Title
Measuring & Modulating Hemispheric Attention

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Publication Date
2012

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Assessment and Modulation of Hemispheric Attention

A dissertation submitted in partial fulfillment of the degree of

Doctor of Philosophy in Psychology

by

Andrew Robert Hill

2012

ABSTRACT OF THE DISSERTATION

Assessment and Modulation of Hemispheric Attention

by

Andrew Robert Hill

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2012

Professor Eran Zaidel, Chair

This dissertation presents a novel behavioral task of lateralized attention: the speeded Lateralized Attention Network Task (sLANT) and establishes behavior and ERP features of single and multiple test administration. In addition, EEG Biofeedback was implemented in a double-blind, randomized, placebo controlled experiment contrasting the effects of EEG training protocols on hemispheric attention as measured by the sLANT. EEG Biofeedback mechanisms were also investigated. Protocols were selected to contrast training hemisphere (C3 vs C4) and reward frequency (SMR: 12-15 Hz, Beta: 15-18 Hz) with active placebo training. Significant protocol by session effects on performance Accuracy and ERP features demonstrate EEG Biofeedback has an effect beyond "Sham", has specific protocol effects by training hemisphere and frequency, and can be successfully blinded in a research context.

The dissertation of Andrew Robert Hill is approved.

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2012

Table of Contents

List of Figures & Tables

Chapter 1

Chapter 2

List of Figures & Tables (continued)

Chapter 3

Appendix: Spectral EEG Change with EEG BFB (Additional Ch 3 Figures)

Acknowledgements

I would like to express my deep gratitude to my advisor and committee chair, Dr. Eran Zaidel, for his support and guidance throughout my PhD program and specifically in supporting the research described in this document. It was a large undertaking both in terms of data gathering and analysis. I grew as a person and a scientist throughout, and I would never have been able to finish without the continued support of Dr. Zaidel and my other committee members, Dr. Dean Buonomano, Dr. Ladan Shams, and Dr. Andrew Leuchter.

I would also like to thank Dr. Larry Hirshberg for his training in the field of Neurofeedback and Dr. Jack Johnstone for his encouragement to apply to UCLA and both of these people for their scientific and professional insight around all things EEG.

Finally, I would like to thank my parents for their encouragement and support, always.

Curriculum Vitae

Education & Academic Status

- 2007 Master of Arts, Psychology / Cognitive Neuroscience, UCLA.
- 2005 GRE Scores: 680 Verbal, 710 Quantitative, 5.5 Analytical Writing
- 1994 Bachelors of Science, Psychology / Neuroscience, University of Massachusetts, Amherst.

Clinical, Laboratory, & Professional Experience

- Teaching Fellow, GE Cluster Program: Frontiers in Human Aging, UCLA, 10/2010 – present
- Editorial Board, Journal of Neurotherapy, 10/2010 – present (from 16:1)
- Graduate Student Researcher, Zaidel Cognitive Neuroscience Lab, UCLA, 10/2007 – present
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Publications

- Hill, A., Zaidel, E. (2011, September) Behavioral and EEG Effects of Lateralized EEG Biofeedback on Lateralized Attention Network Task (LANT) and Lateralized Continuous Performance Task (LCPT); Oral presentation, 19th Annual Conference of the International Society For Neurofeedback & Research, Phoenix, AZ.
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Laboratory Skills & Experience

- Dense array (64-channel) EEG recording and analysis, using BioSemi, NeuroScan, other platforms.
- ERP, EEG, & ICA analysis of EEG using MATLAB, EEGLAB, & ERPLAB
- Additional EEG expertise including Biofeedback training and Quantitative EEG (QEEG) assessment. Interpretation of EEG activation patterns and tracking of behavioral data. Training of EEG with various software & hardware (BioExplorer, EEGer, J&J, Procomp, Pocket Neurobics, etc).
- Hemoencephalography biofeedback using pirHEG & nirHEG.
- Volumetric analysis of MRI with FSL.
- Basic biochemistry including immunoassay, staining, microsurgery, computer-aided cellular analysis.
- Behavioral testing using ePrime and Presention based tasks, including the Lateralized Attention Network Task (LANT), as well as other tests of sustained attention (IVA and TOVA).
- Experience in designing and implementing novel Flanker, Continuous Performance and Go-NoGo tests.

Teaching Skills & Experience

- Teaching Associate for Psychology courses including Physiological Psychology, Sex & the Law, Introductory Psychology, and others.
- Instructor of Record for Teaching Practicum Program: Summer 2010 Intro Psych
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Technology Skills

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Introduction

This dissertation reviews several lines of data gathered from an experiment designed to manipulate attention in each hemisphere of the brain, using EEG Biofeedback. First, we developed a new lateralized test of attention that measures executive Conflict and spatial Orienting in each hemisphere - the "speeded" Lateralized Attention Network Task.

Chapter 1 reviews this test in detail, demonstrating it's sensitivity to behavioral changes in each hemisphere, and shows electrophysiology (ERP) of each test component that can distinguish networks of attention in each hemisphere.

Chapter 2 discusses the sLANT in more detail. It also introduces a series of Biofeedback training sessions and additional sLANT testing, and examines the behavioral and electrophysiological changes caused by EEG Biofeedback. Chapter 2 reviews the effects of giving multiple (3) administrations of the sLANT within 1 week, and contrasts this "practice effect" of behavioral and ERP habituation with attention and EEG changes caused by EEG Biofeedback training

Chapter 3 explores the effects of a dense-sequence of EEG Biofeedback in more depth. First we discuss the ERP evoked by the Biofeedback reward signal itself, and demonstrate differences across 5 sessions of Biofeedback. We also provide evidence of specific frequency bands changing in (spectral) EEG, on Eyes Closed and Eyes Open band power before and after EEG training.

The overall goals of this experiment was to examine a narrow set of EEG Biofeedback protocols that emphasized the effect of (active) protocol vs. Placebo. We also chose active protocols to provide a contrast of hemisphere training (C3 vs. C4) and reward band (SMR vs. Beta). The implementation of a sophisticated Sham allowed gathering a rich set of data that

provided insight into the basic processes of hemispheric attention and into the mechanism of EEG Biofeedback. Further, this research doesn't only answer questions about EEG biofeedback but investigates the sensitivity of Behavior versus Electrophysiology in a fairly standard Cognitive Neuroscience paradigm (the LANT is a version of the Eriksen Flanker Task).

Chapter 1: Measuring attention in the hemispheres: The speeded Lateralized Attention Network Test (sLANT)

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This material is based upon work supported by, or in part by, the U.S. Army Research Laboratory and the U.S. Army Research Office under grant W911NF-07-1-0248 to Eran Zaidel. Citation of trade name does not constitute an official government endorsement or approval of the use of such commercial products. The findings of this report are not to be construed as an official Department of the Army position, unless so designated by other authorized documents.

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Abstract

The Lateralized Attention Network Test (LANT) is a brief test that evaluates independent networks of attention within each hemisphere. We constructed a speeded version of the LANT to optimize use in an Event Related Potential (ERP) paradigm. We evaluated the ability of this new test to behaviorally measure LANT attention networks as well as identify corresponding physiological characteristics of these networks. Speeded trial presentation and increased numbers of trials improved sensitivity of behavioral accuracy measures versus the LANT documented in Greene, et al, 2008. The speeded-LANT (sLANT) validly measured executive Conflict and spatial Orienting in behavior, although omitted an estimate of Alerting in favor of increased trial count. The P3 ERP component correlated with behavioral latency and accuracy sLANT performance; differences between ERP components distinguished networks. The scalp distribution of these ERP components lends weight to existing theories of hemispheric and modular attention networks.

Introduction

Hemispheric Specialization of Attention and its Assessment

Existing research suggests that aspects of selective attention are lateralized and that hemispheric specialization may be observed for both covert orienting of spatial attention and executive response conflict. Evidence comes from both behavioral and physiological research in typical and clinical populations (Posner & Petersen, 1990). Behavioral findings suggest that each hemisphere has it's own independent attention system and that each hemisphere may differ in component networks (Zaidel, 1995). In contrast, physiological results often emphasize exclusive specialization of one hemisphere for specific components of attention, as seen in hemifield neglect. There is also abundant evidence of an anterior/posterior division of attention resources, suggesting parietal cortex is involved in orienting while frontal areas are involved in executive attention. For example, violations of expectation created by conflicts in information processing (Botvinick, Braver, Barch, & Cohen, 2001) are attributed to anterior cingulate cortex and dorsal frontal areas (Fan, McCandliss, Fossella, Flombaum., & Posner, 2005). The right hemisphere may also have a dominant role in orienting attention to locations in space, especially parietal areas (Corbetta & Schulman. 2002). Lateralized attention models suggest each hemisphere is biased towards contralateral space (Spencer & Banich, 2005) although the right hemisphere has greater competence to attend to ipsilateral space (but see Zaidel, Clarke, & Suyenobu, 1990; Zaidel, & Iacoboni, 2003). The right hemisphere may also serve additional attention control and salience tuning functions (Corbeta & Schulman, 2002). This suggests that components of attention are separable along both anterior/posterior and left/right divisions of the cortex, although shared resource models are not ruled out. For this paper we will consider Posner's model of selective attention, including three component networks, namely executive

Conflict, spatial Orienting, and Alerting to a stimulus. To measure these constructs Posner combined an Eriksen Flanker Task (Eriksen & Eriksen, 1974) with the Posner paradigm for measuring covert Orienting of spatial attention in a computerized test called the Attention Network Test (Fan & Posner, 2004). The Eriksen flanker task produces response Conflict between targets and incongruent distractors (flankers). Cues are used to estimate both Orienting and Alerting. Orienting is provided by a spatial cue preceding each target while Alerting is estimated by non-spatial cues.

Zaidel developed a variation of the ANT labeled the Lateralized Attention Network Task (LANT; Greene, Barnea, Herzberg, Rassis, Neta, Raz, and Zaidel, 2008). The LANT presents cues and subsequent targets with flanking distractors, with a force choice identification of the target direction. Target and simultaneous flankers are flashed to one visual field using tachistoscopic presentation. Presenting test stimuli to one hemifield and examining responses made with the ipsilateral hand enables the LANT to estimate Conflict, Orienting, and Alerting in each hemisphere separately. Adding cross-hemifield cue-target sequences enable separating out Orienting Cost from spatial Orienting, as a resource cost from attending to invalid cues; examining trials for the response hand contralateral to target visual field may also distinguish interhemispheric from intrahemispheric resources.

Cue and Flanker effects are present in the ANT and LANT. Targets with congruent flankers produce faster and more accurate responses than those with incongruent flankers (executive Conflict). Predictive validity of spatial cues facilitates performance (Orienting effect). Cued targets are also faster and more accurate than targets without a cue (Alerting effect). The LANT adds a neutral spatial cue (center or bilateral cue) to the spatially valid or invalid cue presentation. Invalid cues facilitate covert attention to the visual field where a

subsequent target will not occur. Performance differences across valid cues versus invalid cues compared to neutrally cued trials refine Orienting into components of Orienting Benefit and Orienting Cost. Several studies have used variations of the ANT or LANT to measure attention networks. Greene, et al (2008) compared the ANT and LANT and demonstrated that the LANT provides valid and reliable measures of attention networks which are similar to networks as measured by the ANT. Reaction time measures were found to be more sensitive in the LANT, with behavioral accuracy apparently near ceiling.

ERP Correlates of Attention Networks

While performance on the LANT is well characterized, ERPs are not, but may be critical for validating hemispheric results observed in the behavior. Existing theories of attention physiology also often suggest anterior resources provide executive function and posterior source serve sensory function. This division is supported by ERP scalp amplitude differences (Fan, Byrne, Worden, Guise, McCandliss, Fossella, & Posner, 2007) and supports our theory of prefrontal control of inhibitory processes serving Conflict versus posterior sensory and visual cortices acting to Orient visual attention. The degree to which attention can modify the corresponding ERP components is also a relevant question. Combing fMRI and EEG, Di Russo, Martinez, and Hillyard, (2003) showed that early components (50-90 ms) evoked in the visual cortex are unaffected by attention, although subsequent components (150-225 ms) in the same calcarine sources are moduled by attention. The early evoked components are interpreted as representing spatial effects of early selective attention (Luck, Woodman, Vogel, 2000). Later component modulation may be interpreted as salience sensitization by attention via input from non-striate occipital and parietal cortex. Visuospatial attention networks may thus be divided into detection of target occurrence followed by spatial orienting of attention to the target.

Evidence from concurrent fMRI and EEG suggest that a P3 component in this later time range indexes both the activation of a ventral attention network at target onset as well as sustained activation of the dorsal attention network (Mantini, Corbetta, Perrucci, Romani, and Del Gratta, C., 2009) interpreted as "Orienting" here.

Both N1 and P3 components (occurring > 100 ms) are sensitive to attention processes, as shown in recent study by Neuhaus, Urbanek, Opgen-Rhein, Hahn, Ta, Koehler, Gross, and Dettling, M, (2010) using a version of the ANT. Neuhaus demonstrated a parietal N1 that responds with increased negative amplitude for spatially relevant versus spatially neutral cues. Other authors suggest this N1 may be modified by selective attention (Luck et al, 2000), or bottom up processes. This may suggest an early stage of sensory processing is driven by the spatial cue and not as an effect of cognitive stimulus evaluation. Other researchers have shown increased amplitude for early negative ERP components are produced by flanker incongruity (Van Veen, & Carter, 2002) and have tied its activation to anterior cingulate sources. Again, this suggests a frontal scalp source for executive attention network activity.

In contrast to the N1/P2, the later N2 and P3 components are often interpreted as indexing cognitive evaluation of a stimulus (Luck, et al, 2005) and may be sensitive to stimulus salience changes. It is clear that these components are related to attention, although some theories suggest the attention resources indexed by these two ERP features are separable. Using a combined flanker and go-no/go task, Enriquez-Geppert, Konrad, Pantev, and Huster, (2010) illustrated an N2 mainly affected by executive response conflict while a P3 amplitude showed the effects of motor inhibition. Neuhaus (2010) also suggests that parietal P3 amplitude (~ 500 ms) is reduced for incongruent versus congruent targets (Conflict), and showed a slightly later frontal P3 (~ 400 ms) exhibiting increased amplitudes to incongruent targets. Rueda, Posner,

and Rothbart, (2005) have also shown an increased P3 (~ 400 ms) amplitude to incongruent flankers. They identified an anterior distribution for this component in adults but a more diffuse anterior/posterior distribution in children. Given maturational lag of prefrontal areas in children, this also supports an anterior network of executive attention. Other studies investigating the effect of incompatible or incongruent flankers on the P3 have found increased amplitudes at both Fz and Pz electrodes in adults (Wild-wall, et al, 2008) or just Pz (Kopp, et al, 1996). Kopp also shows increased N2 amplitude with incongruent flankers.

This paper explores the relationship between behavior and evoked EEG of attention networks. Specifically, we will demonstrate the first systematic study of behavioral and ERP components of LANT attention networks, including Conflict, Orienting Benefit, and Orienting Cost.

Methods

Participants

40 right-handed UCLA undergraduates (17 men, 23 women, M = 22.65, SD 2.6, age 18-30) were recruited from the UCLA undergraduate population, for behavioral testing with EEG monitoring. Participants were selected to be strongly right handed using a modified version of the Edinburgh Handedness Questionnaire, (Oldfield, 1971) with a cutoff score of 12 out of 14. Exclusion criteria included any current use of psychiatric medication, any history of learning disability or attention deficit, any psychiatric or neurological history, non-corrected vision, or lack of native English fluency, evaluated by self-report. Testing sessions lasted one hour, and participants were compensated $25 for their time. Three participants were excluded for chance behavioral performance and one from an EEG data recording error.

Behavioral task: evaluating hemispheric attention networks

Participants were given a new lateralized test of attention. A speeded version of the Lateralized Attention Network Task was developed to evaluate networks of attention in each hemisphere. Continuous EEG recording was performed during the task, and speeded-LANT (sLANT) event-locked ERPs were created to evaluate time and frequency evoked changes to task events and behavior.

sLANT: A "speeded" Lateralized Attention Network Test

The LANT (Greene et al, 2008; Hill, Barnea, Herzberg, Rassis-Ariel, Rotem, Meltzer, … & Zaidel, 2008) measures covert orienting of spatial attention and provides a measure of Orienting Benefit due to a valid spatial cue and a measure of Orienting Cost due to a spatially invalid cue, both relative to a neutral (center) cue. The LANT also evaluates response Conflict using a lateralized flanker task. Conflict and Orienting are measured by manipulation of Flanker Congruity, Target Visual Field, and Cue Validity. Targets are presented with either congruent or incongruent flankers; cues predict target visual field validly, invalidly, or not at all (center cues). By subtracting reaction time and accuracy difference for averaged trials of Incongruent versus Congruent targets, we cacluate Conflict. Orienting Cost subtracts trials with Invalid Cue and Center Cue; Orienting Benefit is the difference between trials with Center Cue and Valid Cue. We developed a version of the LANT with faster timing than Greene, et al, and also eliminated neutral flankers and double (both visual field) cues. The sLANT also discards the "no cue" condition, eliminating the Alerting measure. The first reason for these modifications was to optimize the LANT for ERP data; an ERP study requires many trials of the same behavior type. The LANT presented by Greene, et al., 2008 only has 16 trials of each of 24 unique trial types (Visual Field (2) x Flanker (3) x Cue (4)). In a pilot ERP study being written up separately, the authors of this paper and Greene ran an ERP pilot study on a LANT without neutral flankers.

That modification produced enough (~ 96) trials for each LANT variable level combination, but required almost an hour of testing time (10 five minute blocks plus self-paced breaks) and introduced fatigue and EEG quality issues.

sLANT Design

Our goals with the sLANT included shorter administration time, increased test effort, and increased trial count for each unique stimulus combination. Eliminating Alerting allowed us to increase Orienting and Conflict component trials, and changed the LANT factorial design from 3 (Flanker congruency: congruent, neutral, incongruent) x 2 (Target Visual Field: left, right) x 4 (Cue validity: none: center, double, valid) as in Greene to a new sLANT factor design of 2 (Flanker congruency: congruent, incongruent) x 2 (Target Visual Field: left, right) x 3 (Cue validity: none, valid, invalid). Also, the LANT has shown accuracy rates above 90% (Greene, et, al, 2008); often much higher (Eran Zaidel, personal communication). To increase sensitivity in the accuracy domain, the sLANT decreased trial time and added variability to make stimuli less predictable and increase test difficulty. LANT trials used an 850 ms SOA between Cue and Target; the sLANT implements a 350 ms SOA Cue to Target. The LANT also uses 1000 ms padding per trial after response while the sLANT implemented padding of 1000ms *minus* reaction time, which adds variability to the inter-trial interval. This approach also produced faster next trial onset after a slow response, effectively speeding or "rushing" the participant. A central feature of the LANT is the vertical, lateralized target/flanker arrow set. The sLANT retained these stimuli as well as the LANT presentation eccentricity of 2 degrees for cue and target stimuli.

- Insert Figure 1 about here -

Measures: Data acquisition and signal processing

EEG & sLANT recording: Dense array EEG was recorded using a BioSemi / ActiveTwo system (64-channel QuickCap plus ear electrodes), with cap CMS-DRL for active reference and ground. Digital codes for sLANT unique trial type were sent from E-Prime computer to BioSemi computer via parallel cable. Trial codes were embedded in the EEG record at target+flanker stimulus onset.

EEG preprocessing: Before analysis, the 66-channel data set was visually inspected to remove EMG artifact and excessive noise. A small number of bad electrodes were removed and interpolated. EEG was filtered to remove frequencies below 0.16 Hz and above 50 Hz, and referenced to averaged ears ((A1+A2)/2) for analysis.

ERP Analysis: Three-second epochs were constructed from the continuous EEG, +/- 1500 ms to each sLANT target event. Each unique trial type was averaged in the frequency domain to produced ERPs. A pre-target baseline of –500 to –400 ms was used for ERP epochs to avoid contamination of target locked ERPs with cue-evoked activity before target onset. Within-participant ERP component peak latency and peak amplitude were measured for waveform regions that varied by sLANT stimulus type across the trial interval. N1, P2, and P3 components were measured at 150, 250, and 550 ms respectively. A time window for 100 ms was used around the center of the N1 and P2 waveforms. The P3 component was measured across a 500 ms window from 300-800 ms after target onset.

Combination of ERP and Behavior: The ERP component measurements and sLANT behavioral measures to Cue and Target effects were subjected to separate ANOVAs. In addition, we performed a Pearson correlation between ERP measures and behavioral performance on different sLANT stimuli types (N = 37; 36 df). Given the large number of correlations possible

across ERP components and sLANT stimuli, we restricted our analysis to correlation between electrophysiology and behavioral measures for identical sLANT trial types.

Estimating scalp EEG measures of sLANT: On finding significant but similar ERP components for all sLANT variables, we created subtraction waves to mimic the sLANT construct of Orienting Benefit, Orienting Cost, and Conflict. Testing individual participant data using repeated measures ANOVAs on combinations of ERP and behavioral data (post hoc) may increase Type I errors. Adding additional electrodes to a general linear model would also increase the risk of Type 1 error by adding multiple comparisons. We implemented an alternative method for ERP statistical analysis that considers scalp distribution, as implemented by David Groppe's "Mass Univariate Toolbox" for EEG (Groppe, Urbach, & Kutas, 2011). To determine if significant differences in scalp distribution existed between ERPs for these sLANT measures, the following difference waves were created: Conflict waves were created from valid-flankers minus invalid-flanker, Orienting Cost was produced for center-cues minus invalid-cues, and Orienting Benefit was produced for center-cues minus valid-cues. N.B. We subtracted from center or valid for all of these waves to enable visual comparison. The ERPs from these sLANT analogs were submitted to a repeated measures, two-tailed permutation test based on the tmax statistic (Blair & Karniski, 1993) using a family-wise alpha level of 0.05. Identical time windows were used for the subtraction waves as the trial averaged ERPs although the sign often changes in the subtraction. For all sLANT measures, windows of 100-200 ms, 200-300 ms and 300–800 ms were used. All time points for the time window at 64 scalp electrodes were included in the test (i.e., 3328 total comparisons for N1 or P2 component, and 16448 total comparisons for the P3). 2500 random within-participant permutations of the data were used to estimate the distribution of the null hypothesis (that there is a real difference between conditions

used to produce the difference wave). This permutation analysis was used to supplement our earlier ANOVA-based findings because it provides better spatial and temporal resolution than conventional ANOVAs when used to across multiple electrodes, while maintaining a desired family-wise alpha level. The tmax statistic we used here has also been shown to have relatively good power for data whose dimensions are highly correlated (Hemmelmann, Horn, Reiterer, Schack, Susse, & Weiss, 2004). The highly correlated of points along an ERP waveform suggest that tmax may be a more appropriate measure than an ANOVA, as ERP component measurements data will violate the strict independence requirement of the GLM. To ensure this measure was stringent we chose 2500 permutations to estimate the distribution of the null hypothesis; this is over twice the number recommend by Manly (1997). Based on these tmax estimates, critical t-scores of +/- 3.94 (df=35) were derived for N1 and P2, which corresponds to a test-wise alpha level of 0.000371. For the P3 component critical t-scores were determined at +/- 4.17, corresponding to a test-wise alpha level of 000193. Therefore any differences that exceeded the relevant t-score were deemed reliable.

Apparatus & Testing Procedure

Participants were seated in front of a computer. A BioSemi / ActiveTwo system was applied to the participants head, and 66-channel EEG was recorded using (64-channel QuickCap using CMS/DRL reference, plus ear electrodes). Several minutes of resting baseline EEG was recorded and then instructions for the sLANT were given. General instructions emphasized both speed and accuracy, as well as maintaining visual fixation on a crosshair in the center of the screen. The main task instruction was to report the direction of a middle arrow in lateralized vertical line of 5 arrows. sLANT stimuli were presented via E-Prime on a PC with a 2.1 GHz

CPU, running Windows XP. Stimuli were presented at 57 cm from participant on a 17" LCD monitor with a refresh rate of 70 Hz and a resolution of 1280 * 1024 pixels.

Participants performed 4 blocks of the sLANT, with 156 trials per block. A total of 624 trials were presented in a random order within blocks that alternated by response hand, counterbalanced among participants. Unimanual responses were gathered using a serial mouse held at 180 degrees by the non-responding hand. This allowed consistency of the responding hand to indicate ''up'' with the index finger and ''down'' with the middle finger, regardless of hand used. Trials and thus blocks were of variable length; Blocks ranged from 4-6 minutes based on reaction time differences. The sLANT provided self-timed breaks between blocks, which participants often limited to a few seconds.

Before analysis, sLANT trials with reaction times less than 100 ms or greater than 800 ms were discarded, removing 2.5% percent of trials. The remaining trials had a mean reaction time of 326 ms (median 305, SD 121). Three participants were excluded for accuracy below 60%. One subject was excluded due to a loss of behavioral session data. Mean accuracy for the reduced N = 36 was 0.74.

Results

Behavioral Results

We carried out repeated measures ANOVAs on data for 36 participants. The design was a 2 Target Visual Field (TVF: Left, Right), x 3 Cue Validity (Center, Valid, Invalid), x 2 Flanker Congruity (Congruent, Incongruent) ANOVA. We ran separate ANOVAs for behavioral reaction time and accuracy. In these results we will ignore the significant interactions between Flanker and Cue, due to the theoretical complexity of this second order interaction. Examining accuracy, we show main effects of TVF, of Cue Validity, and of Flanker Congruity, as a

significant interaction of Target Visual Field with Flanker. Tables 1 and 2 summarize the significant sLANT variables that show up for reaction time and accuracy.

- Insert Table 1 & Table 2 about here -

Laterality of accuracy performance suggests left visual field targets (M = 0.759) were responded to significantly more accurately than right visual field targets (M=0.739, F = 7.663, p = 0.009). Performance to Center cues (M = 0.739) was significantly more accurate than to Invalid cues (M = .718, F = 6.411, p = 0.016), and performance for Center cues was also significantly less accurate than for Valid cues (M = .774, F = 21.874, p < 0.001). Congruent Flankers produced more accurate (M = 0.870) performance than incongruent flankers (M = 0.618, F = 296.232, p <0.001). Furthermore, Target Visual Field (TVF) and Flanker interactions highlighted a larger difference between Congruent and Incongruent flankers in the right visual field (M = .281, F = 87.189, p <.001) than in the left visual field (M = .215 ms, F = 79.596, p < 0.001). Latency performance failed to show a main effect of TVF (F = 0.039, p = 0.845) although did show main effects of both Flanker and Cue. Congruent flankers produced significantly faster responses (M = 315 ms) than incongruent flankers (M = 359 ms, F = 113.452, p < 0.001). Performance to Center cues was significantly different than performance to Invalid and Valid cues; Center cues produced significantly faster responses (M = 367.25 ms) than did Invalid cues (M = 375.19 ms, F = 8.809, p = 0.005) and significantly slower responses than Valid cues (M = 367.25 ms, F = 14.604, p = .001).

Electrophysiological Results

Continuous EEG gathered during sLANT administration was used to produce Event Related Potentials from epochs time locked to the sLANT target onset. We chose an averaged-ears ((A1+A2)/2) reference to minimize any hemispheric effect of reference while preserving

ERP amplitudes at vertex electrodes. The resulting ERPs demonstrate posterior amplitude changes at electrodes including P3, Pz, & P4 in the first 300 ms after the target. An N1/P2 complex was elicited at these parietal sites by the target stimuli and modified by the cue type. Frontal electrodes, including FP1, FP2, and Fz, showed the largest amplitude changes with a later P300 post-target component that lasted from about 300 to 800 ms. Changes in this posterior P300 tended to vary by Flanker. Given these observations, electrodes of Fz and Pz were chosen as representative of test-evoked activity for measurement and statistical testing. Central electrodes of C3, C4, and Cz were also analyzed to validate visual field effects of Cue and Target. For these 5 electrodes we considered ERP components of N1, P2, and P3 as described in the Methods section. Figure 2 shows the evoked waveforms for Cue and Flanker as they vary around the Fz electrode. ERP components have similar timing at all electrode sites, although patterns of laterality and anterior / posterior differences in ERP components can be observed.

- Insert Figure 2 about here -

When considering all 64 electrodes, the ERP components evoked by both cues and targets show a clear lateralized pattern of scalp distribution. Even cursory inspection shows that ERP components are evoked contralateral to the visual field of sLANT stimuli. Examining instantaneous amplitudes near the middle of the N1, P2, and P3 time windows (150 ms, 250 ms, and 550 ms respectively) we can observe a similar pattern in the scalp distribution across Cue Validity and Flanker Congruity for N1 (Figure 3), P2 (Figure 4), and P3 (Figure 5)

- Inset Figure 3, 4, 5 about here -

The above figures show that N1 and P2 components are more strongly lateralized than the P3 component. Considering only the N1/P2, we see the N1 has a more anterior/posterior scalp distribution (showing a largely central anterior negativity) while the P2

shows more strongly lateralized activation of temporal and posterior scalp sources. Aside from these gross laterality effects driven by visual field of stimuli, scalp distribution of evoked patterns appear to be largely similar across cues and targets.

When examining ERPs at specific electrodes, Target evoked components appear at most electrodes, visible in waveform and scalp distribution above as an N1, P1, N2, and P3. Each evoked component was measured as the dependent variable for a 2x3x2 ANOVA with the same design as above (TVF x Flanker x Cue). The N2 component largely echoed the significant effects of the P3 component, so only the N1, P2, and P3 components were considered. Measurements included peak amplitude, peak latency, and mean amplitude. Mean amplitudes were found to be redundant with peak amplitudes, so only peak latency and peak amplitude were used. In addition, components in the cue to target interval will not be discussed here, although did include a main effect of Cue (P1 amplitude: $F = 8.76$, $p = .044$) and an interaction of TVF x Cue (P1 mean area: $F = 8.76$, $p = .016$; P1 amplitude: $F = 7.90$, $p = .001$). These visual field and cue validity effects on early ERP components are unsurprising and suggest early automatic processes. The ERP components that interact with attention at time of target bear more scrutiny, and significant post-target ERP components were found at all electrodes examined. Peak latency was more often significant than peak amplitude, although this varied by electrode considered. Parietal (Pz) and left central (C3) electrodes showed the largest number of significant effects. Frontal (Fz), and right central (C4) electrodes also showed many significant peak latency effects, but fewer peak amplitude effects. The sLANT showed patterns of significant test variable that diverged by electrode and ERP component. Target Visual Field was significant at all three ERP components at both peak amplitude and latency, although the test statistic was largest for P2 amplitudes (C3: $F = 59.10$, $p < 0.001$; C4: F 22.66, $p < 0.001$; Pz: $F = 11.323$, $p = 0.002$). Cue

validity only demonstrated significant effects on peak latency, and varied by electrode considered (C4 N1: $F = 3.62$, $p = 0.032$; Cz N1: $F = 3.21$, $p = 0.046$; Fz P3: $F = 3.24$, $p = 0.045$; Pz N1: $F = 5.66$, $p = 0.005$; Pz P2: $F = 7.26$, $p < 0.001$). Flanker congruity had significant effects on both peak amplitude and peak latency at Pz (N1 amplitude: $F = 4.50$, $p = 0.041$; P2 amplitude: $F = 6.61$, $p = 0.002$; P3 latency: $F = 37.99$, $p < 0.001$). For the other electrodes around the vertex, Flanker congruity showed only peak latency effects on the P3 component (C3: $F = 18.84$, $p < 0.001$; C4: $F = 43.52$, $p < 0.001$; Cz: $F = 39.00$, $p < 0.001$; Fz: $F = 30.12$, $p < 0.001$). Interactions of sLANT variables also showed significant effects on peak amplitude and latency. TVF * Cue validity interactions on peak amplitude were found at C3 (N1: $F=5.91$, $p = 0.004$; P3: $F = 4.11$, $p = 0.021$), Fz (N1: $F = 3.25$, $p = 0.045$; P3: $F = 4.88$, $p = 0.01$), and Pz (N1: $F = 3.29$, $p = 0.043$). TVF * Cue also showed significant peak latency of the P3 component at C3 ($F = 5.15$, $p = 0.008$) and C4 ($F = 4.2$, $p = 0.019$). TVF * Flanker interactions showed significant effects on N1 peak latency at C3 ($F = 9.28$, $p = 0.004$), C4 ($F = 14.59$, $p < 0.001$), and Pz ($F = 9.94$, $p = 0.003$).

ERP validity & scalp distribution of Orienting Benefit, Orienting Cost, Conflict

Instead of examining unique variable combinations (trial types), the sLANT provides for creation of difference measures to evaluate Conflict, Orienting Benefit, and Orienting Cost. As described in the Methods, the Mass Univariate Toolbox for EEG (Groppe, Urbach, & Kutas, 2011) was used to examine the first positive peak in the sLANT subtraction based components during the 300 – 800 ms post-target interval. Figure 6 shows the difference waves for Conflict and Orienting Cost in each TVF. Orienting Benefit was just below significant for the 300 – 800 ms time region. Conflict and Orienting Cost showed significant changes in the difference waveforms however, e.g. Conflict demonstrated a P3 (peaking ~ 440 ms) distributed parietally

and contralaterally to the TVF as well as a later negativity (~ 700 ms) that was broadly significant across central and parietal electrodes. Orienting Cost showed significant differences in the Cue to Target interval (~ 180 ms, not labeled) as well an early P3 (~ 280 ms) in parietal electrodes, contralateral to TVF (i.e. effect of the preceding Invalid Cue). Orienting Cost also evoked a later P3 (~ 440 ms) significant at posterior electrodes bilaterally or ipsilateral to the target.

- Insert Figure 6 about here -

Figure 6 shows a clear pattern of statistically significant ERPs and their spatial distribution to targets presented in each visual field. The upper panel for each sLANT measure contains the ERP waveform of an sLANT subtraction measure, grand averaged across all participants (N=36), with Target Visual Fields presented side by side. The corresponding lower plot demonstrates an output of the tmax test for that waveform. T-test plots that exceed the red dotted threshold indicate significant differences from the null hypothesis. Each scalp plot shows data corresponding to the waveform time point selected by the vertical black.

The subtraction waves for Conflict (P3) showed stronger anterior scalp amplitude differences but greater posterior statistical differences in flanker type, ipsilateral to Target Visual Field. There was also right parietal activity during Confllict, regardless of TVF. Orienting Benefit (P3) showed anterior scalp distribution and only a weak (non-significant) difference between valid and center cues. Orienting Cost showed frontal and central ERP distribution without strong laterality for invalid versus center cues, although a suggestion of greater contralateral activation than seen in Conflict. We observe from Figures 6 that the laterality of this P3 ERP component is separable across Conflict and Orienting Cost. Using similar methodology

to examine subtraction regions for earlier components (not shown) also demonstrated the expected contralateral visual field effect of N1 and N2 evoked by cue.

Correlation of Electrophysiology with Behavior

With these well-behaved differences in trial level and subtraction measures of attention networks across both electrophysiology and behavioral results, we subjected the ERP components defined above to separate Pearson correlations with performance latency or performance accuracy. When only considering the correlations between behavior and physiology to the same sLANT trial, we found many strong correlations between latency and accuracy performance and both ERP peak amplitudes and latency. Given the large number of possible correlations (sLANT trial type (12) * Behavior DV (2) * ERP Component (3) by Component Measure (3)) we chose to only highlight correlations significant at $p > .01$, or a Pearson R value > 0.42 for d.f. = 34. With this restriction, a clear pattern of Accuracy versus Latency emerged. Significant changes in N1 and P2 amplitude correlated with sLANT behavioral accuracy, while P3 component latency instead correlated with sLANT reaction times. Both visual fields showed this effect across flanker congruency and cue validity for all three ERP components, although N1 and P2 effects appeared at frontal and central sites while the P3 component demonstrated latency effects at both fronocentral and parieal electrodes. Given the large number of positive correlations between sLANT performance latency, accuracy, and evoked N1, P2, & P3 components across all sLANT unique trial types, it would not be useful to list all correlations. The most statistically stringent of these correlations showed P2 ERPs correlating with sLANT Accuracy. For example accuracy to LVF Incongruent flankers with Center cues correlated with P2 amplitude at Fz ($r = 0.543$, $p < .001$) and to trials with Incongruent flankers and Valid cues with P2 amplitude at Cz ($r = 0.512$, $p < .001$). sLANT LVF

reaction time measures correlated with P3 latency. Reaction time to LVF Incongruent flankers with Center cues correlated with P3 latency at C3, C4 ($r = 0.529, 0.489$; $p < 001, .002$) and reaction time to RVF Congruent flankers with Invalid cues correlated with P3 latency at Cz ($r = 0.613$, $p < .001$). At these values, the observed Pearson correlations indicate a strong positive relationship between the behavior and physiology of attention processes as measured by the sLANT. Significant positive correlations obtained between both peak amplitude and latencies, and different ERP components and electrode sites showed different patterns of behavioral sensitivity (reaction time versus accuracy). Before restricting to only the most significant correlations, we observed a large number of significant effects at Pz (not shown). When considering the more stringent p value, most remaining significant effects are observed at C3, Fz, and C4. This suggests a frontocentral executive component of attention networks is highlighted by this correlation. In contrast, as we saw in the scalp distributions of the Orienting and Conflict difference waves earlier, the significant differences between waveforms of sLANT "subtraction measure" constructs were largely parietal.

Discussion

sLANT Validity

The sLANT introduced a modified LANT and demonstrated a valid measure of three networks of lateralized attention in each hemisphere. Behavioral findings were similar to what has been shown in prior work. Main effects for Conflict, Orienting Benefit, and Orienting Cost were found on our speeded version, with significant effects in both performance latency and performance accuracy. We also showed differences in hemispheric performance on test accuracy, demonstrating some right hemisphere superiority for these attention tasks. This is consistent with prior LANT and other flanker task research.

We chose to compress test timing from prior LANT iterations. This provided increased trial numbers in a shorter time, although risked overlapping ERP components. Given the relatively short epoch (~ 1500 ms after a 100 ms baseline) and the quick succession of sLANT trials, interactions were indeed possible; this is one reason we restricted our analyses from 0 to 800 ms after target onset. With the main effects on N1 & N2 amplitude at Pz, and main effects on P3 at Pz and Fz for both peak amplitude and peak latency, it is clear that the sLANT can distinguish different trial and stimuli type by ERP component. The sLANT attention networks were reasonably tracked by changes in the evoked EEG. In addition, many sLANT trial types showed correlation between behavior and physiology that exceeded a Pearson correlation of 0.4 or 0.5. We also presented several significant interactions (Cue, Flanker) with Target Visual Field. These obtained for TVF * Flanker on performance accuracy; for EEG we showed an interaction of TVF * Cue in earlier ERP components (N1) at Pz and a later component (P3) at Fz. We chose not to discuss additional interactions of Cue * Flanker, although increased difficulty or loading of the test variables (e.g. Invalid Cue and Incongruent Flanker) may be demonstrated as additive Conflict/Cost effects; the ERP components for those trials were also strongly positively correlated with behavior (not shown). This suggests an interaction Conflict and Orienting Cost modules of attention, but requires further study.

sLANT versus LANT in measuring behavior

By removing non-cued trials we lose the LANT Alerting measure but retain cue-driven measures of Orienting Benefit and Orienting Cost. Reducing cue improved Orienting and Conflict, but eliminated a direct vigilance measure. The sLANT may not have measured Alerting well even if non-cued trials were retained; the fast-paced sLANT requires careful attending without stimulus-free intervals necessary to capture a decrease in vigilance. If

vigilance measures are important, a Continuous Performance Test (CPT) may be used (Ricco, et al, 2002) alongside the sLANT. We took this approach and will report on a novel lateralized CPT in a separate paper.

Both LANT and sLANT show similar reaction time and accuracy effect on cue validity and flanker congruity. This sLANT data also showed a left visual field / right hemisphere advantage in overall accuracy. This right hemisphere advantage is usually found in other versions of the LANT as well as the ANT.

By establishing the validity of these three measures of Conflict, Orienting Benefit, and Orienting Cost, the sLANT shows a mean accuracy that is much lower than the LANT, and has more variability. The speeded nature of the sLANT may increase task difficulty, reducing accuracy from a possible "ceiling" as reported by Greene. The absolute measures of Conflict and Orienting are also reduced slightly. This appears to be an effect of shortening trial timing, and may be an effect of attention network interactions, simple task difficulty, or a scale effect based on forcing participants to consistently respond quickly.

The ERP Correlates of Lateralized Attention

This sLANT with full-head EEG recording is the first systematic study of a lateralized flanker task looking at combined behavioral and electrophysiological indexes of attention networks in each hemisphere. These measures provide a useful window into understanding stimulus-evoked attention resources, although illustrate a complex interaction of brain laterality and attention network distribution. As mentioned in the introduction, ERP literature often finds Conflict and Orienting in anterior and posterior sources respectively, and finds a right hemisphere bias for attention performance. Our results provide a pattern of significant ERP components suggesting stages of information processing and dissociable effects of Orienting and

Conflict. The N1 and P2 responded to variations in VF of the Target as well as validity of the preceding Cue. The later P3 that occurred at both anterior and posterior sites is a more complex component. The effects summarized suggest that the P3 peak latency is more affected by Flanker, while TVF and Cue variation instead drive changes to peak and mean amplitudes of the P3. Given the larger amplitude of P3 and absence of earlier N1 (and N2) components at frontal sites, it is plausible that these parietal N1 amplitude changes correspond to the sLANT construct of Orienting. In contrast, the P3 may serve to index both Orienting (in amplitude changes) and Conflict (in peak latency changes). We intepret this as early Orienting resources being driven by parietal and occipital sources, while Conflict occurs slightly later (peri-response) and localizes to central and frontal electrodes. While we did not find a largely right-hemisphere network of attention, we did find asymmetrical EEG response in Conflict and Orienting Cost, as well as strong visual field effects of Cue and Flanker.

Behavioral Latency versus Accuracy and sLANT ERPs

The sLANT ERP components showed significant effects across all measurements, even when we eliminated duplicates that did not add to the picture (e.g. N2 was largely redundant with P3 measures; component mean amplitude was redundant with peak amplitude). Comparing different ERP components also illustrated different stages and aspects of attention processing. Speed or accuracy of behavior was also clearly related to the latency or amplitude of an ERP. As mentioned earlier, P3 amplitude is thought shows a relationship of cognition to behavior, changing with the either the speed or accuracy of a decision variable. In the sLANT, we saw both latency and accuracy effects on the P3 component (at both Pz and Fz). The behavioral and ERP correlations we demonstrated suggest that frontal (Fz) ERPs are largely driven by performance latency (RT) differences, while posterior (Pz) ERPs are driven by both reaction

time and accuracy. We interpret these accuracy effects on the ERP as reflecting a decision process, while reaction time effects may have been due to ancillary sensorimotor resource constraints or a task-relevant decision process. As N1 and P2 effects on amplitude correlated with RT, we interpreted these early components as indexing something that is affecting the speed of a complex attention process. There may be some underlying process that shares resources with our attention networks (e.g. "Attention") or this may have indicated changes in processing speed or sensory activation. For example, if a sensory or motor process is fast, this may also affect latency in later ERP components; this interpretation was supported by statistical effects on the N1 and P2 obtaining for later N2 and P3 components as well.

Scalp Distribution of Conflict, Orienting Cost, and Orienting Benefit

When exploring a tmax analysis of ERP difference waves in the sLANT, we observed distinct patterns in each sLANT component. Most of these patterns showed an anterior/posterior distribution of amplitude, but also laterality evoked by visual field of cue and target. It is interesting to note that Orienting Cost (which involves cueing the wrong visual field) has a *more* strongly lateralized effect than pure Orienting Benefit (which only cues one hemisphere). For example, an OC trial has an RVF cue followed by an LVF target. A similar OB trial has an LVF cue preceding an LVF target. In both cases the LVF target activates the right hemisphere visual cortex, but in Orienting Cost the ERP is more strongly lateralized to this right hemisphere when the left hemisphere is first probed by the invalid spatial cue.

Summary & Initial Conclusions

The sLANT demonstrated valid measures of spatial Orienting Cost and Orienting Benefit and executive response Conflict in each hemisphere. It has shown distinct and unique patterns of ERP components that change with LANT variable types. The speeded trials of the sLANT

successfully produced both behavioral and ERP changes to the task variable levels, and the behavioral accuracy captured by the sLANT appears more sensitive than the earlier LANT. The sLANT thus provides an increased ability to test models of hemispheric independence. We have confirmed discrete attention networks in each hemisphere, although the overall performance of attention networks in each hemisphere was somewhat the same.

The interaction of Cue * TVF suggested that Orienting Cost and Conflict share some resources. Aside from that interaction, the sLANT separately evaluated three networks of attention: two involved in spatial attention and one in executive attention. Thus, the sLANT may be useful in understanding attention from a research as well as clinical perspective and may be a powerful tool in assessment of complex hemispheric activity in normal and pathological brains.

The data and interpretation presented above lends weight to the growing body of literature examining not only a right-hemisphere specialization for attention, but also the capacity of each hemisphere as well as interhemispheric function. We hope this introduction to the sLANT may prove useful to other researchers exploring the behavior and physiology of attention.

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Timeline of sLANT stimuli: Example shows a Valid Cue followed by a Congruent Target.

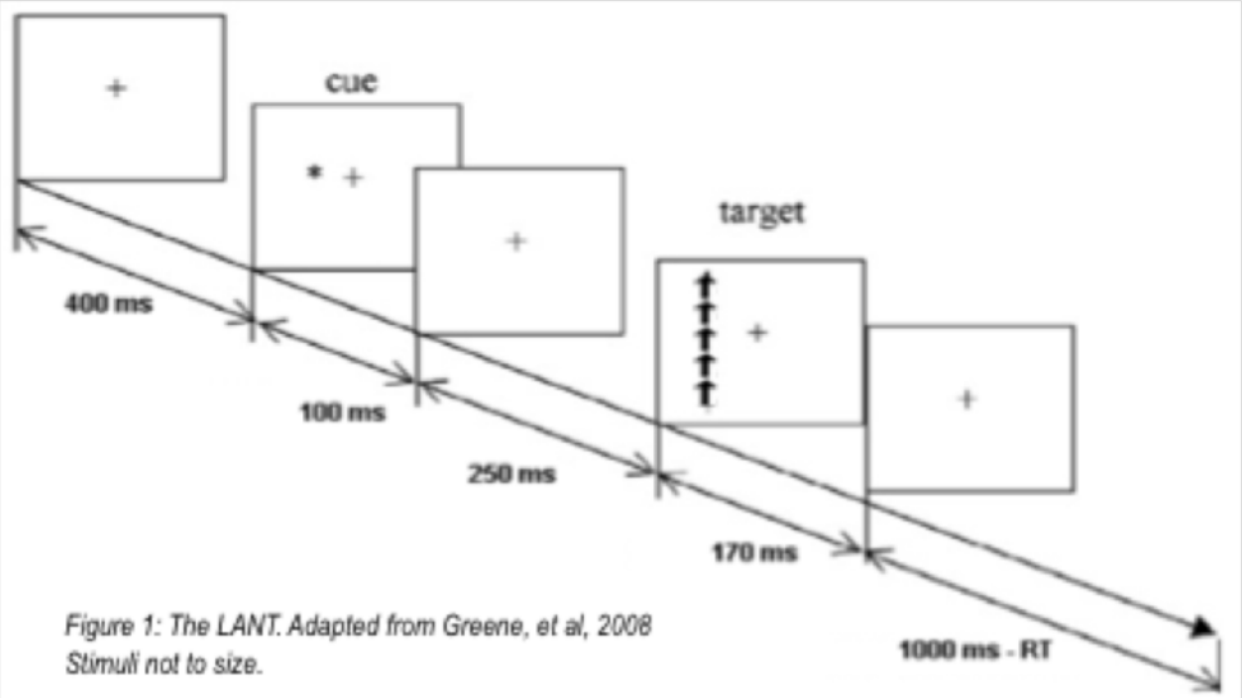


Table 1: sLANT Performance: Reaction Time

sLANT 2x2x3 ANOVA (Reaction Time)		
Variable	F	P
Flanker	79.89	0.001
Cue	18.14	0.001
All results significant at $p < 0.001$		

Table 2: sLANT Performance: Accuracy

sLANT 2x2x3 ANOVA (Accuracy)		
Variable	F	P
Target Visual Field	7.66	0.009
Flanker	97.03	0.001
Cue	18.90	0.001
TVF * Flanker	7.32	0.01
TVF * Cue	7.48	0.001
All results significant at $p < 0.01$		

Figure 2: sLANT ERPs that vary by Cue Validity & Flanker Congruity

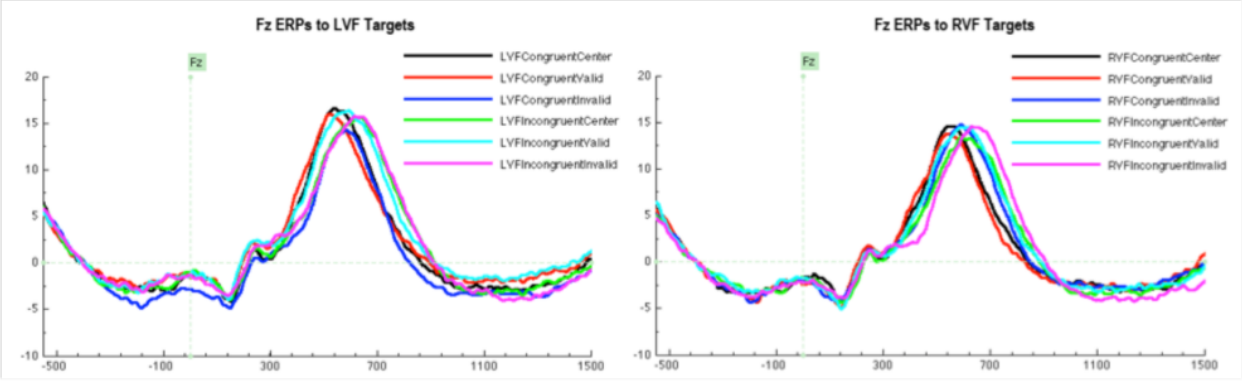


Figure 3: Scalp distribution of N1 ERP evoked by sLANT

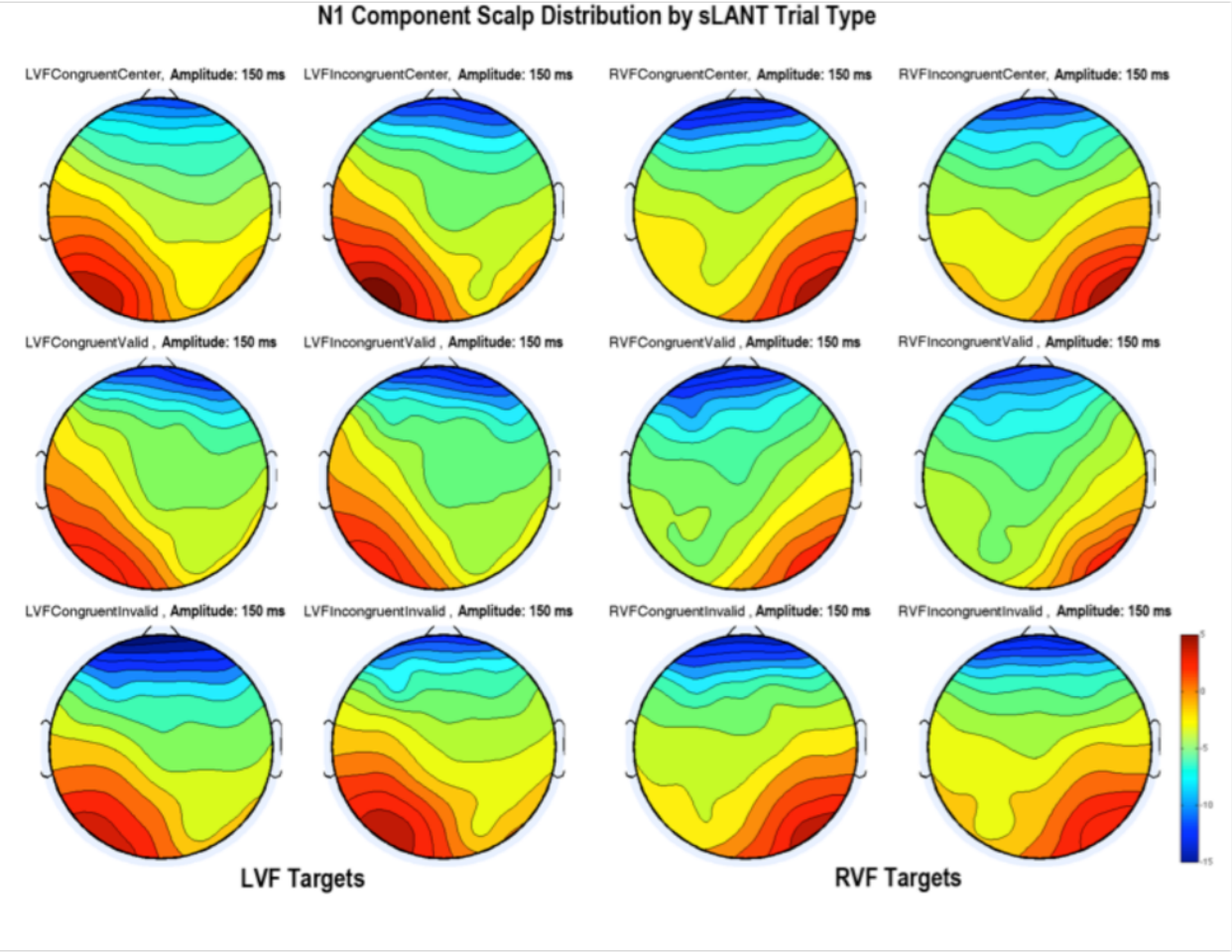


Figure 4: Scalp distribution of P2 ERP evoked by sLANT

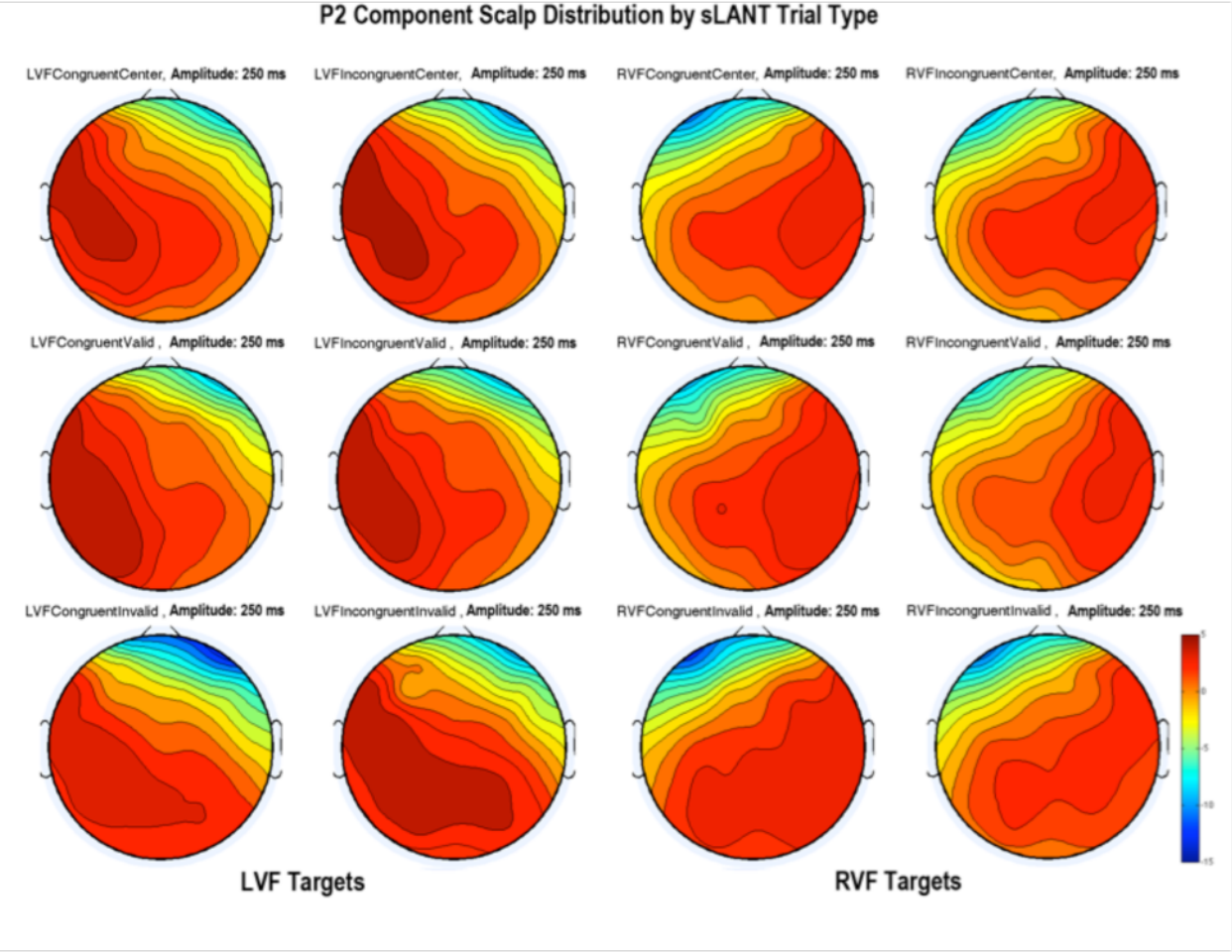


Figure 5: Scalp distribution of P3 ERP evoked by sLANT

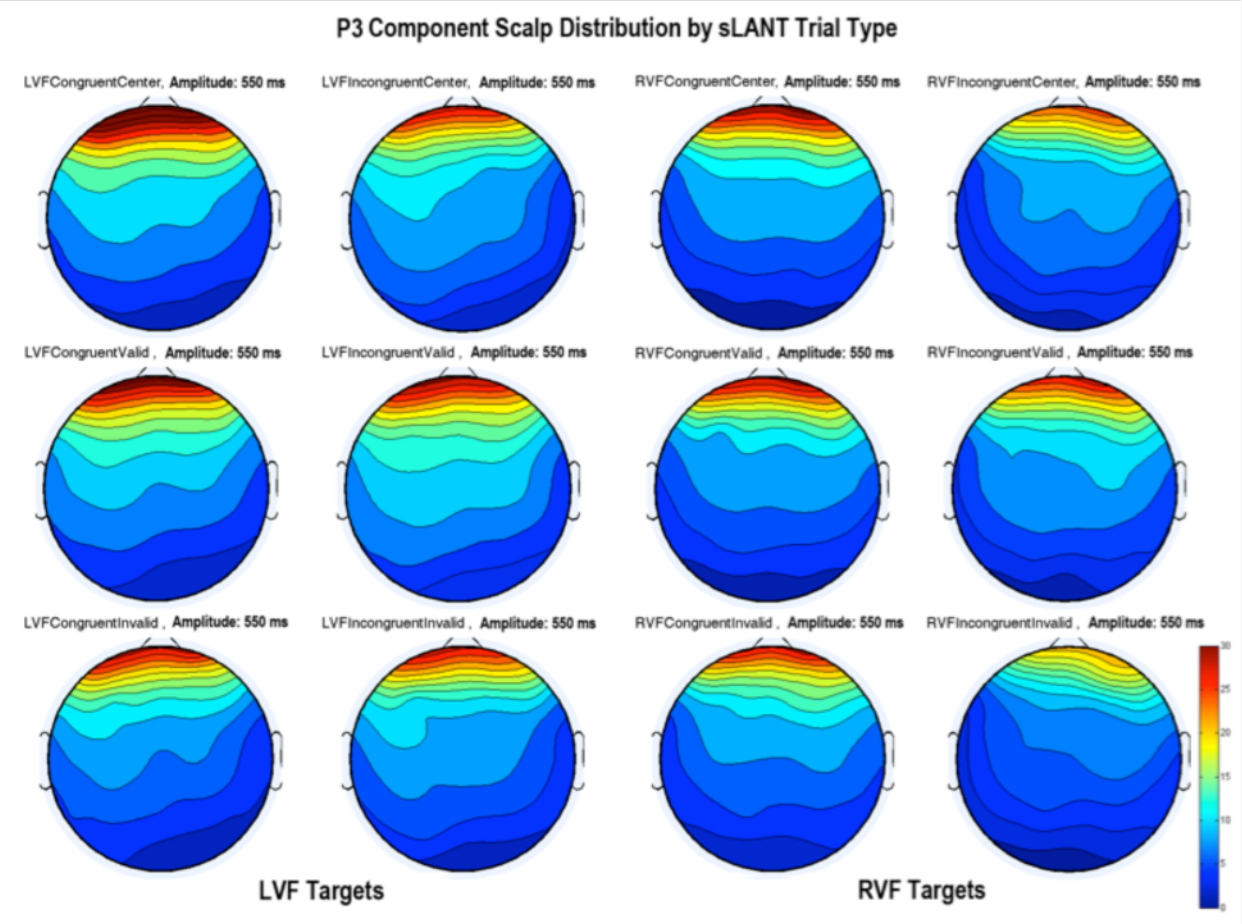
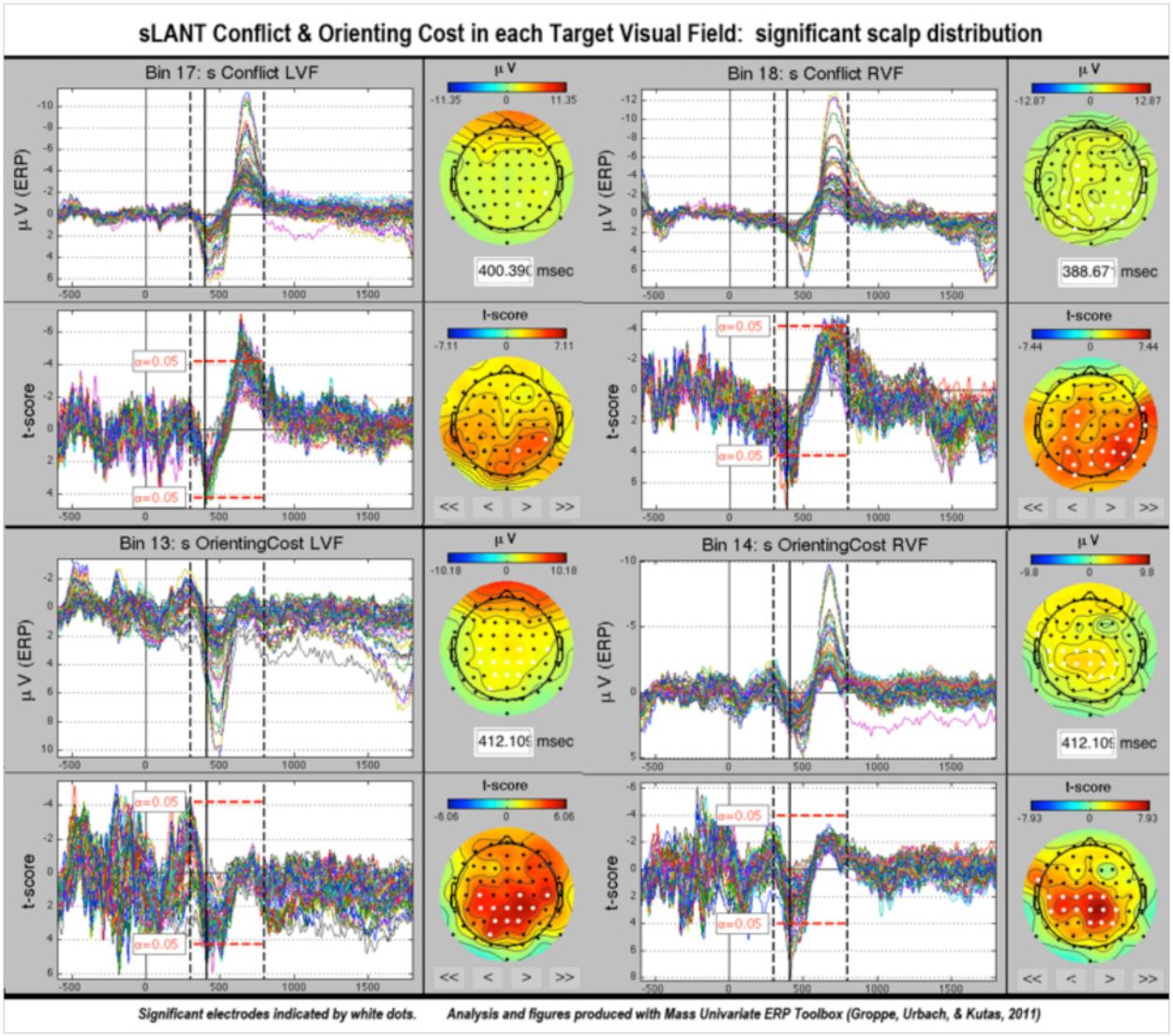


Figure 6: Significant scalp differences of sLANT subtraction measures:



Chapter 2:

Training Hemispheric Attention: EEG Biofeedback effects on the sLANT

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Introduction

Manipulating Hemispheric Attention

Attention appears to have functional independence in each hemisphere, as well as some dominant right hemisphere supervisory function as demonstrated by clinical syndromes such as hemifield neglect, and the typical Left Visual Field / right hemisphere advantage on tests of visual attention. The behavioral results presented in Chapter 1 also demonstrate the ability of each hemisphere to navigate response Conflict and spatially Orient to stimuli in the visual field. Very little is known about the ability of each hemisphere to be changed independently of the other. In addition, the degree to which each hemisphere acts independently on attention tasks versus sharing or transferring information to the other hemisphere remains complex. This Chapter will demonstrate the ability of the sLANT to measure hemispheric attention across multiple administrations, and evaluate the effects of EEG Biofeedback on attention networks in each hemisphere using behavioral and electrophysiological methods.

ERPs & Attention

Several ERP components are routinely studies in research on attention. These include the P50, N1, P2, and P3 components. Early components may represent endogenous events of early stages of processing, while the later components may represent cognitive processing or response evaluation. The earliest negative component (N1) responds to selective attention, and is larger for attended versus unattended auditory stimuli (Hillyard, 1973), suggesting it indexes attention towards a specific set of stimuli. Wang et al (2012) also suggests the N1 amplitude grows with cognitive load of voluntary attention. Training on target/disctractor processing appears to shorten N1 latency to task (Melara, et al, 2012). Mishra et al (2012) also found training to shorten N1 latency. The P2 component also responds to task-relevance. The P2 is larger for

task-relevant ("to-be-attended") stimuli, and smaller for irrelevant (Hillyard, 1973), although Melara et al (2012) found P2 amplitude to increase as distractor discrimination increased on a target recognition task. In contrast to it's amplitude, P2 latency is thought to represent "encoding" of sensory stimuli, and has been positively correlated with task accuracy (Finnigan, et al, 2010). The P3 component has received a great deal of attention; it appears to index cognitive evaluation as well as be sensitive to expectation violation, for example it appears in response to infrequent stimuli (Hillyard, 1972) but is reduced or absent for common stimuli. P3 latency (along with Reaction Time) appears to increase under cognitive load (Korpela and Huotilaninen, 2011). The P3 is also clinically relevant; ADHD children show a longer latency and lower amplitude P3 (Tsai et al, 2012) compared to neurotypicals, suggesting evidence of slower processing speed and reduced inhibition.

The sLANT presented in Chapter 1 demonstrated contralateral ERPs evoked by stimuli in each Target Visual Field (TVF). ERPs with N1, P2, and P3 components were clearly elicited by sLANT trials. The N1 and P2 were more strongly lateralized; the P3 had a frontocentral distribution. We determined that the N1 latency was reduced for Cue of "salient" stimuli (Valid Cues) and longer for Invalid Cues, on N1 Latency. Incongruent Flankers also produced larger and slower P3s than Congruent Flankers, suggesting inhibition and attention loading. TVF * Cue or TVF * Flanker interactions were also found on ERP amplitude and latency, confirming ERP contralateral to trial stimuli (evoked within a hemisphere) were selectively responsive to levels of Flanker or Cue variables. Overall, we found several significant scalp differences across sLANT measures. Cue-derived measures of Orienting related more to posterior scalp ERPs while Flanker-derived measures of Conflict related to anterior scalp ERP sources. As might be expected, Orienting was strongly lateralized in ERP response, while Conflict (sensitive

to the P3) was more fronto-central.

Degree of Hemispheric Specialization: Direct Access vs. Callosal Relay

In the context of measuring normal or typical behavioral laterality, it is useful to establish theoretical limit cases of hemispheric specialization. These methods typically include lateralized stimuli. Some tasks are exclusively specialized to one hemisphere, and when information reaches the "wrong" hemisphere, it needs to be relayed via the corpus callosum before it can be completely processed. We refer to these cases as "callosal relay" tasks. Other tasks may be performed by either hemisphere with different strategies and different degrees of competence. Surprisingly, many tasks show bilateral competence and therefore "Direct Access" to information presented to one hemisphere.

It is possible to develop behavioral criteria to distinguish Direct Access from Callosal Relay. This is often demonstrated using the "processing dissociation" criterion where Visual Field of stimulus input interacts with stimulus parameters (Zaidel, et al 1990). Another approach is to demonstrate a Visual Field by Response Hand interaction. The experimental paradigm used in this experiment (sLANT) combines behavioral and electrophysiological measures. Consequently, the sLANT provides a new index of Direct Access - namely an interaction between Visual Field of Target and laterality of ERP electrode.

Changing the Brain through Central Biofeedback

Neurofeedback (or neurotherapy) includes several biofeedback paradigms, most of which monitor brain events and produce stimulus reward (sound, pictures, animations) in response to brain parameters nearing or staying at the top or bottom of their moving average envelope. EEG Biofeedback (EEG BFB) trains frequency bands in the EEG by shaping amplitude (power, voltage) or by training common information at two electrode sites (coherence or comodulation).

Neurofeedback is distinct from Peripheral Biofeedback measures such as Galvanic Skin Response and Heart Rate Variability in that no cognitive strategy is required to carry out the shaping events; no skill transfer is thus required to perturb the underlying system in a fundamental way, and EEF BFB has been used on animals and profoundly disabled humans (including those who may be nonverbal). Chapter 3 will discuss the background and methodology of EEG Biofeedback more thoroughly, but for purposes of this article consider that EEG Biofeedback first began with shaping of low-Beta or "Sensorimotor Rhythm" SMR (12-15 Hz) on the motor strip of cats (Wyrwicka & Sterman, 1968). Alpha (just below SMR) was also successfully trained in humans very early in the development of this technology (Kayima, 1971). Sterman soon found that SMR training produced suppression of epileptic seizures (Sterman & Friar, 1972). While SMR is much lower amplitude in humans and does not produce the same characteristic eyes-open spindling bursts that it does in cats, SMR does play a functional role as "Sigma" or "sleep spindles" in humans, and may have some regulatory significance not only in sleep, but also in learning (Gais, et al, 2002). Clinical and research use of EEG Biofeedback techniques has often focused on increasing SMR on the left and right central motor strip (C3 and C4 electrode sites, respectively). Other frequency bands that are typically trained using EEG BFB include reducing Theta (4-7 Hz), and increasing Beta (15-18 Hz) as an alternative to SMR. More recently, Neurofeedback training systems have developed multi-channel capability and Z-score and source-localization based training features. Our line of research is designed to address a foundational lack of understanding of how "basic" neurofeedback protocols work. By examining behavioral and brain effects of different training protocols, we will inform clinical decision trees thus far based on little more than clinical "lore".

Methods

Participants

40 right-handed UCLA undergraduates (17 men, 23 women, M = 22.65, SD 2.6, age 18-30) were recruited for a combined lateralized attention and biofeedback experiment. Testing sessions lasted for 5 consecutive days, with 90 minute and 30 min sessions on alternating days. Participants were compensated a total of $150 for their time. Three participants were excluded after testing concluded, one for chance behavioral performance, one for a single session behavior recording error, and one for single session EEG data recording error.

Procedure

Participants were run through alternating 90 min and 30 minute Sessions across 5 consecutive days. Sessions 1, 3, and 5 were 90 minutes and began with Biofeedback electrode placement and 64-channel BioSemi EEG cap placement. Participants then began with 3 minutes of Eyes Closed EEG baselines, and 3 minutes of Eyes Open EEG baselines. The sLANT followed session EEG baselines, with E-Prime events synchronized to BioSemi EEG recording as described in Chapter 1. A Biofeedback protocol lasting 30 minutes followed the LANT. See Chapter 3 for discussion of this process in more depth. Sessions 1, 3, and 5 concluded with an additional Eyes Closed and Eyes Open baseline recording. On days 2 and 4, participants only received the 30 min Biofeedback protocol per Group assignment, with no EEG baselines, sLANT assessment, or full-head EEG.

Group & Biofeedback Protocol Assignment

Participants were blindly partitioned into 3 experimental groups differing in biofeedback training protocol to either: (1) increase sensorimotor rhythm (SMR; 12–15 hz) and decease Theta (4-7 Hz) at C3, (2) increase SMR and decease Theta at C4, or (3) increase Beta (15-18 Hz) and decrease Theta at C3. C3 or C4 electrodes were referenced to ipsilateral ear (A1 or A2,

respectively). Comparing C3 SMR and C4 SMR protocols was designed to highlight hemisphere specific effects of training. Comparing C3 SMR and C3 Beta protocols investigated reward-frequency specific effects of training.

Blinded Placebo-Controlled Biofeedback

See Chapter 3 for an in depth discussion of Biofeedback protocol construction and group assignment. For this article, it is sufficient to understand 16 of 40 recruited participants were assigned a hidden "Placebo" status, within their initial group status. Once the blinding was broken, and for purposes of this discussion, Groups were relabeled Sham, C3 Beta, C3 SMR, and C4 SMR, by reward site and frequency band.

Design: Measuring Hemispheric Attention Changes in Behavior

As described in Chapter 1, we examined performance on the speeded Lateralized Attention Network Task (sLANT). Chapter 1 summarizes the un-manipulated sLANT recording on Session 1 of this 5-day experiment. Considering the larger experiment adds the variable of EEG Biofeedback session count at time of sLANT, and biofeedback protocol, or "Group", for a design of 2 Target Visual Field (TVF: Left, Right), x 3 Cue Validity (Center, Valid, Invalid), x 2 Flanker Congruity (Congruent, Incongruent) x 3 Biofeedback Session (0, 2, 4) x 4 Group (Sham, C3 Beta, C3 SMR, C4 SMR). This model ANOVA was used consistently for any dependent sLANT variables: ERP data (N1, P3; amplitude & latency) and behavioral performance (reaction time, accuracy) for 36 participants.

A key aspect of this design is the intersection of Group * Session, as a two-way effect or as interacting with sLANT variables. Divergence of dependent variables in a group-specific way would suggest biofeedback protocol effects. Planned comparison of restricting Group to 2 (each Active vs. Sham) allow clarification of significant findings from the initial 5-way ANOVA and

further verify effects of Biofeedback vs. Sham on specific test variables.

Design: Measuring Hemispheric Attention Changes in Electrophysiology

ERPs were prepared as described in Chapter 1, for the first, third, and fifth sLANT administration (corresponding to zero, two, and four sessions of biofeedback). Given the ERP waveforms evoked by the LANT stimuli found to be significant in Chapter 1, we only examined components of N1 and P3 components for additional sessions. All component timing and measurement windows are as in Chapter 1, but used component mean amplitude instead of peak amplitude to control for any absolute voltage changes due to differences in session recording offsets. In Chapter 1 we determined the sLANT demonstrates consistency with a hypothesis of frontal executive Conflict and posterior spatial Orienting. To further clarify this, we compared ERP components at electrodes 20% anterior and posterior (Fz, Pz) to vertex (Cz). As our experimental groups had the added variables of left or right hemisphere BFB training (at C3-A1 or C4-A2, also 20% from vertex) we added these electrodes to another planned comparison. One ANOVA design was thus 2 Target Visual Field (TVF: Left, Right), x 3 Cue Validity (Center, Valid, Invalid), x 2 Flanker Congruity (Congruent, Incongruent) x 3 Biofeedback Session (0, 2, 4) x 4 Group (Sham, C3 Beta, C3 SMR, C4 SMR) x 2 Electrode (C3, C4 or Fz, Pz). We also examined ERP components at each electrode with an ANOVA of 2 Target Visual Field (TVF: Left, Right), x 3 Cue Validity (Center, Valid, Invalid), x 2 Flanker Congruity (Congruent, Incongruent) x 3 Biofeedback Session (0, 2, 4) x 4 Group (Sham, C3 Beta, C3 SMR, C4 SMR). Where significant Session * Group interaction were found for ERP measures at C3, C4, Fz, or Pz, we re-examined this interaction, limiting groups to Sham and one Active protocol..

Measures: Concurrent EEG & EEG Biofeedback

sLANT administration followed eyes closed and eyes open EEG baseline recordings, per

methodology described in Chapter 1. Participants then received 30 minutes of EEG Biofeedback, at either C4-A2 or C3-A1, as named in the group assignment (C3Beta, C3SMR, C4SMR) with 64-channel dense-array EEG, and a second set of baselines following biofeedback. This combined sLANT/Biofeedback block of testing/training was administered on the first, third, and fifth day of the concurrent 5-day experimental protocol. On the second and fourth day of the protocol, participants received only the biofeedback segment of the protocol for 30 min, without concurrent dense array EEG or preceding sLANT.

Controlling for Multiple Comparisons

Given the redundant ANOVAs on somewhat correlated dependent variables, we chose a p-value of .01 to reduce the number of comparisons by two. This seems appropriate, as we ran ANOVAs for two ERPs (N1, P3) using two different DVs (mean amplitude, peak latency), and also used two behavioral DVs (reaction time, accuracy).

Planned Comparisons

The Biofeedback protocols suggest several between group tests. A total of five comparisons at the group level are appropriate. The first three may provide evidence for efficacy of biofeedback our our dependent variables, e.g. Sham vs. C3 Beta, Sham vs. C3 SMR, Sham vs. C4 SMR. Two additional comparisons examine training hemisphere (C3 SMR v. C4 SMR) and reward frequency (C3 Beta v. C3 SMR). Where significant Session * Group interactions were found for behavioral or electrophysiological variables in any of the above analyses, the ANOVA was re-run, restricting Group to each planned pair. In the C3 SMR versus C4 SMR pairing, we are especially interested in TVF * Group * Session interactions.

Results: sLANT Behavioral Performance

Reaction Time

There was a main effect of Cue ($F = 27.43$, $p < .001$) and of Flanker ($F = 71.4$; $p < .001$) on Reaction Time. Post-hoc tests determined that Valid Cues were significantly faster (M=292.37 ms ;$F=41.84$, $p < .000$) than Center Cues (M = 308.9 ms) and Invalid Cues were significantly slower (M = 314.55 ms; $F=8.91$, $p = .005$) than Center Cues. Congruent Flankers (M = 297.8 ms) were also responded to faster than Incongruent Flankers (M =322.61 ms; $F = 78.97$ p <.000). We also found a second order effect of Flanker * Session ($F = 7.13$, $p = .002$), shown in figure 1. Post hoc tests show significant performance difference to Congruent Flankers across Session 1 (M = 315.15 ms), Session 3 (M = 283.6), and Session 5 (M = 264.6 ms; F =26.55 p<.001). Incongruent Flankers show a significant Session change as well, across Session 1 (M=358.67 ms), Session 3 (M = 316.30 ms) and Session 5(M=292.85 ms; $F=29.11$, $p<.000$). Lastly, Reaction Time also shows a a four way interaction of TVF * Flanker * Session * Group ($F = 2.54$, $p = .029$). A post-hoc comparison of Sham versus C3Beta performance reproduced this 4-way effect ($F=5.39$, $p=.009$). Figure 1 plots the TVF * Electrode for each flanker type for this comparison.

Figure 1: TVF * Electrode Effects per Flanker Congruency: C3Beta vs Sham (Reaction Time)

Accuracy

There was a main effect of Cue ($F = 18.5$, $P < .001$) on Accuracy. Post-hoc tests determined this to be due to significantly better performance on Center Cues (M = .73) than Valid Cues (M=.67; $F=63.77$,$p <.000$). Invalid Cues (M = .73) were not significantly different from Center Cues. Accuracy also showed a main effect of Flanker ($F = 88.56$, $p < .001$). Mean accuracy to

Congruent Flankers (M=.82) was significantly better than to Incongruent Flankers (M=.61; F=156.35, p <.001). We also found a second order effects of TVF x Flanker (F = 5.2; p = .029). Post-hoc tests within each flanker type determined that RVF Congruent Flankers (M = .95) were significantly more accurate than LVF Congruent Flankers (M=.84, F=473.26, p < .001) and LVF Incongruent Flankers (M = .73) were significantly more accurate than RVF Incongruent Flankers (M=.68; F =6.09, p = .019). Figure 2 shows this double-dissociation. Performance Accuracy showed no significant interactions involving Session * Group. Thus, there was a larger Conflict in the RVF than LVF.

Figure 2: TVF * Flanker Effects (Reaction Time)

Performance Accuracy also showed a second order effect of Flanker x Session (F = 8.7, p < .001). Refer to Figure 1 for one by-Group comparison that demonstrates this effect in a post hoc test.

Figure 3: Flanker * Session Effects (Reaction Time)

Results: sLANT Electrophysiology

sLANT ERPs show a maximal amplitude in fronto-central scalp areas (figure 4).

Figure 4: Scalp Distribution of sLANT ERPs (64 electrodes)

sLANT ERPs demonstrate differences by Cue/Flanker type and by Target Visual Field at vertex (figure 4).

Figure 5: sLANT ERPs to Cue Validity, Flanker Congruity in each TVF

These ERPs may also be created for difference waves corresponding to sLANT constructs of Conflict, Orienting Cost, and Orienting Benefit in each Target Visual Field (figure 6).

Figure 6: sLANT ERPs to Orienting Benefit, Orienting Cost, and Conflict in each TVF

sLANT difference wave components identified in Chapter 1 remain distinct with the addition

of two additional sLANT testing sessions to the grand mean.

sLANT ERPs Around Vertex: N1

The C3 N1 component's mean amplitude demonstrated a main effect of TVF ($F=54.42$, $p < .001$) a main effect of Session ($F=8.52$, $p=.001$), and a two way interaction of TVF * Cue ($F=6.9$,$p=.002$). C3 N1 peak latency showed a main effect of TVF ($F=20.49$,$p=.001$), a main effect of Cue ($F=6.73$,$p=.002$), and a two way effect of Flanker * Session ($F=5.03$, $p=.009$).

The C4 electrode N1 mean amplitude also showed a main effect for TVF ($F=47.57$, $p<.001$) and a main effect of Session ($F=9.57$,$p<.001$). C4 N1 latency showed a main effect of TVF ($F=27.1$,$p<.001$), a main effect of Cue ($F=7.67$,$p=.001$), and a second order effect of TVF * Flanker ($F=4.05$, $p = .011$).

The Fz N1 mean amplitude demonstrated a main effect of Session ($F=12.28$,$p<.001$) and no significant latency effects. The Pz N1 mean amplitude demonstrated a main effect of Cue ($F=5.81$,$p=.005$). The Pz N1 latency also demonstrated a main effect of Cue ($F=17.19$,$p<.001$). Pz N1 amplitude at the vertex electrode (Cz) showed a main effect of Session ($F=8.05$, $p=.001$)

The Cz N1 latency showed a three way interaction of TVF * Session * Group ($F = 3.17$, $p = .009$). Post hoc comparison at the Group level shows that this is significant for the paired Group comparison of Sham v. C3 SMR. Figure 7 shows N1 Latency to targets in each visual field, at each Session for these groups. On Session 1, the N1 is slightly faster in the LVF in both groups - an LVF "Latency Advantage". On subsequent Sessions, the Sham group loses the LVF (right hemisphere) latency advantage and develops an RVF (left hemisphere) advantage. The C3 SMR group maintains and increases it's LVF N1 Latency Advantage by Session 2, and maintains this lateralized pattern through Session 5 (see Figure 7)

Figure 7: N1 Peak Latency: TVF by Group, per Session: Sham vs. C3 SMR

sLANT ERPs Around Vertex: P3

Examining sLANT variables on ERPs at and 20% from Cz vertex (C3, C4, Fz, Cz) we find the C3 P3 mean amplitude has a main effect of TVF ($F = 39.33$, $p < .001$) and a second order effect of Session * Group ($F = 3.69$, $p = .003$). C3's P3 latency showed a main effect of TVF ($F = 10.1$, $p = .003$), a main effect of Flanker ($F=41.01$, $p < .001$), a main effect of Cue ($F =4.98$, $p = .01$), and a three way interaction of Cue * Session * Group ($F = 2.4$, $p = .008$). Table 1 shows the post-hoc paired-Group comparisons for this three-way interaction; only the Sham v. C3 SMR and C3 Beta v. C3 SMR pairings were significant. Figure 8 shows that in the Sham v. C3 Beta comparison, this is due to increased P3 latency in the C3 Beta group only, on Center and Invalid Cues (but not Valid Cues) from the Session 1 to Session 2 of the sLANT. When examining C3 Beta v. C3 SMR (Figure 9) we see that the C3 SMR group also demonstrates this Session 1 to Session 2 increase in P3 latency, but only at Invalid Cues.

Figure 8: P3 Peak Latency: Session by Group, per Cue Validity: Sham vs. C3 Beta

Figure 9: P3 Peak Latency: Session by Group, per Cue Validity: C3 Beta vs. C3 SMR

C4 P3 mean amplitude showed a main effect of TVF ($F=16.34$, $< .001$). C4 P3 latency showed a main effect of TVF ($F=7.46$, $p = .01$), a main effect of Flanker (82.52, $p < .001$), as well as a second order effect of TVF * Group ($F=4.46$, $p=.01$).

Fz P3 latency demonstrated a main effect of Flanker ($F=55.78$, $p<.001$), a main effect of Cue ($F=10.48$, $p < .001$), and a three way effect of TVF * Session * Group ($F = 3.42$, $p = .005$). Table 1 shows this interaction is significant for the Sham vs. C3 SMR pairing (plotted in Figure 10) and also significant for the C4 SMR vs. C3 SMR pairing (plotted in Figure 11). From these two figures it can be seen that both C4 SMR and Sham groups increased (worsened) P3 Latency to Valid Cues on Session 2.

Figure 10: P3 Peak Latency: Session * Group, per Cue Validity: Sham vs. C3 SMR

Figure 11: P3 Peak Latency: Session * Group, per Cue Validity: C3 SMR vs C4 SMR

Pz P3 mean amplitude showed a main effect of TVF (F=8.66, p=.006) and a two way effect of Session * Group (F = 3.25, p = .007). Pz P3 latency demonstrated a main effect of Flanker (F=40.49, p<.001) and a two way effect of Flanker * Session (F =7.74, p=.001).

ERPs at Cz showed no significant P3 amplitude effects, but did show P3 latency main effects of Flanker (F=51.54, p<.001) and Cue (F=5.57, p=.006).

Laterality of ERPs at C3 versus C4

N1 Component

When adding C3 and C4 to the above ANOVA as levels of "Electrode", the N1 component amplitude showed a main effect of Session (F=9.67,p<.001), a two way effect of TVF * Electrode (F=78.71,p<.001), three way effects of TVF * Cue * Electrode (F=7.13, p=.002) and TVF * Electrode * Session (F=7.61, p=.001). N1 peak latency showed a main effect of Cue (F=9.92,p<.001) and a two way effect of TVF * Electrode (F=37.52,p<.001).

P3 Component

The P3 component mean amplitude demonstrated significant two-way effects TVF * Electrode (F=48.76, p<.001) and Session * Group (F = 3.13, p = .009). P3 peak latency showed a main effect of Flanker (F=64.79, p<.001), a main effect of Cue (F=4.93, p=.01), and a two way effect of TVF * Electrode (F=18.14, p<.000).

Anterior Posterior Distribution of ERPs at Fz versus Pz

N1 Component

When instead using Fz and Pz as levels of "Electrode", the N1 component mean amplitude showed a main effect of Electrode (F=21.41, p<.001) and a main effect of Session (F=10.68,

p<.001) as well as a two way interaction of Electrode * Session (F=8.86, p<.001) and a two way interaction of Cue * Electrode (F=6.79, p=.002). N1 latency showed a main effect of Electrode (F=2.31, p =.011), a main effect of Cue (F=16.33,p<.001), and an interaction of Cue * Electrode (F=6.39,p=.003).

Anterior Posterior Distribution of ERPs at Fz versus Pz

P3 Component

The P3 component mean amplitude showed a main effect of Electrode (F=8.68,p=.006), a two way effect of Session * Group (F = 3.06, p = .011), a three way interaction of TVF * Cue * Electrode (F=5.97,p=.004), a three way interaction of Flanker * Electrode * Session (F5.35, p=.007), a four way effect of Flanker * Electrode * Session * Group (F=3.00, p=.012). And a four way interaction of TVF * Electrode * Session * Group (F=3.06, p =.011). This last four-way interaction is particularly important for theoretical reasons. It illustrates that the sLANT shows a Direct Access pattern, and demonstrates systematic shifts in hemispheric specialization. Specifically, C4 SMR group begins with a greater right hemisphere specialization and ends with greater left hemisphere specialization after four sessions of Biofeedback. In contrast, C3 Beta's Direct Access pattern changes from a left hemisphere specialization to an equal competence in both hemispheres. The Sham group shows a strong right hemisphere specialization throughout the experiment.

Figures 12-15: P3 Mean Amplitude: Target Visual Field (LVF_RVF) at C3 vs C4 Electrode (Each Group * Session)

Table 1 shows the post-hoc paired-Group comparisons for these four-way interactions; only the Sham v. C3 SMR and C3 Beta v. C3 SMR pairings were significant for P3 Amplitude. P3 Latency demonstrated a main effect of Electrode (F=16.58, p<.001), a main effect of Flanker

(F=68.55, p<.001), and a main effect of Cue (F=6.43, p=.003) as well as a two way effect of Flanker * Session (F=11.44, p<.001), but not Session * Group effects..

Table 1: Planned Group Comparisons (ERPs)

Discussion

Changes in Behavior

Adding two additional sessions to the single sLANT administration reported in Chapter 1 produced similar behavioral effects of sLANT variables of Cue and Target. Thus, the sLANT appears valid across multiple administrations. Performance means across session were similar to those reported in in Chapter 1, although demonstrated a slight improvement overall in RT and Accuracy. The observed Flanker * Session speeding of RT suggests a practice effect. The first-session main effect of Target Visual Field on Accuracy becomes nonsignificant in this analysis ($F = 3.06$, $p < .09$), although the LVF advantage is still visible in three of the four protocol groups. The trending of this TVF effect to non-significance over the week of training and testing may be practice related, although could also the result of divergent effects across groups averaging out (as appears to be the case - two groups keep their LVF advantage in Accuracy with sessions, two groups lose it).

Flanker shows a Session effect of decreasing Accuracy, although this appears largely happen in the third sLANT session (Figure 3). Cross-session Accuracy suggests an overall RVF advantage on Incongruent Flanker, thus larger Conflict in the RVF. Post-hoc tests confirmed an interesting dissociation on Flanker Congruency by TVF, such that Congruent Flankers were more accurate in the LVF and Incongruent Flankers were more accurate in the RVF, suggesting

hemispheric specialization of Conflict to left hemisphere. The overall behavior performance gains for Sham group over testing sessions may suggest the magnitude of the practice effect on sLANT.

sLANT ERPs: N1 and P3

As in Chapter 1, clear ERPs emerge from our analysis. The N1 and P3 components were again most relevant; each component was measured at mean amplitude and peak latency, and main effects of sLANT variables on ERPs remained when averaging in additional sessions. There was also almost always an effect of "Session" on the ERPs; this may be due to ERPs attenuating / habituating, but some ERPs only habituate in Sham, and instead or enhanced in Active groups. For instance, N1 Latency slowed in Sham, but only in LVF, while it improved in LVF across session for C3 SMR group.

sLANT ERP and EEG Biofeedback: the N1

As shown by the significant Sham vs C3 SMR group-wise comparison for TVF * Group * Session (Figure 7), the LVF / right hemisphere N1 Latency at Cz became reversed in the Sham group over training. This suggests the initial right hemisphere dominant attention to the reward stimulus becomes later and slower with repeated test taking, or put another way, that a fatigue, boredom, or attenuation effect appears to occur, specifically in the right hemisphere, in Sham. This result also suggests that C3 SMR training (to the left hemisphere) predominantly affects the LVF, or right hemisphere, possibly reducing inhibition and accelerating the N1 component and selective attention.

sLANT ERP and EEG Biofeedback: the P3

Considering the Sham vs C3 Beta pairing, we see P3 peak latency at C3 electrode has a significant effect of Cue and Session with regards to training protocol. The Sham group shows a

relatively monotonic enhancement of P3 latency, 20-30 ms across sessions, while C3 Beta group shows slowed latencies of P3 component to Center and Invalid Cues, but not Valid Cues, on the second sLANT administration (and 2 sessions of biofeedback). Furthermore, C3Beta doesn't show any overall change in P3 latency across from first to third sLANT testing sessions (4 biofeedback training sessions). This suggests C3Beta training is keeping P3 latency slower for the intra-hemispheric conditions. E.g. P3 Latency for Valid Cue trials shows a small improvement across sessions and only requires direct access strategies of hemispheric attention. The selective gain-impairment of Center Cues and Invalid Cues latency suggest the C3 Beta protocol may increase laterality at the expense of resources requiring intrahemispheric transfer. Note that in Chapter 1 we found the P3 response to Cue (Orienting) to be more sensitive in amplitude, while Flanker (Conflict) was more related to P3 latency. The change in P3 Latency produced by the C3 Beta protocol may thus be related to reducing the implicit hemispheric competition, or "unloading" the Orienting response to Valid Cues.

Intra vs Interhemispheric Attention: Direct Access and Intrahemispheric Transfer

In addition to the laterality findings of Biofeedback emphasized by the Active vs. Sham comparisons, that demonstrated the N1 Latency at Cz indexing TVF effects and a P3 Latency at C3 changing with laterality, we can also compare the effect of TVF at C3 and C4 to distinguish Direct Access conditions from those requiring Intrahemispheric Transfer (or "Callosal Relay"). Figures 12-15 show that the sLANT demonstrates a Direct Access pattern on the first day of testing, with systematic shifts in hemispheric specialization with repeated testing (Sham) or testing/training (Active). Specifically, C4 SMR protocol appears to eliminate a right hemisphere specialization and ends with greater left hemisphere specialization after four sessions of Biofeedback. In contrast, C3 Beta's Direct Access pattern changes from a left hemisphere

specialization to an equal competence in both hemispheres. The Sham group shows a strong right hemisphere specialization throughout the experiment; this LVF-evoked difference in ERPs (between C3 and C4 electrode) is stable across testing. The large C3 vs C4 session-differences seen in Sham's RVF P3 amplitude (which may represent a late cortical response of trial evaluation) in the left hemisphere was quite poor and unstable. This suggests the Sham group began without a strong lateralized P3 to RVF targets, and while their left hemisphere changed (with amplitudes increasing), there was no clear pattern of laterality to RVF targets throughout sLANT testing. The LVF targets, in contrast, have a stable C3 vs C4 ERP relationship; this is somewhat expected. The right hemisphere likely has a stronger attention response and the ERP stability mirrors the "LVF advantage" that we often see in Flanker Task or LANT administration (sLANT or otherwise). In contrast, all three Active groups initially presented with slightly asymmetrical P3 amplitudes, but became more symmetrical and stable over testing/training sessions.

Electrophysiology vs Behavior

This chapter has demonstrated a clear pattern of behavior in the Biofeedback trained groups that diverges both from Sham and by Active protocol, both in behavior and electrophysiology. Clear lateralized results also obtain, in the behavior to some extent but certainly many more examples of the electrophysiology. The most obvious difference in sensitivity of behavior versus electrophysiology may be in the overall Target Visual Field effect. This was significant in behavior for Session 1, but trended to nonsignificance after a second sLANT administration. This may be due to practice effects, or due to poor sensitivity of the test to measure TVF in the behavioral domain given these small groups (7-13) versus the un-manipulated 36-participant data set from Session 1, before Biofeedback. Earlier versions of the

LANT have also failed to find TVF effects occasionally, on either Accuracy or Reaction Time, or both. In contrast, the ERPs are strongly lateralized even when viewed at midline electrodes, e.g. Target Visual Field is a successful manipulation of laterality, measurable at scalp electrodes. When dense-array EEG is considered, as in the Mass Univariate tests in Chatper 1, extremely clear patterns of contralateral activation from sLANT stimuli emerge.

EEG Biofeedback Protocol Specificity and Efficacy

From the somewhat montonic change in Sham group, on both behavior and electrophysiology, and similar string divergent patterns in the Active groups - from each other, and from Sham - we find that EEG Biofeedback can have a strong effect on hemispheric attention in as little as two sessions. The large number of Session * Group effects in both behavioral performance (RT) and ERPs suggest specificity of Biofeedback protocol. The choice of electrode site appears to matter greatly, as does the choice of reward frequency. Given the sensitivity of ERPs that index stimulus salience or selective attention modulation (N1) and cognitive evaluation task (P3), we believe ERPs have been established as a valuable tool in researching the effect of EEG Biofeedback on behavior as well as cortical processes.

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Figure 1: TVF * Electrode Effects per Flanker Congruency: C3Beta vs Sham (R T)

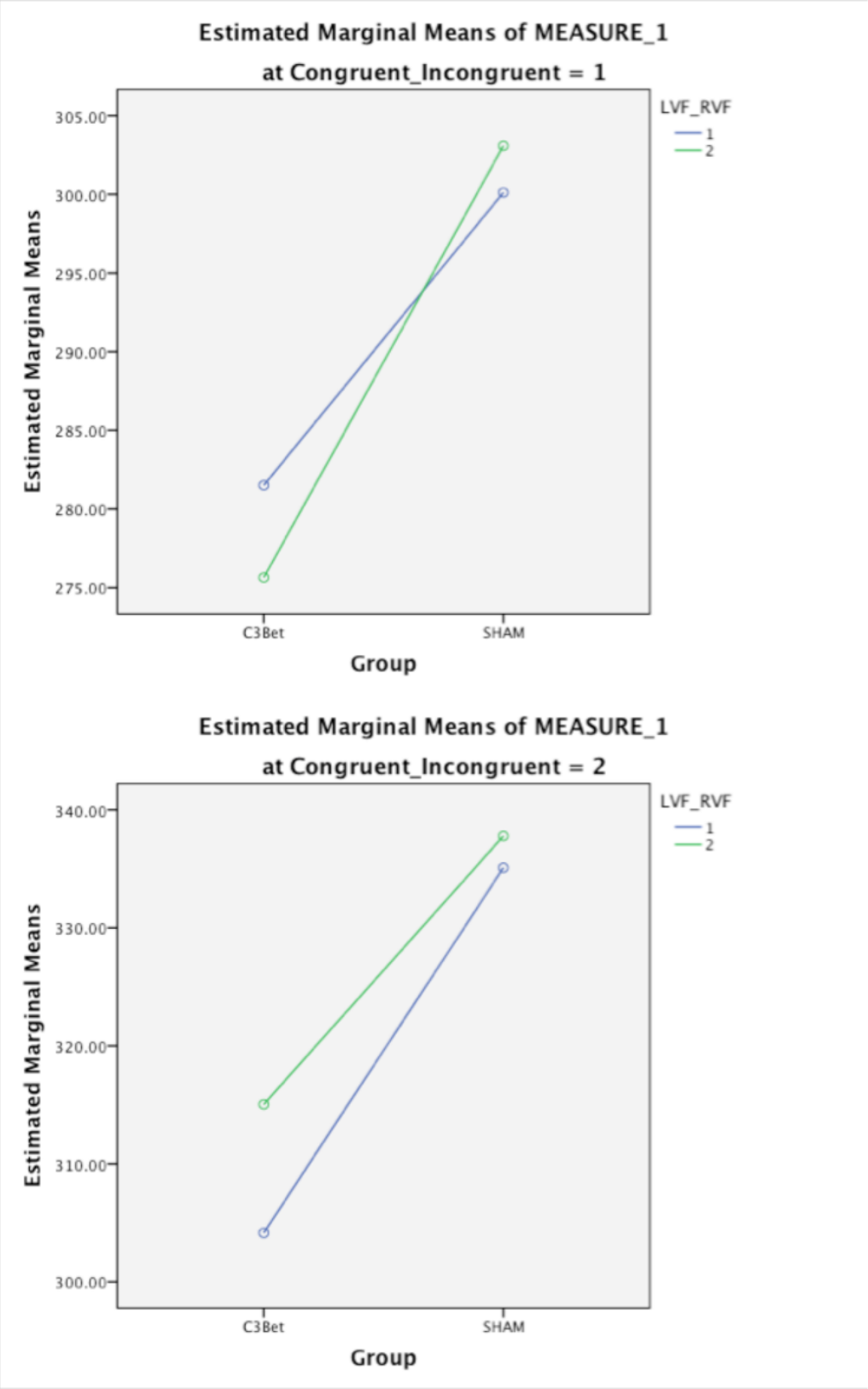


Figure 2: TVF * Flanker Effects (Accuracy)

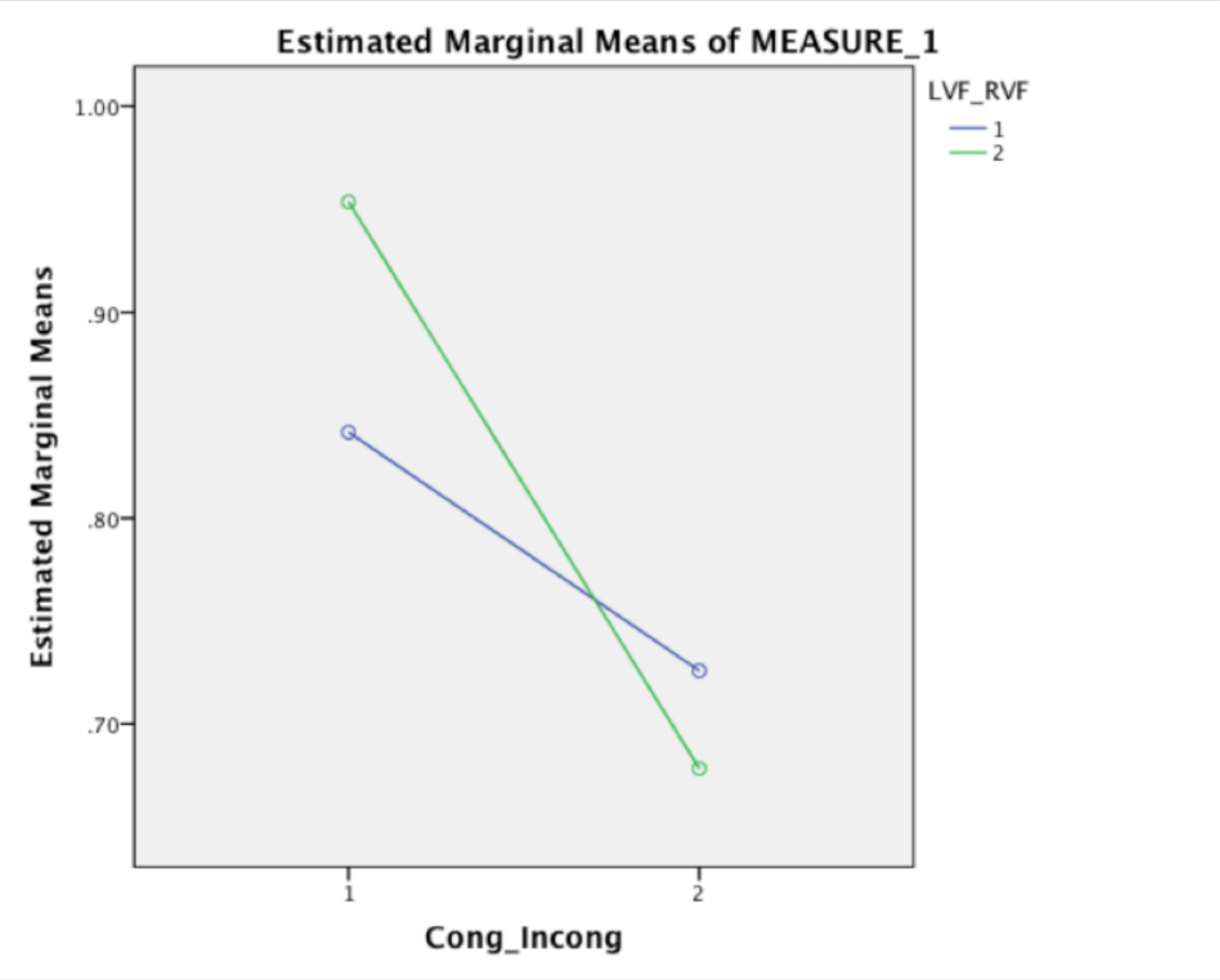


Figure 3: Flanker * Session Effects (Reaction Time)

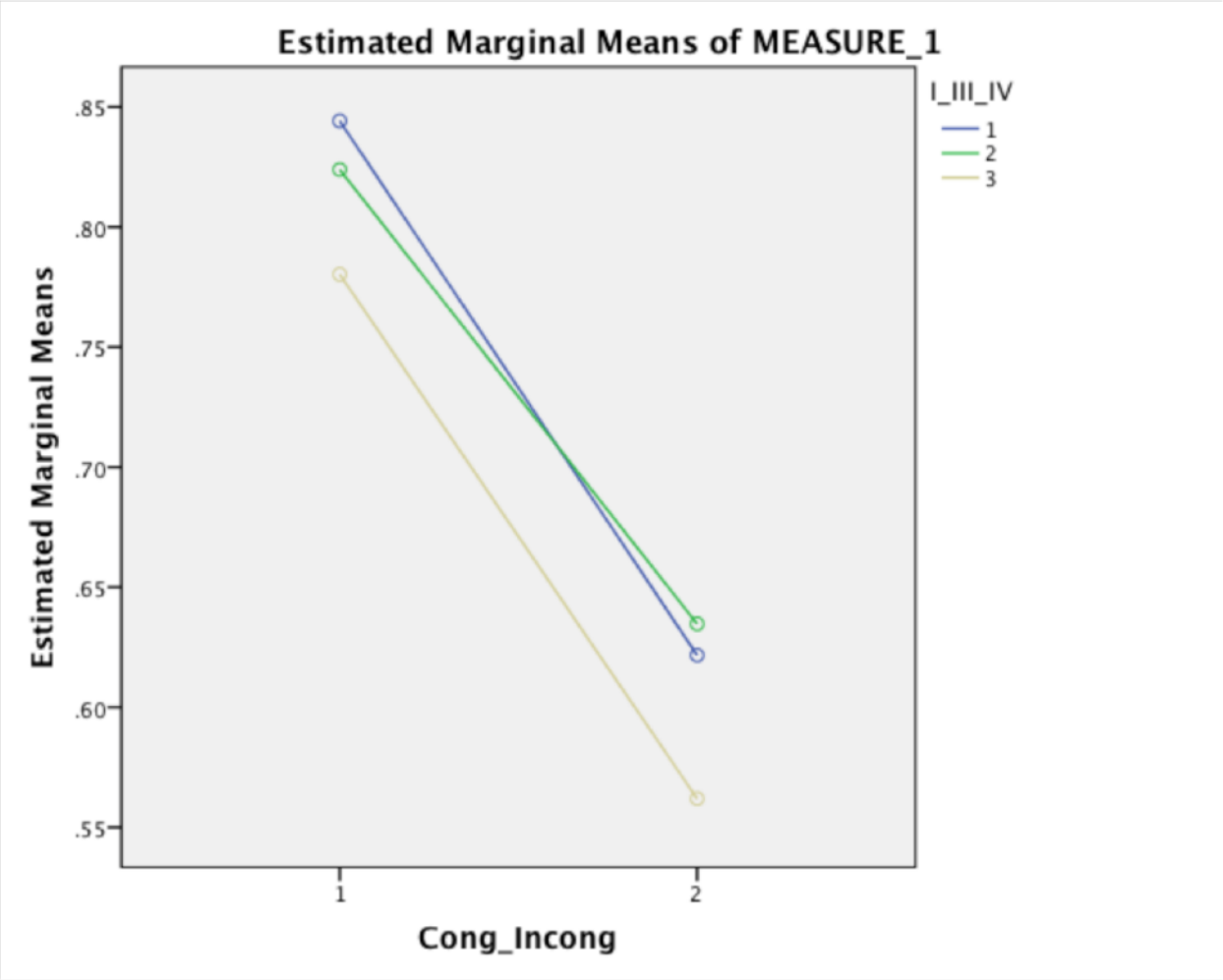


Figure 4: Scalp Distribution of sLANT ERPs (64 electrodes)

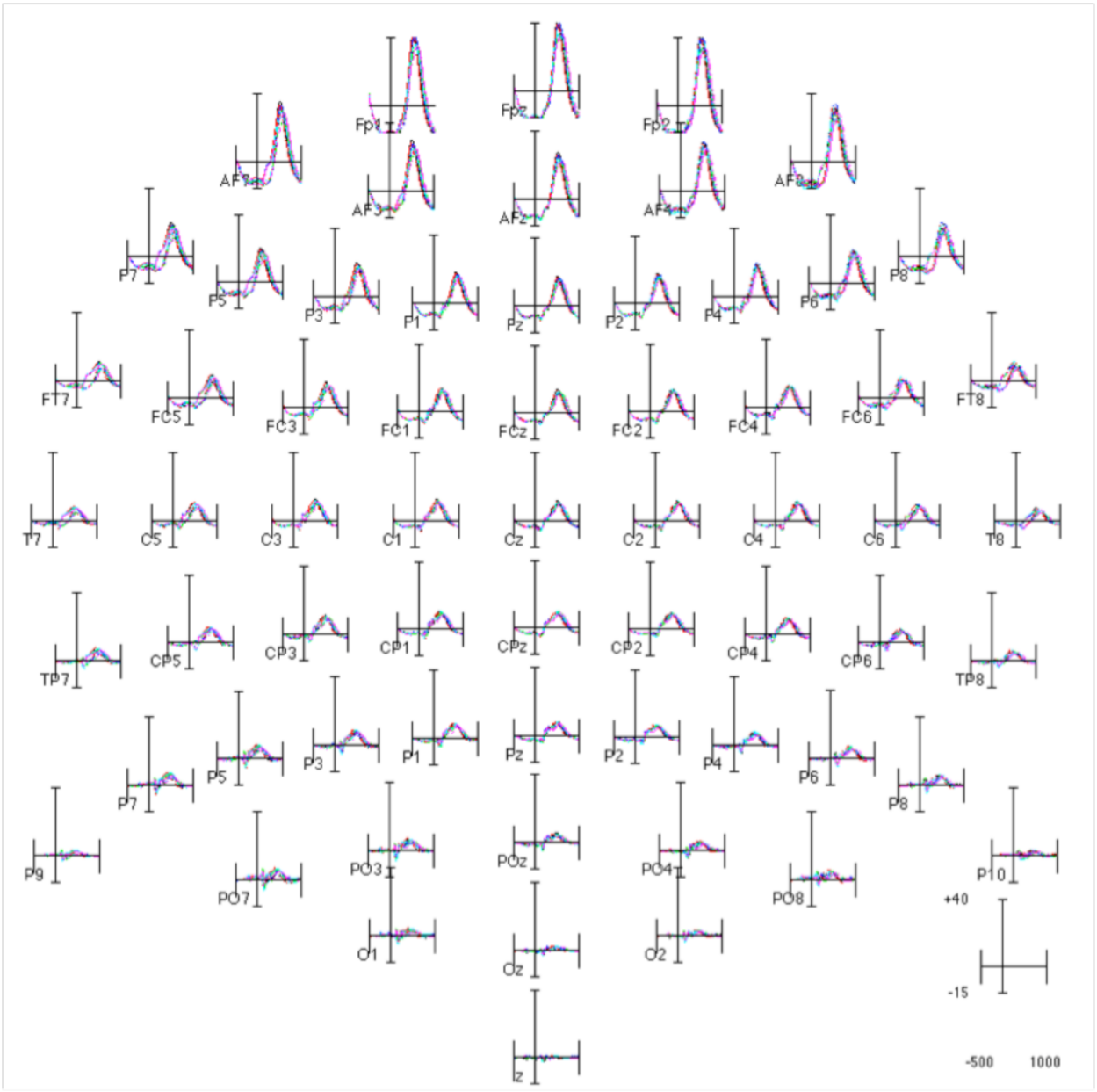


Figure 5: sLANT ERPs to Cue Validity, Flanker Congruity in each TVF

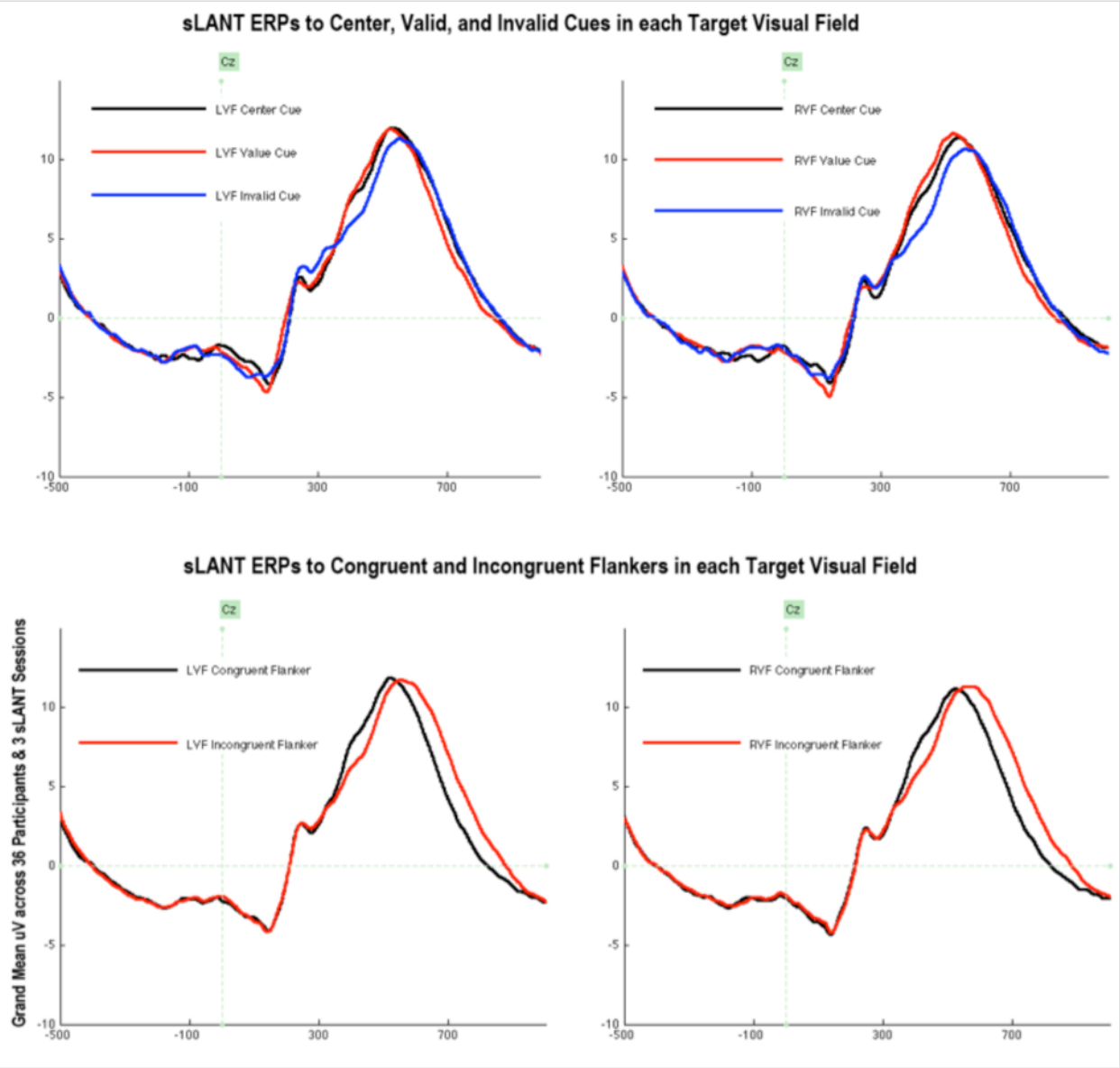


Figure 6: sLANT ERPs to Orienting Benefit, Orienting Cost, and Conflict in each TVF

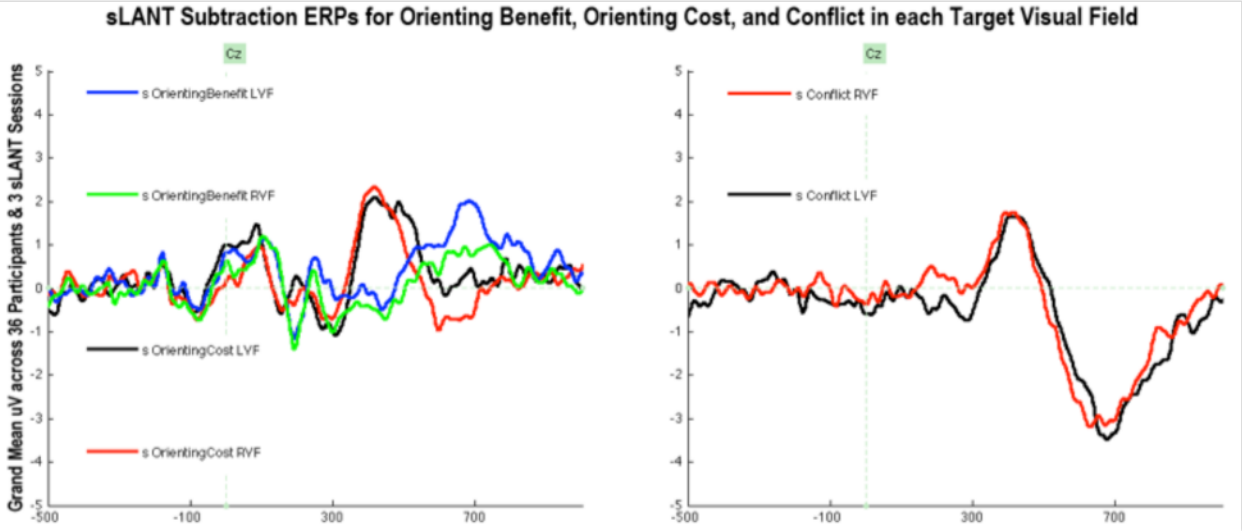


Table 1: Planned Group Comparisons (ERPs)

Planned Comparisons: Repeat sLANT ERP ANOVAs with sig. Session * Group, at each 2-level Group comparison												
Electrode Component (DV)			Sham v C3 Beta		Sham v C3 SMR		Sham v C4 SMR		C3Beta v C3SMR		C4 SMR v C3 SMR	
Single	ERP	sLANT Variables	F	P	F	P	F	P	F	P	F	P
C3	P3 Amplitude	Session * Group			2.01	0.006			5.72	0.008	2.92	0.072
C3	P3 Latency	Cue * Session * Group	4.85	0.002	4.29	0.003	***2.24***	***0.073***				
Cz	N1 Latency	TVF * Session * Group			4.74	0.015						
Fz	P3 Latency	TVF * Session * Group			5.31	0.009					8.80	0.001
Pz	P3 Amplitude	Session * Group			7.54	0.002			4.90	0.015	5.99	0.007
Comparison	ERP	sLANT Variables										
C3 v C4	P3 Amplitude	Session * Group			5.08	0.011			4.69	0.018	***2.75***	***0.083***
C3 v C4	P3 Amplitude	TVF * Cue * Electrode * Session * Group							***2.09***	***0.094***		
Fz v Pz	P3 Amplitude	Session * Group			4.83	0.014			4.09	0.028	**2.66**	**0.089**
Fz v Pz	P3 Amplitude	TVF * Electrode * Session * Group			5.69	0.007	***2.79***	***0.075***	4.01	0.029		
Fz v Pz	P3 Amplitude	Flanker * Electrode * Session * Group			5.15	0.01	***2.99***	***0.065***	3.96	0.031		

Figure 7: N1 Peak Latency: TVF by Group, per Session: Sham vs. C3 SMR

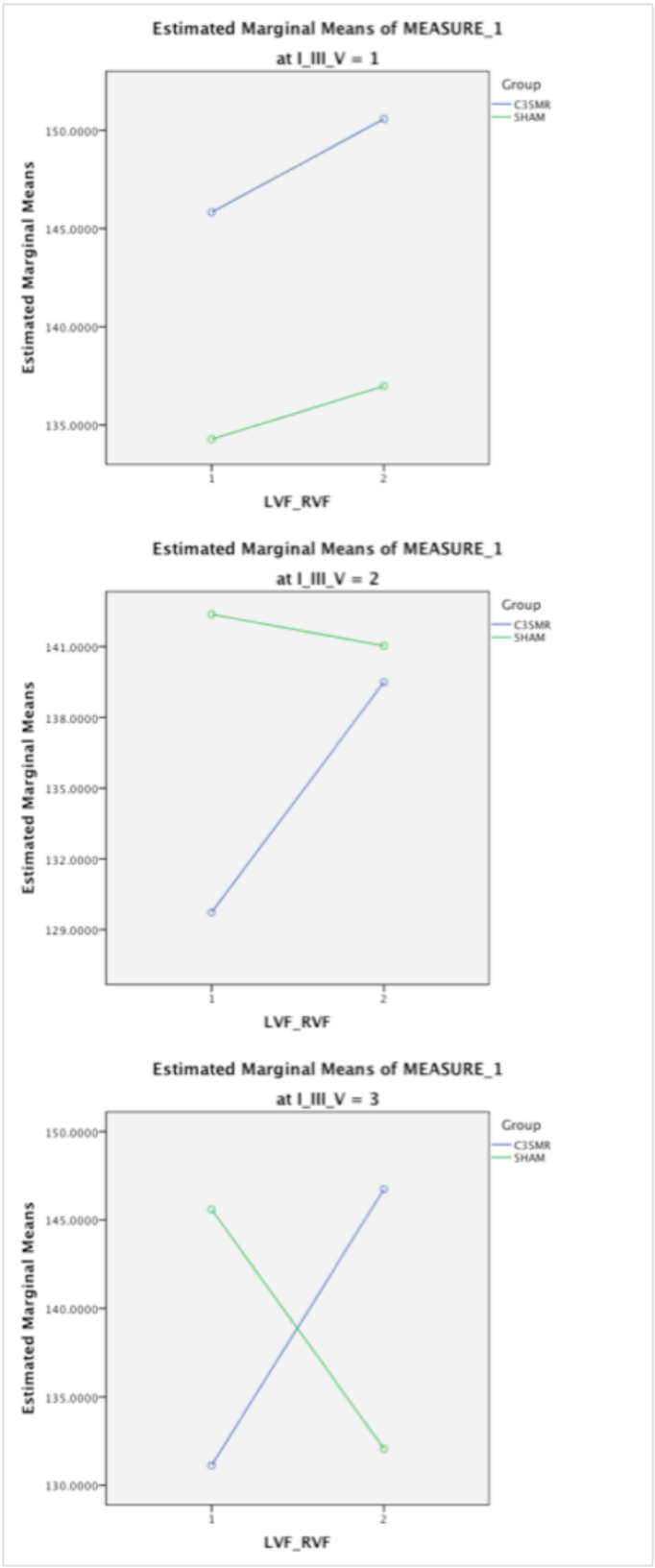


Figure 8: P3 Peak Latency: Session by Group, per Cue Validity: Sham vs. C3 Beta

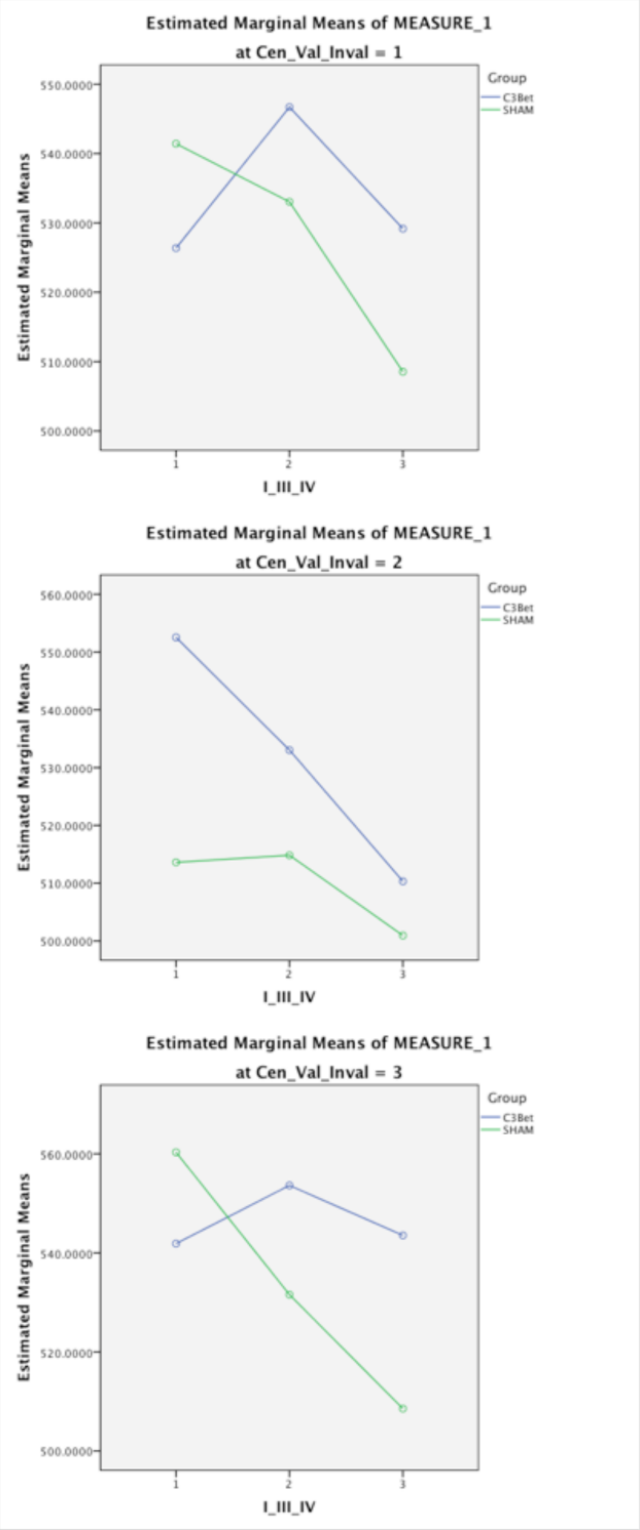


Figure 9: P3 Peak Latency: Session by Group, per Cue Validity: C3 SMR vs. C3 Beta

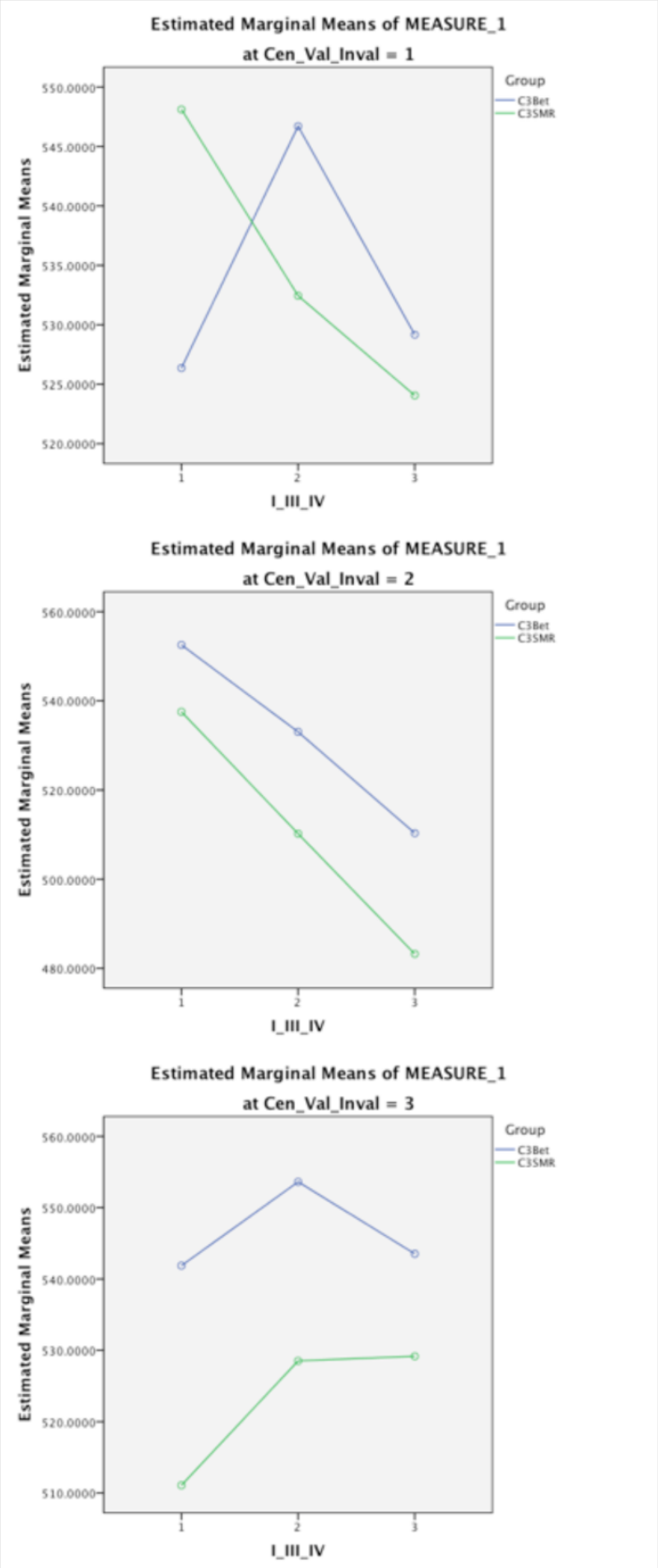


Figure 10: P3 Peak Latency: Session * Group, per Cue Validity: Sham vs. C3 SMR

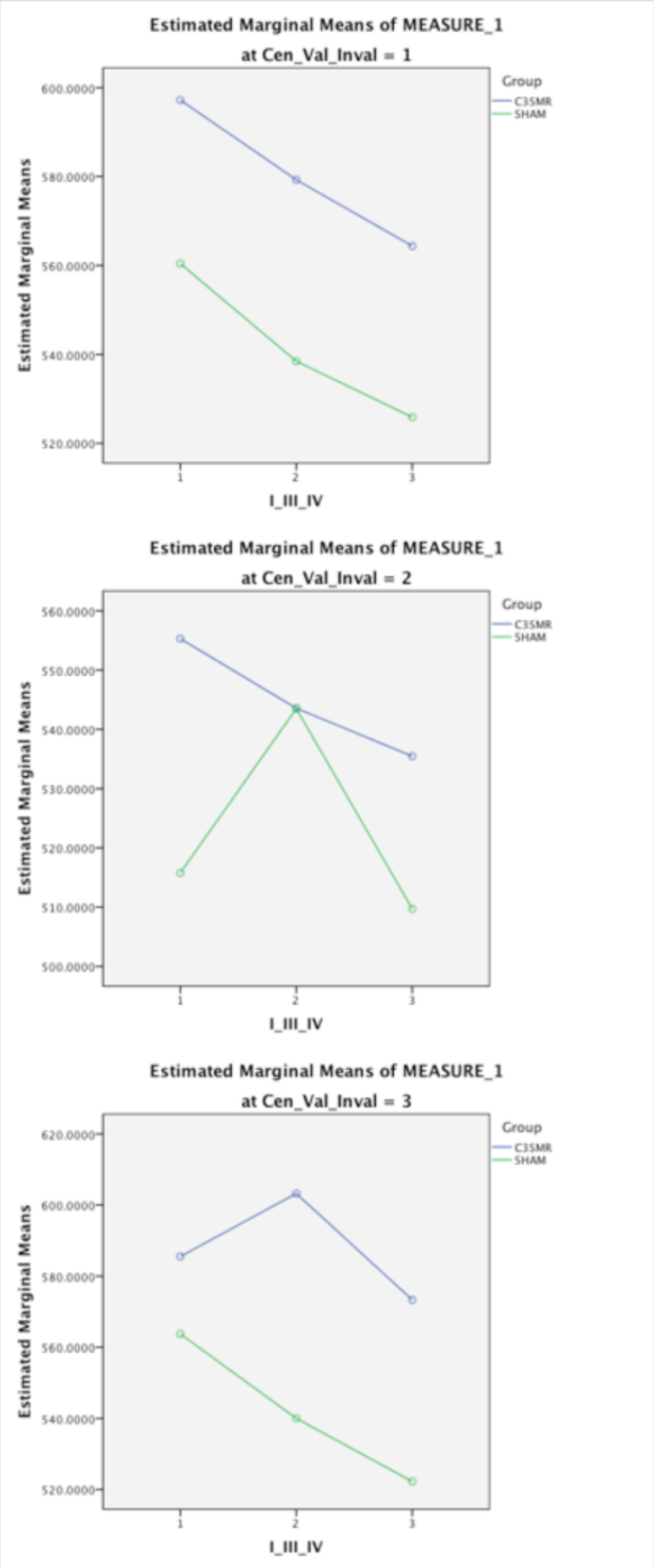
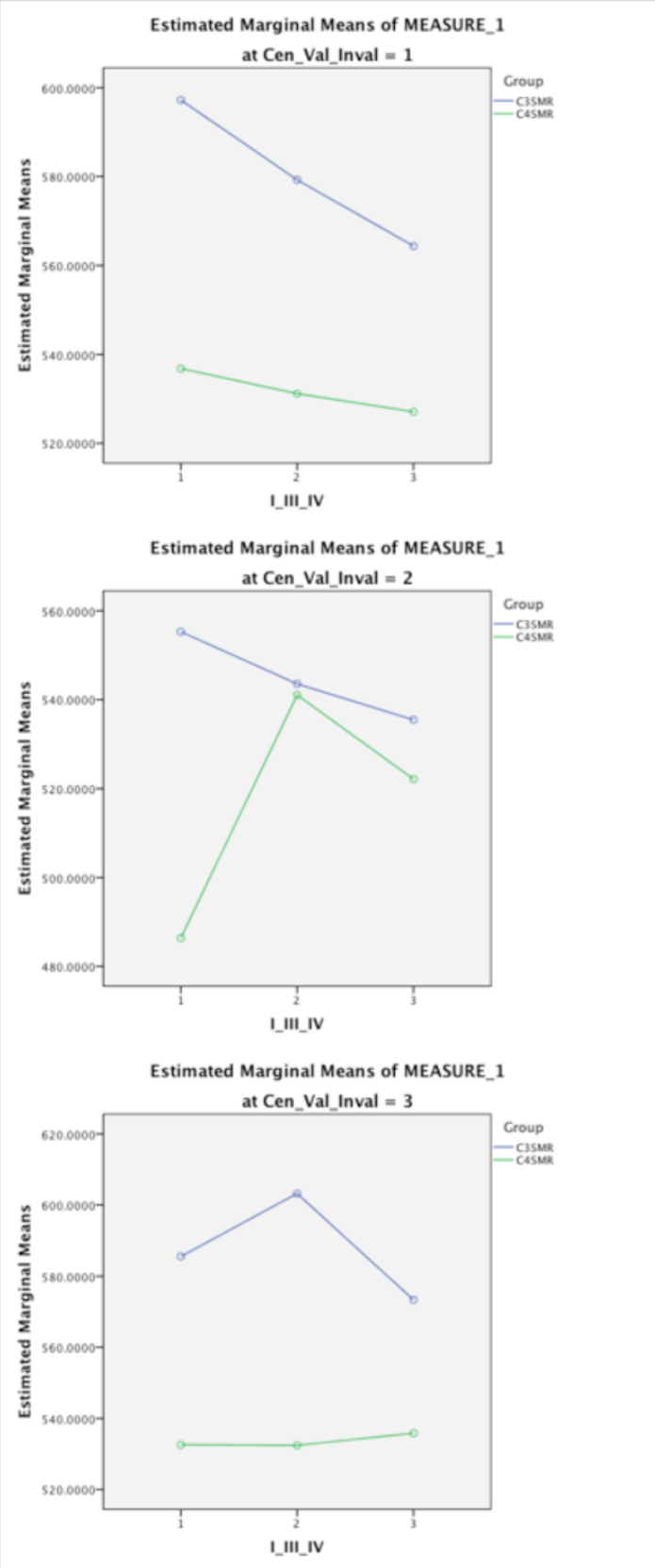
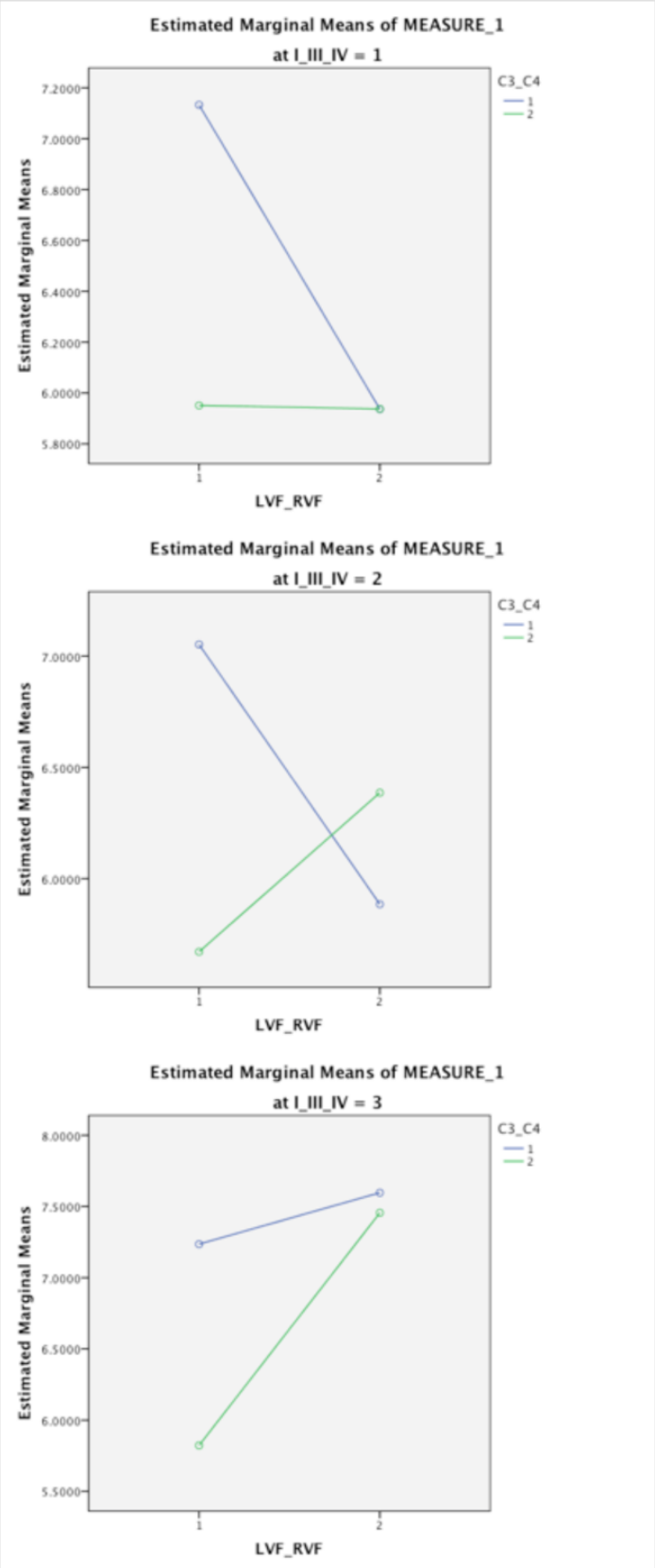


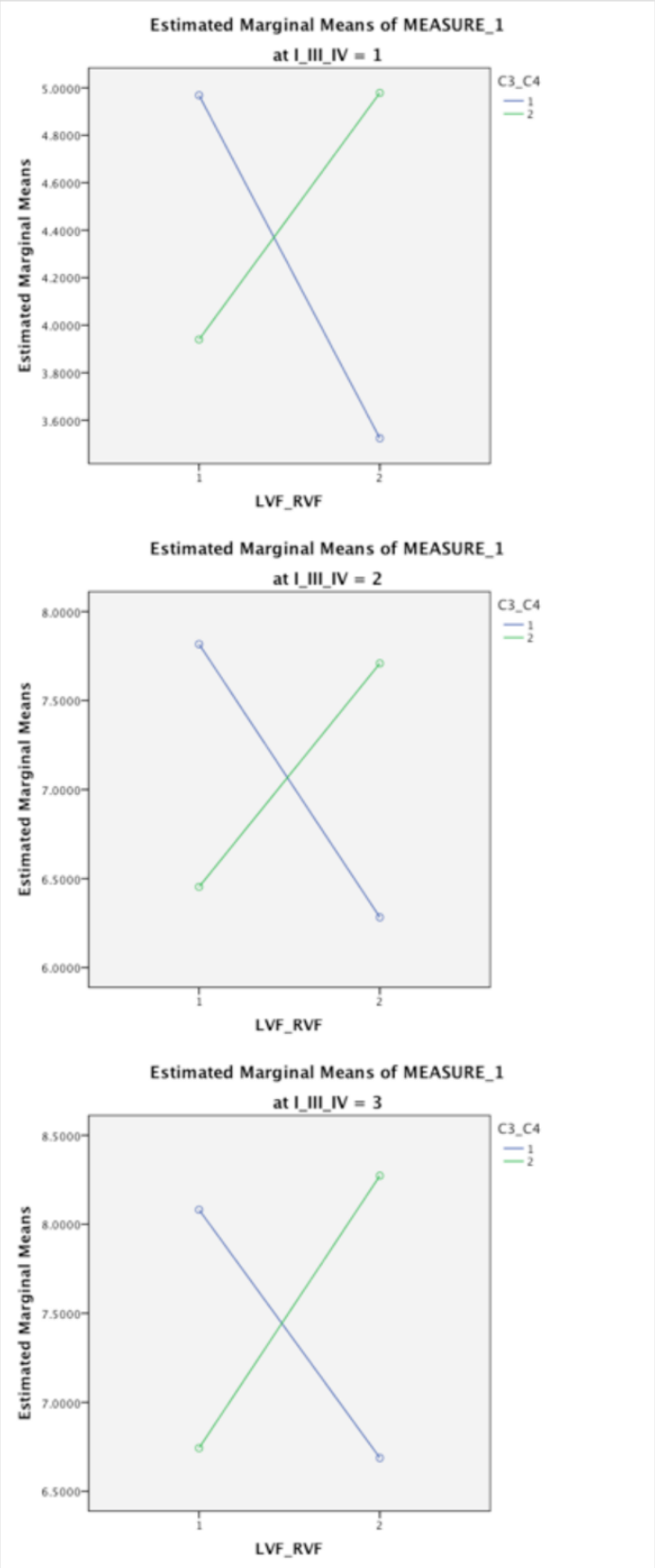
Figure 11: P3 Peak Latency: Session * Group, per Cue Validity: C3 SMR vs C4 SMR



Figures 12: P3 Mean Amplitude: TVF by Electrode (C3 vs C4): SHAM Group * Session



Figures 13: P3 Mean Amplitude: TVF by Electrode (C3 vs C4): C3 BETA Group * Session



Figures 14: P3 Mean Amplitude: TVF by Electrode (C3 vs C4): C3 SMR Group * Session

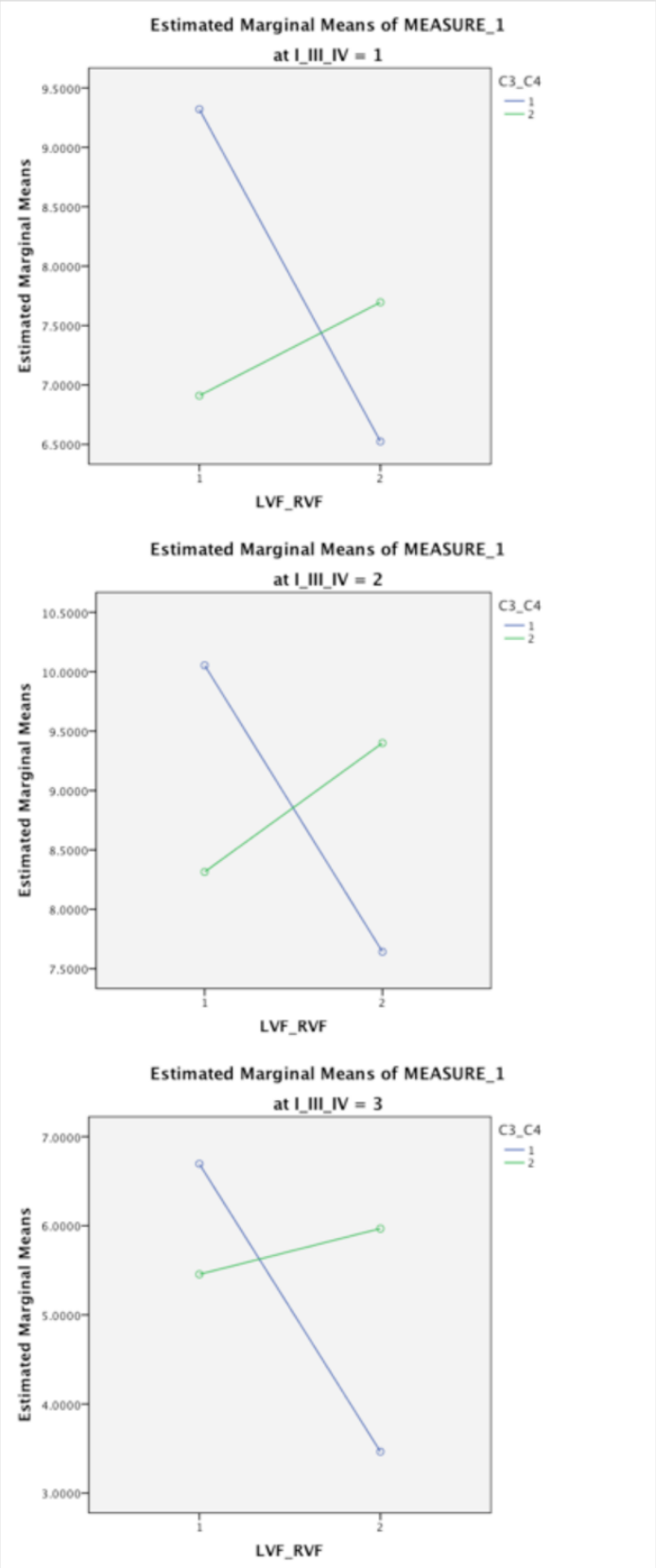
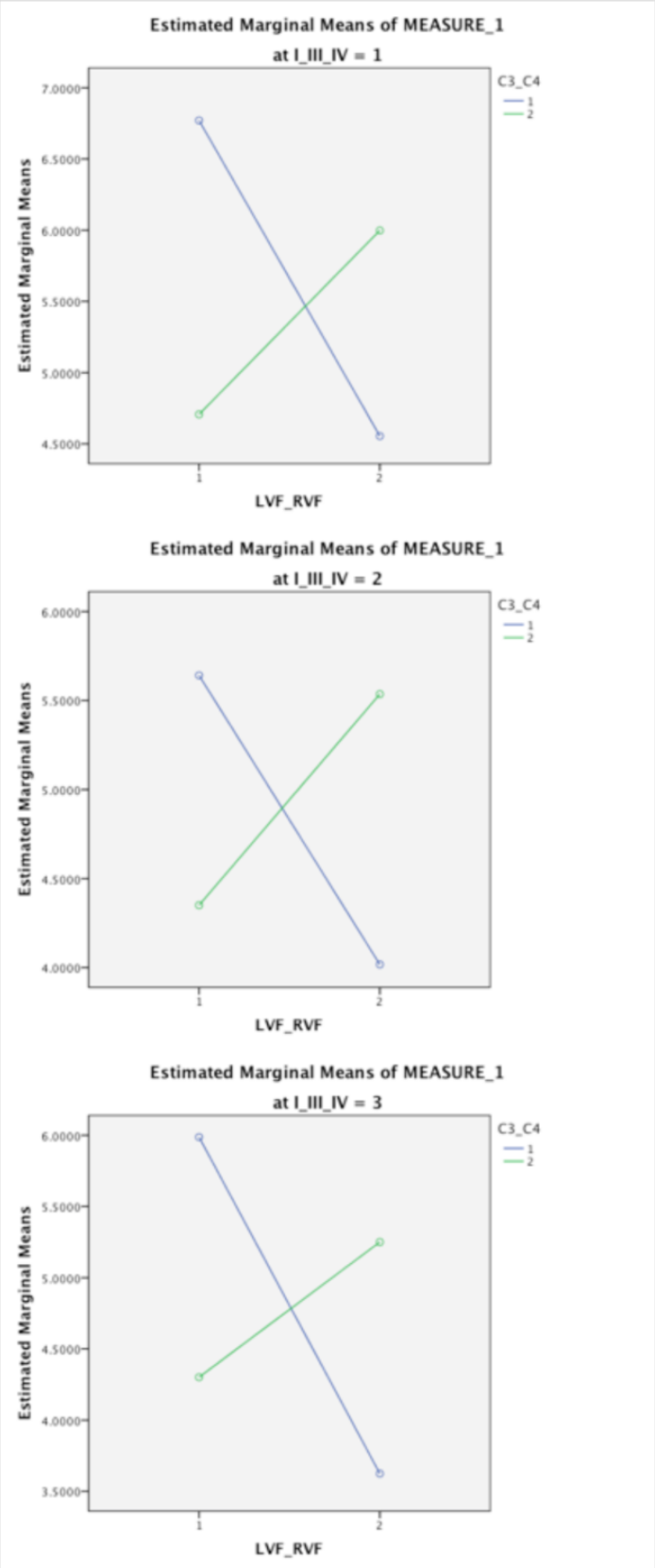


Fig 15: P3 Mean Amplitude: TVF by Electrode (C3 vs C4): C4 SMR Group * Session



Chapter 3:

Evoked Responses to EEG Biofeedback: Placebo Controlled Double Blind Evidence

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Introduction

EEG Biofeedback

In the late 1960s Sterman performed several experiments with cats, training increases in SMR EEG amplitude in cats (Wyrwicka & Sterman, 1968; Sterman M.B., 1977). in an operant conditioning paradigm using a milk reward. An inadvertent effect of this produced seizure resistance in these cats, suggesting some inhibitory or regulatory process had been affected.(Sterman, 1972). Intracranial recordings on these cats showed a marked decrease in spontaneous firing during and after the training process. Kamiya (1969) trained human EEG rhythms about the same time. Over 40 years later there are thousands of "Neurofeedback" clinics and practitioners throughout the world, in a variety of professional settings, and EEG Biofeedback is emerging as an efficacious treatment for attention problems alone (Hirshberg, 2005; Arns, 2009; Nelson, 2003) or with medication. Fox et al (2005) reviewed efficacy studies, and concluded EEGBF is efficacious when compared with typical medication treatment. Work by Monastra et al. also concluded that EEGBF is effective in treating attentional disorders (Monastra, 2003; Monastra & Lubar, 2000; Monastra et al., 1999, 2002) but some methodological issues do persist (Loo, 2003).

EEG BFB techniques have, in general, not been sufficiently scrutinized in rigorous controlled double-blind trials. Worse, extremely little is known about how the process of neurofeedback works or how it may be manipulating human EEG.

Types and Difficulty of EEG Biofeedback in Clinical and Research Settings

EEGBF involves an individual modifying the amplitude, frequency, coherence,

synchrony or other derived measures of the electrical activity of his/her own brain. Many authors have demonstrated control of various electroencephalographic (EEG) parameters in animals and humans (Birbaumer, 1977; Birbaumer, 1984; Birbaumer et al., 1981; Kamiya, 1969; Plotkin, 1976; Sterman, 1977). There are few controlled experiments on the effects of EEGBF training on hemispheric specialization and interhemispheric interaction in the normal brain, mostly using the slow cortical potential shift approach (e.g. Hardman et al., 1997; Kotchoubey et al.,1996; Rockstroh et al., 1993; Pulvermuller et al., 2000), however, the evidence for hemispheric engagement is at best indirect.

Primary improvement on attentional symptoms has shown effectiveness of EEGBF to address ADHD symptomology (Monastra, 2005; Gruzelier & Egner, 2005), although much research still needs to be done to validate the methods of action. As mentioned earlier, Sterman produced motorically "calm" cats, with a trained increase of sensorimotor rhythm (12-15 Hz) on cortical motor strip.

Similar motor calming has been assumed to have a beneficial effect on attention and impulsivity. Many clinicians only train attentional symptoms on the motor strip, at C3, Cz or C4, even though there is strong support for a frontal hypoarousal model of ADHD (Liotti, et. al., 2005; Max, et. al., 2005) along with central and midline cortical slowing (Mann, et. al., 1992; Chabot, et. al., 1996; Monastra, et. al., 1999; Clarke, et. al., 2001).

For protocol frequency selection, inhibiting slower frequency ranges including theta (4-7 Hz) is typical, and reward frequency ranges include SMR (12-15 Hz) and low Beta (15-18 Hz). Clinicians often reward SMR at C4 and low Beta at C3, and either at Cz. In addition, clinicians often reward slower frequencies posterior to the motor strip, and faster frequencies anterior to the

central motor strip. Interhemispheric training (C3-C4) may is also used, rewarding frequencies in the 12-18 Hz range. Many other frequencies and pairs of scalp sites are also used. The subjective nature and variety of these choices adds to the difficulty of performing systematic research on efficacy or mechanism of action.

Even given the range of EEG Biofeedback techniques being practiced in clinical settings today, and the many different software and hardware packages for training EEG at one or many scalp sites available, most clinicians still tend to train at 1 or 2 sites, reward EEG somewhere in the 7-18 Hz range, and inhibit bands above and below that range. This is perhaps driven by the "Othmer Approach", from early instruction on EEG Biofeedback, validated by Sue and Siegfried Othmer (Kaiser & Othmer, 2000). The Othmers began teaching a low-frequency inhibit, medium-frequency reward, and high-frequency inhibit style; most EEGBF software provides this as a standard mode of training, and most clinicians do some version of this, even if guided by presenting complaints or QEEG pre-assessment

Sham Biofeedback

Due to the real-time signal monitoring of EEG by both biofeedback software and training technician, developing a convincing placebo biofeedback was challenging. Typically movement and other major signal artifacts would result in pausing of the training "game". Thus, training from stored EEG versus realtime EEG is immediately apparent to the non-naive trainee or any trainer or EEG researcher. The author of this paper worked with EEGer, Inc to develop a functional placebo, used in this experiment sequence (see Methods).

Attention & Sensory Evoked ERPs

As mentioned in Chapter 2, several ERP components are routinely studies in research on attention. In addition to the N1, P2, and P3 reviewed there, an early-latency component labeled P50 is of special interest in our investigation of the Biofeedback process. The P50 is thought to be involved in sensory gating. It is reduced in disorders with cognitive or sensory processing difficulties (for example Schizophrenia) and is increased by attention to stimuli in healthy subjects (Gjini, et al, 2011). The gating aspect of the P50 appears closely tied to engagement with sensory stimuli stream, of "reality"; even healthy subjects with lower P50 amplitudes have an increase of perceptual anomalies (Croft, et al, 2001). Our Biofeedback paradigm produced a simultaneous "beep" that was presented ~ 1000 times during 30 minutes. If the brain encodes this signal as relevant and changing information, the P50 should be enhanced with training; if the repetitive beep simply produces a sensory habituation, participant ERP should show reduced P50 amplitude.

Methods

See Chapter 1 for a discussion of Participant recruitment and research design, including EEG analysis methods relevant to ERP pre-processing. See Chapter 2 for a discussion of the 5-session Biofeedback protocol and sLANT testing procedure before EEG Biofeedback and after 2 and 4 sessions of Biofeedback.

EEG Biofeedback Training

The EEGer software package (EEG Education & Research Inc) was used to deliver standard 3-band training protocol EEG Biofeedback. Whole-band EEG was acquired at either C3-A1 or C4-A2 and band-pass filtered to display Theta (4-7 Hz) and high Beta (22-40 Hz) as well as either SMR (12-15 Hz) or Beta (15-18 Hz). Initial reward thresholds were set at 70% of band voltage for "rewarded" bands (SMR, Beta) or 20% of amplitude for "inhibited" bands

(Theta and high Beta). As EEG band-power fluctuates from moment to moment, the instantaneous band power changes from threshold value. When all three EEG band-thresholds were met for one half-second interval, a "reward" was presented. The reward even for the EEGer "4-Play" game we used consisted of a simultaneous auditory "beep" and reveal of a picture grid element.

EEG Protocols and Placebo-Controlled Blinding of Biofeedback

After assignment to one of three protocol groups, 16 of 40 participants were assigned a "Sham" status in the biofeedback software, on a hidden, password protected configuration screen. Sham status assignment was performed by a researcher unaffiliated with this experiment or lab in any other way. After sham/veridical assignment was made, resulting group sizes were Sham (16), C3SMR (8), C3Beta (8), and C4SMR (8). After performance and data cleaning exclusions, group sizes were Sham (13), C3 Beta (8), C3 SMR (8), and C4 SMR (7). Sham group subjects were considered as veridical by experimenters, and electrodes placed at C3-A1 or C4-A2 and reward frequency per group assignment. 15 clean 3-minute segments of EEG previously recorded by EEGer at C3 and C4 were used as a Sham "pool" of data. When detecting sham status during biofeedback session start, the EEGer biofeedback software assembled pre-recorded segments in random order to produce 30 minutes of EEG. EEGer then scaled the resulting EEG to within range of the participant realtime EEG, and derived all training parameters and reward events from the constructed file. EEGer's sham implementation also merged real-time signal changes including discontinuity and artifact with the sham data file. The resulting experience was of an EEG screen that responded as expected to blinks, muscle artefacts, and loss of signal, but otherwise mimiced realtime EEG and EEG-driven biofeedback events convincingly. EEGer was also set to auto-threshold reward bands to 70% of current

power and inhibit bands to 20% of current power during every 30 seconds of training.

Biofeedback Data Acquisition and Signal Processing

Dense EEG and Biofeedback EEG recording:

Dense array (66-channel) EEG was recorded using a BioSemi / ActiveTwo system (64-channel QuickCap plus ear electrodes). EEG for Biofeedback was recorded with a 1-channel ProComp+ into EEGer software. The ProComp+ was optically isolated from participants and run on AA batteries; the BioSemi Active2 was also DC-based. There appeared to be no interaction of EEG recording via EEGer software with EEG recording via BioSemi software. Audio reward events from EEGer were embedded at reward onset time in the ongoing BioSemi EEG recording. BioSemi EEG recordings were high-pass filtered at 0.16 Hz to remove active electrode voltage offset and then imported into MATLAB, specifically the EEGLAB toolbox (Delorme & Makeig, 2004) and low-pass filtered at 40 Hz.

Design and Analysis: Measuring EEG of Biofeedback

EEG of multiple types was imported in EEGLAB and examined to determine effect of veridical Biofeedback versus habituation of EEG. This included spectral analysis of resting EEG (post and pre each BFB session) during Eyes Closed and Eyes Open, as well as BFB Reward signal evoked ERPs. Spectral baseline recordings were band-pass filtered from 1 – 50 Hz, visually inspected and artifacted, and referenced to Averaged Ear ((A1+A2)/2). Average amplitude of Theta (4-7 Hz), Alpha (7-11 Hz) SMR (12-15 Hz), and Beta (15-18hz) at each electrode was subjected to an ANOVA on 3 Session * 4 Group, and corrected for multiple comparison using EEGLAB false discovery routine. ERPs were constructed using EEGLAB and ERPLAB.

Reward Epoch Preprocessing

Biofeedback recordings were filtered and created using identical methodology to sLANT

ERPs in Chapter 1. Two-second epochs were then created from the continuous EEG file; 500 ms before to 1500 ms after reward event onset (reward of instantaneous picture display and 125 ms "beep"). Each reward-locked epoch was averaged in the frequency domain to produce ERPs and averaged in the time domain to produce Event Related Spectral Perturbation (ERSP) highlighting event related frequency changes within each group. A pre-stimulus baseline of –100 ms to 0 ms was used for Biofeedback epochs. Approximately 600-700 trials were used, per-subject and per-session, after removing artifactual epochs. Within participant ERP peak latency and mean amplitude were then calculated for the three components in the ERP, namely P50: or most positive peak from 40-80 ms, an N1: most negative peak from 80-140ms, and a P2 component: most positive peak from 140-260 ms. These three ERP components are standard sensory evoked ERPs. As in Chapter 2, we chose to explore ERP effect at electrodes 20% from vertex (C3, C4, Cz, Fz, Pz) and ran ANOVAs with a design of 3 Session * 4 Group for ERPs at each of these electrodes. We also used an ANOVA of design 3 Session * 4 Group * 2 Electrode (C3, C4) for comparing protocol effects at target electrodes.

Planned Comparisons

The Biofeedback protocols suggest five group-wise comparisons of Sham vs. C3 Beta, Sham vs. C3 SMR, Sham vs. C4 SMR. Two additional comparisons contrast effect of protocol hemisphere (C3 SMR v. C4 SMR) and reward frequency (C3 Beta v. C3 SMR). We are especially interested in the effects of EEG at the location of "training electrode", namely left center scalp (C3) and right center scalp (C4), so the ANOVA with Electrode (C3, C4) was run for all group-wise comparisons regardless of Session * Group effects at individual electrode.

Results

See Chapter 2 for an in-depth discussion of how both behavior and ERPs of hemispheric

attention changed during a week of Biofeedback, in protocol-specific ways. When considering the ERP to the Biofeedback reward signal, we see the following:

The Biofeedback "Reward ERP"

An ERP with P50, N1, and P2 components is clearly visualized on averaging Reward-event locked epochs. Qualitatively, these differ slightly when examined at central scalp electrodes. Figure 1 shows the BFB Reward-evoked ERP at C3, Cz, and C4 electrodes referenced to averaged-ears.

- Figure 1: BFB Reward ERP at Central Electrodes-

Many ERP components showed a main effect of "Session" in our analyses; it would be non-informative to repeat these test statistics at each electrode, as they were significant for all participants. Qualitative inspection of the ERPs to the BFB reward signal across each of 3 biofeedback sessions shows subtle differences between groups.

- Figure 2: Vertex Waveform BFB ERP drop per session for all Ss

For the individual analysis of the vertex-surround electrodes, we will only report on Session * Group effects. When contrasting two electrodes (C3 v. C4) we will report main effects of Session as well as Session * Group.

Biofeedback Reward ERPs: The P50

Testing the peak latency and amplitude of the P50 component at each vertex-surround electrode separately revealed a significant interaction of Session * Group on P50 mean Amplitude at C4 ($F=3.85$, $p = .018$). Figure 3 shows the absolute level of mean P50 Amplitude to be higher in Active vs. Sham groups. Qualitatively, the C3 groups both show an initial enhancement of this P50 Amplitude and then a drop; the C4 SMR group shows an initial drop in P50 amplitude, and then an increase. P50 amplitude at Pz also demonstrated an effect of Session

* Group (F=2.6, p=.025) with similar Session patterns (not shown) to those at C4.

Figure 3: C4 P50 Amplitude Change across Session by Group

Planned group-wise comparisons of the changes shown in Figure 3 determined the P50 amplitude effect to be present at C4 for both the Sham v. C3 SMR comparison (F=4.07, p=.025), and the C4 SMR v. C3 SMR condition (F = 6.57, p = .005) (not plotted separately). The Pz electrode also showed a significant P50 amplitude effect of Session * Group between C4 SMR and C3 SMR (F=10.25, p <.001). Figure 4 shows that the C3 SMR and C4 SMR protocols had an opposite effect on the P50 Amplitude. This is similar to what was observed at C4 electrode above.

Table 1: Planned Group-Wise Comparisons

Figure 4: Pz P50 Amplitude Change across Session: C4 SMR v. C3 SMR

Biofeedback Reward ERPs: The N1

Testing the peak latency and amplitude of the N1 component at each vertex-surround electrode separately revealed a Session * Group effect on mean N1 Amplitude at the Pz electrode (F=2.65, p = .024) (Figure 5). Planned group-wise comparison determined N1 amplitude to be significantly different at C4 electrode across session for the Sham v. C3 SMR pairing (F=3.92, p =.028). N1 amplitude at the Pz electrode also showed this Session * Group effect for the Sham v. C3 Beta comparison (F=5.25, p = .034) as well as Sham v. C3 SMR (F = 3.41, p = .043). Group-wise planned comparisons were not plotted separately.

Figure 5: Pz N1 Amplitude Change across Session by Group

Biofeedback Reward ERPs: The P2

Neither the P2 latency nor amplitude showed a significant Session * Group effect when including all participants. Our planned group-wise comparison did show a barely significant

effect on P2 Amplitude when comparing C4 SMR and C3 SMR groups, at the C4 electrode ($F=3.59$, $p = .042$). From Figure 6 it is apparent the two SMR groups diverge in N1 Amplitude by the 3rd Session of Biofeedback.

Figure 6: C4 P2 Amplitude Change across Session by Group: C3 SMR vs C4 SMR

Laterality of ERP at C3 versus C4: P50, N1, P2

The P50 amplitude showed an interaction of Session * Electrode when comparing C3 and C4 electrodes ($F = 4.45$, $p = .016$). Figure 7 demonstrates the P50 Amplitude starts off higher at C4 and lower at C3; this pattern is reversed after 3 training sessions.

Figure 7: C3 vs C4 Electrodes: P50 Amplitude Changes by Session & Electrode

The N1 amplitude also showed a main effect of Session ($F=5.75$, $p=.005$). The P2 amplitude also demonstrated a main effect of Session ($F=17.0$, $p <.001$). N1 Latency showed a main effect of Electrode ($F=4.75$, $p =.037$). A main effect of Electrode as also found on the P2 amplitude ($F=6.02$, $p=.02$). No Session * Group interactions on these ERP components were found when including all participants in the comparison of C3 versus C4 electrodes. When subjecting each of our group-wise pairings to the same ANOVA, a significant Session * Group effect was found on the P50 amplitude ($F=3.97$, $p = .027$) on the comparison of Sham vs. C3 SMR groups. Figure 8 shows that the Sham group presented a larger P50 at C3 electrode; this pattern persisted across 3 Sessions of placebo Biofeedback. In contrast, C3 SMR group begins with a much larger P50 than Sham in at both electrodes, which is slightly larger at C4 during Session 1, By Session 5 of Biofeedback, C3 SMR group's P50 has developed a larger amplitude at C3, and has dropped at both electrodes to within the range of the Sham group P50.

Figure 8: C3 vs C4 Electrodes: P50 Amplitude Change across Session by Group: Sham vs. C3 SMR

Event Related Spectral Perturbation

When viewed in frequency domain versus time domain, we find that the ERPs to the Biofeedback Reward signal produce characteristic frequency bands to each "beep". Figures 9 and 10 plot this Event Related Spectral Perturbation (ERSP) for each Group (in columns), and plot the first and last 10 minutes of the first and fifth session of Biofeedback. Figure 9 shows the evoked frequencies at the C3 electrode; Figure 10 showed the ERSP at C4. It is immediately apparent from inspection that each group produces an Event Related Desynchronization (ERD) in their group-specific Biofeedback reward band. Eg. C3 Beta has a blue stripe in the 15-18 Hz range while C3 SMR and C4 SMR have this ERD in the 12-15 Hz range. The Sham group produces no ERD to the BFB reward. The plots below each group-column show the significant within-group band power changes across frequencies. C3 Beta has a significant high-beta change (> 18 Hz), C3 SMR has significant changes in the middle Beta (14-15 H) as well as higher Beta range (15-18 Hz). C3 SMR shows a significant change in low-SMR (12-14 Hz) as well as Alpha (8-10 Hz). The Sham group shows no Beta changes, but may have some Alpha change. The SMR groups and the Sham group also show Event Related Synchronizations (ERS) in Theta (4-7 Hz), which was inhibited in our Active groups. C3 Beta has a gradual decrease of Theta ERS, both within and across session, while C3 SMR has a gradual increase of Theta ERS within and across session. Both C4 SMR and Sham group's Theta ERS decreases within session only.

Figure: ERSP to Reward Signal at C3 Electrode: Group by Session

Figure: ERSP to Reward Signal at C4 Electrode: Group by Session

Spectral EEG (Eyes Open, Eyes Closed)

The final EEG analysis we will present concerns the 3-minute Eyes Closed and Eyes Open baselines that were recorded at the beginning and end of each session. The Appendix to Chapter 3 shows 8 figures that systematically test EC and EO Theta, Alpha, SMR, Beta bands, comparing post-session recording to pre-session recording. Only significant plots were included, and statistically significant patterns emerged. The C3 Beta and C4 SMR groups both showed a significant change on EC Theta on Session 1; The Sham group showed a significant change on EO Theta on Session 1. The same pattern obtained for EC Alpha (C3 Beta, C4 SMR) versus EO Alpha (Sham). Session 1 EC Beta was also significantly affected, in both C3 Beta and C3 SMR groups. For Session 5, EC SMR was significantly changed across session for C3 Beta group. EO SMR showed significant changes in both C3 SMR group and C4 SMR group. Lastly, EO Beta showed significant changes in all three Active groups.

Discussion

How does the brain know about EEG? How does feedback work? A Theory:

By coupling some external signal to changing cortical parameters, and emphasizing that signal at the "edge" of a physiological range or parameter envelope, "shaping" may occur. The "reward" events of EEG Biofeedback may thus utilize an operant or instrumental conditioning process to shape band-power up or down. Several important questions remain open. First - how does the brain "apprehend" or integrate the training signal as provided by a computer? For example, often a simple "beep" or image display sequence is yoked to a band-power (Theta, Alpha, Beta, etc) that is filtered from of the on-going EEG. How the brain perceives that a "beep" is indexing the upper edge of SMR power, for example, remains unclear. It is unlikely the brain has a "power meter" for a somewhat arbitrary setting of the biofeedback software band-pass filter.

Instead, it is more likely the brain uses existing sensory and attention resources to internalize this stream of training information and somehow make use of it. The EEG signal and specifically the reward-event evoked EEG provides insights into this process. EEG Biofeedback may actually change band-power and thus the brain, or may instead provide some less direct mirroring effect, or perhaps something analogous to cortical exercise. Put more simply, an important question is: does band power have to change in trained bands for effects on self-regulation or attention to occur?

Biofeedback Reward ERP Components:

The BFB Reward-evoked ERP has proven to be a complex ERP with distinct components that respond to training with EEG Biofeedback. In this data the P50 Amplitude appears most affected by the training protocols, although not changed much in the Sham group (Figure 3). Specifically, the P50 amplitude appears to be suppressed by the C3 SMR training protocol, specifically at the C4 electrode (when compared to C3). The C4 SMR group had the opposite effect - with enhancement of P50. This provides evidence for a different role of each hemisphere in producing the P50, since the only difference in protocol is hemisphere of training electrode, showing opposite effects on the P50 amplitude. Also, the P50 may index the brain acquiring the Neurofeedback signal; the fact that our C3 SMR group had many more significant results than our C4 SMR group may suggest that the continued increase of P50 in the C3 SMR group is related to BFB efficacy.

The N1 Amplitude was also affected by training protocol, with significant Sham vs. C3 Beta and Sham vs. C3 SMR results (Figure 5). This plot shows that N1 mean amplitude was reduce (less negative) on those two training protocols, faster than they were in Sham. E.g. By the 3rd session of Biofeedback, N1 Amplitudes had dropped to much smaller in those two Active versus

Sham group, but by the end of the week all groups were again within the same approximate N1 Amplitude. This suggests some impairment of selective attention would occur in the C3 SMR group especially, with their near-zero N1 on Session 2. Because the BFB protocols were run after the sLANT, however, we do not have a direct test of selective attention on that same day of BFB N1 change.

The P2 Amplitude comparison of C3 SMR and C4 SMR also showed a large divergence, by the end of the week. Both groups showed increasing P2 amplitudes on the 3rd session of BFB; the C3 SMR group continued to increase the P2 Amplitude through the 5th session as well. This change suggests both groups are identifying the training signal as relevant information to be attended.

EEG Biofeedback Protocol Efficacy & Specificity

The Group * Session findings throughout this Chapter and Chapter 2 suggest that EEG Biofeedback has protocol specificity on behavior and on ERP measures. Changes caused in P50 support theories of feedback signal acquisition. Changes in the N1 support theories that subject-brains find the "beeps" to be "relevant", although Sham does not.

Aside from waveform component specificity, the ERSP band plots derived from ERPs show striking Event Related Desynchronization and Synchronization, in the Reward and Inhibit bands, respectively. This particular finding suggests that the brain is phase-resetting in the frequency range of the reward band. Again, the absence of the effect on Sham supports efficacy.

The resting (spectral band) EEG gathered Eyes Open / Eyes Closed before and after the day testing/training session also diverges by Active vs. Sham groups, providing further evidence of efficacy and specificity. Eyes Closed slow band (Theta and Alpha) changed for two Active groups, but not the Sham, while Eyes Open slow band changed for Sham group. This suggests

Alpha habituation to the repetitive "beep" in the Sham group; their brains did not find the training signal meaningful. Lastly, SMR and Beta (Eyes Open) changed in all Active groups, but not in Sham.

This divergence of Active vs. Sham, in the presence of real changes in Sham's ERP and behavior, have allowed us to distinguish effects on due to "active placebo" from those caused by EEG Biofeedback. While we did not discuss this in detail, on band that bears further scrutiny is the Theta (4-7 Hz) band, which was "inhibited" in our training protocols, but changes both for Active and for Sham. Examining Theta on the ERSP plots across the four 10-minute segments (beginning, end of Sessions 1, 5) provides the observation that the Theta ERS is changing largely across Sessions for C3 Beta (decreasing) as well as for C3 SMR (increasing) while it's mostly decreasing only within Session for C4 SMR and Sham. This ERS (at time of P2) may be showing habituating versus learning in these later two groups.

In Conclusion:

We have presented compelling evidence of both successful placebo-blinding of EEG Biofeedback and protocol-specific effects on the ERPs and EEG bands of the training process. The active placebo and auto-thresholding protocols allowed little to no "intervention" from investigators to guide training. Even when aware of sham-training possibility, no investigator could determine sham/viridicial status from the EEGer training interface. Given the divergent effects on spectral EEG, ERP, ERSP, and (from Chapter 2) behavior, this Chapter provides strong support for the ability of EEG Biofeedback to affect attention, and of the ability of researchers to study it using double-blind methods. More analysis and development of this data set remains to be done; please see the Dissertation Conclusion for a survey of future related efforts.

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Table 1: Planned Group-wise Comparisons

Planned Comparisons: Repeating BFB ERP ANOVAs at each 2-level Group comparison											
@ Electrode	ERP	Sham v C3 Beta		Sham v C3 SMR		Sham v C4 SMR		C3Beta v C3SMR		C4 SMR v C3 SMR	
Session * Group		F	P	F	P	F	P	F	P	F	P
C4	P50 Amplitude			4.07	0.025					6.57	0.005
	N1 Amplitude			3.92	0.028						
	P2 Amplitude									3.59	0.042
Pz	P50 Amplitude									10.25	0.001
	N1 Amplitude	5.25	0.034	3.41	0.043			*2.68*	*0.088*	*3.00*	*0.068*
Electrode * Session * Group											
C3 v C4	P50 Amplitude			3.97	0.027						

Figure 1: ERP to BFB Reward Signal at Central Electrodes

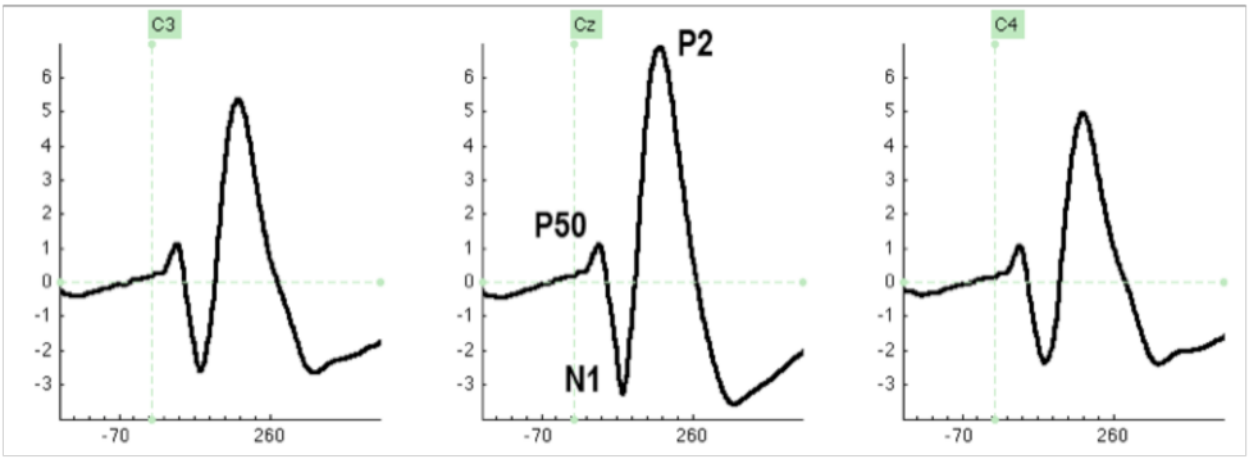


Figure 2: Vertex Waveform BFB ERP change per session for each group:

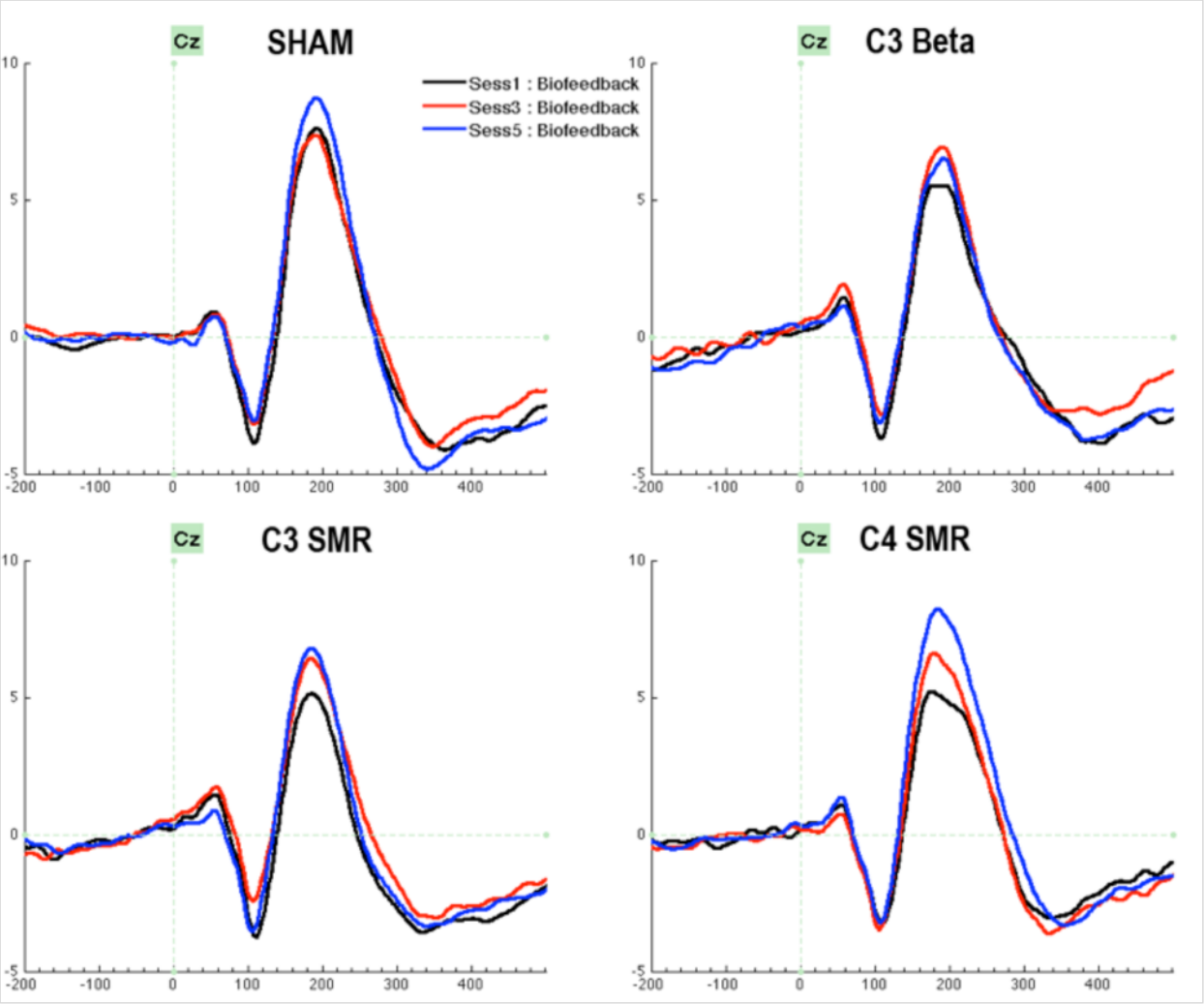


Figure 3: C4 P50 Amplitude Change across Session by Group

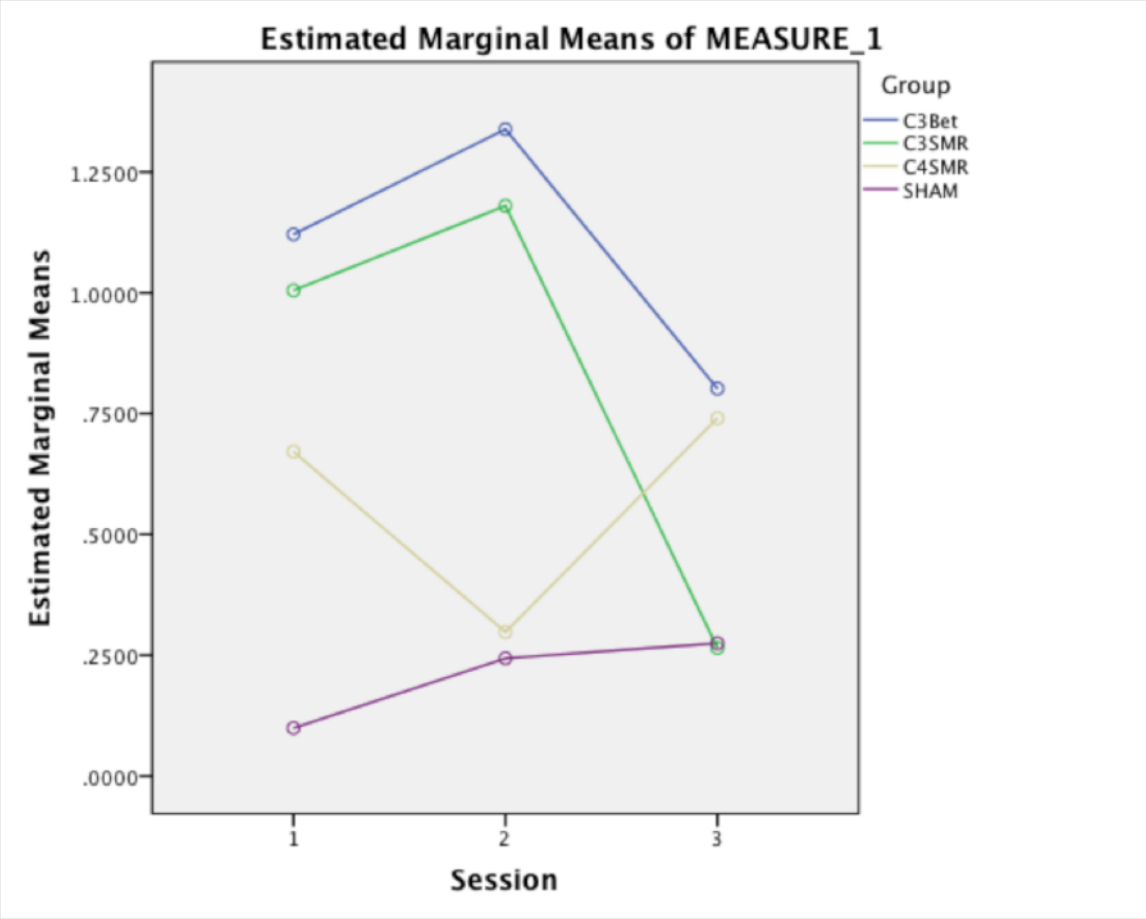


Figure 4: Pz P50 Amplitude Change across Session: C4 SMR v. C3 SMR

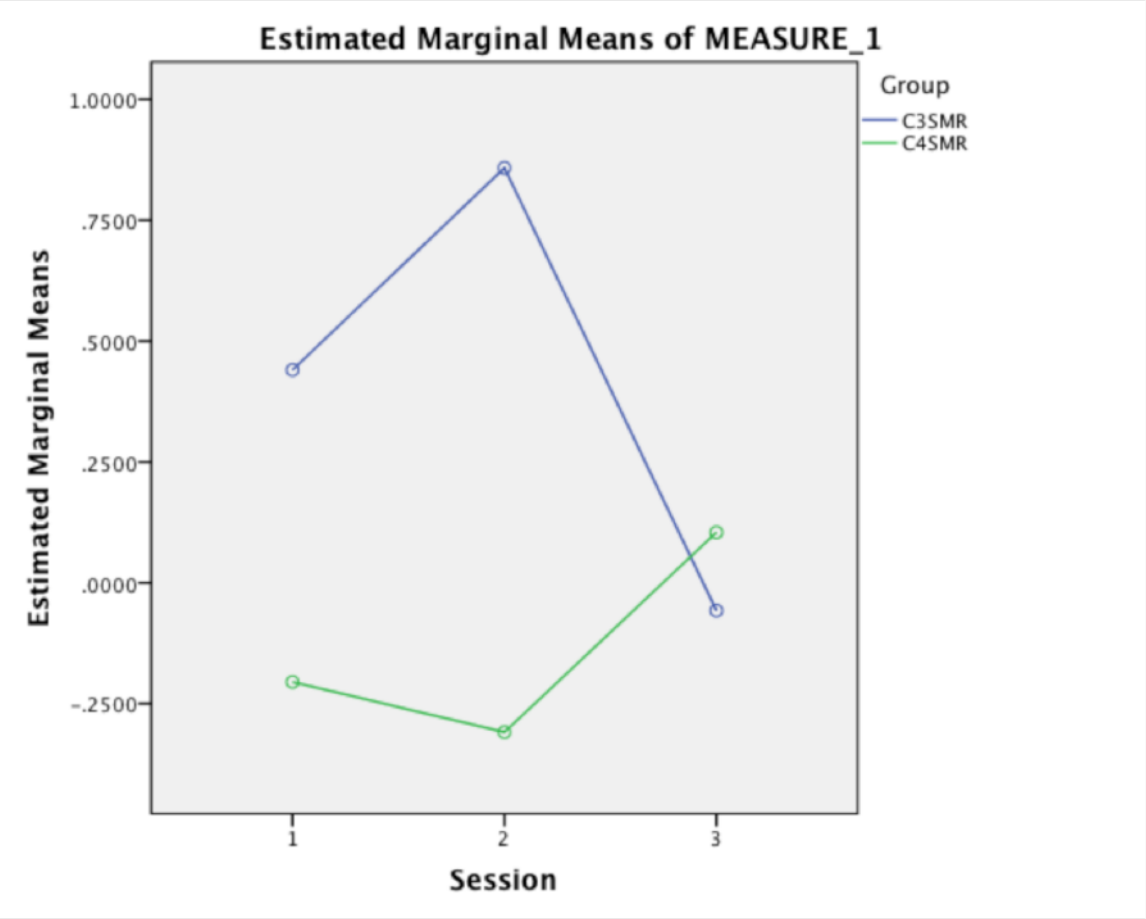


Figure 5: Pz N1 Amplitude Change across Session by Group

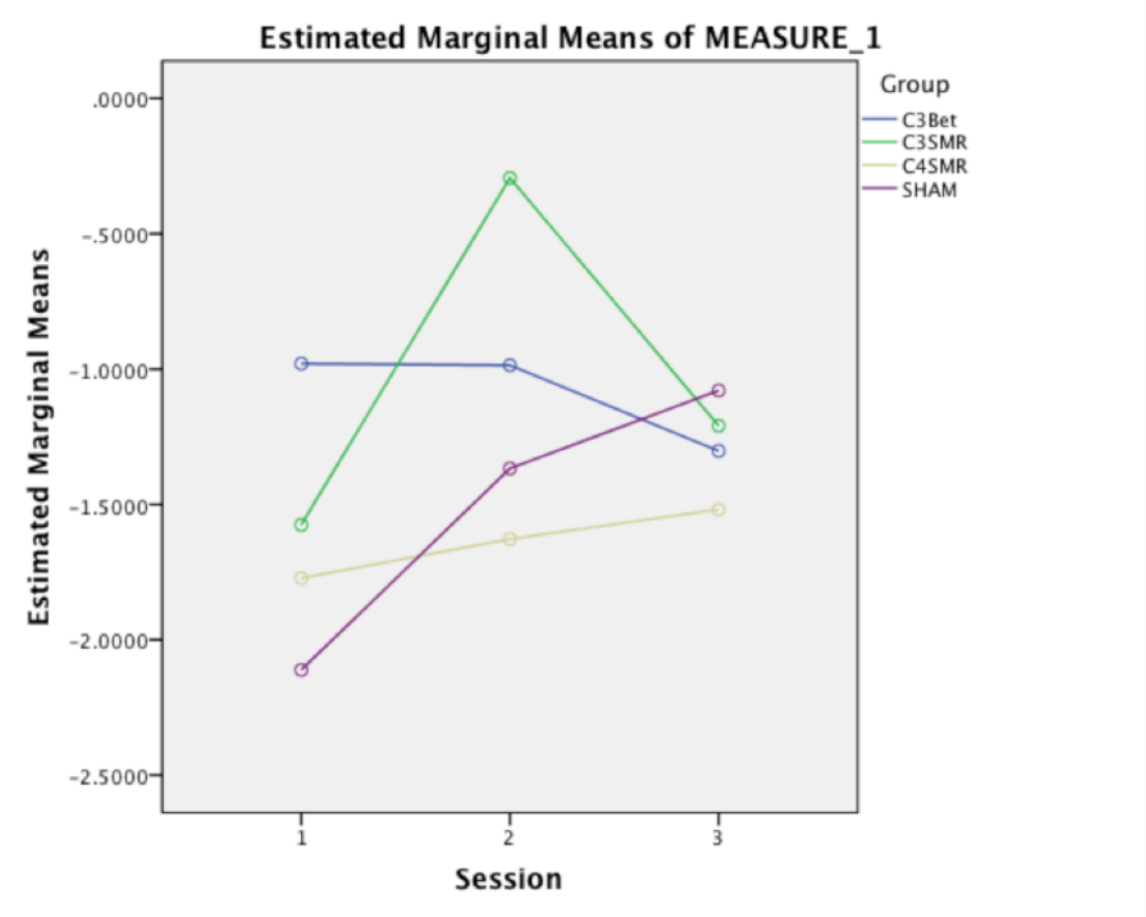


Figure 6: C4 P2 Amplitude Change across Session by Group: C3 SMR vs C4 SMR

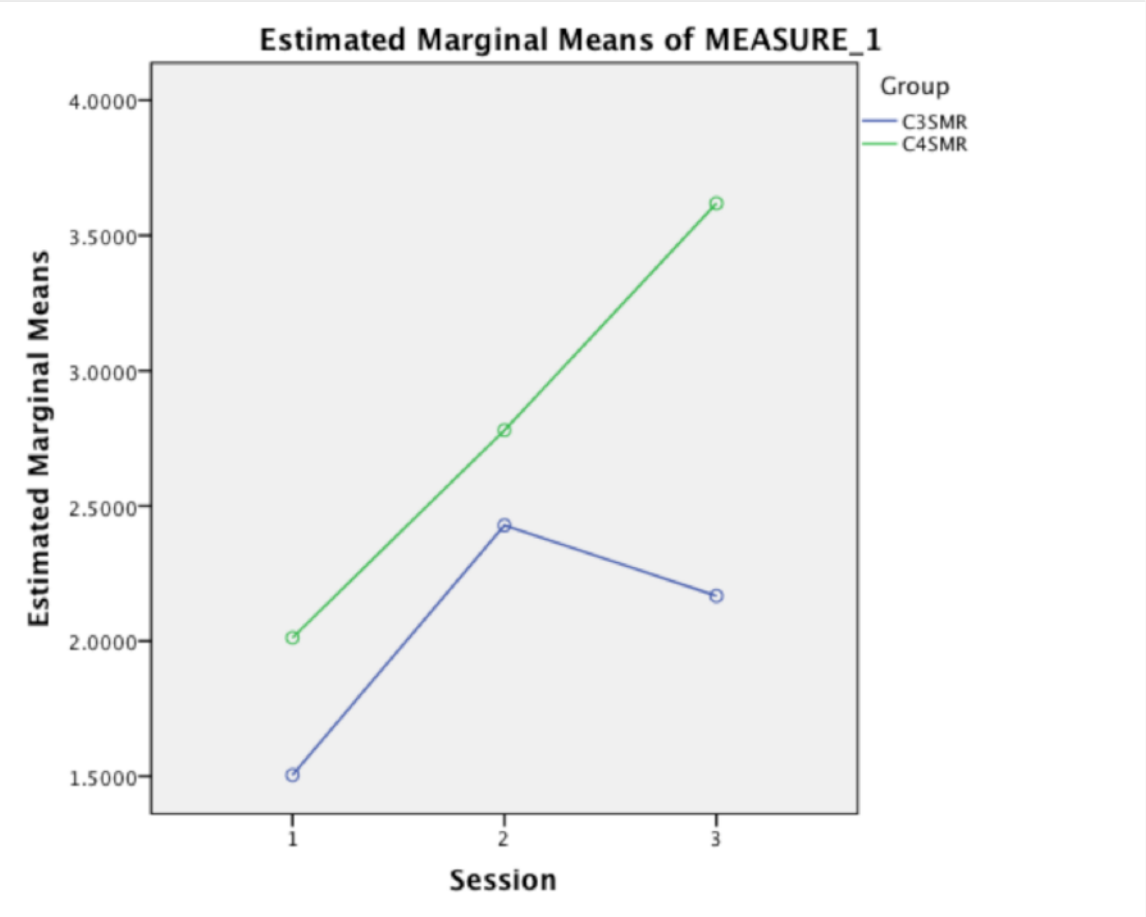


Figure 7: C3 vs C4 Electrodes: P50 Amplitude Changes by Session & Electrode

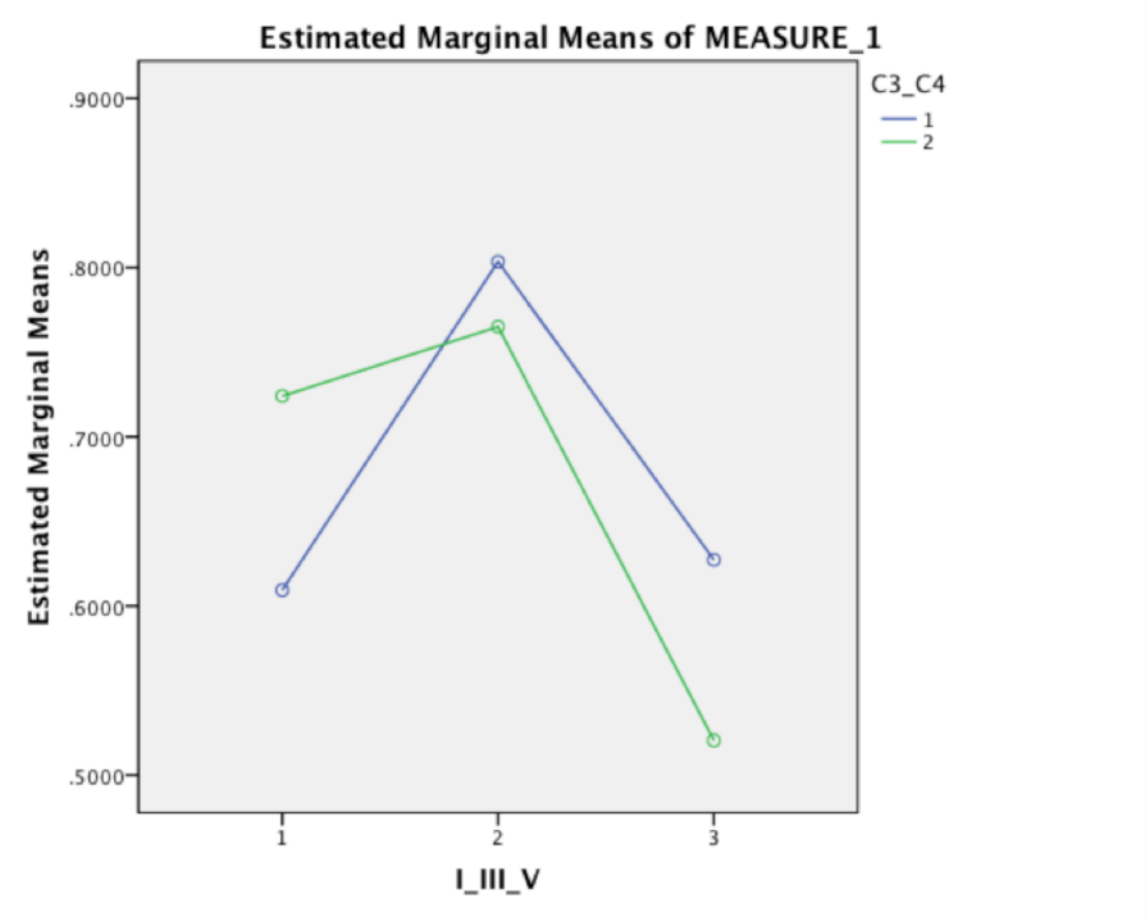


Figure 8: C3 vs C4 Electrodes: P50 Amplitude Change across Session by Group: Sham vs. C3 SMR

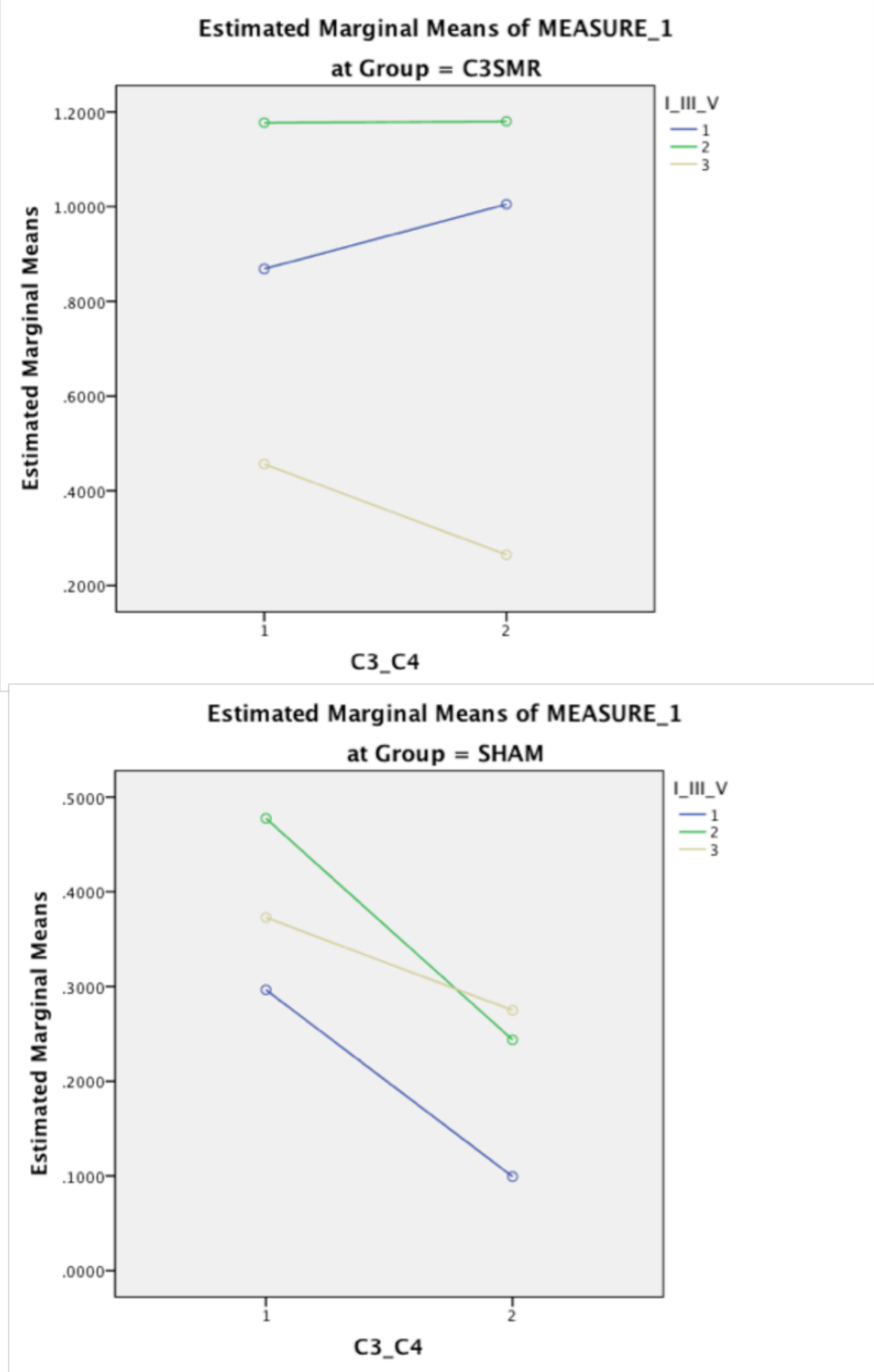


Figure 9: ERSP to BFB Reward Signal at C3 Electrode

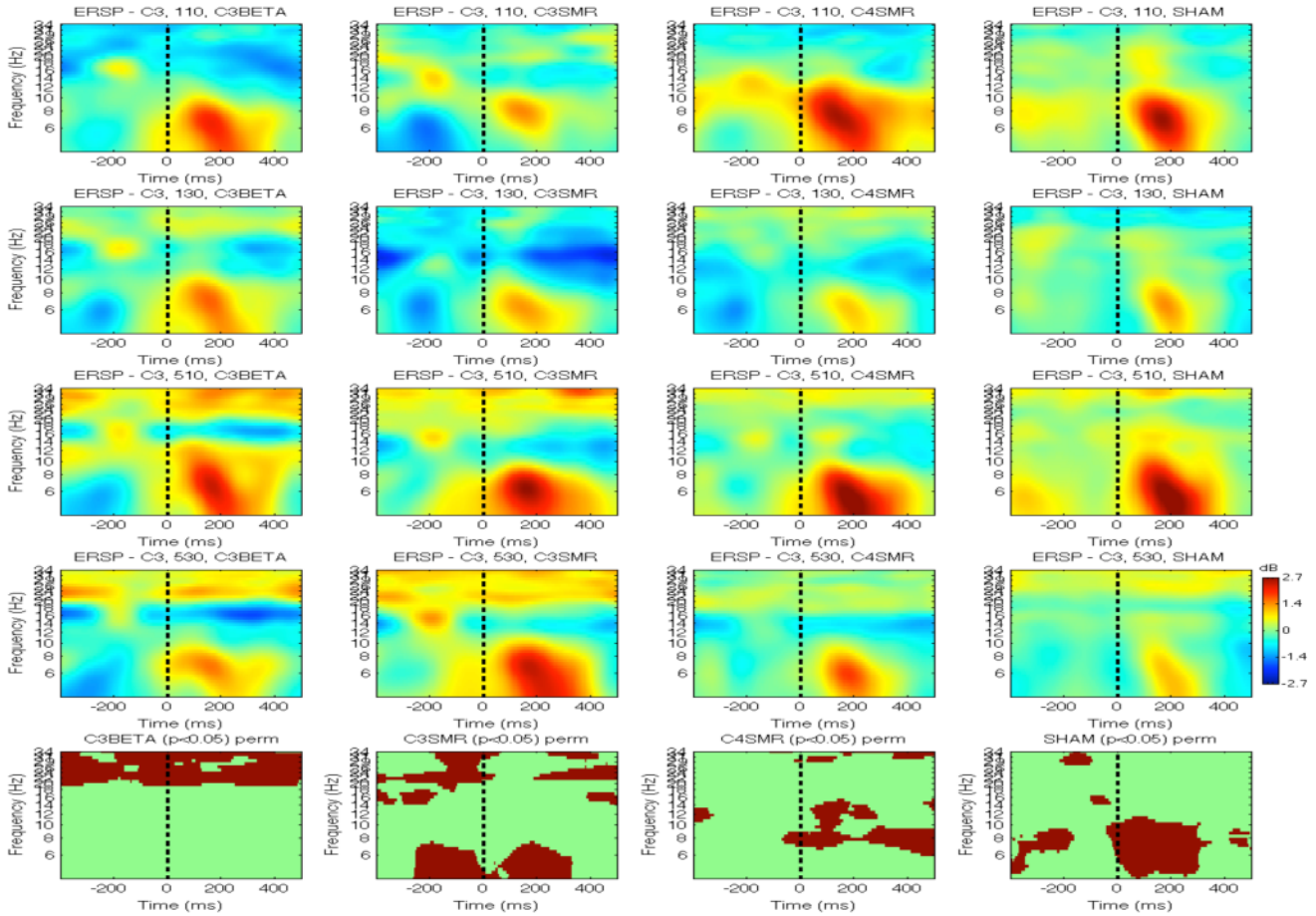
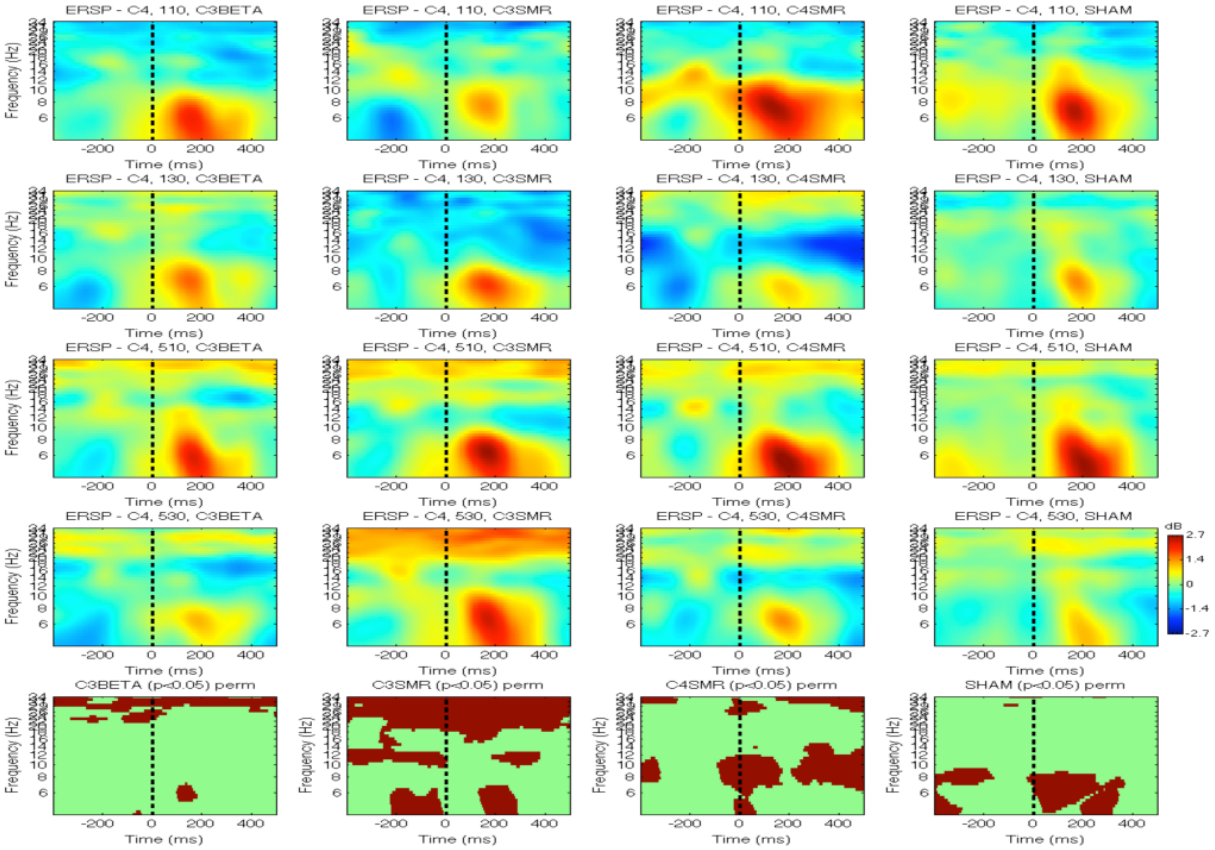


Figure 10: ERSP to BFB Reward Signal at C4 Electrode



Spectral EEG Baseline Changes – please see Appendix

In Conclusion

The preceding chapters have presented a coherent and systematic research effort around Hemispheric Attention and EEG Biofeedback. Several key areas of methodology and knowledge were advanced, including a novel and elegant placebo-controlled EEG Biofeedback method. This is the first active-placebo, double-blind study of Neurofeedback that we know of, and is among the first if not the first double-blind placebo controlled trial of EEG Biofeedback examining dense-array EEG concurrent with single channel Biofeedback. The active nature of our Sham condition was also crucial, and bears emphasis. We made choices that were "clinically poor" by the standards of most practitioners, including frequent auto-thresholding and a feedback signal that is both unified and discrete. A signal reward "event" allowed ERP methodology to be applied, however clinical "lore" suggests that multiple feedback parameters (different tones, animation objects, etc) that each index an EEG band or parameter of interest may provide stronger training. Another "flaw" in our design from a clinical standpoint was identical reward frequency for each participant (within a group) regardless of underlying EEG peak Alpha frequency. Peak Alpha is often used to adjust "SMR" or "Beta" per patient. Given the compromises we made in training approach, the success we had in 1) successfully blinding an EEG experiment and 2) producing group-wise changes with EEG Biofeedback should be emphasized. Even "weak" training has produced "strong" effects. Also, our goals were not to produce lasting clinical change beneficial to one individual. For example we have not answered questions about training permanence or the trajectory of the "learning" effect across weeks, but have shed light on how EEG Biofeedback perturbs the brain and specific aspects of attention.

Future and Ongoing Research

Over the course of this project I gathered several other data sets and performed additional

analyses. The following data sets and analyses are in progress:

sLANT & EEG Biofeedback - additional analysis:

- QEEG database comparison of pre/post data by group
- ICA (MPT) and LORETA analysis of BFB evoked changes: Is there a change in the Default Mode Network?
- Effect of BFB training protocols on connectivity: intra/interhemispheric during training? Coherence afterwards?
- Determine the relationship between the resting state EEG and peformance on sLANT
- Develop QEEG database of sLANT un-modified ERP means. Can that predict BFB effects?
- Responders vs. Nonresponders: Of the "Active" participants, examine LORETA and ERP measures for discriminants.
- BFB Within vs. Between Session: Intriguing (qualitative) patterns within vs. between session may inform BFB theories.

L-CPT / GoNo & EEG Biofeedback:

As part of the initial design of the BFB experiment, I developed a compound Continuous Performance / Go-NoGo test, using lateralized targets and distractors, that can be administered in 24 minutes. The ERP and behavior of this test was also acquired for our 36 participants discussed in these Chapters. This L-CPT/GNG has shown some promise as a complementary test to the sLANT, with signal detection measures that should allow constructing measures of non-transient attention resources such as vigilance and impulsivity.

Handeness and Lateralized Attention

The largest separate data set is a 26 participant EEG set on a long version of the LANT, contrasting 13 left handed and 13 right handed UCLA students. The LANT results were very similar to those reported in Chapter 1, although the LANT was not "speeded" so ERP component timing and behavior were both slowed compared to this sLANT. The behavioral findings were also rather weak on that LANT administration - main effects of Cue, Flanker, and TVF obtained, but only one $p = .06$ interaction with Group. ANOVA of ERPs, on the other hand, produced a

rich set of components that significantly distinguished Cue, Flanker, TVF, and had several Cue * Group interactions. This emphasizes how electrophysiology can provide insights into behavioral processes like attention when behavior may lack sensitivity. As an aside, one possible reason for the lack of TVF effect and somewhat weak behavior * Group results could be the long test time - that LANT version took over an hour to administer, with a heavy 64-channel EEG cap (Neuroscan), and fatigue may have washed out performance differences.

Attention in the Split Brain:

We developed a slow trial version of the LANT with larger, more eccentric stimuli for use with children and atypical populations. This LANT was given to a "split brain" patient (NG) in 2007. QEEG analysis of that data set was abandoned due to technical reasons: 1) QEEG databases don't have good norms for NG's age (70+) and 2) we neglected to record A1 and A2 references at the time, which QEEG databases require. LANT analysis was also problematic; NG performed at chance. Restricting our analysis to EC/EO QEEG measures that did not require earlobe references (coherence) determined that the subject had both hypo- and hypercoherence in all bands between and within hemispheres. It is likely this was an issue with database norms. There is still much to be learned from LANT use with commisurotomy patients, however. A valid avenue would be to administer the sLANT with EEG, as now proven, to younger split-brain subject(s).

Refining the sLANT:

Compressing the timing of the LANT has improved it's behavioral sensitivity and also improved it's ERP trial count sufficiently to provide high correlation between ERP measures and behavior. One remaining design flaw in this type of lateralized Flanker task is that it confounds the Orienting Cost measure (which uses Invalid Cue) with Interhemispheric Transfer. Adding

an Invalid Cue that is within visual field is a design goal to separate these aspects of the test.

Larger Research Context:

Several recent papers have emerged that touch on this line of research. The Brain-Computer-Interface research field is growing rapidly, and Neurofeedback is essentially a BCI system with operant conditioning rules. Current work with animals is making progress on Neurofeedback at the single-unit level (O'Doherty, et al, 2009), and other researchers studying EEG Biofeedback on humans are exploring Slow Cortical Potential training (Kisil &Birbaumer, 1992). We are not the first lab to research SMR biofeedback of course, although even recent SMR research has used dependent variables such as relaxation level (Gruzelier & Egner, 2006) or subjective ADHD scale reports, or at best a CPT test and QEEG. Very few studies have examined the ERP as it's related to EEG Biofeedback, the ones that do (Egner & Gruzelier, 2004) have not used blinding or large numbers of participants.

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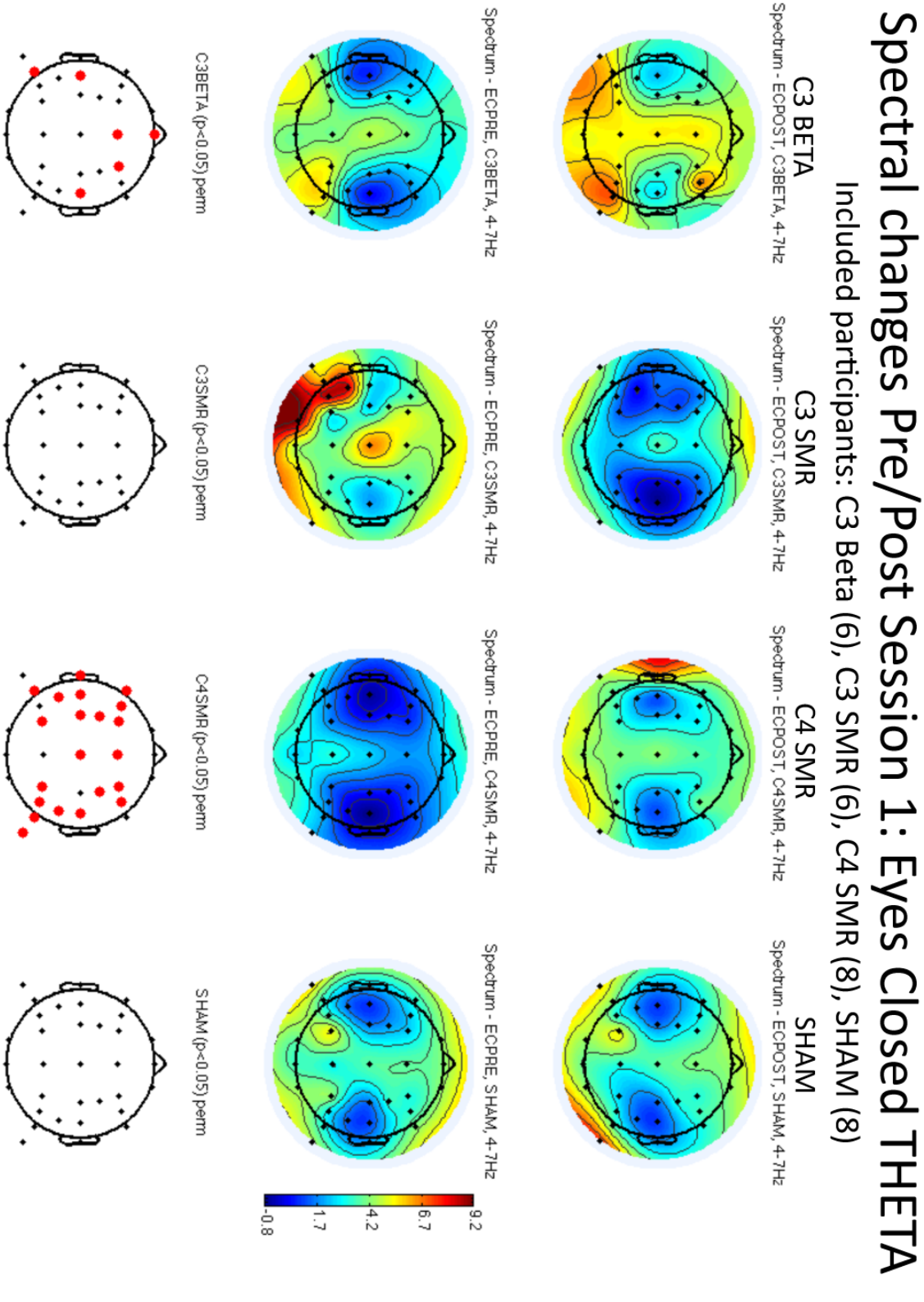
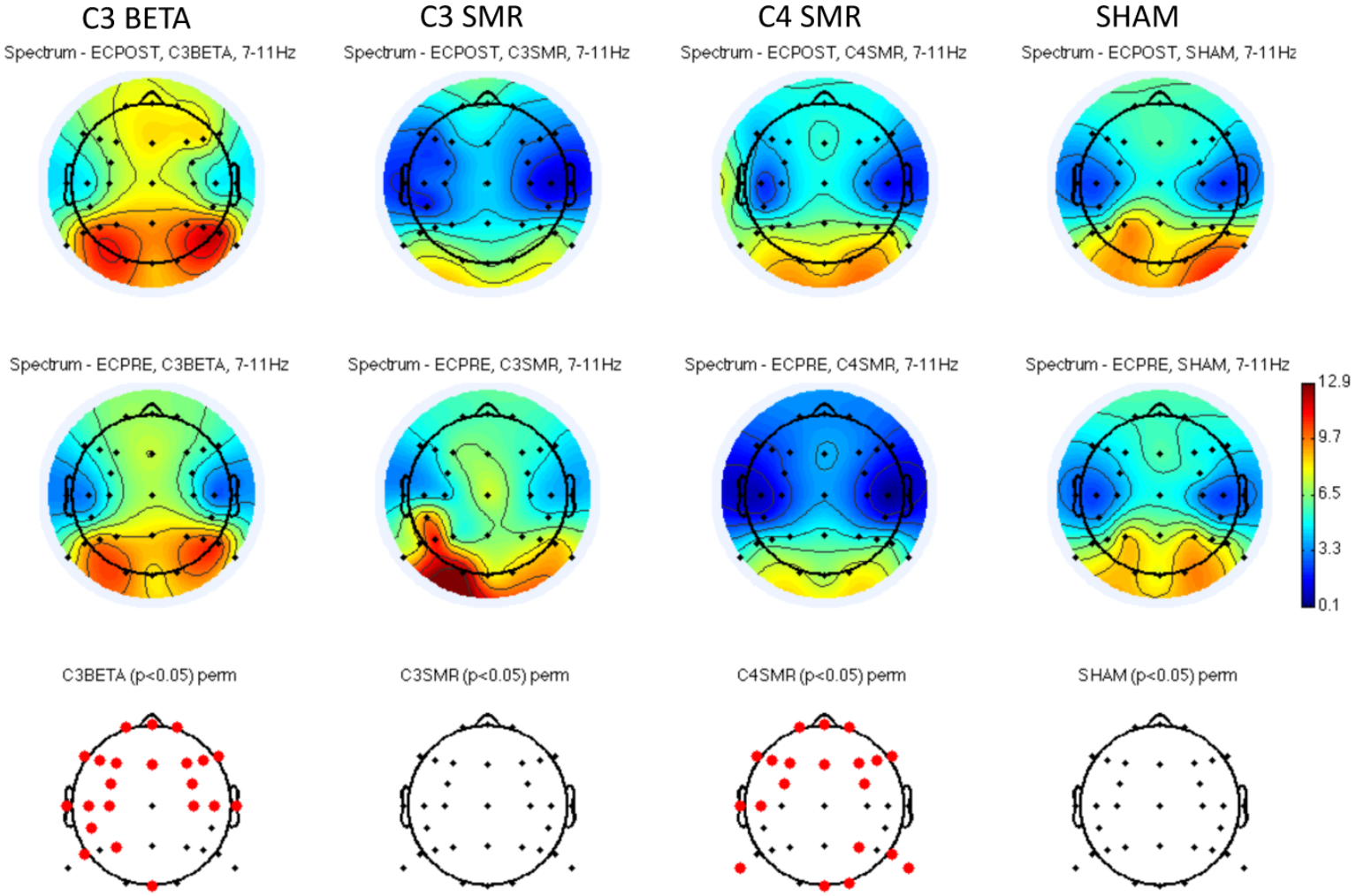
Appendix: Spectral EEG Changes for each Band, Session 1 and Session 5 of EEG BFB:



Spectral changes Pre/Post Session 1: Eyes Closed ALPHA

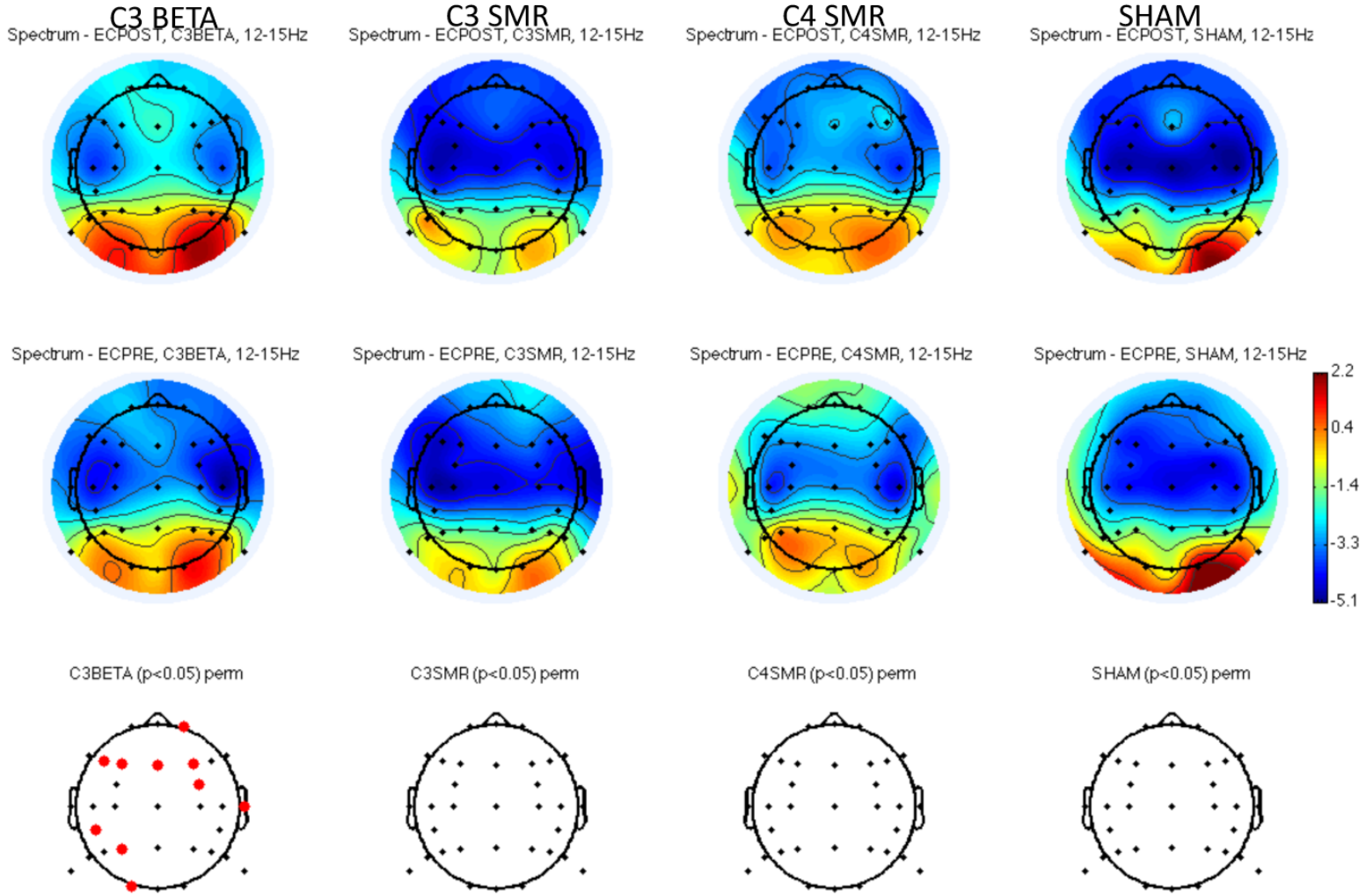
Included participants: C3 Beta (6), C3 SMR (6), C4 SMR (8), SHAM (8)



32-channel, average reference. Red dots signify $p < .05$

Spectral changes Pre/Post Session 5: Eyes Closed SMR

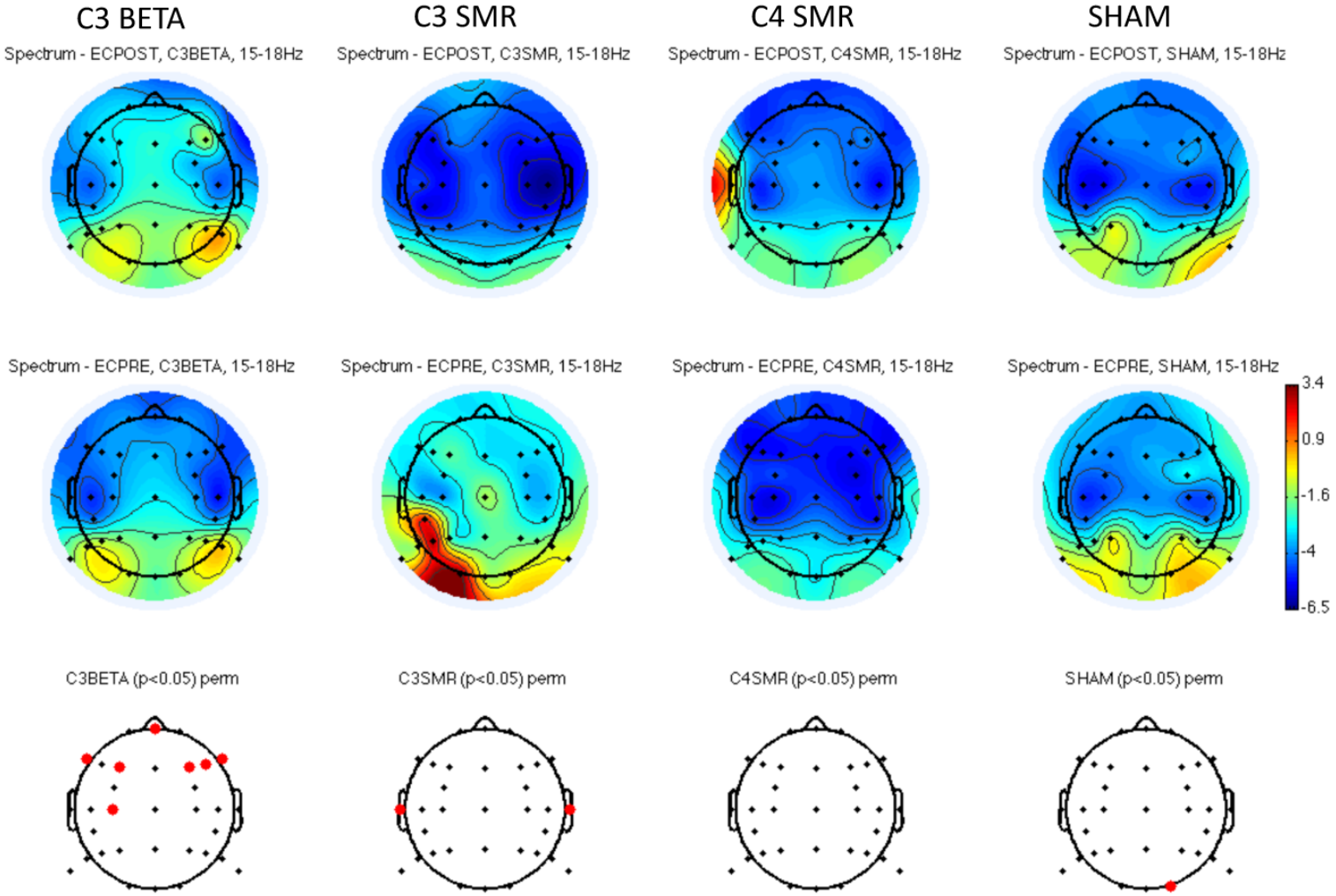
Included participants: C3 Beta (6), C3 SMR (6), C4 SMR (8), SHAM (8)



32-channel, average reference. Red dots signify $p < .05$

Spectral changes Pre/Post Session 1: Eyes Closed BETA

Included participants: C3 Beta (6), C3 SMR (6), C4 SMR (8), SHAM (8)

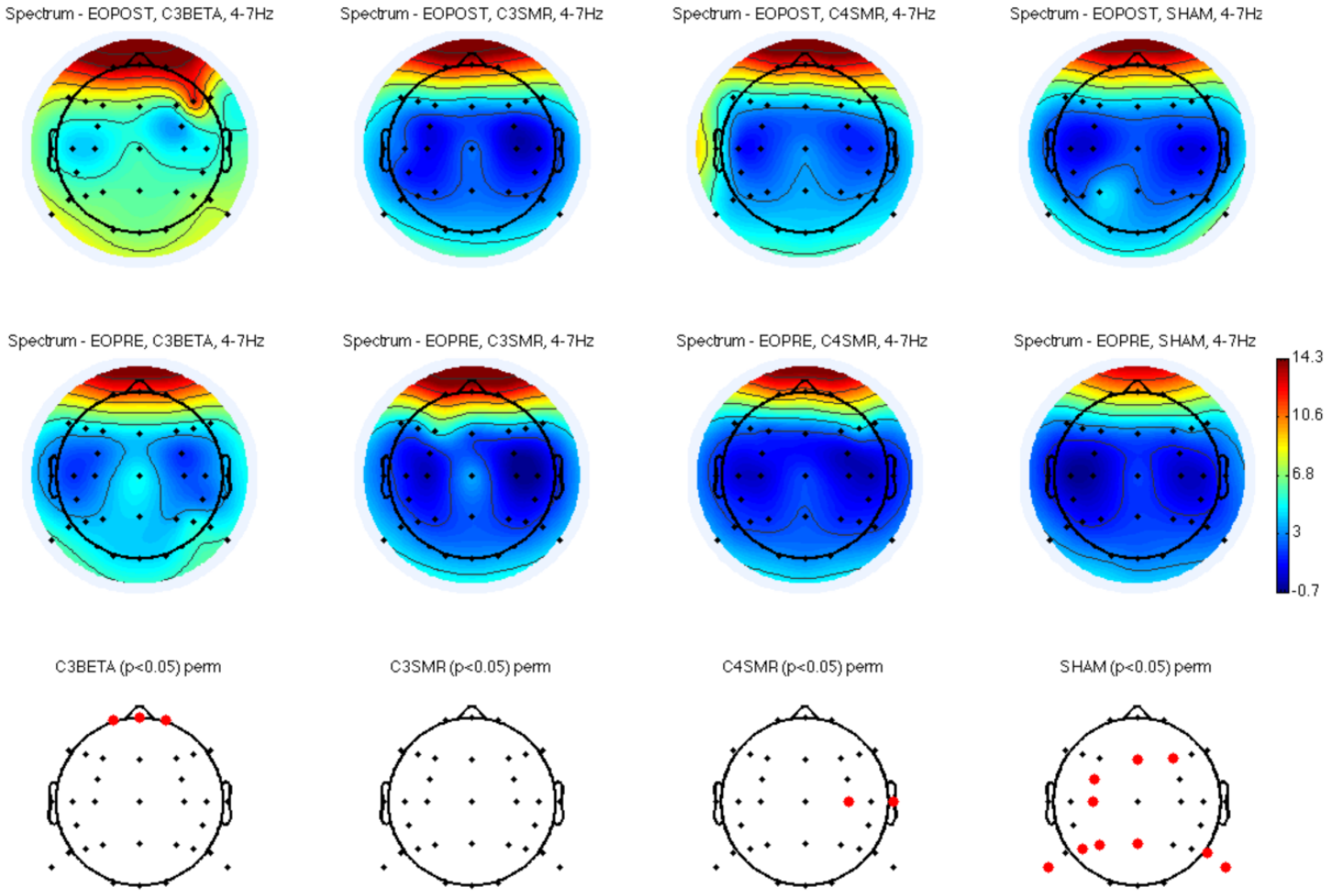


32-channel, average reference. Red dots signify $p < .05$

Spectral changes Pre/Post Session 1: Eyes Open THETA

Included participants: C3 Beta (6), C3 SMR (6), C4 SMR (8), SHAM (8)

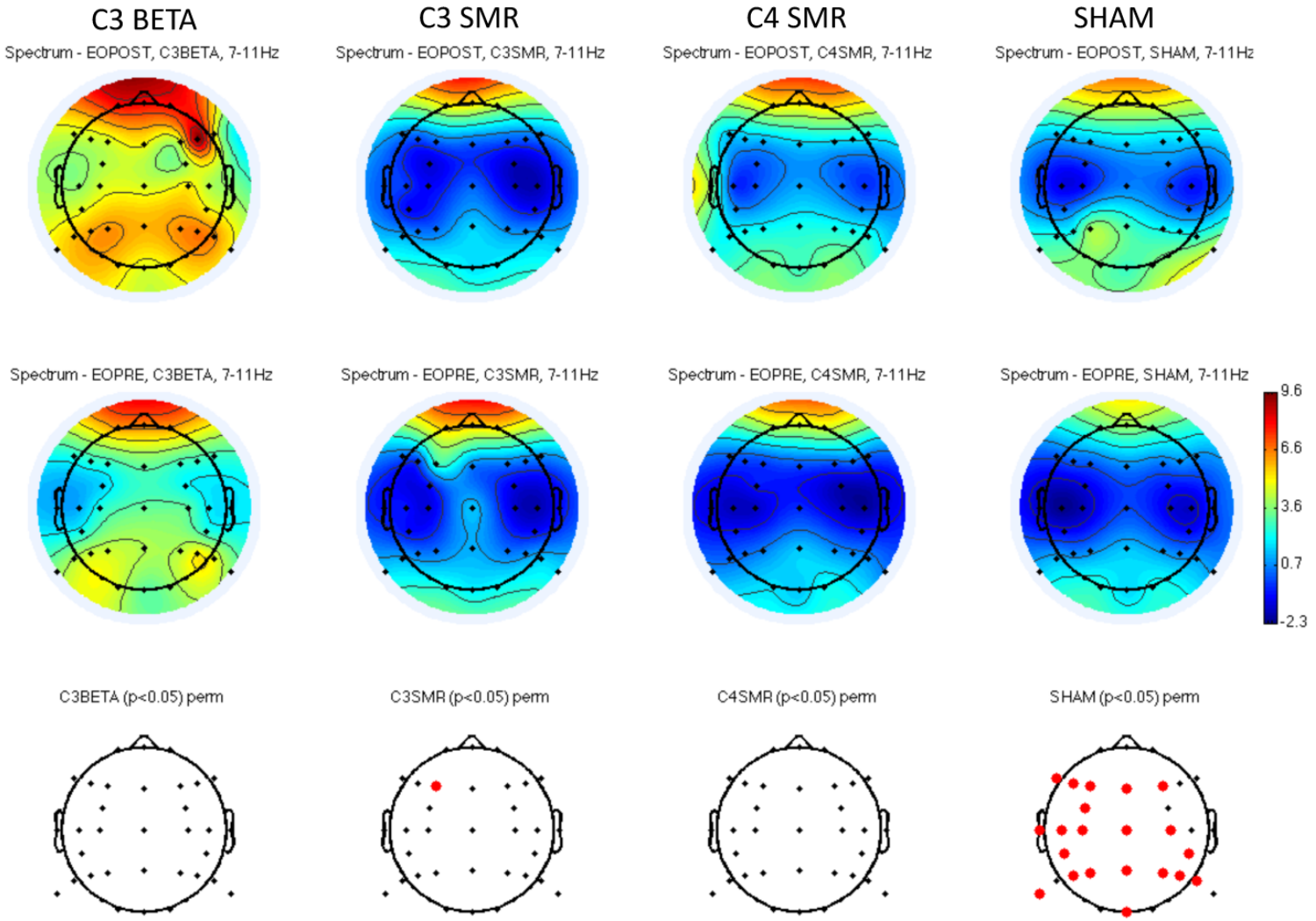
C3 BETA | C3 SMR | C4 SMR | SHAM



32-channel, average reference. Red dots signify $p < .05$

Spectral changes Pre/Post Session 1: Eyes Open ALPHA

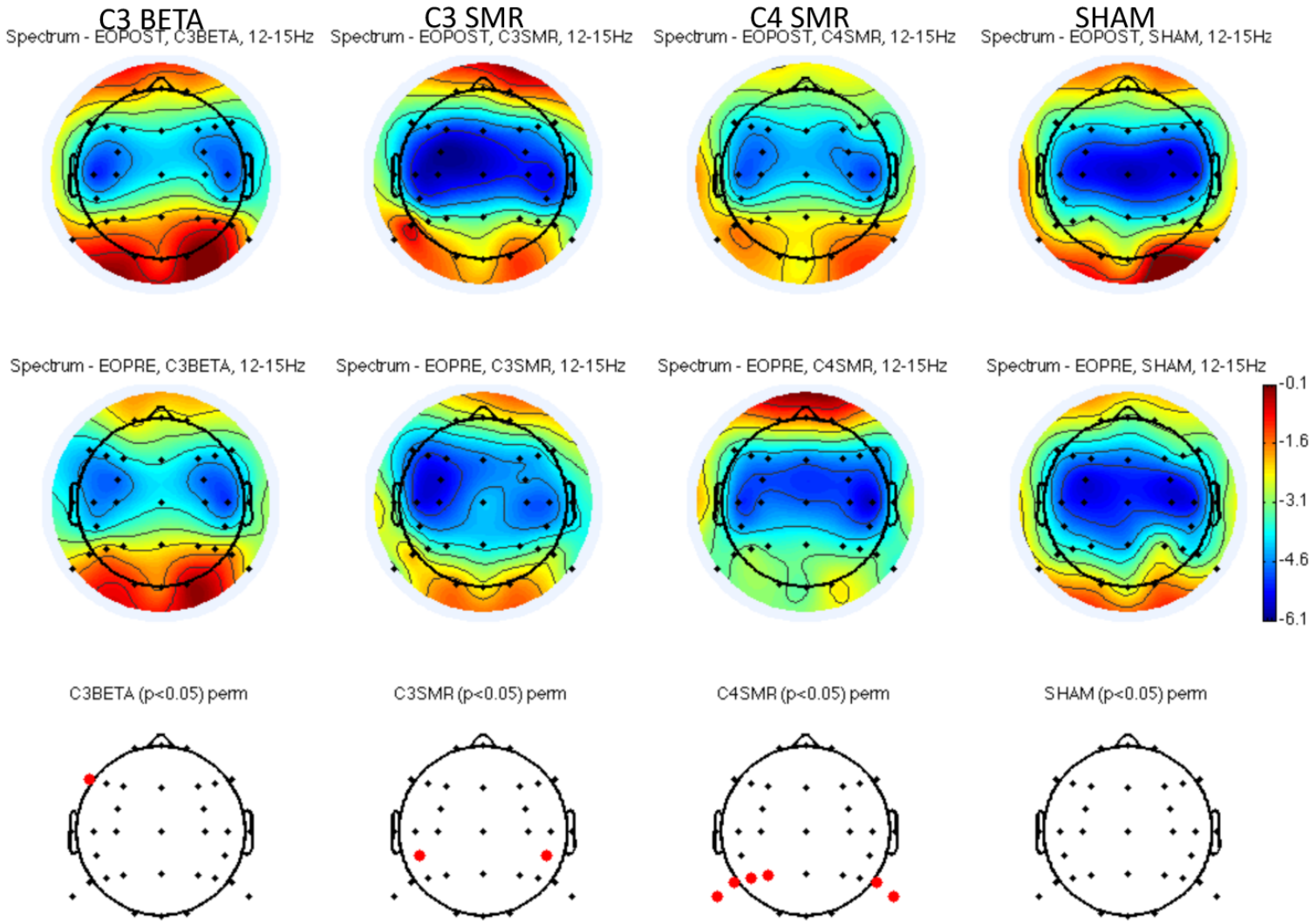
Included participants: C3 Beta (6), C3 SMR (6), C4 SMR (8), SHAM (8)



32-channel, average reference. Red dots signify $p < .05$

Spectral changes Pre/Post Session 5: Eyes Open SMR

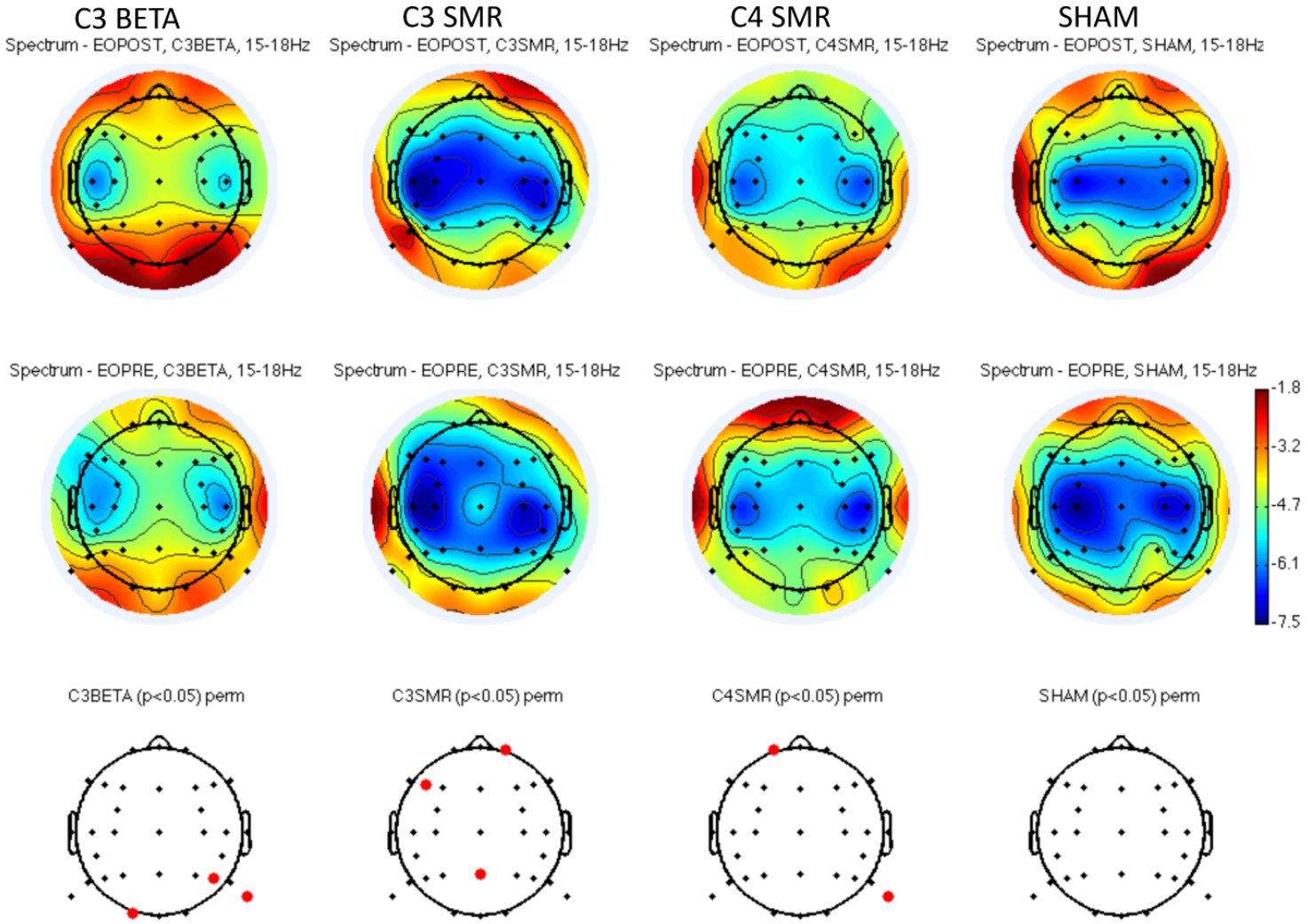
Included participants: C3 Beta (6), C3 SMR (6), C4 SMR (8), SHAM (8)



32-channel, average reference. Red dots signify $p < .05$

Spectral changes Pre/Post Session 5: Eyes Open BETA

Included participants: C3 Beta (6), C3 SMR (6), C4 SMR (8), SHAM (8)



32-channel, average reference. Red dots signify $p < .05$