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Letter to the Editor

Transcranial alternating current stimulation reveals atypical 40 Hz phosphene thresholds in synaesthesia

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1. Introduction

Grapheme-colour synaesthesia is a condition characterized by atypical binding in which letters and numerals involuntarily elicit colour photisms (Ward, 2013). Previous research using transcranial magnetic stimulation (TMS) demonstrated that synaesthetes display enhanced cortical excitability selectively in primary visual cortex (Terhune, Tai, Cowey, Popescu, & Cohen Kadosh, 2011), as measured by phosphene thresholds (Cowey & Walsh, 2000). Further research found that variability in TMS phosphene thresholds covaries with individual differences in the visuospatial phenomenology of synaesthesia. In particular, projectors, who experience colour photisms as spatially co-localized with the inducing grapheme (Dixon, Smilek, & Merikle, 2004; Ward, Li, Salih, & Sagiv, 2007), exhibit lower phosphene thresholds (reflecting elevated cortical excitability) than associators, who experience colour photisms as endogenous images, and non-synaesthete controls (Terhune et al., submitted for publication). Insofar as top-down visuospatial attention enhances visual cortex excitability (Bestmann, Ruff, Blakemore, Driver, & Thilo, 2007), these results are consistent with the proposal that projectors and associators differ in spatial reference frames (Ward, et al., 2007).

Here, we examined whether projectors' low phosphene thresholds were frequency-dependent. A previous study showed that transcranial alternating current stimulation (tACS), a non-invasive brain stimulation technique for modulating brain oscillations, applied to visual cortex can produce phosphenes in a frequency-dependent manner (Kanai, Chaieb, Antal, Walsh, & Paulus, 2008), suggesting that phosphene thresholds result from an interaction between the stimulation frequency and resting state oscillations. We expected that projectors would display lower phosphene thresholds than associators and controls at 40 Hz. Synchronization of neuronal assemblies in this frequency range is believed to be instrumental in perceptual binding (Boudreau, 1964; Freeman, 1975; Singer, 2001) and may contribute to the enhanced visuospatial binding observed in projectors. Toward this end, we measured tACS phosphene thresholds at 40 Hz and three other control frequencies in controls, associators, and projectors.

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2. Methods

Sixteen controls (9 females, $M_{Age} = 24$, $SE = 1.7$), 9 associators (6 females, $M_{Age} = 23$, $SE = 1.4$), and 4 projectors (2 females, $M_{Age} = 21$, $SE = 3.3$), matched for age and years of education, all of whom were right-handed, consented to participate in this study in accordance with local ethical approval. Synaesthetes were classified as associators or projectors if they reported experiencing colour photisms as mental images or as spatially co-localized with graphemes, respectively, when viewing the achromatic digits 0-9 against a grey background during a structured interview (see also Dixon, et al., 2004; Ward, et al., 2007). Synaesthetes displayed lower values ($M = 39.9$, $SE = 5.0$), reflecting greater consistency, than controls ($M = 226.5$, $SE = 29.5$) on a measure of grapheme-colour consistency (mean Euclidean colour distance between colours matched to the numerals 0–9 in three back-to-back blocks (Rothen, Seth, Witzel, & Ward, 2013)), unequal variance $t(27) = 6.23$, $p < .001$, $d = 2.1$ (CIs: 1.5, 3.5).

We measured phosphene thresholds at 5, 10, 20, and 40 Hz as previously described (Kanai, et al., 2008) using a neuroConn DC-Stimulator PLUS (neuroConn® GmbH, Ilmenau, Germany) in a lit room. One 5 × 7 cm electrode was placed on the vertex and a 5 × 5 cm electrode was placed 4 cm above the inion. Order of tACS frequency presentation was counterbalanced across participants. For each frequency, tACS was administered for 5s (1s ramp up/down) starting at an intensity of 750 μA while participants sat with open eyes, passively viewing a black curtain. After each stimulation, participants reported whether they experienced a phosphene and the stimulation intensity was adjusted on a trial-to-trial basis (minimum: 25 μA; maximum: 1500 μA) using a modified binary search algorithm (Terhune et al., submitted for publication). The experimenter who administered the stimulation was blind to participant group.

3. Results

A series of one-way ANOVAs revealed that controls, associators, and projectors did not differ in phosphene thresholds at 5 Hz, $F(2,26) = .62$, $p = .55$, $\eta^2 = .04$ (95% CIs: .00, .30), 10 Hz, $F(2,26) = 1.90$, $p = .17$, $\eta^2 = .13$ (CIs: .01, .49), or 20 Hz, $F(2,26) = 1.03$, $p = .37$, $\eta^2 = .07$ (CIs: .01, .32) (see Fig. 1a). However, as predicted, there was a main effect of Group on 40 Hz phosphene thresholds, $F(2,26) = 6.83$, $p = .004$, $\eta^2 = .34$ (CIs: .16, .71). *Post hoc* Tukey tests revealed that projectors displayed significantly lower phosphene thresholds than controls ($p = .004$) and associators ($p = .008$), who did not differ ($p = 1.0$). This effect remained stable when controlling for tACS frequency order and the three other phosphene thresholds, $F(2,22) = 3.77$, $p = .039$, $\eta_p^2 = .26$ (CIs: .01, .47), with projectors differing from controls ($p = .014$) and associators ($p = .023$) (see Fig. 1b). Bootstrap resampling of 40 Hz phosphene thresholds further showed that 95% confidence intervals (bias-corrected and accelerated percentile method; 10,000 samples; see Fig. 1a) for the projectors' mean threshold (.45, .95) did not overlap with those of controls (1.18, 1.45) or associators (.98, 1.47). Furthermore, each of the projectors' individual thresholds fell outside the CIs of the controls and associators.

We next explored whether the groups differed in the perception of coloured phosphenes. A series of chi-squared tests indicated that there were linear trends for an increasing incidence of coloured phosphenes during tACS from controls to associators to projectors, respectively, at 10 Hz (0%, 11%, 50%), $\chi^2 = 7.73$, $p = .007$, $phi = .55$ (CIs: .22, .86), 20 Hz (0%, 22%, 75%), $\chi^2 = 11.56$, $p = .001$, $phi = .67$ (CIs: .28, .90), and 40 Hz (6%, 22%, 50%), $\chi^2 = 4.23$, $p = .040$, $phi = .39$ (CIs: .07, .69), but not at 5 Hz (6%, 11%, 25%), $\chi^2 = 1.07$, $p = .30$, $phi = .21$ (CIs: .01, .40). Subsidiary Fisher's exact tests showed that across frequencies associators did not differ in incidence rates from projectors, $ps > .20$, or controls, $ps > .11$, although projectors displayed greater incidence rates than controls at 10 Hz, $p = .03$, OR = 15[2] (CIs: .90, 251.07) and 20 Hz, $p = .004$, OR = 45 (CIs: 2.16, 937.37), but not at 5 Hz or 40 Hz, $ps > .08$. Owing to the sample sizes of the three groups, low expected cell counts in controls, and the exploratory nature of these analyses, they are susceptible to both Type I and II errors and thus should be interpreted with caution. For these reasons, we collapsed across synaesthesia subtypes and contrasted the incidence rates of coloured phosphenes in the two groups using Fisher's exact tests. Synaesthetes reported a greater incidence of coloured phosphenes than controls at each stimulation frequency although this was only significant at 20 Hz, 39% *vs* 0%, $p = .011$, OR = 9.38 (CIs: .93, 94.65) [5 Hz: 15% *vs* 6%, $p = .57$, OR = 2.73 (CIs: .22, 34.01); 10 Hz: 23% *vs* 0%, $p = .08$, OR = 4.5 (CIs: .41, 49.63); 40 Hz: 31% *vs* 6%, $p = .14$, OR = 6.67 (CIs: .64, 69.35)].

4. Discussion

Projector synaesthetes displayed lower phosphene thresholds than associator synaesthetes and controls during 40 Hz tACS, but not during three other stimulation frequencies. These group differences accounted for approximately one third of the variance in 40 Hz phosphene thresholds and remained stable when controlling for both tACS frequency order and phosphene thresholds at the three other frequencies. Furthermore, the effect was individually present in all projectors, as demonstrated by the finding that each projector's 40 Hz phosphene threshold fell outside the 95% CIs for the mean thresholds of both associators and controls. These analyses suggest that atypically low thresholds in projectors are specific to 40 Hz and extend previous TMS results demonstrating visual cortex hyperexcitability in projectors (Terhune et al., submitted for publication), which we propose is related to the recruitment of different visuospatial reference frames in synaesthesia subtypes (Bestmann, et al., 2007). The relationship between oscillatory synchrony at 40 Hz and perceptual binding (Singer, 2001) further suggests that the observed differences may reflect the cortical processes supporting the enhanced visuospatial binding that underlies the perceived spatial co-localization of colour photisms with inducing graphemes in projectors (Ward, et al., 2007).

[2] 0% incidence rates in controls were modified to 6% (corresponding to 1 participant) to allow for the computation of ORs. This results in a marginal underestimation of the actual OR and expansion of its CIs.

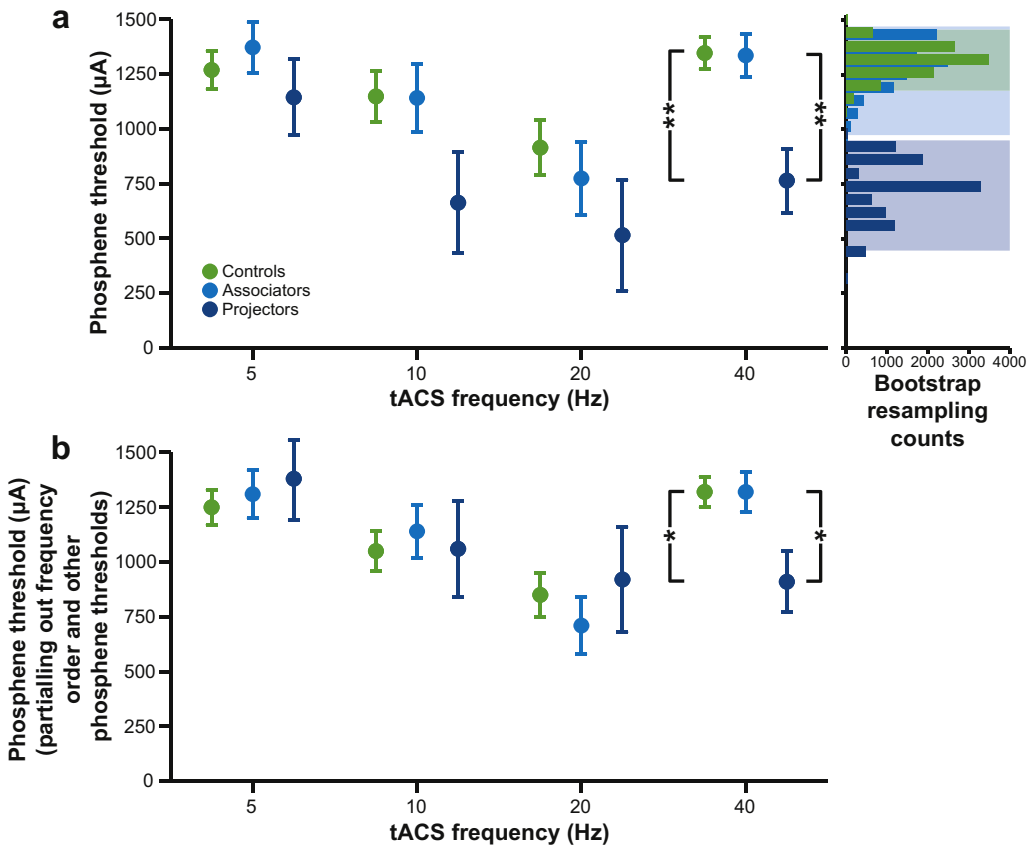

Fig. 1 – Phosphene thresholds as a function of tACS frequency and Group. (a) Uncorrected phosphene thresholds (left) and Bootstrap resampling counts for mean 40 Hz phosphene thresholds (right). (b) Phosphene thresholds corrected for tACS frequency order and the three other respective phosphene thresholds. Error bars represent one standard error of the mean; shaded regions reflect Bootstrap 95% confidence intervals. *$p < .05$, **$p < .01$.

The observed differences at 40 Hz phosphene thresholds are also significant in light of controversies regarding the source of tACS-induced phosphenes (Kanai, et al., 2008; Paulus, 2010; Schutter & Hortensius, 2010). The available evidence suggests that tACS phosphene thresholds reflect an admixture of retinal and visual cortex effects varying on the stimulation frequency, and this limits the interpretation of tACS phosphene thresholds. However, insofar as projectors display neurophysiological and neuroanatomical differences in primary visual cortex (Rouw & Scholte, 2010; Terhune et al., submitted for publication), the observed differences are most likely of cortical origin. Accordingly, the present results provide evidence for a uniquely cortical contribution to individual differences in 40 Hz tACS phosphene thresholds.

In a set of exploratory analyses, we also found that synaesthetes exhibited a greater incidence of coloured phosphenes during 20 Hz tACS than controls (indicating that the odds of experiencing coloured phosphenes are 9 times higher in synaesthetes than in controls). This result is consistent with enhanced colour processing in synaesthetes (Ward, 2013) and may relate to our recent observation that both associators and projectors displayed lower phosphene thresholds than controls (Terhune et al., submitted for publication) because 20 Hz tACS is known to enhance TMS phosphene thresholds (Kanai, Paulus, & Walsh, 2010). Together these results suggest that the previous observation of visual cortex hyperexcitability in synaesthetes (Terhune, et al., 2011) is not driven solely by projectors although further research will be necessary to clarify the relation between TMS and tACS phosphene thresholds.

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