1 **Frequency but not phase specific modulation of binocular rivalry with transcranial alternating**

2 **current stimulation**

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ABSTRACT

Recent transcranial alternating current stimulation (tACS) literature suggests that tACS effects can in principle be both frequency and phase specific. In a series of three experiments using 69 participants used binocular rivalry percepts as a read-out for the effects of phase-synchronized tACS stimulation. To test for phase specificity, with frequency the same in each eye, we visually stimulated each eye with 3Hz, with stimuli in each eye presented in temporal in antiphase. The frequency-specific paradigm visually stimulated the right eye with 3Hz, and the left eye with 5Hz. Each experiment was accompanied by 3Hz tACS, whose phase with respect to the visual stimulus was varied by 0°, 90°, 180°, or 270° in relation to the right eye's stimulus. A baseline no-tACS block preceded the stimulation blocks and two more followed, immediately and ten minutes after. Individual blocks lasted 4 minutes. Additionally, a no-tACS control experiment identical to the 3 Hz anti-phase visual stimuli setup was conducted, keeping all parameters the same but eliminating tACS. During stimulation, the 3 Hz anti-phase visual stimuli setup slowed the rate of rivalry in both eyes. Conversely, the 3Hz-right, 5Hz-left setup slowed the right (targeted) eye significantly while leaving the left (unstimulated) eye unchanged. In both experiments, durations returned to baseline after 10 minutes. Our results are consistent with the frequency-specific model of tACS, and with the Leveltian hypothesis that stimulation weakens the stimulated eye, as the right eye got weaker when it was directly targeted, and both eyes got weaker when targeted in antiphase. tACS does not appear to preferentially modulating percept durations in one phase more than in another.

64   **INTRODUCTION**

65

66   Neural activity can be modulated by electric fields generated by electrodes placed on

67   the scalp – a technique referred to as transcranial electrical stimulation (tES). Three commonly

68   used tES methods differ in the temporal profile of the applied current, *e.g.* direct current

69   (transcranial direct current stimulation; tDCS), alternating current (transcranial

70   alternating current stimulation; tACS), or random noise currents (transcranial random noise

71   stimulation; tRNS). In comparison to TDCS or TRNS, tACS is a particularly effective method to

72   address possible modes of action as it can be delivered at frequencies that are designed to

73   interact both with natural brain-wave rhythms (Antal and Paulus, 2013; Helfrich et al., 2014) as

74   well as responses to externally applied periodic sensory stimuli (Neuling et al., 2012).

75   Prior work on the mechanism of action of tACS has used invasive recordings in animal

76   models and has suggested several mechanisms by which the imposed tACS field could affect

77   with ongoing neural activity, either instantaneously (Liu et al., 2018) or as a (partially) sustained

78   after-effect (Stagg et al., 2018). One of the proposed instantaneous mechanisms is stochastic

79   resonance, in which cells whose membrane potential is near firing threshold can be induced to

80   fire by the addition of an external field (Ozen et al., 2010). Related to stochastic resonance, the

81   "rhythm resonance" mechanism involves precisely timed fields that are coordinated with the

82   depolarizing phase of neurons whose membrane potential is spontaneously fluctuating in an

83   oscillating fashion (Deans et al., 2007; Frohlich and McCormick, 2010; Reato et al., 2010, 2013).

84   That is, tACS may act by summation with the membrane potential of active neurons such that

85   when tACS is in-phase with the ongoing or membrane potential fluctuations, spiking rates

86   increase. External fields may combine with internal fields in such a way to cluster spiking,

87   without actually increasing or decreasing the overall firing rate (Liu et al., 2018). Finally,

88   external fields of high strength can entrain local networks by overwhelming the ongoing activity

89   (Liu et al., 2018). Proposed non-instantaneous mechanisms include various forms of synaptic

90   plasticity that effect synaptic efficacy (Stagg and Nitsche, 2011; Stagg et al., 2018).

91   Of present interest, tACS has been paired with periodic sensory stimulation that is

92   expected to drive cortex at a specific frequency and its harmonics. This approach has the

93   potential to provide strong evidence for instantaneous or "on-line" effects, as well as non-

94   instantaneous ("off-line") effects. An example of the former is the finding that hearing

95   threshold for periodic tone bursts can be modulated by frequency-matched tACS in a phase-

96   dependent fashion (Neuling et al., 2012).

97   Here we used tACS and periodic visual stimulation to measure online and offline effect

98   of tACS on visual perception, using the phenomenon of binocular rivalry as a perceptual read-

99   out. Binocular rivalry occurs when images presented to each eye are not fusible into a single

100   percept. Instead of seeing a single image, as in normal viewing, perception alternates between

101   the images presented to each eye. We reasoned that if tACS modulates neural activity in a

102   frequency or phase-specific fashion, it could alter the balance of perceptual salience for images

103   presented to each eye and this alteration may be reflected in the statistics of the perceptual

104   alternations. Importantly for present purposes, the dynamics of the perceptual alternation

105   depend on the relative perceptual strength of the two images and these dynamics have been

106   formalized into a set of laws which can be used as an interpretive framework (LeVeldt, 1965;

107   Brascamp et al., 2015). We test both the phase and frequency specific models of tACS, looking

108   to see if tACS might have constructive or destructive effects when presented in phase or out of

109   phase with visual stimulation of the same frequency, or if merely being frequency matched is all

110   that is required of tACS for it to have an effect, either online or offline.

111

112   **METHODS**

113

114   **Participants**

115   Participants in this study were 34 females and 35 males from Stanford and the

116   surrounding community who received either credit in a psychology course or monetary

117   payment of $30. Participants were screened to have a stereo acuity better than 50 arc-seconds

118   on the RanDot stereo-acuity test, averaging 31.28 arc-seconds. Participants had an average

119   right eye visual acuity of -0.068 and an average left eye visual acuity of -0.061 on the Bailey-

120   Lovie chart. Eye dominance was measured with the hole in the card test and revealed that 19

121   participants were left eye dominant and 50 were right eye dominant. Procedures were

122   approved by the Stanford Institutional Review Board and each participant provided written

123   informed consent.

124

Visual Stimulation

126   For each of three experiments, 10% Michelson contrast, dichoptic Gabor patches (3

127   c/deg, sigma 1 deg) were presented to the participants. The Gabor patches were oriented at

128   135 degrees in the left eye and 45 degrees in the right eye. The patches flashed either at 3Hz or

129   5Hz, depending on the experiment.   The stimulus was generated using in-house software and

130   presented on a 55-inch, LG passive 3D OLED screen at a mean luminance of $10cd/m^2$. The

131   Gabor patches were viewed by participants from 80cm from the stimulus display. Three

132   concentric circles, visible to both eyes acting as a fusion and focus lock surrounded the test

133   stimulus. Participants wore polarizing-filter glasses and placed their head on a head-rest that

134   had been pre-measured to be 80cm from the stimulus display. The experiments were

135   performed in a darkened room and participants signaled their rivalry percepts by via button

136   presses. They were instructed to press the left button if the bars on the screen appeared to be

137   oriented up and to the left, and the right button if the bars on the screen appeared to be

138   oriented up and to the right. They were instructed to press neither button in the case of mixed

139   percepts. They were also given a practice period and the opportunity to ask for any

140   clarification.

141   In the first two experiments described below, the stimulus flashed at 3Hz in each eye,

142   with left eye stimulus being shifted in phase by 180 degrees relative to the right eye. In the

143   third experiment, the left eye visual stimulus was presented at 5Hz and the right eye stimulus

144   was presented at 3Hz. Electrical stimulation, when present was delivered at 3 Hz.
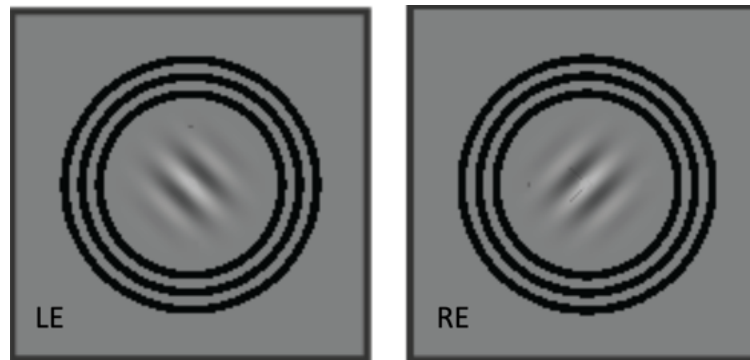
Figure 1: *Visual stimulus schematic. The two Gabor patches with orthogonal carrier orientations were overlaid on one another on the 3D screen. The left eye saw the image on the left, while the right eye only saw the image on the right.*

145

tACS Stimulation

147   Sinusoidal electrical stimulation was delivered via a StarStim system (NeuroElectrics,

148   Barcelona). For every participant, the protocol before starting stimulation involved: hair-

149   washing with baby shampoo, electrode cap sizing, abrasive skin preparation via Lectron II gel

150   application to clean the targeted scalp regions, electrode placement, and electrode gel

151   application. Impedances were kept below 10k. The two source electrodes were placed at P07

152   and P08, while the common sink electrode was placed at O_Z. Stimulation current amplitudes

153   were 1 mA at each of the source electrodes and 2 mA at the sink electrode. This "tri-polar"

154   montage was designed to minimize current flow through the eyes and thus to minimize the

155   chance of inducing phosphenes (Kar and Krekelberg, 2012) and to focus the stimulation on the

156   central field (~2 deg) representations in V1, V2 and V3 that are located on the occipital

157   pole(Dougherty et al., 2003). Current distributions were visualized with StarStim BEM modeling

158   software.

159   The StarStim system was controlled over Bluetooth. Because the start time of the

160   electrical stimulation upon initiating a request for stimulation over Bluetooth was not

161   deterministic, the computer generating the visual stimulus monitored the phase of

162   the tACS stimulation in real time by recording the differential signal between electrodes

163   at Oz and PO8. The visual-stimulation software monitored the tACS waveform in real time and

164   scheduled the start of visual-stimulation so it began at each of 4 pre-determined phase offsets

165 of 0, 90, 180 or 270 degrees relative to the tACS stimulus. This allowed the system to match

166 the current and visual stimulus phase relationships with a maximal error of 1 video frame

167 duration (16.6 msec or 18 deg of phase at 3 Hz).

168   Electrodes were also monitored via the Bluetooth stimulator, which displayed real-time

169 feedback on the impedance and waveforms of the stimulating current, so that the

170 experimenter could visualize the functionality and impedance of all three electrodes and the

171 output of the tACS stimulator that was connected to the electrodes.

172

173 **Experimental procedure**

174   The protocols were designed to assess rivalry before, during and after tACS, testing

175 whether tACS is phase or frequency specific. We also included a control experiment to

176 determine the stability of rivalry parameters over the duration of the active tACS experiments.

177 This psychophysical control was used to determine whether there was any "drift" in the

178 rivalry process after being exposed to the same stimulus for the duration of the experiment.   In

179 this control experiment, referred to below as the no-tACS control, the stimulus conditions and

180 experiment duration were identical to the ones to be described for the first tACS experiment (3

181 Hz anti-phase visual stimuli), but no electrical stimulation was applied at any time.

182   A pilot study was conducted to investigate whether orientation (45/135 deg), temporal

183 frequency (3Hz/5Hz) or eye (left/right) biased overall rivalry distributions. We measured rivalry

184 durations for each of the 8 pairwise combinations in 5 observers. By testing these various

185 iterations of the same paradigm, we established that there was no effect of any of the three

186 factors on overall rivalry modulation, allowing us to pick fixed pairings of eye and orientation

187 and a fixed targeted eye.

188   In each experiment, an initial, non-stimulated block was presented to measure the

189 participant's baseline rate of rivalry. This first block lasted 4 minutes and was comprised of two

190 trials, each lasting approximately two minutes. Next, blocks with 4 different tACS relative

191 phases were run consecutively, but in random order for every subject to control for temporal

192 order. Each block contained 4 trials, lasting approximately two minutes. For the duration of

193 these blocks, participants received tACS stimulation at four different relative phases: 0°, 90°,

194 180°, or 270°. This portion of the experiment lasted 28 minutes. tACS stimulation was on for

195 the entire 28-minute period. Immediately after the completion of the four blocks with tACS

196 stimulation, participants completed a 6th, non-stimulated block of two trials, lasting 4

197 minutes. Participants were then given a 10-minute break in which they could wash their hair

198 but not leave the room. After the 10 minutes, participants completed condition 7, which also

199 had no stimulation but featured the exact same stimulus. This was done in order to measure a

200 possible persistent effect of tACS.

201 In the first tACS experiment (Experiment 2) and in the psychophysical control

202 experiment, both Gabor patches flashed at 3Hz, but they were offset by 180° of one another.

203 This made the sign of polarization opposite in the two eyes and was our test of phase

204 specificity. During blocks 2-5, tACS was presented at 3Hz for the entire duration. When

205 electrical stimulation was applied, tACS was synchronized with the 3Hz visual stimulus, such

206 that it was at either 0°, 90°, 180°, or 270° offset in relation to the visual stimulus in the right

207 eye.

208 In Experiment 3, the visual stimulus was presented at two different frequencies. This

209 was our test of frequency specificity. The right eye's Gabor patch flashed at 3Hz, while the left

210 eye's Gabor patch flashed at 5Hz. tACS was presented at 3Hz, targeting the right eye. During

211 blocks 2-5, when tACS stimulation was applied, the tACS was synchronized with the 3Hz

212 stimulus, such that it was at 0°, 90°, 180°, or 270° phase in relation to the visual stimulus. The

213 relative phase of tACS with respect to the right eye precessed through all possible phase

214 angles.

215

216 **Data Preprocessing**

217 The raw data was exported into MATLAB files for analysis.   After exporting, data was

218 then sorted into left and right presses. Next, duration lengths were calculated for each subject

219 and each trial. The button hardware occasionally resulted in very short durations of non-press

220 during periods of button press. These durations were cleaned up by consolidating any user

221 non-press that lasted <0.5 seconds to the previous button press, provided it was the same

222 button.   Figure 2 shows raw button durations for three observers each with very different

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223   duration distributions spanning the range observed in the experiment.   To characterize these

224   distributions, all data was transformed into log-seconds and then fitted utilizing a normal

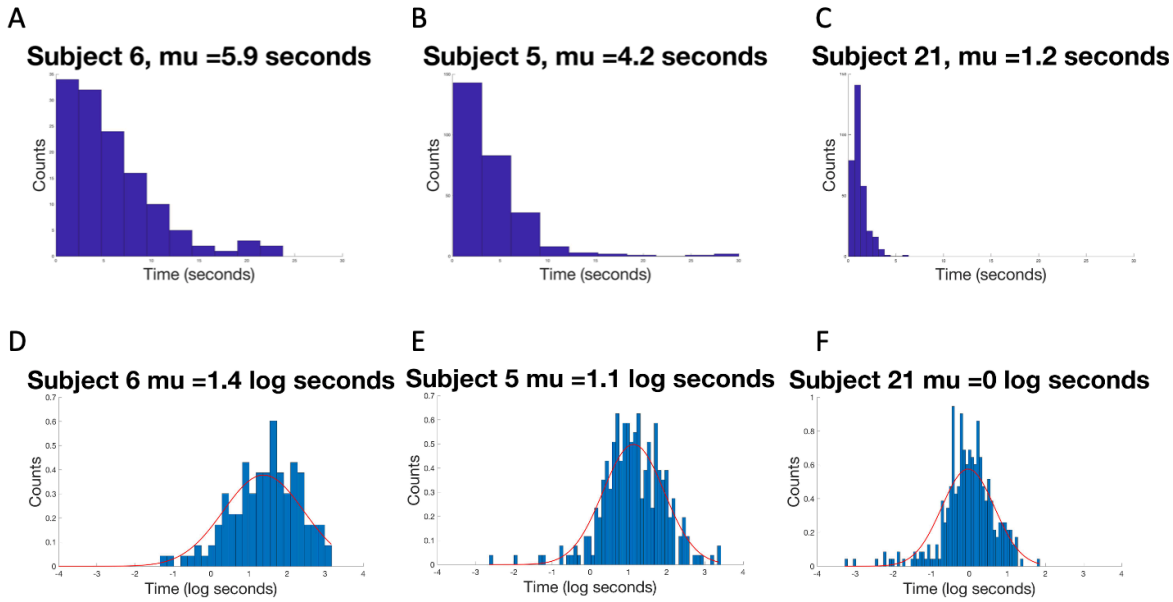225   distribution. The log-normal fits were better than traditional gamma fits.

Figure 2: *Unprocessed and log-normalized data. A: Representative example of a participant with a longer mean rivalry duration. B: Representative example of a participant with an average mean rivalry duration. C: Representative example of a participant with a shorter mean rivalry duration. D-F: Log-transforms of the corresponding distributions A-C, demonstrating that the log-normal fit (red curve) accurately represents data for all rates of rivalry.*

226

Outlier exclusion

228   We noted that some participants had extremely long rivalry durations, suggesting that

229   their rivalry process was far from being balanced. As this imbalance would likely reduce the

230   sensitivity of the rivalry read-out to tACS perturbation, we developed an outlier screening

231   procedure based on the raw durations. A 1.5IQR test was utilized to exclude outliers from each

232   of the three experiments. For this exclusion, only means from condition 1 in each experiments

233   were considered. This was done to ensure that we were excluding subjects who didn't have

234   typical rivalry alternations in their baseline reading, not running the risk of excluding someone

235   who might have been significantly affected by the electrical stimulation.
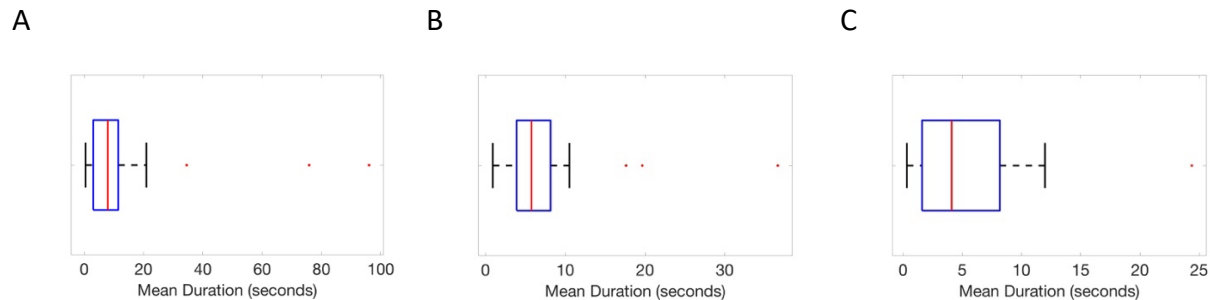
236

237

238

A   B   C

Figure 3: *Outlier detection. Detection of mean durations that fell outside of the pre-determined 1.5IQR of the data. A: Box and whisker plot for the 3Hz/5Hz visual stimulation Experiment. B: Box and whisker plot for the 3 Hz anti-phase visual stimuli setup. C: Box and whisker plot for the no-tACS control experiment. Outliers were data points that fell beyond 1.5*IQR + Q3 and are indicated by the red dots outside of the boxplot. These participants (n=3, 3 and 1 for A, B and C, respectively) were excluded from further analysis, as they did not show typical rivalry alternations.*

239

240   **Data normalization**

241   As can be seen from Figure 2, the mean of each subject's log-durations varied

242   significantly significant variation between the baseline mean durations. This variation arose

243   because of the variable rate at which the subjects rivaled, with some rivaling faster than

244   others.   As the goal of the experiment is to assess the effects of tACS on perception within

245   participants, we normalized all means to the participants value in the baseline condition by

246   subtracting each condition's values from that of condition 1. Normalization was performed for

247   both the log mean duration and switch-rate metrics. The effect of the normalization on

248   duration measurements is shown in Figure 4 which plots the data from all conditions for the

249   three observers shown in Figure 2. Panels A-C show the un-normalized log durations that have

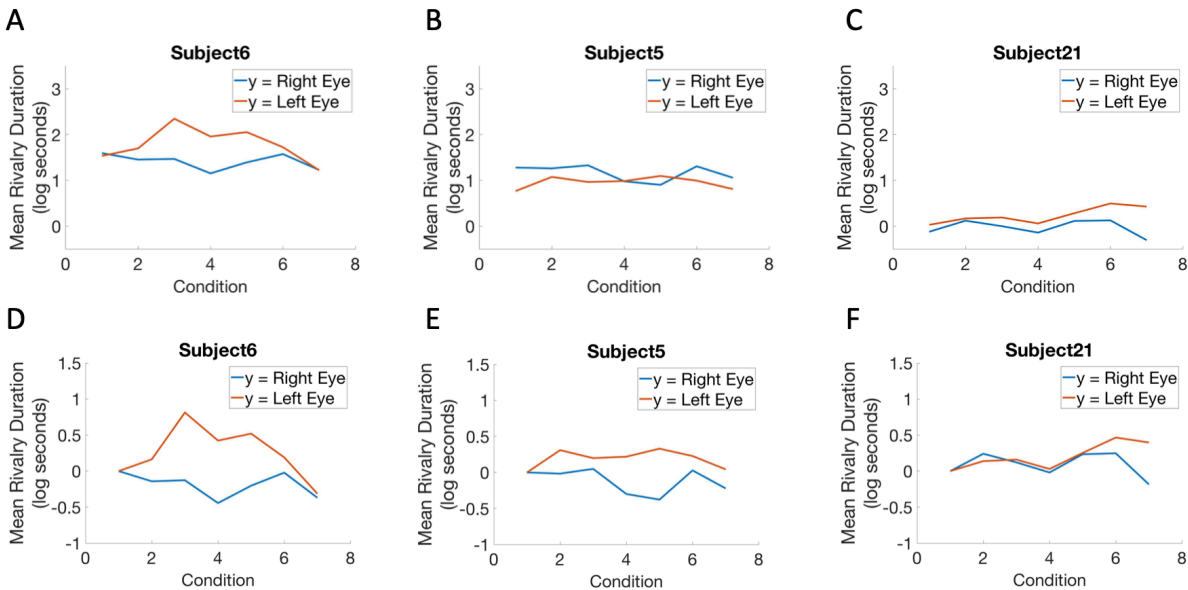250   a larger range than after normalization (panels D-F).

Figure 4: *Normalizing duration data to a set baseline. A-C: Representative participants (same as those shown in Figure 2) showing the variability in the baseline and overall rivalry durations. D-F: Normalized participant data obtained by setting condition 1 as the subtracted baseline.*

251

252   Once normalized, these data were averaged to generate graphs of mean normalized

253 duration for right and left button presses and graphed over condition. For each condition, we

254 also calculated the rivalry switch rate by counting how many times each subject switched

255 buttons throughout the experiment and dividing that number by the duration of the

256 experiment.

257

258 **Statistical Analysis**

259   To assess the impact of the phase of tACS on rivalry, paired t-tests were performed for

260 all pair-wise combinations of the four test conditions, and then corrected utilizing the

261 Bonferroni adjustment for multiple comparisons. If these tests revealed no significant

262 differences, data from the four test conditions were pooled and tested against zero. This test

263 determined the effectiveness of tACS at modulating rivalry in a phase-independent manner.

264   For the post-tACS conditions, paired t-tests compared condition 6 to condition 7

265 (immediately post-tACS to 10 minutes post-tACS) to determine if there were any significant

266 lasting effects of the stimulation. The two conditions were also t-tested against zero (the

11

267   baseline condition) to see if there was any overall effect of tACS. If the t-tests revealed that

268   conditions 6 and 7 were statistically indistinguishable, the two conditions were pooled first and

269   then compared to zero.

270

271   **RESULTS**

272

273   **Behavioral control experiment without tACS**

274   This experiment was performed to determine the degree to which rivalry features

275   remain constant over the long duration of the tACS experiments. Drift in rivalry parameters

276   over the duration of the experiment, if it occurred, would complicate the interpretation of the

277   tACS data. Therefore, to test rivalry stability, we used the same number of trials and

278   experiment duration as in the tACS experiments. The participants viewed 3 Hz anti-phase

279   stimuli in each eye and reported which eye was dominant by holding down one button for left

280   eye and a second button for right eye dominant periods.
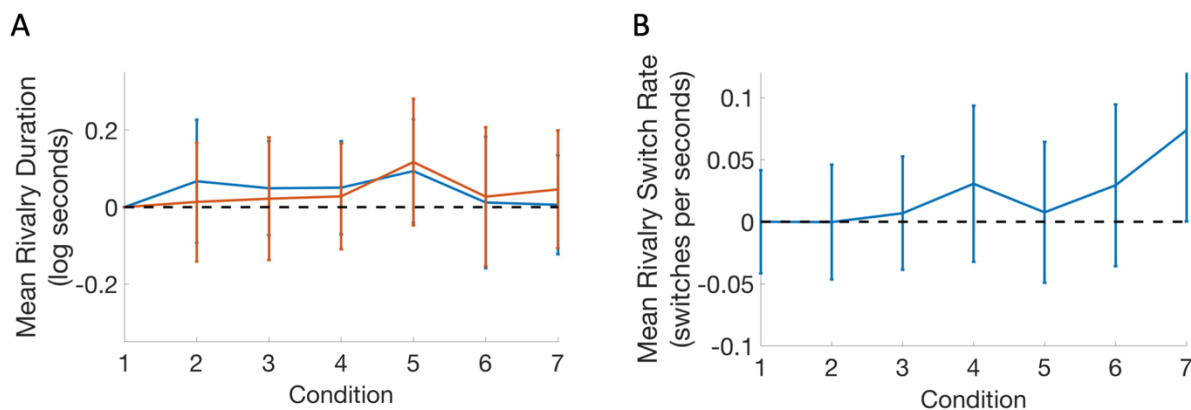

Figure 5: No tACS control experiment: 3 Hz right eye stimulation, 3Hz left eye stimulation without tACS stimulation. Panel A plots left- (red) and right-eye (blue) normalized mean durations. Panel B plots normalized mean rivalry switch rates over blocks of the experiment. Error bars plot +/- 1 s.e.m.

281   We observed no significant deviations from baseline durations or switch rates over the

282   course of the experiment which lasted ~50 minutes. Note that conditions 2-5 were presented

283   in random over a period of 28 minutes, so to determine whether rivalry durations change over

284   the period used in the active tACS phases of Experiments 2 and 3, we pooled the data across

285   conditions 2-5 to obtain estimates of duration and switch rates at an average of 14 minutes

286   after baseline. The immediate post-test (condition 6 data reflect rivalry at and average of 30

287   minutes after baseline and the final post-test (condition 7), 42 minutes. In each case we tested

288   the durations against the baseline value of zero. Each of the pooled condition 2-5 duration

289   values were non-significant (p=0.33; left eye, p= 0.55. right eye). Similarly tests of the periods

290   corresponding to the post-tACS conditions also revealed no significant changes in mean

291   duratione from baseline. For the immediate post-test the right eye p-value was 0.95 and the

292   left eye vlaue was 0.88. The corresponding values for the 10-minute post-tACS condition were

293   0.96 and 0.77, respectively). For the switch rate parameter estimated at 14 minute, there was

294   no measurable deviation from baseline for either eye (p=0.83), nor were there measurable

295   changes in the immediate post-test (p=0.70) or final post-test (p=0.39).

296

297   **Phase-specificity of tACS**

298   The purpose of the next experiment was to determine whether tACS can modulate

299   rivalry durations or switch rates in a phase-specific fashion. To make this measurement, we

300   presented 3Hz visual stimulation to both eyes, but with 3Hz anti-phase tACS. Because we don't

301   know the precise timing of the visual activity we are reading out, we presented tACS at 4

302   different relative phases to span one full cycle of the visual and tACS stimulation (blocks 2-5). In

303   each case tACS was in antiphase, given that the visual stimuli were always presented in anti-

304   phase to the two eyes. The phase-specific hypothesis predicts that a tACS phase that is

305   maximally suppressive in one eye will be maximally facilitative in the other eye which is

306   receiving the opposite polarization, and vice versa, once the proper absolute delay between the

307   visual system's internal response and the instantaneous tACS field is matched. We defined the

308   relative phase of tACS with respect to the right eye's visual stimulation. If tACS was phase

309   specific, we should see weakening in one eye accompanied with a strengthening in the other

310   eye at a particular absolute phase value and the opposite effect at a phase value shifted by 180
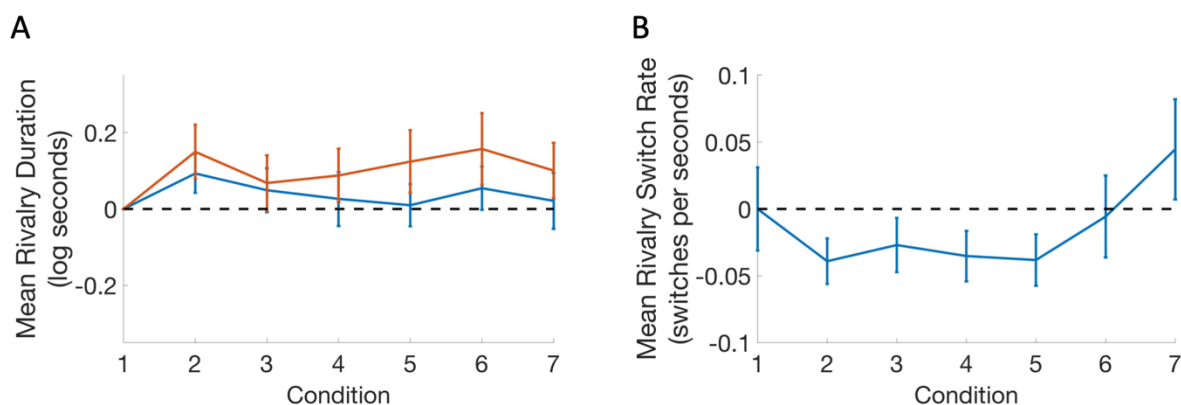
311   deg.

13

Figure 6: 3 Hz right eye stimulation, 3Hz left eye stimulation with 3Hz anti-phase tACS. Panel A plots left- (red) and right-eye (blue) mean durations B: Mean rivalry switch rate over blocks of the experiment. Error bars plot +/- 1 s.e.m.

312

313   The data for this experiment are presented in Figure 6, with left-eye data plotted in red

314   and right-eye data plotted in blue for each block of the experiment. We first tested whether

315   relative tACS/visual phase affected rivalry durations by performing all pair-wise comparisons

316   between the four relative phase values (conditions 2-5 in Figure 6). We observed no phase-

317   specific effect during the application of tACS. All Bonferroni adjusted p-values for the left and

318   right eye pair-wise comparisons were 1.

319   While tACS did not modulate rivalry in a phase-dependent fashion, it could still exert an

320   effect that is independent of relative phase. To test for this possibility, we pooled all of the

321   mean duration measurements for each eye made during tACS stimulation and compared them

322   to 0. The mean durations increased by a factor of 1.28 in the left eye compared to baseline and

323   by a factor of 1.11 in the right eye. The shift for the left eye was highly significant (p= 0.004) but

324   was marginally significant for the right eye (p= 0.13).

325   Another important parameter of the rivalry distribution is the rate of switches. Figure

326   6B shows the rivalry switch rates. All pair-wise Bonferroni corrected tests over the tACS-present

327   conditions had p-values = 1 and thus showed no phase specificity. By contrast, switch rates

328   during tACS decreased by a factor of 1.22 (p< 0.000).

14

329   We then asked whether any of the effects on mean duration and switch rate observed

330   during tACS persisted immediately after cessation of tACS or after 10 minutes after tACS

331   cessation. Mean durations for the immediate post-tACS condition were not significantly

332   different from baseline for the right eye (p=0.35), but there was a non-significant trend for

333   longer durations in the left eye (p=0.11). There were no measurable effects on mean duration

334   for the 10-minute post-tACS condition (right eye 0.78, left eye 0.18). Switch rates in the

335   immediate post-tACS condition were not measurably different from baseline (p=0.90), nor were

336   they different from baseline in the 10-minute post-tACS condition (p=0.36).

337

338   **Frequency Specificity of tACS**

339   Having found no phase specificity of tACS stimulation, we moved on to test whether the

340   tACS effects were frequency specific. This experiment visually stimulated the right eye at 3Hz

341   and the left eye at 5Hz. We applied 3Hz tACS during the four middle "test" conditions and again

342   varied tACS/visual phase. Thus, the right eye received synchronous 3 Hz tACS stimulation at

343   different relative phases, but the left eye received asynchronous tACS/visual stimulation as the

344   visual stimulus was presented at 5 Hz. If tACS' effects were frequency specific, the effects of

345   tACS should be most apparent in the synchronously stimulated right eye.
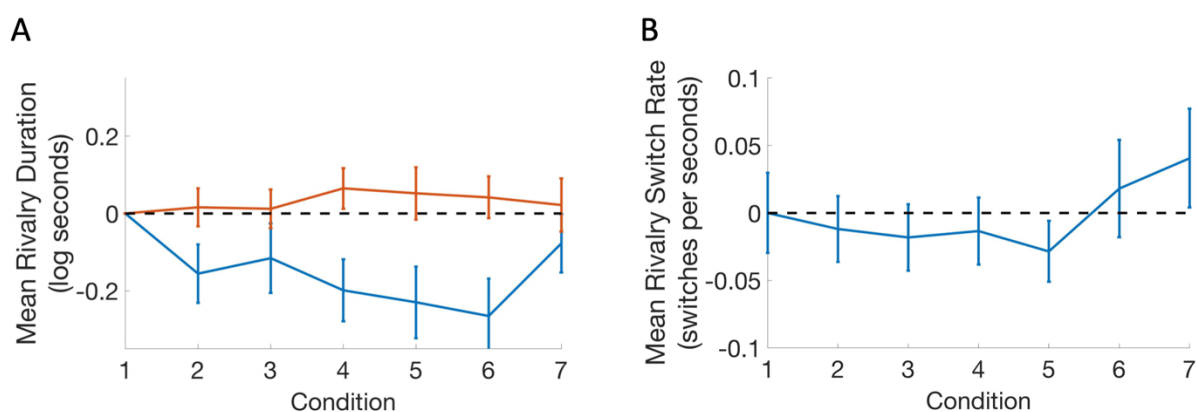

Figure 7: 3 Hz right eye visual stimulation, 5Hz left eye visual stimulation. 3Hz tACS reveals a slowing of percept durations in targeted eye and no change in nontargeted eye.

Panel A shows rivalry durations for both left (orange) and right (blue, targeted) eyes. Panel B shows rivalry switch rates. Rivalry slows in the targeted eye, and switch rates decrease.

15

346

347   The data from this experiment are shown in Figure 7. As in Experiment 2, we observed

348   no phase-specific effects on mean rivalry duration during the application of tACS. All pair-wise,

349   Bonferroni-corrected p-values were 1 for both eyes. We thus pooled all of the mean duration

350   measurements for each eye made during tACS stimulation and compared them to 0 to detect

351   any significant modulation from baseline in the two eyes' percepts. The mean durations

352   increased by a factor of 1.08 in the left eye and *decreased* by a factor of 1.50 in the right eye.

353   The shift for the right eye was highly significant (p< 0.000) but was marginally significant for the

354   left eye (p= 0.19).   Figure 7B shows the rivalry switch rates. The switch rates did not differ by

355   phase on pair-wise Bonferroni corrected tests (all p-values = 1), but they decreased overall by a

356   factor of 1.28 (p< 0.000). The fact that the two eye durations change in opposite directions in

357   this experiment, versus changing in the same direction as 3 Hz anti-phase experiment, plus the

358   fact that switch rates decrease suggests tACS is effective and is frequency specific.

359   We then asked whether any of the effects on mean duration and switch rate observed

360   during tACS persisted immediately after cessation of tACS or after 10 minutes post tACS. Mean

361   durations for the immediate post-tACS condition were significantly different from baseline for

362   the right eye (p=0.01) but were not significantly different from baseline for longer durations in

363   the left eye (p=0.44). There were no measurable effects on mean duration for the 10 minute

364   post-tACS condition (right eye 0.32, left eye 0.75). Switch rates in the immediate post-tACS

365   condition were not measurably different from baseline (p=0.78), nor were they different from

366   baseline in the 10-minute post-tACS condition (p=0.45).

367

368   **DISCUSSION**

369   Our results using bi-stable rivalry percepts as a readout suggest that the effects

370   of tACS on visual perception depend on matching the frequency of visual and tACS stimulation,

371   but not on the relative phase of matched-frequency stimulation. The lack of phase specificity

372   was found in both the 3 Hz anti-phase and 3Hz/5Hz experiments. When 3Hz/5Hz frequencies of

373   visual stimulation were used, tACS that matched the visual stimulation rate (3Hz) decreased the

374   mean durations in that eye, and there was a marginally significant increase in duration in the

16

375   other (5Hz). By contrast, when anti-phase tACS of the same frequency (3Hz) was presented to

376   each eye, both eyes durations increased.   Together, these results indicate that the effect

377   of tACS was frequency, but not phase specific. Levelt's laws of rivalry allow us to deduce that

378   that tACS acted to reduce internal response strength, as described in the next section.

379   Our findings are largely interpretable within the framework of Levelt's laws governing

380   rivalry as recently updated by Brascamp and co-workers (LeVeldt, 1965; Brascamp et al.,

381   2015). Levelt's original laws were based on the results of psychophysical studies of rivalry

382   including situations that varied the relative stimulus intensities in the two eyes. Here, we

383   consider whether tACS effectively modulates internal response strength in a way similar to

384   changes stimulus intensity. There are four Levelt's laws and we interpret our data with respect

385   to each of them in the order that they have been traditionally stated. Levelt's first law states

386   that increasing the stimulus strength in one eye increases the perceptual dominance of that

387   eye's stimulus, and conversely, decreasing the stimulus strength in one eye decreases its

388   perceptual dominance.   Here we do not manipulate visual stimulus strength, but we sought to

389   manipulate the strength of the internal neural response via tACS.   In our test of frequency-

390   specificity with 3Hz/5Hz stimulation, we observed a phase-independent decrease in the right

391   eye's perceptual dominance reflected by its shorter mean durations consistent with this eye's

392   internal representation being weakened. Weakening of the representation in traditional rivalry

393   experiments would come about by decreasing stimulus intensity, so we interpret the effect of

394   tACS in this experiment as being effectively suppressive.

395   Levelt's second law states that "increasing the difference in stimulus strength between

396   the two eyes will primarily act to increase the average perceptual dominance duration of the

397   eye with the stronger stimulus." In the 3Hz/5Hz experiment, tACS targeted the right eye, acting

398   to shorten its durations, consistent with its response being weakened based on the above

399   prediction from the first law.   According to the second law, this should have the effect of

400   increasing the mean duration of the opposite eye. We see a trend in this direction, but the

401   effect is larger on the targeted eye. While the original second law stipulated that this increase

402   in the non-targeted eye should have been larger than the effect on the (weakened) targeted

403   right eye, more recent findings have shown that the second law is only valid for a relatively

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404   restricted range of stimulus intensities and thus internal response intensities, as studied here

405   and can even reverse sign (Brascamp et al., 2006). Second law predictions are thus not strongly

406   proscriptive in the present context.

407   Levelt's revised third law states that "increasing the difference in stimulus strength

408   between the two eyes will reduce the perceptual alternation rate" (Brascamp et al., 2015). The

409   data from 3Hz/Hz experiment are relevant here and we indeed see a reduction in the

410   perceptual alternation rate from baseline when the two eyes are stimulated asymmetrically,

411   *e.g.* only the right eye received synchronous tACS stimulation. Related to this, bistable percept

412   alternation rates have been shown to be maximal when competing percepts are perceptually

413   balanced, as they would have been at baseline (Moreno-Bote et al., 2010). A modulatory effect

414   of tACS (in either direction) is thus predicted to lower the alternation rate, which is what we

415   observe.

416   Levelt's fourth law states that "increasing stimulus strength in both eyes while keeping it

417   equal between eyes will generally increase the perceptual alternation rate…." (Brascamp et al.,

418   2015). The converse is true and more relevant to our observations. Switch rates decrease in

419   the 3Hz/3Hz condition, suggesting that internal response strength decreased, which is

420   consistent with mean durations having also decreased, as suggested above for the first law

421   interpretation of the mean duration data of the 3Hz/5Hz experiment which used asymmetric

422   stimulation.

423

424   **Possible mechanisms underlying observed tACS effects**

425   Prior work in animal models has suggested that tACS can exert phase-specific effects via

426   interactions between the imposed field and cell membrane potentials (Deans et al., 2007;

427   Frohlich and McCormick, 2010; Reato et al., 2010, 2013). Two non-invasive studies in human

428   have varied the relative phase of synchronous tACS and periodic sensory stimuli. The first study

429   (Neuling et al., 2012) reported that psychophysical thresholds for detecting brief 500 Hz tones

430   in noise depended on the timing of the tones relative to 10 Hz tACS.   This effect was

431   subsequently replicated with 4 Hz tACS (Riecke et al., 2015). A similar approach has not been

432   taken in the visual modality, to our knowledge. In the visual modality, Ruhnau and co-workers

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433   (Ruhnau et al., 2016), presented visual flicker at 7 and 11 Hz in presence of frequency-matched

434   or non- matching tACS. They found tACS effects to be frequency-specific, as we report here.

435   They could not assess phase-specificity as their visual and electrical stimuli were not phase-

436   synchronized as they were in the present experiments.

437   The relative lack of phase-specificity in our experiment relative to that reported

438   previously with auditory stimuli could arise for a number of different reasons. First, the

439   effective current strength delivered to cortex could differ for auditory vs visual stimulation

440   montages. The auditory experiments used a bipolar montage with electrodes over auditory

441   cortex where the skull is much thinner than it is over the occipital pole where our 3-electrode

442   array was located. Instantaneous, phase-specific modulation effects are expected to depend

443   strongly on delivered field strength and recent estimates have suggested that the deposited

444   field in human transcranial stimulation experiments is weak relative to that needed to influence

445   membrane potential (Opitz et al., 2016; Huang et al., 2017; Voroslakos et al., 2018). Secondly,

446   the rivalry stimuli were highly supra-threshold, rather than being near threshold as in the

447   auditory detection experiments. tACS effects may depend on the strength of the internal

448   response, which is very small for near threshold stimuli and larger for supra-threshold stimuli.

449   Network-level activity may thus have differed substantially. Finally, the effect of tACS not only

450   depends on electrical path length between the electrodes and the active tissue, but it also

451   depends on tissue orientation (Opitz et al., 2011).   We attempted to minimize this effect by

452   using small visual stimuli that will produce relatively small patches of cortical activation.

453   Because there are multiple representations of the visual field, the separate representations of

454   the patches in different visual areas may have sufficiently different orientation to eliminate the

455   effect of tACS phase which could invert depending on tissue orientation.

456   Transcranial Electrical Stimulation can also act via non-instantaneously through

457   mechanisms that modulate synaptic efficacy (Zaehle et al., 2010; Jackson et al., 2016; Kronberg

458   et al., 2017). These effects are necessary to explain the offline effect we have observed, as

459   there is no imposed field present to interact with cell membrane potentials in the offline

460   conditions. Recall that we showed an immediate offline effect on targeted-eye rivalry duration

461   in the 3Hz/5 Hz condition. It is possible that these mechanisms also underlie the effects we

462   observe during tACS stimulation. Consistent with this, the sign of the offline effect is the same

463   as the effect during tACS stimulation.

464   In conclusion, tACS stimulation can modulate visual perception and under our

465   conditions its net effect is consistent with a weakening of the internal visually-driven signal.

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