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Editorial

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It is with great honor that we present the second year of *NeuroRegulation* to the world. As the new Editor-in-Chief I look forward to bringing more valuable content to our members and the public in general. I would like to express sincere gratitude to Dr. Adam Clarke and Dr. Randall Lyle for their efforts in bringing our new journal to life, as well as its evolution into its current state. We also express many thanks for the sponsorship provided by the International Society for Neurofeedback & Research (ISNR) and Mount Mercy University for making *NeuroRegulation* an open-access, non-fee publishing venue for disseminating research, clinical, review, and theoretical papers across disciplines.

NeuroRegulation is proud to announce its Editorial Board has been formed and this group of scientists will also serve as the Scientific Review Council (SRC) for ISNR. The role of the SRC will be to serve as an advisory panel for the ISNR Board of Directors with regard to promoting sound science, evidence-based research, ethical principles, and high quality education in the promotion of the field of neurofeedback and neuromodulation. The Editorial Team and SRC are:

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The contents of the current issue include a number of interesting topics. Michelle Montopoli and colleagues present data on the effects of chocolate on the EEG and blood pressure. The findings of this study reaffirm the effects of chocolate for individuals that have a particular fondness for this substance. Dr. Mark Jones provides an analysis of DC offset and impedance measures in the assessment of electrode connection quality. The findings emphasize the need to examine our methods in great detail. Mohammad Ali Salehinejad and colleagues examine transcranial direct current stimulation (tDCS) in major depression with visual working memory and reduction in symptoms as outcome measures. This study provides a theoretical and practical concentration on left prefrontal cortex in the interaction between cognition and emotion in major depressive disorder. Dr. John Davis provides a review of "Clinical handbook of biofeedback: A step-by-step guide for training and practice with mindfulness" by Inna Z. Khazan. Finally, Dr. Nancy Wigton provides news from other journals.

NeuroRegulation is an open-access journal devoted to disseminating research, clinical data, reviews, and applied neuroscience to the world. We invite authors to submit original research, clinical case or group data, reviews, and theoretical papers. The target time from submission to first review completion and feedback is typically in the range of 14–20 days; thus affording an expedited submission to publication timeline. One change you will see in this volume of *NeuroRegulation* is an implementation of an editorial model similar to that of the *Frontiers* open-access scientific journals, where individual editors are selected to manage the editorial process of separate articles. Upon publication, the manuscript editor and reviewers are then listed on the article as being responsible for their respective roles in the editorial process.

I thank the authors who submitted to this issue of and welcome future submissions to the journal. Together, as a scientific community, we have the opportunity to fashion *NeuroRegulation* into a reputable peer-reviewed publication, with high impact, and make significant contributions to the scholarly literature of our respective fields.

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The Acute Electrocortical and Blood Pressure Effects of Chocolate

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Abstract

Objective: The present study investigated the effects of consuming chocolate on electroencephalograph (EEG) frequencies and localization and on blood pressure. **Method:** Across six conditions, 122 participants consumed either higher (60%) cacao chocolate, low (0%) cacao chocolate, higher cacao chocolate + L-theanine, high sugar water, low sugar water, or water. EEGs, blood pressure, and mood were measured before and after a 60-min digestion period. **Results:** Analyses indicated a decrease in frontal, parietal, and temporal theta and an increase in occipital beta EEG following the consumption of a 60% cacao confection compared with control conditions. Diastolic blood pressure increased with the consumption of higher cacao chocolate when compared to water alone and to higher cacao chocolate + L-theanine. Diastolic and systolic blood pressure decreased following consumption of higher cacao + L-theanine chocolate, averaging 4–8 mmHg. No condition-specific mood changes or gender differences were found. **Conclusions:** This study suggests an acute stimulating effect of cacao on the human brain and vasoconstrictive effects on peripheral vasculature, the latter of which appear to be offset by an L-theanine additive. **Significance:** This is the first known study to investigate acute EEG effects of consuming chocolate and suggests a potential attention-enhancing effect.

Keywords: chocolate, cocoa, cacao, L-theanine, EEG, blood pressure

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Introduction

Few food products have garnered such attention or have reached such cultural and mythological significance as chocolate. Indeed, chocolate is frequently heralded as an aphrodisiac, a broad-spectrum medicinal agent, a mood-altering substance, a nutritional supplement, an antihypertensive, a stimulant, and as the most frequently craved food in the Western world (Bruinsma & Taren, 1999; di Tomaso, Beltramo, & Piomelli, 1996; Dillinger et al., 2000; Hill & Heaton-Brown, 1994; Rozin, Levine, & Stoess, 1991; Weingarten & Elston, 1991). Research over the past decades has generally been supportive of these effects, if only of minimal magnitude in some cases. Chocolate is made from the cocoa bean—which is actually the seed of the fruit of the *Theobroma cacao* tree—and was originally cultivated by the Olmec, Mayan, and Aztec aristocracy in Mesoamerica and by the Inca in South America. Ancient codices from Mesoamerica indicate that foods made from the raw, fermented, roasted, shelled, and ground cocoa bean (called cacao) were used for a variety of medicinal purposes such as relieving cough, gastrointestinal aids, improving angina and heart palpitations, and even as a sexual stimulant (Dillinger et al., 2000). Modern research has linked the ingestion of flavanols, polyphenolic compounds highly concentrated in the cocoa bean, to stimulation of nitric oxide synthase production (Fisher, Hughes,

Gerhard-Herman, & Hollenberg, 2003). Nitric oxide synthase increases levels of nitric oxide in arterial endothelial cells producing peripheral vasodilation. Cocoa (processed cacao with the cocoa butter removed) and chocolate (processed cacao with cocoa butter not removed) also contain trace amounts of compounds thought to potentially alter brain activity, such as anandamide, a naturally occurring neuromodulator which can bind to cannabinoid-receptors and very mildly mimic the psychoactive properties of plant-derived cannabinoid drugs (di Tomaso et al., 1996).

By far the most heavily researched and most convincing effect of cacao and chocolate ingestion is the effect on blood pressure and vasodilation. The evidence is now highly suggestive that the flavanols in cacao products have vasodilation effects through increases in nitric oxide (NO), which may result in small decreases in blood pressure (Engler et al., 2004; Fraga et al., 2005; Grassi, Lippi, Necozione, Desideri, & Ferri, 2005; Grassi, Necozione, et al., 2005; Taubert, Roesen, Lehmann, Jung, & Schomig, 2007). Taubert, Roesen, and Schomig (2007) conducted a meta-analysis of randomized controlled studies of the effects of cocoa use over a median period of 2 weeks on blood pressure and reported a mean decrease in systolic blood pressure (SBP) of 4.7 mmHg and in diastolic blood pressure (DBP) of 2.8 mmHg. These results translate into a 20%, 10%, and 8% risk reduction in stroke, coronary heart disease, and all-cause mortality, respectively. And, in a cross-sectional study of 470 elderly men, those who consumed the equivalent of 2.3 g of cocoa powder per day over a 5-year period had a significantly lower SBP (-3.7 mmHg) and DBP (-2.1 mmHg) relative to men with low cocoa intake, translating prospectively into a 45–50% decrease in cardiovascular and all-cause risk (Buijsse, Feskens, Kok, & Kromhout, 2006). Such decreases in blood pressure following prolonged consumption of cacao products have been strongly linked in acute effect studies to peripheral vasodilation resulting from endothelium-dependent relaxation of vascular smooth muscles induced by nitric oxide, which is thought to be increased primarily by the flavanol monomer, epicatechin, in cacao products (Fisher et al., 2003; Heiss et al., 2006; Karim, McCormick, & Kappagoda, 2000; Schroeter et al., 2006). This vasodilation has been generally observed to peak at 1–2 hr following consumption of a flavanol-rich chocolate product (Schroeter et al., 2006; Taubert, Rosen, Lehmann et al., 2007). These supportive outcomes notwithstanding, Egan, Laken, Donovan, and Woolson (2010) have pointed to important inconsistencies in outcomes, designs, type, and chemical constituents of cacao confections, dose and time-dependent effects, subject blood pressure (BP) variability, and BP measurement devices, which leave the cardiovascular effects of cacao uncertain at the present time.

The endothelium-dependent relaxation (EDR) effects of cacao are somewhat paradoxical, as cacao also contains a number of sympathomimetics, which have vasoconstrictive and generally stimulatory effects, most notably the biogenic amines, tyramine and phenylethylamine (PEA), and the methylxanthines, caffeine and theobromine (Bruinsma & Taren, 1999; Hurst, Martin, & Zoumas, 1982). Although these substances occur in different amounts in various confections, PEA and theobromine generally are found in larger quantities and tend to potentiate the release of catecholamines, thus causing vasoconstriction and elevations in blood pressure. It is not clear at the present time whether these vasoconstrictive effects are offset by the more prominent EDR vasodilatation effects reported above, or whether the time course of these phenomena are different, resulting in more immediate stimulation followed by a delayed vasodilatation effect. Furthermore, these stimulant effects may well explain the general increase in arousal often reported by chocolate consumers (Bruinsma & Taren, 1999; Dillinger et al., 2000).

If chocolate indeed has an immediate arousing effect, one might expect to see increased arousal in the brain. However, our review of the chocolate literature over the past decades reveals no studies of the effects of chocolate consumption on central nervous system (CNS) arousal. Martin (1998) investigated the electroencephalographic (EEG) effects of olfactory stimulation with the aroma of chocolate, but did not examine the consumption of chocolate in his research. Small, Zatorre, Dagher, Evans, and Jones-Gotman (2001), in a positron emission tomography (PET) study of brain changes following eating chocolate, were interested only in the immediate (within 10 s) reward characteristics of consuming chocolate and did not allow a sufficient time course for cacao constituents to have an effect on cerebral blood flow following digestion. Francis, Head, Morris, and Macdonald (2006) conducted functional magnetic resonance imaging (fMRI) on 16 healthy young women following 5 days of consumption of a flavanol-rich cocoa beverage compared to a low flavanol beverage and examined blood flow changes 1.5 hr after consumption of the beverage during the performance of a cognitive switching task. Although they found no flavanol-specific effects on reaction times, error rates, or

heart rate, they did observe increased fMRI blood oxygenation level-dependent (BOLD) cerebral blood flow (CBF) during the cognitive task following the flavanol-rich cocoa regimen relative to the low flavanol regimen. In a separate pilot study with 4 participants of the time course of CBF changes following an acute dose of flavanol-rich cocoa, Francis et al. reported a peak blood flow response at approximately 2 hr post-ingestion with return to baseline after approximately 6 hr. Reported fMRI images were specific to the cognitive task and not to flavanol ingestion. Although these researchers suggest that the observed effects on CBF may be due to NO-induced EDR, they also point out that the fMRI BOLD response is a neurovascular phenomenon and may result from changes in vascular tone as well as neural activity influenced by stimulants, such as caffeine, in the cocoa product. Nonetheless, these results suggest a flavanol-induced increase in cerebral blood flow consistent with the vasodilation reported in other studies. And, more recently, Camfield et al. (2012), in a study of 61 middle-aged adults who consumed a daily chocolate beverage containing 250 mg or 500 mg of cocoa flavanols compared with a low cocoa flavanol beverage over a 30-day period, found no changes in behavioral measures of accuracy or reaction time on a spatial working memory task but did observe condition-specific amplitude and latency differences on EEG visual evoked potentials (VEP) during the same task. These authors interpreted the observed VEP changes as reflective of increased neural efficiency following the chronic ingestion of cocoa flavanols.

A recent comprehensive review of the neurobiological effects of cocoa flavanols on cognition and behavior indicates rather strong support for neuroprotective effects of long-term consumption of flavanols on age-related and disease-related cognitive decline but less support for the more immediate effects of cocoa consumption on specific brain mechanisms involved in neurogenesis and neuronal function and connectivity, particularly in humans (Sokolov, Pavlova, Klosterhalfen, & Enck, 2013). These authors encourage and offer a template for future research into effects of cacao on human cognition, mood, and behavior.

Given the long-term neuroprotective and neuromodulatory effects of cocoa consumption, the suggested stimulant characteristics of cacao, and the glaring absence of published acute CNS arousal studies, we elected to conduct a controlled EEG study of the comparative effects of consuming a higher cacao-content chocolate (with a high flavanol content) with a low-cacao content chocolate (with no flavanol content) and with balanced sugar and water controls. Sugar controls were included in the present study to control for reported general arousal effects of glucose (Hoffman & Polich, 1998; Hoffman, Friedmann, Saltman, & Polich, 1999). Additionally, as a partial test of the hypothesized acute sympathomimetic effects of cacao, we included a third chocolate condition by the addition of L-theanine to the same higher cacao-content chocolate formulation. L-theanine, an extract of green tea, has been shown in numerous animal and human studies to counteract the stimulating effects of caffeine and stressors, apparently by its ability to bind to the glutamate receptor and to block binding of L-glutamic acid in cortical neurons (Kimura, Ozeki, Juneja, & Ohira, 2007; Mason, 2004;). L-theanine has been found to reduce blood pressure (Yokogoshi et al., 1995; Yokogoshi & Kobayashi, 1998), to elevate posterior EEG alpha activity (Kobayashi et al., 1998), to reduce the psychological and physiological response to a mental stressor (Kimura et al., 2007), and to improve learning in animal models (Juneja, Chu, Okubo, Nagato, & Yokogoshi, 1999). We hypothesized that consumption of the higher cacao-content condition, relative to the low cacao-content, sugar, and water controls, in human volunteers would result in increased activation of the neocortex and increased blood pressure within 1 hr after ingestion and that these effects would be reversed in the higher cocoa-content plus L-theanine condition.

Methods

Participants

A power analysis was conducted to determine the optimal sample size required to detect the hypothesized effect of chocolate on EEG and blood pressure (Howell, 2002). A complex multivariate design was modeled employing 11 dependent variables (9 EEG frequency and 2 blood pressure variables) studied across two repeated measures (pre- and post-ingestion) for each of six treatment conditions. For an alpha level of .05 and a power of .80, sample sizes in each of the 6 treatment cells of 20 allowed a hypothesized medium effect size to be detected.

Consequently, 125 participants (10 males, 10 females in each of the six treatment cells, plus 5 extra participants to allow for possible attrition and outliers) were recruited from the Psychology Department undergraduate voluntary research pool. After exclusion of outliers (3 participants had

clinically-elevated blood pressure readings and were referred to the health center), 122 participants completed the study and were analyzed. Participants were between the ages of 18 and 25 years and were excluded if they used illicit drugs, stimulant or depressant medications, or nicotine, if they had diabetes mellitus, or if they were allergic to chocolate or nuts. Women were not tested during their premenstrual or menstrual phase due to the potentially confounding effect of chocolate cravings during this time and because hormone imbalances during these menstrual phases have been shown to affect the EEG (Dusser de Barenne & Gibbs, 1942; Solis-Ortiz, Ramos, Arce, Guevara, & Corsi-Cabrera, 1994). All participants abstained from caffeine and chocolate intake 24 hr prior to the EEG study. The present study was approved by the NAU Institutional Review Board for the Protection of Human Subjects in Research.

Materials and Equipment

A standard weight scale was used to weigh each participant 1 week prior to study in order to determine the amount of chocolate to administer. Participants were weighed by a same-sex research assistant, and female participants at weigh-in were given a menstrual calendar on which to plot their predicted menstrual cycle. At the initial weigh-in, the participant was briefed as to the nature of the study and the requisite informed consent documents were completed. Blood pressure readings for the study were taken by a HoMedics Automated Blood Pressure Monitor with participants seated and left arm resting at heart level.

The three chocolate treatments were prepared by The Hershey Company, individually wrapped in 40 g squares of identical appearance and coded by contents. The *higher cacao-content chocolate* contained 60% cacao with 15 mg/g of total polyphenols, and 0.37 g/g of sugar; the *low cacao-content chocolate* was a white chocolate (colored with 5% Hansen Brown) that contained 0.4 mg/g of total polyphenols, and 0.56 g/g of sugar; the *higher cacao-content + L-theanine chocolate* contained the identical components as higher cacao-content chocolate above plus 128 mg (3.2 mg/g) of L-theanine (L-theanine has a Generally Recognized as Safe [GRAS] designation by the FDA and, with recommended dosages of 50–200 mg/serving, the amounts used in this study were well within the recommended dosages). Table 1 presents total ingredients of the three chocolate treatments. Three control treatments were also prepared, comprised of a *high sugar beverage treatment* containing an equivalent amount of sugar as the low cacao-content chocolate (23 g/40 g bar or 0.57 g/kg body weight) dissolved in 350 ml (1.5 cups) of water; a *low sugar beverage treatment* containing an equivalent amount of sugar as the higher cacao chocolate (14 g/40 g bar or 0.35 g/kg body weight) dissolved in 350 ml of water; and a 350 ml *water treatment*. For the chocolate and sugar conditions, each participant received 1 g of chocolate for each kg of body weight, with an equivalent amount of sugar for each kg of body weight for the sugar conditions. For example in standard units, a 150 lb participant would receive 2.4 ounces of either of the three chocolate treatments, approximately equivalent to a standard size chocolate bar, 1.38 ounces of sugar in 1.5 cups water, 0.84 ounces of sugar in 1.5 cups water, or 1.5 cups water.

The Positive and Negative Affect Scale (PANAS) was used as a brief measure of emotional changes following chocolate consumption (Watson, Clark, & Tellegen, 1988). The PANAS was administered at the beginning of the study prior to treatment before the EEG was attached, immediately following administration of each condition, and again 1 hr 10 min later after a digestion period and second EEG.

A Mitsar 201 24-channel EEG acquisition system was used to measure each participant's EEG frequencies (Mitsar Co. LTD, 1996). The Mitsar 201 DC amplifiers have a 500 Hz digital sampling rate and input impedance not less than 200 MΩ. EEG data were recorded and preprocessed using WinEEG software (Mitsar Co. LTD, 1996), double visually artifacted by two independent artifactors, and power spectral FFT analyzed utilizing NovaTech EEG Eureka and MHyT software (Nova Tech EEG, Inc., 2006). FFT analysis employed Hamming time domain tapering, Blackman frequency domain smoothing, an overlapping FFT windows advancement factor of 8, and a moving average smoothing filter of 3. The International 10–20 placement system was used to attach 19 Ag/AgCl monopolar electrodes on the scalp with mathematically linked-ear references utilizing the Electro-Cap System (Electro-Cap International, Inc., 2006). Electrode impedances were adjusted to < 5 kohms and to within 1 kohm of each other. All data were recorded in a sound attenuated research suite, appointed with the requisite EEG and blood pressure monitoring equipment. Participants were seated comfortably in a recliner and were able to read magazines during the digestion phase and to sit quietly during the EEG recording phases.

Table 1
Ingredients of the three chocolate confections used in the present study

	High Cacao-Content Chocolate	Low Cacao-Content Chocolate	High Cacao-Content + L-theanine Chocolate
Component	per g	per g	per g
Calories	4.65	4.88	4.65
Fat, g (calculated)	0.339	0.311	0.339
Sat fat, g	0.209	0.173	0.209
Trans fat, g	0.001	0.0016	0.001
Cholesterol, mg	0.078	0.1456	0.078
Sodium, mg	0.153	1.6	0.153
Carbohydrates, g	0.548	0.556	0.548
Dietary fiber, g	0.1099	0	0.1099
Sugar, g	0.37	0.555	0.37
Protein, g	0.0803	0.084	0.0803
Vitamin A, IU	0.9297	6.27	0.9297
Vitamin C, mg	0	0.0117	0
Calcium, mg	0.576	3.13	0.576
Iron, mg	0.107	0	0.107
Magnesium, mg	2.00	0.28	2.00
Potassium, mg	5.27	2.27	5.27
Caffeine, mg	0.63	0.05	0.63
Theobromine, mg	7.14	0.07	6.5
Fat, % (analyzed)	40.1	36.7	38.8
Total polyphenols, mg	15	0.4	22
ORAC, micromoles TE	360	19	250
Catechin, mg	0.16	0.01	0.17
Epicatechin, mg	0.88	0.03	0.95
DMAC, mg	10.10	0.03	12.6
PAC-10, mg/whole product	4.60	< 0.001	5.69
PACs 1 mers	0.83	< 0.001	0.99
PACs 2 mers	0.61	< 0.001	0.78
PACs 3 mers	0.56	< 0.001	0.62
PACs 4 mers	0.56	< 0.001	0.73
PACs 5 mers	0.49	< 0.001	0.51
PACs 6 mers	0.42	< 0.001	1.1
PACs 7 mers	0.36	< 0.001	0.35
PACs 8 mers	0.32	< 0.001	0.22
PACs 9 mers	0.23	< 0.001	0.26
PACs 10 mers	0.24	< 0.001	0.12

Note: Nutrition information calculated using Genesis® R&D *SQL* nutritional analysis and labeling system (ESHA Research, Salem, OR 2007). DMAC = 4-dimethylaminocinnamaldehyde total flavanol content; ORAC = Oxygen Radical Absorbance Capacity general antioxidant activity; PACs = proanthocyanidin flavanol polymers.

Catalogs and magazines were available for participants to read following the ingestion of the treatments. These materials were reviewed in order to remove any overly emotional or stimulating articles that could have potentially affected arousal. Reading materials included clothing, climbing, and hiking catalogs and computer, health-related, and men's and women's magazines.

Procedure

Participants were randomly assigned to 1 of 6 conditions: higher cacao-content, low cacao-content, higher cacao-content + L-theanine chocolates, high sugar water, low sugar water, and water. To preclude blood sugar spikes from an overnight fast from affecting the EEG but to allow more direct effects of each of the conditions without the interference of recent food intake, participants were required to eat breakfast or a meal and then to fast for 4 hr before the experiment. Although cortisol levels were not measured in this study, in order to keep them at their nadir, all participants were run between the hours of 1 and 6 p.m. (Dmitrieva, Almeida, Dmitrieva, Loken, & Pieper, 2013; Karlamangla, Friedman, Seeman, Stawksi, & Almeida, 2013). The type of chocolate condition for each participant was known only to the primary author, who, prior to each test session, carefully weighed out, packaged, and secretly labeled the substance. This package was then passed to a blind research assistant (RA) who conducted the actual test. The sugar water and water conditions were prepared in a similar fashion and the RA was blind as to the nature of the liquid in the cup, with the exception that the RA could visually differentiate the liquid water/sugar water controls from the solid chocolate conditions. Participants were similarly partially blind as to the exact nature of the substance they were consuming, either an unknown chocolate substance or sugar water.

When the participant arrived at the laboratory, they were seated in the recliner and were given the first PANAS to complete; blood pressure was then recorded and the Electro-Cap and EEG equipment were attached, during which time the participant completed a brief questionnaire to substantiate lack of drug use over the past 2 days and lack of caffeine and food intake for the past 24 and 4 hr, respectively. A 10-min, eyes-closed resting baseline EEG was then recorded. Afterwards, each participant was administered their respective chocolate, sugar water, or water treatment, was given 5 min to ingest the substance, and was administered the PANAS again. Sixty min were then allowed for digestion and absorption of the chocolate or water treatments; participants were also visually monitored for alertness. Following the 60-min period, a second 10-min, eyes-closed resting EEG was recorded, then blood pressure was taken, and a final PANAS was administered. The Electro-Cap was then removed and the participant was debriefed. Figure 1 presents the timeline for the study.

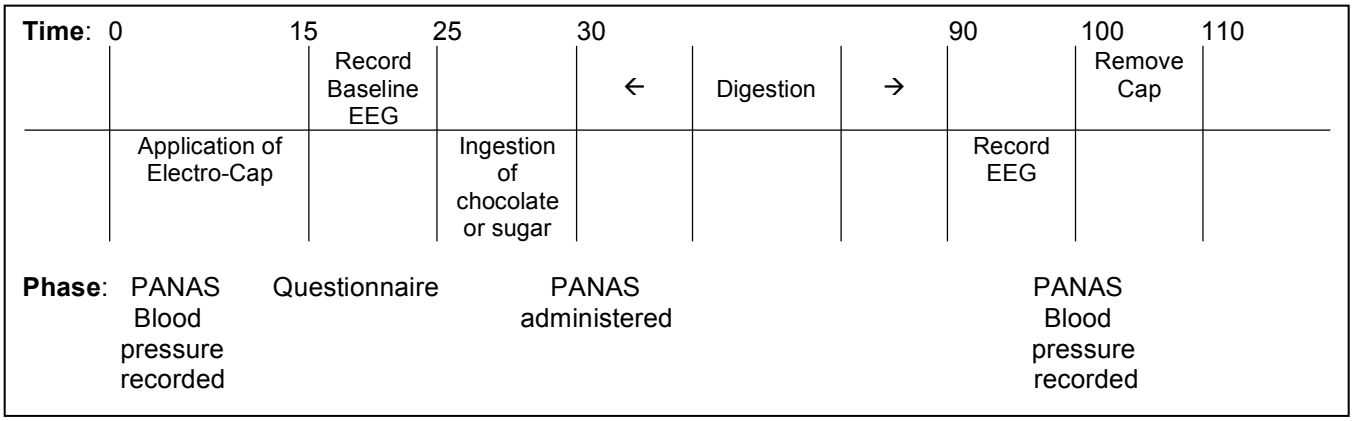

Figure 1. Timeline for the study in minutes.

Design and Analysis

Nine frequency bins were identified for analysis: delta = 0–3.99 Hz, theta = 4–7.99 Hz, low theta = 4–5.99 Hz, high theta = 6–7.99 Hz, alpha = 8–11.99 Hz, low alpha = 8–9.99 Hz, high alpha = 10–11.99 Hz, beta = 12–29.99 Hz, and gamma = 30–60 Hz. Following FFT power spectral analyses, absolute power values for each frequency and for each of the

19 electrode sites were identified and post-treatment minus pre-treatment difference scores for each frequency and site were tabulated, in order to determine the direction and magnitude of change from baseline in absolute EEG power for each condition. Absolute power differences for each electrode were grouped into traditional functional clusters of frontal (Fp1, Fp2, F7, F3, Fz, F4, F8), central (C3, Cz, C4), parietal (P3, Pz, P4), occipital (O1, O2), and temporal (T3, T4, T5, T6) regions. A factorial Analysis of Variance (ANOVA) was then conducted on each functional cluster for each frequency across each of the treatment conditions. In order to investigate the secondary effect of gender, an additional independent variable was included in each analysis, making separate 2 (between-groups: gender) x 6 (between-groups: treatment condition) analyses of post-treatment minus pre-treatment EEG differences for each functional cluster. As this was an investigational study and the percent cacao in the maximal treatment condition was relatively low (60%) thus lowering the magnitude of effect, simple effects analyses of EEGs were conducted utilizing LSD post-hoc *t*-tests. Blood pressure and PANAS effects were assessed utilizing ANOVA with simple effects comparisons made by Tukey HSD tests.

Since surface EEG recordings are aggregates of far-field potentials generated across a 3-dimensional, quasi-spherical cortical space, we wondered what deeper cortical structures might be most impacted by the biochemical constituents of chocolate following our neutral reading task. Low-resolution brain electromagnetic tomography (LORETA) is a neuroimaging software companion to contemporary EEG analyses which allows the triangulation of these surface scalp potentials to their cortical source generators (Pascual-Marqui, 1999; Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002; Pascual-Marqui, Michel, & Lehman, 1994). LORETA algorithms compute a 3-dimensional inverse solution space of cortical gray matter and hippocampi mapped onto a probabilistic Talairach atlas partitioned into 2394 7 mm^3 volumetric units, or voxels. Brodmann anatomical labels may be reported for relevant regions of interest utilizing the Montreal Neurological Institute (MNI) realistic head model (The KEY Institute for Brain-Mind Research, 1995). For the present study, LORETA mapping was utilized in a purely descriptive fashion *post hoc* to identify cortical regions of interest involved in obtained effects. LORETA Current Source Density (CSD) maps were generated from between-groups comparisons of the natural log transformation of FFT power spectral output for each statistically significant frequency and functional cluster.

Results

Participant Characteristics

Our sample of 122 participants was a young, healthy group of undergraduate student volunteers. Mean baseline blood pressures were 73.75 (7.75) mmHg DBP and 117.12 (9.98) mmHg SBP. Males had significantly higher SBP at baseline, 120.32 (8.50) mmHg SBP, than females, 114.03 (10.39) mmHg SBP; $t(120) = 3.65$, $p < .0001$; but these values were within normal limits and there was no significant gender by condition interaction at baseline, $F(1, 5) = 1.37$, $p = .24$.

Analysis of Mood Changes

PANAS scores before, immediately after, and 70-min after consumption of each treatment and for males and females were analyzed by a 2 (gender) x 6 (conditions) repeated measures ANOVA separately for positive and negative moods. Neither analysis revealed significant main effects for treatment, Positive Mood: $F(5, 110) = 1.42$, $p = 0.22$; Negative Mood: $F(5, 110) = 1.56$, $p = 0.18$; or gender, Positive Mood: $F(1, 110) = 0.22$, $p = 0.64$; Negative Mood: $F(1, 110) = 3.06$, $p = 0.08$. There was a trend for males to show slightly higher negative moods across all conditions.

Analysis of EEG Changes

EEG Absolute Power values for each of five primary frequencies for each electrode across each condition at Baseline, at Post-Treatment, and for Difference Scores are presented in Tables 2 through 6 in the Appendix. Values in each table are Absolute Power values for that frequency with decimals removed for ease of presentation (i.e., 608 = .0608, or .0608 x 10^4). In the presentation of these results, a negative difference score indicates that the specified EEG power decreased following treatment (post-treatment – pre-treatment).

For the functional cluster analyses (i.e., frontal, central, parietal, occipital, and temporal), EEG regional cluster scores for individual participants which exceeded 3.29 standard deviation units from the mean for that cluster were identified as outliers and were replaced by the next lower score for that cluster (Tabachnick & Fidell, 2013). Subsequent tests for departures from normality and homogeneity of variance revealed no significant departures for the tested independent variables, with the exception of gamma parietal, which showed a significant departure for the homogeneity of variance

assumption. This latter variable was Log10 transformed, subsequently tested for normality and homogeneity of variance, and was found to meet requirements for analysis. Regional cluster scores for each frequency and condition were then entered into separate 2 x 6 ANOVAs. These results are presented in Table 7.

These ANOVA analyses revealed significant main effects for Condition for frontal theta, $F(5, 110) = 3.12$, $p = .011$, $\eta^2 = .124$; parietal theta, $F(5, 110) = 2.38$, $p = .043$, $\eta^2 = .097$; and temporal theta, $F(5, 110) = 2.72$, $p = .024$, $\eta^2 = .110$; with a trend for central theta as well, $F(5, 110) = 2.00$, $p = .085$, $\eta^2 = .083$. A significant main effect for Gender was also found for frontal theta, $F(1, 110) = 5.94$, $p = .016$, $\eta^2 = .051$, with males showing significantly greater decreases in frontal theta than females across all conditions. No interactions were found to be statistically significant. Planned comparisons revealed frontal theta decreases from Baseline to Post-Ingestion to be significantly greater for the higher cacao-content chocolate condition relative to the water ($p = .006$), high sugar ($p = .001$), low sugar ($p = .005$), and low cacao-content chocolate ($p = .006$) conditions, with these latter conditions actually showing increases in frontal theta. Figure 2 presents these effects graphically for frontal theta. (For Figures 2 through 6, the ordinate scale is set to be equivalent across all figures for ease of magnitude comparisons.)

Similar effects were found for parietal theta and temporal theta with the higher cacao-content chocolate confection showing significant decreases with consumption relative to water ($p = .021$, $.026$), high sugar ($p = .009$, $.002$), and low cacao-content chocolate ($p = .005$, $.008$), which each showed increases across the conditions. Additionally, the higher cacao-content chocolate + L-theanine condition showed significantly smaller increases ($p = .042$) in temporal theta compared to the high sugar condition across treatment. Figures 3 and 4 present these outcomes graphically. These results indicate significant decreases in frontal, parietal, and temporal theta EEG frequencies following the consumption of a 60% cacao confection relative to increases across these cortical regions following consumption of water, high sugar, an approximately 0% cacao-content confection, and, for frontal theta, a low sugar condition.

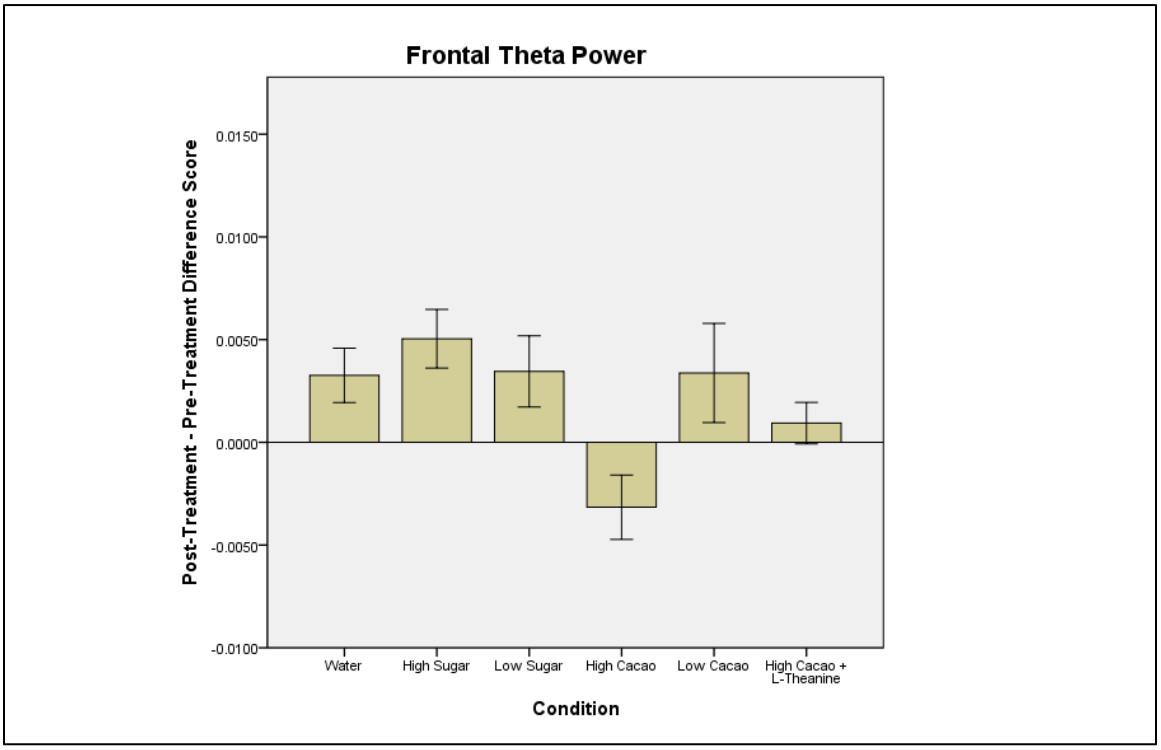

Figure 2. Frontal theta EEG absolute power changes post-treatment minus pre-treatment for each condition, showing significant decreases for higher cacao relative to water, high sugar, low sugar, and low cacao. SE bars = +/- 1 SE.

Table 7
EEG Results for Each Frequency and Regional Electrode Cluster by Condition

	Chocolate Condition		Gender		Interaction	
Cluster	**F (*p*) (η^2)**	**Effect**	**F (*p*) (η^2)**	**Effect**	**F (*p*) (η^2)**	**Effect**
Delta Frontal	.54 (.74) (.02)		.16 (.69) (.001)		.68 (.64) (.03)	
Delta Central	1.01 (.42) (.04)		.16 (.69) (.001)		.46 (.81) (.02)	
Delta Parietal	.70 (.63) (.03)		.17 (.68) (.002)		.58 (.72) (.03)	
Delta Occipital	.44 (.82) (.02)		.08 (.78) (.001)		1.16 (.33) (.05)	
Delta Temporal	.75 (.59) (.03)		.01 (.93) (.000)		.56 (.73) (.03)	
Theta Frontal	**3.12 (.01) (.12)**	d < a,b,c,e	**5.94 (.02) (.05)**	m < f	.52 (.76) (.02)	
Theta Central	2.00 (.09) (.08)		2.61 (.11) (.02)		.16 (.98) (.01)	
Theta Parietal	**2.38 (.04) (.10)**	d < a,b,e	1.67 (.20) (.02)		.41 (.84) (.02)	
Theta Occipital	1.57 (.17) (.07)		.11 (.74) (.001)		.48 (.79) (.02)	
Theta Temporal	**2.72 (.02) (.11)**	d < a,b,e; f < b	2.92 (.09) (.03)		.70 (.63) (.03)	
Low Theta Frontal	**2.46 (.04) (.10)**	d < a,b,c,e	**6.31 (.01) (.05)**	m < f	.32 (.90) (.01)	
Low Theta Central	1.95 (.09) (.08)		2.79 (.10) (.03)		.12 (.99) (.005)	
Low Theta Parietal	**2.75 (.02) (.11)**	d < a,b,c,e	3.45 (.07) (.03)		.20 (.96) (.01)	
Low Theta Occipital	1.99 (.09) (.08)		.05 (.83) (.000)		.06 (.998) (.003)	
Low Theta Temporal	**3.24 (.01) (.13)**	d < a,b,c,e; f < e	3.80 (.054) (.03)		.34 (.89) (.02)	
High Theta Frontal	**3.11 (.01) (.12)**	d < a,b,c,e	**4.88 (.03) (.04)**	m < f	1.13 (.35) (.05)	
High Theta Central	1.98 (.09) (.08)		1.62 (.21) (.02)		.36 (.87) (.02)	
High Theta Parietal	1.79 (.12) (.08)		.92 (.34) (.008)		.77 (.58) (.03)	
High Theta Occipital	1.64 (.15) (.07)		.32 (.57) (.003)		.52 (.76) (.02)	
High Theta Temporal	**2.31 (.049) (.10)**	c,d < b	1.46 (.23) (.01)		.95 (.46) (.04)	
Alpha Frontal	**2.93 (.02) (.12)**	c < a,b,e; d < b,e	1.09 (.30) (.01)		.44 (.82) (.02)	
Alpha Central	1.63 (.16) (.07)		1.31 (.26) (.01)		.67 (.65) (.03)	
Alpha Parietal	1.21 (.31) (.05)		.04 (.84) (.00)		.76 (.58) (.03)	
Alpha Occipital	.74 (.59) (.03)		.21 (.65) (.00)		.57 (.73) (.03)	
Alpha Temporal	1.10 (.37) (.05)		.04 (.84) (.00)		.57 (.72) (.03)	
Low Alpha Frontal	2.38 (.04) (.10)		.51 (.48) (.01)		.78 (.57) (.03)	
Low Alpha Central	1.93 (.10) (.08)		.91 (.34) (.01)		.71 (.62) (.03)	
Low Alpha Parietal	1.61 (.16) (.07)		.13 (.72) (.00)		.72 (.61) (.03)	
Low Alpha Occipital	.91 (.48) (.04)		.00 (.99) (.00)		1.15 (.34) (.05)	
Low Alpha Temporal	1.41 (.23) (.06)		.05 (.82) (.00)		.83 (.53) (.04)	
High Alpha Frontal	1.70 (.14) (.07)		.81 (.37) (.01)		.20 (.96) (.01)	
High Alpha Central	.77 (.57) (.03)		1.64 (.20) (.02)		.51 (.77) (.02)	
High Alpha Parietal	.47 (.80) (.02)		.00 (.95) (.00)		.39 (.86) (.02)	
High Alpha Occipital	.70 (.63) (.03)		.87 (.35) (.01)		.16 (.98) (.01)	
High Alpha Temporal	.45 (.81) (.02)		.30 (.58) (.00)		.19 (.97) (.01)	
Beta Frontal	**2.80 (.02) (.11)**	a,c,d,f < b	.25 (.62) (.00)		1.22 (.30) (.05)	
Beta Central	**3.59 (.005) (.14)**	a,c,d,f < b,e	1.78 (.19) (.02)		.86 (.51) (.04)	
Beta Parietal	1.71 (.14) (.07)		.46 (.50) (.004)		.99 (.43) (.04)	
Beta Occipital	**2.45 (.04) (.10)**	a,c < b; a < d	.13 (.72) (.001)		1.08 (.38) (.05)	
Beta Temporal	.74 (.60) (.03)		.22 (.64) (.002)		1.23 (.30) (.05)	
Gamma Frontal	.67 (.64) (.03)		.61 (.44) (.005)		.78 (.57) (.03)	
Gamma Central	.85 (.51) (.04)		2.66 (.11) (.02)		1.59 (.17) (.07)	
Gamma Parietal	1.25 (.29) (.06)		1.39 (.24) (.01)		1.57 (.18) (.07)	
Gamma Occipital	.52 (.76) (.02)		2.48 (.12) (.02)		2.17 (.06) (.09)	
Gamma Temporal	.33 (.89) (.02)		.43 (.51) (.004)		1.77 (.13) (.07)	

Note: For all analyses, Condition df = 5; Gender df = 1; Condition x Gender df = 5; Error df = 110. All Effects are Post-Condition – Pre-Condition for a = water, b = high sugar, c = low sugar, d = higher cacao-content, e = low cacao-content, f = higher cacao-content + L-theanine; m = male, f = female.

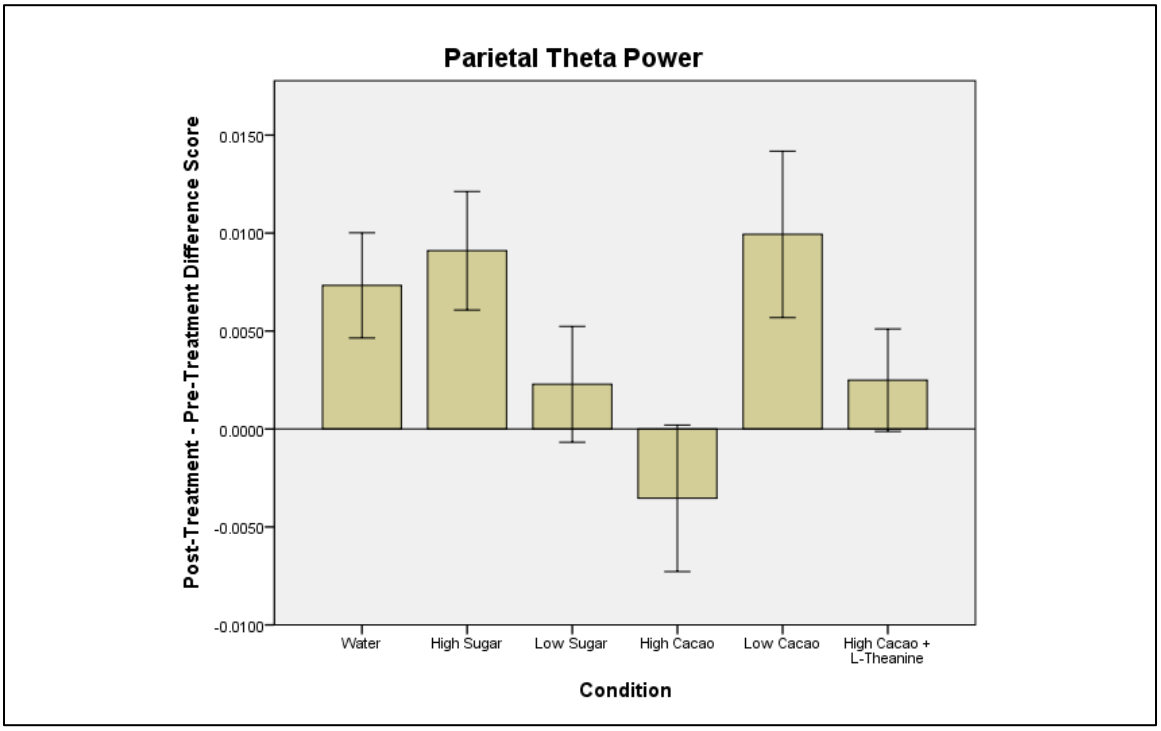

Figure 3. Parietal theta EEG absolute power changes post-treatment minus pre-treatment for each condition, showing significant decreases for higher cacao relative to water, high sugar, and low cacao. SE bars = +/- 1 SE.

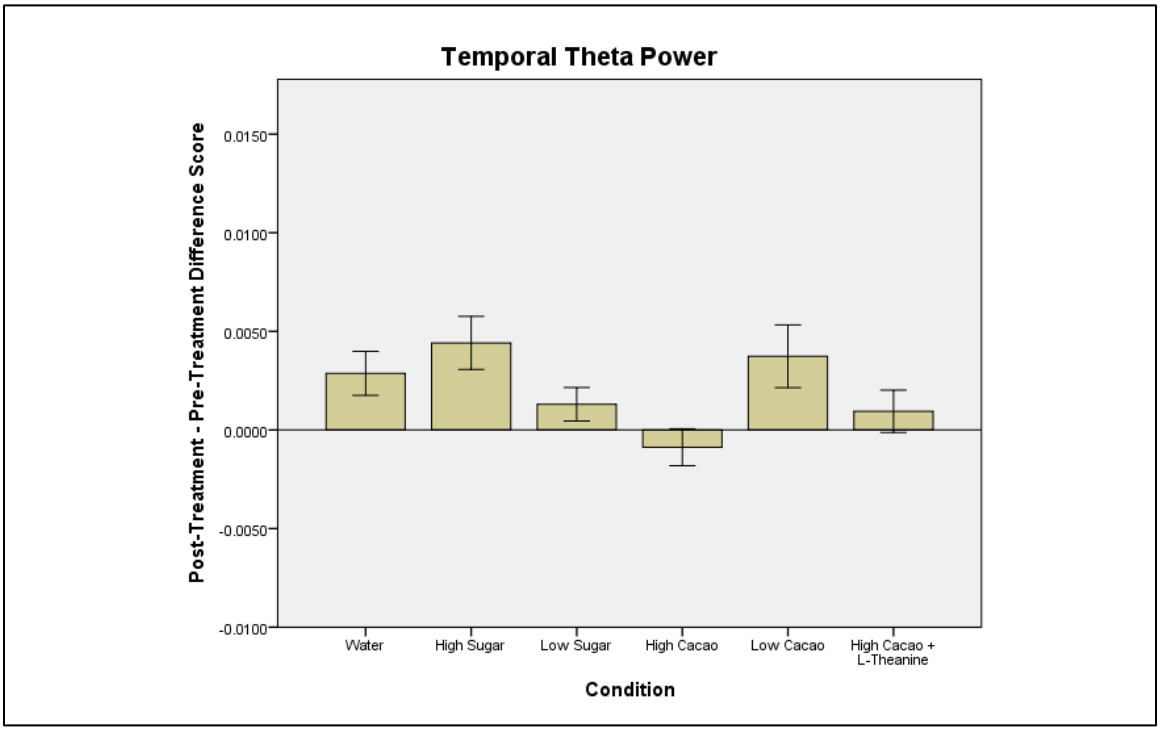

Figure 4. Temporal theta EEG absolute power changes post-treatment minus pre-treatment for each condition, showing significant decreases for higher cacao relative to water, high sugar, and low cacao. SE bars = +/- 1 SE.

Examining narrower frequency bins within the theta band revealed corresponding changes to those reported above for the higher cacao-content chocolate in frontal, parietal, and temporal low theta (4–5.99 Hz) relative to water (p = .030, .010, .011), high sugar (p = .014, .010, .004), low sugar (p = .005, .010, .007), and low cacao-content chocolate (p = .008, .003, .002). Within the high theta (6–7.99 Hz) bin, only the frontal region reached statistical significance for higher cacao-content chocolate relative to water (p = .009), high sugar (p < .0001), low sugar (p = .028), and low cacao-content chocolate (p = .009). These consistent changes in high and low theta frequency bins, primarily in frontal regions, suggest a suppressant effect of cacao on these frequencies. High theta frequency in the temporal region showed very small increases with consumption of low sugar (p = .008) and higher cacao-content chocolate (p = .009) relative to larger high sugar condition increases, an apparent enhancing effect of sugar on the high theta frequency in this region since the higher cacao-content chocolate contained the same amount of sugar as the low sugar condition.

Significant main effects were also obtained for frontal alpha across treatment conditions, $F(5, 110) = 2.93$, p = .016, η^2 = .117. There were no gender or interaction effects for any clusters or alpha frequencies, nor did analysis of any narrow alpha frequency bins result in significant effects. Examination of simple effects for frontal alpha revealed decreases across treatment for the low sugar and higher cacao-content chocolate conditions relative to increases for high sugar (p = .003, .025) and low cacao-content chocolate (p = .006, .047) conditions and for low sugar relative to water (p = .018). Given that low sugar and higher cacao-content chocolate conditions were identical for low sugar levels and that high sugar and low cacao conditions were identical for higher sugar levels, these results suggest an effect of sugar on increasing alpha frequencies in frontal regions. These frontal alpha effects are presented graphically in Figure 5.

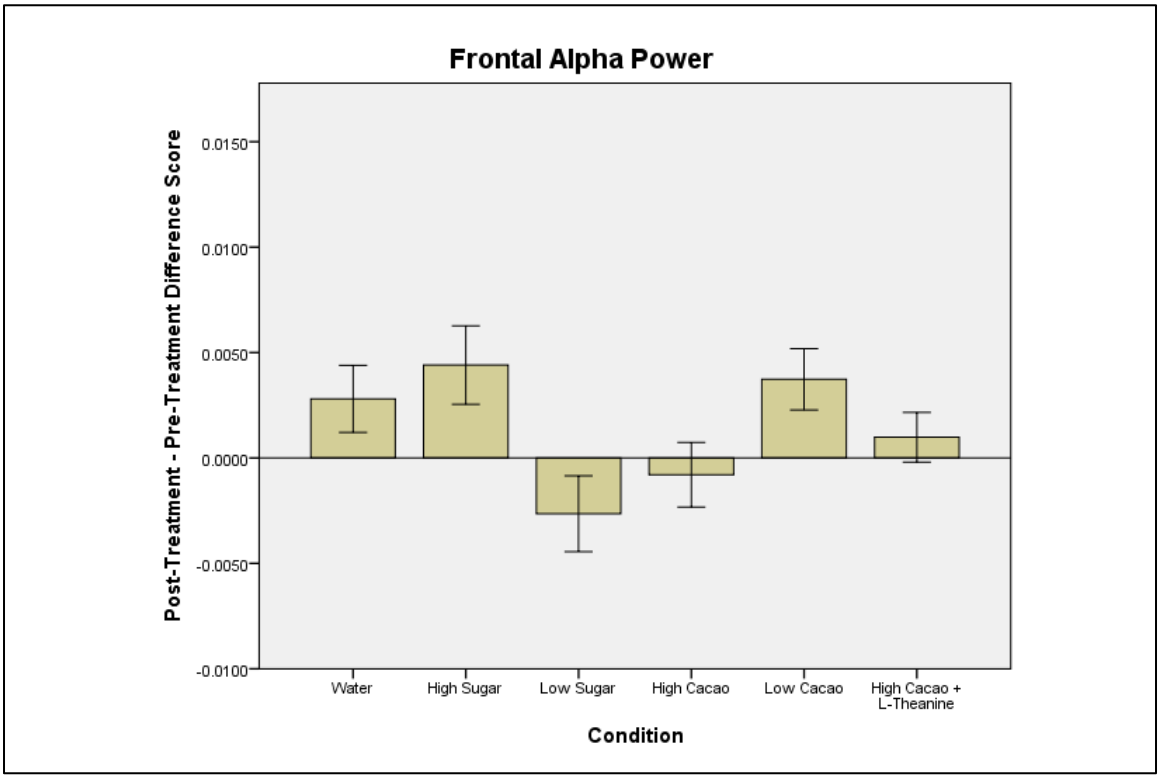

Figure 5. Frontal alpha EEG absolute power changes post-treatment minus pre-treatment for each condition, showing significant decreases for low sugar and higher cacao relative to increases for high sugar and low cacao and for low sugar relative to water. SE bars = +/- 1 SE.

Significant main effects were obtained for frontal beta, $F(5, 110) = 2.80$, $p = .02$, $\eta^2 = .113$; central beta, $F(5, 110) = 3.59$, $p = .005$, $\eta^2 = .14$; and occipital beta EEGs, $F(5, 110) = 2.45$, $p = .038$, $\eta^2 = .10$. No significant gender or interaction effects were obtained. Planned and post-hoc comparisons revealed that for frontal and central regions high sugar was associated with beta increases relative to decreases for water ($p = .003, .006$), low sugar ($p = .019, .016$), higher cacao-content chocolate ($p = .002, .004$), and higher cacao-content chocolate + L-Theanine ($p = .049, .022$), and that for central regions low cacao-content chocolate was associated with beta increases relative to decreases for water ($p = .009$), low sugar ($p = .025$), higher cacao-content chocolate ($p = .007$), and higher cacao-content chocolate + L-Theanine ($p = .035$). In occipital regions, high sugar was also associated with increases in beta relative to decreases for water ($p = .002$) and low sugar ($p = .016$). Again, these beta increases following the consumption of high sugar water in frontal, central, and occipital regions and in central regions following the consumption of a low cacao-content chocolate confection containing comparable high sugar levels, suggest a beta EEG enhancement effect of sugar in these cortical regions. However, an additional, marginally significant ($p = .05$) increase in beta EEG for the higher cacao-content chocolate condition relative to a decrease for water in occipital regions, in the absence of a corresponding increase for the low sugar condition, suggests a potential specific beta enhancement effect for the higher cacao confection. This beta enhancement effect is graphically presented in Figure 6.

No significant main or interaction effects were obtained for delta or gamma EEG frequencies. The absence of these outcomes suggests no statistically significant effect of any of the six conditions on delta and gamma EEG frequencies within the cortical regions studied.

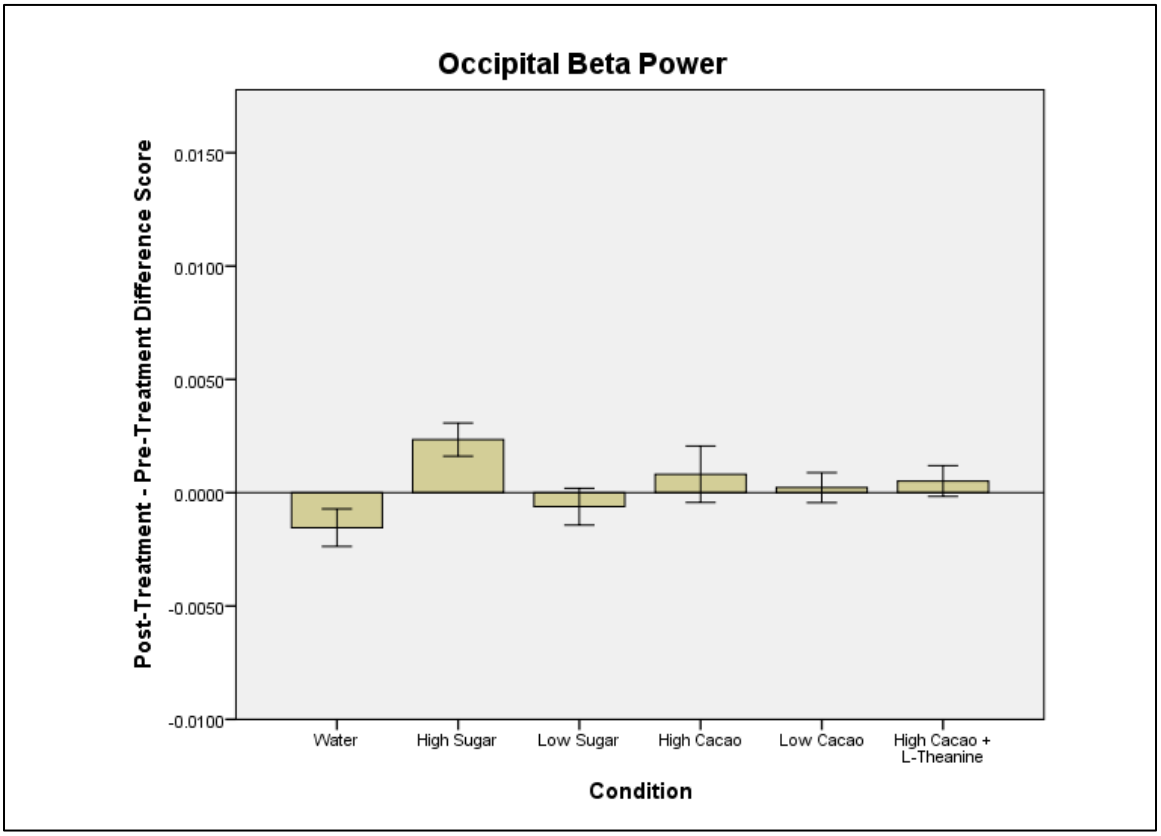

Figure 6. Occipital beta EEG absolute power changes post-treatment minus pre-treatment for each condition, showing significant increases for higher cacao relative to decreases for water. SE bars = +/- 1 SE.

LORETA Source Localization Effects

In order to separate the effects of cacao from sugar in our study, we compared the higher cacao-content condition with the low sugar condition and examined Current Source Density for the higher cacao-content constituents free of sugar effects. Figures 7 and 8 show cortical generators for the low theta and beta frequencies respectively, with relevant neuroimaging parameters reported. The parahippocampal gyrus and sub-gyral hippocampus in the right posterior limbic lobe reflect areas of maximal difference between conditions for the obtained low theta suppressant effect. Maximal differences for the obtained beta enhancement effect involved posterior portions of the medial frontal gyrus and the paracentral lobule in the frontal lobe and the anterior cingulate gyrus in the limbic lobe. Implications of these CSD localization findings are discussed below.

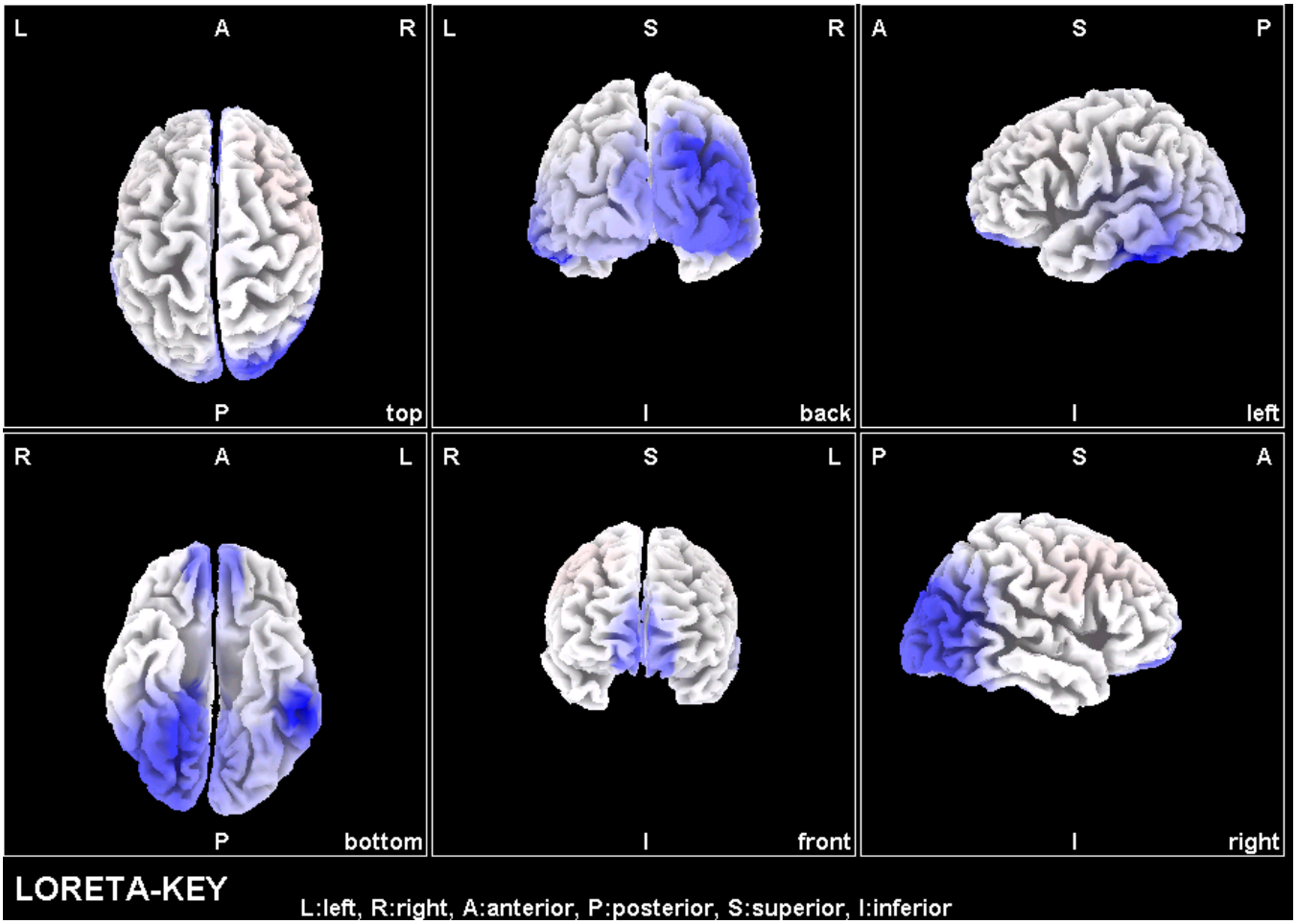

Figure 7. LORETA low theta maximal CSD for the higher cacao-content condition minus the low sugar condition. (Blue color indicates diminished activity.) Mean t = -0.393; SD = 0.420; Maxim t = 4.00; Scale range = +/- 1.36.

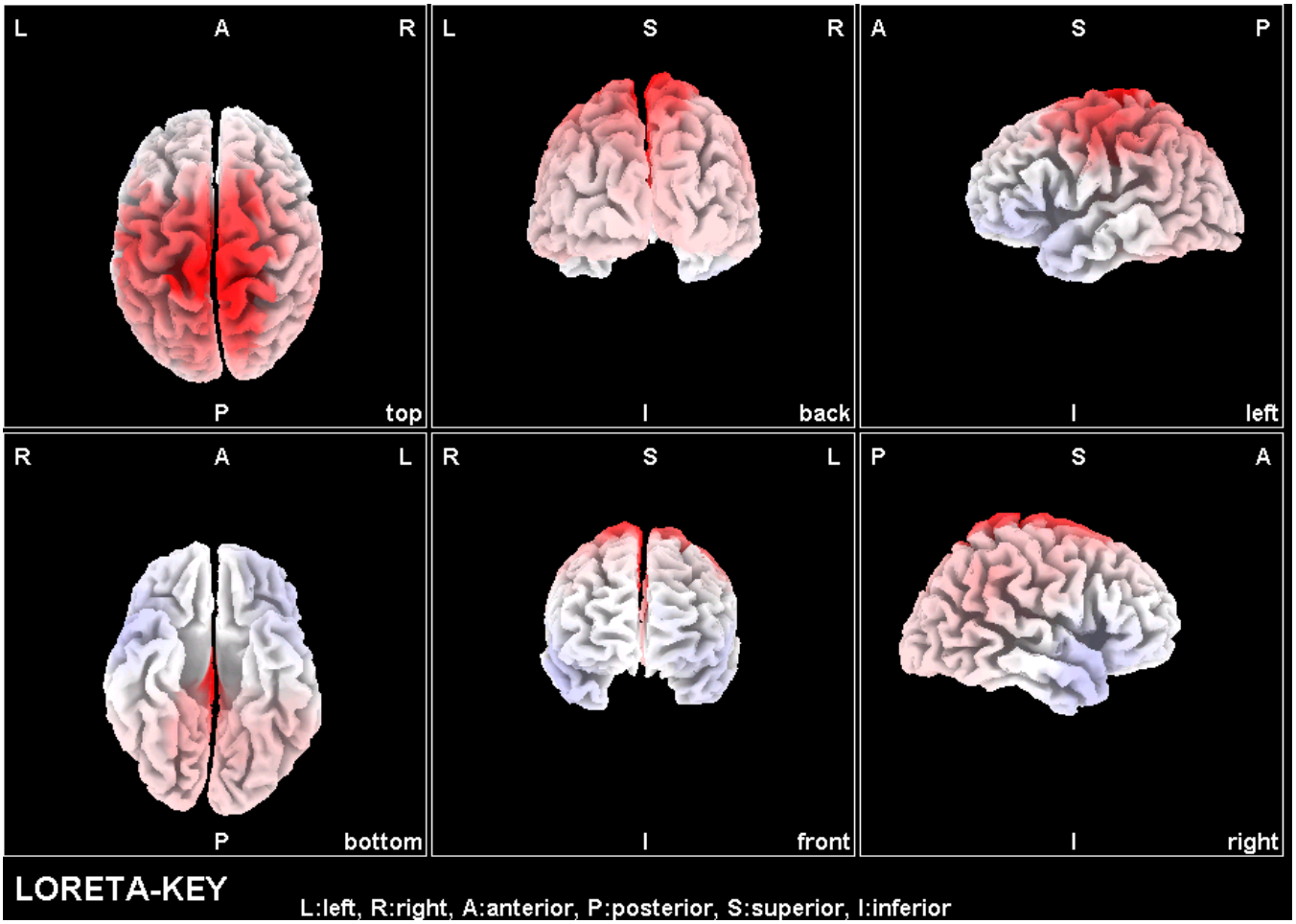

Figure 8. LORETA beta maximal CSD for the higher cacao-content condition minus the low sugar condition. (Red color indicates increased activity.) Mean t = 0.52; SD = 0.76; Maxim t = 4.00; Scale range = +/- 1.92.

Analysis of Blood Pressure Changes

Diastolic and systolic blood pressure changes from baseline to 70-min after ingestion for each treatment and for each gender were analyzed by separate 2 (genders) x 6 (treatments) ANOVAs. For DBP, a significant treatment main effect was found, $F(5, 110) = 6.57$, $p < .0001$, $\eta^2 = .23$, but no significant gender effect, $F(1, 110) = 0.002$, $p = .96$, $\eta^2 < .0001$, and no significant interaction effect, $F(5, 110) = 0.74$, $p = .59$, $\eta^2 = .03$, were obtained. Planned comparisons across treatments for DBP revealed higher cacao-content chocolate DBP to be significantly greater than the higher cacao-content chocolate + L-theanine and water conditions, and higher cacao-content chocolate + L-theanine DBP to be significantly lower than the higher cacao-content chocolate, low cacao-content chocolate, low sugar, and high sugar conditions ($p < .05$). These effects are presented in Table 8 and Figure 9.

For SBP, a significant condition main effect was found, $F(5, 110) = 4.02$, $p = .002$, $\eta^2 = .16$, but no significant gender effect, $F(1, 110) = 0.14$, $p = .71$, $\eta^2 = .001$, and no significant interaction effect, $F(5, 110) = 1.32$, $p = .26$, $\eta^2 = .06$, were obtained. Planned comparisons across conditions for SBP revealed higher cacao-content chocolate + L-theanine SBP to be significantly lower than the higher cacao-content chocolate, low cacao-content chocolate, low sugar, and high sugar conditions ($p < .05$). These effects are presented in Table 8 and Figure 10.

Table 8
Systolic and Diastolic Blood Pressure Changes (Post-Ingestion – Pre-Ingestion)

	Condition Mean (S.E.) BP Change (+ Value = BP Increase)					
	A	B	C	D	E	F
Blood Pressure	Water	High Sugar	Low Sugar	High Cacao	Low Cacao	High Cacao + L-theanine
Systolic	-0.52 (0.72)	+2.55 (1.57)	+1.25 (1.20)	+1.70 (1.65)	+0.57 (1.25)	-5.15 (1.65)** F < B, D, C, E
Diastolic	-0.43 (0.63)	+1.65 (0.71)	+0.85 (0.89)	+4.70 (1.42)* D > F, A	+1.71 (1.06)	-3.65 (1.39)* F < D, E, B, C
N	21	20	20	20	21	20

* = Statistically significant at $p < .05$; ** = Statistically significant at $p < .0001$. All Effects are Post-Condition – Pre-Condition effects for A = water, B = high sugar, C = low sugar, D = higher cacao-content, E = low cacao-content, F = higher cacao-content + L-theanine.

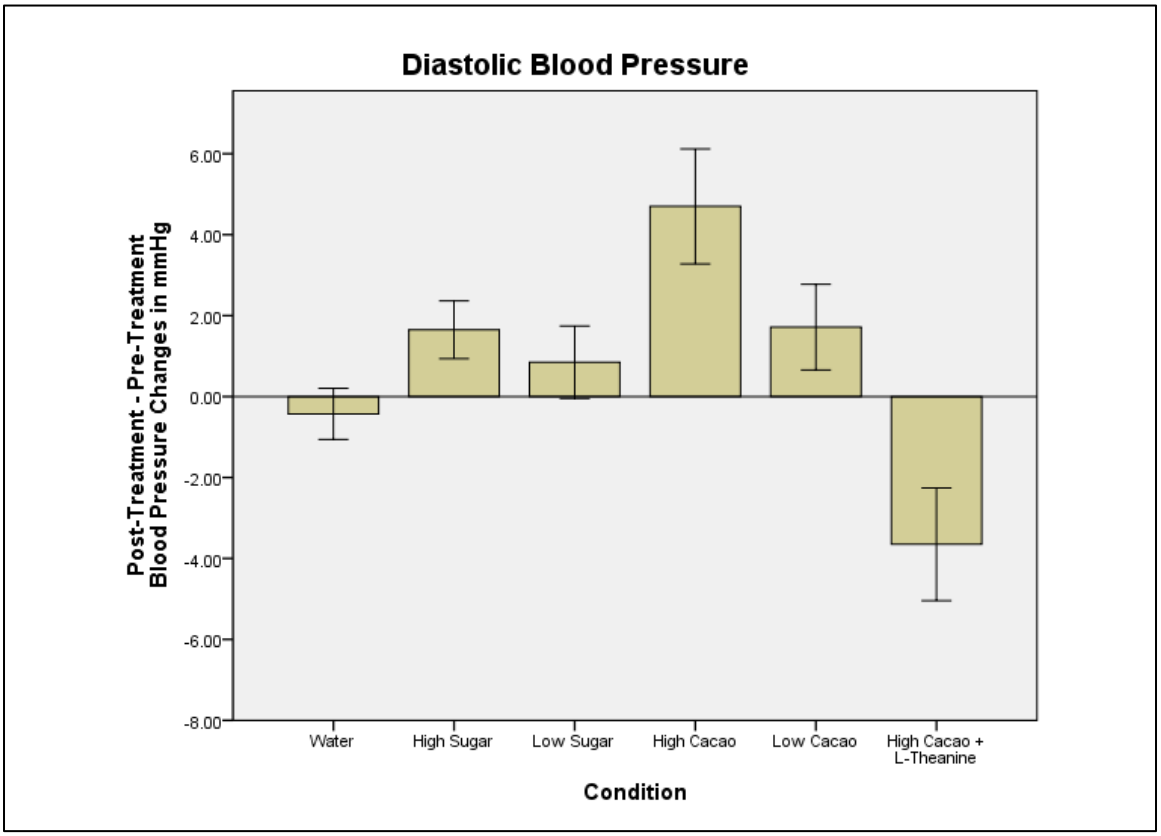

Figure 9. Diastolic blood pressure changes post-treatment minus pre-treatment for each condition, with higher cacao significantly greater than higher cacao + L-theanine and water, and higher cacao + L-theanine significantly lower than higher cacao, low cacao, low sugar, and high sugar. SE bars = +/- 1 SE.

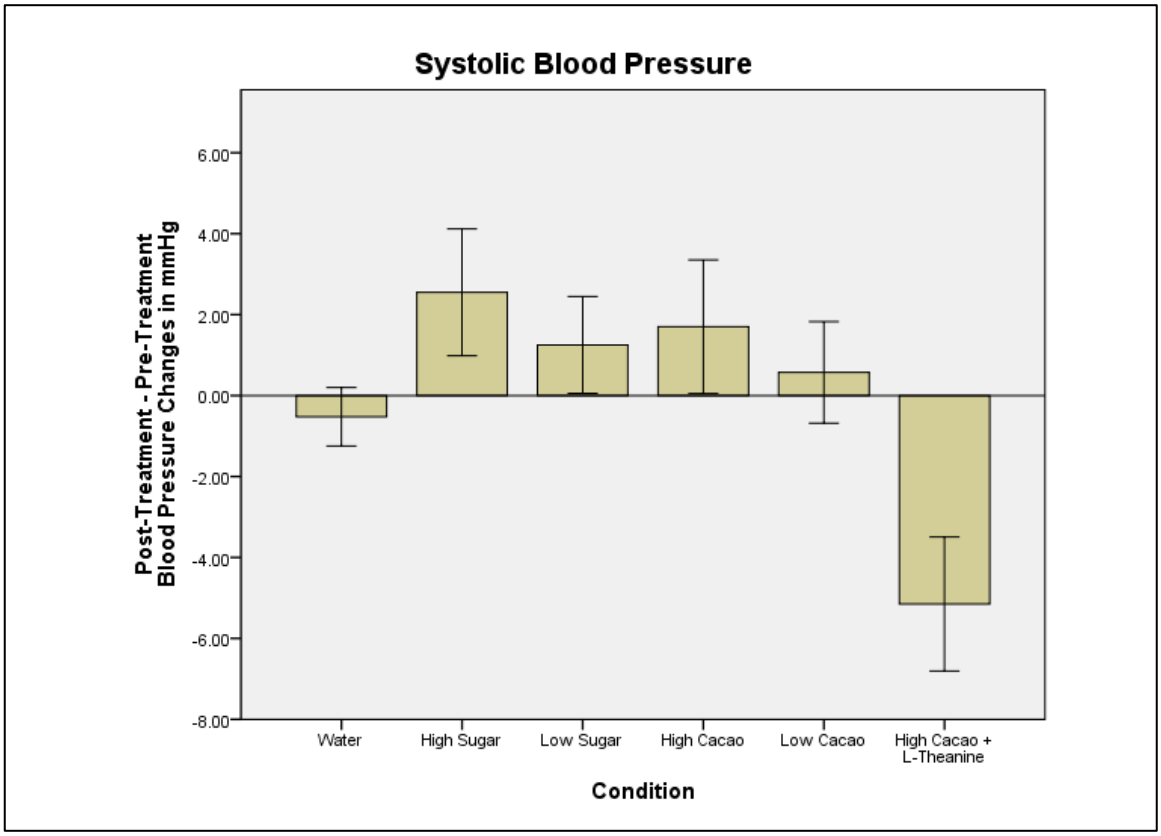

Figure 10. Systolic blood pressure changes post-treatment minus pre-treatment for each condition, with higher cacao + L-theanine significantly lower than higher cacao, low cacao, low sugar, and high sugar. SE bars = +/- 1 SE.

Discussion

General Findings

Consistent with our hypotheses, it appears that chocolate does have an acute stimulatory effect on components of both the central (CNS) and peripheral nervous systems (PNS). In order to understand the nature and implications of these outcomes, it is important to examine the effects on CNS and PNS arousal of specific treatment conditions. The act of sitting quietly and reading neutral magazines during the water condition for our sample of healthy college students tended to diminish CNS arousal, as attested to by general decreases in posterior beta and increases in anterior theta EEG frequencies. The combination of decreased beta and increased theta is commonly seen in attentional disorders and often reflects inattention and "spacing out" (Lubar, Swartwood, Swartwood, & O'Donnell, 1995; Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992), not to be unexpected among college students sitting quietly and reading uninteresting magazines. This diminution of the CNS arousal was inhibited by the consumption of a high sugar drink (increased diffuse beta) and by the consumption of a higher cacao-content chocolate (decreased anterior theta and increased posterior beta). Interestingly, although the high sugar drink was very effective in increasing cortical beta in general, it was not effective in decreasing theta across the cortex, whereas the higher cacao-content chocolate condition was statistically equivalent to high sugar in increasing posterior beta but far more effective in decreasing more diffuse theta activity, even though the higher cacao-content condition contained less sugar (0.35 g/kg body weight) than the high sugar condition (0.57 g/kg body weight). This effect is further supported by a significantly diminished beta enhancement by the low sugar condition relative to high sugar, the former containing an equivalent amount of sugar to the higher cacao-content conditions but none of the cacao bioactive components.

Furthermore, the possibility of these effects being also due to changes in mu rhythms during page turning and lambdoid waves during saccadic eye movements while reading seems unlikely in that both the pre-ingestion and post-ingestion EEGs were recorded eyes closed before and after, respectively, the reading of magazines, with approximately 5 minutes intervening after stopping reading and before post-ingestion EEG recording while the Electro-Cap was repositioned, impedances were checked, and good clean EEG traces were obtained. These observations suggest a supplemental and differential stimulating effect of the bioactive compounds in cacao (such as biogenic amines and/or methylxanthines) over that of sugar, with sugar increasing cortical beta and cacao decreasing cortical theta.

Potential Biogenic Amines Underlying EEG Cacao Effects

Changes in biogenic amine neurotransmission are associated with distinctive patterns of EEG change. In Fischer rats for example, small declines in EEG slow wave activity have been associated with administration of dopamine agonists (Dimpfel, 2005). These declines were followed, 90 min later, by increases in theta, delta, and alpha 2 activity in the hippocampus and frontal cortex. The administration of the highest L-Dopa dose replicated the biphasic low dose finding but predominately in the frontal cortex. It is noteworthy that increases in theta spectral power have been associated with reports of increased tiredness and sedation in humans (Dimpfel, 2008; Dimpfel & Schober, 2001; Vyazovskiy & Tobler, 2005) and also with increased attentional demands during mental work (Schober, Schellenberg, & Dimpfel, 1995; Schwarz-Ottersbach & Goldberg, 1986). Also, administration of direct D2 agonists was found to decrease alpha 2 power in the frontal cortex, hippocampus, and striatum but not in the reticular formation. Predictably the administration of a DA2 antagonist dramatically increased alpha 2 power in the frontal cortex 3 hr after administration of the highest dose. Our data, collected on humans within an hour after the administration of varied cacao doses (with or without theanine) from frontal, temporal, and parietal sites, are consistent with these acute theta wave declines reported by Dimpfel (2008).

Given the known relationship between dopamine (D) regulation and acetylcholine (ACh) neurotransmission, these low dose agonist effects are thought to be associated with the activation of heterosynaptic presynaptic D2 receptors located on cholinergic neurons involving the cAMP inhibition of activity in the b-arrestin pathway (Dimpfel, 2008). Data presented by Zhang, Zhou, and Dani (2004) demonstrating increased dopamine release following administration of an ACh esterase inhibitor supports this conclusion. Conversely, declines in alpha 2 activity have been associated with the administration of an ACh M1 antagonist. Clearly, the availability of different receptor subtypes and their pharmacological selectivity in different neuroanatomical circuits (cortical and subcortical) help regulate both DA and ACh neurotransmission and EEG frequency pattern alterations. However, the precise subcortical neuroanatomical circuitry responsible for these changes has yet to be elucidated and behavioral data collected concurrently are limited. Moreover, these effects are dose-dependent and area specific, as well as time-, drug-, and task-dependent. To complicate matters further, norepinephrine reuptake inhibitors have been demonstrated to increase theta wave activity in the septo-hippocampal area (Hajós, Hoffman, Robinson, Yu, & Hajós-Korcsok, 2003) and administration of the antihypertensive, anxiolytic, and alpha 1 adrenergic receptor agonist clonidine has also been demonstrated to increase theta EEG activity (Dimpfel & Schober, 2001). With regard to the biogenic amines, alterations in EEG outcomes not only appear to involve differing signal activity in different cortical and subcortical neuroanatomical pathways, but also the integration of differing subcellular neuronal processes involved in complex neuronal patterns and behavior associated with cacao-induced electrocortical changes.

For example, cacao flavanols are known to cross the blood brain barrier, to increase blood circulation in brain, to exert antioxidative effects, to increase nitric oxide production, and to trigger protein-receptor synthesis via mitogen-activated protein, phosphoinositide 3-kinase, and extra-signal regulated subcellular cascades, all of which are associated with the neuromodulation of long-term potentiation integral to the formation of memories and neurocognitive function (Sokolov et al., 2013). The neurological impacts of cacao flavanols have also been reported to exert neuroprotective and neuromodulatory effects that promote synaptic connectivity, alter cognition and behavior and promote endothelium-dependent vasodilation (Sokolov et al., 2013). Flavanoids have also been demonstrated to promote neurogenesis and memory formation and to protect against neuronal cell death by increasing the expression of brain derived neurotrophic factor in the hippocampus. And, with regard to acute and chronic consumption effects, the

short-term oral exposure to 100 mg/100 g body weight of cacao exerted an anxiolytic effect on elevated T-maze behavior in rats, whereas exposure to cacao for 2 weeks increased brain serotonin concentration and turnover rate but failed to alter elevated T-maze behavior (Yamada, Yamada, Okano, Terashima, & Yokogoshi, 2009). Nonetheless, in humans, the effects of cacao-derived flavanols on cognitive function and mood have not been clearly elucidated and the effects of acute vs. long-term exposure to flavanols on arousal and EEG changes relating to these processes have not been adequately investigated.

L-theanine EEG Effects

L-theanine has a documented EEG alpha enhancement effect in the research literature (Juneja et al., 1999; Kimura et al., 2007; Kobayashi et al., 1998). While we did not find such an effect with our higher cacao-content + L-theanine confection, we theorize this to be due to the sympathomimetic ingredients in chocolate suppressing slow wave (alpha and theta) and enhancing fast wave (beta) activity. The absence of a significant alpha suppression effect with the higher cacao-content condition is noteworthy. EEG alpha has been historically associated with quiet rest and relaxation. Activation of the brain with increased beta and decreased alpha could actually be perceived by participants as an increase in anxiety and agitation. The finding of increased beta, decreased theta, and a stable alpha frequency with a moderate cacao-content confection suggests that our participants were neurologically activated but without the agitation that might have been perceived had alpha actually been suppressed as well. These CNS arousal without anxiety effects are supported by the absence of significant changes in PANAS mood scores, particularly those related to anxiety/agitation. As noted above, our results suggest that a high sugar beverage can actually increase alpha over our 60% cacao confection, perhaps having implications for a combination of these two substances.

Cortical Source Generators

LORETA cortical source localizations of the surface potentials generated by cacao consumption, independent of sugar effects, suggest some intriguing implications for the impact of cacao on the human brain. Although theta rhythms have been associated with visual imagery, problem solving, perceptual processing, attentive performance in cognitive tasks, creativity, and dissociative states (Stevens et al., 2004), low theta during quiet waking predicts the subsequent development of sleep slow-wave activity and an increase in sleep propensity (Makeig, Jung, & Sejnowski, 2000; Vyazovskiy & Tobler, 2005). Therefore, the suppression of low theta following the consumption of cacao in the present study indicates a counteracting of natural drowsiness induced by an hour of quiet reading of neutral magazines. Since the structures activated are primarily involved with the encoding and recognition of scenes such as landscapes, cityscapes, etc., the content of many of the magazines available during the digestion phase, and with episodic memory (Orrison, 2008), these results suggest an activation of task-related processes in the brain following the consumption of the higher cacao-content confection independent of sugar. Similarly, the enhancement of posterior frontal and anterior cingulate beta frequencies indicates an activation of such executive functions as the recognition of similarities and differences, retention of long term memories, learning, problem-solving, and mental conflict resolution (Orrison, 2008). Taken together, the localization of cortical source generators of the observed surface potentials suggests an enhancement of task-related activities following consumption of cacao in our study. Furthermore, the nature of these brainwave changes directly counteracts those specific frequencies seen during diminished attention.

Acute Blood Pressure Effects

Peripherally, the acute effects (1 hr after consumption) of higher cacao-content and of higher cacao-content + L-theanine ingestion on blood pressure were rather remarkable, with BP changes on the order of 3–5 mmHg. It is noteworthy that while the higher cacao-content condition significantly increased DBP relative to the water condition, it did not significantly do so when compared with the low cacao-content condition. These higher and lower cacao conditions differed considerably in the presence of the psychoactive biogenic amines, tyramine and, particularly, PEA, and the methylxanthines, caffeine and, particularly, theobromine, and would be expected to have a stronger differential effect on blood pressure. Although not statistically significant, these differences were in the predicted direction and were on the order of 3 mmHg different. As mentioned below, it is likely that the only moderate levels of cacao used in this study contributed to this small effect. It is also possible that more prominent vasoconstrictive effects of these sympathomimetics were counteracted by beginning vasodilatation effects of the epicatechin polyphenols in the higher cacao-content product, thus diminishing treatment differences. One can only speculate at this point

what these differences would have been for a higher cacao-content chocolate containing more of these psychoactive compounds.

While the more immediate effect of consuming a higher cacao-content confection was an increase in diastolic BP of 4.7 mmHg on average, the higher cacao-content + L-theanine confection actually counteracted this effect by lowering diastolic BP 3.65 mmHg on average and systolic BP 5.15 mmHg. The potential antihypertensive effect of lowering diastolic blood pressure from the 4.7 mmHg increase seen with higher cacao-content to the 3.65 mmHg decrease seen with higher cacao-content + L-theanine represents an 8.4 mmHg decrease in diastolic blood pressure. These blood pressure lowering outcomes following a single recommended dose of the L-theanine additive represent approximately one-third to one-half the effects of sustained use of standard antihypertensive medications, and without documented side effects (Mason, 2004; Wu et al., 2005). Given the apparent ability of L-theanine to inhibit the more immediate sympathomimetic effects of cacao and to acutely lower blood pressure, combined with the documented longer term antihypertensive effects of polyphenols in cacao, there is clearly the possibility of an application of this combination of L-theanine and cacao in the treatment of hypertension. This exciting possibility is certainly speculative at the present time and awaits further directive research into the longer term consequences of cacao + L-theanine use, particularly for higher doses of both constituents.

Limitations

Overall, these CNS arousal effects suggest that the constituents in cacao (polyphenols, biogenic amines and/or methylxanthines) can inhibit naturally occurring deactivation of the brain during mundane and less interesting tasks. The relative enhancement of beta and suppression of theta frequencies found in this study indicate that higher cacao-content chocolate may have an impact upon electrocortical processes implicated in diminished attention, a common complaint among college students attending lectures and reading academic material. A limitation of this study was that we did not directly measure attentional behavior. Given our findings, it would be of interest in future studies of the effects of chocolate to do so. It is also important to note that this same combination of suppressed beta and enhanced theta has been reported in diagnosed Attention Deficit Disorder (ADD; Lubar, et al., 1995; Mann, et al., 1992). While our participants were not ADD patients, it would be interesting to replicate this study and to observe not only EEG changes but also measures of attentional performance with such a clinical sample.

For reasons of palatability and availability, our study utilized a dark chocolate confection containing only moderate amounts (60%) of cacao. This choice of chocolate confections was a major limitation of this study and quite likely resulted in the small effect sizes (< .25; See Cohen, 1988) found in our analyses, even though the results reported were statistically significant. There are quite palatable chocolate preparations publicly available containing up to 90% cacao. Certainly this study should be replicated with a palatable chocolate confection containing higher percentages of cacao or increased concentrations of cacao bioactives to increase the magnitude of effect and to better understand which cacao constituents are predominantly responsible for these effects. Also of interest for future research would be to examine these enhanced effects for more individualized frequency bins, as suggested by Klimesch (1999).

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Appendix

Table 2

*Absolute **Delta** Power for each electrode site for each condition at Baseline, after Treatment, and Differences (Post Treatment – Baseline)*

Electrode Position	Mean Values	Water Control	High Sugar Control	Low Sugar Control	High Cacao	Low Cacao	Theanine + High Cacao
Fp1	Baseline	608	679	696	669	731	382
	Post-Rx	537	793	651	823	790	449
	Difference	-071	114	-045	153	058	067
Fp2	Baseline	605	657	717	714	702	467
	Post-Rx	538	786	668	850	796	468
	Difference	-066	129	-049	137	095	001
F7	Baseline	481	557	565	693	632	304
	Post-Rx	411	665	621	647	649	317
	Difference	-069	108	055	-046	018	012
F3	Baseline	494	573	582	593	649	356
	Post-Rx	502	651	644	593	719	380
	Difference	008	078	062	-001	070	024
Fz	Baseline	537	571	592	620	669	387
	Post-Rx	555	677	693	589	756	408
	Difference	018	106	101	-030	087	022
F4	Baseline	487	520	551	677	626	350
	Post-Rx	480	610	624	547	724	366
	Difference	-007	090	074	-130	098	018
F8	Baseline	449	454	504	591	544	244
	Post-Rx	374	602	520	531	552	264
	Difference	-075	148	016	-060	007	020
T3	Baseline	247	305	311	307	348	194
	Post-Rx	229	333	344	298	396	203
	Difference	-018	028	034	-008	048	009
C3	Baseline	410	522	514	519	623	320
	Post-Rx	438	591	595	478	692	340
	Difference	027	069	081	-041	069	021
Cz	Baseline	545	654	649	725	760	436
	Post-Rx	606	752	774	623	923	460
	Difference	062	098	125	-102	163	024
C4	Baseline	413	481	486	537	565	341
	Post-Rx	432	549	564	488	742	347
	Difference	019	068	079	-049	177	007
T4	Baseline	208	240	263	265	283	259
	Post-Rx	197	289	324	254	325	169
	Difference	-012	049	060	010	042	-090
T5	Baseline	309	416	372	372	426	246
	Post-Rx	319	458	420	376	503	252
	Difference	011	042	048	004	077	007
P3	Baseline	413	550	525	541	633	334
	Post-Rx	431	618	581	523	701	346
	Difference	018	068	055	-018	069	012
Pz	Baseline	502	628	596	655	712	393
	Post-Rx	518	709	667	620	828	407
	Difference	016	081	071	-035	115	014
P4	Baseline	416	549	500	549	601	335
	Post-Rx	431	611	559	523	692	340
	Difference	015	062	059	-026	091	004
T6	Baseline	301	406	356	459	447	294
	Post-Rx	318	447	402	358	496	259
	Difference	017	041	047	-101	048	-035
O1	Baseline	431	582	511	532	569	362
	Post-Rx	483	658	546	550	647	371
	Difference	053	077	035	001	077	009
O2	Baseline	421	586	516	533	510	333
	Post-Rx	476	671	551	535	608	364
	Difference	054	085	035	002	098	031

NOTE: Values in the table are Absolute EEG Power uV^2 x 10^4 for ease of presentation.

Table 3

*Absolute **Theta** Power for each electrode site for each condition at Baseline, after Treatment, and Differences (Post Treatment – Baseline)*

Electrode Position	Mean Values	Water Control	High Sugar Control	Low Sugar Control	High Cacao	Low Cacao	Theanine + High Cacao
Fp1	Baseline	241	301	302	322	378	268
	Post-Rx	263	342	324	302	419	275
	Difference	022	041	023	-020	041	007
Fp2	Baseline	242	290	298	317	359	271
	Post-Rx	260	331	319	304	402	269
	Difference	019	041	021	-013	044	-001
F7	Baseline	195	255	239	280	314	221
	Post-Rx	206	287	266	252	346	221
	Difference	012	032	026	-028	033	000
F3	Baseline	307	450	432	445	562	347
	Post-Rx	359	518	480	392	645	362
	Difference	052	068	049	-053	083	015
Fz	Baseline	352	498	472	504	604	392
	Post-Rx	420	577	533	441	711	405
	Difference	069	079	061	-064	107	013
F4	Baseline	297	417	340	449	491	330
	Post-Rx	348	482	447	384	580	349
	Difference	051	065	048	-064	089	019
F8	Baseline	171	203	200	239	230	165
	Post-Rx	175	230	216	214	256	178
	Difference	004	027	016	-025	026	013
T3	Baseline	154	224	199	216	254	176
	Post-Rx	160	251	218	205	287	185
	Difference	006	026	018	-011	034	009
C3	Baseline	304	485	448	454	518	341
	Post-Rx	353	545	481	399	618	360
	Difference	049	060	033	-055	100	019
Cz	Baseline	423	618	578	657	698	446
	Post-Rx	509	700	651	533	843	466
	Difference	086	082	073	-124	145	020
C4	Baseline	300	475	440	466	507	351
	Post-Rx	354	523	453	399	611	364
	Difference	054	049	013	-067	104	013
T4	Baseline	115	167	162	172	170	148
	Post-Rx	123	182	168	158	196	141
	Difference	008	015	006	-014	026	-007
T5	Baseline	226	460	334	368	360	265
	Post-Rx	276	531	354	379	468	283
	Difference	050	071	020	010	108	018
P3	Baseline	336	633	508	516	597	385
	Post-Rx	400	732	528	494	695	408
	Difference	064	099	019	-022	098	022
Pz	Baseline	437	737	585	607	690	447
	Post-Rx	522	841	613	563	838	475
	Difference	084	104	027	-044	015	028
P4	Baseline	336	682	466	481	535	370
	Post-Rx	407	752	487	441	641	395
	Difference	072	070	022	-040	106	025
T6	Baseline	225	436	299	361	379	261
	Post-Rx	276	500	307	341	451	279
	Difference	051	064	008	-020	072	018
O1	Baseline	321	625	470	443	488	405
	Post-Rx	417	744	498	554	605	441
	Difference	096	119	028	111	117	035
O2	Baseline	313	722	446	460	420	365
	Post-Rx	400	850	492	437	525	395
	Difference	087	128	047	-023	105	031

NOTE: Values in the table are Absolute EEG Power uV^2 x 10^4 for ease of presentation.

Table 4

*Absolute **Alpha** Power for each electrode site for each condition at Baseline, after Treatment, and Differences (Post Treatment – Baseline)*

Electrode Position	Mean Values	Water Control	High Sugar Control	Low Sugar Control	High Cacao	Low Cacao	Theanine + High Cacao
Fp1	Baseline	282	384	305	291	296	270
	Post-Rx	308	425	274	282	321	279
	Difference	025	040	-031	-009	025	009
Fp2	Baseline	277	373	296	281	284	267
	Post-Rx	298	413	267	273	310	273
	Difference	021	040	-029	-008	026	006
F7	Baseline	220	320	240	237	260	209
	Post-Rx	242	347	221	229	284	219
	Difference	022	027	-019	-008	025	011
F3	Baseline	368	560	460	400	425	374
	Post-Rx	405	614	417	391	475	387
	Difference	037	054	-043	-009	051	013
Fz	Baseline	406	607	496	434	448	421
	Post-Rx	451	675	453	427	505	429
	Difference	045	068	-043	-007	058	008
F4	Baseline	350	526	427	383	386	362
	Post-Rx	385	581	390	374	440	372
	Difference	035	054	-037	-008	054	010
F8	Baseline	188	266	196	191	196	175
	Post-Rx	199	291	185	184	219	186
	Difference	011	025	-011	-007	023	012
T3	Baseline	196	336	249	219	257	193
	Post-Rx	214	361	227	231	288	206
	Difference	019	025	-021	012	031	013
C3	Baseline	435	804	630	478	553	452
	Post-Rx	465	817	559	484	633	469
	Difference	030	013	-071	006	080	017
Cz	Baseline	551	875	693	592	644	531
	Post-Rx	597	945	620	578	736	547
	Difference	047	070	-073	-014	091	016
C4	Baseline	447	820	649	477	548	484
	Post-Rx	483	852	540	455	627	490
	Difference	036	032	-109	-022	079	006
T4	Baseline	162	271	183	176	191	188
	Post-Rx	173	279	162	168	214	193
	Difference	011	007	-021	-008	023	005
T5	Baseline	641	1149	652	690	676	556
	Post-Rx	746	1200	573	686	858	599
	Difference	105	051	-079	-004	181	044
P3	Baseline	885	1474	1014	954	1072	754
	Post-Rx	998	1521	870	915	1181	797
	Difference	113	047	-144	-039	108	043
Pz	Baseline	1063	1716	1234	1140	1171	869
	Post-Rx	1151	1763	1067	1083	1369	925
	Difference	088	047	-166	-057	198	056
P4	Baseline	937	1623	1036	976	1019	828
	Post-Rx	1046	1643	892	933	1123	898
	Difference	109	020	-143	-043	105	070
T6	Baseline	758	1147	682	698	985	651
	Post-Rx	854	1209	584	791	1000	769
	Difference	096	062	-099	092	016	118
O1	Baseline	1689	2328	1513	1327	1550	1505
	Post-Rx	1839	2505	1325	1399	1717	1620
	Difference	151	177	-188	072	166	115
O2	Baseline	1663	2651	1538	1639	1608	1370
	Post-Rx	1710	2826	1430	1696	1864	1543
	Difference	047	175	-108	058	256	173

NOTE: Values in the table are Absolute EEG Power uV^2 x 10^4 for ease of presentation.

Table 5

*Absolute **Beta** Power for each electrode site for each condition at Baseline, after Treatment, and Differences (Post Treatment – Baseline)*

Electrode Position	Mean Values	Water Control	High Sugar Control	Low Sugar Control	High Cacao	Low Cacao	Theanine + High Cacao
Fp1	Baseline	063	049	050	051	046	045
	Post-Rx	055	060	049	050	049	048
	Difference	-009	011	-001	-001	004	003
Fp2	Baseline	075	049	046	047	051	044
	Post-Rx	058	060	047	046	047	045
	Difference	-017	011	001	-001	-004	002
F7	Baseline	043	054	040	043	043	037
	Post-Rx	040	057	039	041	046	040
	Difference	-004	004	-001	-002	002	004
F3	Baseline	060	065	059	059	058	052
	Post-Rx	056	075	060	056	064	053
	Difference	-004	010	001	-003	005	000
Fz	Baseline	062	064	060	060	059	055
	Post-Rx	057	076	060	059	064	054
	Difference	-005	012	000	-001	006	-001
F4	Baseline	067	061	056	057	055	051
	Post-Rx	058	071	057	055	061	051
	Difference	-008	011	001	-002	005	000
F8	Baseline	036	042	032	036	033	030
	Post-Rx	035	044	032	033	038	032
	Difference	-001	002	000	-003	005	002
T3	Baseline	063	067	042	050	051	040
	Post-Rx	053	068	038	045	050	045
	Difference	-009	001	-003	-005	-001	005
C3	Baseline	065	077	064	064	065	054
	Post-Rx	058	083	061	062	074	054
	Difference	-007	006	-004	-002	009	000
Cz	Baseline	071	076	069	075	071	062
	Post-Rx	064	087	067	074	078	060
	Difference	-006	011	-001	-001	007	-002
C4	Baseline	064	075	064	065	062	056
	Post-Rx	056	082	059	064	068	054
	Difference	-008	007	-005	-001	006	-003
T4	Baseline	040	077	054	039	059	041
	Post-Rx	036	067	046	034	047	033
	Difference	-003	-009	-008	-005	-012	-008
T5	Baseline	071	086	066	072	071	060
	Post-Rx	068	096	065	090	081	067
	Difference	-003	010	-000	018	010	007
P3	Baseline	086	091	078	094	086	071
	Post-Rx	079	101	074	110	087	072
	Difference	-007	010	-004	017	002	001
Pz	Baseline	095	094	087	106	090	077
	Post-Rx	086	106	081	123	093	077
	Difference	-009	013	-006	017	002	-000
P4	Baseline	087	092	078	096	084	072
	Post-Rx	079	102	074	107	084	071
	Difference	-007	010	-005	011	-000	-002
T6	Baseline	072	075	061	073	078	054
	Post-Rx	065	084	057	081	074	061
	Difference	-007	009	-004	008	-003	007
O1	Baseline	145	142	120	156	123	129
	Post-Rx	128	166	113	181	123	129
	Difference	-017	024	-007	025	-001	000
O2	Baseline	138	141	116	170	119	117
	Post-Rx	124	164	111	187	124	127
	Difference	-014	023	-005	017	006	010

NOTE: Values in the table are Absolute EEG Power uV^2 x 10^4 for ease of presentation.

Table 6

*Absolute **Gamma** Power for each electrode site for each condition at Baseline, after Treatment, and Differences (Post Treatment – Baseline)*

Electrode Position	Mean Values	Water Control	High Sugar Control	Low Sugar Control	High Cacao	Low Cacao	Theanine + High Cacao
Fp1	Baseline	020	013	014	013	012	012
	Post-Rx	016	014	014	012	013	014
	Difference	-003	001	-000	-001	001	001
Fp2	Baseline	027	014	012	012	017	011
	Post-Rx	019	016	012	011	012	012
	Difference	-008	003	000	-001	-005	001
F7	Baseline	012	024	009	011	013	008
	Post-Rx	010	021	008	009	012	011
	Difference	-002	-003	-001	-002	-001	003
F3	Baseline	009	011	008	008	007	006
	Post-Rx	008	010	007	007	008	007
	Difference	-001	-000	-000	-001	001	001
Fz	Baseline	007	007	006	006	006	005
	Post-Rx	006	007	005	006	006	005
	Difference	-001	000	-000	-001	-000	000
F4	Baseline	013	009	007	007	008	006
	Post-Rx	009	009	007	006	009	006
	Difference	-003	-000	-000	-001	001	001
F8	Baseline	009	016	006	009	009	006
	Post-Rx	009	014	006	007	012	008
	Difference	000	-003	-001	-002	003	002
T3	Baseline	022	032	010	014	015	010
	Post-Rx	017	026	008	010	012	012
	Difference	-005	-005	-003	-004	-003	001
C3	Baseline	007	013	007	008	007	005
	Post-Rx	006	011	006	005	010	005
	Difference	-001	-002	-001	-003	003	001
Cz	Baseline	006	007	006	006	006	005
	Post-Rx	006	007	006	006	006	005
	Difference	-001	000	-000	-000	000	000
C4	Baseline	007	012	006	007	007	005
	Post-Rx	006	011	005	006	009	005
	Difference	-001	-001	-001	-001	003	001
T4	Baseline	013	035	014	010	021	013
	Post-Rx	009	027	012	007	017	009
	Difference	-003	-008	-003	-003	-004	-004
T5	Baseline	007	009	007	009	007	008
	Post-Rx	006	009	007	006	008	011
	Difference	-001	001	-001	-003	000	004
P3	Baseline	006	007	006	007	006	005
	Post-Rx	006	007	006	006	007	005
	Difference	-001	000	-001	-001	000	000
Pz	Baseline	007	007	006	007	007	005
	Post-Rx	006	007	006	006	006	005
	Difference	-001	000	-000	-000	-000	-000
P4	Baseline	007	007	007	006	007	005
	Post-Rx	006	008	006	006	006	005
	Difference	-000	000	-001	-000	-000	000
T6	Baseline	009	009	007	007	007	007
	Post-Rx	007	011	007	007	007	007
	Difference	-002	001	-000	000	000	001
O1	Baseline	011	010	016	015	011	014
	Post-Rx	009	012	013	010	011	010
	Difference	-002	002	-002	-005	-000	-003
O2	Baseline	011	012	015	012	013	012
	Post-Rx	012	014	014	015	012	013
	Difference	001	002	-001	003	-001	001

NOTE: Values in the table are Absolute EEG Power uV^2 x 10^4 for ease of presentation.

NeuroRegulation

Comparing DC Offset and Impedance Readings in the Assessment of Electrode Connection Quality

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Abstract

Electroencephalograph (EEG) electrode impedance measurements of 5,000 ohms or less are required by common standards of practice to minimize artifacts due to electro-magnetic interference (EMI). Some amplifiers geared toward the neurofeedback market do not include on-board impedance monitoring, but provide direct current (DC) offset measurements. To examine if DC offset is a reliable measure of connection quality, measurements of DC offset and impedance, each independently taken by students in a university graduate level course in neurofeedback over a one-year period were analyzed retrospectively. DC offset was not found to have predictive value of a standard impedance level. Additionally, 19 channel EEGs collected within manufacturer recommended parameters of DC offset using a high-impedance amplifier were analyzed to assess the level of EMI pollution of quantitative EEG (QEEG) data. Visible peaks of EMI in the spectra in at least one channel in each of these recordings were identified. A sample of EMI pollution of QEEG results is presented. Together, these findings suggest that DC offset may not be a reliable measure of electrode connection quality.

Keywords: EEG, electrode, interference, impedance, DC offset, QEEG

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Introduction

Many factors are inherent in the quality of an electroencephalograph (EEG) recording, among which are artifact reduction, electrode stability, and the highest possible signal-to-noise ratio. Electro-magnetic interference (EMI) can potentially invade the EEG recording. The 50 Hz or 60 Hz signature of the building's electrical mains is a primary source of EMI. Other sources of EMI, such as radio, may be present in the recording environment. Since the typical neurofeedback provider may not be operating in a shielded room, these sources of EMI are often present, as indicated by artifacts in the traces and characteristic peaks in the spectra. Traditionally, the quality of the electrode connection has been seen as instrumental to ameliorating these factors as achieved by attaining low impedance between the leads. The importance of low impedance for achieving electrode connection quality is well established and continues to be recommended in EEG textbooks (Tatum, 2014; Tyner, Knott, & Mayer Jr., 1983). Impedance measurement below 5,000 ohms remains the adopted standard for EEG recordings (American Association of Sleep Technologists, 2012; American Clinical Neurophysiology Society, 2008).

Modern high-impedance amplifiers reduce the effect of EMI considerably to the extent that some have suggested that the 5,000-ohm impedance standard is no longer relevant or safe if it requires skin abrasion (Ferree, 2001). Historically, some amplifiers have been manufacturerd without on-board impedance measurement and instead include software-assessable direct current (DC) offset measures as an indication of connection quality.

Kappenman and Luck (2010) reported that high electrode impedance may decrease the signal-to-noise ratio and statistical power in event-related potentials (ERP) recordings, even with equipment

designed to tolerate high impedance levels. Though they found that these effects may be ameliorated with a cool and dry recording environment, they recommended that high impedance EEG equipment manufacturers accommodate the need for skin abrasion and impedance monitoring for experiments that require high statistical power.

Whereas impedance is a measure of the conductance of electricity through the skin between a pair of leads, DC offset is a by-product of the DC potentials generated at the junction of the skin and electrolyte solution under the electrodes resulting in a voltage at the amplifier inputs (Kamp, Pfurtscheller, Edlinger, & Lopes da Silva, 2005). Theoretically, it is assumed that the lower the offset, the better the connection.

This study examines the relationship between DC offset and impedance as measurements of electrode connection quality. The hypothesis under investigation in this study is that if DC offset is a reliable measure of electrode connection quality, it will correlate with impedance.

The significance of this study is not merely academic but is intended to be applied to the clinical practice of neurofeedback. Neurofeedback practitioners, as a whole, utilize equipment of various levels of quality, in environments with various levels of EMI, and with various levels of skill in assessing the quality of the EEG signal they are training. Furthermore, a summary of case studies will be presented that indicates the distortion of quantitative EEG (QEEG) results by EMI using high impedance equipment. If, in the clinical practice of neurofeedback practitioners, EMI can adversely affect the processing of the EEG, having a reliable way to assure electrode connection quality is important.

Methods

Measurements of DC offset and impedance, each independently taken by students in a university graduate level course in neurofeedback over a 1-year period using standardized data collection procedures, were analyzed retrospectively. The retrospective study of DC offset and impedance was approved by the Institutional Review Board of the University of Texas at San Antonio. For the retrospective study of EEG recordings, the subjects were protected and the data was collected in accordance with the Declaration of Helsinki.

Procedures

For the DC offset and impedance study, the following procedures were followed. Initial site preparation was done by cleaning with a 91% isopropyl alcohol-soaked cotton ball, scrubbing with an alcohol-soaked gauze impregnated with an abrasive (PDI Electrode Prep pads), and additional scrubbing with an abrasive skin prepping gel (Nuprep). A single channel set of electrodes was then placed on the scalp using conductive paste (Ten20). Central placements according to standard 10–20 EEG placements were used for the active electrode with bilateral mastoid placements for the reference and ground electrodes. Ag/AgCl snap electrodes were used, which were inspected to insure that the pellet coating was not worn, and each set of pellets were used no more than three times. DC offset was measured using high-impedance amplifiers and accompanying software. After DC offset was measured, impedance was measured between active and reference, active and ground, and reference and ground electrodes. Only the active-reference impedance values were used in the comparative analysis, since the DC offset measurements recording in the software reflect the active-reference connection only. The data consist of 181 points measuring two variables, impedance (1000's ohms) and DC offset (+/- 1000's microvolts).

To evaluate the effects of EMI on EEG recordings, 27 19-channel recordings made in a single private practice setting over a period of 8 months were analyzed. Vendor-recommended preparation procedures were used to insure that DC offset readings via the accompanying software read between +/- 25,000 uV for all channels.

Equipment

The following equipment was used for the DC offset and impedance study. Each measurement utilized one of four amplifiers, consisting of three NeXus-4 (Mind Media, The Netherlands) and one NeXus-10 amplifiers (input impedance > 10 Tohm) with accompanying BioTrace software. Since the EEG systems utilized LEMO or ODU brand connectors (push-pull circular shielded connectors with six pins) an adapter was used to connect to a 1089NP Checktrode impedance meter with standard DIN connectors. The recordings analyzed for the EMI case study were all made using one NeXus-32 high-impedance amplifier (input impedance > 10 Tohm) with accompanying BioTrace software and manufacturer-supplied caps.

Analysis

For the retrospective DC offset and impedance study, two analyses were used. The first analysis involved simply plotting the data and computing the sample correlation. Since there were only two variables, plots provide good evidence of the type of relationship between impedance and DC offset, and a correlation close to 1 would indicate a strong linear relationship. The second analysis was a more detailed evaluation that computes confusion tables between DC offset above and below different thresholds and impedance above and below 5,000 ohms. Confusion tables are 2 x 2 tables that calculate the number of true positive, true negative, false positive, and false negative samples. Various statistical performance measures and the receiver operating characteristic (ROC) curve were calculated to show how well DC offset predicted a good connection. The statistical performance measures used were accuracy, precision, and sensitivity. Accuracy was calculated as the number of correct classifications divided by the total (true positives + true negatives divided by the total). Precision was calculated as the positive predicted value (true positives divided by true positives + false positives). Sensitivity was calculated as the true positive rate or hit rate (true positives divided by true positives + false negatives). All performance measures range from 0 to 1. For DC Offset to be a reliable predictor of impedance, it was hypothesized that there should be high levels of accuracy, precision, and sensitivity (close to 1). Also, to reflect high predictability of DC offset to impedance, the area under the ROC curve should be close to 1.

Using spectral analysis, one channel was selected from each of the 27 19-channel recordings that reflected the highest power at 60 Hz. For comparison purposes, these single-channel spectra were combined into one FFT spectra graph (Figure 5). The QEEG statistics were then examined for the recordings to determine if the suspected peaks corresponded with a distortion of the data and *Z*-score statistics.

Results

The results of the study are presented here in three parts. Two analyses were conducted for the DC offset and impedance measurements: (1) plots and correlation, and (2) confusion matrices and receiver operating characteristic curve. The third section presents the results of a case study of EMI in a group of 19-channel EEG recordings.

Analysis 1 of DC Offset and Impedance Measurements: Plots and Correlation

The Pearson Sample Correlation between impedance and DC offset was computed to be 0.092. The plots of impedance vs. DC offset (Figures 1, 2, and 3) and a correlation of 0.092 suggest there is not a linear relationship between impedance and DC offset. Figure 1 reflects the range of all samples collected, Figure 2 plots impedance readings < 15K ohms, and Figure 3 includes plots of DC offset readings < 50K uV.

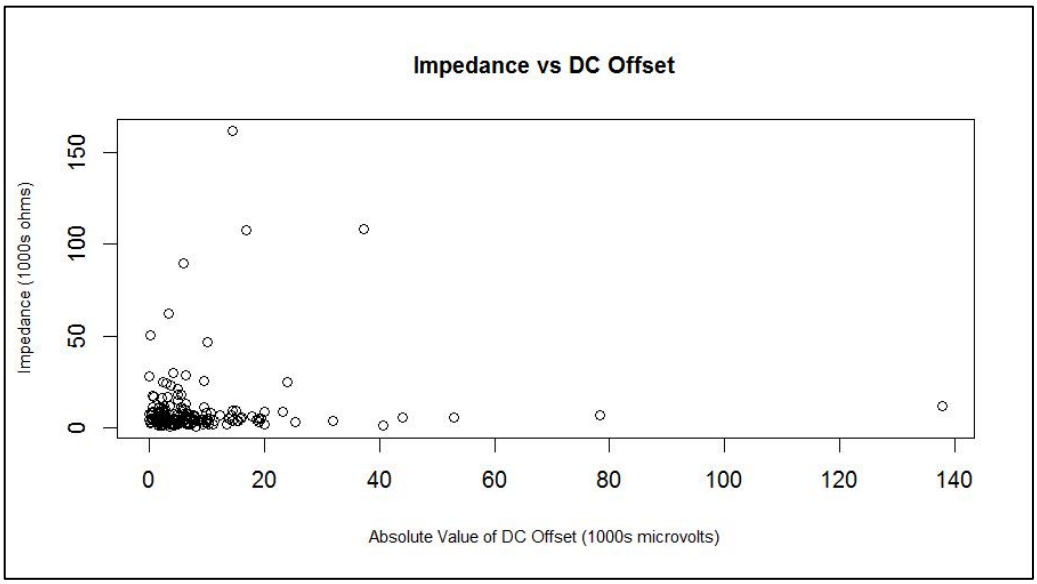

Figure 1. Impedance vs. DC offset reflecting the range of all samples collected.

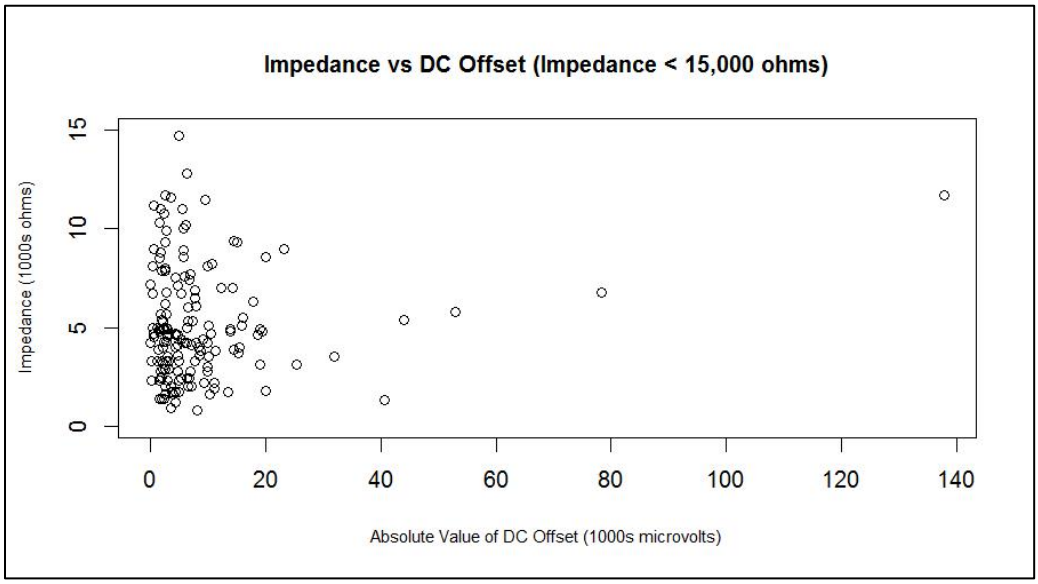

Figure 2. Impedance vs. DC offset showing plots of impedance readings < 15K ohms.

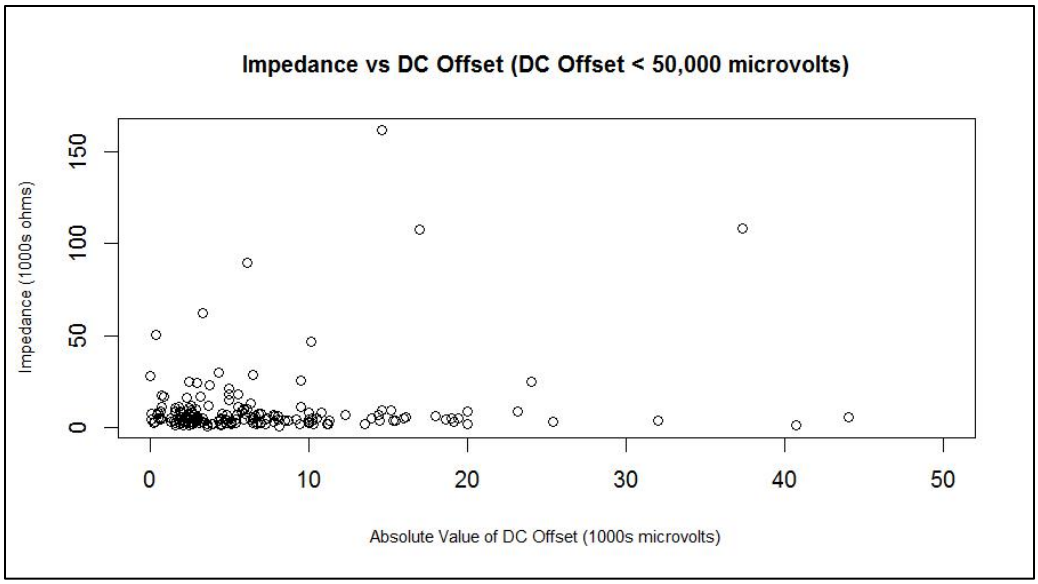

Figure 3. Impedance vs. DC offset showing plots of DC offset readings < 50K uV.

Analysis 2 of DC Offset and Impedance Measurements: Confusion Matrices and Receiver Operating Characteristic Curve

Using impedance less than or equal to 5,000 ohms as a good connection, and greater than 5,000 ohms as a bad connection, four confusion matrices are shown below for good levels of DC offset at less than or equal to 5,000; 15,000; 25,000; and 35,000 microvolts (Table 1). The analysis used the absolute value of the DC offset measures, referred to as |DC Offset|.

The confusion matrices analysis shows accuracy and precision all below 60% for four different thresholds of DC offset, which indicates poor predictability of impedance above and below 5,000 ohms. The low precision and accuracy levels are a result of the relatively high number of false positives (refer to the upper right hand corner of each confusion table). While sensitivity is high (above 90%) for |DC Offset| thresholds above 15,000, this comes with low precision and accuracy.

Table 1
Confusion Matrices

Confusion Matrix 1	Impedance ≤ 5,000 (ohms)	Impedance > 5,000 (ohms)
|DC Offset| ≤ 5,000 (microvolts)	54	39
|DC Offset| > 5,000 (microvolts)	45	43
Accuracy	Precision	Sensitivity
0.536	0.581	0.545

Confusion Matrix 2	Impedance ≤ 5,000 (ohms)	Impedance > 5,000 (ohms)
|DC Offset| ≤ 15,000 (microvolts)	89	69
|DC Offset| > 15,000 (microvolts)	10	13
Accuracy	Precision	Sensitivity
0.564	0.563	0.899

Confusion Matrix 3	Impedance ≤ 5,000 (ohms)	Impedance > 5,000 (ohms)
|DC Offset| ≤ 25,000 (microvolts)	96	77
|DC Offset| > 25,000 (microvolts)	3	5
Accuracy	Precision	Sensitivity
0.558	0.555	0.970

Confusion Matrix 4	Impedance ≤ 5,000 (ohms)	Impedance > 5,000 (ohms)
|DC Offset| ≤ 35,000 (microvolts)	98	77
|DC Offset| > 35,000 (microvolts)	1	5
Accuracy	Precision	Sensitivity
0.569	0.560	0.990

Note: |DC Offset| refers to the absolute value of DC Offset.

A more robust measure of how well DC offset predicts impedance is to calculate the ROC curve, as shown below (Figure 4). The ROC curve shows the true positive rate vs. false positive rate at 1,000 equally spaced thresholds of DC offset from 0 to 140,000 microvolts. Here once again, a good connection represents impedance less than or equal to 5,000 ohms. To reflect high predictability of DC offset to impedance, the area under the ROC curve should be close to 1 (the ideal test line) on the true positive scale rather than close to the random guess line. The results of the ROC analysis shows area under the ROC curve is approximately 0.50. This suggests that DC offset is no better at predicting the quality of a connection than randomly guessing.

Case Study of EMI in 19-Channel EEG Recordings

For the retrospective case study, the one-channel spectral graphs selected from all 27 recordings were combined to enable visual examination (see Figure 5). Based on this examination, four suspected EMI-related peaks were identified. A tabulation of the percent of samples with visible peaks in four suspected frequencies ranges was done to determine how many recordings displayed a visible peak against the background (see Table 2).

All of the recordings had at least one channel that displayed a visible peak at 60 Hz; at least half with visible peaks in the other three suspected frequencies. The sites in question appeared randomly located; they were not confined to specific sites. As seen in the combined spectra, the power of the peaks suggests that they are of artifactual origin, i.e., they do not follow the 1/frequency characteristic and appear higher than would be expected from cortical sources. Furthermore, in visual inspection of the recordings, the suspected peaks appear to rise and fall together with the 60 Hz peak, suggesting they may share a common EMI source or a common sensitivity to EMI at these respective frequencies.

Table 2
Percent of samples with visible peaks in four suspected frequencies ranges.

Peaks	19-21hz	31-33hz	47-49hz	59-61hz
Visible	50%	88.5%	57.7%	100%

 doi:10.15540/nr.2.1.29

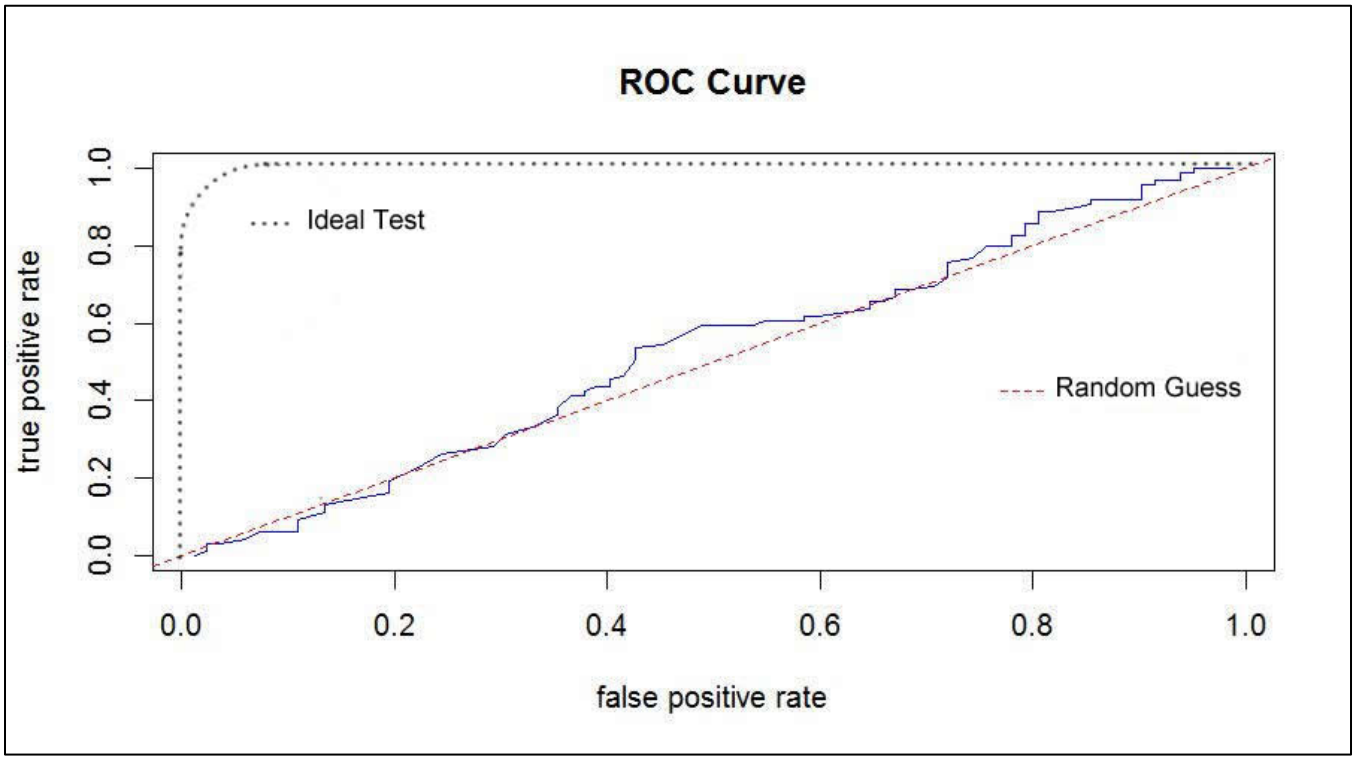

Figure 4. Receiver Operating Characteristic (ROC) curve showing true positive rate vs. false positive rate.

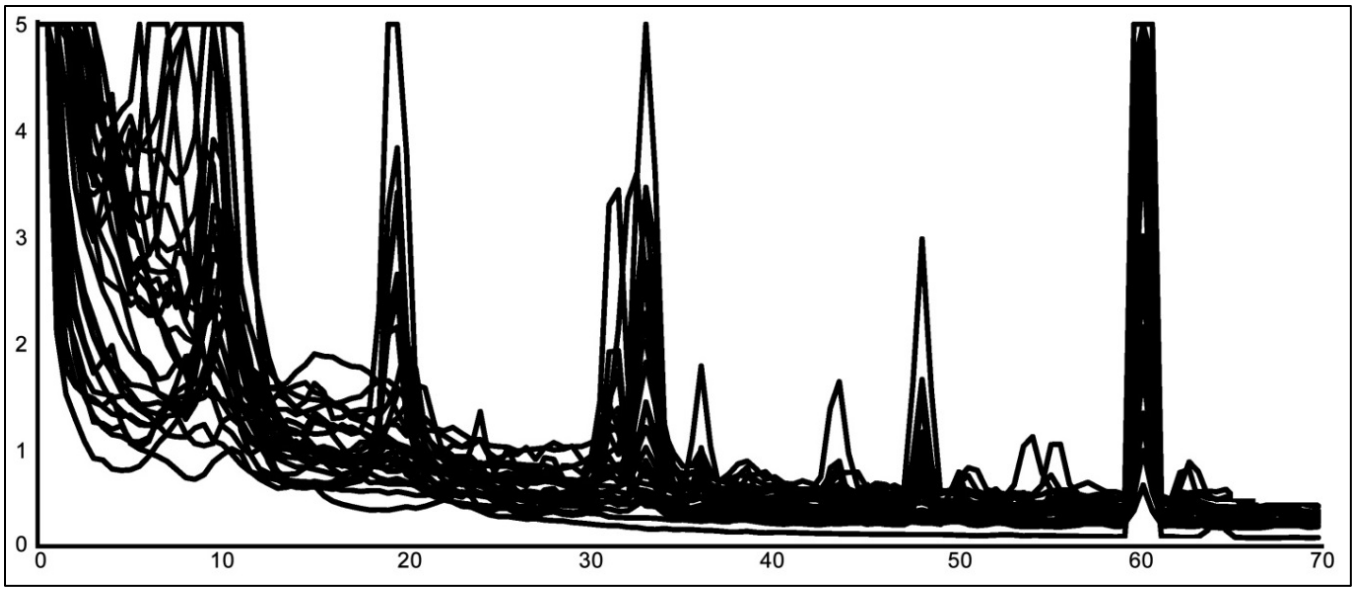

Figure 5. Combined FFT spectra from selected channels from 27 recordings, y-axis-range 5.00 uV peak-to-peak, x-axis-range 0–70 Hz, 512 samples/s, FFT epoch 2 s, FFT points 1024 samples, BIN size 0.50 Hz, Hanning windowing, overlap step 250 ms. All channels in all recordings had DC offset readings of +/- 25K uV.

Upon examination of QEEG *Z*-scores (1–30 Hz), it was found that the 19–21 Hz peak was represented in the data. Figure 6 is an example of the *Z*-score absolute power spectrum of a 19-channel recording with significant EMI artifact, showing a 19–21 Hz peak. For QEEG databases capable to processing activity higher than 30 Hz, it is assumed that the 31–33 Hz peak would also distort the *Z*-score data.

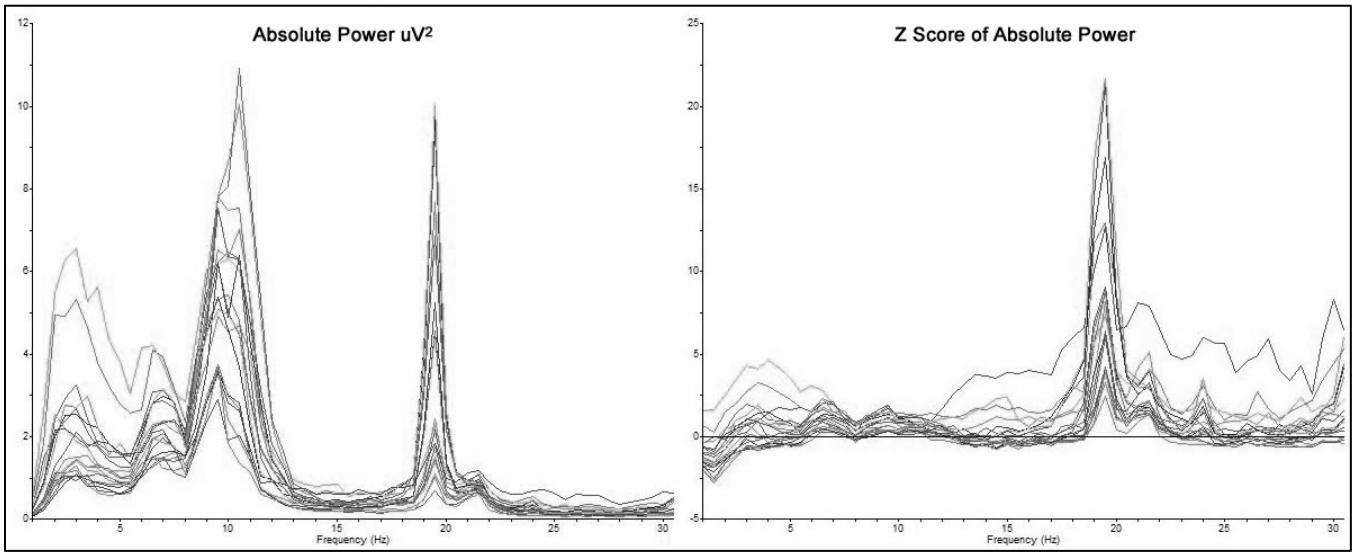

Figure 6. Example of the absolute power (left) and *Z*-score absolute power (right) spectra of a 19-channel recording with significant EMI artifact, showing a ~19 Hz peak in multiple channels. All channels had DC offset readings of +/- 25K uV.

Conclusion

Statistical analysis of common DC offset and impedance measurements suggests that DC offset may not be a reliable measure of electrode connection quality as compared to impedance. A linear relationship between the two measures was not found. A significant number of false positives demonstrated that DC offset may be a poor reflection of connection quality. Plotting the ROC curve showed that DC offset is no better at predicting the quality of a connection than randomly guessing in this study. Furthermore, analysis of case study recordings was presented which suggested the possibility that poor connection quality may result in the distortion of QEEG results.

The analysis of the case study data was included to illustrate the possibility of EMI artifact encroachment into the QEEG data at frequencies generally associated with cortical activity (up to approximately 40 Hz or more). Since many neurofeedback systems do not have the capability of measuring 60 Hz activity, such encroachment would be difficult to detect and might present as localized over-arousal or some other mystifying finding. It also follows that the ability to measure EMI artifact at 60 Hz (or 50 Hz) is one possible way to assess the electrode connection quality.

Impedance remains the conventional means of testing the quality of electrode connection. The current impedance requirements by the American Clinical Neurophysiology Society and the American Association of Sleep Technologists appear to be validated by the findings presented in this paper.

It is assumed that the software-based DC offset measurements available in the systems used in this study measure the effects of voltage difference between the active and reference electrodes only. This allows for no assessment of the quality of the ground electrode connection. Some impedance measurements in the study data showed a poor ground connection, which wasn't accessible via the DC offset measurements. This highlights an additional problem of using DC offset measures as a method of determining electrode connection quality; without a sufficient ground connection, the EEG signal can become unstable. To insure a good quality electrode connection, it is important to measure impedance between active, reference, and ground leads.

Given the technological limitations of the methods used in this study, further research into the relationship between DC offset and impedance, as well as the susceptibility of EMI artifact in the often-uncontrolled environments where neurofeedback is practiced, is warranted. Such future research would be strengthened with the inclusion of a representative variety of equipment manufacturers with duplication in the number of devices. Additionally, the independent analysis of commonly used equipment in a laboratory setting would be advantageous. Beyond the research arena, it is recommended that certification of neurofeedback practitioners include the evaluation of skills needed to adequately assess the quality of electrode connection, including the importance of monitoring impedance.

Another limitation of the study was the subjective nature of the assessment in the QEEG case study. The spectra of the 27 recordings were inspected in order to identify the channel with the highest level of 60 Hz interference. These channels were then combined into a single spectral graph where peaks were identified by visual examination. A more statistically robust method of selecting the relevant channels and finding significant variations would strengthen the conclusions regarding EMI interference.

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NeuroRegulation

Transcranial Direct Current Stimulation of Dorsolateral Prefrontal Cortex in Major Depression: Improving Visual Working Memory, Reducing Depressive Symptoms

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Abstract

Recent studies on major depression (MD) have used noninvasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) to improve impaired emotion and cognition in MD. However, such experiments have yielded mixed results, specifically with respect to cognition in MD. This study aimed to investigate whether anodal and cathodal tDCS applied over the dorsolateral prefrontal cortex (DLPFC) would significantly improve visual working memory and reduce depressive symptoms in patients with MD. Thirty patients with major depression (n = 30) were randomly assigned to receive either experimental (active) or control (sham) tDCS. To measure cognitive functions, the participants underwent a series of visual memory neuropsychological tasks; and to measure depression symptoms, the Beck Depression Inventory (BDI) and Hamilton Depression Scale (HDRS) were used. The parameters of active tDCS included 2 mA for 20 min per day for 10 consecutive days, anode over the left DLPFC (F3), cathode over the right DLPFC (F4) region. After 10 sessions of anodal and cathodal tDCS, patients showed significantly improved performance in visual working memory tasks. The same results were observed for depression symptoms. This study showed that anodal tDCS over left DLPFC, concurrently with cathodal tDCS over right DLPFC, improved cognitive impairment (specifically visual working memory), as well as reduced depressive symptoms in patients with MD. This finding provides evidence that supports effectiveness of a specific montage of tDCS to improve impaired cognition in MD, specifically in visual working memory.

Keywords: major depression; memory; tDCS; visual memory

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Background

With a lifetime prevalence estimated at 16%, major depression (MD) is a serious public health issue (Gohier et al., 2009). Previous studies have shown MD to be associated with a variety of cognitive correlates such as the ability to think, concentrate, make decisions, formulate ideas, reason, and remember (Marazziti, Consoli, Picchetti, Carlini, & Faravelli, 2010). It unquestionably affects specific cognitive domains including executive functions (Marazziti et al., 2010; McDermott & Ebmeier, 2009), different types of memory (e.g., episodic memory, semantic memory, visuospatial memory), and information processing speed (McDermott & Ebmeier, 2009).

MD is usually accompanied by alterations of cortical activity, especially in prefrontal areas (Nitsche, Boggio, Fregni, & Pascual-Leone, 2009). The prefrontal cortex (PFC) consists of regions including the dorsolateral PFC (DLPFC) and ventromedial PFC (VMPFC) that are involved in depression psychopathology in terms of cognition and emotion,

respectively. Functional imaging, lesion and brain stimulation studies, suggest that the DLPFC is primarily associated with “cognitive” or “executive” functions, whereas VMPFC is largely associated with “emotional” or “affective” functions (Koenigs & Grafman, 2009), suggesting that cognition and emotion, which are seriously malfunctioned in MD, are associated with altered cortical activity in the PFC. It is beyond the scope of this paper to review how the PFC is involved in cognitive, executive, and emotional processes. However, we can briefly outline that the PFC is a collection of interconnected cortical regions, in which diverse information converge; and that these areas have interconnections with virtually all sensory systems, with cortical and subcortical motor system structures, and with limbic and midbrain structures involved in affect, as well as memory (Miller & Cohen, 2001).

It is indicated that the activity of the PFC is pathologically altered in MD, mostly in the direction of decreased bilateral or predominantly left-sided activation (Davidson, Pizzagalli, Nitschke, & Putnam, 2002). Some studies suggest an imbalance of function between right and left DLPFC activity as an important causal factor in MD psychopathology (Grimm et al., 2008; Nitsche et al., 2009), suggesting a causal relationship between hemispheric imbalances of function (especially in the PFC) and depressive cognitive and emotional symptoms. More specifically, a decrement of cortical activity exists in the left DLPFC, whereas an increment of cortical activity is seen in the right DLPFC (Davidson et al., 2002; Nitsche et al., 2009; Speer et al., 2000).

A similar imbalance of function is shown in the activity of the PFC that affects memory processing in MD (Nitschke, Heller, Etienne, & Miller, 2004). Numerous electroencephalography (EEG) and neuroimaging studies have reported more right than left PFC activity in depression, indicating hypoactivity in the left DLPFC and hyperactivity in the right DLPFC (Grimm et al., 2008; Nitschke et al., 2004). This imbalance of function is suggested to be associated with memory impairment in MD (Nitschke et al., 2004). The importance of the PFC for visual and spatial working memory is also well documented (Dockery, Liebetanz, Birbaumer, Malinowska, & Wesierska, 2011; Petrides, 2000; Schecklmann et al., 2011). A number of studies have demonstrated that impaired working memory in patients with MD is related to the PFC; however, the relationship between the underlying brain activity and working memory function in MD, and their clinical characteristics, is not yet clear (Pu et al., 2012).

DLPFC imbalance of function is not only associated with cognitive impairment in MD, but also is suggested to be involved in emotional processing in MD (Davidson & Irwin, 1999; Grimm et al., 2008; Phan, Wager, Taylor, & Liberzon, 2002). This would imply that the PFC region is engaged in cognition-emotion interaction (Phan et al., 2002). Studies suggest that the PFC, specifically the medial PFC, is actively engaged during cognitively bound emotional processing of stimuli. For example, it is shown that the PFC plays a crucial role in affective working memory (Davidson & Irwin, 1999). But studies are needed to investigate how the PFC is associated with both cognition and emotion—to address specific questions, such as, “Which subregions of the PFC are mostly responsible for cognition-emotion interaction?”

Recent studies have highlighted the importance of noninvasive brain stimulation as a means of modulating cortical excitability (Brunoni et al., 2012; Nitsche et al., 2009). The development of noninvasive brain stimulation techniques made it possible to modulate cognitive functions in both healthy subjects and clinical populations (Brunoni et al., 2012; Pereira et al., 2013). Transcranial direct current stimulation (tDCS) is a neurostimulation technique in which a weak direct current, applied on the scalp, reaches the brain and induces shifts in membrane resting potentials (Nitsche et al., 2009); thus, modulating cortical excitability. Anodal stimulation increases cortical excitability, whereas cathodal stimulation has the reverse effect (Nitsche & Paulus, 2001). Studies have also demonstrated prolonged aftereffects of tDCS up to 90 min in the human motor cortex (Utz, Dimova, Oppenländer, & Kerkhoff, 2010).

Neuromodulation studies have shown that an increase of excitability of left DLPFC modulates working memory (Boggio, Ferrucci, et al., 2006; Fregni et al., 2005), declarative memory (Javadi & Walsh, 2012), verbal memory and word recognition (Cerruti & Schlaug, 2009; Ferrucci, Mameli, et al., 2008), digit span (Fregni, Boggio, Nitsche, Rigonatti, & Pascual-Leone, 2006), and visual recognition memory (Boggio et al., 2009). Several studies showed that tDCS might modulate cortical excitability in the human motor cortex (Boggio, Castro, et al., 2006; Boggio et al., 2007; Boros, Poreisz, Münchau, Paulus, & Nitsche, 2008), visual cortex (Accornero, Li Voti, La Riccia, & Gregori, 2007; Antal et al., 2004), and parietal cortex

(Sparing et al., 2009; Stone & Tesche, 2009) and also could have clinical implications (Brunoni et al., 2012). In addition to motor and visual learning tasks, tDCS has been effectively used in memory studies, especially working memory (Boggio, Ferrucci, et al., 2006; Ferrucci, Marceglia, et al., 2008; Fregni et al., 2005; Jo et al., 2009), episodic memory, and declarative memory (Javadi & Walsh, 2012; Marshall, Mölle, Hallschmid, & Born, 2004).

Although a number of neuropsychological studies suggest an association between the PFC and working memory function in MD, the results are mixed (Pu et al., 2012). In addition, the neuropsychological characterization of the left DLPFC hypoactivity and right DLPFC hyperactivity, and its association with negative emotional processing in MD, remains poorly understood (Grimm et al., 2008). Studies with specific designs based on neuropsychological characterizations of MD would be more useful and less likely to produce mixed results. Such studies are more facilitative when it comes to the study of the PFC as an interconnected brain region that sends and receives projections from many subcortical areas (Miller & Cohen, 2001), although studying such a region with its many neural connections and networks is very difficult.

Based on neuroimaging studies that suggest an asymmetry of function in bilateral DLPFC in depression, which is associated with cognitive impairments in MD, we suggested a specific tDCS montage. Therefore, this study aims primarily to investigate whether applying tDCS with a specific montage of anodal tDCS over the left DLPFC and cathodal tDCS over the right DLPFC would result in cognitive improvement, especially in visual working memory, which is the most impaired neuropsychological domain in MD (Egerhazi et al., 2013). We are also interested to see if this tDCS montage could reduce depressive symptoms in MD. The left DLPFC was selected as the main site of anodal stimulation, which is hypothesized to increase cortical activity in left DLPFC; and the right DLPFC was selected as the main site of cathodal stimulation, which is hypothesized to decrease cortical activity in right DLPFC. We suggest this specific design to be more helpful in interpreting results, as it is based on a research hypothesis derived from neuropsychological and neuroimaging findings of the PFC, and considers both the left and right DLFPC. Also, we used a series of cognitive assessment measures that are sensitive to cortical functions and are designed with a focus on neuropsychological functions of frontal lobe regions in depression (Egerhazi et al., 2013; Sahakian et al., 1990). Finally, this study aims to examine visual aspects of memory, which is one of the most impaired cognitive domains in MD (Egerhazi et al., 2013; Sahakian et al., 1990); yet to date no tDCS studies have investigated effects of brain stimulation on visual memory in MD.

Materials and Methods

Participants

Thirty participants, aged 18–44, with a MD diagnosis, who were administered the Beck Depression Inventory (BDI; Beck, Ward, & Mendelson, 1961) and the Hamilton Rating Depression Scale (HDRS; Hamilton, 1960), took part in this study. The subjects were recruited from the Atieh Clinic at Tehran, Iran. Demographic characteristics are shown in Table 1 and 2. Inclusion criteria were: (1) failure in response to antidepressant pharmacotherapy for at least 2 weeks *before* tDCS sessions; (2) not on antidepressant or other psychotropic medications *during* the study; (3) moderate to severe depression scores on the BDI (scores close to 29 and higher); (4) HDRS scores of at least 20 (scored by an experienced psychiatrist); and (5) MD diagnosis based on a clinical interview by an experienced psychiatrist, according to DSM-IV criteria. Patients with schizophrenia, substance use disorders, personality disorders, mental retardation, and other severe medical conditions were excluded. The study was performed according to the Declaration of Helsinki ethical standards and approved by the local Institutional Review Board and the Ethical Committee of the University of Tehran. Patients gave their informed consent before participation.

It is notable that, although the BDI baseline scores of both control and experimental groups showed a moderate to severe level of depression, the BDI baseline scores of the control group were lower than the experimental group, which may bring to question whether both groups are different. For this reason, we used the HDRS, in addition to the BDI, to ensure participants met the inclusion criterion of MD severity.

Table 1
Demographic data of patients

Patient	Gender	Age	Antidepressant Use	Onset Age	Baseline BDI/HDRS
1	F	28	Yes	24	41/26
2	M	28	Yes	27	30/27
3	M	26	Yes	24	34/24
4	M	27	Yes	26	25/22
5	M	22	No	22	29/20
6	F	33	Yes	33	27/29
7	F	29	Yes	26	39/25
8	F	37	Yes	34	46/22
9	F	25	Yes	24	35/27
10	M	22	Yes	20	28/23
11	M	29	Yes	28	31/24
12	F	32	Yes	29	39/26
13	F	24	Yes	23	40/21
14	F	44	Yes	40	38/28
15	M	25	Yes	22	31/27
16	F	24	No	23	31/ 21
17	F	31	Yes	30	26/22
18	F	36	Yes	35	32/21
19	M	21	Yes	20	29/23
20	M	28	Yes	26	27/24
21	M	41	Yes	37	25/22
22	F	18	No	17	27/21
23	F	32	Yes	30	31/27
24	F	27	Yes	27	29/20
25	M	26	Yes	25	33/24
26	M	28	Yes	26	27/22
27	F	30	Yes	28	26/24
28	F	25	Yes	20	29/26
29	F	29	Yes	28	27/25
30	M	22	Yes	21	26/21

Table 2
Descriptive statistics of demographic data

	Experimental Group	Control Group
Sample size (*n*)	15	15
Antidepressant medication use	14	13
Age in years – Mean (*SD*)	28.7 (28.73)	27.9 (27.86)
Onset age in years – Mean (*SD*)	26.8 (26.80)	26.2 (26.20)
Baseline BDI score – Mean (*SD*)	34.2 (6.09)	28.3 (2.46)
Baseline HDRS score – Mean (*SD*)	24.7 (3.05)	22.8 (2.06)

Experimental Protocol

Participants were randomly assigned in two groups (experimental or active tDCS, *n* = 15; control or sham tDCS, *n* = 15). Participants in the active group received one 20-min stimulation session per day, for 10 consecutive days. Participants in the control group received sham stimulation, but the stimulator was turned off after 30 s of stimulation. Therefore, participants in the control group felt the initial itching sensation but received no current for the rest of the stimulation period. Cognitive functions and mood were assessed once before the first tDCS session as baseline, and once after the tenth tDCS session for each condition (active and sham). Subjects in the sham stimulation condition were recruited for other therapeutic protocols by the end of the study.

tDCS

Direct current generated by an electrical stimulator was bilaterally delivered through a pair of saline-soaked surface sponge electrodes. We used the tDCS Stimulator Model 101 (TCT Research Limited, Hong Kong, China). Stimulation was applied at an intensity of 2 mA for 20 min once a day for 10 consecutive days. The anodal electrode was positioned over area F3 (left DLPFC) according to the 10–20 EEG international system, and the cathode electrode was positioned over F4 (right DLPFC). The electrodes were thick (0.3 cm), and were placed in rectangular saline-soaked synthetic sponges (surface area of 35 cm^2). All patients were blind to the type of tDCS delivered in each session.

Cognitive Assessment

Cognitive functions were assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB; CeNeS, Cambridge, UK). The CANTAB is designed with a significant focus on neuropsychological functions, subserved by frontal lobe regions, such as frontostriatal circuitry that mediate motor, cognitive and behavioral functions within the brain (Fray, Robbins, & Sahakian, 1996). It has been extensively validated for assessing brain–behavior relationships and is sensitive to detect brain dysfunctions in the frontal, temporal, and amygdalo-hippocampal regions (Clark, Chamberlain, & Sahakian, 2009; Owen, Sahakian, Semple, Polkey, & Robbins, 1995; Sahakian et al., 1990).

Over the last decade, the CANTAB has been used in cognitive studies of both neurodegenerative disorders, such as dementia and Huntington's disease (Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999; Sahakian et al., 1990), and psychiatric disorders, such as schizophrenia, MD, and bipolar disorder (Egerhazi et al., 2013; Levaux et al., 2007; Porter, Gallagher, Thompson, & Young, 2003; Roiser & Sahakian, 2013). It has also been used successfully to detect deficits in visuospatial short-term memory in neurosurgical patients with temporal or frontal lobe excision (Owen et al., 1995). Specifically, Falconer et al. (2010), in a study involving Electroconvulsive Therapy (ECT), showed that the CANTAB can assess the cognitive impact of ECT on visual working memory.

Since the CANTAB is sensitive to brain dysfunctions in frontal and temporal regions, it is highly appropriate for assessing cognitive functions, especially in studies involving passage of electrical current on the frontal and temporal regions, by means of bilateral electrodes (Falconer, Cleland, Fielding, & Reid, 2010). Considering that our study involves applying direct current stimulation to the brain, we decided to use this battery. Moreover, it is believed that performance on the CANTAB is dependent on change in cortical activity, our particular tDCS montage is supposed to modulate prefrontal activity, and the CANTAB is precisely sensitive to cortical activity changes. In addition, the CANTAB is shown to be correlated with traditional and well-validated neuropsychological testing instruments. For example, the CANTAB memory tests are associated with performance on traditional measures assessing visual memory and working memory, such as the "Green Story Recall Test Immediate and Delayed Recall" and the "Digit Span Forwards and Backwards" (Smith, Need, Cirulli, Chiba-Falek, & Attix, 2013).

Moreover, the CANTAB has a specific battery called the CANTAB Depression Battery, which is an accurate assessment system for measuring cognitive functions in MD (Egerhazi et al., 2013; Papakostas, 2014; Roiser & Sahakian, 2013). Studies show that the CANTAB Depression Battery can discriminate the cognitive profile of depression from other disorders and is uniquely sensitive to MD; also, some tests such as the Delayed Matching to Sample (DMS) and Pattern Recognition Memory (PRM) can specifically detect visual memory deficits in MD (Egerhazi et al., 2013). Finally, the CANTAB has been specifically developed to assess the nature of memory deficits (Falconer et al., 2010), especially visual memory, which makes it an efficient measure to assess memory deficits. From an administration standpoint, the CANTAB has highly standardized administrations, with automated response recording and millisecond precision.

In this study, a two-test CANTAB battery was used (15–20 min duration), selected from the CANTAB Depression battery and CANTAB Memory tests: DMS and PRM. This battery was selected to evaluate visual aspects of memory in MD, including visual working memory and visual recognition memory (Rock, Roiser, Riedel, & Blackwell, 2014). The DMS test assesses visual recognition memory by presenting a target pattern and requiring the subjects to pick out the target pattern from an array of four patterns in immediate, 4- and 12-s delay conditions (Robbins et al., 1994). This test is proposed to be primarily sensitive to damage in the medial temporal lobe area, with some input from the frontal lobes (Egerhazi et al., 2013). It lasts about ten 10 minutes and the outputs include the number and percentage of correct responses and response latency.

The PRM is a test of visual recognition memory following a two-choice forced discrimination paradigm. The participant is presented with a series of 12 visual patterns, one at a time, in the center of the screen. These patterns are designed so that they cannot easily be given verbal labels. In the first recognition phase, the participant is required to choose between a pattern they have already seen and a novel pattern. The second recognition phase can be administered either immediately or after a 20-min delay. The tasks last about 5 minutes. The outputs for the PRM include number and percentages of correct and incorrect responses, and response latency.

Mood Measurement

Depressive symptoms and mood were evaluated using two well-known depression inventories and scales: the BDI and the HRSD. The evaluation was made once before the tDCS sessions, and once after 10 sessions. The original form of the BDI, which is used in this study, is a self-reported 21 questions inventory about how the subject has been feeling in the last week, where each question has four answers ranging in intensity. The HRSD is a multiple items questionnaire designed for measuring adult depression and is administrated by a health care professional. HDRS is currently the most common depression measure used worldwide (Marijnissen, Tuinier, Sijben, & Verhoeven, 2002). Both measures are designed to indicate the presence of depressive symptoms in a past number of days.

Statistical Analysis

We used PASW Statistics 18.0 for data analysis. Baseline demographic and clinical data were compared using the Fisher's exact test for categorical variables and a paired-samples *t*-test for continuous variables. This study adopted a 2 x 2 mixed factorial design. The effect of tDCS was assessed with a stimulation condition (pre-stimulation/post-stimulation) as a within-subject factor, group (active/sham) as a between-subject factor, and scores on the CANTAB (cognitive performance) as the dependent variable. A similar 2 x 2 mixed factorial design was used for measuring the effects of tDCS on mood. Our analyses of variance (ANOVA) met linear assumptions and the Leven's test was used to examine homogeneity of variances. A significance level of $p < .05$ was used for all statistical comparisons.

Results

All subjects tolerated the tDCS treatment well and no adverse effects were reported. The effects of tDCS on the DMS were investigated. For correct responses, the ANOVA results showed that the effect of tDCS on DMS scores depends on group, indicated by a significant interaction effect, $F(1, 28) = 8.270$, $p < .008$. A significant main effect of stimulation condition was also observed, $F(1, 28) = 5.120$, $p < .032$; however, no significant main effect of group was observed, $F(1, 28) = 0.471$, $p < .498$. Regarding latency time, ANOVA results indicated a significant main effect of stimulation condition, $F(1, 28) = 17.571$, $p < .001$; no significant main effect of group, $F(1, 28) = 0.192$, $p < .664$; and a significant interaction between the two factors, $F(1, 28) = 6.790$, $p < .014$. These results show that anodal stimulation of left DLPFC and cathode stimulation of right DLPFC, significantly improved visual recognition memory, as assessed by the DMS and effect of stimulation condition (pre/post) depends on group factor (active/sham).

Table 3
F and P values of ANOVAs for cognitive functions

Cognitive Functions	Degree of Freedom	*F*	*p*
DMS (correct)			
Stimulation	1.28	5.120	**.032**
Group	1.28	0.471	.498
Stimulation*group	1.28	8.270	**.008**
DMS (latency)			
Stimulation	1.28	17.571	**.001**
Group	1.28	0.192	.664
Stimulation*group	1.28	6.790	**.014**
PRM immediate phase (corrects)			
Stimulation	1.28	28.255	**.001**
Group	1.28	3.319	.079
Stimulation*group	1.28	3.469	.073
PRM immediate phase (latency)			
Stimulation	1.28	7.038	**.013**
Group	1.28	3.990	.056
Stimulation*group	1.28	3.499	.072
PRM delay phase (corrects)			
Stimulation	1.28	25.779	**.001**
Group	1.28	3.066	.091
Stimulation*group	1.28	0.818	.373
PRM delay phase (latency)			
Stimulation	1.28	0.006	.940
Group	1.28	2.507	.125
Stimulation*group	1.28	0.050	.826

$p < .05$; DMS = Delayed Matching to Sample; PRM = Pattern Recognition Memory.

Table 4
Performance on DMS and PRM

Cognitive Functions	Mean	Standard Deviation	SEM
DMS (correct)			
Pre-stimulation (PG)	60.33 (54.93)	13.88 (17.26)	3.58 (4.45)
Post-stimulation (PG)	66.43 (57.80)	12.04 (13.71)	3.11 (3.54)
DMS (latency)			
Pre-stimulation (PG)	5167.8* (5267.40)	1734.6 (1598.40)	447.8 (412.70)
Post-stimulation (PG)	4551.3 (4848.40)	1527.8 (1301.41)	394.4 (336.15)
PRM immediate phase (corrects)			
Pre-stimulation (PG)	62.55 (55.17)	11.51 (10.32)	2.97 (2.66)
Post-stimulation (PG)	75.53 (63.68)	17.46 (16.68)	4.50 (4.30)
PRM immediate phase (latency)			
Pre-stimulation (PG)	4316.6* (5000.20)	1753.5 (1789. 30)	452.7 (461.90)
Post-stimulation (PG)	2925.1 (3946.50)	1318.5 (1348.40)	340.4 (348.10)
PRM delay phase (corrects)			
Pre-stimulation (PG)	37.22 (36.11)	10.01 (8.02)	2.58 (2.07)
Post-stimulation (PG)	60.75 (48.24)	18.01 (18.49)	4.64 (4.77)
PRM delay phase (latency)			
Pre-stimulation (PG)	2974.7* (3899.21)	1403.4 (1449.10)	362.3 (374.14)
Post-stimulation (PG)	2913.3 (3772.13)	891.7 (960.52)	230.2 (248.11)

PG = Placebo Group; DMS = Delayed Matching to Sample; PRM = Pattern Recognition Memory; * = Values marked by (*) are in ms.

The effect of stimulation on visual recognition memory was again analyzed through PRM using a 2 x 2 mixed factorial design with stimulation condition (pre-performance/post-performance) and group (active/sham) as within-subject factors and between-subject factors, respectively. For the immediate recognition phase, the results showed a significant main effect of stimulation condition, $F(1, 28) = 28.255$, $p < .001$; no significant main effect of group, $F(1, 28) = 3.319$, $p < .079$; and no significant interaction between the two factors, $F(1, 28) = 3.469$, $p < .073$. The same results were noted in the late recognition phase, in which were observed a significant main effect of stimulation condition, $F(1, 28) = 25.779$, $p < .001$; no significant main effect of group factor, $F(1, 28) = 3.066$, $p < .091$; and no significant interaction between the two factors, $F(1, 28) = 0.818$, $p < .373$. This shows that anodal stimulation of the left DLPFC and cathode stimulation of the right DLPFC significantly improved visual recognition memory; however, the effect of the stimulation condition did not depend on group (active/sham). Results for latency output showed a significant main effect of stimulation type in the immediate phase, $F(1, 28) = 7.038$, $p < .013$, but not in the delay phase, $F(1, 28) = 0.006$, $p < .940$; no significant interaction between stimulation condition and group in the immediate and delay phase; and no significant main effect of group (active/sham) in the immediate and delay phase.

In addition to visual working memory, the effect of stimulation on mood was also measured. Using a 2 x 2 mixed factorial design with stimulation condition (pre-performance/post-performance) and group (active/sham) as within-subject factors and between-subject factors, respectively, results showed a significant interaction effect of stimulation condition and group on BDI scores, $F(1, 28) = 118.849$, $p < .001$. This indicates our stimulation significantly reduced depressive symptoms and that the effect of stimulation condition depends on group. In addition to the interaction effect, also of significance are the main effect of the stimulation condition, $F(1, 28) = 159.201$, $p < .001$; and group, $F(1, 28) = 18.834$, $p < .001$. Results of the HDRS also show the same pattern with significant interaction effect, $F(1, 28) = 35.973$, $p < .001$; which means, depending on group, stimulation condition significantly reduces HDRS scores. Also of note from the results shown in Table 5 are the main effect of stimulation condition, $F(1, 28) = 131.822$, $p < .001$; and group, $F(1, 28) = 21.971$, $p < .001$.

As Figure 1 clearly depicts, the effect of stimulation condition depends on the group (active/sham). In other words, tDCS effects on mood and depressive symptoms of patients depend on receiving active or sham stimulation. We see a significant reduction in depressive scores after 10 sessions of tDSC only in the experimental group. It is also notable that the baseline scores of the BDI are different, which may give rise to a question about group homogeneity in terms of severity of depression in both control and experimental groups. Although both groups' BDI baseline score indicates a moderate to severe level of depression, this baseline difference could be due to the subjective nature of the BDI self-report. To make sure both groups' depression severity is similar, we used the HDRS (completed by an experienced psychiatrist) in addition to BDI to make sure participants met inclusion criterion of MD severity. As left graph in Figure 1 shows, the baseline HDRS scores of both groups indicate that both groups suffered from severe MD.

Table 5
F and P values of ANOVAs for depression scores

Cognitive Functions	Degree of Freedom	*F*	*p*
BDI			
Stimulation	1.28	159.201	.001
Group	1.28	18.834	.001
Stimulation*group	1.28	**118.849**	**.001**
HDRS			
Stimulation	1.28	131.822	.001
Group	1.28	21.971	.001
Stimulation*group	1.28	**35.973**	**.001**

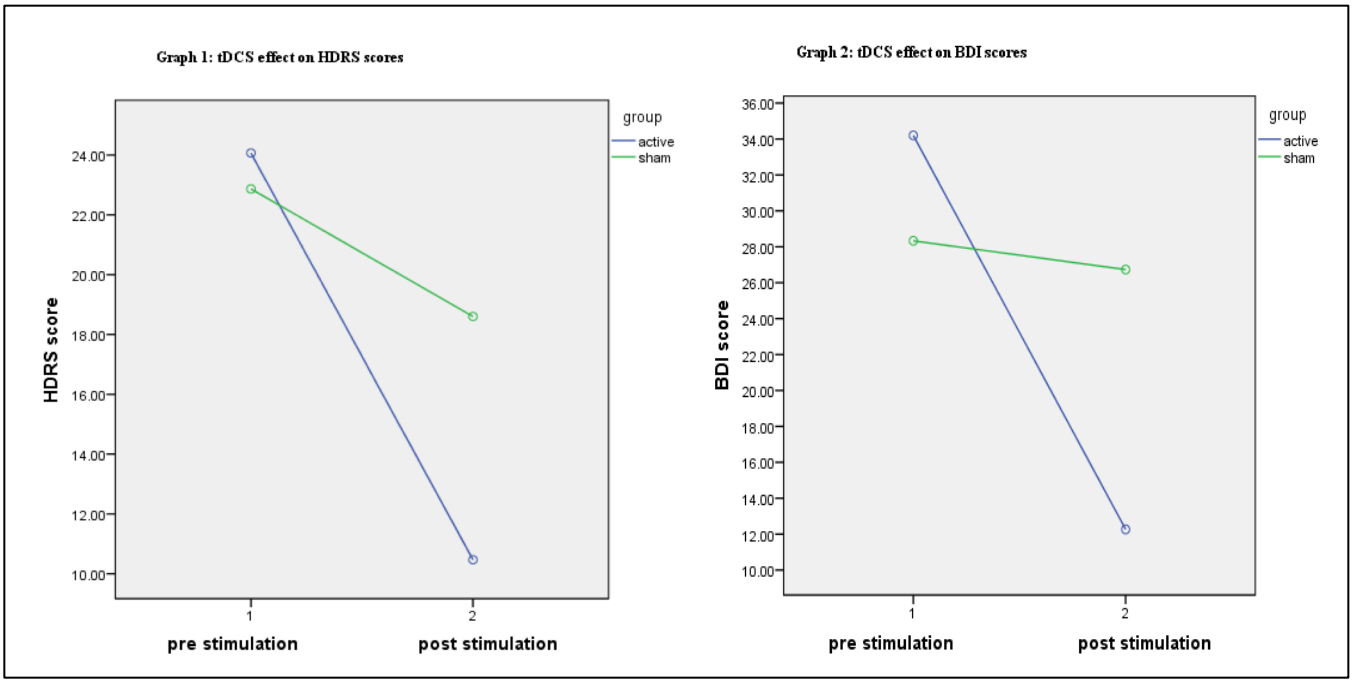

Figure 1. Interaction effect of stimulation condition and group (active/sham) on HDRS scores (left) and BDI scores (right).

Discussion

This study primarily showed that anodal tDCS over DLPFC for 10 consecutive days improved visual working memory in patients with MD. Visuospatial memory, in which its function is associated with prefrontal cortex function (Church, Petersen, & Schlaggar, 2010; Dockery et al., 2011; Fregni et al., 2005), is impaired in patients with MD, and some recent studies suggest that visual memory is the most impaired cognitive domain in MD (Smith et al., 2013). This is proposed to be the result of large alterations in cortical activity of the PFC in major depression (Nitsche et al., 2009). Therefore, we can expect to observe improving effect on visual memory if we modulate cortical activity of the PFC in MD. To modulate cortical activity of the PFC, we applied anodal tDCS of the left DLPFC concurrently with cathodal stimulation of the right DLPFC. We applied this specific treatment montage according to pathological cortical activity of PFC in MD. This study also indicated that our specific stimulation montage significantly reduced depressive symptoms.

There is an imbalance of function between the right and left DLPFC in MD (Grimm et al., 2008; Nitsche et al., 2009; Nitschke et al., 2004). It is suggested that there is a higher than normal cortical activity in the right DLPFC and a lower than normal activity in the left DLPFC in MD, which is responsible for impaired visual memory deficits in depression. A similar imbalance of function is suggested to be associated with negative emotional processing in MD (Grimm et al., 2008). We modulated this imbalanced activity in the left and right PFC by applying anodal tDCS on the left DLPFC and cathodal tDCS on the right, and we observed improved performance in visual spatial memory tasks after a 10-session tDCS protocol using this montage. In other words, we tried to alter pathologic cortical activity in depression to normal cortical activity using this specific stimulation montage.

What our study claims to find is considerable from several points. First of all, visual memory impairment is one of the most impaired cognitive function in MD (Smith et al., 2013); although numerous studies showed effectiveness of tDCS on memory, specifically working memory (Boggio, Ferrucci, et al., 2006; Ferrucci, Mameli, et al., 2008; Fregni et al., 2006; Jo et al., 2009), few studies have evaluated visual aspects of memory using tDCS; and no study has investigated these aspects of memory in MD specifically. However, an animal study conducted by Dockery et al. (2011) found anodal and cathodal tDCS of the frontal cortex improved visuospatial working memory in rats.

Secondly, and more importantly, our study suggests a specific stimulation montage for MD tDCS studies, based on findings of neuroanatomical and neuroimaging studies. Results of this study propose that application of anodal tDCS over the left DLPFC concurrently with cathodal tDCS over the right DLPFC can enhance visual working memory and visual recognition memory in MD. Previous brain stimulation studies on depression targeted left DLPFC for anodal stimulation, and usually did not apply cathodal stimulation on right DLPFC, as part of treatment protocol. This could be partly due to the fact that tDCS studies on depression are fairly new, especially when it comes to the study of cognitive functions in MD, and more studies are needed to replicate findings and suggest more accurate treatment protocol. By applying cathodal stimulation of the right DLPFC, we suggest a specific tDCS montage and treatment protocol, especially when we are concerned about improving cognitive impairments of MD.

The PFC and DLPFC are suggested to be engaged in cognitive functions. More specifically they are directly involved in different aspects of memory, including visual-spatial memory (Dockery et al., 2011; Petrides, 2000). Dysfunction of distributed cortico-subcortical, bihemispheric regions in the DLPFC network, with higher activity in the right hemisphere and lower activity in the left hemisphere, has been found central in depression pathology (Brunoni & Vanderhasselt, 2014; Nitsche et al., 2009). Thus modulation of PFC and DLPFC cortical activity is supposed to be accompanied by cognitive improvement in depression. Our study suggests improving effects of tDCS on visual working memory and recognition memory of patients with MD, by targeting left DLPFC for anodal stimulation and right DLPFC for cathodal stimulation. This has important theoretical implications for MD studies too, in terms of how the DLPFC contributes to MD cognitive impairments. As mentioned, the relationship of the PFC and working memory has been supported by previous studies; however, results are still mixed, especially in MD studies (Pu et al., 2012). This study attempted to investigate this relationship in a brain stimulation context.

This proposed mechanism of how our tDCS montage improves cognitive visual memory is a suggestion based on our controlled study. However, it is possible that cognitive improvement is a positive side effect of general improvement in depression severity. Memory deficit in depression is secondary to other cognitive dysfunctions, such as attention deficits and impaired cognitive initiative, rather than the ability of short-term memory storage (Marazziti et al., 2010). Thus, tDCS over the DLPFC, the brain region involved in cognitive functions and emotional processing, is associated with therapeutic effect, and it is reasonable to hypothesize that altering this pathological state could be associated with cognitive improvement. We altered this pathological state in MD patients by modulating cortical activity of the DLPFC through anodal and cathodal tDCS.

Although the main purpose of this study was to investigate the effect of transcranial brain stimulation on visual working memory in MD, we also observed reduced depression scores, which support previous brain stimulation studies of MD. One way we can explain such findings is that the PFC regions, specifically tumors, ischemia and epileptogenic zones of the left hemisphere, are frequently accompanied by depressed mood (Nitsche et al., 2009). Both excitability enhancement of the left DLPFC and excitability reduction of the right DLPFC to treat depression have been studied; however, mechanism of action is certainly not proven (Nitsche et al., 2009). It is also known that the VLPFC is involved in emotional processing, rather than cognitive processing (Marazziti et al., 2010). One explanation from a brain-stimulation mechanism perspective is that, by applying anodal tDCS, we increased cortical activity in the left DLPFC that is pathologically decreased in major depression; and by applying cathodal tDCS, we decreased cortical activity in the right DLPFC that is pathologically increased in major depression.

Although the results are encouraging, our study had several limitations. First of all, we did not evaluate the long-term effects of the intervention in terms of follow-up study. Further studies should evaluate visual-spatial memory improvement after tDCS treatment in fixed intervals. Secondly, although our sample is theoretically representative for a clinical intervention study, a larger sample size is preferred.

Our study is a pilot study that has an exploratory nature using small sample. Pilot studies are not adequate to test the clinical efficacy of tDCS for a particular condition for the first time (Brunoni et al., 2012). Therefore, despite of promising results, future studies that compare tDCS effect versus another therapy are needed to validate tDCS as an effective treatment. Finally, even though significant effects of tDCS on memory was observed in patients with MD, the mechanisms underlying tDCS-induced visual memory enhancement still remain unclear and they should be the focus of investigation in further controlled studies. Using neuroimaging measures

such as fMRI, PET, and some measure of neural changes such as ERPs and qEEG, would be more beneficial and yield more accurate results.

In conclusion, our study demonstrated that anodal stimulation of the left DLPFC concurrently with cathodal stimulation of the right DLPFC improved visuospatial aspects of memory (visual working memory, visual recognition memory) in MD, after 10 consecutive sessions of tDCS. This effect is suggested to be the result of cortical activity modulation of DLPFC through tDCS. By increasing cortical activity of the left DLPFC and decreasing it in the right DLPFC, we altered pathologic imbalanced activity of the PFC in MD and visual memory performance improved after such a treatment protocol. A mood improvement was also observed after 10 sessions of tDCS treatment. Although further controlled studies with larger sample sizes and longer stimulation periods are needed, our results encourage using this stimulation montage for improving both cognitive and emotional impairment in MD.

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NeuroRegulation

Book Review – *Clinical Handbook of Biofeedback: A Step-by-Step Guide for Training and Practice with Mindfulness*

by Inna Z. Khazan. Wiley-Blackwell, Malden, MA, 2013, 354 pages, ISBN: 978-1119993711.

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Inna Khazan has written a book on biofeedback that does three things very well. First, it provides clear and accessible descriptions of applied psychophysiology methods. Second, it reviews the research base that supports these methods and makes them credible treatments for a range of significant health problems. Third, it creatively integrates biofeedback with the practice of mindfulness meditation, a major component of the newest generation of cognitive-behavior therapy (Hayes, Luoma, Bond, Masuda, & Lillis, 2006).

As Khazan writes in her introductory chapter, "Mindfulness allows people to become truly aware of the present moment, to tell the difference between what they can and cannot change, and then focus their attention on the things they *can* change" (p. xiii, original italics). Applying mindfulness in biofeedback, as in psychotherapy, transforms what symptoms mean and overcomes treatment impasses.

Chapters are excellently researched and provide salient reference citations. Khazan's writing is direct and clear. Tables, illustrations, and formatting make the text readable and accessible as a practical reference. The chapters are organized into four sections: Foundations, Assessment, Biofeedback Modalities, and Biofeedback Applications.

The Foundations section begins with a basic introduction to mindfulness, research supporting its effects, and directions for integrating mindfulness with biofeedback. As the title advertises, methods are presented in a concise step-by-step fashion. A number of meditation scripts are offered in appendices. This first section concludes with two brief chapters. One briefly reviews general issues in biofeedback, such as goals, modalities, and important training parameters (e.g., rapport, rationale, self-monitoring, and homework). The other describes large-scale multi-modality devices, and small-scale devices, and provides vendor information.

Assessment is presented in four chapters. The first of these outlines an interview structure for collecting information about the presenting problem and relevant background history. Psychophysiological stress assessment is described next, including sensor placement, specific steps for each phase of assessment, and guidelines for interpreting results. Khazan then outlines rationale and methods for completing a relaxation profile. This type of assessment profile induces relaxation with several methods in turn and determines which produces the best physiological response. Last, Khazan reviews the often-overlooked stage of treatment planning. She does this by integrating methods of stress assessment interpretation from a previous chapter with illustrations of common psychophysiological profiles. Levels of research evidence (Moss & Gunkelman, 2002) are outlined, and used to classify biofeedback methods for representative disorders. For example, surface EMG biofeedback for adult tension headache is reported as having sufficient evidence to reach Moss and Gunkelman's Level 5 ("efficacious and specific"), whereas heart rate variability training for PTSD achieves only Level 2 ("possibly efficacious"). Thus, Khazan provides methods for data collection, interpretation, and integration with empirically supported biofeedback techniques. This then enables client-therapist collaboration for evidence-based decision-making.

Khazan's third section reviews Biofeedback Modalities: breathing, heart rate variability, surface electromyography, temperature, and skin conductance. Chapters concisely present the physiology of each system. Step-by-step protocols are outlined for assessment and treatment, together with methods for including mindfulness. In many cases, sample therapist scripts are offered. Specific assessment and treatment variations are described for particular client presentations. Checklists and trouble-shooting guides are also included. Appendices present useful client logs for self-monitoring symptoms and skill practice.

The final section, Biofeedback Applications, addresses representative disorders for which biofeedback may be an effective treatment. These are anxiety, asthma, migraine headache, tension-type headache, essential hypertension, irritable bowel syndrome, Raynaud's phenomenon, temporomandibular joint disorders, and chronic pain. Emerging directions for the use of biofeedback are presented for major depressive disorder, heart disease, diabetes, arthritis, and insomnia. The organization of these chapters includes sections on symptoms, physiology, etiology, assessment, conventional treatment, and biofeedback. Presentation of biofeedback protocols is succinct and well organized. Brief scripts and client recording tools are included.

Khazan's book is informative, practical, and readable. It should be on the shelf of every serious biofeedback practitioner. The author perceptively notes that the book may also be of value to psychotherapists who wish to consider how biofeedback can be included in their existing practice in order to provide more holistic care. That is, the book does a service to build bridges between practitioners who treat maladies of the body and those who treat disorders of the mind.

Despite the book's absence of neurofeedback coverage, it should be read by neurofeedback practitioners for several reasons. Most importantly, it presents mindfulness skills and how they can be integrated with biofeedback to further develop self-awareness and self-regulation, consequently strengthening the effects of biofeedback. This point can be easily and directly extrapolated to the practice of neurofeedback. Formats for assessment and tools for symptom monitoring will also be welcomed by neurofeedback practitioners. Khazan's book should also be read by neurofeedback practitioners because it provides ideas for planning and conducting treatment that can improve outcomes.

In sum, Khazan's integration of mindfulness with biofeedback is easily extended to neurofeedback. Integrated with neurofeedback, these methods are likely to bear much fruit. For clients, they will facilitate the more ready acquisition of self-awareness and self-regulation skills, enable compassionate detachment from experiences beyond one's control, and accelerate the application of newly learned skills to effectively change what can be controlled. Khazan's book is an excellent introduction to biofeedback for new students of the field, as well as to seasoned therapists from a range of mental health disciplines who are interested in strengthening their practice by treating both the mind and the body. Scientists will welcome Khazan's book for the testable hypotheses it suggests.

For established practitioners of both biofeedback and neurofeedback, Khazan's innovative integration of mindfulness will be greatly appreciated because it articulately presents methods to augment self-awareness and self-regulation that will result in better clinical outcomes.

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NeuroRegulation

Neuroregulation News from Other Journals

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Abstract

In the following section selected articles related to neuroregulation modalities are summarized. While most have a focus on EEG-based neurofeedback, some come from the growing fMRI-based neurofeedback approaches as well as transcranial magnetic stimulation neuromodulation. Of particular note, is the increase in prevalence of offerings from open access journals; many included here are from such journals, with direct URL links to the articles. The timeframe of these articles encompass from October 2013 through December 2014.

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Applied Psychophysiology and Biofeedback

Escolano, C., Navarro-Gil, M., Garcia-Campayo, J., Congedo, M., & Minguez, J. (2014). The effects of individual upper alpha neurofeedback in ADHD: An open-label pilot study. *Applied Psychophysiology and Biofeedback,* 39(3–4), 193–202. http://dx.doi.org/10.1007/s10484-014-9257-6

This study of 20 children with ADHD, evaluated an individualized approach to neurofeedback by incorporating alpha peak frequency in the protocol development. Neurophysiological tests, outcome measures such as parent rating scales, and assessed learning curves were included to evaluate efficacy.

Sokhadze, E. M., El-Baz, A. S., Tasman, A., Sears, L. L., Wang, Y., Lamina, E. V., & Casanova, M. F. (2014). Neuromodulation integrating rTMS and neurofeedback for the treatment of autism spectrum disorder: An exploratory study. *Applied Psychophysiology and Biofeedback, 39*(3–4), 237–257. http://dx.doi.org/10.1007/s10484-014-9264-7

This study investigated the effects of repetitive transcranial magnetic stimulation (rTMS) in combination with EEG neurofeedback (TMS-NF) as compared to a waitlist control group for the treatment of Autism spectrum disorder. The study found improved behavioral and function outcomes from the 18 sessions of TMS-NF, more so over the waitlist control group.

Steiner, N. J., Frenette, E., Hynes, C., Pisarik, E., Tomasetti, K., Perrin, E. C., & Rene, K. (2014). A pilot feasibility study of neurofeedback for children with autism. *Applied Psychophysiology and Biofeedback*, *39*(2), 99–107. http://dx.doi.org/10.1007/s10484-014-9241-1

This was a study focusing on neurofeedback for children with high functioning autism spectrum disorders and difficulties with attention. It examines the feasibility of neurofeedback with this population.

Biofeedback

Koberda, J. L., Koberda, P., Moses, A., Winslow, J., Bienkiewicz, A., & Koberda, L. (2014). *Z*-score LORETA neurofeedback as a potential therapy for ADHD. *Biofeedback*, *42*(2), 74–81. http://dx.doi.org/10.5298/1081-5937-42.2.05

This is a single case study report of the use of both surface and low-resolution brain electromagnetic tomography (LORETA) *z*-score neurofeedback with an 8-year-old male with ADHD. Cognitive testing demonstrated improvements in symptoms as a result of the *z*-score neurofeedback. There were also improvements in academic functioning.

Thatcher, R. W. (2014). Advances in assessment and treatment of ADHD using network analyses. *Biofeedback*, *42*(2), 58–67. http://dx.doi.org/10.5298/1081-5937-42.2.07

A review article discussing *z*-score neurofeedback, the article discusses the benefits of *z*-score neurofeedback derived from the neuroscience underpinnings of brain networks. Specific networks (such as attention or default mode) can be directly addressed through the implementation of LORETA *z*-score neurofeedback; thus allowing improved specificity in the linking of symptoms with brain dysregulation.

Biological Psychology

In January 2014, the Biological Psychology journal published a special themed issue where all articles in the volume focused on neurofeedback. Included in that issue were 13 articles that encompassed a wide variety of topics within the field of neurofeedback. The titles of those articles are as follows, and all are found in Volume 95:

Arns, Heinrich, and Strehl. Evaluation of neurofeedback in ADHD: The long and winding road. http://dx.doi.org/10.1016/j.biopsycho.2013.11.013

Dekker, Sitskoorn, Denissen, and van Boxtel. The time-course of alpha neurofeedback training effects in healthy participants. http://dx.doi.org/10.1016/j.biopsycho.2013.11.014

Enriquez-Geppert et al. Modulation of frontal-midline theta by neurofeedback. http://dx.doi.org/10.1016/j.biopsycho.2013.02.019

Gruzelier, Foks, Steffert, Chen, and Ros. Beneficial outcome from EEG-neurofeedback on creative music performance, attention and well-being in school children. http://dx.doi.org/10.1016/j.biopsycho.2013.04.005

Gruzelier et al. Replication of elite music performance enhancement following alpha/theta neurofeedback and application to novice performance and improvisation with SMR benefits. http://dx.doi.org/10.1016/j.biopsycho.2013.11.001

Kober et al. Near-infrared spectroscopy based neurofeedback training increases specific motor imagery related cortical activation compared to sham feedback. http://dx.doi.org/10.1016/j.biopsycho.2013.05.005

Maurizio et al. Comparing tomographic EEG neurofeedback and EMG biofeedback in children with attention-deficit/hyperactivity disorder. http://dx.doi.org/10.1016/j.biopsycho.2013.10.008

Meisel, Servera, Garcia-Banda, Cardo, and Moreno. Reprint of "Neurofeedback and standard pharmacological intervention in ADHD: A randomized controlled trial with six-month follow-up." http://dx.doi.org/10.1016/j.biopsycho.2013.09.009

Reiner, Rozengurt, and Barnea. Better than sleep: Theta neurofeedback training accelerates memory consolidation. http://dx.doi.org/10.1016/j.biopsycho.2013.10.010

Ros, Munneke, Parkinson, and Gruzelier. Neurofeedback facilitation of implicit motor learning. http://dx.doi.org/10.1016/j.biopsycho.2013.04.013

Ruiz, Buyukturkoglu, Rana, Birbaumer, and Sitaram. Real-time fMRI brain computer interfaces: Self-regulation of single brain regions to networks. http://dx.doi.org/10.1016/j.biopsycho.2013.04.010

Schabus et al. Enhancing sleep quality and memory in insomnia using instrumental sensorimotor rhythm conditioning. http://dx.doi.org/10.1016/j.biopsycho.2013.02.020

Staufenbiel, Brouwer, Keizer, and van Wouwe. Effect of beta and gamma neurofeedback on memory and intelligence in the elderly. http://dx.doi.org/10.1016/j.biopsycho.2013.05.020

Child and Adolescent Psychiatric Clinics of North America

Holtmann, M., Sonuga-Barke, E., Cortese, S., & Brandeis, D. (2014). Neurofeedback for ADHD: A review of current evidence. *Child and Adolescent Psychiatric Clinics of North America, 23*(4), 789–806. http://dx.doi.org/10.1016/j.chc.2014.05.006

This article is an overall review of neurofeedback. The authors call for more studies, which are methodologically sound, well controlled, and include larger samples. However, there is acknowledgement that neurofeedback has gained empirical support more recently and fits within in multimodal treatment therapy approaches.

Clinical EEG and Neuroscience

Cannon, R. L., Baldwin, D. R., Diloreto, D. J., Phillips, S. T., Shaw, T. L., & Levy, J. J. (2014). LORETA neurofeedback in the precuneus: Operant conditioning in basic mechanisms of self-regulation. *Clinical EEG and Neuroscience*, *45*(4), 238–248. http://dx.doi.org/10.1177/1550059413512796

A research study evaluating low-resolution brain electromagnetic tomography (LORETA) neurofeedback in the precuneus with 13 participants (five non-clinical, eight with heterogeneous clinical diagnoses). Outcome measures in the form of neurophysiological data, a personality inventory, and an executive function rating scale were assessed to determine the effects of the neurofeedback. This study provides support for the use of LORETA neurofeedback for enhancement of executive function and improvement in psychological symptoms.

Clinical Neurophysiology

Mottaz, A., Solcà, M., Magnin, C., Corbet, T., Schnider, A., & Guggisberg, A. G. (2014). Neurofeedback training of alpha-band coherence enhances motor performance. *Clinical Neurophysiology.* Advance online publication. http://dx.doi.org/10.1016/j.clinph.2014.11.023

This is a research article evaluating neurofeedback to address functional connectivity. The sample included one stroke patient and 10 healthy subjects. The frequency of interest was the alpha band.

Frontiers in Human Neuroscience

Arns, M., Feddema, I., & Kenemans, J. L. (2014). Differential effects of theta/beta and SMR neurofeedback in ADHD on sleep onset latency. *Frontiers in Human Neuroscience, 8*(1019), 1–10. http://dx.doi.org/10.3389/fnhum.2014.01019

This is a research study evaluating the role of sensory motor rhythm (SMR) neurofeedback versus theta beta ratio neurofeedback and the impact of sleep and attention-deficit/hyperactivity disorder (ADHD). The study compared adult ADHD patients to control group participants. Relationships were found between inattention in adults and self-reported sleep problems. The SMR neurofeedback resulted in more improvement in sleep symptoms. Possible differential effects of SMR and theta beta ratio neurofeedback are discussed.

Gevensleben, H., Moll, G. H., Rothenberger, A., & Heinrich, H. (2014). Neurofeedback in attention-deficit/hyperactivity disorder – different models, different ways of application. *Frontiers in Human Neuroscience, 8*(846), 1–10. http://dx.doi.org/10.3389/fnhum.2014.00846

A review article discussing two hypothetical neurofeedback framework models informed by either slow cortical potential or frequency band neurofeedback modalities. The authors suggest the underlying model impacts how the neurofeedback is evaluated and applied. They argue the importance of stating theoretical perspectives of frameworks and models when reporting on neurofeedback research.

Kober, S. E., Witte, M., Ninaus, M., Neuper, C., & Wood, G. (2013). Learning to modulate one's own brain activity: The effect of spontaneous mental strategies. *Frontiers in Human Neuroscience, 7*(695), 1–12. http://dx.doi.org/10.3389/fnhum.2013.00695

This research compared 10 neurofeedback sessions of either sensorimotor rhythm based or gamma (40–43 Hz) based protocols. Also investigated were mental strategies on neurofeedback performance. Participants who reported having no specific mental strategy demonstrated linear improvements in neurofeedback performance whereas participants reporting specific mental strategies did not.

Ros, T., Baars, B. J., Lanius, R. A., & Vuilleumier, P. (2014). Tuning pathological brain oscillations with neurofeedback: A systems neuroscience framework. *Frontiers in Human Neuroscience, 8*(1008), 1–22. http://dx.doi.org/10.3389/fnhum.2014.01008

This paper is a review article providing a broad overview of the neurophysiological underpinnings of neurofeedback. Also discusses a proposed mechanism for the workings of neurofeedback in terms of tuning brain oscillations in a framework of network stability and flexibility.

Strehl, U. (2014). What learning theories can teach us in designing neurofeedback treatments. *Frontiers in Human Neuroscience, 8*(894), 1–8. http://dx.doi.org/10.3389/fnhum.2014.00894

A review article exploring various aspects of learning theory as applied to neurofeedback. The author also provides a reminder of the importance of psychotherapeutic dynamics in the neurofeedback process.

Strehl, U., Birkle, S. M., Wörz, S., & Kotchoubey, B. (2014). Sustained reduction of seizures in patients with intractable epilepsy after self-regulation training of slow cortical potentials – 10 years after. *Frontiers in Human Neuroscience, 8*(604), 1–7. http://dx.doi.org/10.3389/fnhum.2014.00604

This article is a long-term follow-up study of slow cortical potential (SCP) neurofeedback for intractable epilepsy. The study was conducted 10 years after the neurofeedback and is reported to be the longest follow-up study for psychophysiological epilepsy treatment. The study suggests participants were still able to self-regulate their SCPs and continued to experience reduced frequency of seizures.

Human Brain Mapping

Zhang, G., Yao, L., Shen, J., Yang, Y., & Zhao, X. (2014). Reorganization of functional brain networks mediates the improvement of cognitive performance following real-time neurofeedback training of working memory. *Human Brain Mapping.* Advance online publication. http://dx.doi.org/10.1002/hbm.22731

This real-time fMRI neurofeedback study investigated connectivity between the working memory network and default mode network. Results suggest training on the identified regions of interest improved cognitive performance.

Memory

Guez, J., Rogel, A., Getter, N., Keha, E., Cohen, T., Amor, T., … Todder, D. (2014). Influence of electroencephalography neurofeedback training on episodic memory: A randomized, sham-controlled, double-blind study. *Memory*. Advance online publication. http://dx.doi.org/10.1080/09658211.2014.921713

A research study evaluating neurofeedback effects on memory using a double-blind sham-controlled design. The study participants included 30 healthy adults who engaged in 10 neurofeedback sessions. Results of pretest and posttest memory assessment are reported.

NeuroImage: Clinical

Stoeckel, L. E., Garrison, K. A., Ghosh, S. S., Wighton, P., Hanlon, C. A., Gilman, J. M., … Evins, A. E. (2014). Optimizing real time fMRI neurofeedback for therapeutic discovery and development. *NeuroImage: Clinical, 5*, 245–55. http://dx.doi.org/10.1016/j.nicl.2014.07.002

This paper is a review article discussing real time functional magnetic resonance imaging (rtfMRI) neurofeedback applications. The authors propose guidelines for rtfMRI studies and call for clinical trials of this modality. They believe that rtfMRI neurofeedback can be a personalized intervention approach to address maladaptive brain patterns.

NeuroRehabilitation

Munivenkatappa, A., Rajeswaran, J., Indira Devi, B., Bennet, N., & Upadhyay, N. (2014). EEG neurofeedback therapy: Can it attenuate brain changes in TBI? *NeuroRehabilitation, 35*(3), 481–484. http://dx.doi.org/10.3233/NRE-141140

This is a case review study of two individuals with histories of traumatic brain injury. Both participants received 20 neurofeedback sessions over a period of 2 months. Cognitive functions for both individuals were improved upon post testing.

Neuroscience and Biobehavioral Reviews

Gruzelier, J. H. (2014). EEG-neurofeedback for optimising performance. I: A review of cognitive and affective outcome in healthy participants. *Neuroscience and Biobehavioral Reviews, 44*, 124–141. http://dx.doi.org/10.1016/j.neubiorev.2013.09.015

Gruzelier, J. H. (2014). EEG-neurofeedback for optimising performance. II: Creativity, the performing arts and ecological validity. *Neuroscience and Biobehavioral Reviews, 44*, 142–158. http://dx.doi.org/10.1016/j.neubiorev.2013.11.004

Gruzelier, J. H. (2014). EEG-neurofeedback for optimising performance. III: A review of methodological and theoretical considerations. *Neuroscience and Biobehavioral Reviews, 44*, 159–182. http://dx.doi.org/10.1016/j.neubiorev.2014.03.015

A three-part series of review articles discussing neurofeedback from the perspective of optimizing performance. Part one is an overview of the neurofeedback field in general and reviews studies evaluating healthy and elderly participants. Of those reviewed, the authors indicate 23 controlled studies report outcomes that are beneficial. Part two primarily focuses on the use of neurofeedback for enhancement of creativity in the performing arts, to include acting, music, and dance. Part three is germane to researchers and practitioners in discussing theoretical and methodological issues as it pertains to the scientific study and practice of neurofeedback.

Pediatrics

Steiner, N. J., Frenette, E. C., Rene, K. M., Brennan, R. T., & Perrin, E. C. (2014). In-school neurofeedback training for ADHD: Sustained improvements from a randomized control trial. *Pediatrics, 133*(3), 483–492. http://dx.doi.org/10.1542/peds.2013-2059

This randomized controlled study evaluated sustained gains from 40 sessions of neurofeedback, cognitive training, or a control condition, 6 months after the training. The sample included 104 children ages 7- to 11-years-old who were all diagnosed with attention-deficit/hyperactivity disorder (ADHD). Outcome measures were three behavioral rating scales and changes in medication dosages. Greater improvements in ADHD symptoms were attained by the neurofeedback group over the cognitive training or control group; moreover, these gains were sustained at the 6-month follow-up. Also of note was that, at the 6-month follow-up, both the cognitive training and control groups had increases (statistically and clinically) in medication, while only the neurofeedback group maintained the same dosage levels.

PLoS ONE

Neuner, I., Arrubla, J., Werner, C. J., Hitz, K., Boers, F., Kawohl, W., & Shah, N. J. (2014). The default mode network and EEG regional spectral power: A simultaneous fMRI-EEG study. *PLoS ONE, 9*(2), e88214, 1–8. http://dx.doi.org/10.1371/journal.pone.0088214

This is a study evaluating fMRI and EEG data simultaneously as it relates to the default mode network. The EEG was investigated using a region of interest approach with Low Resolution Electromagnetic Tomography (LORETA). The results suggest support for EEG band specific associations with various default mode network functions.

Psychology of Addictive Behaviors

Keith, J. R., Rapgay, L., Theodore, D., Schwartz, J. M., & Ross, J. L. (2014). An assessment of an automated EEG biofeedback system for attention deficits in a substance use disorders residential treatment setting. *Psychology of Addictive Behaviors*. Advance online publication. http://dx.doi.org/10.1037/adb0000016

This research study was conducted to evaluate the effectiveness of neurofeedback in a residential treatment setting for substance use. Here an automated neurofeedback protocol was compared to clinician-guided protocols, as well as to participants who received additional therapy sessions as a control condition. All groups received 15 sessions of each protocol or additional therapy and group sample sizes ranged from 30 to 33. Both the neurofeedback groups resulted in post treatment improvements in the computerized performance test outcome measure, with no improvement for the control group. No significant difference between the automated or clinician-guided neurofeedback was found.

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