Effects of Cranial Electrotherapy Stimulation on Brain Activity in the Resting State

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Introduction

Cranial electrotherapy stimulation (CES) is an FDA-approved treatment for insomnia, depression, and anxiety that consists of a pulsed, alternating microcurrent applied to the head using electrodes placed on the earlobes (Fig. 1).

The mechanism of action of CES remains unclear, but the primary effect is postulated to be cortical and subcortical inhibition in the brain[1]. Electrical current may reach the brain via cranial afferents near the earlobe. Previous studies have shown highest levels of brain current are recorded in the thalamus[2], a region that may be important in the pathophysiology of anxiety[3,4]. However, no study has investigated the direct effects on brain activity of acute CES.

Aim: To determine effects of acute CES stimulation on patterns of brain connectivity in healthy control subjects. We studied the effects of two commonly-used stimulation frequencies (0.5 Hz and 100 Hz) on brain activity in the resting state in 11 healthy control subjects while using functional magnetic resonance imaging (fMRI).

Objective: To provide a preliminary overview of the immediate effects of CES stimulation on brain activity patterns.

Hypothesis: Acute CES will be associated with deactivation in cortical and subcortical regions (including the thalamus), which will differ for the 100 Hz relative to the 0.5 Hz frequency. Stimulation will also be associated with changes in connectivity between the posterior cingulate cortex and others regions of the default mode network (DMN).

Methods

Safety and artifact testing
- The CES device was safety tested in the MR environment before subject participation using a whole-body phantom, thermister, and voltmeter. Simultaneous CES activation and MR scanning did not produce heating or significant changes in voltage or current, and no artifacts were observed in the MR image.

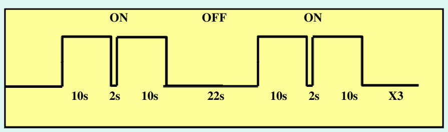
Subjects
- 11 healthy right-handed male and female subjects, 18-65 years old, were recruited from the community.

Current intensity determination
- Subjects underwent testing outside of the scanner to determine individual sensory thresholds for CES current
- Using this individualized current intensity, we performed a forced-choice test to ensure that each subject was unable to guess if the device was ON vs. OFF above chance level.

Scanning procedure
- Instructions: patients were told to "Please keep your eyes closed for the duration of the scan, but try not to fall asleep. You do not have to think about anything in particular."
- CES device: stimulation cycled between 6 ON blocks of 22 sec (2 sec off in middle due to device constraints) and 6 OFF blocks of 22 sec, for a total of 5 min 35 sec. (Fig. 2)
- fMRI acquisitions: two fMRI scans were collected at 0.5 Hz and 100 Hz, order was counterbalanced across subjects.
- Behavioral assessment: the "State" portion of State-Trait Anxiety Inventory (STAI) was administered before and after scan session.

Figure 1: Alpha-Stim® device

Figure 2: Alpha-Stim® 100 microcurrent



fMRI
- 3-Tesla Trio (Siemens) MRI scanner T2*-weighted EPI gradient-echo pulse sequence. TR = 2.5 s, TE = 21 ms, Flip-Angle = 75º

Statistical Analyses
- Functional neuroimaging: we used FEAT in FSL[5] for voxel-wise analysis:
  - Performed a random-effects analysis with subject as random factor.
  - Analyzed data using multiple regressors to model hemodynamic changes associated with contrasts:

    contrast 1 = 0.5 Hz CES "ON" vs. "OFF"

    contrast 2 = 100 Hz CES "ON" vs. "OFF"

Region of interest (ROI) analysis
- Compared mean % signal change in thalamus (Harvard-Oxford probabilistic atlas, anatomical ROI) for ON vs. OFF with paired t-tests

Current intensity regression analysis
- Voxel-wise analysis of brain activation/deactivation with demeaned individual current intensity values as the regressor

Functional connectivity analysis
- Psychophysiological interaction analysis (PPI)[6] using bilateral posterior cingulate (4 mm spherical ROI)[9] as anatomical seed region to investigate effects of CES stimulation on resting state brain activity.
  - BOLD time-course regressor from seed
  - ON vs. OFF regressor, convolved with the HRF
  - Interaction term models the effects on connectivity in seed region-correlated time-course of ON vs. OFF stimulation

Results

Behavioral data:
- No significant change in STAI after CES (mean ± SD: before= 21.9 ± 3.9 after = 22.6 ± 3.1, P=.67).

Thalamus ROI analysis:
- No significant differences for ON vs. OFF were observed for 0.5 or 100 Hz (P=.22 and .99, respectively).

ON vs. OFF and current intensity analyses (see Table 2 and Figs. 3 and 4)
- 0.5 Hz stimulation was associated with decreased activation in bilateral precuneus, supplementary motor area, posterior cingulate, pre- and post-central gyrus, left frontal pole, and left middle frontal gyrus.
- 100 Hz stimulation was associated with decreased activation in bilateral SMA and precentral gyrus, right superior parietal lobule, and right supramarginal gyrus.

PPI Analysis:
- CES device ON was associated with changes in connectivity in the right hemisphere between posterior cingulate seed and several regions known to be part of the default mode network (DMN) as well as those known to be anticorrelated with the DMN (see Fig. 5)
  - 0.5 Hz stimulation was associated with decreased connectivity with the right postcentral gyrus.
  - 100 Hz was associated with increased connectivity with the right insula.

Table 1: Individual subject data

Subject ID	Age	Gender	% correct lobe .5	% correct lobe 100	current lobe .5	current lobe 100
1001	50	female	66	50	100	100
1002	54	male	50	-	300	300
1003	24	female	33	25	200	200
1004	27	female	33	50	150	150
1005	28	male	58	33	100	150
1007	52	male	58	58	150	300
1008	29	female	50	50	250	250
1009	55	male	50	50	10	100
1010	23	female	33	50	150	200
1011	20	male	58	66	150	150
1012	21	male	58	66	150	50
Mean	34.8	5F/6M	49.7	49.8	155.5	177.3
SD	14.5	X	11.7	12.9	77.0	81.7

Table 2. Local maxima for significant activations for ON vs. OFF

0.5 Hz Deactivation	Z score	x, y, z
Bilateral paracingulate cortex	3.34	6, 12, 50
Pre-and post-central gyrus	3.30	40, -10, 52
Bilateral precuneus	3.13	-2, -74, 46
Middle frontal gyrus	2.86	-30, 6, 54
Left frontal pole	2.85	-38, 52, 6
100 Hz Deactivation	**Z score**	**x, y, z**
Postcentral gyrus	3.16	42, -34, 58
Precentral gyrus	3.12	-22, -18, 70
Right superior parietal lobule	2.94	12, -50, 70

Results (cont.)

Fig. 3: Regional deactivation associated with 0.5 Hz (blue) and 100 Hz (yellow)

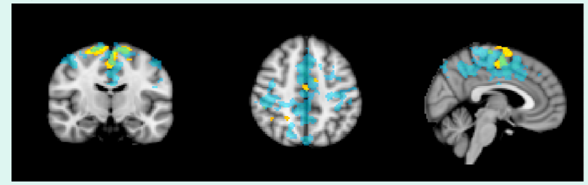


Fig. 4: Regions positively associated with current intensity for 0.5 Hz

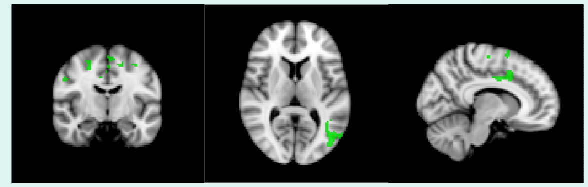
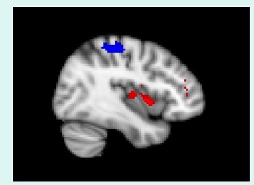


Fig. 5: Changes in connectivity in intrinsic brain networks using posterior cingulate seed associated with ON stimulation:

- **Increased connectivity in right insula for 100 Hz (red)**
- **Decreased connectivity in right postcentral gyrus for 0.5 Hz (blue)**



Conclusions

- CES stimulation altered connectivity between the posterior cingulate and several regions that may represent correlated and anticorrelated nodes of the default mode network.
- CES stimulation is associated with **cortical deactivation** for 0.5 Hz and 100 Hz frequencies in bilateral frontal, parietal and posterior midline regions.
  - No significant regional difference evident between the two frequencies, but greater and more extensive effects for 0.5 Hz
- Cortical deactivation may depend more on frequency of stimulation than on current intensity.
- Whether cortical deactivation may relate to decrease in EEG frequencies found in other studies[7,8] (and to therapeutic action for anxiety and sleep) needs to be directly tested in future studies

Limitations:
- Non-clinical population
- Small sample size

Future studies:
- Pre- and post- 6 weeks of daily treatment in clinical population: to understand the therapeutic mechanism of action and how it may relate to cortical deactivation and/or changes in resting state networks

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