Announcements 3/25/19

- Paper/Proposal Guidelines available on course webpage (link in D2L too)
- Two paragraph prospectus due (on D2L) no later than Monday April 8
- 3x5 time

Fourier Series Representation

- Pragmatic Details
  - Lowest Fundamental Frequency is 1/T
  - Resolution is 1/T
- Phase and Power
  - There exist a phase component and an amplitude component to the Fourier series representation
  - Using both, it is possible to completely reconstruct the waveform.

Fourier Series Representation

- If a signal is periodic, the signal can be expressed as the sum of sine and cosine waves of different amplitudes and frequencies
- This is known as the Fourier Series Representation of a signal

From: Curham & Allen (submitted)
Pragmatic Concerns

- Sample fast enough so no frequencies exceed Nyquist
  - Signal bandwidth must be limited to less than Nyquist
  - Violation = ERROR
- Sample a long enough epoch so that lowest frequency will go through at least one period
  - Violation = ERROR
- Sample a periodic signal
  - If subject engaging in task, make sure that subject is engaged during entire epoch
  - Violation = ??, probably introduce some additional frequencies to account for change

Demo of EEG Data

- CNT Data to Frequency Domain Representation

Frequency-domain EEG applications and methodological considerations

Applications

- Emotion Asymmetries
  - Lesion findings
    - Catastrophic reaction (LH)
    - RH damage show a belle indifference
  - EEG studies
    - Trait (150+ 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)

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

Oakes et al, 2004, Human Brain Mapping

EEG Asymmetry, Emotion, and Psychopathology

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

State Anger and Frontal Asymmetry

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

Individual Subjects’ Data

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.


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.”
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

Relative Left Frontal, Anger, & Aggression as a Function of Condition
Frontal EEG asymmetry predicts Anger and Aggression
Not in Neutral condition … no relationship
Strongly in Insult condition
\[ r = .57 \text{ for anger} \]
\[ r = .60 \text{ for aggression} \]
Note: partial \( r \) adjusting for baseline indiv diffs in asymmetry and affect

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

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)

Motivational Styles and Depression

\[ r = 0.45 \]

Mid-Frontal Asymmetry and BAS Scores
Mid-Frontal Asymmetry and PA Scores

\[ r = 0.00 \]

Harmon-Jones & Allen, 1997

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.

Motivational Styles and Depression

Replications

Coan & Allen, 2003

Smaller L>R 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

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

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
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**
  - Stranger/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)

States – how short can they be?

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

DAVID N. TOWERS AND JOHN J. B. ALLEN
Department of Psychology, University of Abertay, Dundee, Scotland, UK

Abstract
Frontal alpha asymmetry is typically computed using alpha power averaged across many overlapping epochs. Previous research has estimated the internal consistency reliability of asymmetry by dividing rating EEG sessions into segments of approximately 10 epochs. Here we present an estimation of the internal consistency reliability of frontal EEG asymmetry using the Spearman–Brown prophecy formula. The Spearman–Brown formula partly depends on the number of data, such that this approach may underestimate reliability in using less than the number of defined items available. Reliability estimates for accepting H06 data in the present study (N_04 subjects, 8 sessions) were obtained using mean split-half correlation with epoch alpha power co-variantized at separate times. Estimates of all scalp sites and reference schemes approached .90 with as few as 108 epochs, suggesting the internal consistency of frontal asymmetry is greater than that previously reported.
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)

Middle Income Countries

- Lower Respiratory Infections
- Diarrhoeal Diseases
- Unipolar Depression
- Ischemic Heart Disease
- Cerebrovascular Disease
- Road/Traffic Accidents
- Lower Respiratory Infections

Upper Income Countries

- Lower Respiratory Infections
- Diarrhoeal Diseases
- Unipolar Depression
- Ischemic Heart Disease
- Cerebrovascular Disease
- Alzheimer's and Other Dementias
- Alcohol Use Disorders

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

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

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 of the probit MD, to open-cohort and panic disorder (PD) in affected siblings. These results are obtained from a Cox proportional hazard model controlling for age, sex, and birth cohort. We fitted these results pairwise models with a single inflection point using a grid search to find the single inflection point that maximized the model -2 log likelihood.

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

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; 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; Possiel, Lo, Fritz, & Seeman, 2008; Schaffer, Davidson, & Saron, 1983; Vuga, et al., 2006);
- 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);

PMDD

Assessed at
- Late-Luteal
- Follicular

Specificity or Spectrum: PMDD

Accortt & Allen, 2006
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
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

Reference Effects

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

Figure 2. Panel A shows frontal alpha asymmetry scores (0.13 Hz at Fz-F1, Fz-F2, F6-F5, F8-F7) by lifetime MDD status for each reference montage across all four frontal regions depicted on the head inset. 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(\(\text{AUG}_C\)) for AVG, C2, and LM references, and ln(\(\text{AUG}_C\)) for CSD-referenced data. MDD = major depressive disorder; AVG = average; CSD = current source density; C2 = 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 54 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, Bio Psychology 2018

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
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”

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

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?

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<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</td>
<td>.35</td>
<td>.45</td>
</tr>
</tbody>
</table>

Stewart, Bismark, Towers, Coan, & Allen 2010, J Abnormal Psychology
Prospective Pilot Data

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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)
Multi-modal Imaging

- Tether EEG asymmetry to other measures neural systems known to be involved in MDD
- 23 subjects with simultaneous EEG and fMRI during resting state

TIME AND SPACE

Multi-modal Imaging

- Tether EEG asymmetry to other measures neural systems known to be involved in MDD

Mayberg et al., 2005

Remove Artifacts from Resting EEG

EEG Alpha Asymmetry is Negatively Correlated with IFG Connectivity in Two ACC-seeded Resting State Networks

Spatially-enhanced EEG asymmetry (using CSD transform) at sites F8-F7 is related to resting state connectivity between left inferior frontal gyrus and two ACC-seeded networks.

Allen, Hewig, Wittner, Hecht, & Schneyer, In preparation
EEG-fMRI Synopsis

- Less relative left frontal activity (indexed by EEG) is related to increased connectivity of left IFG to two ACC-seeded RS networks
- Consistent with:
  - Hyper-connectivity in RSfMRI emotion networks in MDD (e.g., Grecius et al., 2007; Sheline et al., 2010)
  - Frontal EEG asymmetry findings of less relative left frontal activity in risk for MDD.
- Alpha power may regulate network connectivity
  - Note: Between vs Within Subjects

**Within Subjects’ Moderation of RSfMRI Connectivity**

- Calculate F8-F7 alpha asymmetry for each TR
  - EEG leads TR by 4.096 seconds
  - Median split into high (left) and low (right)
  - Entered as moderator in PPI approach (cf. Friston et al., 1997)
    - Tests whether strength of connectivity to seed region varies as a function of the moderator

Within (red) and Between (blue) Within-subject effects more extensive

**Cognitive Control over Emotion**

- IFG has a key role in mediating the success of cognitive control over emotional stimuli
Cognitive Control over Emotion

- **Left IFG:** Language and self-referential processing
- **Right IFG:** Attentional control, behavioral inhibition, suppression of unwanted thoughts, attention shifting, efforts to reappraise emotional stimuli

**Working Hypothesis:**
- Hyperconnected left IFG and emotion networks: rumination
- Hypoconnected right IFG: difficulty disengaging from emotion