

Quantitative analysis of the electroencephalogram during cranial electrotherapy stimulation

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Abstract

Objective: Normal individuals were used to quantitate electroencephalographic (EEG) changes during concurrent administration of 0.5 and 100 Hz cranial electrotherapy stimulation (CES).

Methods: Twelve normal, right-handed males were used in a randomized, double-blind crossover design study. A 3 amplifier system incorporating noise-cancellation was used to collect one channel of EEG (O1-Cz configuration) for 30 min. Either 0.5, 100 Hz, or sham CES treatment was administered for 20 min of each session. Statistical analyses were applied to time- and frequency-domain EEG variables.

Results: Relative to sham control, 0.5 and 100 Hz CES caused the alpha band mean frequency to shift downward. Additionally, 100 Hz CES also caused a decrease of the alpha band median frequency and beta band power fraction.

Conclusions: Both 0.5 and 100 Hz CES provide frequency distribution shifts that suggest beneficial changes in mental state. However, compared to 0.5 Hz CES, 100 Hz CES effected a greater overall change. It is suggested that similar tests be performed on individuals with various behavioral and neurological disorders to determine if comparable EEG changes can be realized and correlated with beneficial effects of CES therapy. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Mental and behavioral disorders such as depression, insomnia, and anxiety are ubiquitous problems seen throughout the health arena today. Often, unfavorable responses to external stress factors are the underlying cause of these disorders. In fact, it has been shown that stress is linked to immune suppression and that reducing its effects can produce immune enhancement (Peavey, 1982). Additionally, the American Institute of Stress reports that 75–90% of all visits to the physician are linked to stress (Nowroozi, 1994).

Some of the recommended techniques used to treat stress-related mental and behavioral disorders are meditation, exercise, diet, cognitive behavioral therapy, medication, biofeedback, and cranial electrotherapy stimulation (CES). Of these, the newest to modern medicine, and often most controversial is CES, a treatment that involves stimulation of the brain by passing a small electrical current through it.

One main topic of controversy is the unease of both the patient and the medical establishment on passing electrical current through the head, and therefore, the brain. Another concern remains on whether low current CES devices actually produce enough current to stimulate brain tissue. To date, minimal work has been done to assure adequate brain tissue stimulation or determine whether electroencephalographic changes occur during CES.

CES is primarily used for the treatment of insomnia, depression, and anxiety. Numerous experimental and clinical studies have been performed to investigate the efficacy of CES therapy for these disorders (Jarzembki, 1985; Klawansky et al., 1995; Rosenthal, 1971; Shealy et al., 1989). Studies have used a variety of CES devices with current levels generally ranging from 50 μ A to 5 mA and treatment sessions of approximately 30 min over 5–15 days. Most have concluded positive results immediately following the final treatment with effects lasting from 1 week to 2 years. However, many CES studies did not have a control group or were not blinded during the experiment, leaving some doubt on the reliability of the results. Other areas in which CES has been investigated are chemical dependency,

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attention to task, post-traumatic amnesia, and relaxation (Smith, 1982; Schmitt et al., 1984, 1986; Klawansky et al., 1995). A comprehensive research review on CES can be found in Smith (1985).

The mechanism by which CES produces its effects is not yet fully understood. It is postulated that the stimulation of brain tissue causes increased amounts of neurotransmitters to be released, specifically serotonin, beta endorphin, and norepinephrine (Shealy et al., 1989). These neurotransmitters, in turn, permit a return to normal biochemical homeostasis of the limbic system of the brain that may have been imbalanced by a stress-related condition.

In determining how CES can best be used as a therapeutic tool, it is important to quantify and correlate electroencephalographic (EEG) changes with the administration of various CES waveform shapes and frequencies. Although there has been research to investigate quantitative EEG changes before and after CES application (Itil et al., 1972), minimal literature exists on quantitative EEG changes *during* the application of CES (Ferdjallah et al., 1991). This is due mostly to the difficulty of eliminating the CES signal from the EEG. To date, over a dozen different CES devices, some containing multiple signal types and frequencies have been utilized (Smith, 1985). However, quantitative comparison of EEG changes due to CES applied at different frequencies has not been reported. The objective of this research is to investigate quantitative changes in the EEG due to CES administration to normal individuals by acquiring relatively noise-free EEG in the presence of CES at 0.5 and 100 Hz. Statistical analyses are performed on numerous EEG parameters to investigate significant changes during and after application of this relatively new medical technology.

2. Methodology

2.1. Instrumentation and data acquisition

The CES device used in this work is the Alpha-Stim® 100 Microcurrent Stimulator (Electromedical Products International, Inc., Mineral Wells, TX, USA). This is a battery-powered device that can be used as both a CES device and a transcutaneous electrical nerve stimulator (TENS) device. It provides constant current levels up to 600 μ A and has settings of 0.5, 1.5, and 100 Hz. The current delivered is in the form of a biphasic, square pulse with a variable pulse width for the 0.5 and 1.5 Hz settings, as shown in Fig. 1a. Each change in current level is initiated by a spike in the direction of the pulse step. The 100 Hz setting provides a similar current profile but a 100 Hz signal rides atop a slower frequency signal of about 0.4 Hz.

Upon application to the head, the CES current corrupts the EEG signal as shown in Fig. 1b. This 'noise' presents difficulties when EEG information is desired. The degree to which the EEG is corrupted is dependent upon, among other

things, the level of CES current produced at the site of the recording electrodes.

To minimize the presence of CES in the EEG, a basic noise-canceling method is used. First, the EEG signal obtained from the EEG surface electrodes, $EEG_{CES}(t)$, is considered to consist of the true EEG signal, $EEG(t)$, plus the undesired CES signal, $n_{CES/EEG}(t)$. The actual CES signal recorded from the CES device is also considered to be a noise signal, $n_{CES}(t)$. Then, assuming that

$$n_{CES/EEG}(t) = n_{CES}(t), \quad (1)$$

one can recover the EEG signal by subtracting the actual CES signal from the noisy EEG signal,

$$\begin{aligned} EEG(t) &= EEG_{CES}(t) - n_{CES}(t) \\ &= EEG(t) + n_{CES/EEG}(t) - n_{CES}(t). \end{aligned} \quad (2)$$

Of course, the assumption of Eq. (1) will not always be met exactly, but an approximation of it will provide a sufficient $EEG(t)$ waveform.

The instrumentation setup by which this was accomplished is shown in Fig. 2. The CES signal, $n_{CES}(t)$, was measured by placing a resistor in line with a CES electrode and measuring the voltage across the resistor, thus providing a measurement of current coming from the CES device. By adjusting the CES amplifier gain (DC Amp 2) and matching the CES amplitude to the CES artifact within the EEG (DC Amp 1), an estimate of the noise-free EEG waveform can be accomplished by subtracting one signal from the other through the use of a third amplifier (AC Amp).

Matched amplifiers/filters were used for DC amplifiers 1 and 2 of Fig. 2. These were Gould Universal amplifiers with isolated input preamplifiers (Gould Inc., Cleveland, OH, USA). Gains were set at approximately 4000 V/V and lowpass filters set at 30 Hz with a roll-off of 6 dB/octave. The AC coupled amplifier (AC Amp 3) was a Gould EEG Coupler with Universal Preamplifier. The gain was set at approximately 10–20 V/V and bandpass filter set at 1–30 Hz with 12 dB/octave roll-off.

The output from the noise-canceling circuit is shown in Fig. 1(c). The power spectra of the EEG before and after CES noise cancellation are shown in Fig. 3. Prior to noise cancellation, the EEG spectrum shows large amounts of power in the low end of the spectrum at the odd harmonics of 0.4 and 0.5 Hz. After noise cancellation, most of the CES signal has been removed from the spectrum and the recognizable portion of the EEG spectrum remains intact. In this example, the noise-cancellation procedure reduced the amount of power by a factor of 7, from 21.7 to 3.1 $V \times V/Hz$.

Data epochs of 16 s were collected every minute for 30 min at a sampling rate of 256 Hz using a 486 personal computer via a National Instruments PC-LPM-16 12 bit analog input card (National Instruments, Austin, TX, USA). LabVIEW™ software (National Instruments, Austin, TX, USA) was used and a LabVIEW™ program was written

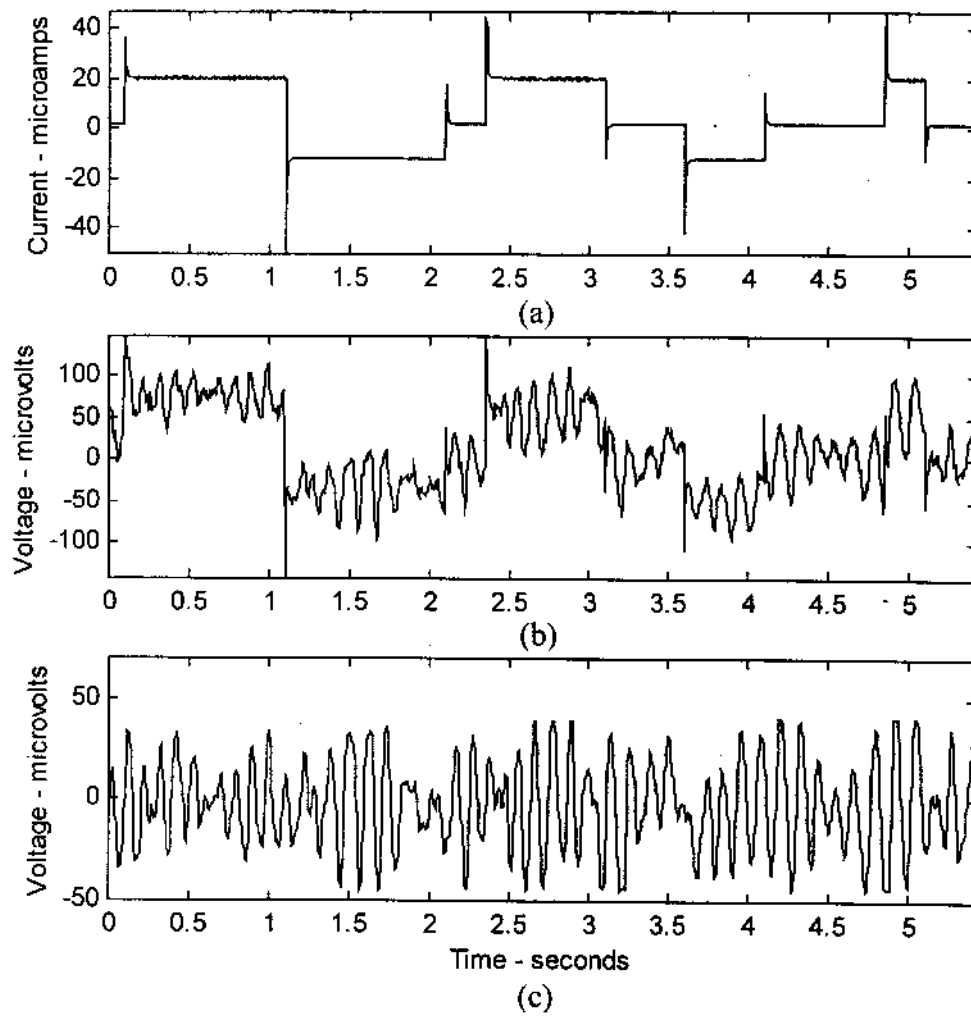


Fig. 1. Noise cancellation of CES from the EEG: (a) CES at 0.5 Hz, (b) EEG corrupted with CES and (c) EEG after noise-cancellation.

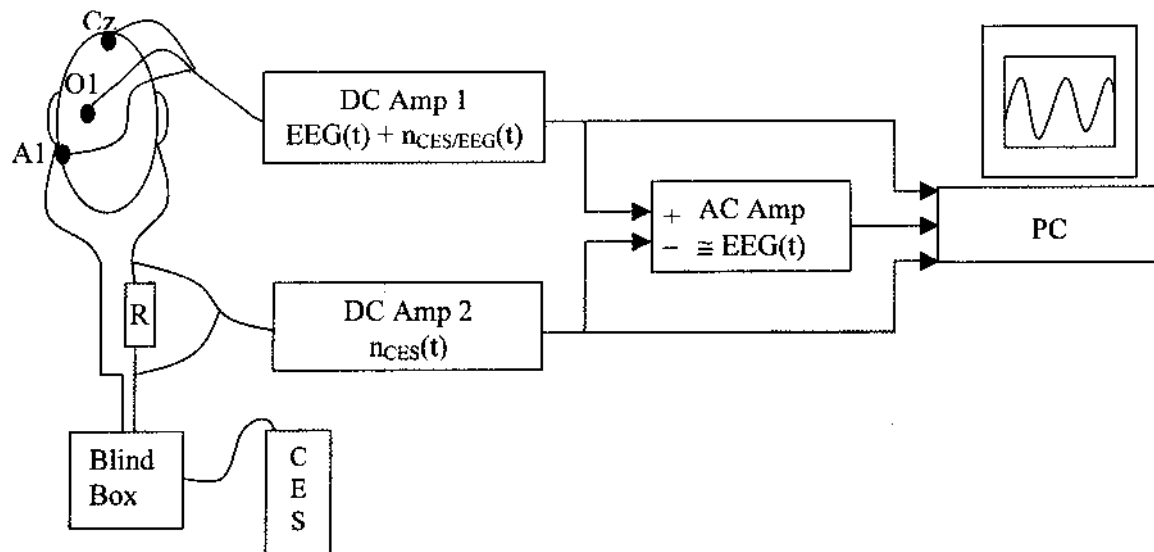


Fig. 2. Noise-cancellation instrumentation setup.

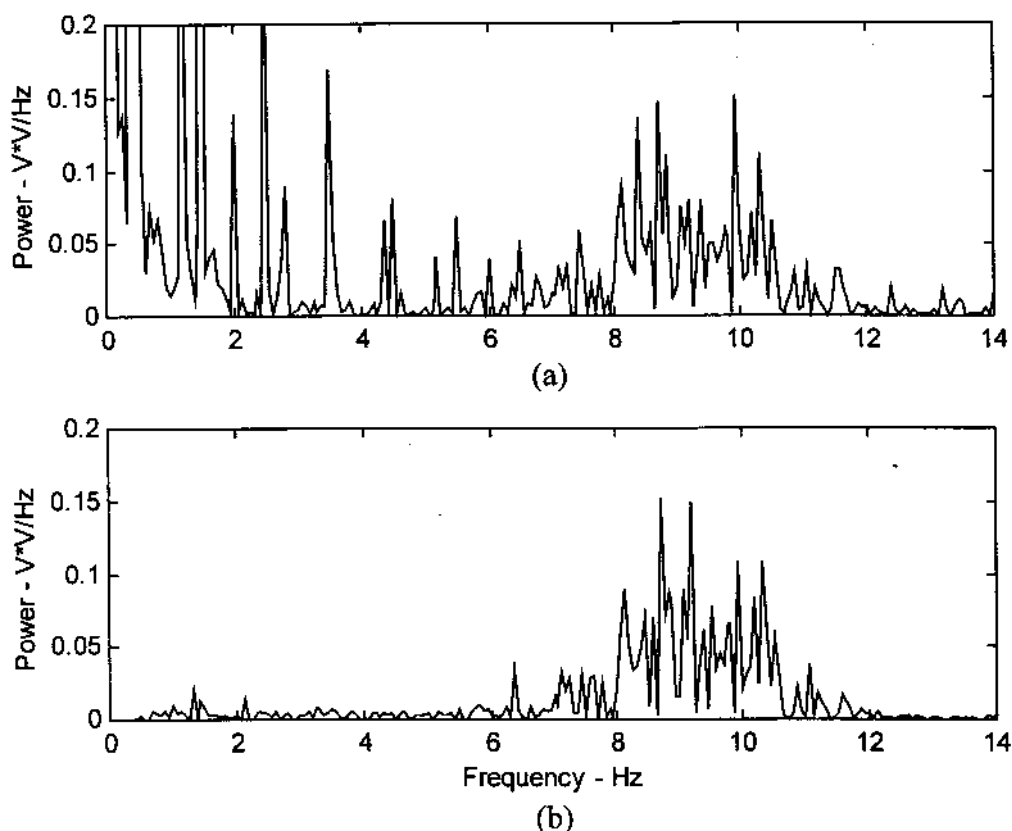


Fig. 3. Power spectra of EEG with CES at 0.5 Hz. (a) Before noise cancellation. (b) After noise cancellation.

to provide a user interface for data collection and data viewing. An example of data collected by the noise-cancellation method is shown in Fig. 1. The CES signal and noisy EEG signal from the DC amplifiers are shown in Fig. 1a,b, respectively. Fig. 1c shows the output of AC amplifier 3 upon taking the difference of the CES and noisy EEG signals, and further amplification and filtering. On-line processing yielded a clean signal and offered proof of system flexibility for later applications, such as biofeedback.

2.2. Subjects

Twelve right-handed male subjects between the ages of 20 and 35 years old participated in a randomized, double-blind, crossover study with no compensation. All subjects signed a consent form granted by the University of Texas at Austin Institutional Review Board verifying that they were not using prescription drugs that influence the central nervous system, have not suffered a head injury that required medical attention, have not experienced epileptic seizures or convulsions, and have never been medically treated for insomnia or psychiatric depression.

2.3. Experimental protocol

A trial session with CES was administered to the subject for the purpose of familiarizing him with the environment

and methodology. Subsequent to the trial session, 3 additional randomized sessions were administered to each subject on different days. These 3 sessions included a sham control (no CES), 0.5 Hz CES, and 100 Hz CES.

One channel of EEG was collected using the O1-Cz bipolar configuration and the left mastoid (M1) as the isolated ground. This montage produced a near equipotential distribution of CES current relative to the EEG electrodes, thus allowing easier cancellation of the CES noise. Ag/AgCl electrodes were used for the measurement and were cleaned with an abrasive gel and rechlorided after each use according to established methods (Geddes et al., 1969; Webster, 1992). Skin preparation consisted of first cleaning the site with alcohol and then rubbing an abrasive skin prepping gel onto the electrode site. Then an electrode filled with EEG paste was applied to the site with a cotton ball placed over the back of the electrode. This procedure was repeated when necessary until a measured electrode impedance of less than 2 k Ω was achieved. The electrodes were then given approximately 25 min to allow for electrode–gel–skin interface potentials to stabilize prior to the DC potential recording. During this time, the subject was placed in a Faraday cage and the CES electrodes were applied to the earlobes after first wetting the electrode pad with saline solution. The subject was asked to remain fairly still and relaxed and was allowed to read.

After the 25 min electrode stabilization period, a CES

Table 1
EEG metrics used to quantify changes^a

EEG metrics	
Frequency domain	Intraband mean and median frequencies (8)
	Interband mean and median frequencies (2)
	Band power fractions (4)
Time domain	RMS power
	DC potential
	Alpha index
	Alpha modulation index

^a Numbers in parentheses indicate number of variables within the category.

sensation threshold was determined for the subject by switching the CES device to either 0.5 or 100 Hz and adjusting the current level until the subject could feel sensation at the electrode site. The current was then reduced to a subthreshold level. The CES device was temporarily switched to 0.5 Hz and both the EEG and CES signals were observed on the data acquisition computer. The CES amplifier gain was then adjusted to match the level of the CES magnitude within the EEG. The amplifier gain adjustments were performed with the CES device set at 0.5 Hz since the amplitude levels were more easily observed and matched. The CES device was then reset to the appropriate frequency. Overall, the current settings for all subjects had a mean of 48 μ A and a range of 10–100 μ A.

The CES unit was then turned off and plugged into a predetermined, randomly assigned, real or sham input of a blinding box. The subject was asked to close his eyes and remain relaxed and still for the next 30 min during which time data epochs were recorded. The CES device was powered on after the first 5 min and shut off automatically after 20 min. No CES was administered during the last 5 min of the session. To prevent the subject from falling asleep during the study, the investigator would ask the subject if he was awake approximately every 5 min, more often if the subject appeared particularly drowsy. All subjects were vigilantly monitored to insure that they maintained a wakeful state and to minimize any other observed changes in behavioral state.

2.4. EEG analysis

EEG analysis was performed in both the time and frequency domains using custom designed Matlab[®] programs (The MathWorks, Inc., Natick, MA, USA). The EEG parameters used in this study are shown in Table 1 with the number of categorical parameters shown in parentheses. Four EEG intraband frequency ranges were defined as follows: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz). A total of 18 variables were calculated.

Power spectra were determined for each epoch of data for the frequency-domain analysis. Mean and median power

frequencies were calculated within each of the 4 EEG frequency bands (intraband) and over the entire EEG range (interband). Also, the band power fractions or relative amount of power within an EEG band with respect to the total amount of spectrum power were determined.

The time-domain analysis consisted of calculating the RMS power, alpha index, alpha modulation index (AMI), and DC potential for every epoch of data. The DC potential was calculated as the average value of the EEG data epoch from the DC coupled amplifier. The alpha index and AMI were calculated using complex demodulation (Schroeder and Barr, 2000). These are measures of the percent of time that alpha activity and alpha modulation are present in an epoch of data, respectively. The AMI is differentiated from the alpha index by the presence of predefined characteristics of amplitude modulation or the waxing and waning of alpha activity. Non-CES EEG artifact was minimal and no additional efforts were made to remove artifact from the EEG data that were analyzed.

2.5. Statistical analysis

The double-blind crossover design in which each subject received both the CES treatments and a sham treatment was used in an attempt to reduce experimental variance. The statistical analysis methods consisted of paired *t* tests and analysis of variance (ANOVA) tests. The paired *t* tests compared the change in variable from before CES administration to after CES (i.e. the first 5 min versus the last 5 min of a session). The one factor ANOVA used time as the factor to investigate significant differences throughout the treatment session where every 5 min division was considered a level of the factor. All statistical tests were performed relative to the sham treatment group by directly subtracting a subject's sham value from his treatment value at each point in time. Thus, only the change in each variable relative to its sham value was analyzed. The predetermined level of significance for all tests was $P \leq 0.05$.

3. Results

Time–frequency plots in Fig. 4 show the EEG spectra for each treatment after normalization and averaging. Most of the power is visible in the alpha band and centered around 10 Hz. A noticeable attenuation of power occurs around or shortly after the first 5 min in each case. Slightly more low alpha and high theta activity is demonstrated throughout the sessions of active CES.

Statistical analysis results for the 0.5 and 100 Hz active treatments (relative to sham) are shown in Table 2. The tests resulting in a *P*-value equal to or less than 0.05 are considered to be significant and are shown in bold type. The *t* tests for 0.5 Hz CES indicate a significant change only for the alpha mean frequency ($P = 0.037$), whereas no significant parameters are indicated using the ANOVA test. The 100 Hz CES treatment also shows a significant change in the

alpha mean frequency, where both the t test ($P = 0.014$) and the ANOVA test ($P = 0.016$) are significant. Additionally, 100 Hz CES induces a significant change in the alpha band median frequency according to both the t test ($P = 0.042$) and ANOVA test ($P = 0.036$) and the beta power fraction

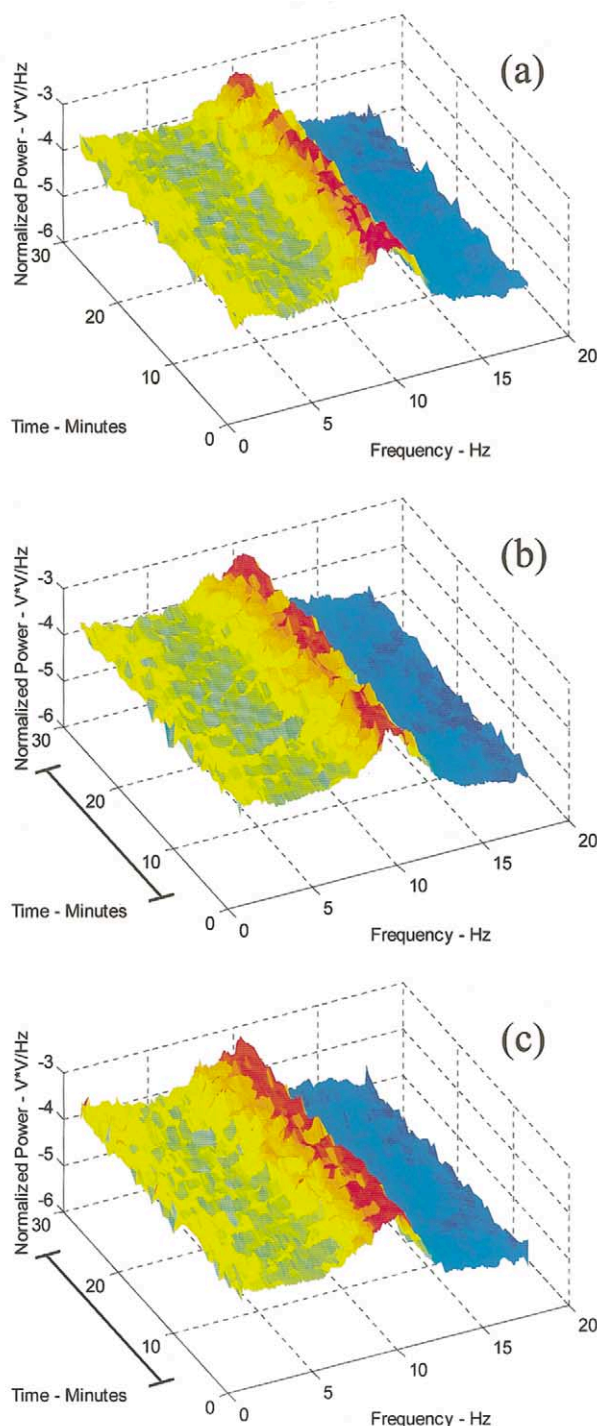


Fig. 4. Normalized and averaged power spectra of all subjects over 30 min study duration: (a) sham treatment, (b) 0.5 Hz CES treatment, and (c) 100 Hz CES treatment. Power is log based. Bar indicates time of active CES.

Table 2
Results of statistical analysis^a

Parameter	0.5 Hz		100 Hz	
	t test	ANOVA	t test	ANOVA
Interband mean frequency	0.300	0.953	0.773	0.931
Interband median frequency	0.284	0.853	0.943	0.803
Delta mean frequency	0.481	0.572	0.759	0.506
Theta mean frequency	0.329	0.678	0.255	0.746
Alpha mean frequency	0.037 ↓	0.433	0.014 ↓	0.016 ↓
Beta mean frequency	0.689	0.356	0.628	0.187
Delta median frequency	0.422	0.620	0.456	0.295
Theta median frequency	0.166	0.420	0.194	0.576
Alpha median frequency	0.076	0.184	0.042 ↓	0.036 ↓
Beta median frequency	0.613	0.593	0.942	0.270
Delta power fraction	0.186	0.835	0.719	0.931
Theta power fraction	0.380	0.511	0.766	0.96
Alpha power fraction	0.175	0.853	0.682	0.790
Beta power fraction	0.766	0.296	0.065	0.036 ↓
Alpha index	0.093	0.489	0.661	0.697
Alpha modulation index	0.291	0.356	0.549	0.906
RMS power	0.312	0.913	0.129	0.150
DC potential	0.605	0.910	0.726	0.986

^a Bold values indicate $P < 0.05$; arrows indicate the parameter trend.

changes significantly according to the ANOVA test ($P = 0.042$).

Plots of the t test variables showing significance are shown in Fig. 5 and indicate each subject's change from before the CES treatment to after the treatment relative to his sham treatment session. The plots also show the mean and the standard error of the mean (SEM) for the group. All 3 cases indicate a group decline in the parameter as very few subjects show a positive change.

The significant ANOVA plots, in Fig. 6, illustrate the change of the group mean (\pm SEM) throughout the entire treatment session relative to the sham treatment. All 3 plots are for the 100 Hz CES case. The alpha band mean and median frequencies decline gradually from the beginning to the end of the session. However, the beta band power fraction exhibits a large initial decrease during the first 5 min of CES followed by a recovery toward its starting point during the second 5 min of CES. The remaining 15 min show a steadily decreasing trend toward the value achieved during the first 5 min of active CES.

4. Discussion

A double-blind crossover design experiment was performed on normal subjects to quantify and compare the effects of two different CES frequency treatments before, during, and after treatment. Results showed a decreasing trend in the alpha band mean frequency for both the 0.5

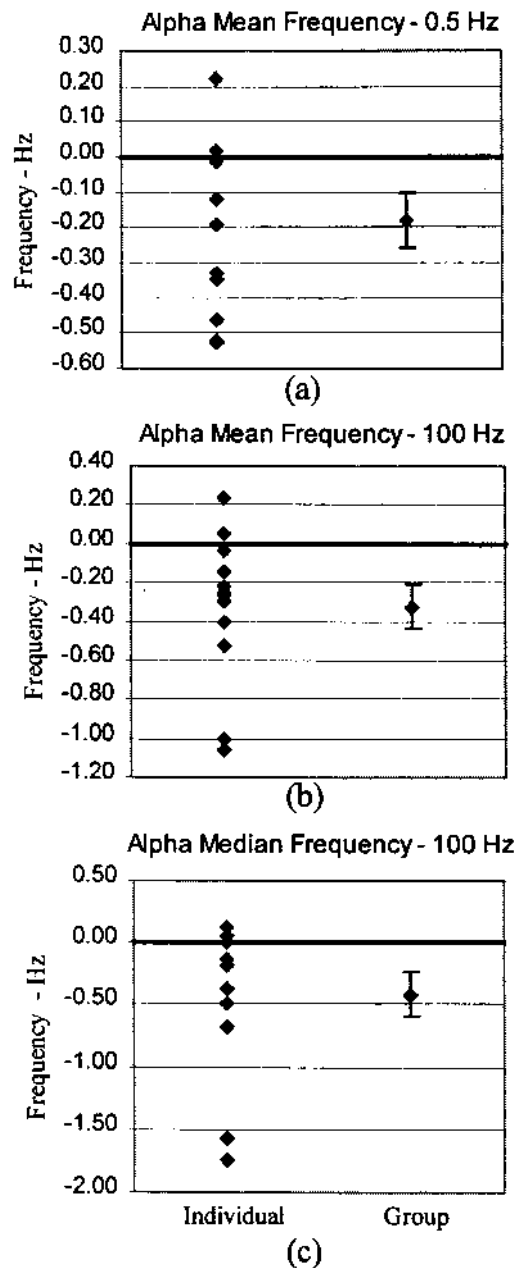


Fig. 5. Pre- to post-treatment changes of significant *t* test cases: individual subjects and group (mean \pm SEM): (a) 0.5 Hz CES alpha band mean frequency; (b) 100 Hz CES alpha band mean frequency; (c) 100 Hz CES alpha band median frequency.

and 100 Hz CES settings. Additionally, a decreasing trend occurred in the alpha band median frequency and beta band power fraction for 100 Hz CES. Thus, both CES frequencies caused a downward shift of the power in the alpha band but 100 Hz CES caused a greater overall change in the EEG.

Although the statistical significance of these findings may be diminished due to the large number of tests performed, the consistency across treatments and agreement with other studies lends support to these results. Both the 0.5 and 100 Hz CES cases, two separate test cases, show significant

changes in the alpha mean frequency variable, suggesting that the finding was not an aberration of the number of tests performed. Also, the alpha median frequency, a variable somewhat analogous to the alpha mean frequency, demonstrated a significant change for the 100 Hz CES case.

The statistically significant findings presented here are also corroborated by previous studies. Itil et al. (1972) showed that CES treatment resulted in an increase in power in the theta and low alpha range and a decrease in power in the high alpha and beta ranges, results that are consistent with those presented here. Additionally, a study by Taylor (1991) showed that, in general, the higher frequency 100 Hz CES treatment used in his study effected a greater change in the measured variables than did the slower 5 Hz CES signal. Again, these results agree with those presented here.

The significance of these findings is realized when compared to unique spectral changes in the EEG spectra of trained meditators (Banquet, 1973). In that study, alpha activity was shown to decrease in frequency by 1–2 Hz during meditation, whereas no such change was noticed in the matched control group. The frequency resolution of the Banquet study was only 1 Hz. Although shifts of such magnitude were not realized in our study, the decrease in alpha band frequency may indicate that CES facilitates a more relaxed state.

Additionally, since the beta band is associated with arousal, problem solving, and stress, 100 Hz CES may be beneficial due to its apparent attenuating effect on this band. Thus, the double effect of decreasing the amount of relative beta power and shifting the alpha frequency distribution downward suggests that 100 Hz CES may be more beneficial than 0.5 Hz CES in affecting the EEG mental state.

This study, for the first time, demonstrates the ability to collect EEG data during concurrent application of CES, thus allowing EEG changes to be quantified throughout a treatment without the interruption of CES power that might otherwise elicit sporadic physiologic changes. The plots of Fig. 5 show a relatively steady decline in alpha band parameters over time during 100 Hz CES. However, a more unique trend was realized for the beta power fraction in which a sudden decline was noticed during the first 5 min of active 100 Hz CES. This was followed by a recovery towards pre-treatment levels during the next 5 min and a steady decline thereafter. It is difficult to conclude whether a longer duration of CES would have caused greater changes in these or other variables. However, this type of information can be clinically valuable towards understanding when and to what extent a treatment has evoked a desired response.

The quantified EEG changes realized in this study coincide with the claims of CES proponents and no side effects were reported. Though only normal subjects were used in this work, significant quantitative EEG changes due to both 0.5 and 100 Hz CES were found. These findings raise the question of whether additional beneficial CES effects would

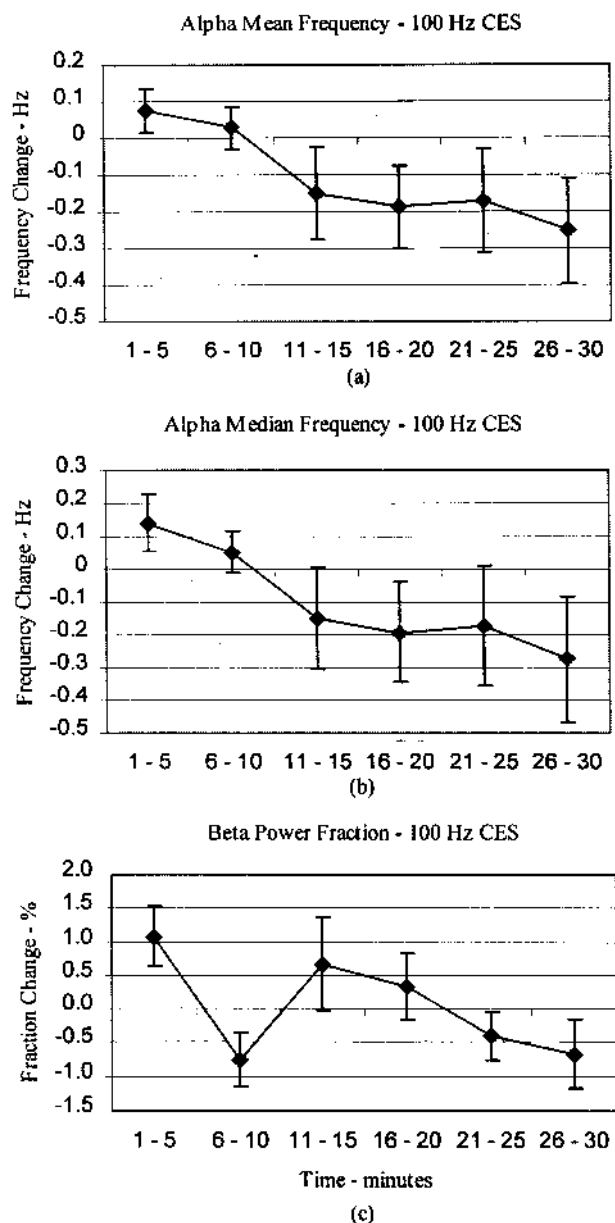


Fig. 6. Trends of significant ANOVA cases (mean \pm SEM): (a) 100 Hz CES alpha band mean frequency; (b) 100 Hz CES alpha band median frequency; (c) 100 Hz CES beta band power fraction change.

be detected in a clinically abnormal population such as insomniacs or depressed individuals. The investigation of EEG changes in combination with behavioral changes of such a population would provide valuable insight toward the understanding and usefulness of CES as a mainstream clinical modality.

4.1. Limitations

Exactly precise double-blindness was not achieved in this study. Both the subject and the investigator were unaware of the random treatment to be administered prior to and during the first 5 min of the study. After that time, even though the

CES device was connected to a blinding box, the investigator became aware of whether or not the subject was receiving CES by viewing the EEG data collection monitor. Interaction was minimal after this point since the investigator was only allowed to ask the subject if he was awake.

In order that 'clean' EEG data be obtained during application of CES, only one channel of EEG was collected, severely reducing the amount of information available from which to quantify changes. However, the complexity of applying noise cancellation to reduce the CES in the EEG increases with each additional EEG channel. A more elaborate system including additional amplifiers and automatic noise-cancellation electronics would need to be developed to perform such a task. Additionally, the non-symmetrical current distribution of the biphasic CES signal throughout the head increases the degree of difficulty of performing a multi-channel EEG.

There are concerns regarding the low CES current level applied to the subjects. The range of current levels used in this study was generally between 30 and 80 μ A depending upon the subject's sensation threshold. Other studies using the Alpha-Stim 100 use currents in the 300 μ A range and much higher levels are used for other devices. Without implanting deep brain electrodes, it is difficult to know the extent of stimulus penetration (Ferdjallah et al., 1996), however, the presence of statistically significant results shown in this work provide reason to believe that current does in fact penetrate the brain to some extent.

Another concern is that of the crossover design of treatments on the same subject. It has been suggested that the effects of CES can be long lasting and thus affect the outcome of EEG measurements made during subsequent treatment or control sessions (Frankel et al., 1973). In this study, each subject served as his own control and was also subjected to a trial CES session and two randomized CES treatments. Although concern of the protocol is warranted, this experiment was designed to minimize statistical variance in the subject population at the expense of incurring possible aftereffects of prior CES treatments.

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