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Development of EEG gama indicies of cue reactivity to assess functional outcomes of neurofeedback training in substance use disorder.

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DEVELOPMENT OF EEG GAMMA INDICES OF CUE REACTIVITY TO ASSESS FUNCTIONAL OUTCOMES OF NEUROFEEDBACK TRAINING IN SUBSTANCE USE DISORDER

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DEVELOPMENT OF EEG GAMMA INDICES OF CUE REACTIVITY TO ASSESS FUNCTIONAL OUTCOMES OF NEUROFEEDBACK TRAINING IN SUBSTANCE USE DISORDER

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ABSTRACT

Introduction: In 2006 it was estimated by the Substance Abuse and Mental Health Service Administration (SAMHSA, 2007) that 19.9 million Americans used illicit drugs, computing to roughly 8.0 % of the United States population. In 2007, there were 2.1 million active cocaine users, comprising 0.8 percent of the population. The National Institute on Drug Abuse (NIDA) estimates that the total expenditure of drug-related complications is greater than 500 billion dollars when healthcare, legal procedures and job loss are considered. Research has shown that prolonged drug use has a profound effect on the EEG recordings of drug addicts when compared to controls during cue reactivity tests. Cue reactivity refers to a phenomenon in where individuals with a history of drug abuse exhibit excessive psychophysiological responses to cues associated with their drug of choice. The goal of this research is to develop gamma band EEG indices to determine the effectiveness of neurofeedback therapies which are thought to offer a non-invasive method of mediating EEG abnormalities resulting from prolonged substance abuse.

Method: Ten current cocaine abusers were treated using neurofeedback protocol to simultaneously increase SMR and decrease Theta activity, combined with Motivational Interviewing sessions. Eight of them completed all planned pre and post-neurofeedback cue reactivity tests with event-related EEG recording and clinical evaluations. Cue reactivity tests consisted of a visual oddball task with images from the International Affective Picture System and drug-related pictures. Evoked and induced gamma

responses to target and non-target drug cues were analyzed using wavelet analysis and coherence protocols via custom algorithms implemented in MatLab.

Results: Outpatient subjects with cocaine addiction completed the bio-behavioral intervention and successfully increased SMR while keeping theta practically unchanged in 12 sessions of neurofeedback training. Neurofeedback treatment resulted in a lower EEG gamma reactivity to drug-related images in a post-neurofeedback cue reactivity test. In particular, evoked gamma showed decreases in power to non-target and target drug-related cues at all topographies (left, right, frontal, parietal, medial, inferior); while induced gamma power decreased globally to both target and non-target drug cues. Also, long range coherence was found to increase in specified electrode pairings post neurofeedback. Our findings supported our hypothesis that gamma band cue reactivity measures are sufficiently sensitive to functional outcomes of neurofeedback treatment. Both evoked and induced gamma measures were found capable of detecting changes in EEG responses to both target and non-target drug cues.

Conclusion: Our study emphasizes the utility of cognitive neuroscience methods based on EEG gamma band measures for the assessment of the functional outcomes of neurofeedback-based bio-behavioral interventions for addictive disorders. This approach may have significant potential for identifying both physiological and clinical markers of treatment progress. These methodologies can also be adapted and used in additional pathologies to provide fast and reproducible evidence of treatment outcomes.

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I. INTRODUCTION

Drug addiction is a psychoactive substance use disorder (SUD), which can be characterized by the physiological dependence of an afflicted individual upon a drug of choice. This dependence is coupled with the withdrawal syndrome upon discontinuation of drug use as well as physiological and psychological dependence and craving which motivates an addict to partake in drug-seeking behavior. Drug addiction is a chronic, relapsing mental disorder that results from the prolonged effects of drugs on the brain (Dackis & O'Brien, 2001; Leshner, 1997; Wexler et al., 2001). Addiction leads to behavioral, cognitive and socially adverse outcomes that incur substantial costs to society. In 2006, it was estimated by the Substance Abuse and Mental Health Service Administration (SAMHSA, 2007) that 19.9 million Americans used illicit drugs, computing to roughly 8.0 % of the United States population. In 2007, there were 2.1 million active cocaine users, comprising 0.8 percent of the population. The National Institute on Drug Abuse (NIDA) estimates that the total expenditure of drug-related complications is greater than 500 billion dollars when healthcare, legal procedures and job loss are considered.

Prolonged drug use can have profound effects upon the normal brain activity, which can be recorded and measured through the use of qualitative EEG (qEEG)

techniques. One of the most difficult drug addictions to treat is that of cocaine, as it is associated with a high rate of morbidity and mortality. Patients suffering from cocaine addiction typically show low interest in interventional treatment and hence treatment programs are often plagued by low retention rates. Some qEEG studies have highlighted components of EEG activity that are significantly altered by cocaine abuse. Several studies have indicated that cocaine abusers show increased beta as well as delta and alpha frequencies (Alper et al., 1990, 1998; Costa & Bauer, 1997; Herning et al., 1985, 1994ab; Noldy et al., 1994; Prichep et al., 1996, 1999, 2002). These changes are thought to be caused by the neurotoxic side effects of cocaine use and as a result of the withdraw process (Alper, 1999).

In light of these findings an effective and non-invasive method for treating the qEEG manifestations of addiction, and tracking the EEG changes over the course of treatment is needed. Neurofeedback (NFB) is a technique employed to noninvasively modify the electrical activity of the brain, including EEG, event-related potentials (ERP), slow cortical potentials, and other electrical activity of cortical origin. Detailed review of clinical efficacy of neurofeedback methods in SUD treatment and historic aspects of biofeedback-based behavioral intervention for drug addiction can be found in Sokhadze et al. (2008a) and Trudeau (2005).

Preoccupation with drug and drug-related items is a typical characteristic of cocaine-addicted individuals. It has been shown in multiple accounts that prolonged drug use has a profound effect on the EEG recordings of drug addicts when compared to controls during cue reactivity tests. Cue reactivity refers to a phenomenon in which

individuals with a history of drug abuse exhibit excessive verbal, physiological and behavioral responses to cues associated with their drug of choice (Carter & Tiffany, 1999; Franken et al., 1999), suggesting a rearranging of neuronal networks in the brain of addicted individuals.

In cocaine addiction, items related to cocaine and drug paraphernalia are repeatedly selected by the brain for conscious processing, and drug-related representations are disproportionately tagged as relevant. While studies with active cocaine users have indicated a strong physical reaction to drug-related stimuli (Carter & Tiffany, 1999, Childress et al., 1994, 1999; Grant et al., 1996, London et al., 2000), research examining cognitive aspects, for example attentional processes in cocaine addiction has been limited (Franken et al., 2000; Robbins et al., 1997). Several research studies provided support for the hypothesis that an attention alteration process takes place in addicts (Hester et al., 2006; Lyvers, 2000; Robinson & Berridge, 1993), referred to as the "attentional bias" (Franken et al., 1999, 2000, 2003), resulting in drug-related cues attaining greater salience and motivational significance in substance abusing patients (Garavan et al., 2000; Koob, 1999; Koob & Le Moal, 2001; Robbins et al., 2000).

Cue reactivity expressed in physiological and behavioral responses to stimuli associated with the preferred substance of abuse (alcohol, nicotine, cocaine, heroin, etc.) is relatively well explored (Carter & Tiffany, 1999; Childress et al., 1999; Drummond et al., 1995; Ehrman et al., 1998; Lubman et al., 2000). One of the cognitive components of cue reactivity in substance abusers is the preferential allocation of attentional resources to items related to drugs (Lubman et al., 2000; Stormak et al., 2000). It has been proposed

that conditional sensitization in neural pathways associating incentives with stimulus items may be responsible for cue reactivity (Franken, 2003; Weiss et al., 2001). Several neuroimaging studies have reported effects associated with drug cue-related responses and craving in cocaine addiction (Garavan et al., 2000; Hester & Garavan, 2004; Hester et al., 2006; Johnson et al., 1998; Kilts et al., 2004). Restructuring and reallocation of attentional resources suggests an over-attention to drug related cues believed to be directly tied to the psychological symptoms of craving, which leads to repeated drug use and relapse.

Several studies have been conducted to quantify the changes in qEEG values that result from acute cocaine use as well as changes seen after prolonged abstinence, which validated the findings that cocaine abusers typically elicit increased power in the beta, delta and alpha frequency patterns as compared to controls (Alper, 1999; Alper et al., 1990, 1998; Costa & Bauer, 1997; Herning et al., 1985, 1994b; Kilts et al., 2004; Noldy et al., 1994; Prichep et al., 2002). A more informative method of testing qEEG differences, as compared to resting, eyes closed EEG recordings, is the use of both visual and auditory oddball tasks. SUD patients have been shown to illustrate a much higher response to emotionally salient stimuli. Hence, in a visual oddball task involving neutral (e.g., household items and nature pictures) and drug related images, drug addicts have shown a much higher response to drug-related cues as compared to controls (Sokhadze et al. 2008b).

Attentional bias toward the processing of salient stimuli is hypothesized to be a cognitive process that is poorly controlled. Such automatic processing is similar to the

orienting reflex to novel and significant signals. Drug abuse-related after-effects in the medial prefrontal cortex (PFC) could be accompanied by impairments in emotional regulation, and specifically in the inhibition of all motivations and emotions other than craving (London et al., 2000; Volkow et al., 2003). Diminished PFC control of fronto-striatal circuits allows more habitual responses mediated by the posterior and subcortical (e.g., basal ganglia, striatum) structures to take over behavior regulation.

The gamma band (30-80 Hz), a high frequency rhythm of EEG activity, and more specifically gamma activity within 30-40 Hz range, is thought to represent the allocation of attentional resources and cognitive processes which take place in the brain. The gamma frequency oscillation has been speculated to play a role in several important cognitive functions. Widespread gamma band activity, which can be seen in the EEG recordings, may be connected to feature "binding" from separate parts of the brain in the attempt to make a coherent image from several perceived senses (Tallon-Baudry, 2003; Tallon-Baudry & Bertrand, 1999; Tallon-Baudry et al., 1998, 2005). Additional data involving new techniques such as magnitoencephalogram (MEG) and intra-cortical data collection have implemented the gamma band, especially frequencies around 40 Hz, in several higher level cognitive functions such as memory and learning through the synchronization of cortical cell networks (Gray & Singer, 1989; Muller et al., 2000) . These connections are thought to be reflected through calculating the power of the filtered gamma band at a given electrode of interest when presented with the appropriate stimulus.

The oscillatory gamma response may be broken down into two main groups: evoked and induced responses (Figure 1). These two gamma responses may be discriminated on the basis of temporal localization and if they are time-locked to a stimulus. The early, or evoked, gamma responses occur in the 0-200 ms post-stimulus range. These early responses have been attributed to the early information processing which have been linked to the sensation and perception of stimuli. These responses are also time locked to a specific stimulus. In contrast, the late or induced gamma response manifests in the 250-450 ms post-stimulus time window, depending on stimulus modality and complexity. These induced responses are not time locked to a stimulus and are seen in task conditions which require pattern recognition or a higher-order processes of the short-term memory. As such, these patterns have been linked to the possible indication of perceptual and cognitive processes. Based on these variable responses it is hypothesized that the gamma band is multifunctional and represents a broad based integration of attentional resources and cognitive patterns.

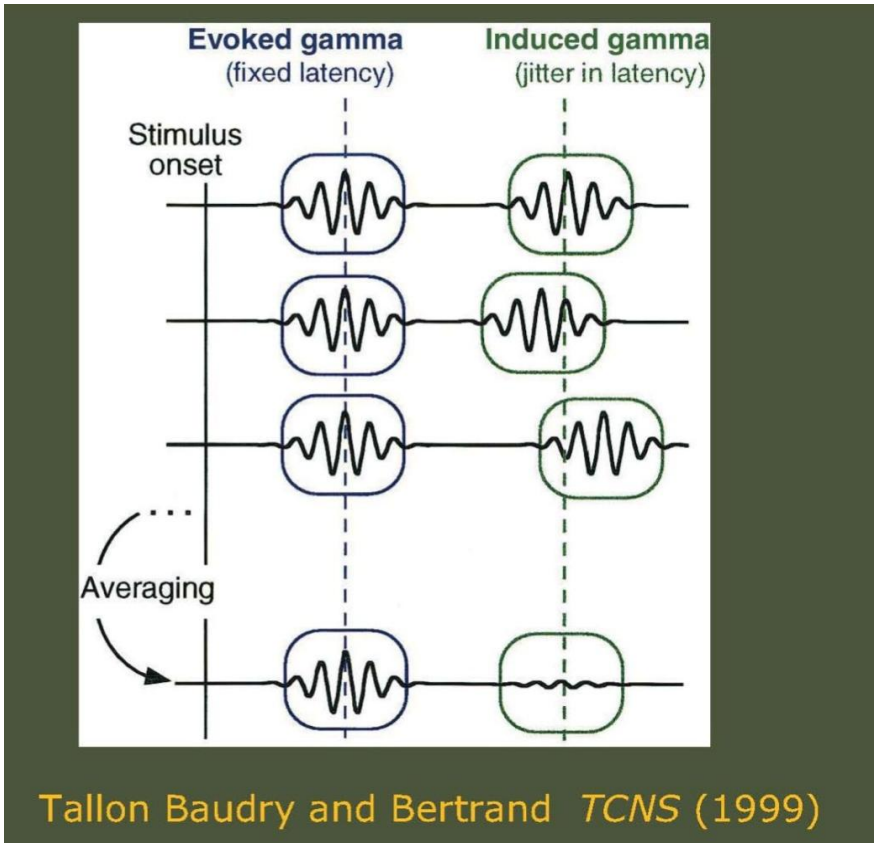

Figure 1: Illustration of time locked early evoked gamma and late induced gamma responses

It should be noted that the early time locked gamma response is less affected by changes in stimulus type, task descriptions and level of task complexity. As a result of these findings it has been suggested that early, time locked gamma is actually a sensory oriented process.

An additional measurement indicator used to highlight differences in attentional resources altered during drug addiction is dense-array event-related potentials (ERP). The most commonly studied ERP is the so called P300 which looks at the window 300-600 ms post stimulus. It has been suggested that the amplitude of this waveform may be attributed to the brain allocating attentional resources while the latency period has been

correlated to the stimulus classification processes. The P300 may be subdivided into amplitudes occurring over either the frontal regions or centro-parietal regions, and are named P3a and P3b respectively. When collected during the administration of an oddball task, as was done during this research, the P3a is correlated with an orientation of attention to a stimulus, while P3b is thought to represent sustained attention upon the stimulus (Katayama & Polich, 1998).

It has already been reported by the authors that significant changes result in the ERP as a result of chronic cocaine use and are observable even after long periods of abstinence in recovering cocaine addicts (Sokhadze et al., 2008b). Changes reported included extended P300 latency. It was also shown that larger P3a and P3b amplitudes would be seen in addicts in response to drug cues as compared to controls. The results clearly demonstrated heightened ERP responses to drug-related cues in addicted individuals. It is reasonable to propose that excessive reactivity during exposure to drug cues in addicts can be detected not only in ERP but also in evoked and induced gamma responses. It is possible that evoked gamma responses may be even more sensitive than the P300 component of ERP which is known to be a pre-morbid trait in SUD and many other psychopathologies such as schizophrenia, bipolar disorder, affective disorders (Polich & Herbst, 2000).

It is thought that neurofeedback may be a non-invasive method of treatment, which can lower drug-oriented attention and behavior, including craving. These changes may be measurable through the use of qEEG techniques such as gamma power analysis and gamma coherence calculation. Wave coherence is defined as a measure of

destructive interference between two waves. EEG coherence analysis is a technique that investigates the pair-wise correlations of power spectra obtained from different electrodes. It measures the functional interaction between cortical areas in different frequency bands. A high level of coherence between two EEG signals indicates co-activation of neuronal populations and provides information on functional coupling between these areas (Franken et al., 2004). EEG coherence abnormalities have been reported in patients with cocaine (Roemer et al., 1995), heroin (Fingelkurts et al., 2006ab), and marijuana dependence (Struve et al., 1989, 1999, 2003). In our research the EEG data was segmented into the appropriate frequency bands and the coherence calculated over time for a given frequency range. Coherence between electrode pairs was evaluated using the Brain Electrode Source Analysis software package. Bitmap images produced using this software package were then passed to MatLab for quantitative analysis using a custom algorithm.

Gamma power, representing the relative amount of gamma activity at a given electrode in time, was estimated using a waveleting technique implemented in MatLab. Wavelet transforms are a multi-resolution analysis technique, which allows for the EEG signal to be split into a user-defined number of sub-bands. When implemented in code it may be visualized as a series of high and low pass filters which result in the signal being split into smaller and smaller portions. These resulting sub-signals can then be passed to a band pass filter written to allow the passage of gamma band frequencies. After passing all sub-band signals through the band pass filter it is then possible to summate these waveforms to attain an accurate estimate of the gamma frequency of a given electrode in time.

It is our hope that through measuring pre and post-treatment normalized power indices of gamma band activity and long range coherence, we will be able to show mediated responses to drug related items in post-neurofeedback cue reactivity tests in cocaine addicts. Both evoked and induced gamma power were analyzed at pre and post-neurofeedback training time points and then compared for any statistical differences between topographic groupings of electrodes in the hope of highlighting topographic differences in the left and right hemispheres as well as in the anterior and posterior regions of the brain.

Our neurofeedback training protocol included up to 3 motivational interviewing (MI, Miller & Rollnick, 2002) sessions as an integral part of biobehavioral intervention in outpatients, since we always emphasized that outpatient treatment programs were more effective in drug abusers when neurofeedback training is combined with additional cognitive-behavioral therapy treatment modalities (Sokhadze et al., 2008a). Several studies of brief MI with cocaine abusers (Stotts et al., 2001, 2006), including our own pilot study (Sokhadze et al., 2005), report that cocaine dependent patients presenting with lower initial motivation to change habits were more likely to achieve abstinence following brief MI intervention than those who did not receive MI intervention. Our hypothesis in this study was that following 12 sessions of neurotherapy (SMR/theta neurofeedback and MI) outpatient cocaine users will show decreased evoked and induced gamma frequency response to both target and non-target drug-related stimuli and higher long range coherence during post neurofeedback cue reactivity tests.

II. SUBJECT RECRUITMENT AND DEMOGRAPHICS

A. Subjects: recruitment process

Patients with current cocaine use or a cocaine dependence record were referred from the University of Louisville Hospital drug abuse treatment outpatient services, such as Jefferson County Alcohol and Drug Abuse Center (JADAC), and other psychiatric ambulatory units. Dr. Stewart, a Medical Director at JADAC and a clinical consultant at two residential addiction treatment centers located in the Louisville Metro Area, provided referrals through these programs and conducted Motivational Interviewing sessions. Participating subjects with SUD were provided with full information about the study including the purpose, requirements, responsibilities, reimbursement, risks, benefits, alternatives, and role of the local Institutional Review Board (IRB). The consent forms were reviewed and explained to all subjects who expressed interest in participating. If the individual agreed to participate, she/he signed and dated the consent form and received a copy countersigned by the investigator who obtained consent.

All procedures were conducted within the facilities of the Department of Psychiatry and Behavioral Science and the University of Louisville Hospital Outpatient Clinic. Initial contact with prospective participant was typically made via telephone screening to ensure participants met inclusion criterion. Subjects participating in the research study were reimbursed for their time and transportation costs. Payment methods followed the University of Louisville Health Science Center's Committee for the Protection of Human Subjects' guidelines concerning reimbursement for research time and parking. Participants were paid $20/hour for completing required research activities (e.g., EEG/ERP tests, providing urine sample, completing self-report forms, neurofeedback session, etc.) at each visit.

B. Psychiatric status questionnaires, drug use and psychosocial functioning screening

The Structured Clinical Interview for DSM-IV (SCID I) (First et al., 2001) was used for Axis I diagnoses. Posttraumatic Stress Disorder (PTSD) was assessed using The Post-traumatic Symptom Scale - Self Report (PSS-SR) (Foa et al., 1989, 1997) questionnaire. The Beck Depression Inventory (BDI-II, Beck et al., 1996) was used to measure symptoms of depression. PTSD and depression scores were assessed both before and after treatment. Handedness of patients was assessed using the Edinburgh inventory (Oldfield, 1971). Scores from the Addiction Severity Index (ASI) were used to measure problem severity in the areas of medical, employment, drug abuse, legal, family, social, and psychiatric difficulties (McLellan et al., 1980). Cocaine Negative Consequences Checklist (Michalec et al., 1996) was used to assess short-term and long-

term adverse effects resulting from cocaine use. Psychosocial adjustment was assessed using the Social Adjustment Scale (SAS) (Weissman & Bothwell, 1976).

Qualitative urine toxicology screens (DrugCheck 4, NxStep, Amedica Biotech Inc., CA) were conducted in each subject to confirm cocaine abuse. In addition, qualitative urine toxicology screens for amphetamines, opiates and marijuana were performed to assess presence of additional abused substances. A positive test for marijuana was not considered an exclusion criterion. Qualitative Saliva drug test (ALCO SCREEN, Chematics, Inc., IN) was used during each visit to rule out current alcohol use. Urine drug screens were conducted at the intake stage, and at the post-neurofeedback assessment stage.

C. Subjects Demographics

Ten cocaine abusing/dependent subjects (two females, eight males) mean age, 44.6 ±8.3, range 35-54 years, 70% Afro-Americans) participated in the study. Eight of them were current cocaine users and all subjects displayed no additional comorbid mental conditions. Seven subjects tested positive for cocaine, and seven of them also tested positive for marijuana use. One tested positive for opiates and admitted the use of heroin along with crack cocaine. Two subjects who did not test positive were recovering addicts enrolled in this study after the inpatient JADAC rehabilitation course with an abstinence period less than 30 days. Hospital records confirmed their use of cocaine within one month of the baseline cue reactivity test. One of them tested non-conclusive positive for cocaine at intake, but a repeated test on the following week did not confirm drug use.

Therefore the majority of our outpatient population consisted of current cocaine users, with more than half of them using marijuana as a second drug of choice.

The preferred method of drug administration was smoking crack cocaine. Only one of the cocaine addicts in this study used cocaine intravenously. The majority of addicted subjects (80%) reported regular use of nicotine/smoking. None of the subjects were simultaneously in any treatment program other than Narcotics Anonymous (NA), Alcoholic Anonymous (AA), or local church-based anti-drug counseling programs. All of the subjects except one were right-handed. Subjects enrolled in the study were fully informed about the nature of this research and signed informed consent forms approved by the Institutional Review Board (IRB) of the University of Louisville. For biological specimen collection (urine drug screens and alcohol saliva tests), subjects signed a separate consent form also approved by the IRB within the same study protocol.

III. DATA COLLECTION

All stimulus presentation, behavioral and subjective response collection was controlled via computer running E-prime software (Psychology Software Tools [PST], PA). E-Prime is a graphical programming language that allows for the creation of psychology experiments according to a user-defined hierarchy of stimulus presentation and signal recording. Visual stimuli were presented on a 15" flat-panel display. Behavioral responses (e.g., reaction time) were collected with a 5-button keypad (Serial Box, PST, PA). Subjects were instructed to press key number 1 when they were presented with a target category picture, and to not press any key when presented with a non-target category images. In all experiments subjects were seated in a chair with their chin in a chinrest. The chinrest was placed so that subject's eyes were 50 cm from the center of the flat panel screen. Breaks were provided every 10 minutes. All EEG data were acquired with a 128-channel Electrical Geodesics system (Net Station 200, v. 4.0) (Electrical Geodesics Inc. [EGI], OR) running on a Macintosh G4 computer.

EEG data were sampled at 500 Hz, 0.1 - 100 Hz analog filtered, and referenced to the vertex (C3). The Geodesic Sensor Net was a lightweight elastic thread structure containing silver/silver-chloride electrodes housed in a synthetic sponge on a pedestal. The sponges were soaked in a potassium chloride solution to render them conductive.

Sensor impedance was maintained below the range recommended by the EGI manual (40 kOhm). Stimulus-locked EEG data were segmented off-line into 1000 ms epochs spanning 200 ms pre-stimulus to 800 ms post-stimulus around the critical stimulus events (Figure 2).

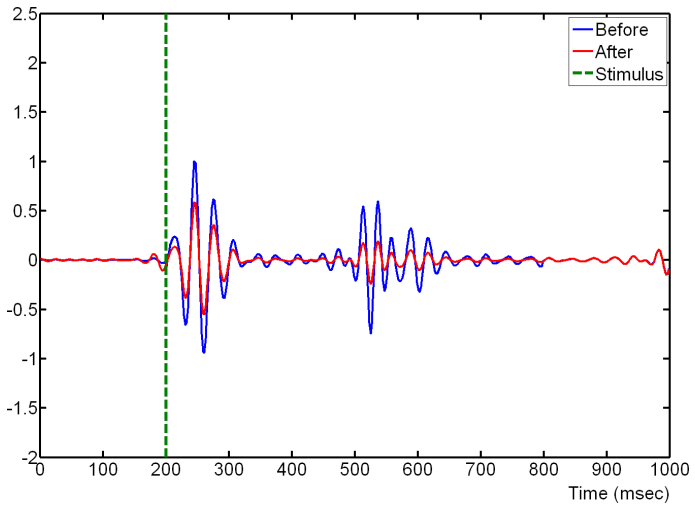

Figure 2: Illustration of a single trial epoch with a stimulus presentation at 200 msec. Early and Evoked Gamma waveforms are shown.

For example in our cue reactivity task the events were: (1) neutral target of household category, (2) neutral non-target of household category, (3) neutral target of animal category, (4) neutral non-target of animal category, (5) drug target, (6) drug non-target, and (7) neutral non-target nature images (standards). Frequency of targets for each category (household, animals, and drug) was 25%. There were always 50% of neutral pictorial (all non-drug, neutral other than household or animal category) standards in each block of trials. Data were digitally screened for artifacts (eye blinks, movement, etc.) and bad trials were removed using built-in EGI Net Station artifact rejection tools. The remaining data were sorted (segmented) by condition and exported for further analysis using MatLab and BESA routines described below in the data analysis section. EEG sites

presented in Figure 3 were selected for evoked and induced gamma response analysis and Figure 4 shows the major regions of the brain to allow for location comparison.

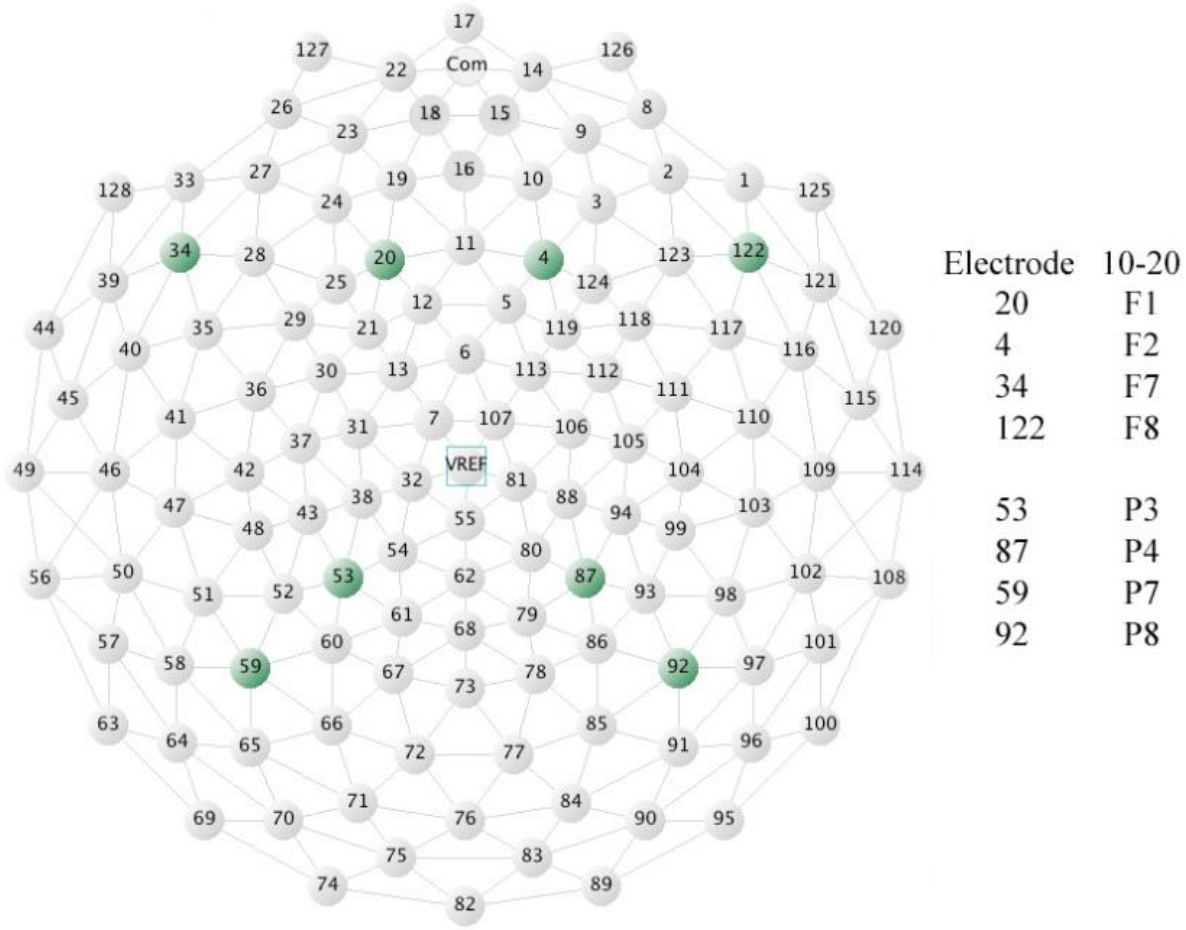

Figure 3: Illustration of the 128 electrodes used to collect EEG data with the eight electrodes selected for analysis highlighted in green. The list to the right yields the electrodes respective numbers and the corresponding name in the 10-5 naming system. Electrodes labeled with an F are located in the frontal lobe while those labeled with a P are located in the parietal lobe.

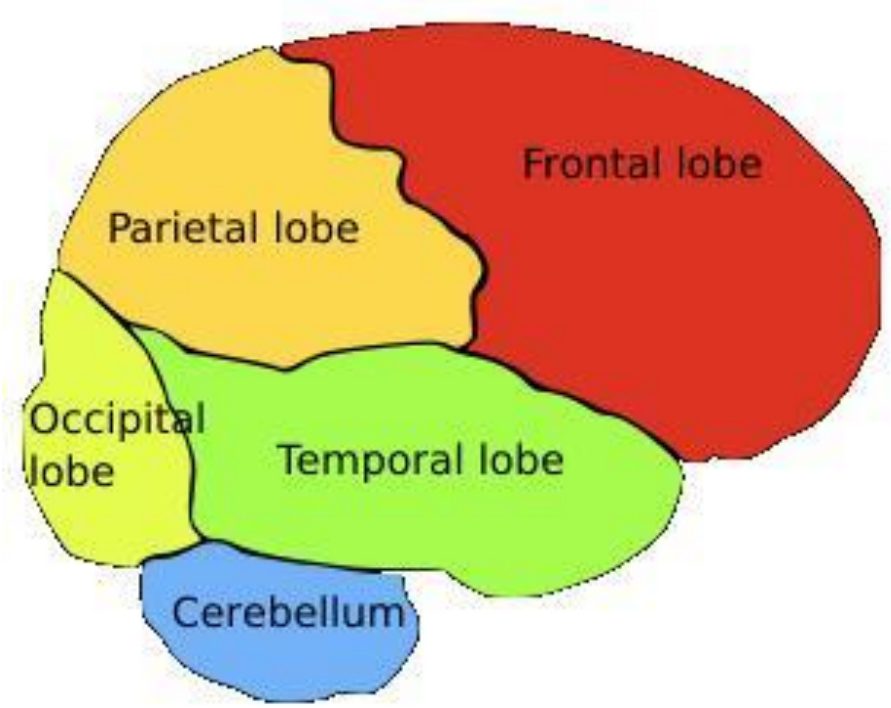

Figure 4: Pictorial representation of the brain split into the five major regions. All regions can be found on both the left and right hemispheres. All of our electrodes are found within the parietal and frontal lobes. In Figure 3, all electrodes beginning with the letter F represent a frontal electrode, and likewise all those beginning with the letter P represent a parietal electrode.

The pictorial material was taken from the International Affective Picture System (IAPS, Lang et al., 2001). Numbers of each IAPS picture used in the study are available upon request. Cocaine images were selected and validated by a co-author (ES) during his post-doctoral fellowship at Rice University (Houston, TX). In that prior study (Potts, Martin, Stotts, George, & Sokhadze, unpublished report), 25 cocaine-abusing patients rated 115 cocaine-related images on a 5-point scale (1 being low and 5 being high) as to how evocative each drug image was. The mean rating for the entire set was 2.66, SD=0.48. Thirty images of high rating (all 30 with a mean rating above 3.0) were selected for use in this study. Valence, arousal, and dominance rates were matched

within each set of images in neutral categories using ratings from the IAPS database (Lang et al., 2001). The experiment used pictures from two neutral categories as targets: neutral (household items, animals), and one drug category (cocaine and drug paraphernalia). Three examples of each image category are shown in Figure 5 below, additional images used in this experiment may be found in the appendix section.

A. Neutral Household photos:

B Neutral Nature photos:

C. Cocaine and Drug Paraphernalia Photos:

Figure 5: Examples of images used in the cue reactivity test for the following three blocks; A.) Neutral Household, B.) Neutral Nature and C.) Cocaine and Drug Paraphernalia.

Subjects were instructed to respond to stimulus items from one of the categories, ignoring the others within each block (e.g., targets were household items in a "neutral" block, Figure 6). The order of blocks (with 240 trials per block) was counter-balanced. In the task a stimulus was presented on the screen for 200 ms, whereas recording of EEG data occurred for 1000 ms (200 ms pre-stimulus and 800 ms post-stimulus). Inter-trial interval varied in 1100~1300 ms range to avoid anticipation effects. Each of the three blocks of trials was followed by a short break. The experiment took approximately 30 minutes to complete. The cue reactivity test was followed by a 10-15 min cool-down to allow cocaine cue-induced craving to fade out. Repeated cue reactivity was administered within a week after completion of 12 sessions of neurofeedback training.

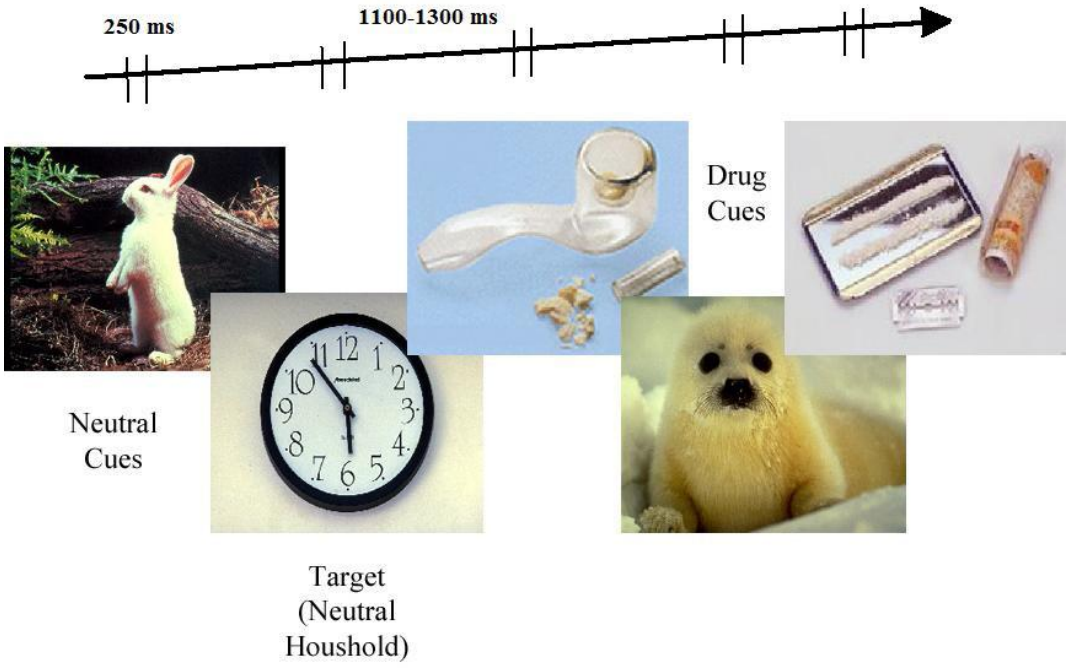

Figure 6: Illustration of cue reactivity experiment protocol. Each stimulus is presented for 200 ms and a variable weight period of 1100-1300 ms is observed between stimuli.

A. Neurofeedback procedure:

During neurofeedback treatment the subjects were trained to enhance amplitude of SMR within a specified frequency band (12-15 Hz at C3 monopolarly referenced to the left mastoid) and/or decrease (suppress) amplitude of Theta frequency bands (4-7 Hz at F3 monopolarly referenced to the left mastoid) over 12 sessions (2 sessions/per week rate). Visual and auditory real time online feedback was provided using a C-2 J&J Engineering device with Physiodata software (J&J Engineering Inc, Poulsbo, WA). Each session in the SMR/Theta protocol was conducted using a standardized procedure lasting no more than 30 min.

Immediately after attachment of electrodes, impedance check (< 5 kOhms) and four min long baseline recording, subjects performed four, seven-min long blocks of neurofeedback training (operant conditioning of specified EEG frequencies – suppression of Theta and enhancement of SMR). EEG was recorded at a sampling rate of 1024 Hz recorded from C3 with reference on the left mastoid and the ground electrode placed on the right earlobe. The EEG biofeedback procedure was based on Lubar's ADHD protocol in its late modifications (Lubar, 2003), and the first part of Scott & Kaiser's modification of Peniston's brainwave training protocol for alcohol/drug abuse treatment (Scott et al., 2005). During neurofeedback training, patients were trained to increase their SMR amplitude and decrease their slow wave activity (e.g., theta). Our neurofeedback training protocol therefore consists of rewarding enhanced EEG amplitudes at the sensorimotor strip (C3) in the 12-15 Hz frequency range, while simultaneously inhibiting

excessive low frequency (4-7 Hz) at the frontal F3 site. Self-adjusting thresholds were used for continuous visual and auditory feedback.

B. Motivational Interviewing procedure

Motivational Interviewing (MI) (Miller & Rollnick, 2002; Treasure, 2004) is a brief psychotherapeutic intervention for behavioral change aimed to bring about rapid commitment to changing addictive behaviors. The MI (also referred to as Motivation Enhancement Therapy [MET]) was designed to increase the compliance and probability of treatment entry and abstinence (Burke et al., 2003). This behavioral therapy is considered to be especially useful for the drug-dependent individuals who are ambivalent about changing their habits, since MI was specifically targeted to less motivated individuals. Dr. Stewart, a specialist in addiction psychiatry, who is trained in MI, conducted forty- five minute MI sessions. Each subject received at least 2 sessions of MI, while 5 subjects from the group volunteered for a third (optional) MI session. There was at least a one-week waiting period between MI visits.

IV. DATA ANALYSIS

A. Wavelet Power Analysis

Data were collected and stored using Net Station (EGI). Immediately following the cue reactivity test the EEG data were tagged according with the appropriate triggers in Net Station and segmented into the appropriate response categories (e.g. drug-target, drug-non target, neutral-target and neutral-non target) and exported to MatLab for wavelet analysis. Waveleting was used to elucidate the frequency components of a signal as they vary in time. By plotting the result of the filtered wavelet data it was possible to measure the precise timing and strength of the gamma response, both early evoked and late induced, in relation to a given stimulus. The data were subjected to wavelet analysis using the continuous wavelet transform (Eq. 1), which can be found in the wavelet toolbox of MatLab.

$$CWT\,\frac{\psi}{x}(\tau, s) = \frac{\mathbf{1}}{\sqrt{[s]}}\int [x(t)\psi * \left(\frac{t-\tau}{s}\right)] dt \qquad (1)$$

The mother wavelet (ψ) used in this application was the Morlet window, and 128 coefficients were found for each signal. Using this window implies subtracting a user-defined constant from the wave followed by localization using a Gaussian window. A pictorial representation of the Morlet Window is shown below in Figure 7. The mathematical representation of the Morlet window is also outlined in equations 2, 3 and 4.

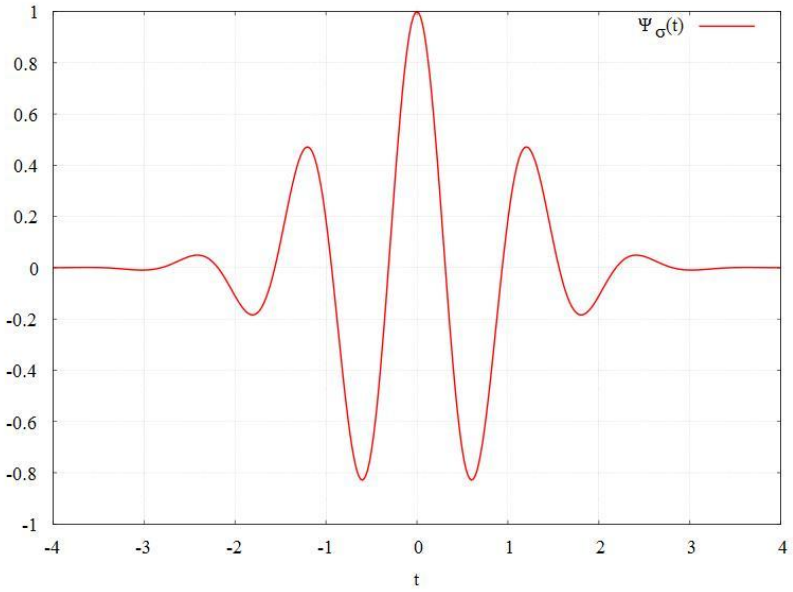

Figure 7: Plot of the Morlet window used in our continuous wavelet transform.

$$\textbf{Morlet Window} = \Psi v(t) = Cv\Pi^{\frac{-1}{4}} e^{\frac{-1}{2}t^2} (e^{ivt} - Kv) \qquad (2)$$

$$Kv = e^{\frac{-1}{2}v^2} \quad (3)$$

Equation 3: Constant subtracted from the base wave for the construction of the Morlet Window

$$Cv = \left(1 + e^{-v^2} - 2e^{\frac{-3}{4}v^2}\right)^{\frac{-1}{2}} \quad (4)$$

Equation 4: Normalization factor used in the construction of the Morlet Window.

The waveleted signal was passed on for band pass filtering using a custom design Harris 7 window (Figure 8). The Harris window used 725 samples and was designed to allow the complete passage of signals from the 30-40 Hz range. An attenuation band of one Hz was present in the system. The resulting signals now only consisted of the gamma band frequency components and could be summated to yield the relative power of the gamma band. A flow-chart representation of data processing is shown on Figure 9.

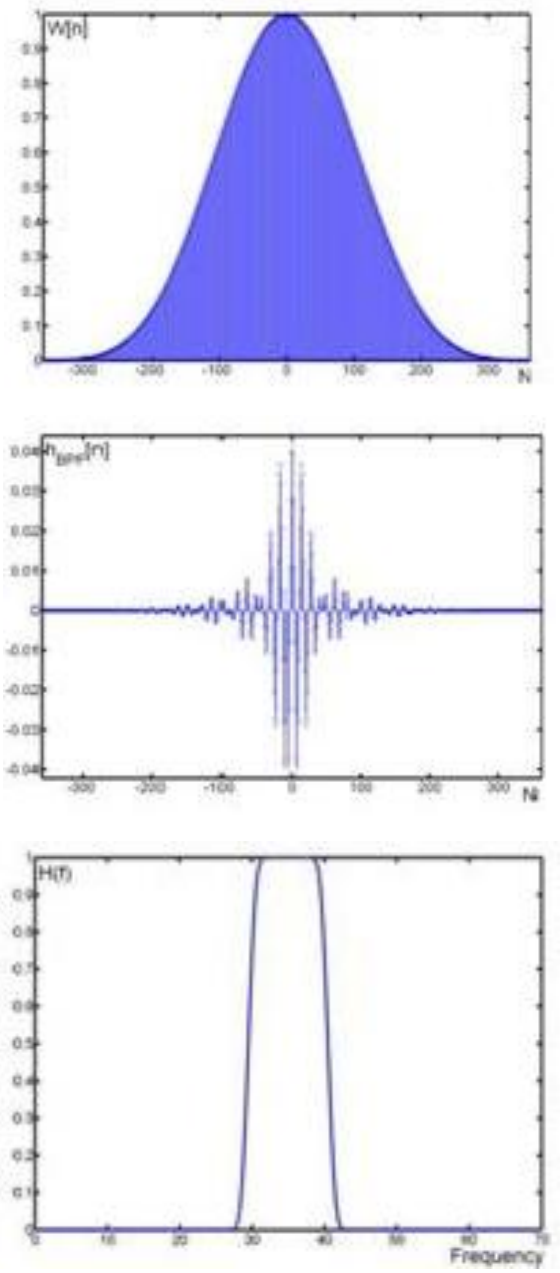

Figure 8: From top to bottom, 1) the custom Harris seven window with 725 samples, 2) the impulse response and of the designed band pass filter 3) the band pass filter displaying a pass band of 30-40 Hz with a 1 Hz transition band on either side of the pass window.

Figure 9: Flow chart representation of the calculation of Gamma Power.

1. Statistical analysis of Gamma Power

Statistical analysis was performed on the subject-averaged data using the subject averages as observations. Each single gamma oscillation trial was analyzed for pre-selected frontal and parietal EEG sites and time window (0-200, 250-450 ms post-stimulus). Data for each dependent gamma EEG variable was analyzed using a repeated-measures ANOVA. Factors included *Stimulus* (target or non target), *Cue* (drug or neutral), *Hemisphere* (right or left) and *Topographic location* (anterior or posterior). Using SPSS (v. 18) analysis packages, a model was created to test for significant interactions between electrodes in both lateral (inferior) and medial locations pre and post neurofeedback training in both the early and late gamma windows. In all ANOVAs, Greenhouse-Geisser corrected p-values were employed where appropriate.

B. Coherence Calculations

Coherence was calculated using a combination of the Brain Electrical Source Analysis (BESA 5.1 Grafelfing, Germany) software packages and custom software programs developed in MatLab. Data was exported in raw format from Net station to

BESA. Toolboxes within BESA allow for the uploading of surface electrode coordination files and stimulus classification. Once the data was loaded and coordinated to the appropriate electrode source, it could be segmented into separate sets according to the cue reactivity test trial (e.g. drug-target, neutral target…). BESA also contains artifact detection protocols, which allow for the elimination of contaminated trials and channels based upon phase, amplitude and low signal thresholds. Raw data was scanned and eliminated of all possible artifacts before coherence values were calculated. Coherence is measured in BESA according to three values. The first is the time-frequency signal, which is simply the amplitude of the signal at a given point in time for the frequency range specified by the user. The second is the actual coherence of the two wave amplitude, which is measured by finding the correlation of the time-frequency signals and normalizing this value over all the trials of that particular cue (ie. target drug…). The final value is the phase locking value, which measures the phase similarities between the two recorded electrode waveforms. Figure 10 shows a summary of the values found in BESA, along with how these values are combined into a final coherence value between zero and one.

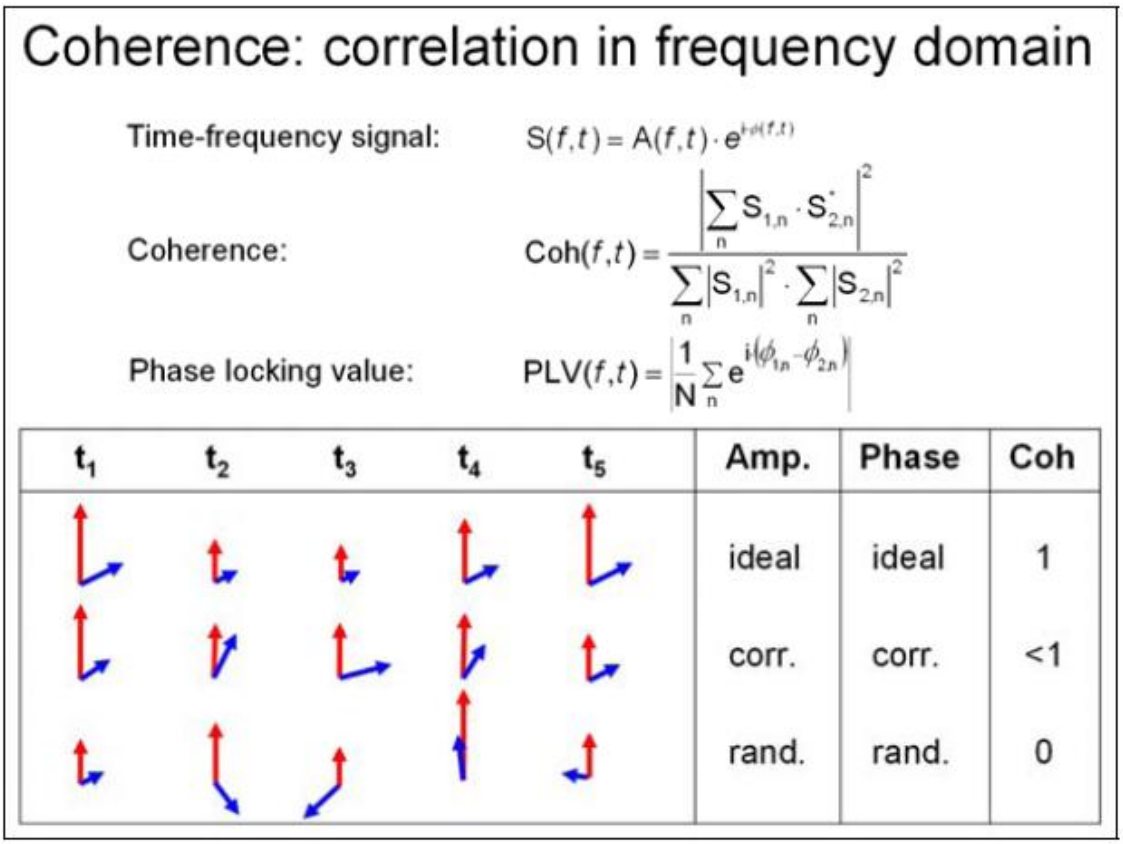

Figure 10: Recreated from BESA instruction manual, this image shows the three relevant values found when calculating the coherence using BESA, namely the time-frequency signal, the coherence and finally the phase locking value. These values are found over all trials and used to yield an overall coherence value according to the bottom table.

Within BESA it was possible to create a montage displaying electrodes of interest. Hence a custom montage consisting of the eight electrodes previously outlined in Figure 4 was created and applied to the raw data prior to artifact scanning and calculation of coherence. Using the coherence toolbox, BESA returns a bitmap image relating coherence in the form of a scaled color mapping system (blue = .0 correlation coefficient to red = 1.0 correlation coefficient). Each image displays a set of mappings, which show each electrode in the montage referenced to a single electrode. Each possible combination of reference electrodes were created (e.g. for the eight electrode

montage, eight images were created, each using one of the eight electrodes as a reference.) An example of the images created in BESA is shown below (Figure 11). These mapping images were then be saved and exported into MatLab for qualitative quantification using a custom computer program.

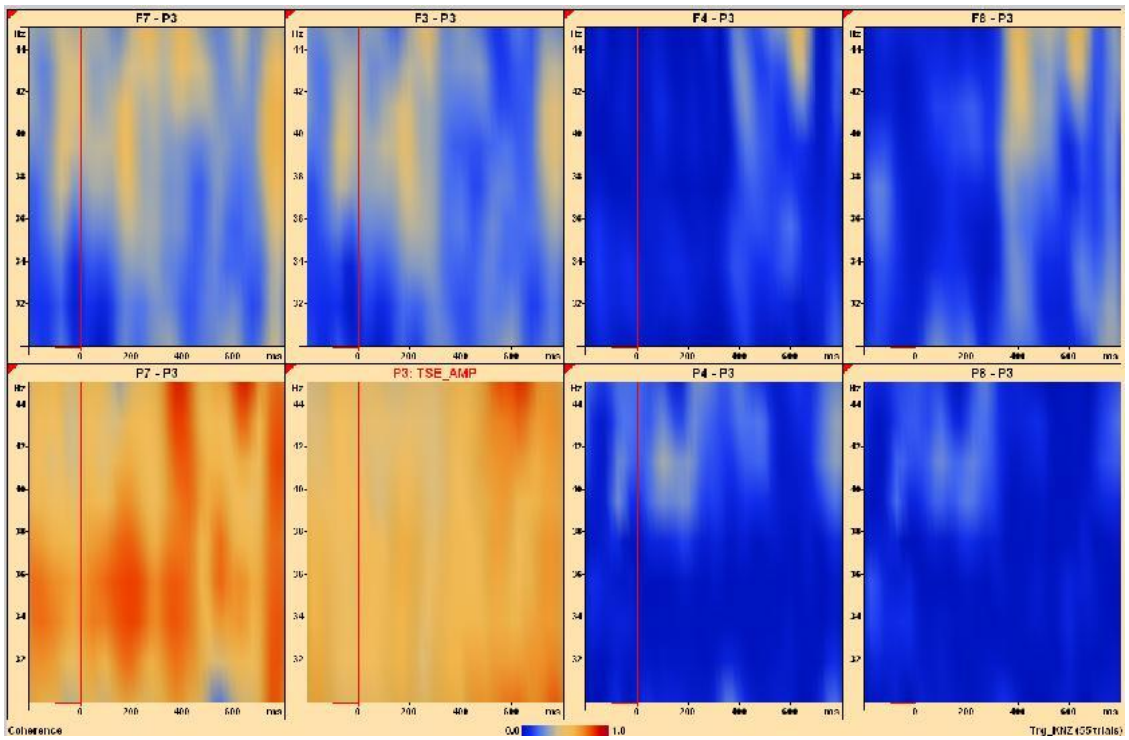

Figure 11: Representative image of the bitmaps created in BESA. Eight such images were created for each patient at each for each condition and stimulus (target vs. non-target) at pre-and post neurofeedback time points.

Using a custom made MatLab program, these bitmap images were segmented into eight smaller images, one for each electrode. The program then segmented each electrode images into a series of windows over a 100 ms width and a 5 Hz height. For each electrode image there were 848 possible windows that cover the 0-200 ms (early) or the 250-450 ms (late) post stimulus time frame and 30-45 Hz frequency band. Once the

windows were created each individual window was analyzed for coherence. To do this each window was loaded and compared pixel by pixel to a color matrix. The color matrix assigns a scaling value over the interval of [0:1] with a step size of 1/512 (512=the number of possible red, green and blue color combinations which compose an individual pixel in the matrix). Each pixel in the image possesses a RGB value which can be compared to the color matrix using the following distance calculation:

$$Distance = \sqrt{(Rpixel - Rscale)^2 + (Gpixel - Gscale)^2 + (Bpixel - Bscale)^2} \quad (5)$$

Equation 5: Distance formula calculation. Used to calculate the Euclidian distance between the RGB values of a given pixels and each RGB combination in the scaling matrix.

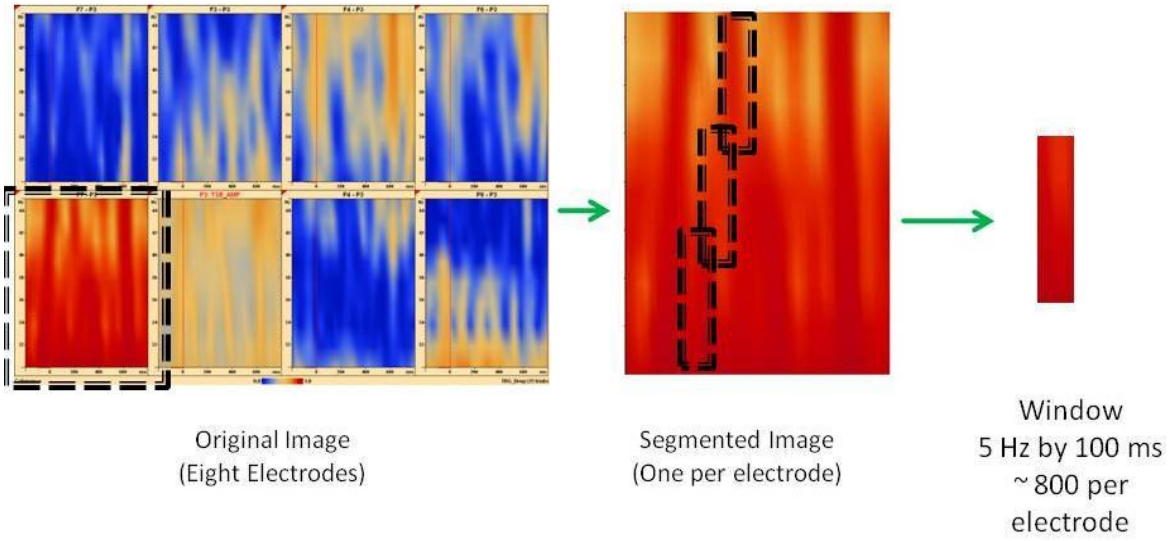

Figure 12: Flow chart illustration of the segmentation process, a complete bitmap image is loaded in MatLab, an individual electrode is then segmented out, and an entire region is iteratively swept to create test windows.

This calculation was made to every point in the scaled color matrix and the minimum value was taken as the coherence value for that pixel. This process was repeated for each pixel contained within the specified window. These values may then be summated to yield the total coherence over the loaded window. Each of the 848 windows for the electrode image was analyzed and the maximum of the 848 resulting values was taken as the gamma band coherence at a given time frame. Images were created and analyzed for each patient for both target and non-target drug cues, and at both early and late time points. Results were then statistically analyzed using a student's t-test to determine which electrodes showed statistically higher responses post neurofeedback.

V. RESULTS

A. SMR and Theta changes in neurofeedback sessions

All subjects successfully completed twelve 25-30 min long sessions of SMR-up/theta-down sessions and at least 2 Motivational Interviewing sessions (conducted by Dr. Stewart and his associate, addiction psychiatry fellow Dr. Husk). The mean increase of the SMR amplitude as compared to daily baseline level across all neurofeedback sessions was 17.06 percent, SD=15.04 ($t=3.20$, $p=0.007$), but mean change of theta amplitude was not significant (0.99 ± 5.71 percent, $t=0.49$, $p=0.311$, n.s.). Regression analysis showed that the increase of SMR as compared to baseline vs. neurofeedback session numbers was not linear ($y=0.808x+10.53$, $r^2=0.24$, $F=3.21$, $p=0.103$, n.s., Figure 13). Considering that out of 10 participants only 8 were available for the post-neurofeedback (within a week after completion) clinical assessments and cue reactivity test, all results are reported for 8 subjects (i.e., hereafter all statistical calculations used N=8/group).

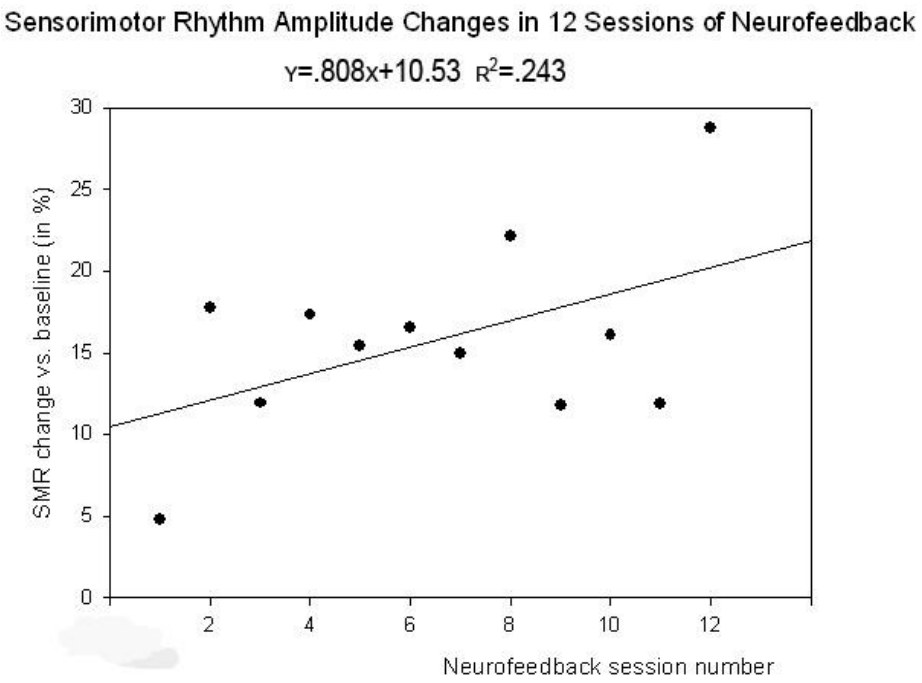

Figure 13: Changes in SMR levels compared to baseline over the course of 12 neurofeedback sessions.

B. Effects of NFB on RT and EEG gamma power in cue reactivity test (post-treatment)

Behavioral responses. There were no significant differences in reaction time (RT, Mean 603.6 ± Standard Deviation 120.6 ms pre- vs. 576.9 ± 122.4 ms for drug targets post-neurfeedback, n.s.) and accuracy (percentage of commission and omission errors, 10.9 ± 11.7 percent pre vs. 11.6 ± 13.2 percent across all targets, n.s.) in the cue reactivity test following neurofeedback treatment.

C. Effects of NFB on evoked (early) gamma responses

Neurofeedback affected predominantly evoked early gamma responses to non-target drug stimuli bilaterally at the frontal and parietal sites (all $p<0.05$). The power of gamma oscillations to non-target drug cues significantly decreased post-treatment with decreases ranging from -23.6 percent (P8) up to -44.94 percent (P3), mean - 35.84 percent with SD across the EEG channels 7.43 percent. Gamma responses to target drug cues were less pronounced (-9.65 ± 7.21 percent) and were significant only at F2, F8, P3, and P7 sites. Changes of gamma power in response to target and non-target drug cues at each EEG recording site are presented in Table 1 below.

TABLE I

CHANGES IN GAMMA POWER IN THE EARLY AND LATE TIME FRAMES

EEG Channel/condition	Early Evoked Gamma Power					Late Induced Gamma Power				
	Pre	Post	% Change	$F_{(1,14)}$	Sig.	Pre	Post	% Change	$F_{(1,14)}$	Sig.
AFz-Non-target drug	0.399	0.347	-15.0	18.8	0.001 **	0.436	0.297	-46.8	182.4	0.000***
AFz-Target Drug	0.520	0.499	-4.2	0.4	0.524	0.563	0.472	-19.3	28.2	0.000***
F1-Non-target drug	0.392	0.321	-22.1	8.5	0.014 *	0.429	0.355	-20.8	8.1	0.014*
F1-Target Drug	0.495	0.467	-6.0	1.0	0.332	0.552	0.436	-26.6	15.0	0.003**
F2-Non-target drug	0.400	0.319	-25.4	18.1	0.001***	0.427	0.360	-18.6	7.3	0.018*
F2-Target Drug	0.523	0.478	-9.4	7.2	0.023*	0.563	0.445	-26.5	17.4	0.002**
F7-Non-target drug	0.382	0.318	-20.1	11.4	0.006**	0.426	0.309	-37.9	59.1	0.000***
F7-Target Drug	0.46	0.485	5.2	0.9	0.376	0.546	0.475	-14.9	6.5	0.029*
F8- Non-target drug	0.388	0.299	-29.8	77	0.000***	0.436	0.314	-38.9	37	0.000***
F8-Target Drug	0.499	0.469	-6.4	2.6	0.139	0.476	0.467	-1.9	0.0	0.924
P3- Non-target drug	0.387	0.276	-40.2	22.5	0.001**	0.419	0.285	-47.0	55.0	0.000***
P3-Target Drug	0.513	0.442	-16.1	4.1	0.071	0.432	0.438	1.4	0.0	0.958
P4- Non-target drug	0.399	0.325	-22.8	5.5	0.039*	0.436	0.322	-35.4	20.5	0.001**
P4- Target Drug	0.465	0.453	-2.6	0.2	0.641	0.536	0.457	-17.3	12.3	0.006**
P7- Non-target drug	0.386	0.281	-37.4	23.7	0.000***	0.417	0.279	-49.5	120.8	0.000***
P7-Target Drug	0.496	0.433	-14.5	3.7	0.082	0.554	0.433	-27.9	24.3	0.001**
P8- Non-target drug	0.379	0.326	-16.3	5.0	0.048*	0.438	0.313	-39.9	38.7	0.000***
P8-Target Drug	0.456	0.465	1.9	0.1	0.71	0.560	0.465	-20.4	26.1	0.001**

Cue (drug, neutral) had main effects both at medial (F1, F2, P3, P4) and lateral (i.e., inferior, F7, F8, P7, P8) EEG channels with more at medial (F=9.43, p=0.001) as compared to lateral (F=5.05, p=0.044). The *Stimulus* (non-target, target) main effect was

highly significant both medially and laterally (medial, $F=268.05$, $p<0.0001$; lateral $F=196.75$, $p<0.0001$).

D. Effects of NFB on induced (late) gamma responses

Neurofeedback affected induced gamma responses to both target and non-target drug stimuli bilaterally at most frontal and parietal sites, except responses to targets at P3. The power of gamma oscillations to non-target drug cues significantly decreased post-treatment (across all channels, mean -47.17 ± 9.88 percent), while decreases to target drug cues were also significant but slightly less expressed (-21.58 ± 5.09 percent).

Cue (drug, neutral) had main effects both at medial and lateral EEG channel groups ($F=34.28$, $p<0.001$, and $F=27.20$, $p<0.001$ respectively). The *Stimulus* (non-target, target) main effect was also significant medially and laterally (medial, $F=80.52$, $p<0.0001$; lateral $F=1173.16$, $p<0.0001$).

E. Topographic differences and interaction effects

Early gamma responses showed a *Stimulus* (non-target, target) X *Treatment* (pre-, post-NFB) interaction both at medial ($F=34.82$, $p<0.001$) and lateral ($F=29.82$, $p<0.001$) channels with more of a pronounced decrease in gamma activity to non-target compared to target cues. A three-way *Stimulus* X *Cue* (drug, neutral) X *Treatment* interaction was significant only at the medial channel group ($F=7.99$, $p=0.015$) and can be described as a more significant decrease to non-target rather than target drug cues following neurofeedback training. There was a tendency for a *Hemisphere* (left, right) X

Topography (anterior, posterior) X *Treatment* interaction, but the effect did not reach significance (F=4.56, p=0.056, n.s.).

Induced gamma responses showed a *Stimulus* (non-target, target) X *Treatment* (pre-, post-NFB) interaction only at lateral EEG channels (F=60.78, p<0.001). Again, the effect manifested as a clearer global decrease in gamma power to non-target cues (Figure 15). A *Stimulus* X *Cue* X *Treatment* interaction was significant both at the medial (F=6.29, p=0.022) and lateral (inferior) channels (F=4.72, p=0.049) and was characterized by more significant decreases in gamma induced by non-target compared to target drug cues post-neurofeedback. Figures 14 shows a relatively more visible decrease of evoked and induced gamma responses to non-target as compared to target drug cues after neurofeedback based therapy.

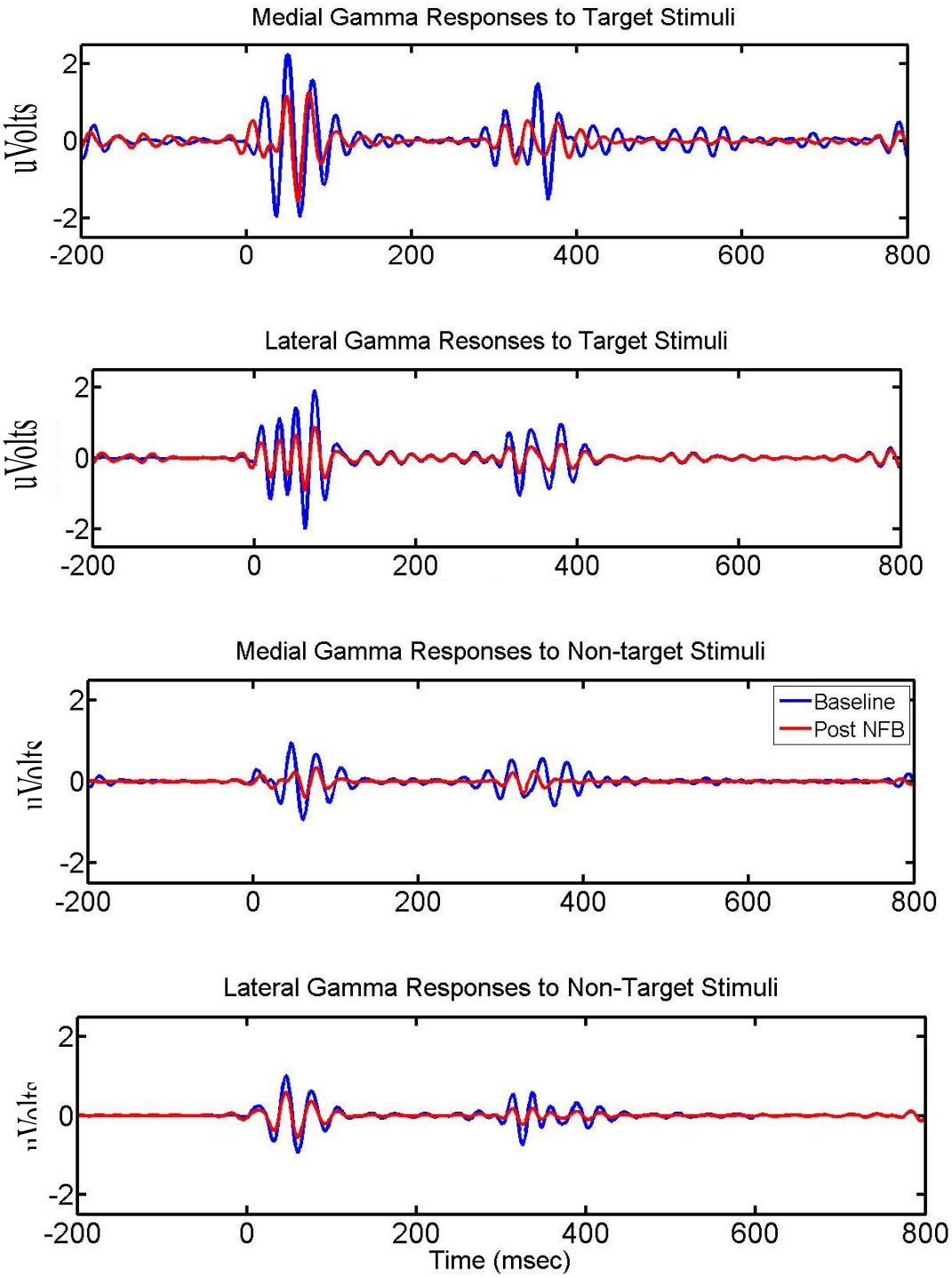

Figure 14: From top to bottom: 1.) Gamma Responses of the grand average of the 4 medial electrodes to target drug stimuli, 2.) grand average of the 4 lateral electrodes to target stimuli, 3.) grand average of the 4 medial electrodes to non-target drug stimuli, and 4) grand average of the 4 lateral electrodes to non-target stimuli.

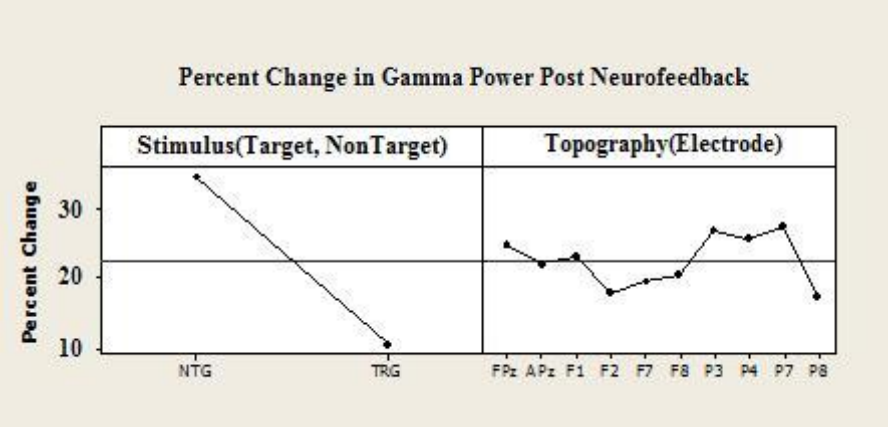

Figure 15: Analysis of gamma response change (in percent) across electrodes. Results show a higher percent change to non-target rather than target stimuli (left), and all electrodes changing in a consistent pattern (i.e. Topography was not a significant factor in percent change of gamma power).

F. Coherence Results

Coherence was shown to increase in for both conditions (ie. target and non-target drugs) in both early and late gamma time frames. Despite the fact that many of the electrodes did show improvement, relatively few were statistically significant. When considering early gamma targets showed statistically significant increased coherence at the F7/F1, F1/P4 and F1/P8 electrode pairs and non-target cues likewise showed statistical improvement at the F7/F1 electrode pair only. In contrast the target cues showed several more statistically significant increases: F7/F1, F7/P4, F7/P8, F1/P4, and F1/P8 all showed a p-value less than .05. Finally, non-target cues showed statistical improvement in only the F7/F1 position. Figures 16-19 show graphical depictions of coherence improvement for each cue in both time frames, as well as which electrode pairs show statistical improvements.

While statistically relevant improvement was seen, it was highly limited and failed to show a widespread improvement in long range coherence. It is the belief of the authors however, that this data may be slightly skewed based upon comparing single electrodes only. It is possible within BESA to create montages of entire brain regions, effectively taking groups of electrodes for a brain region and combining them into a single grand average waveform. With this technique it would be possible to highlight areas of baseline coherence abnormalities between controls and drug addicted patients and also to show increases in regional brain coherence rather than simply a pair-wise electrode comparison which may yield an improved analysis of long range coherence.

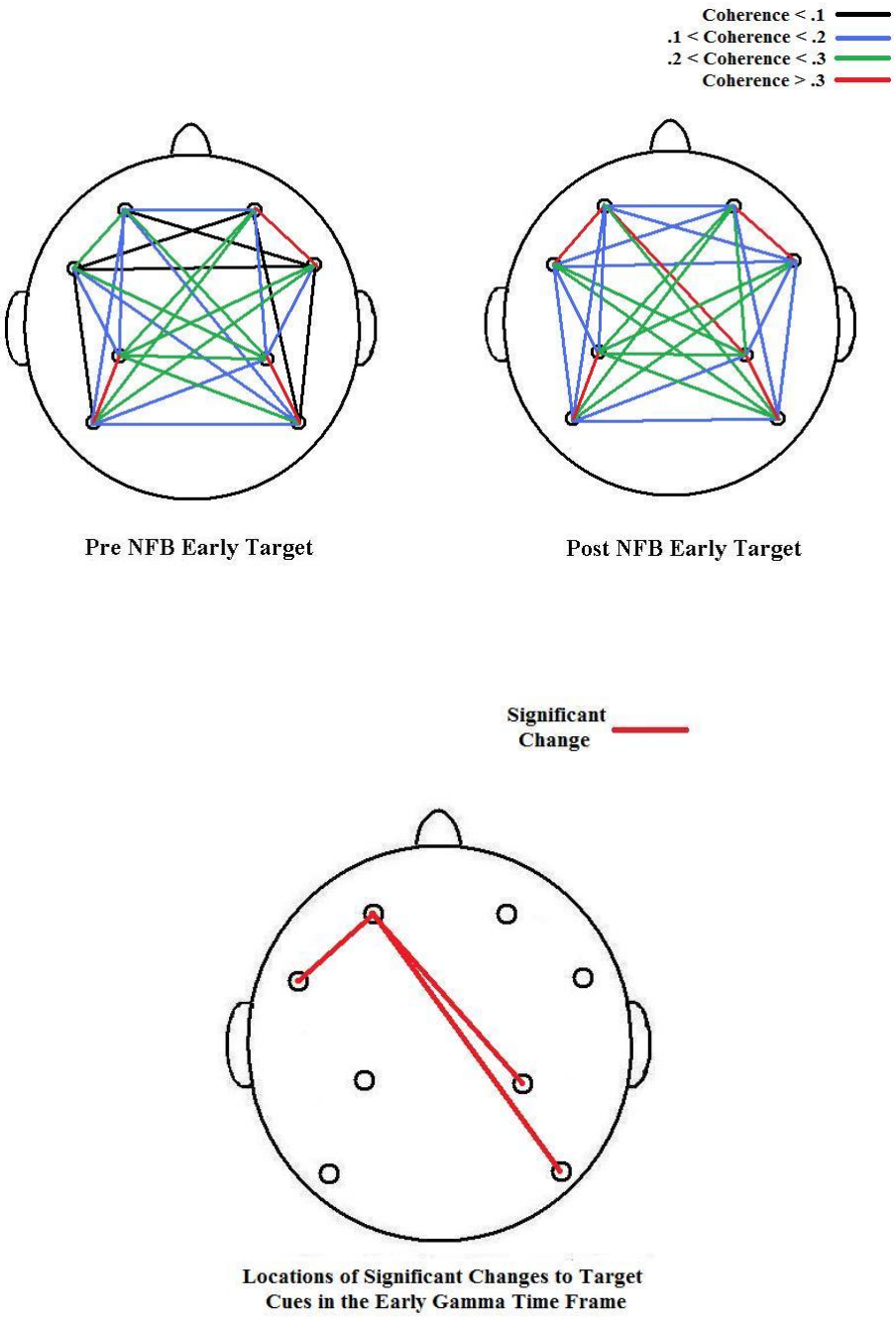

Figure 16: Top: Long range early gamma coherence to target drug cues pre and post NFB. Bottom: Electrode pairs showing statistically relevant improvement according to one sample t-test on difference between the pre and post NFB values.

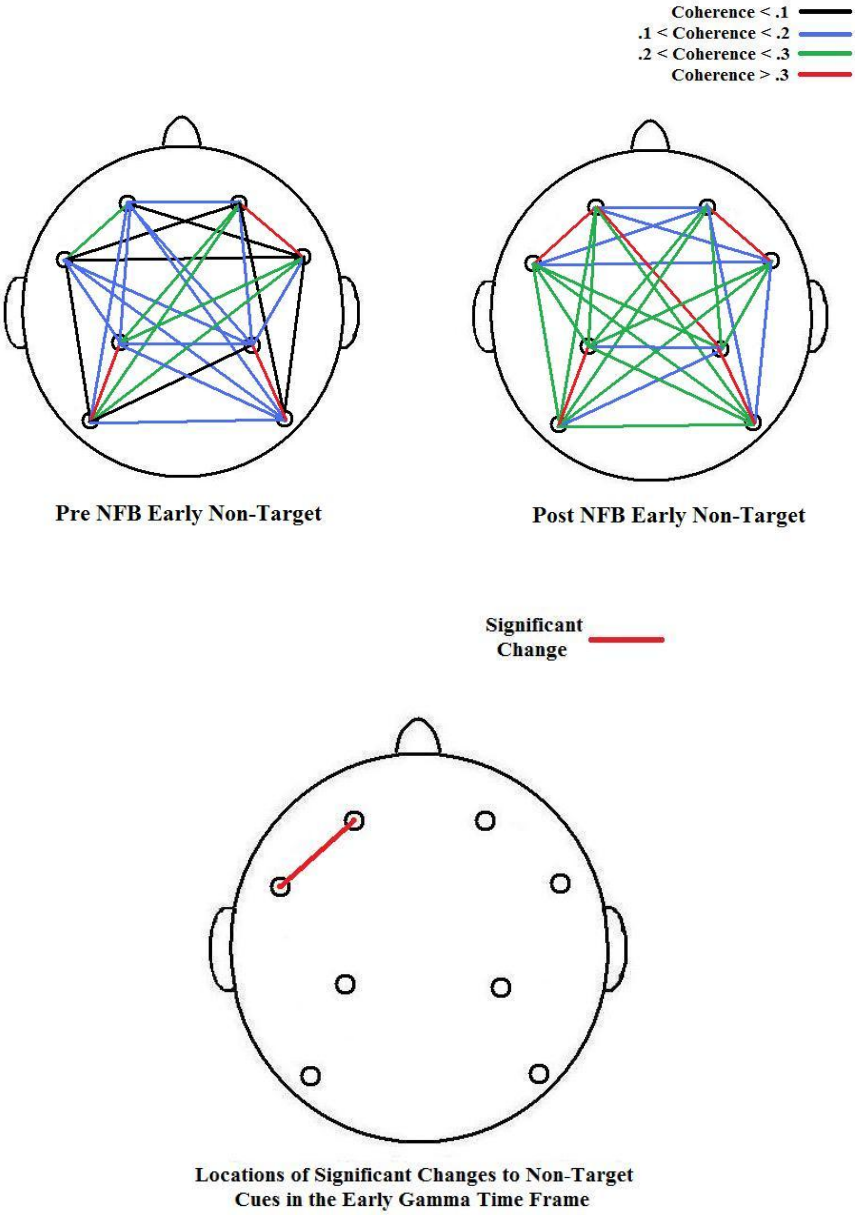

Figure 17: Top: Long range early gamma coherence to non-target drug cues pre and post NFB. Bottom: Electrode pairs showing statistically relevant improvement according to one sample t-test on difference between the pre and post NFB values.

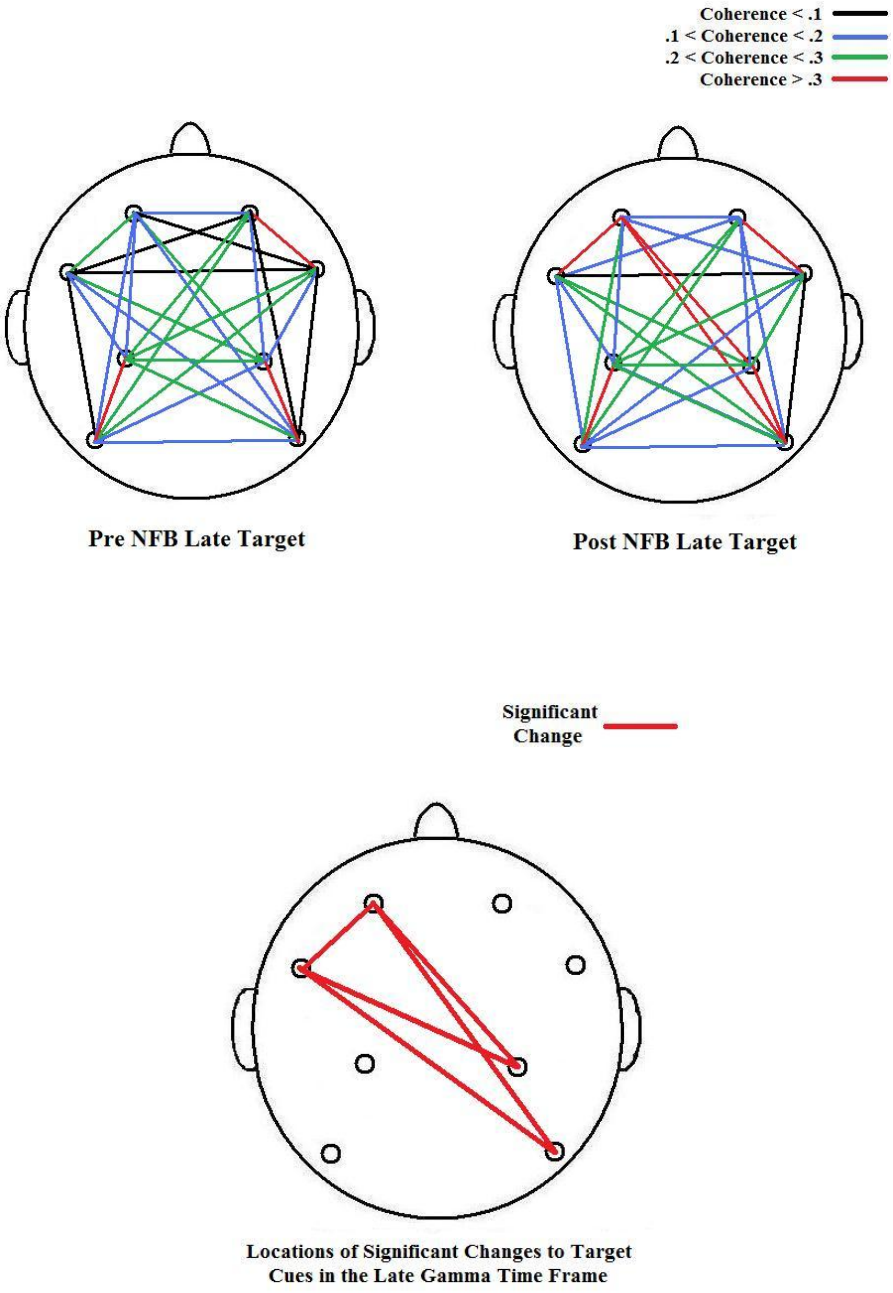

Figure 18: Top: Long range late gamma coherence to target drug cues pre and post NFB. Bottom: Electrode pairs showing statistically relevant improvement according to one sample t-test on difference between the pre and post NFB values.

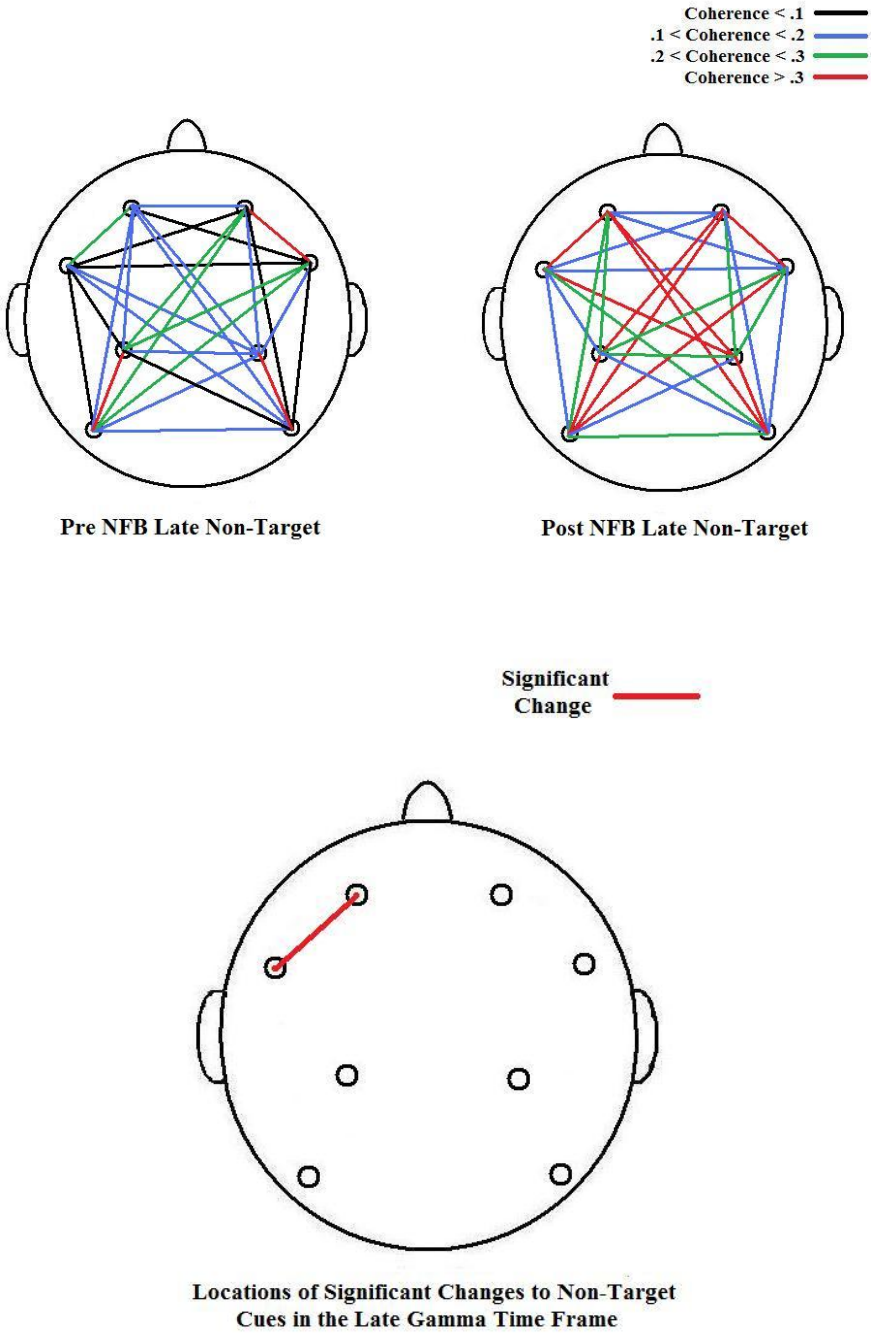

Figure 19: Top: Long range late gamma coherence to non-target drug cues pre and post NFB. Bottom: Electrode pairs showing statistically relevant improvement according to one sample t-test on difference between the pre and post NFB values.

G. Clinical evaluations and drug tests after NFB and MI

Results of the clinical evaluations showed decreased perceived depression and stress. Following neurofeedback sessions subjects reported to have reduced depression scores (from 22.2 ± 6.9 at pre- to 13.6 ± 8.7 at post-NFB, two-tailed Student's t-test, t=3.30, p=0.004) as measured by the BDI-II (Beck et al., 1996); additionally there was a reduced stress score (from 29.9 ± 8.6 to 20.1 ± 13.9, t=1.95, p=0.041) as measured by the PSS-SR (Foa et al., 1989, 1997). Post-neurofeedback urine drug screens showed a marginal decrease in positive cocaine tests (t=1.96, p=0.04) and a significant decrease in positive tests for marijuana use (t=2.44, p=0.018). Most of the patients reported a decrease in the amount of cocaine and marijuana used and improvements in social status (i.e., resuming study at school, employment, housing, financial security, problems with law, etc.); however, in this study we did not have any independent sources (e.g., family members, neighbors or social workers reports) to confirm self-reported data collected from our subjects. Considering that from ten participants originally enrolled in this neurofeedback study all planned clinical, behavioral, and EEG data were collected from eight, an acceptable retention rate was maintained.

VI. CONCLUSIONS

Our study attempts to develop and quantify methods of analytically quantifying the effects of neurofeedback procedures, specifically in cocaine addiction. Substance abuse disorder is a psychoactive disorder, which causes changes in the brain that result in a misallocation of attentional resources to drug related items. These changes are a consequence of both the neurotoxic effects of the drugs being used by the patient and as a result of the withdraw process experienced upon cessation of drug use. Drug addiction as a whole is projected to cost approximately 500 billion dollars when the cost of healthcare, job-loss and legal ramifications are considered.

Previous studies have highlighted specific differences found in the EEG patterns of patients suffering from cocaine addiction. These differences include abnormal levels of theta and delta band frequencies. However, very little work has been done previously to quantify differences in the gamma band, which comprises of frequencies ranging from 30-80 Hz in the EEG waveform. The gamma band may be split into two major components, namely evoked and induced. The evoked gamma response are also referred

to as early gamma responses, as they occur in the 0-200 ms post stimulus range and are time locked to a given stimulus. These responses show very little variance to different types or different complexities of stimuli. Hence they are thought to represent a pre-recognition process within the brain.

In contrast to these findings the induced, or late gamma, occurs in the 250-450 ms post stimulus range, and is not time locked to a stimulus. The induced gamma response also shows a much higher variation in amplitude and latency depending on stimulus type and complexity, suggesting a role in conscious cognitive thought processes. Since it is known that substance abusing patients show an increased response to drug related items in a cue reactivity test, it makes sense to investigate changes in the gamma band as a non-invasive method to quantify the effects of neurofeedback over the course of treatment.

In this experiment we set out to quantify two indices of the gamma band that may be used to track the progress of treatment. Specifically these two methods were the calculation of gamma power and of long-range gamma coherence between electrodes. Gamma power was found by submitting the raw EEG signal from a given channel to a waveleting routine implemented in MatLab. This process allowed for the separation of specific frequency bands as they occur in time. Our custom waveleting routine used 128 coefficients to separate the data, each of which was then passed through a digital band pass-filter designed to allow passage of frequencies between 30-40 Hz. The values of each of the 128 coefficients were then summated to yield the total gamma waveform that could then be used to calculate the gamma power in both the early and late time frame. Statistical analysis was performed to determine changes between baseline values and post

treatment values. In this study our hypothesis was that we would see statistically lower gamma responses post treatment, indicative of less attentional resources being dedicated to the analysis of drug related stimuli.

Long-range gamma coherence is representative of interbrain connectivity during the recognition and analysis of a given stimulus. EEG coherence analysis is a technique that investigates the pair-wise correlations of power spectra obtained from different electrodes. It measures the functional interaction between cortical areas in different frequency bands, with high level of coherence between two EEG signals indicating co-activation of neuronal populations. Coherence was calculated for the 30-45 Hz by passing the raw EEG data to BESA and using its own coherence toolboxes. This process resulted in a bitmap image, which was exported to a custom MatLab algorithm to give a quantitative average coherence value over a 100 ms X 5 Hz window. In this study we expected to see statistically higher coherence values post neurofeedback training.

In this pilot study we selected ten drug addicted patients, (two females, eight males) mean age, 44.6 ±8.3, range 35-54 years, 70% Afro-Americans), to participate in the study. All patients were carefully screened for inclusion in the experiment, informed of all procedures and protocols, and signed the consent form approved by the University of Louisville's IRB. These patients then underwent a baseline cue reactivity test, 12 neurofeedback sessions, at least 2 MI sessions, and a post treatment cue reactivity test. The neurofeedback protocol consisted of simultaneously increasing SMR frequencies (12-15Hz) at the C3 recording sight and decreasing Theta frequencies (4-7Hz) at the F3

recording site. Data from the two cue reactivity tests were segmented and analyzed using the protocols outlined above.

As a result of this study it is the conclusion of the authors that the gamma band indices developed through this research were sufficiently sensitive to changes in the EEG pattern to be indicative of improvement over the course of neurofeedback treatment. As was predicted prior to onset of the study, subjects did show decreases in gamma power to both target and non-target stimuli post neurofeedback, and increases in long-range coherence were also seen.

Despite the positive results of this study there are still several limitations, which need to be addressed. The first major complication is that there was no control group of demographically matched non-addicted patients and our test group was small. The no control group implies that while we know the gamma powers decreased and coherence values increased in addicted patients, we are unable to compare these differences to pre-post NFB differences seen in a non-addicted patient. In a similar fashion our data may be skewed by the small sample size used in this pilot study. Through careful analysis of the gamma power results it was possible to highlight topographical difference that were trending towards significance which may be found if a larger data pool was used.

Another potential setback of this study is the fact that two different treatment modalities were employed simultaneously, namely motivational interviewing and neurofeedback. As a result of this we have no way of isolating the effects seen in this study as being the effect of either modality. While motivational interviewing was used as a method to get patients actively involved in the study and retain them, it is possible that

patients received some benefit through the process that could manifest itself in alterations of the gamma waveform.

The third major limitation of this study comes from the selection of electrodes. We used a 128-electrode net to collect the data, yet only eight channels were analyzed. These eight channels were selected as points of different brain regions to give a widespread view of the brain and to allow for comparisons between medial and lateral as well as frontal and parietal regions. However, by only taking a single electrode we fail to capture large-scale regional comparisons, which may yield more information about long-range coherence in the brain. BESA is capable of creating montages which calculate the average responses of a given brain region which could then be used to calculate coherence and gamma power, allowing the same modality to be used on a more comprehensive data set.

VII. Future Work and Application:

This protocol allows for a large deal of continuation research. As it applies specifically to cocaine related drug addiction, further studies to collect more study subjects, and also the collection of a control group would be greatly beneficial. Also an additional follow-up time point may be added to the research to determine how long beneficial results remain after neurofeedback treatment. This data is currently being collected and analyzed by members of the research lab responsible for the data collected here. Also, all data presented here is representative of drug related cues, not neutral related cues. While it has been shown previously that drug-addicted patients show increased responses to drug related cues as compared to neutral cues, it may be informative to compare changes in both categories after neurofeedback as well.

Additional future work includes expanding this methodology to other areas of research in the neurofeedback field. The methodologies laid out here are applicable to a wide range of psychiatric disorders, including ADHD, schizophrenia and posttraumatic stress disorder (PTSD) with minimal modification. Again research is already being

collected here at the University of Louisville to investigate the effects of PTSD on the gamma band, an area of increasing interest given the large number of returning veterans who may suffer from PTSD. Additionally a study is already underway to study the effects of neurofeedback specifically targeted to provide real time audio and visual feedback based upon the level of gamma activity recorded from the subject. In this study we have already recruited 5 addicts and 5 controls as a pilot data set that we expect to publish results from within the year.

These techniques are also not limited to the gamma frequency band. The waveleting techniques outlined in this paper could be easily modified to isolate frequencies of the alpha, beta, theta or any other sub-band of the EEG waveform. In addition, the coherence calculations made here may be used to analyze a wide range of brain frequencies. The main limitation in the analysis of coherence is the BESA program. BESA has set ranges that may be used to define frequencies for coherence analysis, and these frequencies may not go sufficiently low for analysis of the low frequency bands such as theta and beta. However in this case it should be possible to devise additional custom MatLab programs, which could take the filtered data set and calculate coherence manually. The versatility of the methodologies outlined in this thesis makes them applicable in several areas of EEG analysis with very little change and allow for the quick and repeatable creation of quantifiable data sets.

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Appendix 1: MatLab Codes:

i) Main Runtime

```
clear all
close all
clc
format long
Maximum_Coorelation = 1; % you have to change this number based on the capture
image

Scale  = [0:Maximum_Coorelation./510:Maximum_Coorelation];

load data_file Color_Map_Matrix

for kkk=1:64

        if kkk<10
                File_Name=['PR_00' num2str(kkk) '.bmp'];
        elseif kkk>=10 && kkk<100
                File_Name=['PR_0' num2str(kkk) '.bmp'];
        else
                File_Name=['PR_' num2str(kkk) '.bmp'];
        end

Test_Image=coherence_image(File_Name);%generate individual electrode images
Correlation_Matrix=zeros(1,8); %Initialize Matrix

for j=1:8

Average_Correlation=zeros(1,848);
Window=window_maker(Test_Image(:,:,:,j)); %Create Windows for the given image
[Row_Index Col_Index Layer Image]=size(Window(:,:,:,1));

%Calculate Coherence
        for i=1:848
        Sum_Cor = 0;
        Counter = 0;

        for a=1:Row_Index
                for b=1:Col_Index
                R = double(Window(a,b,1,i));
                G = double(Window(a,b,2,i));
                B = double(Window(a,b,3,i));
```

```
                distance_v = ((R - Color_Map_Matrix(:,1)).^2 + (G -
                Color_Map_Matrix(:,2)).^2
                        + (B – Color_Map_Matrix(:,3)).^2).^(0.5);
                [min_dis pos_value] = min(distance_v);
                Coorelation_value = Scale(pos_value);
                Sum_Cor = Sum_Cor + Coorelation_value;
                Counter = Counter + 1;
                clear distance_v
                end
        end
        Average_Correlation(1,i) = Sum_Cor./Counter;
        end
        Correlation_Matrix(1,j)= max(Average_Correlation);%find highest value of
window
end

%    Correlation_Matrix; %display matrix
%    fprintf('Be sure to remember one value is the reference and should be ignored\n')

Sxls1=['B' num2str(kkk+1) ':I' num2str(kkk+1)];
xlswrite('All_Results.xls',Correlation_Matrix,Sxls1)
kkk

end
```

ii.) Image Segmentation Function

```
function[Test_Image]=coherence_image(File_Name)
%coherence image splitter
%Tim Horrell
%February 22, 2010
%Given a 2,4 image array, this program will produce eight pictures which
%can then be individually tested

Input_Image=imread([cd '\Images\' File_Name]);
Test_Image=zeros(394,295,3,8);

for i=0:3
        for layer=1:3
                for j=1:394
                        for k=1:295
                        Test_Image(j,k,layer,i+1)=Input_Image(20+j,(24+318*i)+k,layer);
                        end
                end
        end
end

% figure
% subplot(2,2,1)
% imshow(Test_Image(:,:,:,1))
% subplot(2,2,2)
% imshow(Test_Image(:,:,:,2))
% subplot(2,2,3)
% imshow(Test_Image(:,:,:,3))
% subplot(2,2,4)
% imshow(Test_Image(:,:,:,4))

for i=0:3
        for layer=1:3
                for j=1:394
                        for k=1:295
                        Test_Image(j,k,layer,i+5)=Input_Image(455+j,(24+318*i)+k,
                layer);
                        end
                end
        end
end
```

iii.) Window Making Function

```
function [Window]=window_maker(Input_Image)
%coherence image splitter
%Tim Horrell
%February 22, 2010
%Given a input image array, this program will produce a specified set of window
%images which can then be individually tested
Window=zeros(130,30,3,848);
counter=1;
for v_shift=1:5:261
        for h_shift=121:2:151
                for layer = 1:3
                        for i= 1:130
                                for j= 1:30
                        Window(i,j,layer,
                        counter)=Input_Image(v_shift+i,j+h_shift,layer);
                                end
                        end
                end
        counter=counter+1;
        end
end
```

Appendix II: Data Tables

TABLE II
T-TEST OF THE DIFFERENCES BETWEEN PRE AND POST NFB EARLY GAMMA COHERENCE TO TARGET DRUGS

One-Sample Test

	Test Value = 0			
	t	df	Sig. (2-tailed)	Mean Difference
F7_F1	3.591	6	.011	.223573
F7_F2	.594	6	.574	.027164
F7_F8	.536	6	.611	.023116
F7_P7	1.050	6	.334	.034787
F7_P3	.175	6	.867	.003330
F7_P4	2.045	6	.087	.066962
F7_P8	.954	6	.377	.051838
F1_F2	-.271	6	.795	-.011503
F1_F8	.930	6	.388	.040995
F1_P7	.771	6	.470	.039371
F1_P3	.384	6	.714	.022367
F1_P4	3.051	6	.022	.145110
F1_P8	3.301	6	.016	.123250
F2_F8	-.531	6	.614	-.074125
F2_P7	.234	6	.823	.007712
F2_P3	.674	6	.525	.035374
F2_P4	.898	6	.404	.046554
F2_P8	1.015	6	.349	.048434
F8_P7	-.150	6	.885	-.005207
F8_P3	-.275	6	.792	-.010297
F8_P4	.294	6	.779	.011803
F8_P8	1.423	6	.205	.034904
P7_P3	-.120	6	.909	-.012001
P7_P4	.697	6	.512	.027238
P7_P8	-.115	6	.912	-.007189
P3_P4	-1.455	6	.196	-.036053
P3_P8	.267	6	.798	.014323
P4_P8	.717	6	.501	.053361

TABLE III

T-TEST OF THE DIFFERECNE BETWEEN PREA AND POST NFB EARLY GAMMA COHERENCE TO NON-TARGET DRUGS

One-Sample Test

	Test Value = 0			
	t	df	Sig. (2-tailed)	Mean Difference
F7_F1	2.613	7	.035	.310625
F7_F2	.620	7	.555	.041250
F7_F8	.964	7	.367	.043250
F7_P7	1.646	7	.144	.146625
F7_P3	1.267	7	.246	.116500
F7_P4	2.197	7	.064	.099375
F7_P8	1.070	7	.320	.105625
F1_F2	.494	7	.637	.047875
F1_F8	.990	7	.355	.060875
F1_P7	1.160	7	.284	.113625
F1_P3	1.285	7	.240	.102750
F1_P4	1.990	7	.087	.125625
F1_P8	1.622	7	.149	.147500
F2_F8	1.041	7	.332	.134500
F2_P7	.307	7	.768	.020125
F2_P3	.837	7	.430	.039875
F2_P4	1.260	7	.248	.139500
F2_P8	1.621	7	.149	.108375
F8_P7	.534	7	.610	.031125
F8_P3	.701	7	.506	.029875
F8_P4	1.412	7	.201	.129750
F8_P8	1.855	7	.106	.079375
P7_P3	-.463	7	.657	-.034875
P7_P4	1.355	7	.218	.059375
P7_P8	1.479	7	.183	.147375
P3_P4	.971	7	.364	.032875
P3_P8	.823	7	.437	.098500
P4_P8	1.217	7	.263	.085250

TABLE VI

T-TEST OF THE DIFFERECNE BETWEEN PREA AND POST NFB LATE GAMMA COHERENCE TO TARGET DRUGS

One-Sample Test

	Test Value = 0			
	t	df	Sig. (2-tailed)	Mean Difference
F7_F1	5.393	6	.002	.232429
F7_F2	.222	6	.832	.010286
F7_F8	.723	6	.497	.021286
F7_P7	1.007	6	.353	.046286
F7_P3	.664	6	.531	.012714
F7_P4	3.165	6	.019	.091286
F7_P8	2.556	6	.043	.091714
F1_F2	-.545	6	.605	-.021429
F1_F8	.748	6	.483	.029143
F1_P7	.940	6	.383	.053429
F1_P3	.345	6	.742	.018143
F1_P4	5.076	6	.002	.173000
F1_P8	2.671	6	.037	.127571
F2_F8	-.351	6	.738	-.047857
F2_P7	-.487	6	.644	-.018714
F2_P3	.801	6	.454	.028429
F2_P4	1.057	6	.331	.025429
F2_P8	2.252	6	.065	.072571
F8_P7	-.997	6	.357	-.025857
F8_P3	.298	6	.775	.006857
F8_P4	-.472	6	.654	-.011286
F8_P8	1.108	6	.310	.022000
P7_P3	-.165	6	.875	-.014143
P7_P4	.263	6	.801	.013857
P7_P8	.783	6	.463	.040286
P3_P4	-.464	6	.659	-.019143
P3_P8	.389	6	.711	.014429
P4_P8	.264	6	.801	.015286

TABLE V

T-TEST OF THE DIFFERECNE BETWEEN PREA AND POST NFB LATE GAMMA COHERENCE TO NON-TARGET DRUGS

One-Sample Test

	Test Value = 0			
	t	df	Sig. (2-tailed)	Mean Difference
F7_F1	2.705	7	.030	.271625
F7_F2	.459	7	.660	.021500
F7_F8	.889	7	.404	.082750
F7_P7	1.587	7	.157	.113750
F7_P3	1.223	7	.261	.102125
F7_P4	2.178	7	.066	.142750
F7_P8	1.323	7	.227	.090750
F1_F2	.439	7	.674	.045625
F1_F8	1.259	7	.248	.114500
F1_P7	.971	7	.364	.089375
F1_P3	1.406	7	.203	.098250
F1_P4	1.573	7	.160	.137250
F1_P8	2.202	7	.064	.179750
F2_F8	.839	7	.429	.112750
F2_P7	.866	7	.415	.063875
F2_P3	.773	7	.465	.053375
F2_P4	1.032	7	.336	.120000
F2_P8	1.674	7	.138	.132375
F8_P7	1.245	7	.253	.112375
F8_P3	.228	7	.826	.009875
F8_P4	1.117	7	.301	.107375
F8_P8	1.848	7	.107	.106625
P7_P3	-.748	7	.479	-.046750
P7_P4	.713	7	.499	.042750
P7_P8	1.631	7	.147	.150000
P3_P4	.886	7	.405	.074125
P3_P8	1.419	7	.199	.102375
P4_P8	1.436	7	.194	.079750

TABLE VI

Compiled coherence results of the early gamma window when presented with a target cue pre NFB.

Ref:	F7							F1						F2					F8				P7			P3		P4
Subject	F1	F2	F8	P7	P3	P4	P8	F2	F8	P7	P3	P4	P8	F8	P7	P3	P4	P8	P7	P3	P4	P8	P3	P4	P8	P4	P8	P8
Patient 1	0.075	0.120	0.137	0.165	0.112	0.108	0.079	0.272	0.106	0.200	0.137	0.137	0.149	0.407	0.226	0.147	0.160	0.203	0.263	0.152	0.060	0.055	0.229	0.083	0.225	0.150	0.123	0.294
Patient 2	0.313	0.055	0.055	0.062	0.086	0.158	0.093	0.071	0.055	0.064	0.098	0.117	0.156	0.391	0.251	0.325	0.137	0.090	0.256	0.341	0.119	0.056	0.476	0.054	0.070	0.169	0.055	0.349
Patient 3	0.216	0.070	0.055	0.121	0.135	0.229	0.176	0.068	0.058	0.110	0.116	0.349	0.257	0.865	0.402	0.379	0.314	0.105	0.385	0.383	0.289	0.085	1.000	0.187	0.081	0.215	0.068	0.344
Patient 4	0.075	0.068	0.070	0.070	0.090	0.260	0.309	0.090	0.071	0.240	0.294	0.056	0.059	0.999	0.363	0.366	0.160	0.089	0.276	0.293	0.242	0.084	0.995	0.141	0.561	0.189	0.387	0.423
Patient 5	0.672	0.219	0.172	0.082	0.113	0.320	0.358	0.253	0.145	0.057	0.143	0.387	0.386	0.727	0.233	0.235	0.069	0.060	0.123	0.283	0.131	0.115	0.304	0.098	0.132	0.754	0.698	0.966
Patient 6	0.277	0.057	0.055	0.059	0.148	0.316	0.369	0.076	0.056	0.081	0.115	0.332	0.126	0.362	0.262	0.281	0.191	0.068	0.167	0.221	0.121	0.056	0.757	0.055	0.108	0.078	0.084	0.251
Patient 7	0.134	0.058	0.059	0.130	0.194	0.144	0.065	0.066	0.077	0.163	0.196	0.127	0.091	0.201	0.193	0.182	0.115	0.061	0.217	0.204	0.057	0.058	0.865	0.104	0.107	0.149	0.120	0.156
Patient 8	0.235	0.056	0.055	0.057	0.061	0.083	0.086	0.065	0.055	0.072	0.078	0.158	0.113	0.356	0.158	0.179	0.132	0.087	0.071	0.156	0.063	0.067	0.336	0.091	0.119	0.070	0.069	0.277
Avg	0.250	0.088	0.082	0.093	0.117	0.202	0.192	0.120	0.078	0.123	0.147	0.208	0.167	0.538	0.261	0.262	0.160	0.095	0.220	0.254	0.135	0.072	0.620	0.102	0.175	0.222	0.200	0.383
STD	0.192	0.057	0.046	0.040	0.042	0.092	0.132	0.088	0.032	0.069	0.069	0.127	0.106	0.286	0.082	0.090	0.072	0.046	0.098	0.084	0.087	0.021	0.320	0.044	0.163	0.221	0.228	0.249

TABLE VII

Compiled coherence results of the early gamma window when presented with a target cue post NFB

Ref :	F7							F1						F2					F8				P7			P3		P4
Subject	F1	F2	F8	P7	P3	P4	P8	F2	F8	P7	P3	P4	P8	F8	P7	P3	P4	P8	P7	P3	P4	P8	P3	P4	P8	P4	P8	P8
Patient 1	0.314	0.117	0.064	0.222	0.123	0.307	0.366	0.130	0.055	0.070	0.068	0.353	0.317	0.276	0.308	0.314	0.134	0.070	0.190	0.232	0.099	0.055	0.782	0.109	0.320	0.083	0.258	0.325
Patient 2	0.375	0.071	0.066	0.105	0.112	0.250	0.280	0.215	0.055	0.142	0.144	0.252	0.292	0.369	0.272	0.311	0.176	0.199	0.261	0.327	0.117	0.058	0.386	0.082	0.055	0.228	0.073	0.364
Patient 3	0.386	0.055	0.055	0.055	0.091	0.159	0.123	0.057	0.055	0.102	0.248	0.336	0.240	0.520	0.377	0.360	0.117	0.064	0.282	0.273	0.070	0.055	0.879	0.056	0.114	0.085	0.055	0.661
Patient 4	0.363	0.277	0.306	0.072	0.141	0.386	0.178	0.141	0.350	0.186	0.112	0.408	0.218	0.367	0.265	0.136	0.323	0.055	0.265	0.136	0.323	0.055	0.742	0.336	0.207	0.091	0.114	0.114
Patient 5	0.912	0.055	0.061	0.293	0.128	0.375	0.341	0.079	0.096	0.135	0.143	0.408	0.383	0.785	0.122	0.374	0.241	0.235	0.119	0.345	0.177	0.236	0.224	0.088	0.094	0.741	0.800	1.000
Patient 6	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Patient 7	0.171	0.205	0.151	0.111	0.109	0.144	0.132	0.120	0.180	0.177	0.134	0.221	0.257	0.191	0.284	0.317	0.291	0.278	0.184	0.166	0.102	0.172	0.715	0.213	0.258	0.135	0.256	0.382
Patient 8	0.765	0.055	0.062	0.073	0.110	0.150	0.109	0.061	0.063	0.369	0.369	0.369	0.369	0.919	0.250	0.247	0.131	0.134	0.254	0.261	0.155	0.135	0.392	0.065	0.197	0.083	0.064	0.337
Avg	0.469	0.119	0.109	0.133	0.116	0.253	0.219	0.115	0.122	0.169	0.174	0.335	0.296	0.490	0.268	0.294	0.202	0.148	0.222	0.249	0.149	0.109	0.589	0.136	0.178	0.206	0.231	0.455
STD	0.266	0.088	0.093	0.090	0.016	0.106	0.109	0.055	0.110	0.097	0.102	0.073	0.063	0.270	0.077	0.081	0.083	0.090	0.059	0.077	0.085	0.073	0.250	0.103	0.095	0.241	0.265	0.289

TABLE VIII

Compiled coherence results of the early gamma window when presented with a non-target cue pre NFB.

Ref:	F7							F1						F2					F8				P7			P3		P4
Subject	F1	F2	F8	P7	P3	P4	P8	F2	F8	P7	P3	P4	P8	F8	P7	P3	P4	P8	P7	P3	P4	P8	P3	P4	P8	P4	P8	P8
Patient 1	0.081	0.055	0.055	0.055	0.055	0.099	0.057	0.121	0.055	0.096	0.055	0.055	0.070	0.392	0.309	0.076	0.055	0.055	0.288	0.083	0.055	0.055	0.081	0.074	0.209	0.055	0.055	0.265
Patient 2	0.292	0.062	0.054	0.097	0.123	0.137	0.086	0.145	0.055	0.087	0.105	0.114	0.082	0.390	0.281	0.260	0.082	0.060	0.232	0.237	0.070	0.055	0.766	0.055	0.097	0.126	0.055	0.279
Patient 3	0.344	0.059	0.055	0.098	0.113	0.188	0.170	0.055	0.055	0.125	0.143	0.351	0.224	0.926	0.373	0.362	0.175	0.055	0.366	0.352	0.160	0.055	1.000	0.189	0.055	0.243	0.055	0.293
Patient 4	0.062	0.055	0.056	0.068	0.107	0.235	0.251	0.228	0.088	0.324	0.309	0.055	0.056	0.969	0.373	0.379	0.133	0.056	0.259	0.295	0.167	0.055	0.919	0.109	0.336	0.160	0.290	0.576
Patient 5	0.475	0.211	0.131	0.055	0.055	0.310	0.295	0.146	0.103	0.176	0.055	0.386	0.342	0.499	0.166	0.242	0.104	0.068	0.110	0.288	0.201	0.138	0.341	0.086	0.062	0.156	0.111	0.744
Patient 6	0.059	0.096	0.055	0.055	0.096	0.188	0.077	0.111	0.056	0.059	0.064	0.156	0.077	0.382	0.202	0.331	0.211	0.055	0.158	0.240	0.131	0.055	0.718	0.055	0.229	0.060	0.185	0.137
Patient 7	0.055	0.055	0.055	0.188	0.204	0.060	0.055	0.054	0.055	0.237	0.265	0.112	0.055	0.341	0.310	0.258	0.056	0.055	0.251	0.273	0.059	0.055	0.847	0.073	0.057	0.097	0.055	0.160
Patient 8	0.250	0.055	0.055	0.056	0.070	0.160	0.106	0.056	0.055	0.056	0.056	0.187	0.174	0.298	0.133	0.158	0.074	0.087	0.073	0.089	0.054	0.081	0.338	0.082	0.080	0.068	0.076	0.378
Avg	0.202	0.081	0.065	0.084	0.103	0.172	0.137	0.114	0.065	0.145	0.131	0.177	0.135	0.525	0.269	0.258	0.111	0.061	0.217	0.232	0.112	0.069	0.626	0.090	0.141	0.121	0.110	0.354
STD	0.161	0.054	0.027	0.046	0.049	0.078	0.092	0.060	0.019	0.095	0.101	0.127	0.104	0.267	0.091	0.103	0.057	0.011	0.097	0.097	0.060	0.029	0.330	0.044	0.105	0.064	0.086	0.208

TABLE IX

Compiled coherence results of the early gamma window when presented with a non-target cue post NFB

Ref:	F7							F1						F2					F8				P7			P3		P4
Subject	F1	F2	F8	P7	P3	P4	P8	F2	F8	P7	P3	P4	P8	F8	P7	P3	P4	P8	P7	P3	P4	P8	P3	P4	P8	P4	P8	P8
Patient 1	0.209	0.055	0.055	0.105	0.057	0.293	0.228	0.058	0.055	0.055	0.055	0.274	0.256	0.513	0.150	0.206	0.125	0.055	0.143	0.168	0.068	0.055	0.383	0.089	0.377	0.055	0.157	0.291
Patient 2	0.357	0.055	0.055	0.055	0.072	0.208	0.209	0.098	0.055	0.076	0.082	0.141	0.190	0.636	0.152	0.200	0.093	0.132	0.108	0.167	0.139	0.059	0.531	0.118	0.083	0.213	0.071	0.379
Patient 3	0.381	0.055	0.055	0.089	0.167	0.242	0.081	0.056	0.056	0.167	0.314	0.372	0.152	0.745	0.352	0.335	0.255	0.054	0.263	0.211	0.164	0.063	0.781	0.097	0.055	0.324	0.055	0.359
Patient 4	0.705	0.100	0.109	0.127	0.227	0.363	0.064	0.064	0.119	0.140	0.214	0.397	0.121	0.462	0.330	0.284	0.055	0.056	0.373	0.333	0.171	0.114	0.990	0.075	0.314	0.055	0.208	0.365
Patient 5	0.923	0.060	0.075	0.377	0.055	0.353	0.339	0.055	0.058	0.309	0.055	0.408	0.383	0.815	0.056	0.276	0.243	0.207	0.065	0.219	0.308	0.316	0.316	0.280	0.255	0.086	0.089	1.000
Patient 6	0.357	0.055	0.055	0.142	0.159	0.139	0.129	0.139	0.067	0.177	0.143	0.145	0.203	0.362	0.325	0.276	0.081	0.070	0.306	0.342	0.077	0.065	0.386	0.072	0.247	0.061	0.057	0.352
Patient 7	0.969	0.540	0.404	0.893	0.951	0.417	0.792	0.763	0.543	0.986	0.892	0.538	0.806	0.953	0.715	0.573	0.931	0.614	0.581	0.513	0.813	0.396	0.977	0.361	0.871	0.288	0.974	0.535
Patient 8	0.201	0.059	0.055	0.058	0.068	0.157	0.100	0.067	0.056	0.159	0.118	0.147	0.151	0.788	0.229	0.233	0.224	0.171	0.145	0.144	0.194	0.115	0.370	0.104	0.105	0.147	0.058	0.234
Avg	0.513	0.122	0.108	0.231	0.219	0.272	0.243	0.163	0.126	0.259	0.234	0.303	0.283	0.659	0.289	0.298	0.251	0.170	0.248	0.262	0.242	0.148	0.592	0.150	0.288	0.153	0.209	0.439
STD	0.309	0.169	0.121	0.287	0.302	0.101	0.240	0.244	0.170	0.304	0.280	0.149	0.227	0.201	0.202	0.120	0.286	0.189	0.171	0.126	0.242	0.133	0.282	0.109	0.262	0.109	0.314	0.242

TABLE X

Compiled coherence results of the late gamma window when presented with a target cue pre NFB.

Ref:	F7							F1						F2					F8				P7			P3		P4
Subject	F1	F2	F8	P7	P3	P4	P8	F2	F8	P7	P3	P4	P8	F8	P7	P3	P4	P8	P7	P3	P4	P8	P3	P4	P8	P4	P8	P8
Patient 1	0.153	0.115	0.065	0.060	0.074	0.098	0.088	0.208	0.134	0.162	0.055	0.189	0.174	0.517	0.355	0.231	0.189	0.082	0.223	0.144	0.138	0.110	0.187	0.079	0.217	0.115	0.116	0.375
Patient 2	0.251	0.055	0.055	0.090	0.116	0.196	0.096	0.097	0.055	0.085	0.092	0.108	0.109	0.441	0.257	0.305	0.112	0.058	0.266	0.301	0.072	0.055	0.390	0.055	0.076	0.180	0.055	0.352
Patient 3	0.153	0.055	0.055	0.082	0.104	0.179	0.191	0.055	0.055	0.085	0.091	0.257	0.197	0.863	0.357	0.364	0.268	0.055	0.375	0.375	0.254	0.055	1.000	0.320	0.057	0.343	0.055	0.287
Patient 4	0.122	0.087	0.093	0.133	0.139	0.225	0.168	0.231	0.093	0.292	0.306	0.061	0.092	0.980	0.330	0.340	0.252	0.073	0.165	0.181	0.311	0.069	0.999	0.162	0.473	0.133	0.351	0.402
Patient 5	0.617	0.257	0.157	0.091	0.173	0.367	0.386	0.271	0.077	0.072	0.245	0.500	0.571	0.731	0.206	0.176	0.085	0.065	0.160	0.340	0.160	0.093	0.268	0.071	0.080	0.805	0.762	0.989
Patient 6	0.133	0.067	0.056	0.064	0.118	0.332	0.369	0.082	0.055	0.077	0.086	0.237	0.128	0.363	0.172	0.255	0.171	0.055	0.191	0.274	0.118	0.055	0.737	0.055	0.202	0.068	0.108	0.251
Patient 7	0.085	0.055	0.064	0.073	0.122	0.100	0.059	0.063	0.075	0.311	0.289	0.071	0.058	0.180	0.159	0.195	0.090	0.110	0.193	0.190	0.129	0.067	0.901	0.064	0.067	0.074	0.071	0.086
Patient 8	0.337	0.055	0.056	0.066	0.093	0.143	0.085	0.068	0.055	0.072	0.117	0.180	0.099	0.348	0.101	0.174	0.182	0.067	0.177	0.150	0.117	0.077	0.319	0.087	0.107	0.063	0.124	0.333
Avg	0.231	0.093	0.075	0.082	0.117	0.205	0.180	0.134	0.075	0.144	0.160	0.200	0.178	0.553	0.242	0.255	0.168	0.071	0.219	0.244	0.162	0.073	0.600	0.112	0.160	0.223	0.205	0.384
STD	0.176	0.070	0.035	0.024	0.030	0.100	0.130	0.087	0.028	0.101	0.102	0.141	0.165	0.278	0.098	0.074	0.070	0.018	0.072	0.090	0.079	0.020	0.345	0.091	0.141	0.252	0.244	0.264

TABLE XI

Compiled coherence results of the late gamma window when presented with a target cue post NFB

Ref:	F7							F1						F2					F8				P7			P3		P4
Subject	F1	F2	F8	P7	P3	P4	P8	F2	F8	P7	P3	P4	P8	F8	P7	P3	P4	P8	P7	P3	P4	P8	P3	P4	P8	P4	P8	P8
Patient 1	0.305	0.063	0.075	0.172	0.093	0.227	0.279	0.113	0.071	0.099	0.113	0.295	0.275	0.303	0.178	0.266	0.198	0.062	0.151	0.141	0.070	0.061	0.633	0.129	0.355	0.144	0.225	0.259
Patient 2	0.384	0.066	0.058	0.060	0.097	0.294	0.205	0.120	0.055	0.093	0.090	0.234	0.299	0.383	0.280	0.312	0.165	0.159	0.180	0.256	0.104	0.060	0.384	0.055	0.059	0.097	0.055	0.392
Patient 3	0.365	0.055	0.055	0.075	0.094	0.219	0.118	0.083	0.055	0.087	0.201	0.368	0.201	0.741	0.360	0.380	0.241	0.059	0.285	0.291	0.154	0.055	0.807	0.055	0.057	0.117	0.055	0.419
Patient 4	0.408	0.248	0.210	0.065	0.079	0.390	0.252	0.199	0.346	0.217	0.135	0.412	0.238	0.369	0.272	0.209	0.246	0.071	0.272	0.209	0.246	0.071	0.914	0.342	0.254	0.149	0.204	0.204
Patient 5	0.985	0.057	0.055	0.383	0.274	0.560	0.566	0.074	0.057	0.310	0.229	0.609	0.500	0.801	0.115	0.366	0.209	0.216	0.151	0.381	0.206	0.214	0.172	0.152	0.171	0.787	0.775	1.000
Patient 6	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Patient 7	0.182	0.203	0.187	0.080	0.139	0.135	0.199	0.198	0.108	0.277	0.187	0.291	0.311	0.185	0.303	0.241	0.170	0.316	0.190	0.198	0.172	0.110	0.670	0.141	0.154	0.192	0.229	0.351
Patient 8	0.715	0.060	0.055	0.085	0.134	0.123	0.097	0.057	0.058	0.369	0.369	0.369	0.369	0.943	0.125	0.209	0.126	0.134	0.150	0.255	0.149	0.108	0.386	0.060	0.306	0.093	0.092	0.303
Avg	0.478	0.107	0.099	0.131	0.130	0.278	0.245	0.121	0.107	0.207	0.189	0.368	0.313	0.532	0.233	0.283	0.194	0.145	0.197	0.247	0.157	0.097	0.567	0.133	0.194	0.226	0.234	0.418
STD	0.276	0.082	0.069	0.117	0.067	0.154	0.156	0.057	0.107	0.116	0.094	0.122	0.098	0.291	0.094	0.071	0.043	0.095	0.058	0.076	0.059	0.056	0.263	0.101	0.116	0.250	0.251	0.267

TABLE XII

Compiled coherence results of the late gamma window when presented with a non-target cue pre NFB.

Ref:	F7							F1						F2					F8				P7			P3		P4
Subject	F1	F2	F8	P7	P3	P4	P8	F2	F8	P7	P3	P4	P8	F8	P7	P3	P4	P8	P7	P3	P4	P8	P3	P4	P8	P4	P8	P8
Patient 1	0.106	0.055	0.055	0.055	0.055	0.092	0.077	0.104	0.055	0.086	0.055	0.091	0.107	0.515	0.305	0.122	0.055	0.055	0.228	0.107	0.070	0.055	0.148	0.070	0.164	0.055	0.055	0.268
Patient 2	0.328	0.071	0.055	0.075	0.092	0.160	0.078	0.176	0.061	0.104	0.081	0.111	0.097	0.388	0.250	0.320	0.106	0.057	0.213	0.323	0.094	0.055	0.627	0.055	0.072	0.074	0.055	0.286
Patient 3	0.342	0.054	0.054	0.090	0.103	0.220	0.210	0.055	0.055	0.081	0.090	0.332	0.197	0.936	0.384	0.374	0.205	0.055	0.388	0.367	0.200	0.055	1.000	0.340	0.059	0.368	0.055	0.283
Patient 4	0.063	0.065	0.075	0.055	0.078	0.128	0.251	0.163	0.088	0.235	0.218	0.055	0.055	0.977	0.300	0.352	0.099	0.055	0.203	0.255	0.113	0.055	0.862	0.097	0.324	0.178	0.260	0.613
Patient 5	0.391	0.247	0.177	0.055	0.055	0.355	0.310	0.226	0.157	0.276	0.055	0.383	0.345	0.774	0.128	0.210	0.058	0.055	0.072	0.270	0.125	0.063	0.315	0.107	0.064	0.141	0.109	0.872
Patient 6	0.074	0.103	0.062	0.064	0.080	0.142	0.055	0.128	0.062	0.068	0.093	0.258	0.067	0.378	0.230	0.302	0.189	0.055	0.176	0.267	0.113	0.055	0.731	0.055	0.146	0.061	0.103	0.123
Patient 7	0.055	0.055	0.055	0.100	0.137	0.074	0.055	0.055	0.054	0.222	0.210	0.073	0.055	0.367	0.273	0.260	0.058	0.077	0.269	0.270	0.080	0.067	0.802	0.055	0.055	0.126	0.055	0.147
Patient 8	0.303	0.055	0.055	0.062	0.104	0.097	0.056	0.083	0.055	0.059	0.057	0.234	0.108	0.329	0.088	0.222	0.137	0.072	0.077	0.112	0.077	0.113	0.352	0.055	0.063	0.094	0.055	0.355
Avg	0.208	0.088	0.074	0.069	0.088	0.158	0.136	0.124	0.073	0.141	0.107	0.192	0.129	0.583	0.245	0.270	0.113	0.060	0.203	0.247	0.109	0.065	0.605	0.104	0.118	0.137	0.094	0.368
STD	0.145	0.066	0.042	0.017	0.027	0.092	0.104	0.061	0.036	0.088	0.068	0.126	0.099	0.270	0.097	0.084	0.059	0.009	0.102	0.092	0.042	0.020	0.301	0.097	0.093	0.102	0.071	0.253

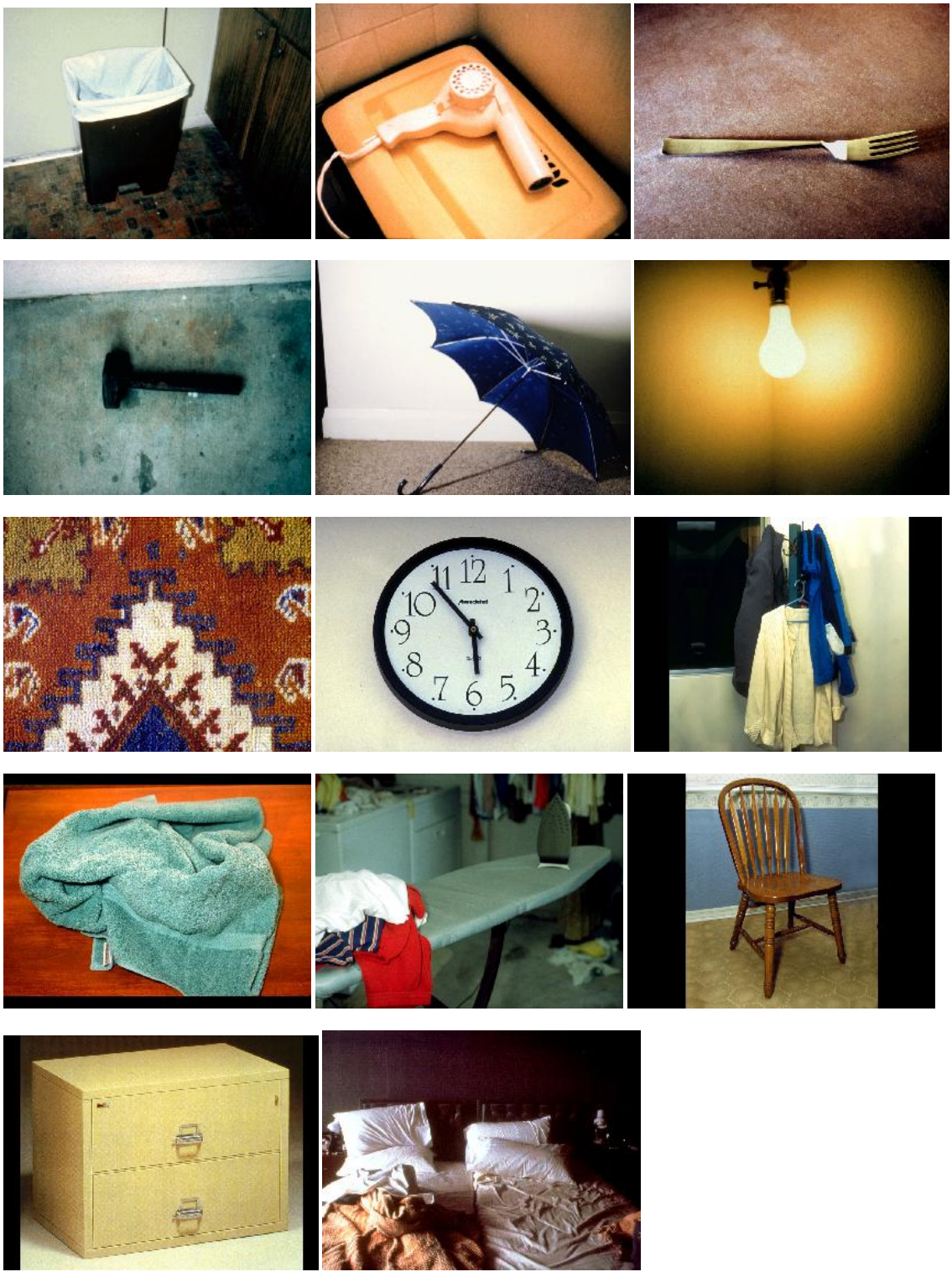
TABLE XIII

Compiled coherence results of the late gamma window when presented with a non-target cue post NFB

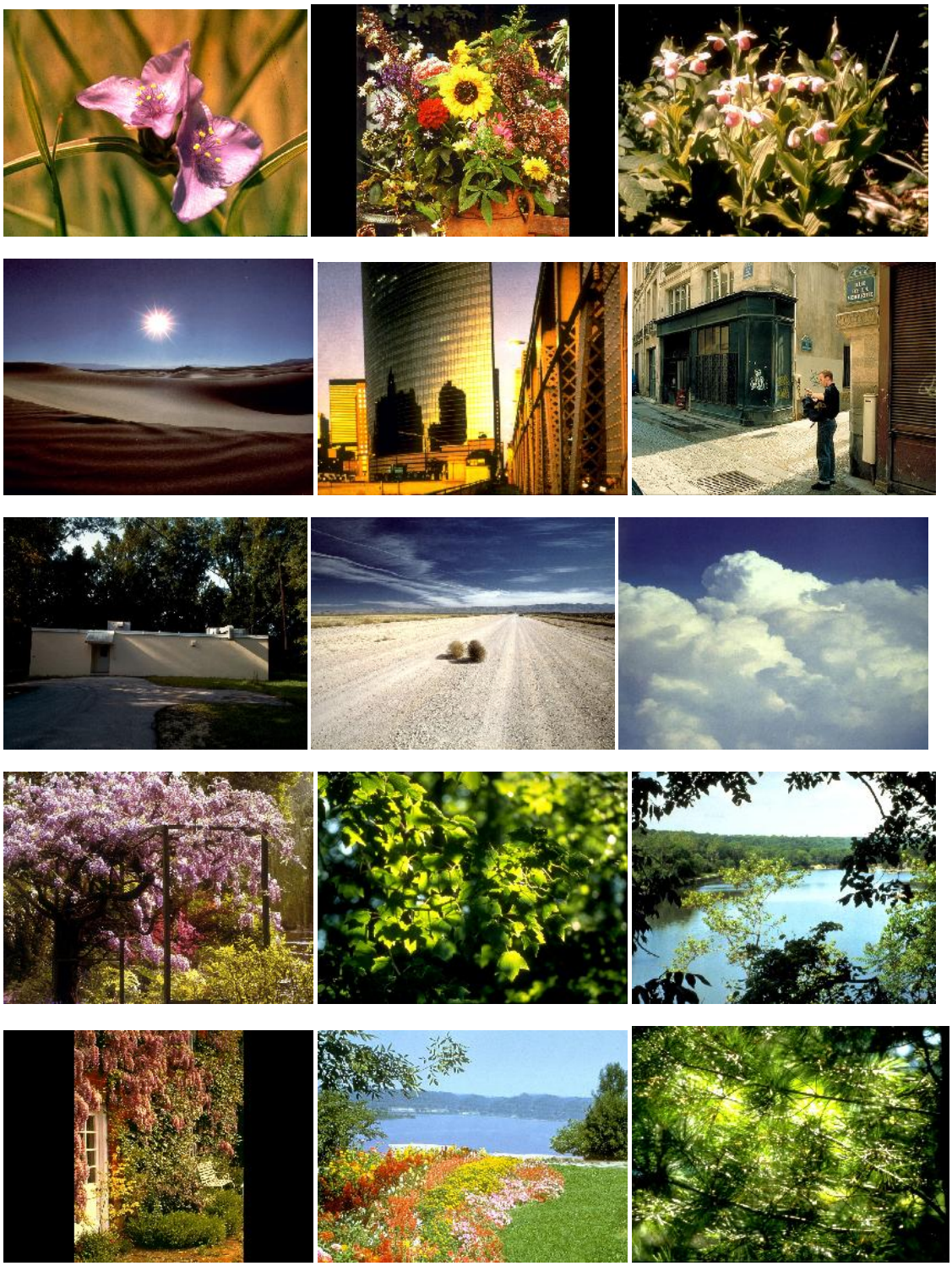
Ref:	F7							F1						F2					F8				P7			P3		P4
Subject	F1	F2	F8	P7	P3	P4	P8	F2	F8	P7	P3	P4	P8	F8	P7	P3	P4	P8	P7	P3	P4	P8	P3	P4	P8	P4	P8	P8
Patient 1	0.165	0.055	0.055	0.062	0.056	0.271	0.178	0.060	0.055	0.055	0.055	0.214	0.245	0.738	0.147	0.232	0.060	0.055	0.177	0.219	0.063	0.055	0.385	0.114	0.372	0.055	0.217	0.304
Patient 2	0.366	0.055	0.055	0.058	0.078	0.172	0.132	0.055	0.055	0.096	0.067	0.197	0.160	0.747	0.195	0.143	0.087	0.087	0.165	0.152	0.091	0.060	0.591	0.105	0.088	0.168	0.116	0.382
Patient 3	0.375	0.055	0.055	0.088	0.162	0.283	0.129	0.065	0.055	0.162	0.312	0.369	0.166	0.665	0.363	0.311	0.216	0.055	0.259	0.198	0.146	0.055	0.803	0.064	0.079	0.284	0.055	0.321
Patient 4	0.626	0.262	0.127	0.110	0.164	0.377	0.134	0.111	0.295	0.091	0.123	0.568	0.264	0.460	0.322	0.278	0.064	0.079	0.369	0.301	0.105	0.089	0.897	0.198	0.252	0.102	0.226	0.470
Patient 5	0.859	0.057	0.061	0.377	0.057	0.313	0.279	0.065	0.105	0.225	0.058	0.373	0.323	0.813	0.068	0.213	0.310	0.298	0.097	0.275	0.248	0.330	0.282	0.141	0.128	0.155	0.166	1.000
Patient 6	0.367	0.059	0.064	0.079	0.137	0.134	0.253	0.106	0.100	0.120	0.143	0.097	0.277	0.366	0.306	0.349	0.100	0.136	0.260	0.277	0.159	0.230	0.363	0.075	0.305	0.058	0.094	0.342
Patient 7	0.782	0.279	0.780	0.633	0.813	0.600	0.549	0.814	0.776	0.924	0.741	0.587	0.755	0.973	0.783	0.732	0.950	0.727	0.958	0.430	0.848	0.483	0.761	0.406	0.812	0.770	0.639	0.495
Patient 8	0.296	0.055	0.054	0.057	0.054	0.259	0.164	0.078	0.062	0.171	0.145	0.232	0.279	0.805	0.283	0.332	0.080	0.104	0.239	0.198	0.071	0.070	0.380	0.073	0.110	0.098	0.055	0.274
Avg	0.479	0.110	0.157	0.183	0.190	0.301	0.227	0.169	0.188	0.231	0.206	0.330	0.308	0.696	0.308	0.324	0.233	0.193	0.316	0.256	0.216	0.172	0.558	0.147	0.268	0.211	0.196	0.448
STD	0.247	0.099	0.253	0.211	0.256	0.143	0.142	0.261	0.251	0.285	0.232	0.178	0.189	0.197	0.216	0.178	0.303	0.230	0.272	0.086	0.262	0.161	0.237	0.113	0.245	0.237	0.191	0.236

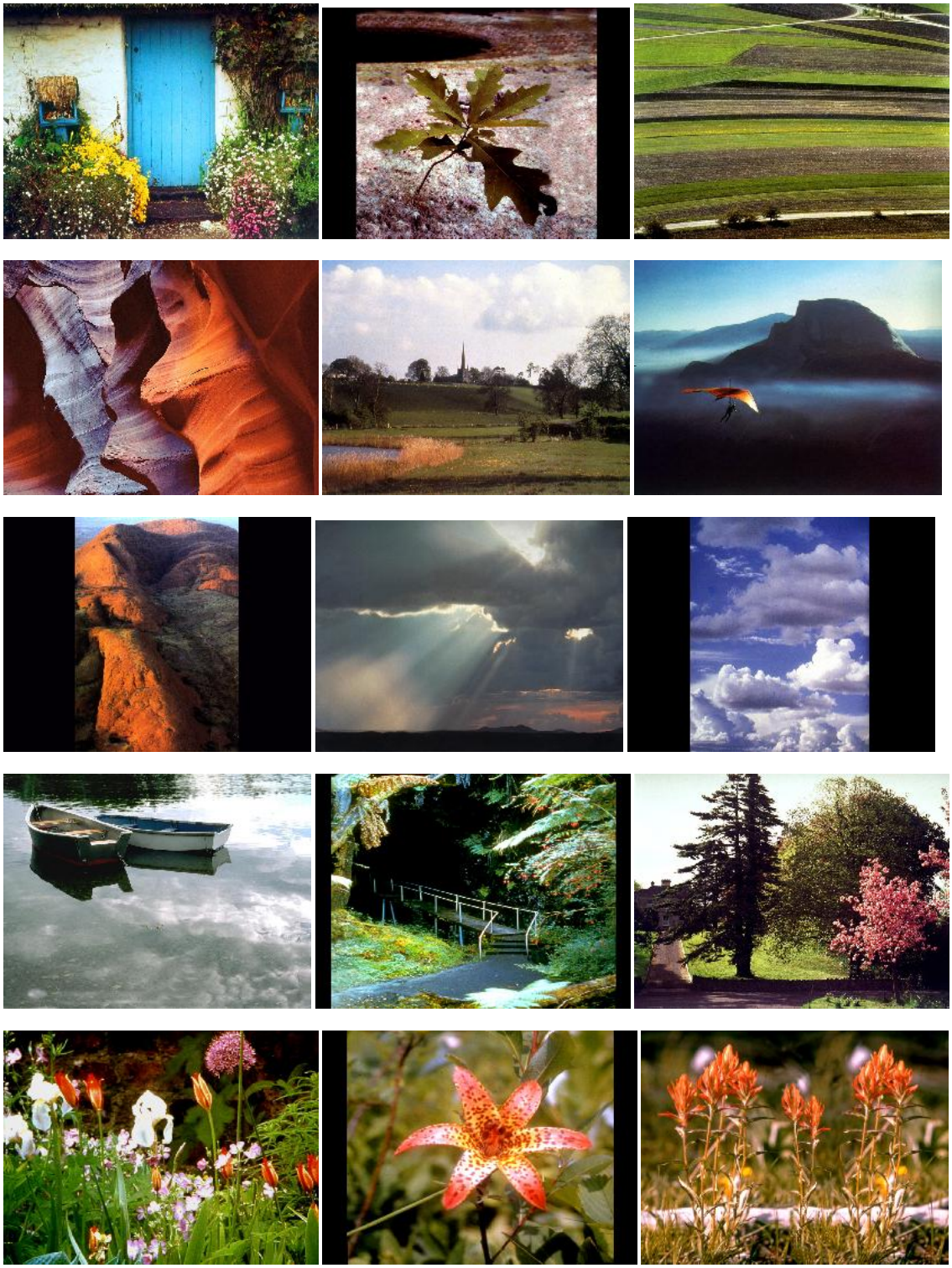
Appendix III: Additional Cue Reactivity Images

i.) Neutral Household Images:



ii.) Neutral Nature Images:





iii.) Drug Images: