1(R) = R$$

$$L_{resid} = L - \hat{L} = L - R$$

Allen, Coan, & Nazarian (2004)

Fancy That!

- Residual values for left hemisphere leads approaches *L* – *R* as the correlation between left and right leads approaches 1.0.
- Residual values for right hemisphere approaches the value *R* – *L* as the correlation between left and right leads approaches 1.0.
- Therefore, this procedure will make it appear that right hemisphere leads correlate with a criterion variable in the same direction and magnitude as the *R* – *L* difference score, and that left hemisphere leads correlate with a criterion variable in the opposite direction but same magnitude as the *R* – *L* difference score.
- Therefore, *don't do that!*

What to do?

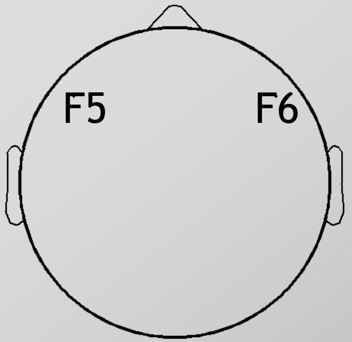
- Residualize only on whole head power, not additionally on homologous lead power
- Use hierarchical general linear models
  - can include both categorical and continuous predictors
  - can be constructed to test a variety of specific hypotheses of interest, including those related to overall power, hemisphere, and even reference scheme, all in a single model

Deconstructing the “resting” state: Exploring the temporal dynamics of resting frontal brain asymmetry as an endophenotype for depression

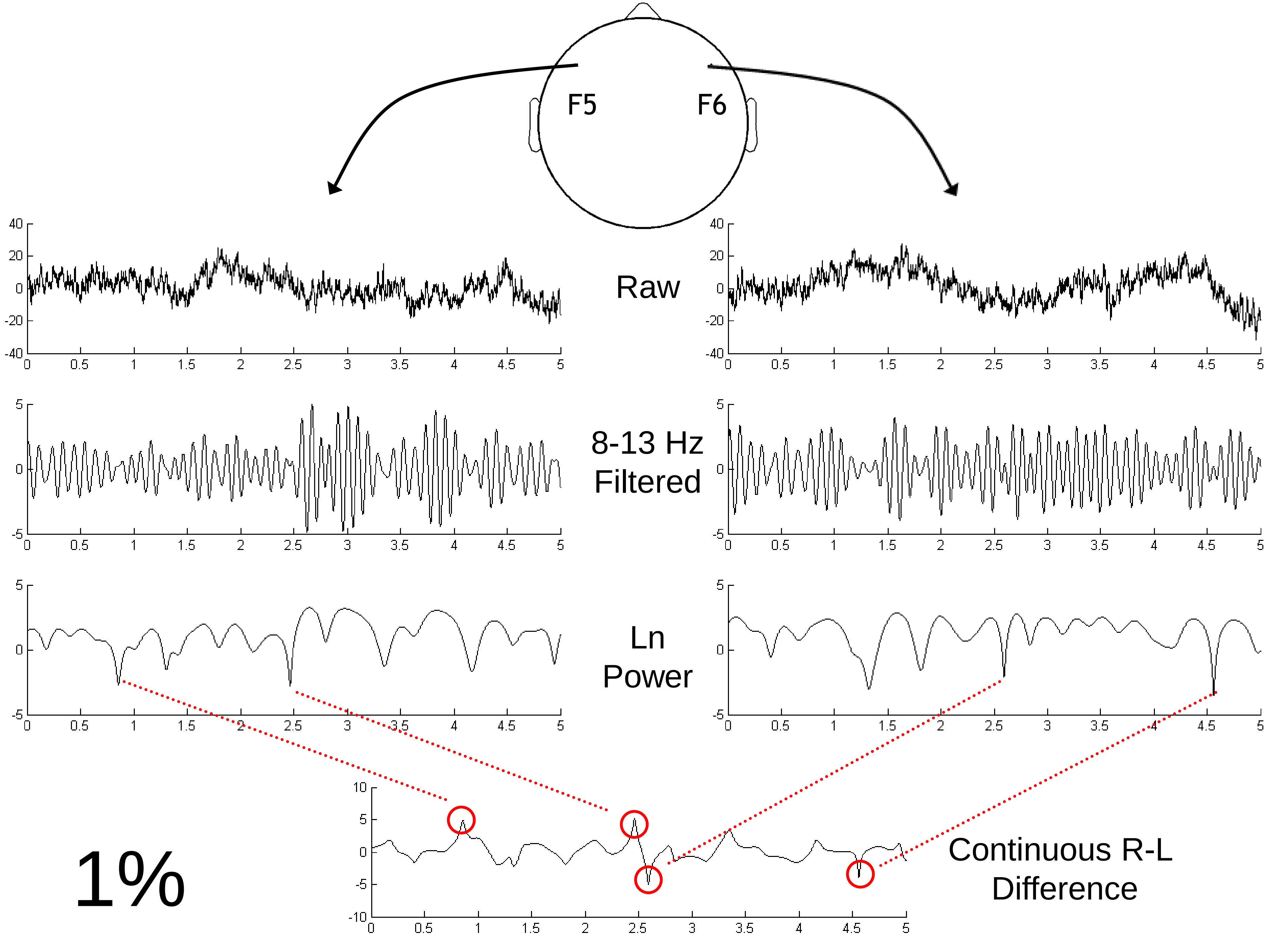
Allen & Cohen, 2010

The Conventional Approach

- One number to summarize several minutes of resting data
- Good reliability, but…
  - Lacks temporal specificity
  - Confuses “more” with “more often”



Asym = Ln(Right)-Ln(Left) Alpha Power


F5
F6
Raw
8-13 Hz
Filtered
Ln
Power
1%
Continuous R-L
Difference

Three Central Questions

- How do the novel peri-burst metrics of dynamic asymmetry compare to the conventional FFT-based metrics?
- Do the peri-burst metrics adequately differentiate depressed and non-depressed participants
- What EEG dynamics surround the asymmetry bursts that are captured by the novel peri-burst metrics?

Three Central Questions

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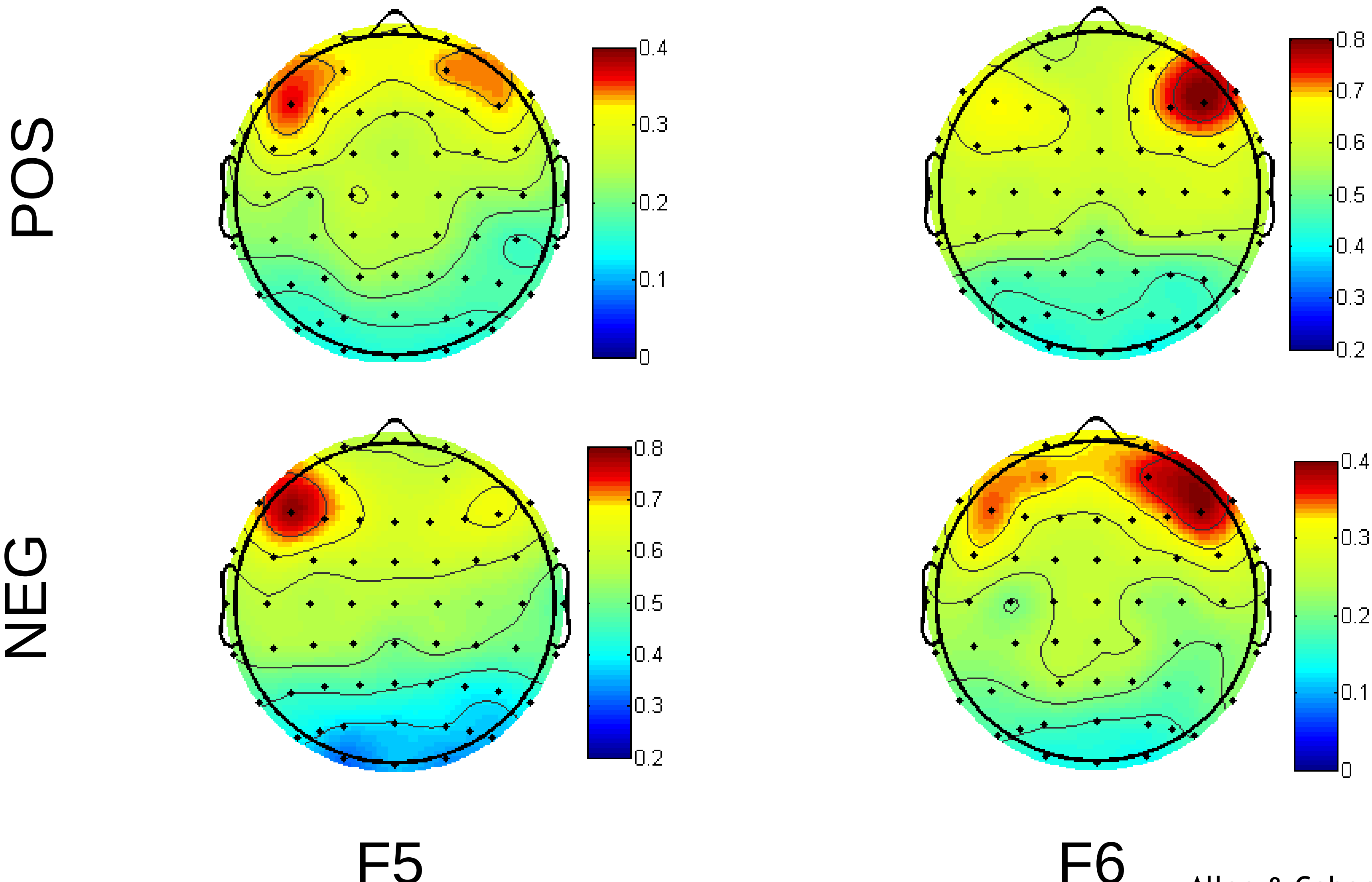
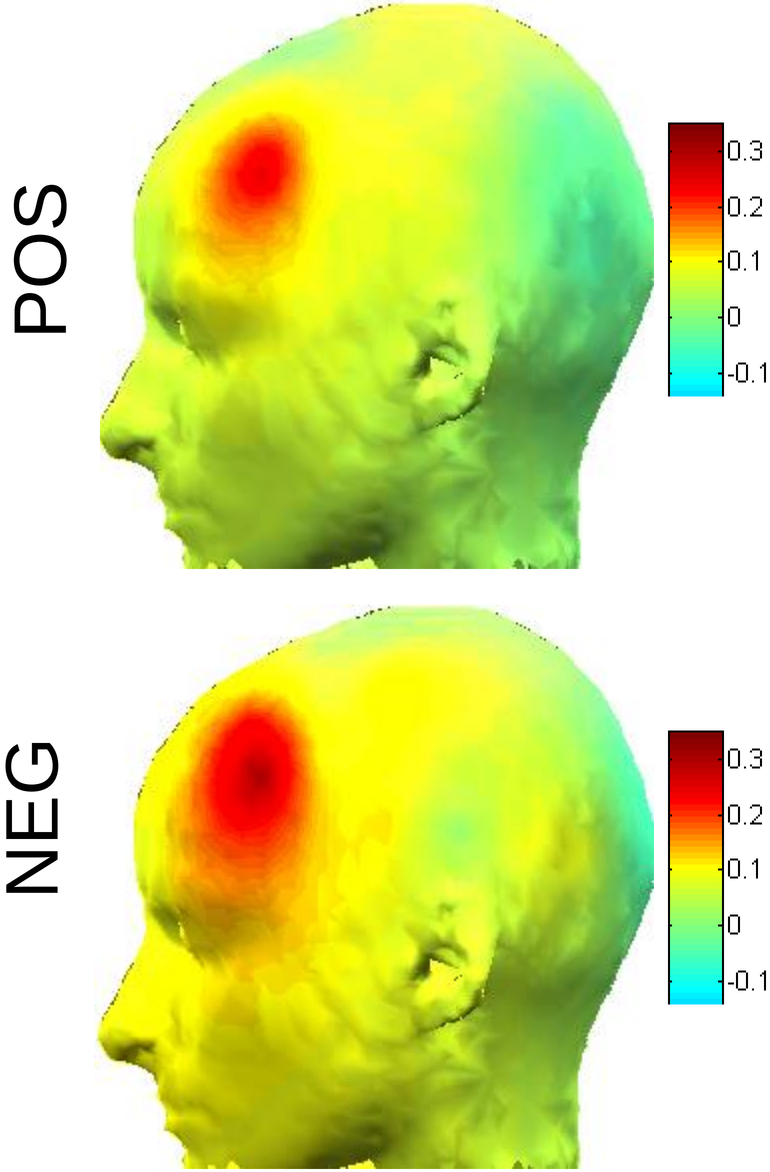
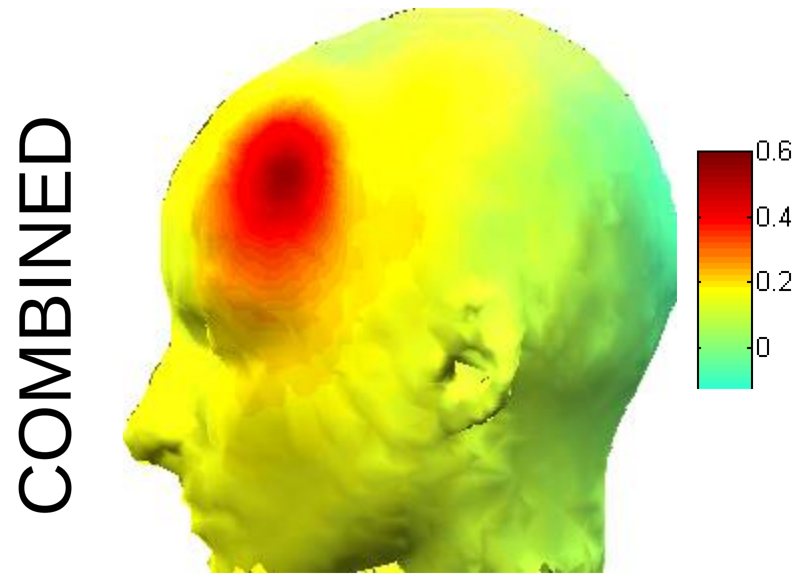
Relationship of Peri-Burst Alpha Power with Conventional FFT-Derived Power



Allen & Cohen, 2010

Relationship of Peri-Burst Alpha Asymmetry at F6-F5 with Conventional FFT-Derived Alpha Asymmetry across the scalp





r^2=.42 !

(1%)

Allen & Cohen, 2010

Three Central Questions

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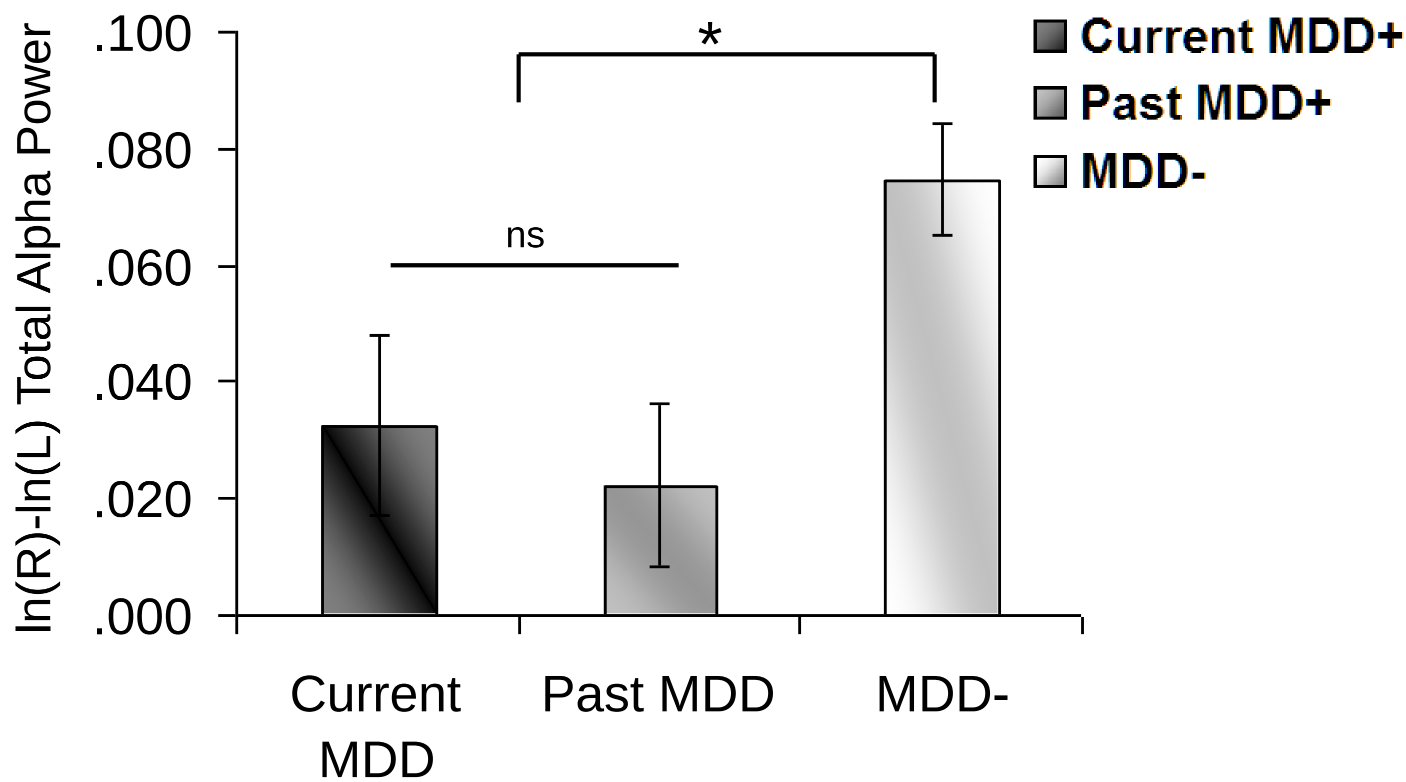
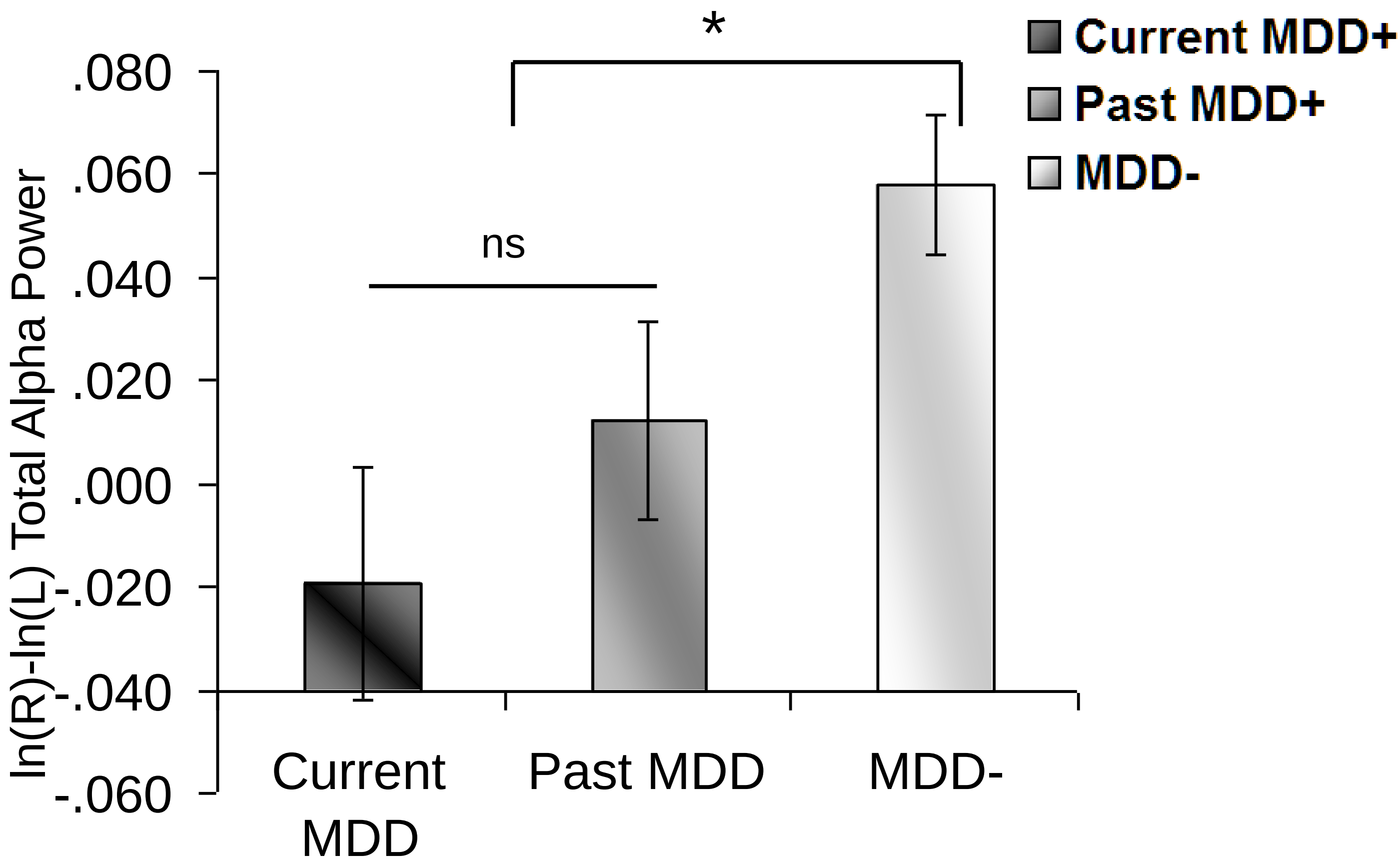
- What EEG dynamics surround the asymmetry bursts that are captured by the novel peri-burst metrics?

Conventional Frontal EEG Alpha Asymmetry by MDD status



Stewart, Bismark, Towers, Coan, & Allen 2010, *J Abnormal Psychology*

Peri-burst Frontal EEG Alpha Power Asymmetry by MDD status

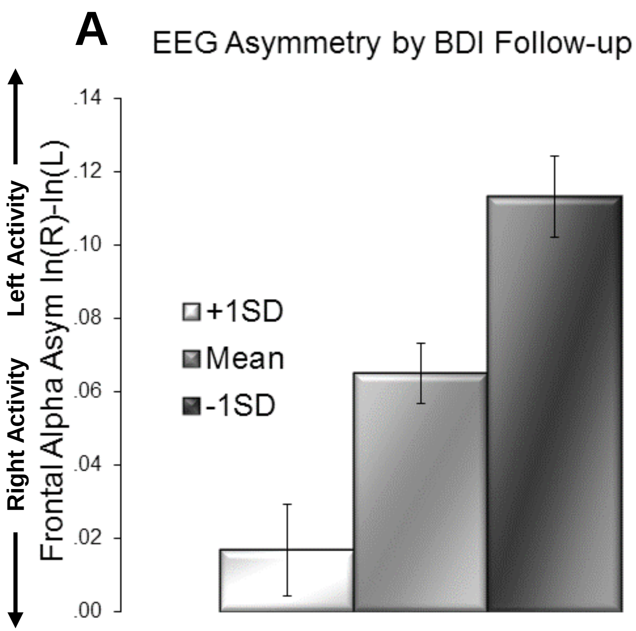


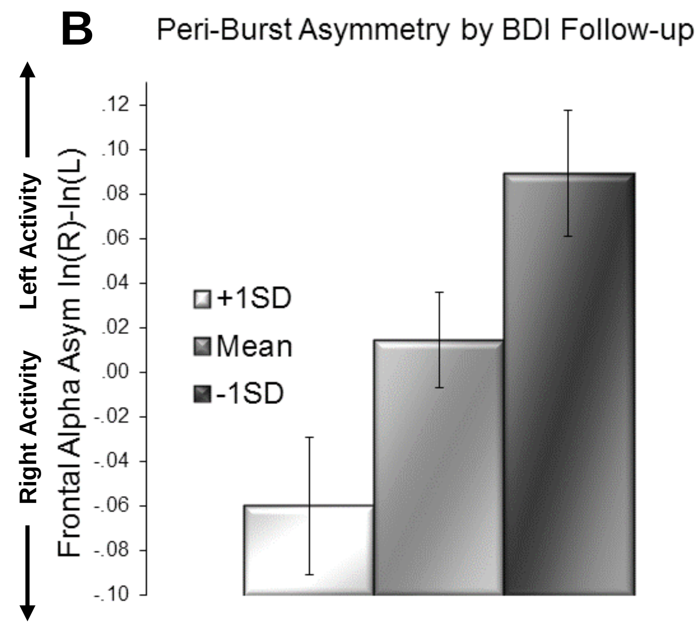
Allen & Cohen, 2010

Table 3. Effect sizes (Cohen's *d*) comparing depressed groups to never depressed controls.

Diagnosis	Conventional	Peri-burst
Lifetime MDD	.43	.38
Past MDD only	.43	.27
Current MDD (with or without Past MDD)	.35	.45

Prospective Pilot Data





Three Central Questions

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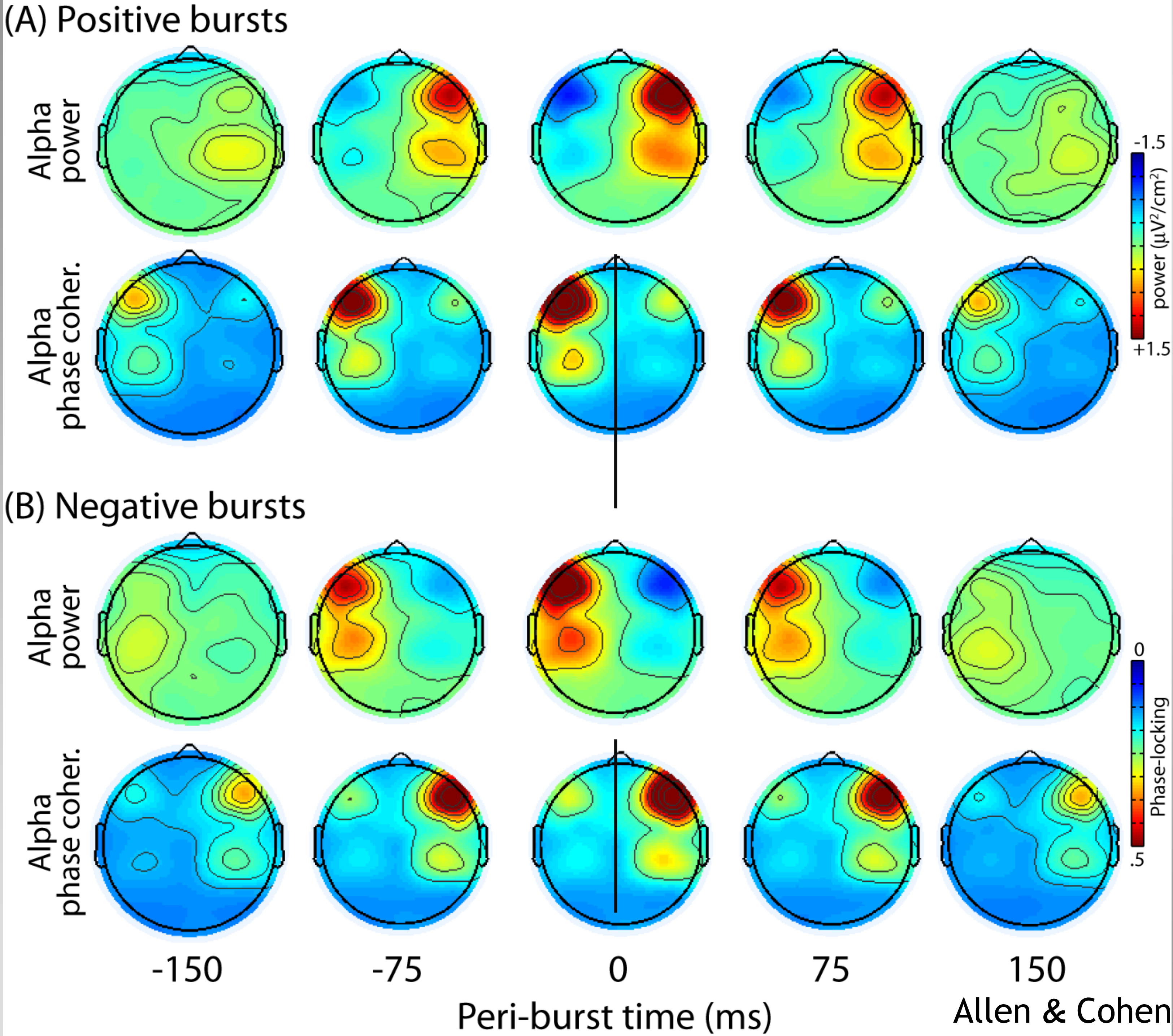


Allen & Cohen, 2010

So?

- Novel peri-burst metrics account for substantial variance in conventional metrics (despite being just 1%)
- Peri-burst metrics differentiate depressed and non-depressed participants, similar to conventional metrics

So?

- Bursts reflect …
  - Transient lateralized alpha suppression that shows a highly consistent phase relationship across bursts
  - Along with concurrent contralateral transient alpha enhancement that is less tightly phase-locked across bursts
- Analogous to ERD/ERS (Pfurtscheller, 1992)?

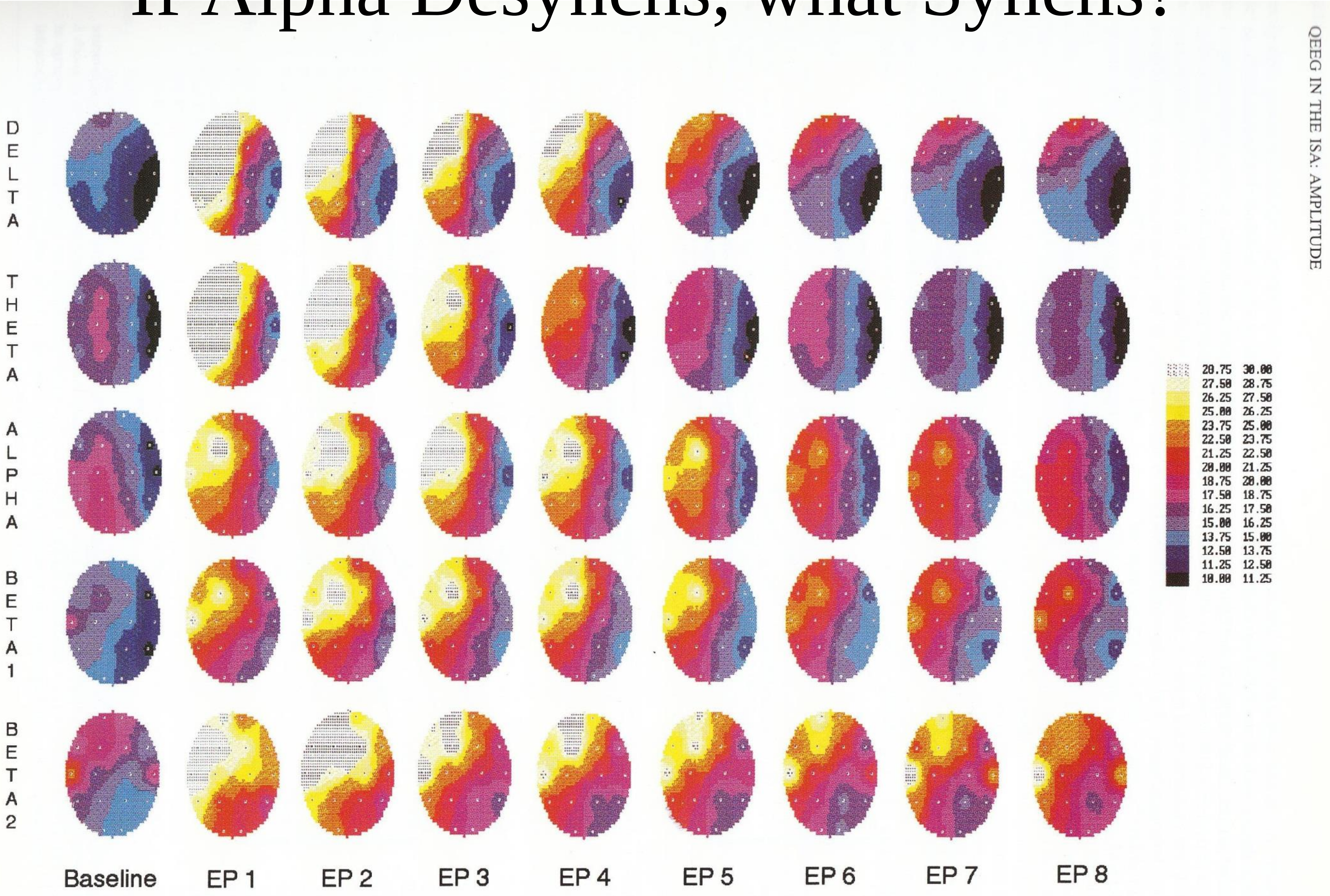
So?

- The fact that the alpha suppression is particularly tightly phase-locked across bursts raises the possibility that the lateralized alpha suppression may drive or regulate cortical processing
- Alpha has been shown to regulate gamma power (i.e., cross-frequency coupling, Cohen et al., 2009)

Synchronization and Desynchronization

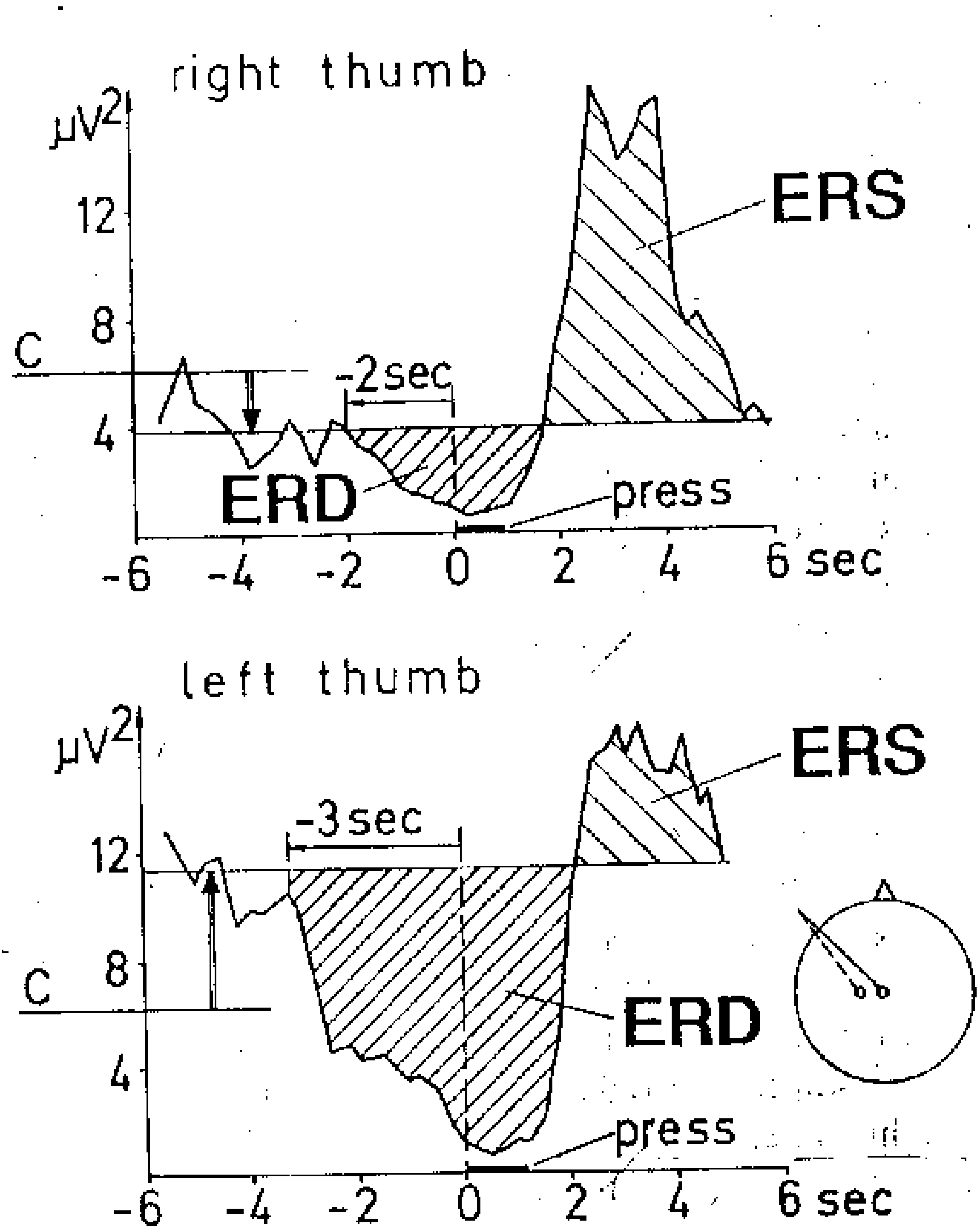
- Supposition that alpha blocking meant that the EEG had become desynchronized
  - Yet the activity is still highly synchronized -- not at 8-13 Hz
  - May involve fewer neuronal ensembles in synchrony

If Alpha Desynchs, what Synchs?

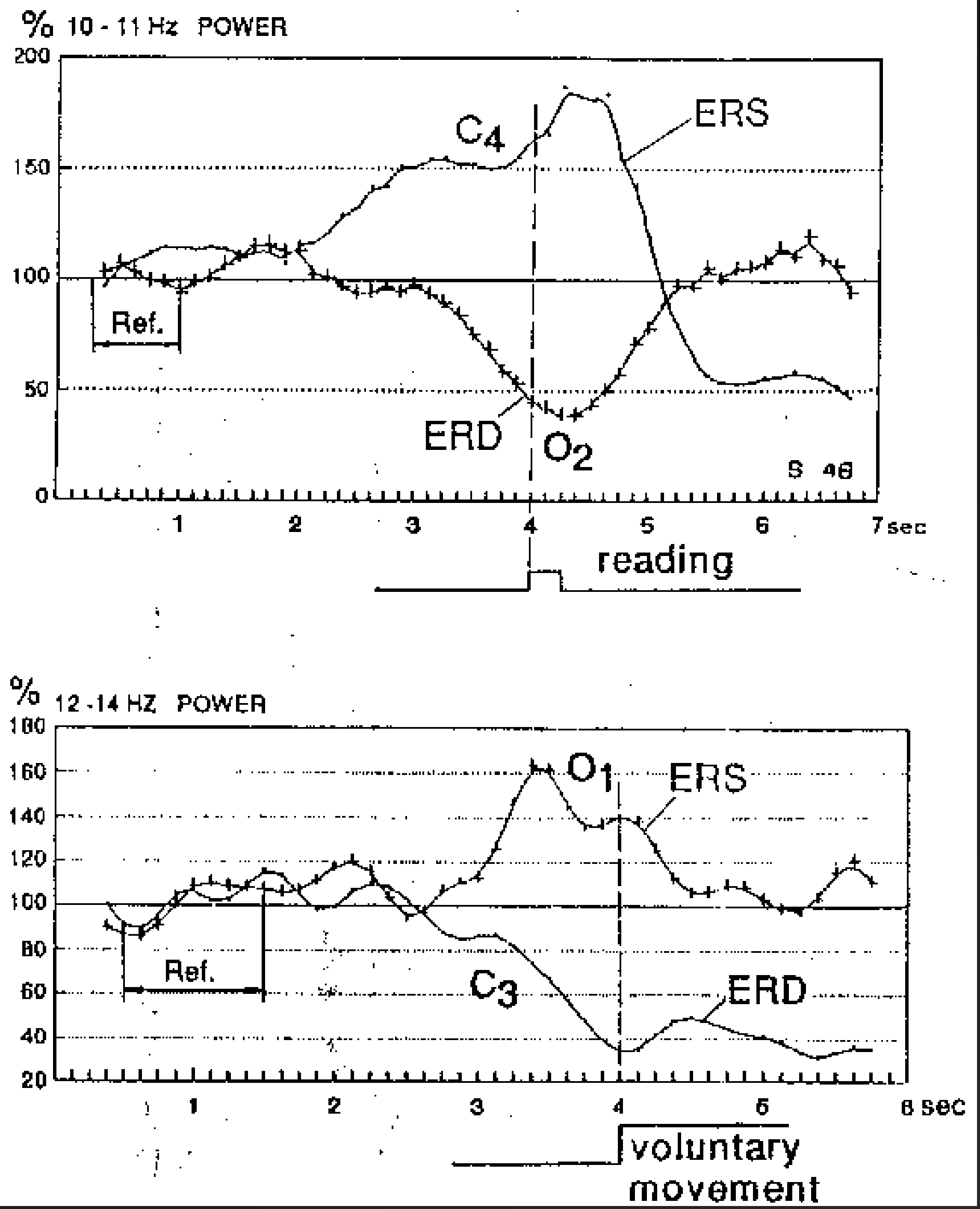


Event-related Synchronization and Desynchronization

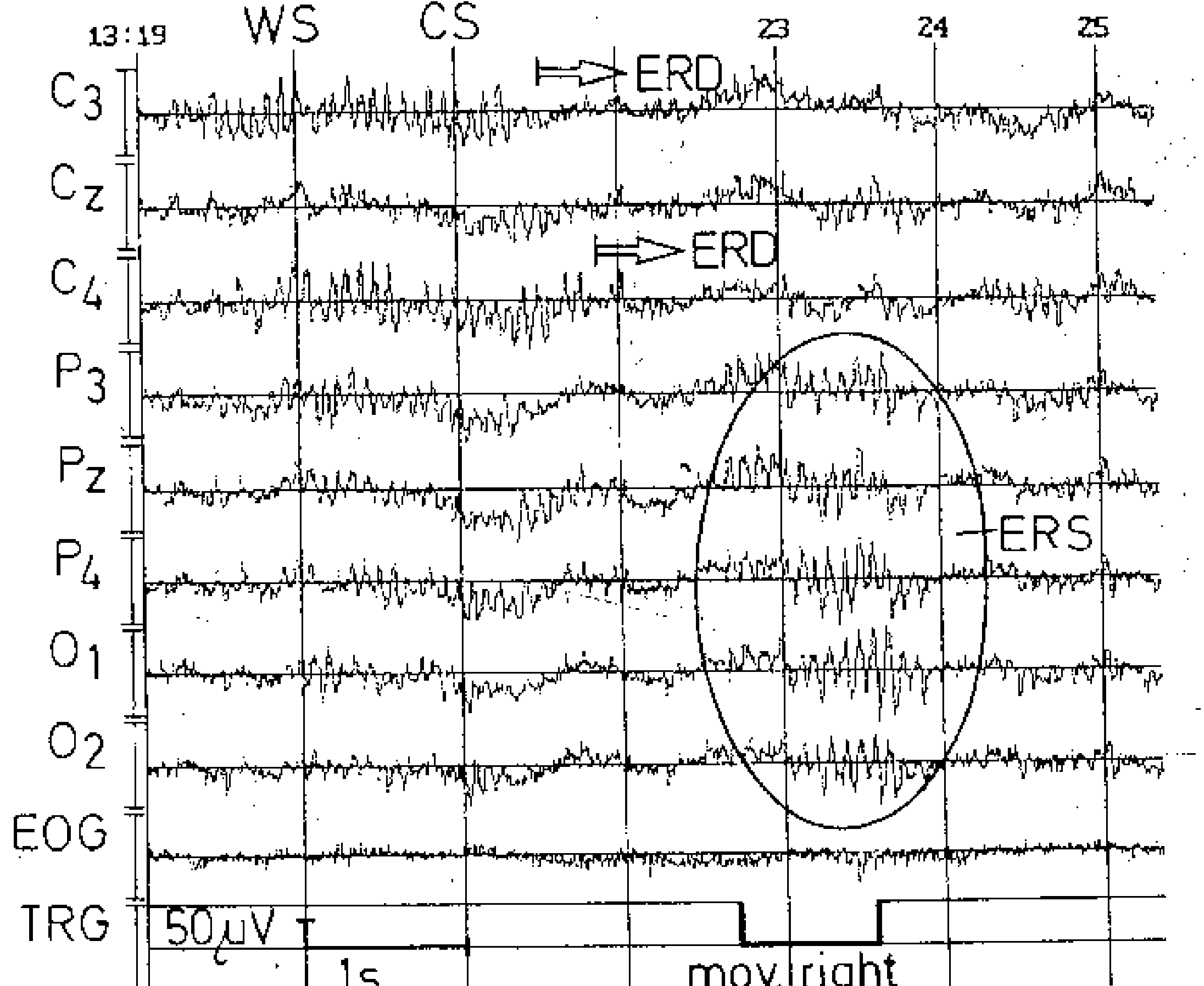
- Pfurtscheller (1992) -- Two types of ERS
  - Secondary (follows ERD)
  - Primary (**Figure 3 & Figure 4**)



Alpha Power time course over left central region during voluntary movements with right and left thumb



Alpha power time course during reading (upper) and voluntary finger movements (lower). Primary ERS is seen over electrodes overlying cortical areas not involved in the task.



Primary ERS seen over parietal and occipital leads during right finger movement. ERD is seen over central electrodes, with earlier onset over hemisphere contralateral to movement.

Frontal Midline Theta
(more later in advanced topics)

- Increased midline frontal theta during periods of high cognitive demand
- This is specifically under conditions in which cortical resources must be allocated for select cognitive processes
  - Attention
  - Memory
  - Error Monitoring

Saueng Hoppe Klimesch Gerloff Hummel (2007)

- Complex finger movement sequences
- Varied Task Difficulty, and Memory Load (2x2 design)
- Task-related Theta Power (4-7 Hz) computed for each condition relative to 5 min. resting baseline
- Phase coherence also examined across sites
  - Phase Locking Value (0-1)
  - Then expressed as percent increase over rest

Theta Power

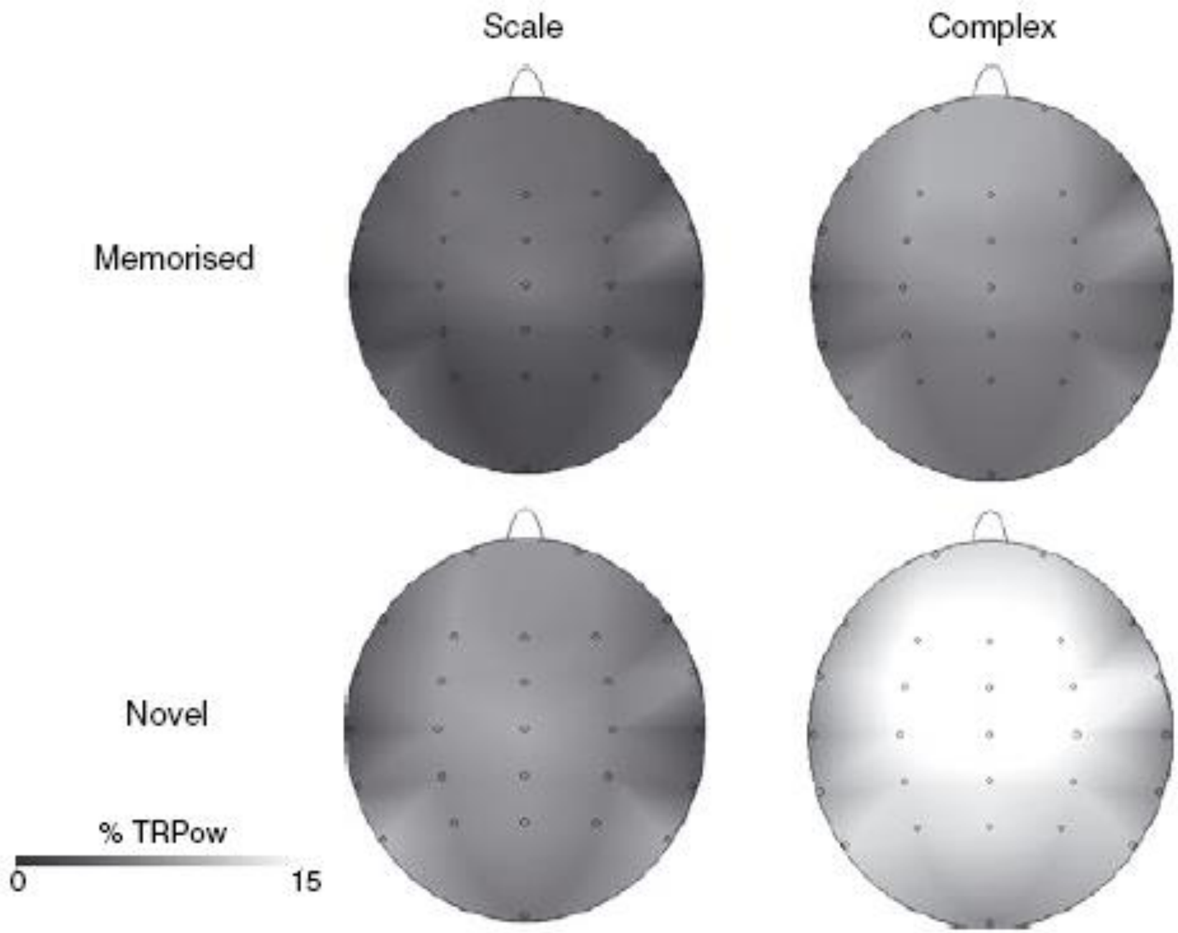
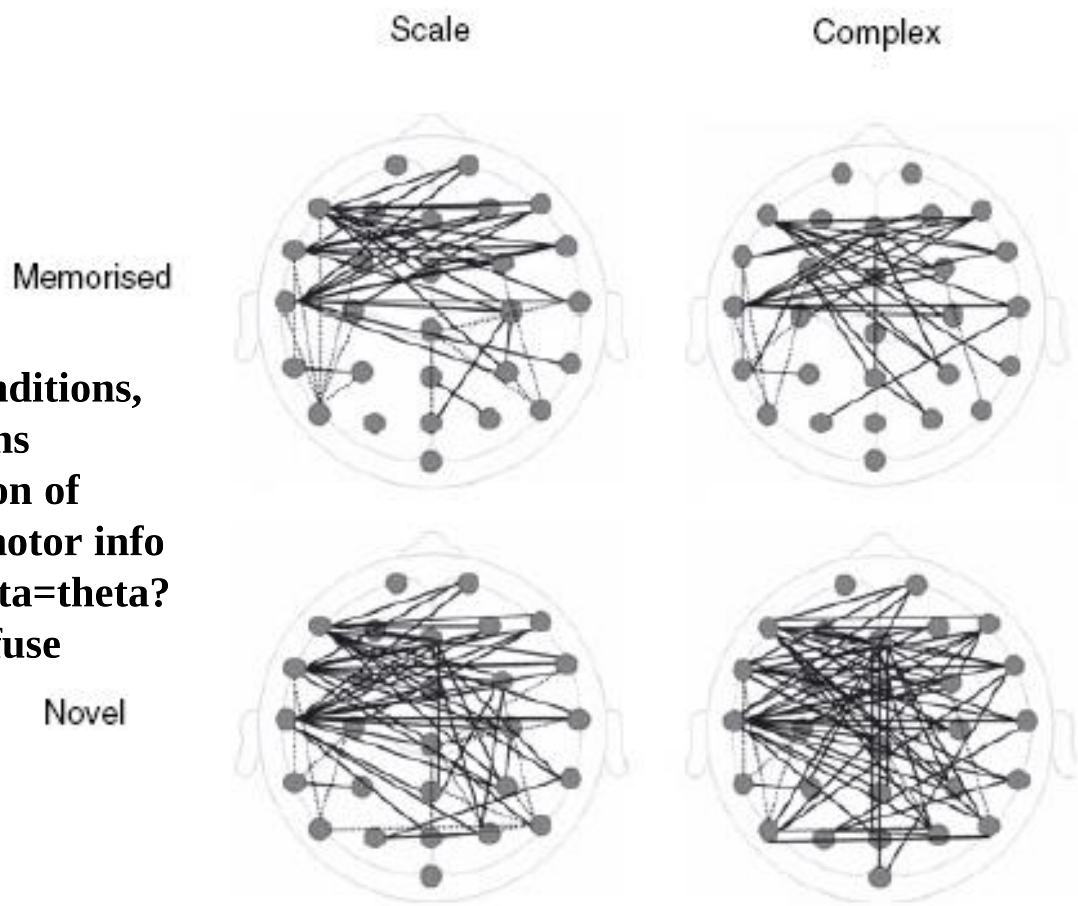


FIG. 1. Task-related theta (4–7 Hz) power increase. White indicates a strong task-related power increase compared with rest. Note that only during execution of novel and complex sequences is strong frontal-midline theta exhibited. This indicates that frontal theta activity reflects both memory load and sequence complexity.

Saueng Hoppe Klimesch Gerloff Hummel (2007)

Theta PLV



- ➢**Higher in Novel conditions, contrary to predictions**
- ➢**Speculate integration of visual with sensory-motor info**
- ➢**But, does theta=theta=theta? Fronto-central vs diffuse**

FIG. 3. Task-related theta phase coupling. Bold connections indicate a significant ($P < 0.005$) increase of theta phase coupling compared with rest, dotted lines indicate decrease of phase coupling. There are more significant electrode pairs during execution of novel sequences compared with performance of memorized ones. This effect is independent of task complexity. During both memorized and novel, there is no significant difference of the distributed theta network between scale and complex sequences.

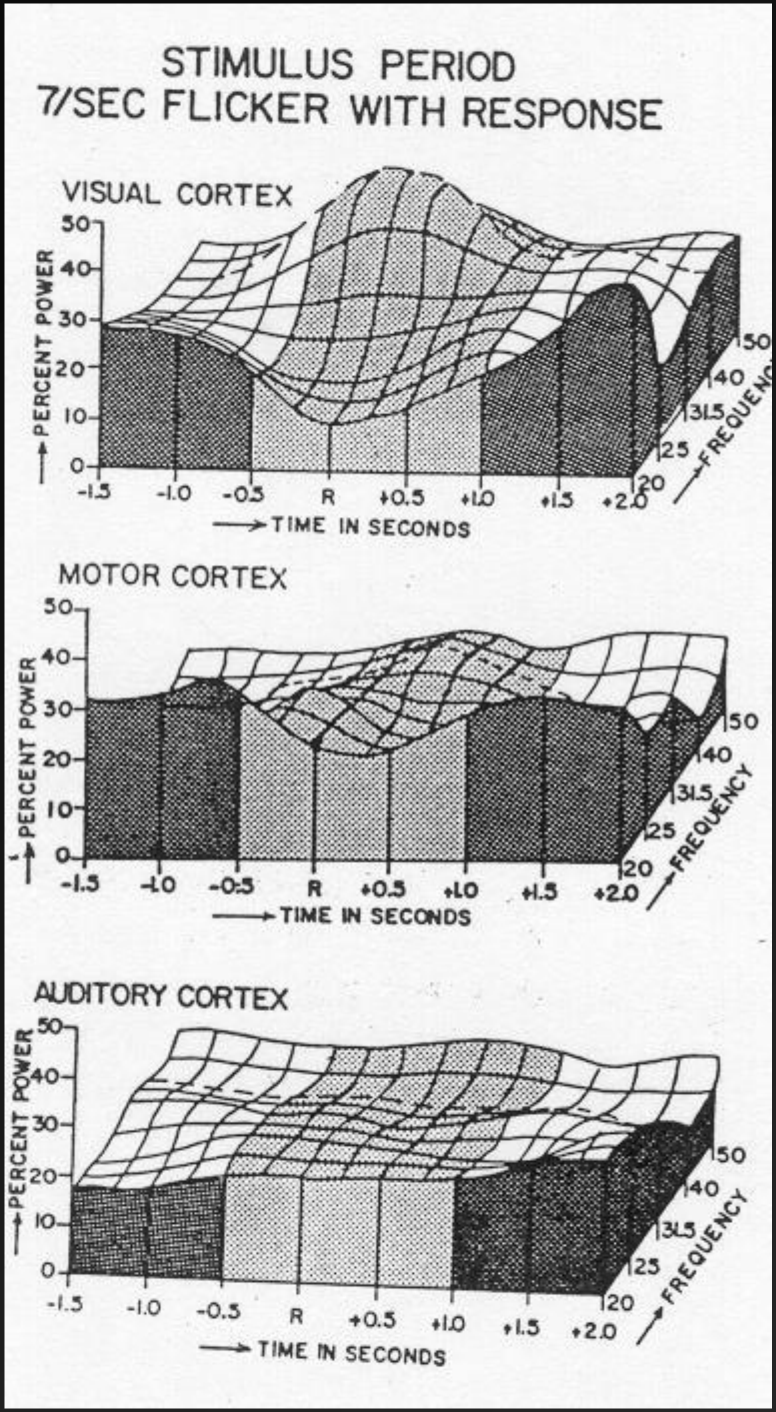
Saueng Hoppe Klimesch Gerloff Hummel (2007)

40 Hz Activity

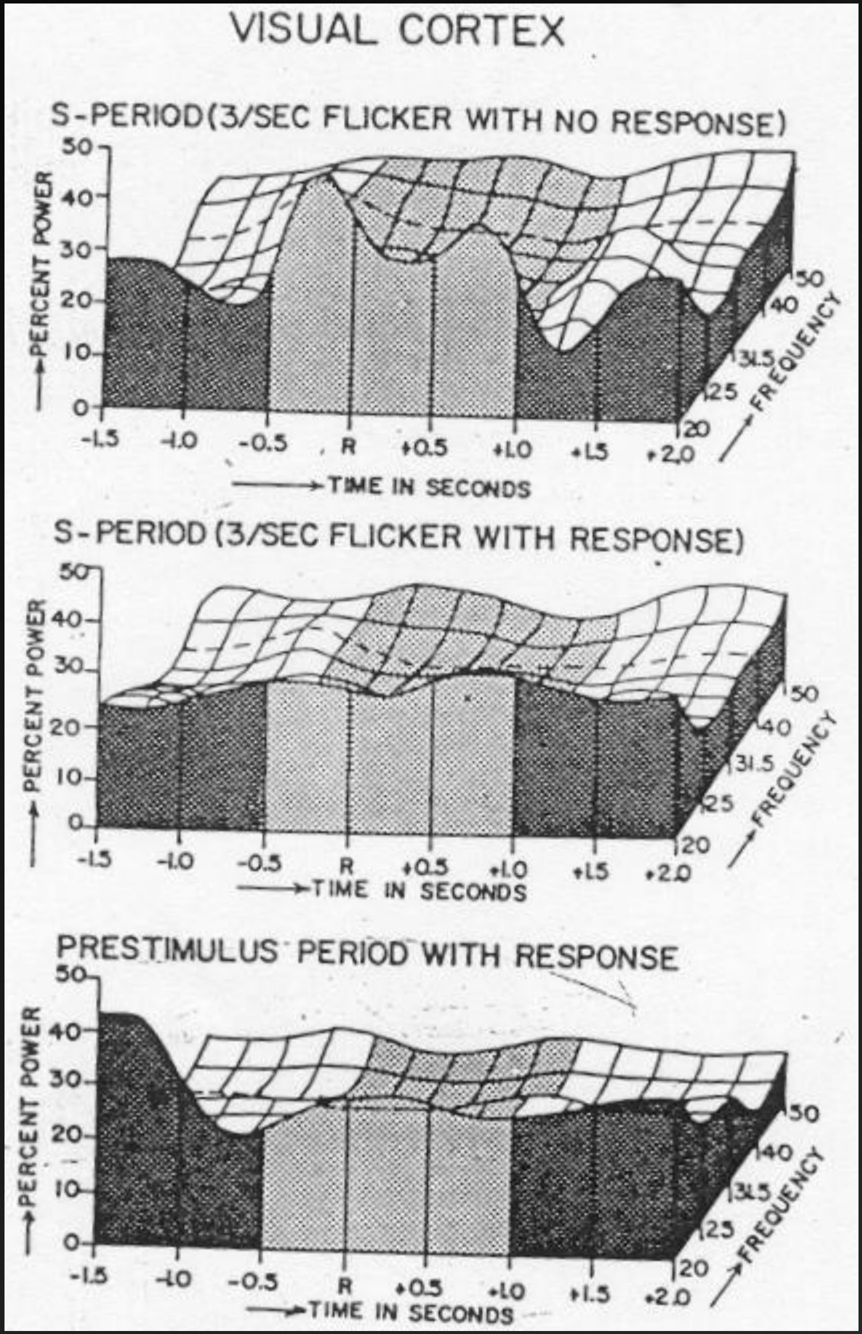
- First reports of important 40 Hz activity
- Sheer & Grandstaff (1969) review
  - pronounced rhythmic electrical bursting
- Daniel Sheer’s subsequent work until his death renewed interest in “40 Hz” phenomena

Sheer work with Cats

- Learning paradigm
- Cat must learn
  - press to S_D (7cps light flicker)
  - not S- (3 cps light flicker)
  - the hypothesis is that the synchronized 40 Hz activity represents the focused activation of specific cortical areas necessary for performance of a task



Note specificity of response to S_D, over visual cortex to discriminative stimulus, in 40-Hz range; Some hint of it later in the motor cortex. Note also decreased activity in slower bands during the same time periods.



Note very different pattern to S-. No 40-Hz change in visual cortex, and marked increase in lower frequencies at same time period.

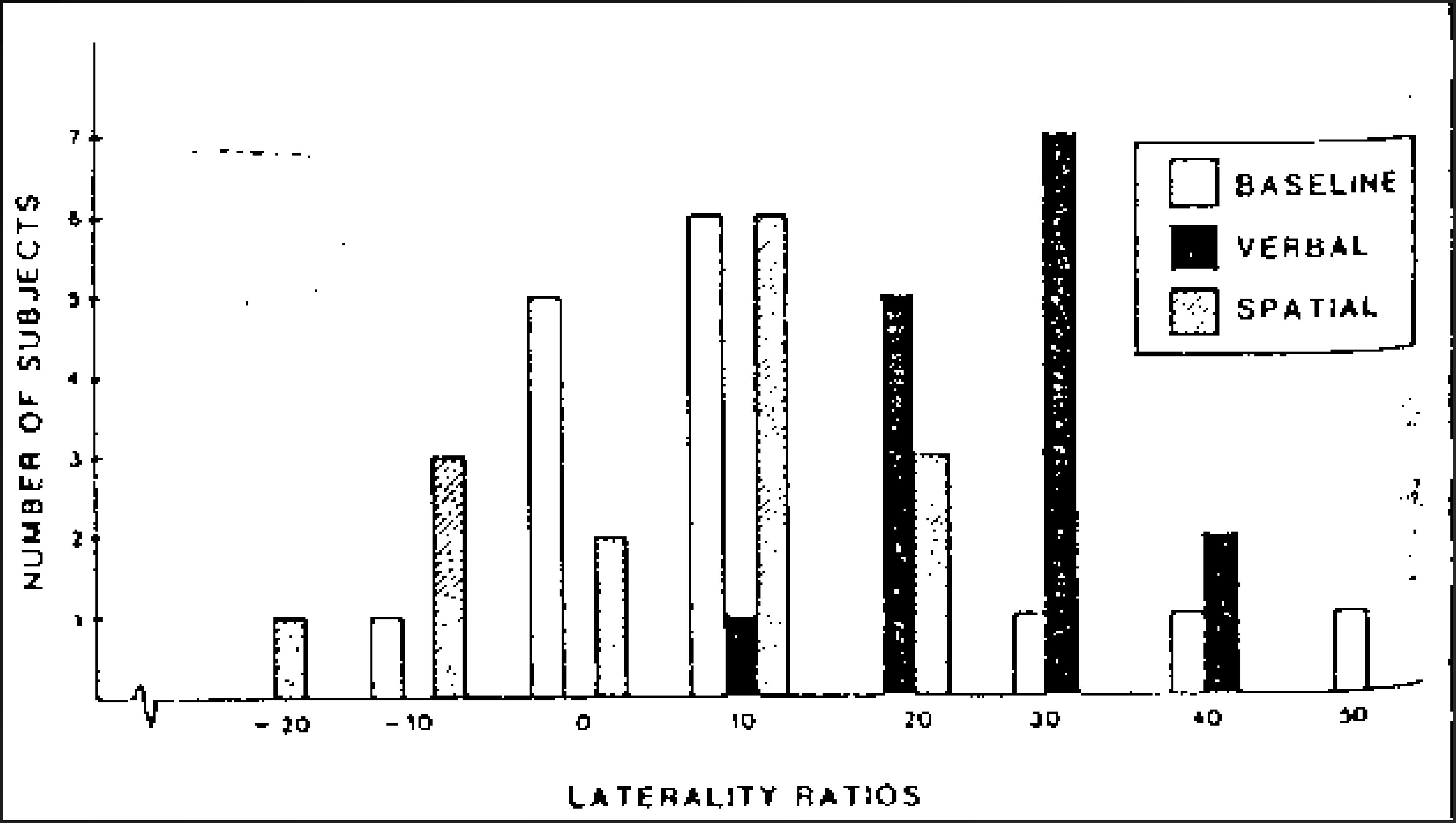
Human Studies

- Hypothesis is that 40 Hz activity correlates with the behavioral state of focused arousal (Sheer, 1976) or cortical activation
  - a "circumscribed state of cortical excitability" (Sheer, 1975)
  - Bird et al (1978)
    - biofeedback paradigm
    - increased 40 Hz activity is associated with high arousal and mental concentration
  - Ford et al., (1980)
    - subjects once trained to voluntarily suppress 40 Hz EEG are unable to maintain that suppression while simultaneously solving problems
    - concluded that problem solving and absence of 40 Hz are incompatible

Lateralized Task Effects

- Loring & Sheer (1984)
  - right-handed students
  - analogies task
  - spatial Task
- Results transformed into laterality ratios:
  - (L-R)/(L+R) 40 Hz
  - higher # => greater LH activity (P3-O1-T5 triangle vs P4-02-T6 triangle);
- Results
  - greatest variability during baseline
  - smallest variability and greatest LH activation during verbal
  - no laterality effects in the 40Hz EMG bands

Laterality of 40 Hz



Controlling for EMG contributions

- Spydell & Sheer (1982)
  - used similar tasks and found similar results
  - using conservative controls for muscle artifact

TABLE 1

Median changes in rate scores

	Median Rate Score Changes									
	Alpha		Beta II		40 Hz Total		40 Hz EEG		40 Hz EMG	
Problems	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Verbal	−36.7*	−52.4*	−20.1*	−20.2*	1.0*	0.1	1.2*	0.1	8.4*	10.6*
Rotation	−36.7*	−37.6*	−15.3*	−15.3*	0.7	1.0*	0.4	0.9*	13.9*	8.9*

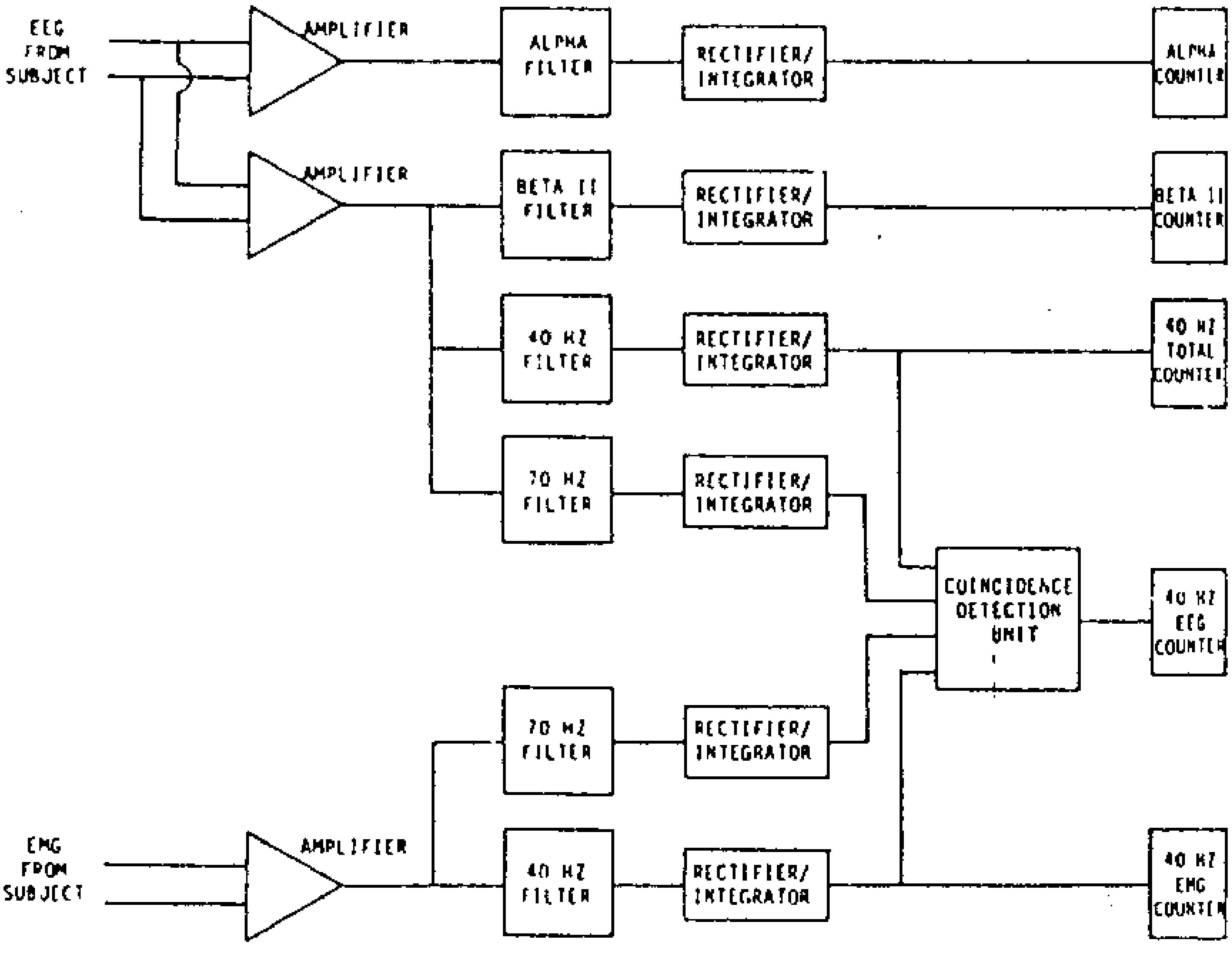
*$p < .05$.

TABLE 3

Spearman rank-order correlations between various 40 Hz activity measures

	Correlations							
	Verbal Left		Verbal Right		Rotations Left		Rotations Right	
40 Hz Measures	40 Total	40 EEG	40 Total	40 EEG	40 Total	40 EEG	40 Total	40 EEG
40 Hz EEG	.74*		.68*		.94*		.78*	
40 Hz EMG	.27	.28	.39	.05	.27	.35	.16	.25

*$p < .05$.

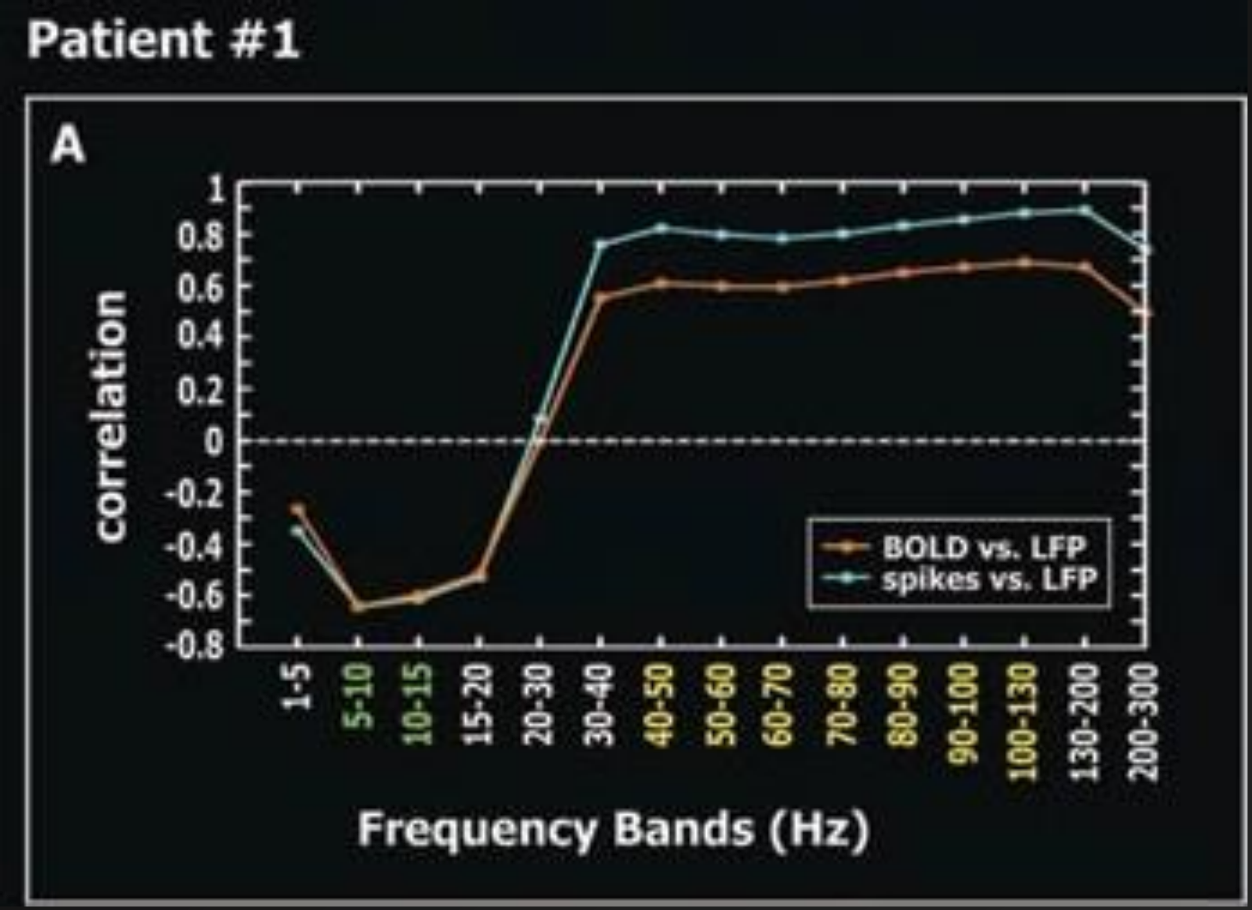

EEG FROM SUBJECT
AMPLIFIER
AMPLIFIER
ALPHA FILTER
BETA II FILTER
40 HZ FILTER
70 HZ FILTER
RECTIFIER/ INTEGRATOR
RECTIFIER/ INTEGRATOR
RECTIFIER/ INTEGRATOR
RECTIFIER/ INTEGRATOR
ALPHA COUNTER
BETA II COUNTER
40 HZ TOTAL COUNTER
COINCIDENCE DETECTION UNIT
40 HZ EEG COUNTER
70 HZ FILTER
RECTIFIER/ INTEGRATOR
EMG FROM SUBJECT
AMPLIFIER
40 HZ FILTER
RECTIFIER/ INTEGRATOR
40 HZ EMG COUNTER

Individual Differences

- Spydell & Sheer (1983), Alzheimers
  - controls showed task related changes in EEG with appropriate lateralization
  - Alz did not
- Schnyer & Allen (1995)
  - Most highly hypnotizable subjects showed enhanced 40 hz activity

So this is exciting, why hasn't this work exploded?

- The EMG concern
  - The concern is likely over-rated (recall **Table 3**)
- Sheer died
- But not all is lost, as there is renewed interest…



Mukamel et al *Science* 2005

recorded single unit activity and local field potentials in auditory cortex of two neurosurgical patients and compared them with the fMRI signals of 11 healthy subjects during presentation of an identical movie segment. The predicted fMRI signals derived from single units and the measured fMRI signals from auditory cortex showed a highly significant correlation.

Singer (1993)

- Revitalized interest in the field

The Binding Problem

- Potentially infinite number of things and ideas that we may attempt to represent within the CNS
  - Cells code for limited sets of features,
  - These must somehow be integrated
  - -- the so-called binding problem
- If there exists a cell for a unique contribution of attributes, then convergent information from many cells could converge on such a cell
  - But there are a finite # of cells and interconnections
- And even the billions and billions of cells we have cannot conceivably handle the diversity of representations

The Functional Perspective -- as yet merely a theory

- There is no site of integration
  - Integration is achieved through simultaneous activation of an assembly of neurons distributed across a wide variety of cortical areas
  - Neurons in such assemblies must be able to adaptively identify with other neurons within the assembly while remaining distinct from other neurons in other assemblies
  - This association with other neurons is through a temporal code of firing (Synchronicity)
    - This even allows for the possibility that a single neuron could be part of two active assemblies (via a multitasking procedure)

Implications

- Also allows for the possibility that there exists no direct neuronal connection between neurons within an assembly
  - merely the fact that they are simultaneously activated that makes the unified experience of the object possible
- This is most likely when there is an oscillatory regularity
  - If networks are tuned to a single frequency, they are easy to synchronize, but difficult to desynchronize – PROBLEM!
  - Therefore it may be adaptive to have a broader-band oscillator (centered on ~40 hz)
  - Cannot be too slow (e.g., alpha) since this would be inadequate to successfully bind percepts together efficiently
  - Cannot be much faster than gamma since the human nervous system cannot allow synchronization at frequencies much beyond gamma

Functional Role of Gamma Synchronization

- Feedforward coincidence detection
  - To summate effectively, signals must arrive at post-synaptic neuron from multiple sources within msec of each other (else decay)
  - Gamma-band synchronization can lead to temporal focusing of inputs from multiple and distributed pre-synaptic neurons
- Rhythmic Input Gain Modulation
  - Excitatory input is most effective when it arrives out of phase with inhibitory input and vice versa
  - Allows for precision and efficiency of signal transmission (or inhibition)

Fries, 2009

Implications

- This view is a dynamic view
  - depends on experience
  - can change with experience
- Synchronously activated units more likely to become enhanced and part of an assembly that will subsequently become synchronously activated
- Singer concludes:
  - Points out the problem of looking for synchronous activation on the micro level, suggesting that a return to the EEG literature looking for task-dependent synchronization in the gamma (aka 40 Hz) band!
- Forty-Hz may indeed make a comeback!
  - "Forty" = 40 $\pm$ some range
  - Gamma! (Stay tuned during advanced topics)