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Transcranial alternating stimulation in a high gamma frequency range applied over V1 improves contrast perception but does not modulate spatial attention

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Spatial visual attention enhances information processing within its focus. Vision at an attended location is faster, more accurate, of higher spatial resolution, and has an enhanced sensitivity for fine changes. Earlier hypotheses suggest that the neuronal mechanisms of these processes are based on the interactions among different neuronal groups by means of cortical oscillations in the gamma range. The aim of the current study was to modulate these oscillations externally, using a new technique called transcranial alternating current stimulation (tACS). We investigated the effect of covert spatial attention within and outside its focus by probing contrast sensitivity and contrast discrimination at high resolution across the visual field of 20 healthy human subjects. While applying 40, 60, and 80 Hz tAC stimulation over the primary visual cortex (V1), subjects' contrast-discrimination thresholds were obtained using two different conditions: in the first condition we presented a black disc as a peripheral cue that automatically attracted the subject's attention, whereas there was no cue in the second condition. We found that the spatial profile of contrast sensitivity was not affected by the stimulation. Contrast-discrimination thresholds on the other hand decreased significantly during 60 Hz tACS, whereas there was no effect of 40 and 80 Hz stimulation. These results suggest that attention plays an important role in contrast discrimination based on V1 activities that are influences by gamma range tACS stimulation.

Keywords tACS; visual cortex; contrast perception; human; spatial attention

Electrophysiologic and biophysical studies have revealed that synchronized oscillatory activities are common in the primate cortex during different perceptual conditions, and even single neurons are able to resonate and oscillate at multiple frequencies.[1] These oscillations are organized in various complex patterns and different frequency bands

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have been linked to distinct functions. Slower theta (4-8 Hz) and alpha (8-12 Hz) oscillations are believed to be associated with interregional, top-down processing, and cognitive functions such as working memory, semantic memory, or risk identification.[2-5] The beta rhythm (12-20 Hz) is usually desynchronized during motor tasks and synchronized (beta rhythm rebound) shortly after movement[6] and reflects the activity of the motor cortices.[7-10] High-frequency gamma-oscillations (30-80 Hz) have been linked to different perceptual and cognitive functions such as feature binding,[11] formation of percepts, long-term memory,[12,13] learning, and selective attention.[14,15]

Amplitude changes of the oscillations are considered to result from the phase synchronization within local neuronal ensembles and have been linked to cognitive functions such as perception and motor control. The synchronization of oscillatory activity, however, is not constrained to local networks, but can also serve as a tool for the interaction between distant brain areas with diverse functional roles. Single and multiunit electrophysiologic recordings from cat visual cortex have revealed that external stimuli could induce strongly synchronized cortical activity within the 20-80 Hz frequency range inside and between different visual areas.[16-18] It has been hypothesized that the temporal synchronization of the neuronal firing patterns in the visual system can be temporarily organized into functional units, which encode information about single features as well as the whole stimulus to achieve their "binding." After introducing binding in the context of feature integration,[19] the concept has been applied to other domains such as object recognition,[20] memory recall,[21] language processing,[22] and attention.[23]

Attention has been shown to enhance gamma-band activity,[24] to increase gamma-frequency synchronization of neuronal oscillations in monkey visual cortex[14] and to enhance gamma-band coherence among V4 neurons.[25] Attentional influences are not restricted to extrastriate visual areas, since electrophysiologic and imaging studies have documented attentional modulation of visual information processing in V1 as well.[26-28]

Voluntary spatial visual attention serves as a mechanism enabling us to selectively and covertly (i.e., without gaze shifts) direct our limited processing capacity to certain locations of the visual field. Several studies across a range of perceptual tasks have demonstrated the effect of covert attention on visual performance and perception.[29-32] Covert attentional allocation can also be attracted transiently in an automatic fashion by sudden, salient stimuli such as a spot of light flashed briefly in the visual periphery.[33] For human observers, it is hard or impossible to ignore transient cues, even when they are known to be irrelevant.[34,35]

Contrast sensitivity is a basic performance parameter of visual systems and therefore well suited to study the effect of attention on visual information processing. In addition, automatic attention captured by the short presentation of a peripheral cue, can increase the apparent contrast of subsequently presented gratings.[35,36]

In humans, noninvasive cortical stimulation techniques have been used to influence the excitability of cortical tissues and to investigate the functions of cortical regions. The most well-known are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Transcranial alternating current stimulation (tACS) in external brain stimulation is a new technique. It aims to interfere with ongoing oscillations in the brain. It has been shown to improve implicit motor learning with 10 Hz stimulation of the motor cortex[37] and to interact with processes in the visual cortex in a frequency-dependent manner.[38,39]

In this study, we hypothetized that alternating current in the gamma range applied to the primary visual cortex interferes with neural synchronization thus changing the effect of attention on contrast perception. We carried out two experiments using a four-alternative forced-choice detection task to determine the effect of attention and electric stimulation on contrast detection thresholds for stimuli placed at four different distances to a cued location. Our results document a significant influence of 60 Hz tACS on contrast-discrimination thresholds, whereas contrast sensitivity was unaffected.

Methods and materials

Subjects

Twenty healthy subjects (nine women; 21-32 years old, mean age: 25.8 $\pm$ 6.2) participated in the studies. All had normal or corrected-to-normal vision. Subjects were interviewed to exclude volunteers with any history of neurologic or psychologic disorders, metallic implants, drug, or alcohol abuse. None of the subjects took regular or acute medication. All the participants gave informed written consent and all the experiments were approved by the Ethics Committee of the University of Göttingen, and conformed to the Declaration of Helsinki.

Apparatus

tACS

A battery-driven Eldith DC-stimulator Plus (NeuroConn GmbH, Ilmenau, Germany) was used with conductive-rubber electrodes, placed in saline-soaked sponges. The size of the electrode placed over Oz (in accordance with the international 10-20 EEG system) was 4 $\times$ 4 cm, whereas the reference electrode over Cz had a size of 7 $\times$ 4 cm. The electrodes were fixed with rubber bands. The electrical stimulation was sinusoidal with a current intensity of 1500 μA. Using this current intensity the maximum current density at the Oz electrode was 93,75 $\mu A/cm^2$, which is below the safety limits accepted for tDCS.[40] Because of the larger electrode size current density was 53.57 $\mu A/cm^2$ at the Cz position. Three stimulation frequencies 40, 60,

and 80 Hz were tested. The stimulation lasted throughout the whole experiment resulting in a stimulation duration of 45 minutes ± 10 minutes in the first experiment and 15 minutes ± 5 minutes per session in the second experiment. The impedance limit was set to ≤ 10 kΩ and the intensity was ramped up and down for 5-10 seconds. For sham stimulation, the current was turned on for 20 seconds before beginning the experiment to achieve the light itching sensation under the electrode. The flickering sensation during the stimulation, which has been reported at lower frequencies[38] was not observed for the higher stimulation frequencies used here. Subjects were blinded for stimulation conditions in both experiments.

Stimulus presentation

Stimuli were generated and controlled using a custom software, running on a G4 Power Macintosh computer. Observers viewed the stimuli on a CRT monitor at a refresh rate of 85 Hz and a resolution of 40 pixels per degree of visual angle. The range of the luminance values used was 18.17-6.95 cd/m^2, with 40 grey value steps available within this range. Background luminance was set to 6.95 cd/m^2.

Stimuli and design

A black square presented in the center of a uniform grey background served as a fixation point. Four black lines (260 pixels long, 1 pixel wide) separated the screen into four quadrants. The fixation point and the four black lines were presented throughout the entire experiment. The peripheral cue was a black disk (10 pixels, 0.25 degree radius in diameter), presented to the left or right of fixation at 240 pixels (approximately 6 degrees) eccentricity along the horizontal meridian. Contrast thresholds were measured using stationary random dot patterns (RDPs) with a dot density of 12-dots per square degree and a diameter of 48 pixels (1.2 degrees of visual angle). Dots surface was 3 × 3 pixels, each single screen pixel measuring 0.025 degree (1600 pixels/degree^2). Luminance of the dots was between 18.17 and 6.95 cd/m^2.

As a contrast measurement we used RMS contrast that is the standard deviation of the mean luminance of the stimulus. For calculation we used the following formula: contrast = $\sqrt{[p_{(i)} \times (L_{(i)} - L_b)^2]}$, where $p_{(i)}$ is the proportion of pixels with luminance $L_{(i)}$ in the stimulus, and L_b is the mean luminance of the background. This metric has been shown to provide a better estimate of contrast in RDPs than the Michelson formula.[41,42]

Subjects' contrast detection performance was measured in two conditions. In the control condition (ctrl) only the target stimuli were presented in eight possible locations (Figure 1A). The eight locations were arranged equidistantly on an invisible circle. In the attention condition (test) the contrast RDPs were presented at the same locations as in the ctrl condition; however, they were preceded by the presentation of a black disk as a noninformative peripheral cue (10 pixels, 0.25 degree radius). The initial display was the same for both conditions and it consisted of four black lines dividing the screen into four quadrants and a fixation point at the center of the screen. Subjects were instructed to maintain fixation on the fixation point. Trials were started by pressing the space bar on the keyboard. In the ctrl condition 223.5 milliseconds after an RDP appeared at one of the eight possible locations (Figure 1A), whereas in case of the test condition 94 milliseconds after trial start a peripheral cue appeared for 70 milliseconds on either the left or the right side. The cue was followed by the test stimulus after 60 milliseconds (Figure 1B). Test stimuli were presented for 47 milliseconds in both conditions. Participants were required to push a key on a computer keyboard (1, 3, 7, 9 on the NumPad) indicating the quadrant where they saw the target stimulus. Subjects pressed the space bar with their left hand and they used their right hand to press the key indicating the quadrant.

To determine the subjects' contrast threshold in the different conditions, we used a weighted staircase method.[43] The up (miss)/down (hit) algorithm of 3/1 converged to the contrast level of 75% correct response rate. For each target position a separate staircase was run. Each staircase was sampled at a fixed number of 20 trials.

Eye positions were not measured during our experiments, but the 177-millisecond interval between cue onset and stimulus offset was too short for the subjects to make an eye movement.[44]

Procedure

All experiments were conducted in a dimly lit room. Subjects maintained a viewing distance of 57 cm with a chin rest restraining head movements and gave their responses through a standard computer keyboard. They were asked to maintain their gaze on the fixation point throughout each trial of the experiment. Each subject participated in a practice block of 60 trials for both conditions and five experimental blocks of 160 trials for the ctrl and 320 trials for the test condition that lasted approximately 2 hours. The first experiment was conducted in a repeated measurement design using a randomized order, with a break of at least 10 minutes between each stimulation session (blocked design). Before applying tACS we performed a no-stimulation session. After that the subjects received 40, 60, 80 Hz tACS and sham stimulation in a randomized order. The order of the test and the control conditions were also randomized and counterbalanced. To avoid the possible after effects of tACS and to control the reproducibility of the data, we conducted another experiment with the same task but in this case the experimental conditions were separated with at least 2 days between them (separated design).

By presenting a black disc on a monitor as a noninformative peripheral cue on a grey background the subjects' attention was automatically drawn to one of two

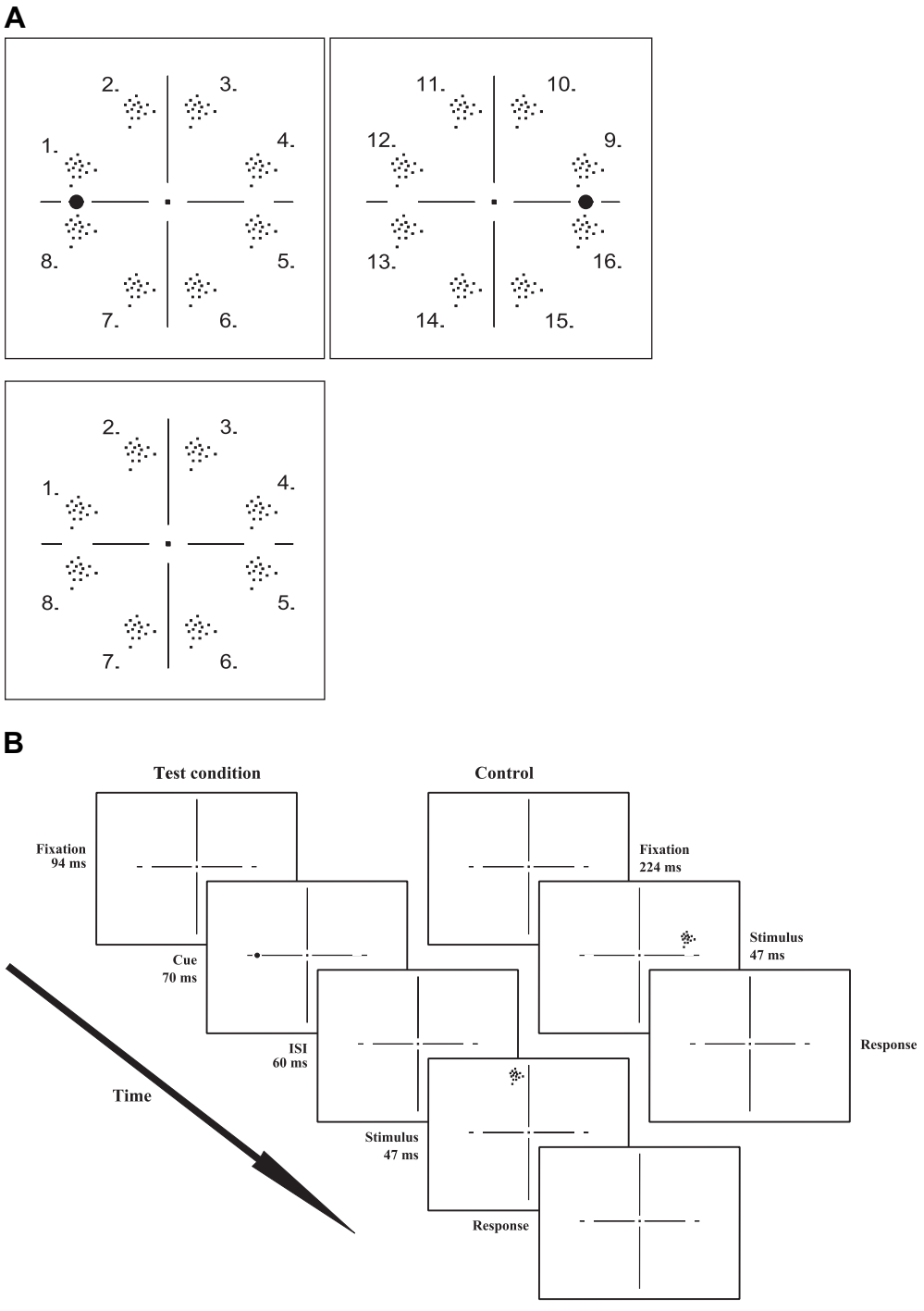

Figure 1 Experimental design. **A**, The eight possible locations of the stimuli during the control and the test conditions. The locations are placed on a circle centered on the fixation point (radius: 6 degrees). The test patterns appear at the following positions relative to the fixation point: 6 degrees to the left and 1 degree up, 1 degree to the left and 6 degrees up, 1 degree to the right and 6 degrees up, 6 degrees to the right and 1 degree up, 6 degrees to the right and 1 degree down, 1 degree to the right and 6 degrees down, 1 degree to the left and 6 degrees down, 6 degrees to the left and 6 degrees down. This layout created four different cue-stimulus distances: (1) 1 degree; (2) 7.75 degrees; (3) 9.2 degrees; (4) 12 degrees. **B**, Task timeline in a single trial. The fixation point and the lines separating the four quadrants were visible throughout the experiment. The subjects started each trial by pressing the spacebar. During the test condition the cue onset followed 94 milliseconds after trial start and the cue was presented for 70 milliseconds. The stimulus pattern appeared 60 milliseconds after the offset of the cue. The timing of the sequence was chosen to maximize the effect of transiently attracting attention to the cue condition and precluded eye movements. The time course in the control condition was identical, except that no cue appeared on the screen. Observers performed a four-alternative forced choice task: they were asked to press one of four buttons according to the quadrant where they saw the stimulus.

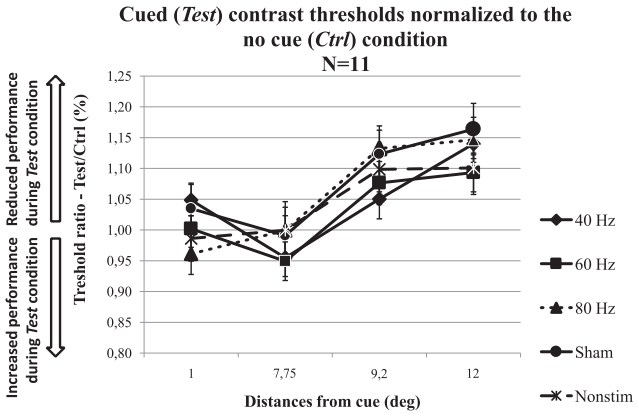

Figure 2 Contrast threshold ratios (Test/Ctrl) during the separated experimental design. This figure demonstrate the attentional modulation on contrast thresholds. An ANOVA revealed significant main effects of position in all stimulation conditions and the nonstimulation condition. Values above 1 indicate that during the test condition the contrast thresholds were higher, i.e., the subjects' performance was worse.

possible locations, either left or right from fixation. By using a four-alternative forced-choice detection task, we quantified facilitatory and inhibitory effects of attention on contrast detection thresholds for stimuli at four different distances to the cued location.

Data analysis

All data were analyzed using MATLAB (Mathworks Co., Natick, MA). Every first three of the 20 trials were excluded from the analysis. Contrast thresholds for the different stimulus positions were obtained by averaging contrast values of each false-choice trial. For both the test and the ctrl condition, the patterns were grouped according to their distance from the cue and their threshold data were averaged (test condition groups: 1-8-9-16, 2-7-10-15, 3-6-1-14, 4-5-12-13; Figure 1A). In case of the ctrl condition, we had only half the number of measurements as we had the same number of positions but we did not have the cue as a reference (ctrl condition groups: 1-8-4-5, 2-7-3-6, 3-6-2-7, 4-5-1-8), so we computed two thresholds and flipped them across space because with the stimulation electrode over the Oz in the midline the stimulation had the same impact on both hemispheres. To evaluate the effect of attention, the contrast values during the test condition have been divided by the contrast values of the corresponding stimuli during the ctrl condition.

Repeated measurements of analyses of variances (ANOVAs) (condition [40, 60, 80 Hz tACS versus sham] × distance [1; 7.75; 9.17; 12 degree]) were used to compare the different conditions. Effects were considered significant if $P < 0.05$. In the case of a significant interaction of distance and stimulation condition, a Fisher least significant difference (LSD) post hoc test was performed.

Results

None of the experimental sessions were interrupted because of side effects of the stimulation, although two of the 20 subjects complained about mild headache after the experiments. Flickering sensation during tACS can be a problem to perform sham stimulation; however, with the applied frequencies and intensity none of our subjects observed any flickering sensation.

Earlier results with the paradigm that we used in this study showed that attention enhances sensitivity for stimuli near the attended location and suppresses it at farther distances. Our results are in correlation with this, as repeated measures ANOVA revealed a significant main effect of position before and during stimulation as well (before stimulation: $F(3,30) = 13.95$, $P = 0.00$ ill. 40 Hz stimulus: $F(3, 30) = 15.28$, $P = 0.00$, 60 Hz stimulus: $F(3, 30) = 9.54$, $P = 0.0001$, 80 Hz stimulus: $F(3, 30) = 8.67$, $P = 0.0003$, Sham stimulus: $F(3, 30) = 5.35$, $P = 0.005$).

In both experimental designs (for explanation of separated and blocked design see the section "Procedure"), with 60 Hz stimulation the subjects' contrast detection performance was improved compared with the sham condition, whereas 40 and 80 Hz had no effect. On the other hand, none of the stimulations was able to modify the effect of attention on the contrast thresholds (Figure 2). In case of the block designed experiment (Figure 3A), repeated measures ANOVA revealed a nearly significant main effect of 60 Hz stimulation ($F(1, 8) = 4.18$, $P = 0.07$), whereas there was no effect of position ($F(3, 24) = 0.78$, $P = 0.52$). The interaction between stimulation and position was also not significant ($F(3, 24) = 1.01$, $P = 0.41$). For 40 Hz stimulation, we found no significant main effect with repeated measures ANOVA neither for stimulation ($F(1, 8) = 0.25$, $P = 0.63$) nor for position ($F(3, 24) = 2.00$, $P = 0.14$). The interaction between stimulation and position was also not significant ($F(3, 24) = 1.52$, $P = 0.24$). During 80 Hz stimulation, we obtained the same results as for 40 Hz stimulation. There was no significant main effect for stimulation ($F(1, 8) = 0.25$, $P = 0.63$) and for position ($F(3, 24) = 0.52$, $P = 0.68$). The interaction between them was also not significant ($F(3, 24) = 0.47$, $P = 0.70$). Fisher LSD test in case of this experimental design revealed significantly better performance during 60 Hz stimulation in the first ($P = 0.006$), second ($P = 0.0003$), and third ($P = 0.0007$) positions and nearly significant in the fourth position ($P = 0.06$).

During the separated experimental design (Figure 3B), repeated measures ANOVA again revealed a significant main effect of 60 Hz stimulation ($F(1, 10) = 5.25$, $P = 0.045$), whereas there was no evidence of a significant effect of position ($F(3, 30) = 0.99$, $P = 0.41$). The interaction between stimulation and distance was also not significant ($F(3, 30) = 0.28$, $P = 0.84$). In case of 40 Hz, there was no significant main effect of stimulation ($F(1, 10) = 0.11$, $P = 0.74$) or position ($F(3, 30) = 2.41$, $P = 0.09$). The

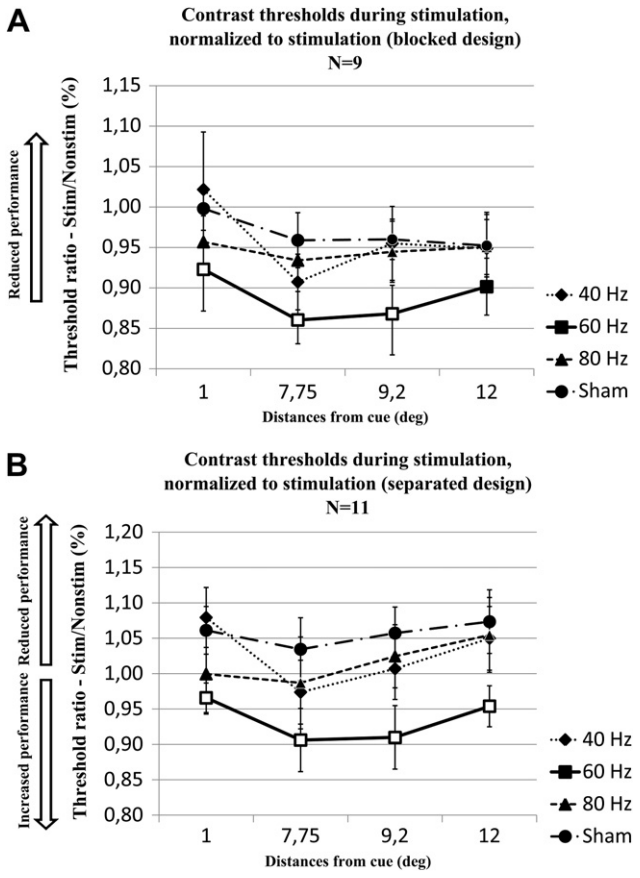

Figure 3 Results of tACS over primary visual cortex. Data contain threshold values for both the test and the ctrl conditions. **A**, Contrast threshold ratios (Nonstimulation/Stimulation) during the block designed experiment for all conditions. The error bars represent standard errors of the mean (SEM). Unfilled symbols indicate significant result compared with sham. Values above 1 indicate that during stimulation the contrast thresholds were lower, i.e., the subjects' performance was better. **B**, Contrast threshold ratios (Nonstimulation/Stimulation) during the separated experimental design. The error bars represent SEM. Unfilled symbols indicate significant result compared with sham.

interaction between stimulation and position was also not significant ($F(3, 30) = 0.83$, $P = 0.49$). For 80 Hz stimulation, there was no main effect for stimulation ($F(1, 10) = 0.56$, $P = 0.47$) and position ($F(3, 30) = 1.31$, $P = 0.29$). The interaction between stimulation and position was also not significant ($F(3, 30) = 0.21$, $P = 0.89$). According to Fisher LSD test, performance under 60 Hz stimulation was significantly better in the second ($P = 0.038$), third ($P = 0.005$), and the fourth ($P = 0.049$) position but not in the first ($P = 0.086$).

Discussion

The aim of our study was to investigate the influence of tACS over V1 on the spatial profile of attention although probing contrast sensitivity at high resolution across the visual field. Our psychophysic paradigm had been developed in the context of a previous study[45] without transcranial stimulation. The results showed that attending to a particular location enhances sensitivity for stimuli near the attended location and suppresses it at farther distances. Our results confirm these findings as the detection thresholds at and around the attended location were lower and they increased with increasing distance (Figure 2). Furthermore, we observed that 60 Hz tACS over the primary visual cortex improved contrast detection during the stimulation (Figure 3).

Several studies reported that tDCS, TMS, and rTMS can modulate visual cortex excitability[46] and can influence contrast sensitivity.[47,48] However, these techniques always only led to decreases in performance. One possible reason for this is that the human contrast sensitivity is highly optimized, so contrast perception cannot be improved by modulating the excitability of neurons in the primary visual cortex. With tACS in the current study, however, we targeted not the excitability of the neurons but the oscillatory activities that are suggested to play an important role in the communication between and within cortical areas.[49] Synchronous oscillatory activity in the gamma range has been suggested as a mechanism by which neuronal linking within and across visual cortices is achieved as a first step in perceptual organization binding.[11,17,49] The various attributes of a visual image might be processed separately in distributed neuronal assemblies across widespread cortical regions and linked by a common gamma-frequency oscillation. The phase-locked discharges of these distributed groups may be responsible for the "binding" of the various features into a coherent cognitive percept. It is conceiveable that our 60 Hz stimulation improved the communication between the neurons within primary visual cortex and possibly with and between the extrastriate visual areas as well. According to our hypothesis, the improved communication increased the signal transmission into, within, and forward of the network and thus, the contrast perception.

Several previous studies investigated the relationship of gamma range EEG activity and visual processing of elementary visual features.[50,51] They reported that during full-field stimulation by vertical gratings with a sinusoidal luminance profile (Gabor-patches) the highest power gamma-frequency activity was observed at the midline over the inion. These studies proposed that high-frequency oscillatory activity can be subdivided into narrower frequency bands, each associated with a different aspect of visual processing. Although 60 Hz was outside the range they investigated (14-55 Hz), our results support this concept as we found no effect after 40 and 80 Hz but after 60 Hz electrical stimulation, suggesting that the different gamma-band frequency ranges may serve different functional roles in visual processing.

When static horizontal black/white square-wave grating patterns are presented to human subjects V1 shows the strongest and most consistent oscillatory responses. The

frequency of these oscillations is in the gamma range (20-60 Hz) with the maximum around 40 Hz.[52,53] This suggests that gamma oscillations in V1 are related to very low-level stimulus attributes (such as luminance contrast). Our results are consistent with these findings and in addition indicate a relationship between gamma-band activity and contrast sensitivity function.

The time-locked evoked response that usually appears in the first 150 milliseconds after stimulus onset, can be modulated by selective attention,[54] spatial frequency,[50,51] and stimulus properties such as size and eccentricity.[55] Busch et al.[55] proposed that stimulus size not only affects the amplitude but also the frequency of the early evoked gamma-band response. Although they could not find significant differences in frequencies, there was a trend toward lower frequencies for bigger stimulus sizes. Therefore, the small stimulus size used in our paradigm might lead to a shift in the optimal stimulation frequency range from 40 toward 60 Hz. In another study Schadow et al.[56] found that the contrast of a visual stimulus strongly modulates the visually evoked gamma-band oscillations. The mean peak latency of the evoked gamma activity (shorter than VEPs P100)[57-59] and the fact that it is strongly influenced by stimulus size and eccentricity suggest that the primary visual cortex is the source of these oscillations.

Late induced gamma frequency is nontime-locked, independent from modality, and appears about 200 milliseconds after stimulus onset. These oscillations seem to be related to top-down processes as they can be modulated by memory,[60] attention,[61] and object recognition.[62] Therefore, our stimulation might not have modulated the induced gamma oscillations but only the visually evoked oscillations, because induced gamma activity is more dependent on the function of higher order areas and thus is harder to modulate with external stimulation.

In a previous study we found that tACS over the primary motor cortex induces only weak if any after effects.[37] In that study we used a stimulation intensity of 400 μA to avoid tACS-induced retinal phosphene perception. With tDCS a minimal intensity of 600 μA was needed to elicit motor cortex plasticity effect. In the current study we used 1500 μA stimulation intensity, nearly four times stronger than what we applied before. Most likely because of the higher stimulation frequencies and to the different position of the reference electrode (vertex instead of forehead), none of our subjects reported flickering phosphenes during the experiments. Although in the present study we did not investigate the after effects of tACS, we showed that during stimulation tACS can modulate cortical activity.

In summary, stimulating over V1 using 60 Hz frequency tACS we observed a reproducible significant improvement in contrast perception. One of the disadvantages of our study is that we did not apply individual gamma frequencies. Indeed a recent paper suggests that spike-timing-dependent plasticity induced by tACS in the alpha frequency range selectively modulates synapses depending on the resonance frequencies of the neural circuits that they belong to.[63] Although the neuronal mechanism of this process is not clear, tACS might interact with ongoing oscillations in V1, providing a new method for noninvasively influencing rhythmic brain activities.

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