

Title: Effects of High Amplitude and Focused tACS on Entraining Physiological Tremor

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Protocol unfocused electrodes – Healthy volunteers

1. Patient consent (20 min)
 - a. Explain the study
 - b. Let subject read & fill in informed consent
2. Patient preparation (1h)
 - a. Clean big regions of the scalp with ethanol around the left motor cortex and the prefrontal cortex
 - b. Measure Cz, C1 and C3 and place the stimulating electrode between C1 and C3.
 - c. Place another stimulating electrode over the PFC (by measuring F5/F6)
 - d. Place the return electrode over the ankle
 - e. Calibrate the accelerometer
 - f. Place the accelerometer on the middle finger of dominant hand
 - g. Ask subject to adopt a tremor inducing pose
 - h. Measure the tremor frequency for 5 minutes and analyse with specTremor
 - i. Check if impedance is below $5\text{k}\Omega$
 - j. If impedance is too high, add more saline
3. Stimulation amplitude dose response (10 min)
 - a. Instruct the subject to report any stimulation related side effects / secondary effects (tingling, pain, phosphenes)
 - b. Apply stimulation with increasing currents, while
 - i. Monitoring impedance
 - ii. Asking the subject about side effects
 - c. As long as no severe side effects are reported and subject wants to increase the current, increase with small steps (e.g. 0.2 mA) until a maximum of 2mA.
 - d. Repeat for second stimulation site
 - e. Determine the maximal amplitude that is tolerable in both regions. So stimulate the two regions at the same amplitude.
4. Phosphene ratings and thresholds (10 min)
 - a. Check phosphene ratings at maximal stimulation amplitude for both stimulation sites
 - b. If phosphenes are reported, determine the phosphene thresholds for both sites by gradually increasing the stimulation amplitude
5. Stimulation protocol (45 min)
 - a. Measure the tremor frequency
 - b. Perform the stimulation protocol at the maximum stimulation amplitude determined in step 3.
 - c. Record one session of 30 sec OFF-1 min MC-30 sec OFF-1 min PFC repeated 4 times in random order
 - d. Repeat 2 more times to have 3 sessions

Protocol focused electrodes – Healthy volunteers

6. Patient consent (20 min)
 - a. Explain the study
 - b. Let subject read & fill in informed consent
7. Patient preparation (1h)
 - a. Clean big regions of the scalp with ethanol around the left motor cortex and the occipital cortex
 - b. Place the electrode cap over the head of the subject
 - c. Measure if Cz of the cap matches the position of the vertex
 - d. Indicate with marker the position of the stimulating electrodes
 - e. Remove the electrode cap
 - f. Measure if the stimulating electrode is at the correct position (C3). If not, repeat a-e.
 - g. Apply EMLA-cream around the stimulating electrode positions
 - h. Calibrate the accelerometer
 - i. Place the accelerometer on the middle finger of dominant hand
 - j. Ask subject to adopt a tremor inducing pose
 - k. Measure the tremor frequency for 5 minutes and analyse with specTremor
 - l. After half an hour after applying the EMLA cream, check if the hair is dry. If the hair is still too wet, dry with paper/towel or a hairdryer.
 - m. Place the electrode cap over the head of the subject
 - n. Measure the head to ensure that the location of the motor cortex matches the position of the plastic electrode holders.
 - o. Add electrolyte gel inside the electrode holders with a syringe
 - i. 2.5 ml for flat electrode holders
 - ii. 5 ml for Gamma
 - p. Add the electrodes and close the electrode holders
 - q. Check if impedance is below $5\text{k}\Omega$
 - r. If impedance is too high, add more gel or attach rubber straps over the electrodes for good contact of the electrode holders and the scalp.
8. Stimulation amplitude dose response (10 min)
 - a. Instruct the subject to report any stimulation related side effects / secondary effects (tingling, pain, phosphenes)
 - b. Apply stimulation with increasing currents, while
 - i. Monitoring impedance
 - ii. Asking the subject about side effects

- c. As long as no severe side effects are reported and subject wants to increase the current, increase with small steps (e.g. 0.5 mA) until a maximum of 5mA.
- d. Repeat for second stimulation site
- e. Determine the maximal amplitude that is tolerable in both regions. So stimulate the two regions at the same amplitude.

9. Phosphene ratings and thresholds (10 min)

- a. Check phosphene ratings at maximal stimulation amplitude for both stimulation sites
- b. If phosphenes are reported, determine the phosphene thresholds for both sites by gradually increasing the stimulation amplitude

10. Stimulation protocol (45 min)

- a. Measure the tremor frequency
- b. Perform the stimulation protocol at the maximum stimulation amplitude determined in step 3.
- c. Record one session of 1min OFF-1 min MC-1 min OFF-1 min OC repeated 3 times in random order
- d. Repeat 2 more times to have 3 sessions

Statistics

Statistics are performed with a significance level $\alpha=0.05$. A two-sided Wilcoxon signed-rank test compares scores for phosphene intensity and thresholds between the different conditions. For phase entrainment the effect of the condition on the entrainment is tested with a non-parametric Friedman test. If significant, a post-hoc analysis is conducted with a two-sided Wilcoxon Signed-Rank test between all pairs of the conditions. p-values are adjusted for multiple comparisons with a Bonferroni correction.