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: Alpha-Stim® 100 microcurrent

•Although the mechanism of action of CES remains unclear, the primary effect has been postulated to be due to the production of cortical and subcortical inhibition in the brain[1]. Current may reach the brain via cranial afferents near the earlobe. Previous studies have shown the 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 the effects of acute CES stimulation on patterns of brain activity 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 eleven healthy control subjects while scanned using functional magnetic resonance imaging (fMRI). The objective was to provide a preliminary overview of the immediate effects of CES stimulation.
Hypothesis: Acute CES will be associated with deactivation in cortical and subcortical regions (including the thalamus) with stimulation, which will differ for the 100 Hz relative to the 0.5 Hz frequency.

Methods

Safety testing:
•The CES device was tested for safety 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, nor where there artifacts in the MR image observed.

Subjects
- 11 healthy right-handed male and female subjects aged 18 to 65 years recruited from the community.

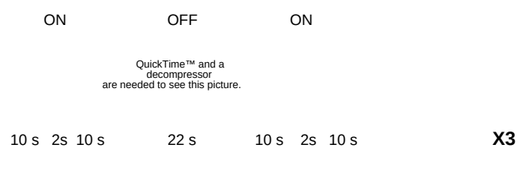
Current intensity determination:

•Subjects first underwent testing outside of the scanner to determine their individual sensory threshold for CES stimulation.

•Using this individualized current intensity, subjects then engaged in a forced-choice test to ensure that he or she could not correctly guess if the device was on at greater than chance level.

Scanning procedure
•Subjects were instructed 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.”
•During scanning, the CES device 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.
•Subjects completed one run each of the 0.5 Hz and the 100 Hz pulse frequencies, the order of which was counterbalanced between subjects.
•Subjects completed the “State” portion of the State-Trait Anxiety Inventory (STAI) before and after the scan.

Fig. 2: Block design for administration of CES



fMRI
3-Tesla Trio (Siemens) MRI scanner T2*-weighted echo planar imaging (EPI) gradient-echo pulse sequence. TR = 2.5 seconds, TE = 21 milliseconds, Flip-Angle = 75◦,

Statistical Analyses
Functional neuroimaging (using FEAT in FSL) for voxel-wise analysis:
-Performed a random-effects analysis with subject as the random factor.
-Analyzed data using multiple regressors to model hemodynamic changes associated with the different contrasts:
1. 0.5 Hz CES “On” vs. “Off”
2. 100 Hz CES “On” vs. “Off”

Region of interest (ROI) analysis
-Anatomical ROI of thalamus derived from Harvard-Oxford subcortical probabilistic atlas
-mean percent signal change in each region and compared between groups using two-sample t-tests
Current intensity regression analysis
-To determine the relationship between current intensity and brain activation/deactivation, we entered demeaned individual current intensity values as a regressor of interest in the voxel-wise analysis.
Functional connectivity analysis
We performed a psychophysiological interaction analysis, using the posterior cingulate as an anatomical seed region to investigate the effects of CES stimulation on resting state brain activity [results are pending]

Results

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	34.82	X	49.73	49.80	155 .45	177 .27
SD	14.52	X	11.74	12.87	76.99	81.74

Behavioral data:
There was little change in the STAI after CES during the scan (mean 21.9±3.9 before and 22.6±3.1 after).

Thalamus ROI analysis:
No significant differences for on vs. off were observed for 0.5 or 100 Hz

Table 2. Local maxima for significant between -groups activations

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	41, -34, 58
Precentral gyrus	3.12	-22, -18, 70
Right superior parietal lobule	2.94	12, -50, 70

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

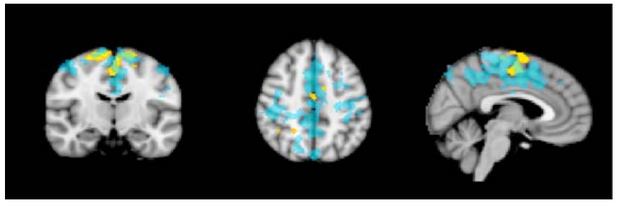
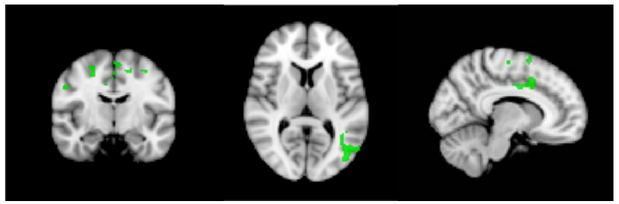


Fig. 4: Regions positively associated with current intensity for 0.5 Hz



Conclusions

•CES stimulation is associated with cortical deactivation for 0.5 Hz and 100 Hz frequencies in bilateral frontal, parietal and posterior midline regions. Although the pattern is slightly different for the frequencies, in a direct comparison we did not find significant differences.

•Current intensity may be less critical than frequency of stimulation in relation to cortical deactivation.

•Midline regions that demonstrated deactivation may represent nodes of the default mode network; however, our results from a functional connectivity analysis to investigate this are still pending.

•Future studies will need to explore the longer-term effects of daily treatment in relation to clinical improvement, and how brain deactivation relates to previously observed decreases in EEG frequencies, in order to further understand the therapeutic mechanism of action.

•Limitations:
- •This study only examined the acute effects of CES and therefore did not provide insight into the changes in brain activity that may arise from a therapeutic course of treatment over several weeks.
- •Non-clinical population limits our ability to generalize findings to individuals with anxiety, depression, or insomnia.

References

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