EEG coherence effects of audio-visual stimulation (AVS) at dominant and twice dominant alpha frequency

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SUMMARY. The effects of a single session of audio-visual stimulation (AVS) at the dominant alpha rhythm and twice-dominant alpha frequency on EEG coherence were studied in 23 subjects. An eyes-closed baseline EEG determined each subject's dominant alpha frequency. Subjects were stimulated at their dominant alpha frequency or at twice dominant alpha frequency for twenty minutes, while EEG was recorded in 5-minute intervals. A post-session baseline was recorded 30 minutes after each session. AVS decreased coherence in the intrahemispheric projections from the occipital region and the parietal midline, and generally increased coherence, with few exceptions, among all other longitudinal pairs. Interhemispheric coherence increased posteriorily and high frequencies, and tended to decrease frontally and low frequencies. Alpha AVS was more effective than twice-alpha AVS at producing interhemispheric synchronization, and tended to produce more effects overall. Although main effects of frequency and time were observed, when individual coherence pairs changed, they almost always changed in only one direction. Overall coherence was greater during the first ten minutes than the last ten minutes, and greatest in the beta 1 and delta 2 bands, and lowest in the alpha and delta 1 bands. Few, if any, significant effects persisted into the post-stimulation baseline. A new method of assessing the effects of multiple comparisons on experimentwise error, based on randomization theory, is proposed and implemented.

INTRODUCTION

The ability of a flashing light stimulus to evoke EEG rhythms related to the stimulus frequency has been studied since the early history of electroencephalography (Adrian & Matthews, 1934). Known as the *photic driving response* (PDR), or *steady state visual evoked potential*, this effect is commonly measured in routine clinical EEG examinations, and has been proven useful for investigating neurological disorders (Takahashi, 1987; Coull & Pedley, 1978; Duffy, Iyer, & Surwillo, 1989).

The diverse perceptual and emotional effects of photic stimulation (Walter & Walter, 1949; Stwertka, 1993; Gizycki, Jean-Louis, Snyder, Zizi, Green et al., 1998), and it's ability to cause seizures in susceptible individuals (Walter, Dovey & Shipton, 1946; Striano, Meo, Bilo, Ruosi, Soricellis et al., 1992) have led many to investigate whether rhythmic auditory and visual stimulation (AVS) might also induce clinically beneficial changes in brain activity. In the 1950's and 60's, many studies focused on the ability of AVS to induce relaxation and hypnosis (reviewed in Morse, 1993). Others have reported AVS to be effective for relieving a diversity of pain symptoms (Solomon, 1985; Anderson, 1989; Shealy, Cady, Cox, Liss et al., 1990), treating dental anxiety (Morse, 1993), premenstrual syndrome (Noton, 1997), fibromyalgia (Mueller, Donaldson, Nelson & Layman, 2001) and for alleviating the cognitive dysfunctions associated with closed head injury (Montgomery, Ashley, Burns & Russell, 1994) and strokes (Russell, 1997; Rozelle & Budzinski, 1995). Since the enhancement of beta (13-21 Hz) and inhibition of theta (4-8 Hz) is a goal of EEG biofeedback for the treatment of attention deficit hyperactivity disorder (ADHD; Lubar & Lubar, 1999; Lubar, Swartwood, Swartwood & O'Donnell, 1995), some have proposed using AVS in neurofeedback as a "priming stimulus" to encourage the endogenous production of desired cortical frequencies, which are then reinforced as the conditioned response. In a study of 25 ADHD children, Patrick (1996) found "photic-driven EEG neurotherapy" effective in improving cognitive, behavioral, and clinical EEG measures in less than half the number of sessions usually required. Meanwhile, Micheletti (1999) found AVS alone effective in improving cognitive and behavioral measures, in a study of 99 ADHD children. Carter and Russell (1993) reported significant improvement in cognitive and behavioral functioning, related to the number of AVS sessions, in learning disabled boys. Joyce and Siever (2000) reported that a 7-week audiovisual stimulation treatment in 8 reading-disabled children, compared to a control group, normalized scores on the Test of Variables of Attention (TOVA), improved scores on the Standardized Test for the Assessment of Reading (STAR), and improved general behavior as noted by teachers and parents.

Mechanisms by which long-term AVS therapies may cause these behavioral changes have been suggested by research in neuronal plasticity. A number of investigators (van Praag, Kempermann & Gage, 2000; Rosenzweig, 2003; Mohammed, Zhu, Darmopil, Hjerling-Leffler, Ernfors et al., 2002) are in essential agreement that ongoing direct experience that evokes persistent neuronal activation alters brain structure and brain functioning. Although most studies have focused on effects of an enriched environment, persistent neuronal activation can also be evoked by trains of sensory stimuli. Human subjects have been shown to respond to flicker frequencies from 1-100 Hz with steady-state activity at all frequencies up to at least 90 Hz with clear resonance phenomena or harmonics at 10, 20, 40 and 80 Hz (Herrmann, 2001). A possible linkage

between steady-state stimulation induced neuronal activation and neuronal plasticity is the increasing evidence that brain electrical activity regulates the synthesis, secretion and actions of neurotrophins (Schindler and Poo, 2000), which promote synaptogenesis.

The most commonly studied PDRs have been the effects of stimulation on alpha (8-13 Hz) power over the occipital region (Iwahara, Noguchi, Yang & Oishi, 1974; Aranibar & Pfurtscheller, 1978). The photic driving response is most reliable when the stimulus approximates the subject's peak alpha frequency (Toman, 1941; Townsend, Lubin, & Naitoh, 1975). However, recent studies have shown that AVS activates a diverse range of EEG frequencies, beyond the primary sensory cortices, and outside of the frequency of stimulation. Using low-frequency theta AVS, Dieter & Weinstein (1995) described a significant reduction in "mean activity" (an increase of delta and theta activity) in frontal, central, and parietal regions, in addition to occipital regions. In a study of 13 college students (Timmermann, Lubar, Rasey & Frederick, 1999), we found that effects of AVS were widely distributed across the standard 10-20, 19-channel montage. AVS at a subject's dominant alpha frequency had no effect in the alpha band, but significantly increased power in the delta 1, delta 2, theta, beta 1, and beta 2 bands. Stimulation at twice the dominant alpha frequency significantly increased theta, alpha, beta 1, and beta 2 power.

While the amplitude and power effects of AVS have been widely studied, relatively little is known about the effects of AVS on EEG coherence. Coherence is a correlational measure, varying between zero and one, of the variability in phase between two signals over time (Shaw, 1981). This frequency-specific signal correlation suggests the extent to which two regions are cooperating on the same task. High coherence indicates a common signal, whether it is synchronous between two locations, or delayed by a constant conduction velocity. Coherence in the eyes-closed baseline reflects the number of synaptic connections between recording sites, and the strength of these connections (Thatcher, 1992). Coherence has been shown to be lower in Alzheimer patients, comatose subjects, and in brain-injured subjects, while it is higher in mentally retarded persons, during sleep, and during epileptic seizures. Between these extremes, "optimal levels" of coherence for normal functioning have been described (Silberstein, 1995). Some have suggested that EEG coherence biofeedback could be used to normalize the coherence deviations seen in dyslexic and head injured subjects (Evans & Park, 1996; Hoffman, Stockdale, Hicks & Schwaninger, 1995).

Differences in photic driving of coherence have been described between normal subjects and patients with Alzheimer's disease (Wada, Nanbu, Kikuchi, Koshino, Hashimoto et al., 1998a), schizophrenia (Wada, Nanbu, Kikuchi, Koshino & Hashimoto, 1998b), and between genders (Wada, Nanbu, Kadoshima & Jiang, 1996). However, the effects of combined auditory and visual stimulation on coherence in normal subjects have not been previously reported.

Although AVS devices are used by many neurotherapists as an adjunct to EEG biofeedback, the overall pattern of effects of AVS on coherence needs to be better understood, to ensure that AVS treatment is influencing coherence in the appropriate direction. To begin to achieve this understanding, we conducted an exploratory study of the effects of AVS on coherence in normal college students. We hypothesized that AVS would increase coherence at the frequency of stimulation, and assumed that effects would be most prominent over the occipital and temporal leads, which are closest to the primary

visual and auditory cortex. Given our previous findings of increased amplitude in multiple frequency bands (Timmermann et al., 1999), we anticipated effects across the coherence spectrum. However, since our goal was to observe the effects rather than to verify any hypothesis about them, beyond the expected increase at the stimulus frequencies, we did not predict directions of change.

METHODS

Participants. This study was a reanalysis, in terms of coherence, of data previously analyzed and reported in terms of power (Timmermann et al., 1999). However, in this study, ten additional participants were added to each stimulation condition. Participants (11 male and 22 female) were recruited from the undergraduate and graduate populations of the University of Tennessee, Knoxville. Participants ranged in age from 20-45 years, with a mean of 25 years. All participants reported no previous history of epilepsy, learning disabilities, attention deficit disorder, or mental illnesses during personal screening interviews. Participants self-reported that they were free of medication use during the study.

Apparatus. Audio-visual stimulation was provided by a Polysync Pro (Synetic Systems) device. This unit consisted of headphones and a pair of "photoscopic" glasses that were connected to a small, portable unit that was programmed to provide specified levels of visual and auditory stimulation. The glasses had eight light emitting diodes (LEDs), four per side, arranged in a cross pattern. The LEDs were situated approximately 1.5 cm from the eyes, and each emitted red light at .166 candle power at the frequencies employed. Audio stimulation consisted of a cycled tone with a pitch of 185 Hz, presented to both ears simultaneously, with a duty cycle of 50% and a loudness level of approximately 77 dB(A scale) for the alpha condition and 81 dB(A scale) for the beta condition. Both auditory and visual stimulation were sinusoidally modulated (Townshend et al., 1975). The Polysync Pro equipment was tested for and did not produce any detectable electrical interference in our EEG recordings (Timmermann et al, 1999).

Procedures. The first thirteen participants came to the laboratory on two different occasions for AVS sessions. These sessions were at least two weeks apart to minimize carry-over effects. The presentation of the AVS condition was counter-balanced; during the first AVS session six of the participants experienced alpha stimulation and seven experienced twice-dominant alpha ("beta") stimulation. For the second session, those who experienced alpha stimulation during the first session received beta stimulation, and those who experienced beta stimulation first received alpha stimulation. The additional twenty participants were randomly assigned to either an alpha AVS or beta AVS group, as part of an experiment measuring the effects of multiple sessions of AVS (Timmermann, 1999). Only results from the first session of this experiment are included in this analysis. The two groups were counterbalanced for age and gender, and did not differ significantly with respect to dominant alpha frequency. The mixing of subjects from both repeated measures and independent groups designs in the present study might compromise the validity of some inferences about the differences between the two stimulation conditions. However, both experimental designs have advantages and risks for detecting such differences: repeated measures designs risk within-subject effects,

while independent group designs risk between-subject effects. We decided that this compromise was worth the increase in statistical power obtained for all other comparisons in this study.

The procedure was the same for either stimulation condition. Participants were seated upright in a plastic chair located in a sound-attenuated, dimly lit room for the EEG recordings. The headphones and glasses were placed over the electrode cap. All participants had an eyes-closed baseline EEG recorded for four minutes at the beginning of the session. This baseline recording was analyzed to determine each subject's dominant alpha frequency, defined as the peak power between 8 and 12 Hz at locations Pz and P4 as measured by power spectral analysis, rounded to the nearest 0.5 Hz. Participants were then provided AVS for 20 minutes, with EEG recording occurring simultaneously. For the alpha stimulation condition, participants were stimulated at their dominant alpha frequency. During the beta stimulation condition each participant received AVS at twice their dominant alpha frequency. Participants were instructed to close their eyes and relax during the 20-minute AVS. Thirty minutes after the stimulation session, a post-session eyes-closed EEG was recorded for 5 min.

EEG Recordings. Quantitative referential EEGs (monopolar montage) were recorded from 19 electrodes following the International 10-20 system for electrode placement, with linked earlobe references. All electrode impedances were below 5 KOhm. Recordings were made using an electrode cap (Electro Cap Inc.). Raw EEG was fed through 19 matched 7P511 pre-amplifiers (Grass Instrument Co.), with bandpass filters set to 0.5 - 100 Hz. A BMSI 12-bit A to D converter digitized the outputs of the amplifiers. Rhythm software (Stellate Systems) was employed to record the raw EEG. The sampling rate was set at 128 samples per second. Under Rhythm, when a sampling rate of 128 Hz is specified, the actual rate employed is oversampled at 256 Hz and each digitized point is replaced by a weighted sum of its neighbors. Every other point of this filtered data is written to disk as a 16 bit value. Signal aliasing was eliminated by the use of a 16 point FIR (finite impulse response) filter, with a sharp low pass cutoff set at 64 Hz and higher. Coherences were analyzed from the raw EEG off-line on a Pentium 233 processor using Rhythm software. Rhythm analysis employs Hanning windowing and cosine tapering of each selected four-second epoch. Eye-blinks, large eye movements, and all observable muscle artifacts were removed prior to analysis by a visual review of the EEG records. Tests of normality, ANOVAs, and sign rank tests were performed with Statistical Analysis Software (SAS Institute). Randomization tests were performed with custom algorithms written in PERL by the first author (available by request).

RESULTS

EEG data were analyzed via Fast-Fourier transformation to derive 8 interhemispheric and 55 longitudinal coherence pairings in each of six bandpasses (delta 1, 0.75-2 Hz; delta 2, 2-4 Hz; theta, 4-8 Hz; alpha, 8-12 Hz; beta 1, 13-21 Hz; and beta 2, 21-31 Hz). Each 20-minute AVS condition was analyzed in four 5-minute blocks (0-5 min, 5-10 min, 10-15 min, and 15-20 min) to examine changes over the course of stimulation. The post measure was a 5 minute EEG recording taken one half hour after the AVS session. Thus, there were six coherence measures per frequency bandpass in this

pilot study: baseline, 0-5 min, 5-10 min, 10-15 min, 15-20 min, and post.

These data were found to have a significantly non-normal distribution by the Kolmogorov-Smirnov test ($p<.01$), so it was determined that all inferential statistics would be performed on ranked data (Conover, 1980). Differences from the pre-stimulation baseline condition were calculated for each stimulation condition, and sorted and ranked by subject. A repeated measures analysis of variance on these data found significant main effects of time ($F=27.84$, $p<.0001$), electrode pairing ($F=41.28$, $p<.0001$), and frequency ($F=43.08$, $p<.0001$). Tukey's post-hoc procedure determined (at $p<.05$) that the overall coherence was higher during the first ten minutes (intervals 1 and 2) and the post-stimulation baseline than during the last ten minutes of stimulation (intervals 3 and 4). Tukey's procedure found three distinct frequency groupings (beta 1& delta 2 > theta & beta 2 > alpha & delta 1). The type of stimulation had no significant main effect (using the more conservative, independent groups ANOVA model; $F=3.03$, $p=.08$). However, interactions between stimulation type and frequency were observed ($F=18.23$, $p<.0001$). Alpha stimulation decreased overall coherence, compared to beta stimulation, in the alpha ($F=17.18$, $p<.0001$) and theta ($F=6.77$, $p<.0093$) bands. Beta stimulation decreased overall coherence, compared to alpha, in the delta 1 ($F=15.69$, $p<.0001$) and beta 2 ($F=40.43$, $p<.0001$) bands. There were no significant differences of stimulation type in the delta 2 and beta 1 bands.

The number of possible interactions of electrode pairing with other variables was considered too great to be approached practically with ANOVA methods and Tukey's procedure. Thus, the difference from baseline for each pairing location was tested for significance with Wilcoxon's sign rank test (at $p<=.01$). Since this procedure was performed on 3780 variables (2 stimtypes X 6 frequencies X 5 times X 63 pairing locations), under the null hypothesis, 3780 x .01 = 37.8 false-positive sign rank tests could be expected by random effects alone, whereas we actually observed 241 positive tests. Although it is highly unlikely that this ratio of signal-to-noise would arise by chance alone in 3780 independent experiments, these variables are highly interdependent. A principal components analysis revealed that at most, 19 independent factors explained 100% of the variance in these data. It is possible that the large number of significant variables is explained, not by the experimental conditions, but by random effects in only one or a few large underlying factors. To test whether this was the case, we constructed empirical distribution functions (EDFs) of the number of significant sign rank tests observed when the baseline was randomized with respect to the stimulation conditions, resampling each of 3780 sign-rank tests 1000 times with replacement. The rank of the actual observed number among the randomized trials (divided by 1000) was thus the probability of type I error (Edgington, 1987). To preserve the covariance relationships among variables, a single random decision determined whether the sign of the difference from baseline would be reversed for all variables for each subject, a total of 23 decisions per trial. The probability of 241 false-positive sign rank tests at $p<=.01$ arising by chance was thereby determined to be $p<.001$.

Similar comparisons demonstrated that a significant number of positive tests had been observed in each stimulation type, frequency, and time, with the exception of the post-stimulation baseline. When random EDFs were generated for each of the 19 electrode locations, the number of positive tests observed/expected was significant at $p<.01$ for most, and at $p<.05$ for all 19 locations. It was then of interest to see how each

of the 63 coherence pairs contributed to this pattern. Seventeen of these comparisons were significant at p<.01 (29 at p<.05). Table 1 shows the number of coherence changes for each variable (positive, negative, and total coherence changes), compared to the number that would be expected from experimentwise error.

The distribution of the positive vs. negative effects in table 1 supports the general findings of the ANOVAs: B1 and D2 had more positive changes than D1, and the first ten minutes had a higher ratio of positive-to-negative changes than the last ten minutes. Alpha and beta stimulation evoked roughly the same ratio of positive-to-negative changes, although alpha stimulation evoked a greater total number of changes. The anatomical distribution of this pattern became clear when plotted on graphical heads (using Vbmapper software; Frederick, 2001), as shown in figures 1 and 2. With few exceptions, the decreasing coherences were longitudinal projections from the occipital leads and Pz. The increasing coherences were always associated with the frontal poles, the interhemispheric pairings, and all the remaining longitudinal projections that did not involve O1, O2, or Pz. An interesting exception was that 4/4 of the significant frontal interhemispheric coherences (FP1FP2 and F7F8) decreased. This tendency toward decreasing frontal interhemispheric coherences became even more apparent at p<=.05. We found that the findings at p<=.05 showed a high degree of consistency with those at p<=.01, so these are also represented (with lighter, less saturated lines) in figures 1 and 2. Most remarkable was the observation that individual coherence pairing locations generally changed in only one direction, regardless of frequency, time, or type of stimulation. For example, the main effect of time appeared to be mediated by the decreasing number of increased frontal intrahemispheric coherences (from 25 in the first five minutes to 8 in the last five minutes), along with the increasing number of decreased posterior intrahemispheric coherences (from 18 to 26).

DISCUSSION

This study has demonstrated a number of anatomical asymmetries in the coherence effects of AVS. AVS decreased intrahemispheric coherences involving the posterior leads Pz, O1 and O2, but increased intrahemispheric coherence frontally and centrally. Meanwhile, the interhemispheric derivations increased posteriorly and at high frequencies, and tended to decrease frontally and at low frequencies. The overwhelming tendency of all the significant effects for a given electrode pair to go in the same direction independently of frequency, time, or type of stimulation, is another striking asymmetry. The segregation of these positive and negative changes into discrete anatomical compartments suggests that descriptions of "coherence" that omit discussion of location are somewhat oversimplified. The many significant decreases in coherence demonstrate that the popular naming and marketing of AVS devices as "brain wave synchronizers" (Morse, 1993) is also oversimplified.

Overall coherence was significantly lower during the last ten minutes of stimulation. During the first five minutes, the ratio of positive to negative changes was 40:18, which changed to 24:32 by the last five minutes. These results suggest that subjects were adapting or habituating to the effects of stimulation. The failure of the effects to persist into the post-stimulation baseline suggests a limitation to the use of

these devices as “stand-alone” treatments for influencing coherence. The AVS experience is essentially a passive one, and we would expect that more persistent effects would be observed if concurrent biofeedback were used to reinforce desired changes in the EEG. However, it is also possible that more persistent effects of AVS alone could be achieved with a variable-frequency stimulus paradigm or a larger number of sessions.

Our finding of a highly consistent inhibitory effect in the occipital intrahemispheric coherences stands in contrast with two recent studies of photic driving of coherence. Wada et al. compared the photic driving of coherence between Alzheimer patients and 10 normal participants (mean age 59; Wada et al., 1998a); and between schizophrenic patients and 30 normal participants (mean age 22.3; Wada et al., 1998b). Although comparisons with the baseline were not statistically tested, graphs comparing the subject groups showed that 5, 10, and 15 Hz photic stimulation (with no auditory stimulus present) increased or tended to increase all intrahemispheric coherences from the baseline in normal subjects. These included O1P3, O2P4, O1T5, and O2T6 in the first study, and O1C3 and O2C4 in the second study. We have, however, replicated these findings in a new sample of 30 participants with new, custom software (coherence algorithms by David Joffe at Lexicor; Frederick & Lubar, 2002). Interestingly, spectral correlation, a measure which is often confused with coherence, did not decrease during stimulation in these same recordings. Possibly, the differences between Wada et al.'s findings and ours might be explained by their use of a more intense, square-wave stimulus, or the lack of an auditory stimulus.

Our statistical analysis of these data has taken a new approach to the problem of type I error from multiple comparisons. Many previous studies (e.g., Dafters, Duffy, O'Donnell & Bouqet, 1999; Wada et al., 1998b) have avoided this problem by "not looking" at more than a small representative subset (6 to 10) of the 171 coherences that are possible among 19 electrodes. We believe that this approach has unacceptable consequences for type II error. Limitations to the Stellate Rhythm software made it impractical for us to look at more than 64 coherence pairs, but at this level of resolution, it is apparent that groups of coherences (e.g. frontal longitudinal) can change reliably while individual members of that group might not. Other studies have simply performed hundreds of univariate tests and relied on the intuitive clarity of the overall magnitude and scope of the effect (e.g., Gevins et al., 1987). We believe that an optimal balance between type I and type II error is achieved not by avoiding or ignoring the problem of multiple comparisons, but by measuring it. When the problem of experimentwise error is framed as a null hypothesis, that "these significant univariate tests arise from random effects," clearly the most direct method of testing this hypothesis is to compare the number of observed effects to the empirical distribution of random effects.

While this study has shown that the coherence effects of discrete-frequency AVS are distributed throughout the frequency spectrum, it should be acknowledged that our stimulus paradigm was highly artificial compared to those used in a clinical setting. Further research is needed to understand the effects of variable-frequency stimulation, auditory vs. visual vs. combined AVS, binaural beat stimulation, EEG-driven AVS, and desynchronized AVS paradigms. Nonetheless, the ability to alter patterns of coherence in the brain is potentially a powerful tool for neurotherapy. The recruitment of alternative pathways and circuits is often essential for recovery from neurological and perhaps psychiatric disorders. Neurons and neural pathways have a much larger connectivity than

their usual territory of functional influence, which can be "unmasked" by disinhibiting or potentiating these connections (Mallet, 2001). Temporally paired (or coherent) inputs are required for associative long-term potentiation to occur (Kelso, Ganong & Brown, 1986.) Synchronous activity has been shown to be an essential signal for synaptogenesis in the developing brain, as well as axonal sprouting after cortical lesions in the adult (Carmichael, 2003). The changes in coherence evoked by AVS in this study suggest that long-term AVS therapies may activate these mechanisms of neuronal plasticity to reorganize functional linkages in the brain.

REFERENCES

Adrian, E. D., & Matthews, B. H. C. (1934). The Berger rhythm: potential changes from the occipital lobes in man. *Brain*, *57*, 355-384.

Anderson, D. J. (1989). The treatment of migraine with variable frequency photostimulation. *Headache*, *29*, 154-155.

Aranibar, A., & Pfurtscheller, G. (1978). On and off effects in the background EEG activity during one-second photic stimulation. *Electroencephalography and Clinical Neurophysiology*, *44*, 307-316.

Carter, J. L., & Russell, H. L. (1993). A pilot investigation of auditory and visual entrainment of brainwave activity in learning-disabled boys. *Texas Researcher: Journal of the Texas Center for Educational Research*, *4*, 65-73.

Carmichael, S. T. (2003). Plasticity of cortical projections after stroke. *Neuroscientist*, *9* (1), 64-75.

Conover, W. J. (1980). *Practical Nonparametric Statistics*. New York: John Wiley & Sons.

Coull, B. M. & Pedley, T. A. (1978). Intermittent photic stimulation. Clinical usefulness of non-conclusive responses. *Electroencephalography and Clinical Neurophysiology*, *44*, 353-363.

Dafters, R. I., Duffy, F., O'Donnell, P. J. & Bouqet, C. (1999). Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence. *Psychopharmacology*, *145* (1), 82-90.

Dieter, J. N. I., & Weinstein, J. A. (1995). The effects of variable frequency photo-stimulation goggles on EEG and subjective conscious state. *Journal of Mental Imagery*, *19*, 77-90.

Duffy, F. H., Iyer, V. G., & Surwillo, W. W. (1989). *Clinical and Electroencephalography and Topographic Brain Mapping.* New York: Spinger-Verlag.

Edgington, E. S. (1987). *Randomization Tests*, 2nd ed. New York: M. Dekker.

Evans, J. R. & Park, N. S. (1996). Quantitative EEG Abnormalities in a Sample of Dyslexic Persons. *Journal of Neurotherapy*, *2* (1).

Frederick, J. A. (2001). Technical Note: Open source method of graphical QEEG analysis using PERL and Visual Basic. *Journal of Neurotherapy*, *4* (4), 63-70.

Frederick, J. A. & Lubar, J. F. (2002). Differences between coherence and spectral correlation during auditory and visual stimulation at dominant alpha frequency. *Journal of Neurotherapy,* 6(1): 70-1.

Gevins, A. S., Morgan, N. H., Bressler, S. L., Cutillo, B. A., White, R. M., Illes, J., Greer, D. S., Doyle, J. C., Zeitlin, G. M. (1987). Human Neuroelectric patterns predict performance accuracy. *Science*, *235*, 580-585.

Gizycki, H., Jean-Louis, G., Snyder, M., Zizi, F., Green, H., Giuliano, V., Spielman, A., & Taub, H. (1998). The effects of photic driving on mood states. *Journal of Psychosomatic Research*, *44* (5): 599-604.

Herrmann, C. S. (2001). Human EEG responses to 1-100 Hz flicker: resonance phenomena in visual cortex and their potential correlation to cognitive phenomena. *Experimental Brain Research*, *137* (3-4):346-53.

Hoffman, D. A., Stockdale, S., Hicks, L. L., & Schwaninger, B. A. (1995). Diagnosis and treatment of head injury. *Journal of Neurotherapy 1* (1).

Iwahara, S., Noguchi, S., Yang, K., & Oishi, H. (1974). Frequency specific and nonspecific effects of flickering lights upon electrical activity of the human occiput. *Japanese Psychological Research*, *16*, 1-7.

Joyce, M., Siever, D. (2000). Audio-visual Entrainment Program as a Treatment for Behavior Disorders in a School Setting. *Journal of Neurotherapy*, *4* (2), 9-25.

Kawaguchi, T., Jijiwa, H., & Watanabe, S. (1993). The dynamics of phase relationships of alpha waves during photic driving. *Electroencephalography and Clinical Neurophysiology*, *87*,

88-96.

Kelso, S. R., Ganong, A. H., and Brown, T. H. (1986). Hebbian synapses in hippocampus. *Proceedings of the National Academy of the Sciences USA*, *83*, 5326-5330.

Lubar, J. F. & Lubar, J. O. (1999). Neurofeedback assessment and treatment for attention deficit/hyperactivity disorders. In Evans, J.R., & Abarbanel, A., (Eds). *Introduction to Quantitative EEG and Neurofeedback* (pp. 103-143). San Diego, CA, US: Academic Press, Inc.

Lubar, J. F., Swartwood, M. O., Swartwood, J. N., & O'Donnell, P. (1995). Evaluation of the effectiveness of EEG neurofeedback training for ADHD in a clinical setting as measured by changes in T.O.V.A. scores, behavioral ratings, and WISC-R performance. *Biofeedback and Self-Regulation*, *20*, 83-99.

Mallet, M. (2001). Plasticity of the human motor cortex and recovery from stroke. *Brain Research Reviews*, *36* (2-3), 169-74

Micheletti, L. S., (1999). The use of auditory and visual stimulation for the treatment of Attention Deficit Hyperactivity Disorder in children (ritalin, adderall). *Dissertation Abstracts International: Section B: The Sciences and Engineering*, *60* (6-B), 2953.

Mohammed, A. H., Zhu, S. W., Darmopil, S., Hjerling-Leffler, J., Ernfors, P., Winblad, B., Diamond, M. C., Eriksson, P. S., & Bogdanovic, N. (2002). Environmental enrichment and the brain. In Hofman, M. A., Boer, G. J., Holtmaat, A. J. G. D., Van Someren, E. J. W., Verhaagen, J., & Swaab, D. F. (Eds.), *Progress in Brain Research*, *138*, 109-133.

Montgomery, D. D., Ashley, E., Burns, W. J., & Russell, H. L. (1994). Clinical outcome of a single case study of EEG entrainment for closed head injury. *Proceedings from the Association for Applied Psychophysiology and Biofeedback*, *25*, 82-83.

Morse, D. R. (1993). Brain wave synchronizers: A review of their stress reduction effects and clinical studies assessed by questionnaire, galvanic skin resistance, pulse rate, saliva, and electroencephalograph. *Stress Medicine*, *9*, 111-126.

Mueller, H. H., Donaldson, C. C. S., Nelson, D. V., & Layman, M. (2001). Treatment of fibromyalgia incorporating EEG-driven stimulation. *Journal of Clinical Psychology 57* (7): 933-952.

Noton, D. (1997). PMS, EEG, and photic stimulation. *Journal of Neurotherapy*, *2* (2), 8-13.

Patrick, G. J. (1996). Improved neuronal regulation in ADHD: An application of 15 sessions of photic-driven EEG neurotherapy. *Journal of Neurotherapy*, *1*, 27-36.

Regan, D. (1966). Some characteristics of average steady-state and transient responses evoked by modulated light. *Electroencephalography and Clinical Neurophysiology 20*, 238-248.

Rosenzweig, M. R. (2003). Effects of differential experience on the brain and behavior. *Developmental Neuropsychology*, *24* (2-3), 523-540.

Rozelle, G.R. & Budzynski, T.H. (1995). Neurotherapy for stroke rehabilitation: A case study. *Biofeedback and Self-Regulation*, *20*, 211-228.

Russell, H. L. (1997). Intellectual, auditory, and photic stimulation and changes in functioning in children and adults. *Biofeedback*, *25* (1), 16-17, 23-24.

Shaw, J. C. (1981). An introduction to the coherence function and its use in EEG signal analysis. *Journal of Medical Engineering Technology*, *5* (6): 279-288.

Shealy, C. N., Cady, R. K., Cox, R. H., Liss, S., Clossen, W. & Culver Veehoff, D. (1990). *Brain wave synchronization (photo-stimulation) with the Shealy RelaxMate (TM)*. Shealy Institute for Comprehensive Health Care: Springfield, MO.

Schindler, A. F., Poo, M. (2000). The neurotrophin hypothesis for synaptic plasticity. *Trends in Neuroscience*, *23* (12), 639-45.

Silberstein, R. B. (1995). Neuromodulation of neocortical dynamics. In P. L. Nunez (Ed.), *Neocortical Dynamics and Human EEG Rhythms* (pp. 591-627). New York: Oxford University Press.

Solomon, G. D. (1985). Slow wave photic stimulation in the treatment of headache-a preliminary

study. *Headache*, *25*, 444-446.

Striano, S., Meo, R., Bilo, L., Ruosi, P., Soricellis, M., Estraneo, A., Caporella, A. (1992). The use of EEG activating procedures in epileptology. *Acta Neurologica*, 14(4-6): 275-289.

Stwertka, S. A. (1993). The stroboscopic patterns as dissipative structures. *Neuroscience and Biobehavioral Reviews*, 17: 69-78.

Takahashi, T. (1987). Activation methods; in Niedermeyer E., Lopez da Silva, F. (eds): *Electroencephalography*, *Basic Principles*, *Clinical Applications and Related Fields*, ed 2. Baltimore, Urban & Scharzenberg 1987, pp 209-227.

Thatcher, R. W. (1992). Cyclic cortical reorganization during early childhood. *Brain and Cognition*, *20*, 24-50.

Timmermann, D. L. (1999). An assessment of the effects of multi-session audio-visual stimulation on cognitive measures and the cortical EEG. *Dissertation Abstracts International: Section B: The Sciences and Engineering*, *60* (3-B), 1343.

Timmermann, D., Lubar, J. F., Rasey, H. W., & Frederick, J. A. (1999). Effects of dominant and twice-dominant alpha audiovisual stimulation on the cortical EEG. *International Journal of Psychophysiology*, *32*, 55-61.

Toman, J. (1941). Flicker potentials and the alpha rhythm in man. *Journal of Neurophysiology*, 4: 51-61.

Townsend, R. E., Lubin, A., & Naitoh, P. (1975). Stabilization of alpha frequency by sinusoidally modulated light. *Electroencephalography and Clinical Neurophysiology*, *39*, 515-518.

van Praag, H., Kempermann, G., & Gage, F. H. (2000). Neural consequences of environmental enrichment. *Nature Reviews Neuroscience*, *1*, 191-198.

Wada, Y., Nanbu, Y., Kadoshima, R., & Jiang, Z. Y. (1996). Interhemispheric EEG coherence during photic stimulation: Sex differences in normal young adults. *International Journal of Psychophysiology*, *22* (1-2), 45-51.

Wada, Y., Nanbu, Y., Kikuchi, M, Koshino, Y., Hashimoto, T., & Yamaguchi, N. (1998a). Abnormal functional connectivity in Alzheimer's disease: Intrahemispheric EEG coherence during rest and photic stimulation. *European Archives of Psychiatry and Clinical Neuroscience*, *248* (4), 203-208.

Wada, Y., Nanbu, Y., Kikuchi, M., Koshino, Y., & Hashimoto, T. (1998b). Aberrant functional organization in schizophrenia: Analysis of EEG coherence during rest and photic stimulation in drug-naive patients. *Neuropsychobiology*, *38* (2), 63-69.

Walter, W. G., Dovey, V. J., & Shipton, H. (1946). Analysis of electrical response of human cortex to photic stimulation. *Nature*, *158*, 340-541.

Walter, V. J., & Walter, W. G. (1949). The central effects of rhythmic sensory stimulation. *Electroencephalography and Clinical Neurophysiology*, *1*, 57-86.

CAPTIONS

TABLE 1. Likelihood of type I error resulting from multiple comparisons (*p*). The number of significant coherence differences (*obs*; sign-rank test $p \leq 0.01$) was counted for each variable across all other variables, and compared to the distribution of false-positive tests observed in 1000 randomized trials. *Pos* denotes the number of increases, *neg*, the number of decreases, *null*, the average number of false-positive tests in random data, **ALPHA**, the alpha stimulus condition; **BETA**, the twice dominant alpha stimulus condition, **D1-B2**, coherence bandpasses; **0-5 min** etc., recording intervals; **F1**, **F2**, etc. individual members of coherence pairs; **F1C3**, **F1CZ**, etc., coherence pairs.

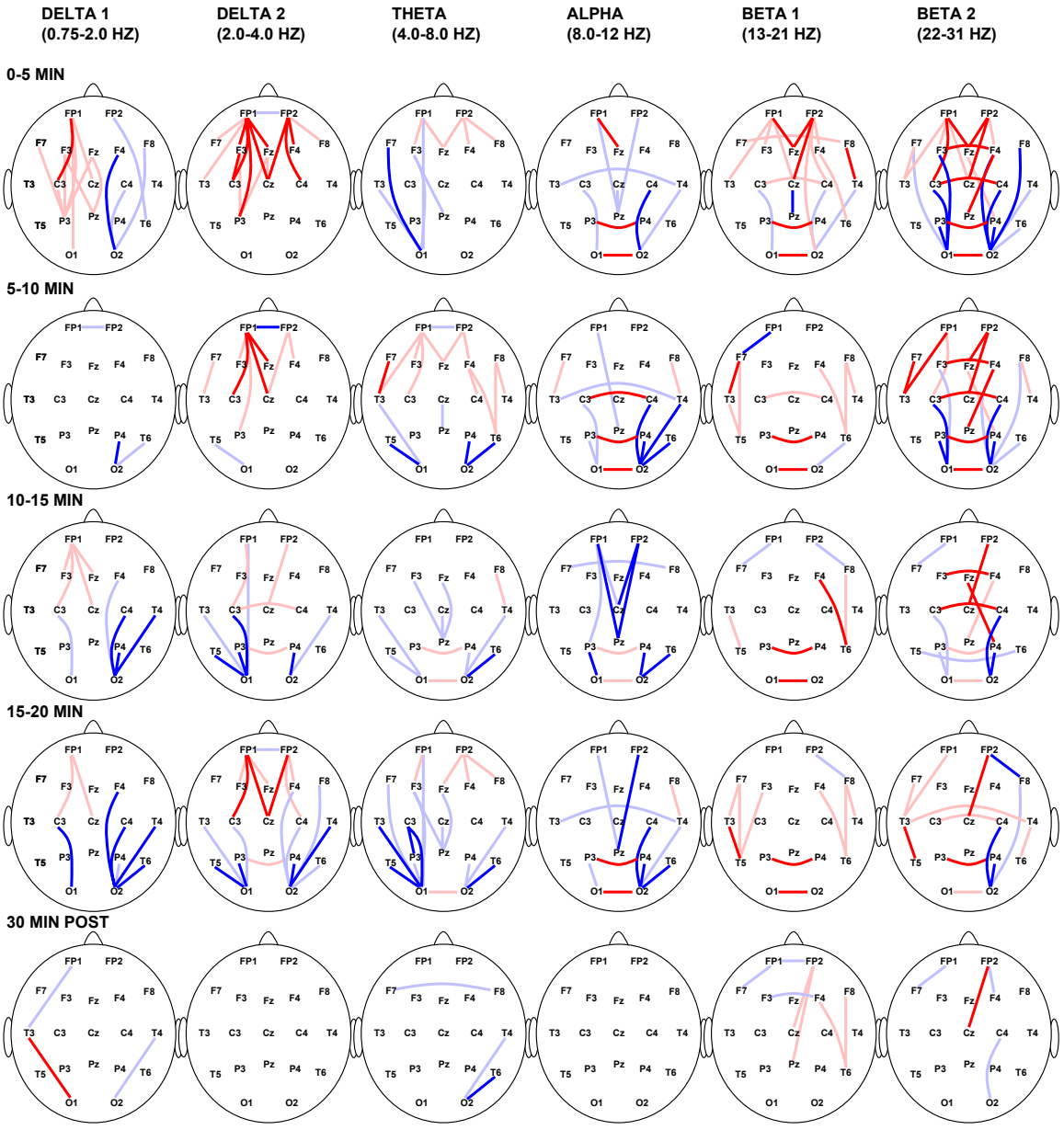
FIGURE 1. Effect of dominant alpha stimulation on EEG coherence. Dark red lines, increases at $p \leq .01$; light red lines, increases at $p \leq .05$; dark blue lines, decreases at $p \leq .01$; light blue lines, decreases at $p \leq .05$.

FIGURE 2. Effect of twice-dominant alpha stimulation on EEG coherence. Dark red lines, increases at $p \leq .01$; light red lines, increases at $p \leq .05$; dark blue lines, decreases at $p \leq .01$; light blue lines, decreases at $p \leq .05$.

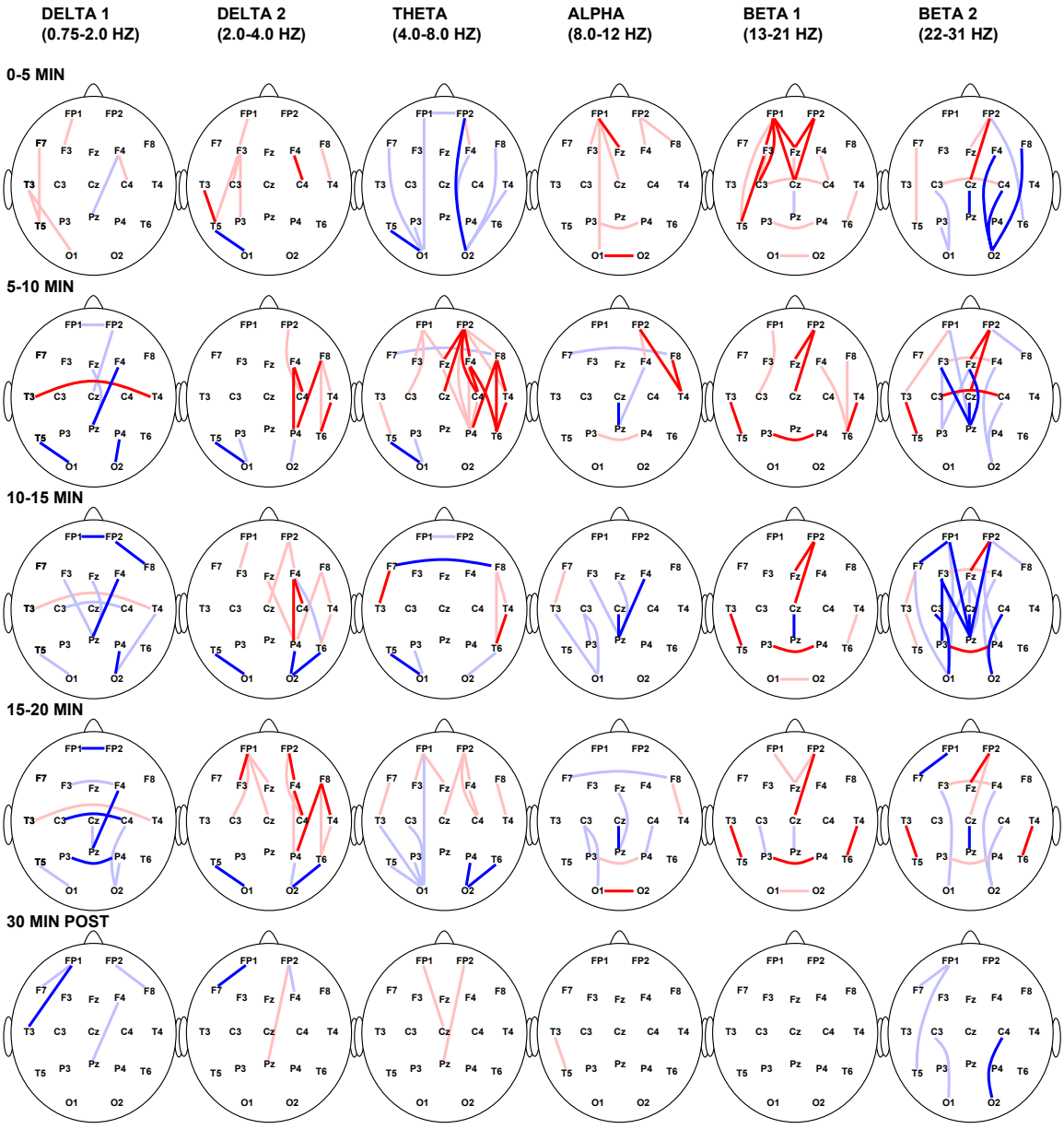
	p	*pos*	*neg*	*obs*	*null*	*tot/null*
ALL	0.001	128	113	241	41.7	5.8
ALPHA	0.001	67	63	130	21.2	6.1
BETA	0.001	61	50	111	20.5	5.4
D1	0.007	3	22	25	7.1	3.5
D2	0.001	28	17	45	7.1	6.3
TH	0.003	13	18	31	6.8	4.6
AL	0.006	13	19	32	7.0	4.5
B1	0.001	35	3	38	6.8	5.6
B2	0.001	36	34	70	6.8	10.2
0-5 min	0.001	40	18	58	8.6	6.7
5-10 min	0.001	45	23	68	8.5	8.0
10-15 min	0.001	17	36	53	8.5	6.2
15-20 min	0.001	24	32	56	8.6	6.5
POST	0.545	2	4	6	7.5	0.8
F1	0.002	22	10	32	7.3	4.4
F2	0.001	31	10	41	7.3	5.7
F3	0.038	8	4	12	4.7	2.6
F4	0.001	17	8	25	4.7	5.3
F7	0.032	4	6	10	4.0	2.5
F8	0.008	8	5	13	4.0	3.3
FZ	0.001	18	1	19	4.1	4.6
C3	0.001	12	8	20	3.2	6.2
C4	0.001	12	13	25	3.3	7.6
CZ	0.001	19	10	29	2.6	11.2
T3	0.008	15	2	17	3.3	5.2
T4	0.001	12	4	16	3.2	5.0
P3	0.001	15	8	23	4.6	5.0
P4	0.001	20	17	37	4.7	7.8
PZ	0.001	2	21	23	4.0	5.8
T5	0.001	9	12	21	4.1	5.2
T6	0.001	9	11	20	4.0	5.0
O1	0.001	12	26	38	5.3	7.2
O2	0.001	11	50	61	5.3	11.6
F1C3	0.003	6	0	6	0.6	9.7
F1CZ	0.021	4	0	4	0.7	6.0
F1F3	0.05	3	0	3	0.7	4.2
F1FZ	0.003	7	0	7	0.7	10.1
F1P3	0.284	1	0	1	0.7	1.5
F2C4	0.109	2	0	2	0.6	3.2
F2CZ	0.001	15	1	16	0.7	24.6
F2F4	0.043	3	0	3	0.7	4.6
F2FZ	0.001	10	0	10	0.7	14.9
F2T4	0.27	1	0	1	0.7	1.5
F3C3	0.298	1	0	1	0.7	1.5
F3F4	0.043	3	0	3	0.6	4.8
F3T5	0.29	1	0	1	0.7	1.5

	p	*pos*	*neg*	*obs*	*null*	*tot/null*
F4C4	0.006	5	0	5	0.7	7.2
F4P4	0.123	2	0	2	0.7	2.9
F4T6	0.111	2	0	2	0.7	3.0
F7T3	0.025	4	0	4	0.7	5.8
F8P4	0.045	3	0	3	0.7	4.5
F8T4	0.022	4	0	4	0.6	6.3
F8T6	0.275	1	0	1	0.7	1.5
FZP4	0.311	1	0	1	0.7	1.4
C3C4	0.006	5	1	6	0.7	9.0
P3P4	0.001	14	1	15	0.7	22.7
T3T4	0.262	1	0	1	0.6	1.6
T3T5	0.003	8	0	8	0.7	12.3
T4T6	0.007	6	0	6	0.7	9.1
O1O2	0.001	11	0	11	0.7	16.9
F1F2	0.047	0	3	3	0.6	5.3
F1F7	0.019	0	4	4	0.6	6.6
F1PZ	0.108	0	2	2	0.7	3.0
F2F8	0.116	0	2	2	0.7	3.0
F2O2	0.297	0	1	1	0.7	1.5
F2PZ	0.039	0	3	3	0.7	4.5
F3P3	0.291	0	1	1	0.7	1.5
F7F8	0.3	0	1	1	0.7	1.4
FZPZ	0.278	0	1	1	0.6	1.6
C3P3	0.25	0	1	1	0.6	1.7
CZPZ	0.001	0	9	9	0.6	14.5
O1C3	0.009	0	6	6	0.6	9.4
O1F3	0.278	0	1	1	0.6	1.6
O1F7	0.276	0	1	1	0.6	1.6
O1P3	0.02	0	5	5	0.6	7.8
O1T5	0.001	0	12	12	0.7	16.9
O2C4	0.001	0	12	12	0.7	18.2
O2F4	0.016	0	4	4	0.7	6.1
O2F8	0.104	0	2	2	0.7	3.1
O2P4	0.001	0	16	16	0.7	22.9
O2T4	0.019	0	4	4	0.6	6.6
O2T6	0.001	0	11	11	0.6	17.7
PZF3	0.1	0	2	2	0.6	3.2
PZF4	0.003	2	4	6	0.7	8.6
F1T3	0.119	1	1	2	0.7	2.9
O1T3	0.106	1	1	2	0.6	3.2
C4P4	0.575	0	0	0	0.6	0.0
F1O1	0.575	0	0	0	0.7	0.0
F1T5	0.575	0	0	0	0.7	0.0
F2P4	0.575	0	0	0	0.7	0.0
F2T6	0.575	0	0	0	0.7	0.0
F7P3	0.575	0	0	0	0.7	0.0
F7T5	0.575	0	0	0	0.7	0.0
FZCZ	0.575	0	0	0	0.7	0.0
FZP3	0.575	0	0	0	0.7	0.0
T5T6	0.575	0	0	0	0.7	0.0

Frederick et al., EEG Coherence Effects of AVS, table 1



Frederick et al., EEG Coherence Effects of AVS, figure 1



Frederick et al., Coherence Effects of AVS, Figure 2