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
Alpha Vs Activity Assumption (AAA)

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
During positive affect, the frontal leads display greater relative left hemisphere activation compared with negative affect and vice versa.
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 (\(\ln[\text{right}] - \ln[\text{left}]\)) and trait anger. Positive correlations reflect greater left activity (less left alpha) is related to greater anger.

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 during 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.
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 I think it will be fun.

Carver & White, 1994
Motivational Styles and Depression

$r = .45$

Mid-Frontal Asymmetry and BAS Scores

$r = .00$

Harmon-Jones & Allen, 1997
Motivational Styles and Depression Replications

Sutton & Davidson, 1997

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

Coan & Allen, 2003
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
Biofeedback provided 3 times per week for 12 weeks
“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)
EEG responds to directed facial actions

From Coan, Allen, and Harmon-Jones (2001)
States – how short can they be?
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 $0.85 \leq r_{TT} < 0.90$ and bold numbers indicating $r_{TT} \geq 0.95$ (the pair C82-C81 was omitted).
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.
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

World Disability Adjusted Life Years (Millions)

- Lower Respiratory Infections: 94.5
- Diarrhoeal Diseases: 62.6
- Unipolar Depression: 65.5
- Ischemic Heart Disease: 72.8
- HIV/AIDS: 58.5

World Health Organization, 2008
Upper Income Countries

World Disability Adjusted Life Years (Millions)

- Unipolar Depression: 10.0
- Ischemic Heart Disease: 4.4
- Cerebrovascular Disease: 4.8
- Alzheimer's and Other Dementias: 7.7
- Alcohol Use Disorders: 4.2

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

Age at Select Percentiles for Onset of MDD

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

Negative Affect and Mood
Behavioral Disengagement
Withdrawal Motivation
Low Behavioral Activation

\[ \text{Ln(R)} - \text{Ln(L)} \] Alpha
Hypothesized Findings

- MDD+
- MDD−
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**

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, & Hernandez-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

mood.swings
marked.anger
irritability depressed.mood
appetite.changes
difficulty.concentrating
fatigue
anxiety
sleep.difficulties
feeling.out.of.control
physical.symptoms
decreased.interest
tension

Accortt & Allen, 2006
PMDD

Assessed at
- Late-Luteal
- Follicular

Accortt & Allen, 2006
Specificity or Spectrum: PMDD

* Accortt & Allen, 2006

Asymmetry by region

\[
\text{ln}(R) - \text{ln}(L) \text{ alpha power}
\]

- **F7F8**
- **F3F4**
- **FTC12**
- **T3T4**

Region

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

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
Completed BDI in Pre-Testing (N = 10,227)

Invited to Participate in Study Screening (N = 1904)

Invited for Interview (N = 520)

Did Not Respond (N = 863)

Excluded After Screening (N = 521)
- Epilepsy (N = 3)
- Unknown (N = 19)
- Did Not Schedule Interview (N = 65)
- Head Injury/LOC (N = 85)
- Psychotropic Medication (N = 104)
- Left-handedness (N = 245)

Eligible and Enrolled in Study (N = 323)

Excluded After Interview (N = 197)
- No Longer Interested (N = 9)
- Psychotropic Medication (N = 11)
- Unknown (N = 14)
- Did Not Show for Interview (N = 15)
- Subsyndromal Past MDD and No Current MDD (N = 18)
- Did not Meet targeted BDI severity range just prior to screening (N = 30)
- Head Injury/LOC (N = 33)
- Comorbid Axis I Diagnoses (N = 67)

Final Sample for Analysis (N = 306)
- Withdrew From Study Prior to EEG Recording (N = 10)
- Excluded for a diagnosis of Current Dysthymia without MDD (N = 7)

Anxiety Disorders
- PTSD (N = 1)
- Social Phobia (N = 2)
- Panic Disorder (N = 3)
- Anxiety NOS (N = 4)
- Specific Phobia (N = 6)
- OCD (N = 7)
- GAD (N = 11)

Substance Use
- Dependence (N = 13)
- Abuse (N = 33)

Psychotic Disorders
- Psychotic NOS (N = 1)
- Schizophrenia (N = 1)
- Bipolar Disorder (N = 4)

Eating Disorders
- Eating NOS (N = 4)
- Bulimia (N = 7)
- Anorexia (N = 8)

Other
- Hypochondriasis (N = 3)

Stewart, Bismark, Towers, Coan, & Allen 2010, J Abnormal Psychology
Reference Effects

AR

CSD

Cz

LM

Resting Eyes Closed Alpha Power

CSD Toolbox

MATLAB®
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 μV² for AVG, Cz, and LM references, and ln μV²/cm² for CSD referenced data. MDD = major depressive disorder; AVG = average; CSD = current source density; CZ = Cz; LM = linked mastoid.
STICK WITH CSD...
Interim Synopsis: Endophenotype Desiderata

- 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)
<table>
<thead>
<tr>
<th>Average Reference</th>
<th>Residualized Power</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Diagram" /></td>
<td><img src="image2.png" alt="Diagram" /></td>
</tr>
<tr>
<td><img src="image3.png" alt="Diagram" /></td>
<td><img src="image4.png" alt="Diagram" /></td>
</tr>
</tbody>
</table>

†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.

Alpha Power at Homologous Sites is *Highly* Correlated

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

Consider residualized left lead power when $L \approx R$

\[ L_{resid} = L - L \]

\[ L = a + b(R) \]

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

\[ L = 0 + 1(R) = R \]

\[ L_{resid} = L - L = L - R \]

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”

\[
\text{Asym} = \ln(\text{Right}) - \ln(\text{Left}) \text{ Alpha Power}
\]
F5
F6

Raw

8-13 Hz Filtered

Ln Power

Continuous R-L Difference

1%
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

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?
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

\[ r^2 = 0.42 ! \]

(1%)

Allen & Cohen, 2010
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?
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.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Conventional</th>
<th>Peri-burst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime MDD</td>
<td>.43</td>
<td>.38</td>
</tr>
<tr>
<td>Past MDD only</td>
<td>.43</td>
<td>.27</td>
</tr>
<tr>
<td>Current MDD (with or without Past MDD)</td>
<td>.35</td>
<td>.45</td>
</tr>
</tbody>
</table>
Prospective Pilot Data

A. EEG Asymmetry by BDI Follow-up

B. Peri-Burst Asymmetry by BDI Follow-up
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?
(A) Positive bursts

Alpha power

Alpha phase coher.

(B) Negative bursts

Alpha power

Alpha phase coher.

Peri-burst time (ms)

-150 -75 0 75 150

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?

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<td><img src="image14.png" alt="Image" /></td>
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*OEEG in the ISA: Amplitude*
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
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.
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.
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

  - right-handed students
  - analogies task
  - spatial Task
- Results transformed into laterality ratios:
  - \( \frac{(L-R)}{(L+R)} \) 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
# Alpha, Beta II, 40 Hz EEG, and 40 Hz EMG Activity

## TABLE 1

*Median changes in rate scores*

<table>
<thead>
<tr>
<th>Problems</th>
<th>Alpha</th>
<th>Beta II</th>
<th>40 Hz Total</th>
<th>40 Hz EEG</th>
<th>40 Hz EMG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Verbal</td>
<td>-36.7*</td>
<td>-52.4*</td>
<td>-20.1*</td>
<td>-20.2*</td>
<td>1.0*</td>
</tr>
<tr>
<td>Rotation</td>
<td>-36.7*</td>
<td>-37.6*</td>
<td>-15.3*</td>
<td>-15.3*</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*p < .05.

---

# Spydell and Sheer

## TABLE 3

*Spearman rank-order correlations between various 40 Hz activity measures*

<table>
<thead>
<tr>
<th>40 Hz Measures</th>
<th>Verbal Left</th>
<th>Verbal Right</th>
<th>Rotations Left</th>
<th>Rotations Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 Hz EEG</td>
<td>.74*</td>
<td>.68*</td>
<td>.94*</td>
<td>.78*</td>
</tr>
<tr>
<td>40 Hz EMG</td>
<td>.27</td>
<td>.28</td>
<td>.39 .05</td>
<td>.27 .35</td>
</tr>
</tbody>
</table>

*p < .05.
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 ± some range
  - Gamma! (Stay tuned during advanced topics)