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Report

Frequency-Dependent Electrical Stimulation of the Visual Cortex

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Summary

Noninvasive cortical stimulation techniques, such as transcranial magnetic stimulation (TMS) [1, 2] and transcranial direct current stimulation (tDCS) [3–6], have proved to be powerful tools for establishing causal relationships between brain regions and their functions [1, 2]. In the present study, we demonstrate that a new technique called transcranial alternating current stimulation (tACS) [7] can interact with ongoing rhythmic activities in the visual cortex in a frequency-specific fashion and induce visual experiences (phosphenes). We delivered an oscillatory current over the occipital cortex with tACS. In order to observe interactions with ongoing cortical rhythms, we compared the effects of delivering tACS under conditions of light ("Light" condition) or darkness ("Dark" condition). Stimulation over the occipital cortex induced perception of continuously flickering light most effectively when the beta frequency range was applied in an illuminated room, whereas the most effective stimulation frequency shifted to the alpha frequency range during testing in darkness. Stimulation with theta or gamma frequencies did not produce any visual phenomena. The shift of the effective stimulation frequency indicates that the frequency dependency is caused by interactions with ongoing oscillatory activity in the stimulated cortex. Our results suggest that tACS can be used as a noninvasive tool for establishing a causal link between rhythmic cortical activities and their functions.

Results and Discussion

Various frequencies of rhythmic activities are observed in the brain across many species [8]. Oscillatory synchrony plays an essential role in visual attention and perception by dynamically modifying neuronal interactions between brain regions [9–11]. In humans, brain activity measured with electroencephalography (EEG) on the scalp and intracranially recorded local field potentials exhibit typical oscillatory activities at various frequencies. We therefore sought to use frequency-specific brain stimulation to entrain oscillatory activity in the visual cortex. We predicted that weak alternating current applied over the scalp would be able to entrain specific EEG frequency bands and induce phenomena specifically related to the functions of a stimulated region and its oscillatory activities. Indeed, a recent study has shown that transcranial application of oscillatory potentials at a low frequency (0.75 Hz) during slow-wave sleep can enhance the consolidation of declarative memory [12].

It is known from tDCS studies that polarization of cortical neurons with transcranially applied electric currents modulates excitability of visual areas under the stimulation electrode [13, 14]. Thus, we expected that tACS would also be able to stimulate those areas with the same electrode montages and chose those areas as our target stimulation sites for phosphene induction with tACS. The question of particular interest here is whether phosphene induction would show any physiologically meaningful dependency on stimulation frequency. Thus we used a broad range of parameters, including the theta (4–8 Hz), alpha (8–14 Hz), beta (14–22 Hz), and gamma (> 30 Hz) ranges. Because EEG displays distinct patterns of dominant frequency as a function of the presence or absence of visual input, we conducted the experiments both in the light and in the dark. Alpha activity recorded over early visual areas is dominant during eyes-closed or in-the-dark resting conditions, whereas in eyes-open, in the light, alpha is suppressed and is replaced by brain activity at higher frequencies, such as the beta range [15–18]. Therefore, differences in the effective tACS stimulation frequencies between the two lighting conditions would be indicative of an interaction between ongoing and induced oscillatory activity. In order to characterize the frequency dependency of tACS over the visual cortex, we measured both subjective and objective measures of cortical excitability by phosphene ratings and threshold measurements, respectively.

To stimulate early visual areas, a small stimulation electrode was placed 4 cm above the inion and a large reference electrode was placed over the vertex (see Supplemental Experimental Procedures, available online). A larger electrode was used for the reference, in order to minimize the current density under the reference electrode [19].

Eight healthy observers (four male, four female) participated in an experiment in which they were asked to rate the presence or absence and the strength of a tACS-induced phosphene at frequencies ranging from 4 Hz to 40 Hz. The experiment was conducted as follows: First, we familiarized the observers with the appearance of phosphenes in the light by applying 16 Hz tACS at a current strength of 1000 μA (the maximum current density at the stimulation electrode corresponded to 83 $\mu A/cm^2$). This stimulation was used as the comparator for both phosphene induction in both Light and Dark conditions, with various combinations of stimulation intensity and frequency (see Supplemental Experimental Procedures).

Observers were unaware of the stimulation frequency on any trial, and frequency was randomized within current intensities. For each frequency, observers were tested both in the light and in the dark (each about 5 s), consecutively, and were asked to give a rating for the phosphenes in each condition. We alternated the Light and the Dark conditions to avoid buildup of adaptation to darkness across trials [20], given

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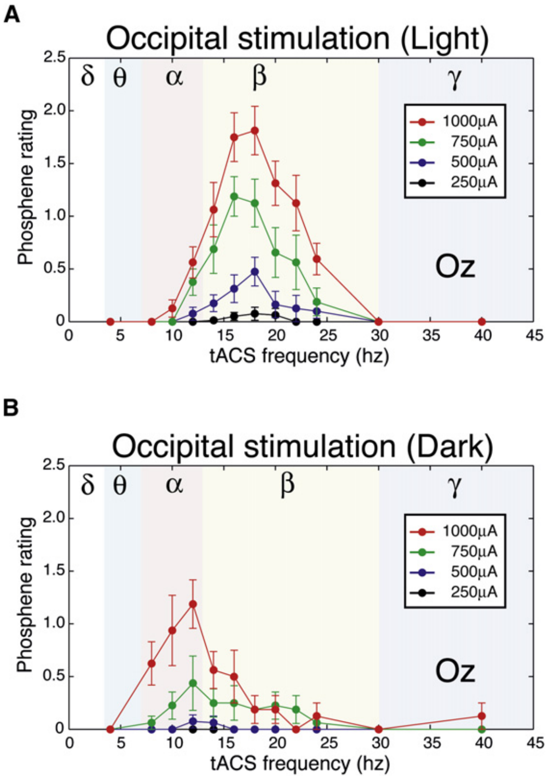

Figure 1. Phosphene Ratings of tACS over Early Visual Cortex

(A) Mean ratings for phosphene strength in the Light condition. Each line corresponds to the rating results for different stimulation intensities (see inset). The error bars correspond to one standard error of the mean (SEM).
(B) Mean ratings for phosphene strength in the Dark condition.

that slow adaptation to darkness is known to change sensitivity to TMS-induced phosphenes [21]. After their report of the presence and strength of phosphenes, observers were also asked to describe the phosphene(s) qualitatively.

Phosphene Rating

In the Light condition, phosphenes were most prominent with tACS in a frequency range of 14 Hz to 20 Hz (Figure 1A), which corresponds to the intermediate beta frequency of the EEG. The perception of phosphenes was also restricted to the beta range when tACS was applied at a weaker intensity (e.g., 250 μA and 500 μA).

When tACS was applied at a high intensity (1000 μA) within the beta range, flickering phosphenes were continuously perceived. When tACS was delivered in darkness, the strongest phosphenes were reported during stimulation at alpha frequencies (10 Hz–12 Hz). The beta frequency stimulation, which was most effective in the Light condition, did not produce phosphenes as strong as those seen in the Light condition. Instead, stimulations at alpha frequencies produced stronger phosphenes in the Dark condition (mean rating of 0.92 ± 0.20 SEM) than in the Light condition (0.23 ± 0.07 SEM) ($T(7) = 3.24$, $p < 0.01$). This shift of the optimal stimulation frequency suggests that the effectiveness of tACS is related to the existing physiological state rather than to the stimulation properties per se. The alpha range is the most dominant frequency in EEG in the absence of visual input [15–18]; thus, it seems that tACS most effectively induces the perception of phosphenes when it is delivered at the known dominant frequency of the area being stimulated.

A three-way repeated-measures ANOVA showed a main effect of stimulation intensity ($F(2,14) = 34.4$, $p < 0.001$), stimulation frequency ($F(11,77) = 15.2$, $p < 0.001$), and lighting condition ($F(1,7) = 21.5$, $p < 0.01$). There was a significant interaction between stimulation frequency and lighting condition ($F(11,77) = 13.2$, $p < 0.001$), supporting the shift of the peak between the Light and Dark conditions. Other interactions were not significant.

During their observations of phosphenes, observers frequently reported qualitatively different phosphenes in the Dark condition. Whereas the phosphenes in the Light condition were perceived as flickering rapidly, phosphenes in the Dark condition were reported to be more diffuse and slowly oscillating. Also, for frequencies at which phosphenes were reported in both Light and Dark conditions, observers reported different positions and orientations of the phosphenes depending on the lighting condition. These observations suggest that the tACS might interact with the visual cortex in a qualitatively different manner depending on the presence or absence of visual stimulation.

Phosphene Thresholds

In a second set of experiments, we measured the threshold stimulation intensity required for induction of a phosphene with a probability of 50%. Four naive observers (two females and two males) participated in this study. As in the phosphene-rating experiment, two lighting conditions (Light and Dark) and twelve stimulation frequencies (4 Hz–40 Hz) were examined. A threshold was estimated for each of the 48 test conditions with the use of a modified-binary-search adaptive staircase [22].

The results are shown in Figure 2. Consistent with the phosphene-rating experiment, thresholds were lowest in the beta frequency range during testing in the Light condition. During testing in the Dark condition, the most sensitive frequency shifted from the beta range to the alpha range: the most effective frequency was 20 Hz in the Light condition, whereas it shifted to10 Hz in the Dark condition.

These results are consistent with the results of the phosphene-rating experiment. For stimulation conditions in which observers reported a strong phosphene, the thresholds were low. However, there was a small discrepancy in these two measurements. In the threshold-measurement experiment, the most effective frequency in the Light condition was 20 Hz, whereas it was slightly lower (16 Hz–18 Hz) in the phosphene-rating experiment. The most effective frequency in the threshold-measurement experiment in the Dark condition peaked at 10 Hz, whereas the peak for the phosphene-rating experiment was 12 Hz.

Thus far, we have shown in two experiments that the most effective stimulation frequency changes depending on the lighting condition. In the Light condition, the most effective tACS frequency corresponded to the beta range in the EEG, whereas it shifted to the alpha range in the Dark condition. This shift corresponds to the known shift of the dominant EEG frequency [15–18] and supports the idea that tACS interacts with the ongoing oscillatory activities measured in EEG.

Appearances of Phosphenes

In order to gain insight into the perception of phosphenes, we conducted a separate experiment in which observers were asked to draw the positions and the shapes of phosphenes.

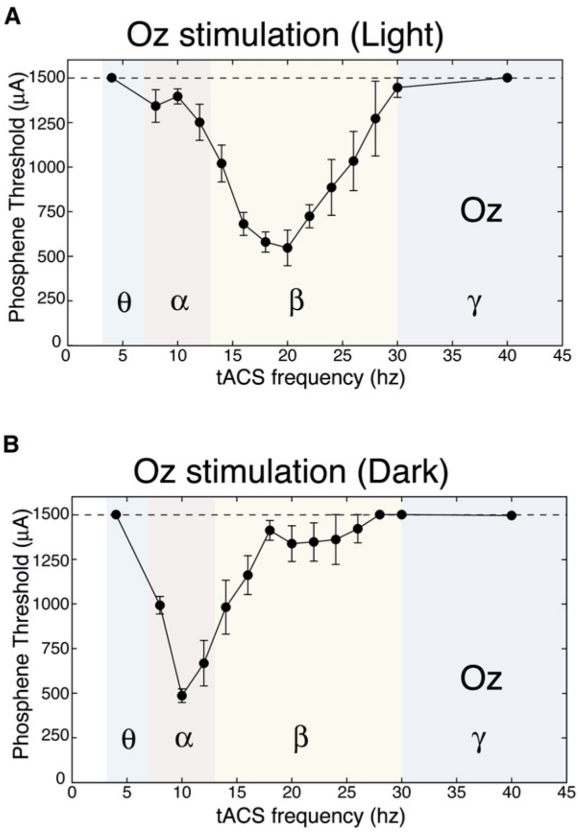

Figure 2. Thresholds for Phosphene Induction

(A) Mean phosphene thresholds in the Light condition. The error bars correspond to one standard error of the mean (SEM).

(B) Mean phosphene thresholds in the Dark condition.

In particular, the position of the phosphene is informative regarding the cortical regions stimulated by alternating current, because the retinotopic organization of early visual areas is well understood [23, 24]. We obtained drawings of phosphenes induced by occipital stimulation in Light and Dark conditions. To maximize the clarity of phosphenes, we used a stimulation frequency of 18 Hz for the Light condition and 10 Hz for the Dark condition.

The drawings of phosphene regions were obtained from six naive observers (Figure 3). All observers reported phosphenes in the periphery of the visual field. The point of phosphenes nearest to fixation was about 15°–20° away. Unlike phosphenes induced by TMS over V1 [25], the phosphenes induced by occipital stimulation were not restricted to the lower visual field; they appeared in both the upper and lower visual fields. In the Dark condition, the phosphene regions generally increased in size.

The fact that phosphenes were reported in the far peripheral vision suggests that tACS stimulated the anterior part of the visual cortex on the medial wall, where the peripheral parts of the visual field are represented. This suggests that current flowed mostly in the cerebrospinal fluid between the two hemispheres and entered the cortex from the anterior part of the visual cortex. Given that the conductivity of cerebrospinal fluid (CSF; 1.25∼1.79 S/m,) is roughly 3–5 times as high as that of the cortical tissues (white matter 0.25 S/m ∼0.48 S/m; gray matter 0.28 S/m∼0.7 S/m) [26–28], it is plausible that current flows in the CSF along the medial wall until it is blocked by the posterior part of the corpus callosum (splenium). The idea that current flows primarily along the CSF will be a useful guide in targeting other cortical areas with tACS. However, this needs to be further confirmed with functional brain imaging and neuronal modeling.

In the literature on intracranial electrical stimulation of the visual cortex, most studies have used repetitive pulses with various frequencies and pulse durations [29–32]. In the visual cortex, it has been shown that perceived brightness of phosphenes increases monotonically as the frequency of pulses increases up to 200 Hz [33]. In the motor cortex, the threshold for evoking a motor response decreased with the frequency of pulsed stimulation up to 90 Hz and then increased for higher frequencies [34]. Thus, experiments with intracranial pulsed stimulation generally show a monotonic increase in efficacy within the frequency range used in our study (i.e., < 40Hz), whereas our stimulation method showed nonmonotonic frequency dependency.

Although it is difficult to estimate current density at the surface of the visual cortex in our tACS experiments, it is clear that the intensity required for stimulation of the cortical surface via tACS is considerably lower than that required for pulsed stimulation of the cortical surface. For example, in Dobelle and Mladejovsky's study [31], the thresholds for 50 Hz pulse stimulation on the pial surface were estimated to be on the order of

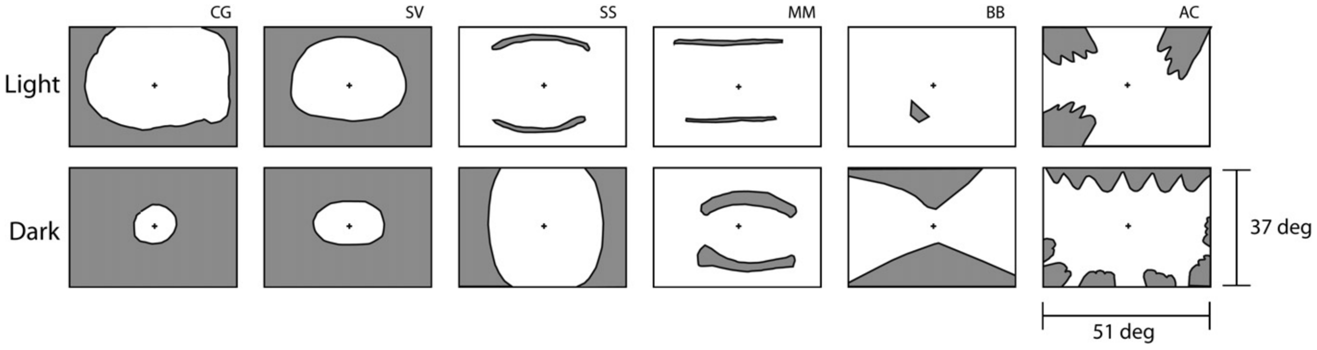

Figure 3. Drawings of Phosphenes

The stimulation frequency was 18 Hz for the Light condition and 10 Hz for the Dark condition. The stimulation intensity was 1000 μA. The phosphenes are represented as the gray regions. Each column corresponds to one observer. The upper panels show the drawings of the phosphenes in the Light condition, and the lower panels show the drawings of the phosphenes in the Dark condition.

1000 ~ 5000 μA in the visual cortex. Given the volume conduction of the scalp and skull, as well as the distance between stimulation electrode and stimulated cortical surface, in our study, the current that reached the surface of the cortex must be much smaller than that of the studies with pulsed stimulation on the pial surface.

In earlier studies of transcranial electric stimulation (TES), brief, high-voltage electric shocks were used to stimulate the cortex [35–37]. In those studies, much stronger current intensity was required for induction of the perception of phosphenes (800 V, with a peak current of 50 A), as compared to our present study (5–15 V, with a peak current of 1.0–1.5 A). This suggests that the visual cortex is more sensitive to electrical stimulations at the frequencies observed in EEG; these frequencies are presumably supported by the visual cortex as a system for a given state (e.g., dark versus light).

The first study with tACS [7] attempted to stimulate the motor cortex. However, the results were somewhat disappointing; no effects of tACS were detected in various measures, such as changes in the MEP amplitude and EEG power. The key differences in the present study are the larger stimulation intensity and the larger number of frequencies. In [7], the stimulation intensity was limited to 400 μA. However, this is about the level of the threshold intensity for the optimal stimulation frequency in our current study (see Figure 2). Therefore, it is likely that positive effects will be observed in other cortical areas when higher stimulation intensity is applied.

Ongoing rhythmic activities in the brain have been known about for many years. Recent studies began finding roles for such activities in attention and sensory awareness [18]. For example, it has recently been shown that fluctuation of ongoing alpha oscillation is related to excitability of the cortex and accounts for trial-by-trial variability of perception to a constant stimulus [38]. Our present technique offers the possibility of directly modifing ongoing activities in given frequency bands to influence behavioral responses by entraining or disrupting such activities.

Supplemental Data

Supplemental Data include Supplemental Experimental Procedures and can be found with this paper online at http://www.current-biology.com/supplemental/S0960-9822(08)01396-1.

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