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Neuromodulation of Early Multisensory Interactions in the Visual Cortex

Silvia Convento[1], **Giuseppe Vallar**[1,2], **Chiara Galantini**[1], and **Nadia Bolognini**[1,2]

Abstract

■ Merging information derived from different sensory channels allows the brain to amplify minimal signals to reduce their ambiguity, thereby improving the ability of orienting to, detecting, and identifying environmental events. Although multisensory interactions have been mostly ascribed to the activity of higher-order heteromodal areas, multisensory convergence may arise even in primary sensory-specific areas located very early along the cortical processing stream. In three experiments, we investigated early multisensory interactions in lower-level visual areas, by using a novel approach, based on the coupling of behavioral stimulation with two noninvasive brain stimulation techniques, namely TMS and transcranial direct current stimulation. First, we showed that redundant multisensory stimuli can increase visual cortical excitability, as measured by means of phosphene induction by occipital TMS; such physiological enhancement is followed by a behavioral facilitation through the amplification of signal intensity in sensory-specific visual areas. The more sensory inputs are combined (i.e., trimodal vs. bimodal stimuli), the greater are the benefits on phosphene perception. Second, neuroelectrical activity changes induced by transcranial direct current stimulation in the temporal and in the parietal cortices, but not in the occipital cortex, can further boost the multisensory enhancement of visual cortical excitability, by increasing the auditory and tactile inputs from temporal and parietal regions, respectively, to lower-level visual areas. ■

INTRODUCTION

Events in the surrounding environment provide multiple sources of information that hit our senses concurrently. The brain can efficiently interpret such a rich sensory experience through mechanisms of multisensory integration, that is, by combining information derived from the different senses in a coherent perceptual experience. This mechanism has clear behavioral advantages: Binding together inputs from different sensory channels allows the brain to amplify minimal signals and reduce their ambiguity, thereby improving the ability of detecting and identifying environmental events and orienting toward them (e.g., Calvert, 2001; Stein & Meredith, 1993).

So far, the neural mechanisms subtending multisensory integration have been mostly ascribed to the activity of higher-order heteromodal areas, where sensory modalities converge through feed-forward pathways arising from primary modality-specific projections. However, recent evidence suggests that sensory interactions take place also in primary sensory areas, which are located very early along the cortical processing streams (see, for reviews, e.g., Driver & Noesselt, 2008; Macaluso, 2006; Schroeder & Foxe, 2005).

In humans, strong support for the involvement of lower-level sensory areas in multisensory processing has been provided by work investigating the cross-modal modulation of phosphene perception (Bolognini & Maravita, 2007, 2011; Bolognini, Senna, Maravita, Pascual-Leone, & Merabet, 2010; Romei, Murray, Cappe, & Thut, 2009; Ramos-Estebanez et al., 2007; Romei, Murray, Merabet, & Thut, 2007). Basically, the application of single-pulse TMS (sTMS) to the occipital areas can elicit phosphenes, which consist of bright spots of light appearing in specific regions of the visual field and reflect the retinotopic organization of human visual cortex (McKeefry, Gouws, Burton, & Morland, 2009; Fernandez et al., 2002). Phosphenes are generated by TMS of virtually all early visual areas, including the striate cortex (V1), the extrastriate areas (V2/V3), and cortico-cortical tracts projecting from V2/V3 back to V1 (Kammer, Puls, Erb, & Grodd, 2005; Kammer, Puls, Strasburger, Hill, & Wichmann, 2005). Because the sTMS output threshold needed to generate phosphenes provides a direct measure of visual cortical excitability (Kammer, Puls, Erb, et al., 2005), the study of cross-modal interactions at the level of phosphene perception can provide a more direct measure of early visual cortical responses to nonvisual stimuli (for a review, see Bolognini & Maravita, 2011). By using this approach, it has been shown that a peripheral somatosensory or auditory stimulus can modify the excitability of the visual cortex in such a way that

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phosphene perception can be induced using a lower sTMS intensity. Such cross-modal modulation of phosphenes follows strict spatial and temporal constraints, and it becomes behaviorally relevant especially under conditions of subthreshold sTMS intensity, suggesting that this type of cross-modal interactions depends on the relative physiological salience of visual information (Bolognini, Senna, et al., 2010; Romei et al., 2007, 2009; Bolognini & Maravita, 2007; Ramos-Estebanez et al., 2007).

The neural substrate of the cross-modal enhancement of phosphene perception has not yet been established. It might be that the auditory or tactile input is transmitted to low-level visual areas through direct, feed-forward projections from primary or associative auditory/somatosensory cortices (Cappe, Thut, Romei, & Murray, 2009; Cappe & Barone, 2005; Schroeder & Foxe, 2005; Rockland & Ojima, 2003; Falchier, Clavagnier, Barone, & Kennedy, 2002). An alternative account posits an indirect pathway, in which feed-forward auditory/tactile inputs reach areas of multisensory convergence (e.g., the superior temporal polysensory region or the posterior parietal cortex [PPC]) and are then transmitted via feedback connections to earlier unisensory visual areas (e.g., Driver & Noesselt, 2008; Stein & Stanford, 2008; Macaluso, 2006; Calvert, 2001; Giard & Peronnet, 1999).

Understanding which conditions can increase our ability to integrate inputs from different sensory modalities and the mechanisms supporting this phenomenon is a question of central interest: not only to better characterize multisensory interactions, but also to uncover ways to enhance multisensory processing in the human brain. In this perspective, we have conducted a first experiment aimed at comparing the effects of different combinations of bimodal (i.e., an auditory or tactile stimulus combined with the occipital sTMS pulse) and trimodal (i.e., an auditory-tactile stimulation combined with the occipital sTMS pulse) stimuli on subthreshold phosphene perception. At variance with previous studies, we examined whether cross-modal stimuli could alter the reported brightness of phosphenes, over and above being able of increasing their detectability. Then, we explored the possibility of enhancing these lower-level cross-modal interactions through the noninvasive modulation of cortical excitability of areas putatively mediating cross-modal influences on phosphene perception. To this aim, we took advantage of transcranial direct current stimulation (tDCS).

tDCS is a noninvasive brain stimulation technique that involves the delivery of weak, constant direct current via electrodes placed on the scalp, in correspondence with target cortical areas. tDCS can up- or down-regulate neural activity in the stimulated regions in a polarity-dependent way, with anodal stimulation enhancing cortical excitability of the underlying cortical areas and cathodal stimulation decreasing it (Brunoni et al., 2012; Nitsche et al., 2008; Nitsche & Paulus, 2000, 2001). The mechanisms of action of tDCS involve the modulation of neuronal signalling by influencing the permeability of ion channels or shifting

electrical gradients, which, in turn, modulate the resting membrane threshold (Ardolino, Bossi, Barbieri, & Priori, 2005). Chemical neurotransmission, either pre- or postsynaptic, may also play a role in tDCS effects (Liebetanz, Nitsche, Tergau, & Paulus, 2002). In humans, tDCS has been successfully used to facilitate modality-specific perception within the visual and somatosensory modalities (for recent reviews, see Vallar & Bolognini, 2011; Utz, Dimova, Oppenlander, & Kerkhoff, 2010; Zimerman & Hummel, 2010) and also to affect plasticity (Berlucchi, 2011; Kolb, Teskey, & Gibb, 2010). Up to now, fewer studies have used this technique to modulate multisensory interactions (Mancini, Bolognini, Haggard, & Vallar, 2012; Bolognini, Rossetti, Casati, Mancini, & Vallar, 2011; Bolognini, Fregni, Casati, Olgiati, & Vallar, 2010; Bolognini, Olgiati, Rosetti, & Maravita, 2010).

Here, we used tDCS to increase auditory and tactile influences on visual cortical excitability, as measured by TMS-induced phosphenes. To this aim, anodal tDCS was applied over the occipital, temporal, or parietal cortices. The choice of these areas was guided by the following considerations. The occipital cortex is the site of phosphene induction, and previous studies have shown that anodal tDCS over this area (including V1) improves the perception of phosphenes (Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004; Antal, Kincses, Nitsche, & Paulus, 2003a, 2003b). Hence, anodal tDCS of the occipital cortex could facilitate phosphene perception, regardless of the presence of cross-modal stimuli. By contrast, the stimulation of the temporal and of the parietal cortices could be able to boost specifically the cross-modal effects of sounds and touches on phosphene perception through the modulation of feedback influences from these heteromodal areas to visual areas (e.g., Driver & Noesselt, 2008; Macaluso, 2006) and by directly facilitating multisensory interactions in the temporal and parietal cortices (e.g., Stein & Stanford, 2008). In both circumstances, the expected effect should be a selective modulation of the facilitation of phosphene perception brought about by the cross-modal stimuli.

EXPERIMENT 1

Methods

Participants

Eight neurologically healthy volunteers took part in Experiment 1 (three men, mean age = 23.6 years, range = 19–34 years). Given the subjective nature of phosphene perception, only participants who reported reliable phosphenes were enrolled in the study (Fernandez et al., 2002). Using this criterion, 8 of the 12 screened participants underwent the experimental session.

All participants had normal hearing and normal or corrected-to-normal vision. None of the participants had neurological, psychiatric, or other relevant medical problems nor any contraindication to TMS or tDCS (Poreisz,

Boros, Antal, & Paulus, 2007). Accepted recommendations for the use and safety of TMS and tDCS were applied (Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Nitsche et al., 2003).

All participants were naive to the experimental procedure and to the purpose of the study. They gave informed consent before being enrolled in the study, which was carried out according to the guidelines of the ethical committee of the University of Milano-Bicocca and in accordance with the ethical standards of the Declaration of Helsinki (British Medical Journal, 1991, Vol. 302, p. 1194).

Training Session

An initial training before the experimental session was carried out to determine the optimal site of occipital stimulation for inducing reliable phosphenes. To this aim, a functional mapping procedure for phosphene induction was used (Fernandez et al., 2002); this type of protocol has been previously used to probe excitability of the visual cortex (Romei, Gross, & Thut, 2012; Bolognini, Senna, et al., 2010; Romei et al., 2007, 2009; Silvanto, Muggleton, Lavie, & Walsh, 2009; Bolognini & Maravita, 2007) based on findings of phosphenes to originate from the striate cortex (V1; Sparing et al., 2002; Cowey & Walsh, 2000; Corthout, Uttl, Walsh, Hallett, & Cowey, 1999; Amassian et al., 1994; Meyer, Diehl, Steinmetz, Britton, & Benecke, 1991) and extrastriate areas V2/V3 (Kammer, Puls, Erb, et al., 2005; Cowey & Walsh, 2000; Potts et al., 1998).

Participants sat in an armchair, wearing a specially designed blindfold to prevent any light perception and an elastic swimming cap to mark the stimulation sites. All participants adapted to darkness for a period of 10 min to stabilize the level of excitability of the visual cortex and to facilitate phosphene perception (Boroojerdi et al., 2000). Single-pulse TMS (sTMS) was delivered over the occipital cortex using a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim Company, Whitland, UK), connected with a 70-mm figure-eight-shaped coil (maximum field strength, 2.2 T). We first determined in each participant the optimal scalp site from which the occipital sTMS pulse induced a phosphene. Then, we established the phosphene threshold (i.e., PT), that is, the minimum intensity of the sTMS needed to evoke a phosphene on 50% of the trials (i.e., 5 of 10 trials). The mean PT was of 66% ($SD =$ 8%) of the maximum stimulator output in Experiment 1.

The TMS coil position was then kept constant for each participant across the different experimental sessions. To this aim, coil location was marked on the elastic swimming cap placed over the head of the participants. In each experiment, only the occipital cortex of the right hemisphere was stimulated, with phosphenes being induced in the left visual hemifield. The optimal stimulation site across participants was localized on average 2.6 cm above the inion ($SD = 1$ cm) and 2 cm ($SD = 0.6$ cm) to the right of the midline. During the experimental session, participants remained blindfolded and sTMS was applied at the previously determined optimal scalp location for phosphene induction at the individual PT.

Noteworthy, the training session also allowed us to monitor the reliability of phosphene perception over time. The optimal TMS coil position over the occipital pole, as well as the shape, size, and position of the perceived phosphenes, remained constant over repeated trials in each participant.

Stimuli and Procedure

Auditory stimuli consisted of a 250-msec (55–75 dB) looming sound (Romei et al., 2009) delivered from an external loudspeaker, placed in the same visual field quadrant, where phosphenes appeared (Bolognini, Senna, et al., 2010). Tactile stimulation was delivered using a custom-made electromagnetic solenoid, attached to the participants' left index finger, releasing 15-msec suprathreshold vibrations (consisting of two 5 msec on phases, with one 5 msec off phases interval); participants were required to place their left hand in the same visual field quadrant of phosphenes, where the loudspeaker was also placed (see Bolognini & Maravita, 2007). Hence, both the auditory and the tactile stimulus were presented at the same spatial location as the perceived phosphene, with respect to both the vertical and the horizontal meridians, in accordance with previous reports from our laboratory, showing that cross-modal influences on phosphene perception are spatially specific (Bolognini, Senna, et al., 2010; Bolognini & Maravita, 2007).

During the experiment, the following stimulus conditions were presented: the unimodal condition, with the occipital sTMS delivered alone, and the cross-modal conditions. The latter conditions comprised either bimodal stimuli, that is, occipital sTMS paired with the auditory stimulus or the tactile stimulus, or trimodal stimuli, that is, occipital sTMS paired with both the auditory and the tactile stimuli. The auditory stimulus always preceded the sTMS pulse by 40 msec, whereas the tactile stimulus preceded the sTMS pulse by 60 msec. These ISIs were chosen in line with previous work, which has elucidated the temporal profile of cross-modal interactions in the visual cortex, by using phosphene induction by sTMS (Bolognini, Senna, et al., 2010; Romei et al., 2009; Ramos-Estebanez et al., 2007). Catch trials, consisting of the presentation of tactile, auditory, or audiotactile stimuli without sTMS, were also presented.

The experiment comprised two blocks, each including 60 trials: 12 unimodal, 12 tactile, 12 auditory, 12 audiotactile, and 12 catch trials, namely with no sTMS. Each block lasted approximately 7 min. Within each block, the different stimuli were presented in a random order with an intertrial interval between 4 and 5 sec to avoid any possible carryover effect of TMS on visual cortical excitability (Walsh & Pascual-Leone, 2003). Stimulus presentation and responses recording were under computer control (E-prime Software, Psychology Software Tools).

Participants were instructed to press on the keyboard of a PC the button "1" with the index finger of the right hand when they saw a phosphene and to press the button "2" with the middle finger of the right hand to indicate that they did not see any phosphenes. The percentage of phosphene detection score was the ratio between the number of reported phosphenes and the number of trials. On each trial, if a phosphene was detected, participants were also asked to indicate its level of brightness on a 5-point scale (1 = *faint gleam percept*, 5 = *very bright phosphene*); the participants' rating was scored manually by the experimenter. Before running the analyses, the percentage of phosphene detection was converted to the arcsin of the square root of the raw values to normalize the data distribution (Zubin, 1935).

Statistical Analyses

Statistical analyses were performed using the Statistica Software (Statsoft, Version 6.0). In Experiment 1, the mean rate of phosphene detection (percentage of phosphene = number of detections/number of trials for each stimulus condition), and their mean brightness in the different conditions (unimodal vs. crossmodal) were analysed via one-way repeated-measures ANOVA with Condition as a within-subject factor: the unimodal condition, that is, sTMS alone, and the cross-modal conditions, that is, sTMS combined with sound, sTMS combined with touch, and sTMS combined with sound plus touch. Whenever necessary, post hoc multiple comparisons were performed by the Student–Newman–Keuls test. The partial Eta square ($p\eta^2$), which measures the proportion of the total variance that is attributable to a main factor or to an interaction (Cohen, 1973), was calculated.

Results

As shown in Figure 1, phosphene detections and their level of brightness increased in cross-modal conditions, with the highest detection and brightness in the trimodal audiotactile condition. The ANOVA showed a significant effect of Condition, $F(3, 21) = 25.23, p < .001, p\eta^2 = .78$: An increase of phosphene detection emerged in every cross-modal condition, as compared with the unimodal condition (sTMS alone = 39% vs. sTMS combined with sound = 49%, $p < .05$; sTMS combined with touch = 67%, $p < .001$; sTMS combined with sound and touch = 77%, $p < .001$). Across the cross-modal conditions, significant differences were found between the effect of sound and touch ($p < .01$), but it was the audiotactile stimulation that induced the greatest increase ($p < .05$, for all comparisons).

The analysis of phosphenes' brightness showed again a significant effect of Condition, $F(3, 21) = 5.67, p < .01, p\eta^2 = .44$: An increase of phosphenes' brightness emerged when sTMS was paired with touch (rating = 1.22, $p < .05$),
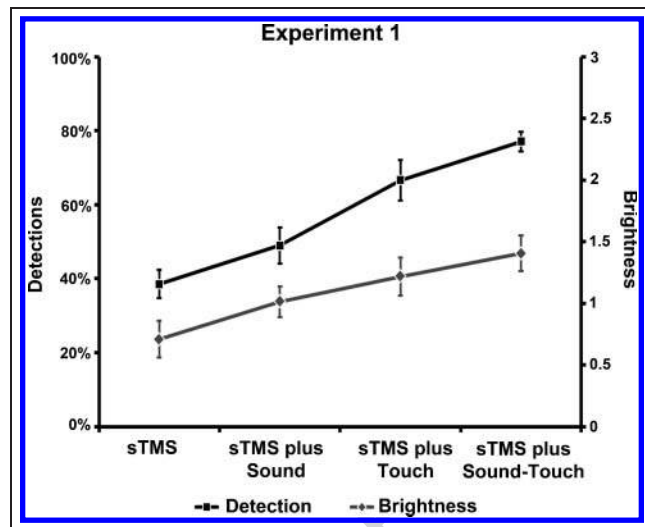

Figure 1. Experiment 1. Mean percentage ($\pm SEM$) of perceived phosphenes (black line) and their perceived brightness (gray line) by sensory condition (Unimodal, sTMS; Cross-modal: sTMS plus Sound, plus Touch, plus Sound and Touch).

or with an audiotactile stimulus (1.41, $p < .01$), but not when it was combined with sound (0.93, $p = .1$), as compared with the unimodal stimulus (i.e., sTMS alone). The effects of auditory and tactile stimuli were not significantly different ($p = .1$).

In the entire experiment, participants committed only a total of 2% false alarms (i.e., less than 3 false alarms of 60 trials), with no differences among conditions; these data were not further analyzed.

EXPERIMENT 2

Participants

Eight participants were tested in Experiment 2 (two men, mean age = 23.8 years, range = 19–34 years); six of them were tested also in Experiment 1. The same general procedure of Experiment 1 was adopted, with the difference that the task was given in four different sessions, after the delivery of tDCS. Moreover, participants were now required to detect phosphenes only, without judging their brightness. The mean PT was of 65.5% (SD = 8%) of maximum stimulator output in Experiment 2.

tDCS

tDCS was transferred by a saline-soaked pair of surface sponge electrodes (5×5 cm, 25 cm^2) and delivered by a specially developed, battery-driven, constant current stimulator (Eldith Ltd., Germany, www.eldith.de/products/stimulator). The device can be set to deliver either the active or the sham stimulation, thus keeping both the participant and the experimenter masked (Gandiga, Hummel, & Cohen, 2006). A constant current of 2 mA intensity

was applied for 10 min before the task (fade-in/fade-out phases = 10 sec), in compliance with safety guidelines (Poreisz et al., 2007; Nitsche et al., 2003).

During stimulation of the temporal cortex, the active electrode was placed over T4: the regions beneath T4 are BA 22 and BA 42 (Talairach & Tournoux, 1988) corresponding mostly to the superior temporal gyrus (STG) and to a less extent to the middle temporal gyrus (Herwig, Satrapi, & Schonfeldt-Lecuona, 2003). For parietal stimulation, the active electrode was placed over P4, a location that overlies the PPC, close to the intraparietal sulcus (Herwig et al., 2003). For both these stimulation sites, the reference electrode was placed over the contralateral supraorbital area, in line with previous experimental work, which suggests the effectiveness of this montage (Bolognini et al., 2011; Nitsche et al., 2008).

For occipital stimulation, the active anode electrode was placed over O2, a site overlying the primary visual cortices, whereas the reference electrode was placed over Cz, in the light of previous studies, which have proved this electrode arrangement to be effective to achieve current-driven cerebral excitability changes in the occipital cortex (Bolognini et al., 2011; Antal et al., 2004).

Each participant underwent four different tDCS sessions randomized across participants: three sessions during which active tDCS was applied to one of three cortical areas of the right hemisphere (i.e., the same hemisphere of the occipital sTMS for phosphene induction) and one session with the delivery of sham (i.e., placebo) tDCS.

For sham tDCS, the electrodes were arranged over one of the target areas (the electrodes montage was randomized across participants; Bolognini et al., 2011), and the current was ramped up over 30 sec but was then immediately switched off. In this way, participants could perceive the initial itching sensation typical of tDCS, but no effective modulation of cortical excitability was induced, allowing their successful blinding for the real versus sham stimulation (Gandiga et al., 2006). Each tDCS session was separated by the following one by a period of at least 60 min to avoid any after-effect induced by the stimulation (Boggio, Zaghi, & Fregni, 2009; Ragert, Vandermeeren, Camus, & Cohen, 2008; Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008; Fregni et al., 2005).

The blindfold mask was removed between tDCS sessions to prevent systematic drifts in PT by carryover effect due to long-lasting adaptation to darkness (Pitskel, Merabet, Ramos-Estebanez, Kauffman, & Pascual-Leone, 2007).

Statistical Analyses

In Experiment 2, the rate of phosphene detection was analyzed via a two-way repeated-measures ANOVA, with tDCS Stimulation (Sham tDCS, Occipital tDCS, Parietal tDCS, and Temporal tDCS) and Condition (same as above) as within-subject factors.

Results

Figure 2 shows the effects of tDCS on phosphene detection for every sensory condition and each stimulation site. In line with Experiment 1, cross-modal stimuli facilitated phosphene perception. Crucially, anodal tDCS affected phosphene detection in a selective manner. Indeed, the ANOVA showed a significant main effect of Condition, $F(3, 21) = 4.05$, $p < .05$, $p\eta^2 = .37$: An increase of phosphene detection was found in every cross-modal condition, as compared with the unimodal ones ($p < .05$, for every comparison). The main effect of tDCS Stimulation was not significant, $F(3, 21) = .34$, $p = .8$, $p\eta^2 = .05$. The tDCS Stimulation by Condition interaction was significant, $F(9, 63) = 2.35$, $p < .05$, $p\eta^2 = .26$.

We explored this interaction by four one-way ANOVAs, one for each sensory condition (sTMS, sTMS plus sound,

Figure 2. Experiment 2. Mean percentage (±SEM) of perceived phosphenes by tDCS session (Sham tDCS, dark gray bars; Occipital tDCS, light gray bars; Temporal tDCS, white bars; Parietal tDCS, black bars) for the unimodal (sTMS) and cross-modal (sTMS plus Sound, plus Touch, plus sound and touch) conditions.
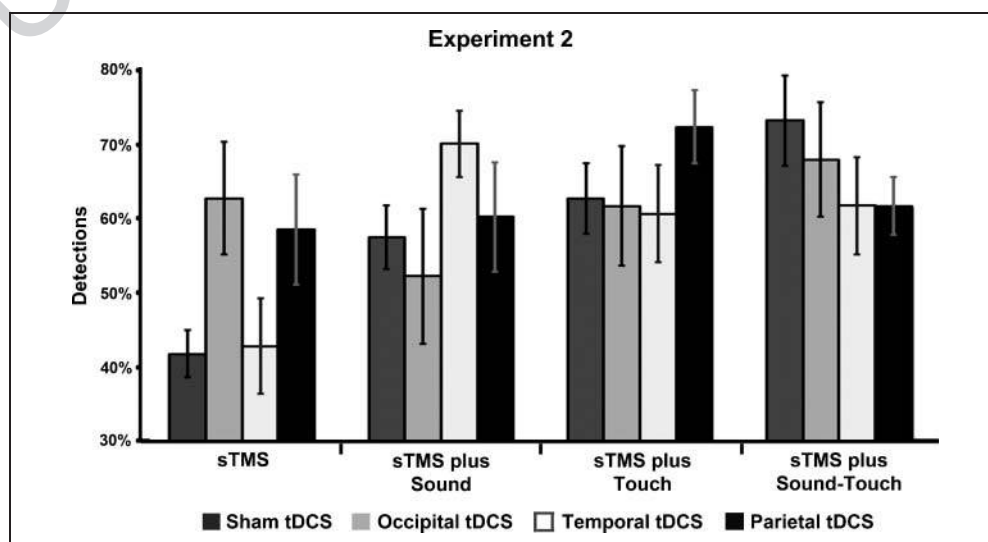
plus touch, plus sound and touch). In the unimodal condition (i.e., sTMS alone), a significant difference was found, $F(3, 21) = 6.05$, $p < .01$, $p\eta^2 = .46$: As compared with Sham tDCS (42%), an increment of phosphene detection occurred after Occipital tDCS (63%, $p < .01$) and after Parietal tDCS (58%, $p < .05$), but not after Temporal tDCS (43%, $p = .9$). Occipital tDCS and Parietal tDCS did not differ from each other ($p = .4$), but they both differed from Temporal tDCS ($p < .05$). For the cross-modal conditions, the ANOVA did not reveal significant differences for sTMS combined with sound, $F(3, 21) = 1.81$, $p = .2$, $p\eta^2 = .2$, with touch, $F(3, 21) = .79$, $p = .5$, $p\eta^2 = .1$, and with sound plus touch, $F(3, 21) = .75$, $p = .5$, $p\eta^2 = .1$.

We also conducted four one-way ANOVAs, one for each tDCS Stimulation (Sham, Occipital, Temporal, and Parietal tDCS). Significant differences were found for Sham tDCS, $F(3, 21) = 7.39$, $p < .01$, $p\eta^2 = .5$, and for Temporal tDCS, $F(3, 21) = 3.85$, $p < .02$, $p\eta^2 = .35$: In both sessions, phosphene detection increased in every cross-modal condition, as compared with the unimodal condition ($p < .05$ for all comparisons). No differences were found for Occipital, $F(3, 21) = 1.68$, $p = .2$, $p\eta^2 = .19$), and Parietal tDCS, $F(3, 21) = 1.04$, $p = .4$, $p\eta^2 = .17$.

On catch trials, in each tDCS session, participants committed less than 3% false alarms, with no differences among conditions; these data were not further analyzed.

To summarize the results of Experiments 1 and 2, phosphene perception improved when subthreshold occipital sTMS was coupled with an auditory stimulus, a tactile stimulus, or both, presented at the expected retinotopic location of the phosphene percept (Experiment 1). Anodal tDCS of the occipital and parietal cortices increased phosphene detection only in the unimodal condition; the facilitatory effect induced by Occipital tDCS was comparable with that induced by cross-modal stimuli (i.e., Experiment 2). Conversely, tDCS did not affect phosphene perception in cross-modal conditions; however, there is a tendency for tDCS-specific facilitatory effects with respect to the type of stimulus. It should be noted that the cross-modal stimulation per se induced a significant increment of phosphene perception, in both experiments; hence, a "ceiling effect" might have precluded any further enhancement by tDCS in the cross-modal conditions (Bolognini, Senna, et al., 2010). To address this issue, we performed two additional experiments, with the same procedure of Experiment 2, but setting the intensity of sTMS based on the subjective PT in the cross-modal conditions, rather than in the unimodal condition.

EXPERIMENT 3

Participants

Twenty-four participants (three men, mean age = 23.7 years, range = 19–34 years) participated in Experiments 3; eight of them had taken part also in Experiment 2.

Stimuli and Procedure, tDCS, and Statistical Analyses

Stimuli, procedures, and statistical analyses were similar to those of Experiment 2. Experiment 3 differed from Experiment 2 in that PT was now determined considering the minimum intensity of sTMS needed to evoke a phosphene on 50% of trials in the cross-modal condition, rather than in the unimodal one, as in the previous experiments. The PT in the cross-modal conditions was determined separately for the auditory and the tactile stimulations. Consequently, we ran two different experiments: 12 participants took part in Experiment 3-A, in which the PT was determined for the cross-modal condition with sound paired to sTMS; 12 participants took part in Experiment 3-B, in which the PT was determined for the cross-modal condition with touch paired to sTMS. The mean PT under cross-modal stimulation was of 63% (SD = 5%) of maximum stimulator output in Experiment 3-A and of 61% (SD = 4%) in Experiment 3-B. Noteworthy, for those participants who took part also in Experiment 2, the PT in Experiments 3 was significantly lower (59%) as compared with that in Experiment 2 (65%, $t = 2.3$, $p < .05$).

During the two experiments, only the cross-modal stimulus was presented: namely the cross-modal condition with sound paired to sTMS (Experiment 3-A) and the cross-modal condition with touch paired to sTMS (Experiment 3-B). Each experiment included 12 stimulation trials and 12 catch trials, for a total duration of about 5 min.

Each participant underwent four tDCS sessions (Sham, Occipital, Parietal, and Temporal tDCS), randomized across participants.

For each experiment, the rate of phosphene detection (see above) was submitted to a one-way repeated-measures ANOVA, with four conditions: Sham, Occipital, temporal, and Parietal tDCS.

Results

The effects of tDCS on cross-modal subthreshold phosphenes are shown in Figure 3. The rate of cross-modal phosphenes increased after both Parietal and Temporal tDCS, but the effect was specific with respect to the cross-modal stimulus. In Experiment 3-A (sound paired with sTMS), the ANOVA showed a significant difference among conditions, $F(3, 33) = 3.28$, $p < .05$, $p\eta^2 = .22$, with an increase of cross-modal phosphenes only after Temporal tDCS (66%, $p < .05$ for all comparisons), as compared with Sham tDCS (48%), Occipital tDCS (53%), and Parietal tDCS (52%). Occipital and Parietal tDCS did not differ from Sham tDCS ($p = .8$), and they also did not differ from each other ($p = .9$). Also in Experiment 3-B (touch paired with sTMS), the ANOVA showed a significant difference among conditions, $F(3, 33) = 3.36$, $p < .05$, $p\eta^2 = .23$, with an increase of phosphene perception only after Parietal tDCS (77%, $p < .05$ for all comparisons), as compared with Sham tDCS (57%), Occipital tDCS (55%),
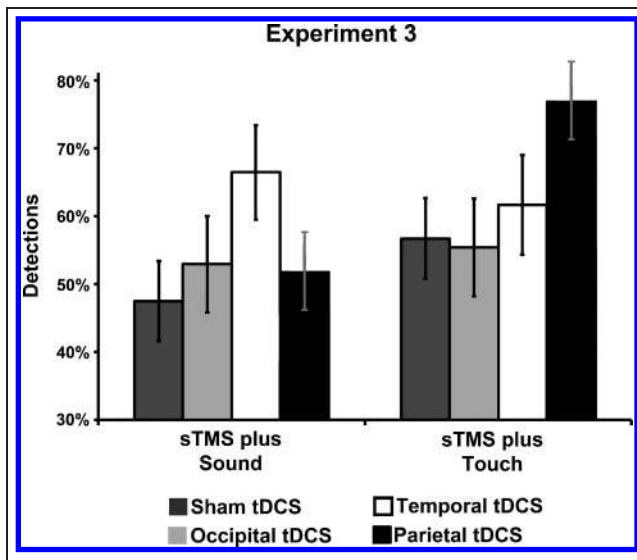
Figure 3. Experiment 3. Mean percentage (±*SEM*) of perceived phosphenes by tDCS session (Sham tDCS, dark gray bars; Occipital tDCS, light gray bars; Temporal tDCS, white bars; Parietal tDCS, black bars), for the two cross-modal conditions: sTMS plus Sound in Experiment 3-A, and sTMS plus Touch, in Experiment 3-B.

and Temporal tDCS (62%). Occipital tDCS and Temporal tDCS differed neither from Sham tDCS ($p = .9$) nor from each other ($p = .6$).

In both experiments, on catch trials, the rate of false alarms was about 3% in each tDCS session, without differences among conditions; these data were not further analyzed.

To sum up, we found a selective modulation of cross-modal phosphenes after brain polarization of the parietal and the temporal cortices: temporal tDCS increased phosphene perception when the cross-modal stimulation was auditory (Experiment 3-A), whereas it was parietal tDCS to increase phosphene perception when the cross-modal stimulus was tactile (Experiment 3-B).

DISCUSSION

The results of this study provide clear evidence that cross-modal interactions can affect processing in low-level visual areas, thereby facilitating phosphene perception. As compared with previous work on this phenomenon (Bolognini & Maravita, 2007, 2011; Bolognini, Senna, et al., 2010; Romei et al., 2007, 2009; Ramos-Estebanez et al., 2007), the main novel finding is that brain polarization can facilitate phosphene perception in a specific manner, being dependent on the area targeted by tDCS and the type of the sensory input to be processed (unimodal vs. crossmodal).

The first experiment further featured the cross-modal influences on phosphenes perception by comparing the effects of auditory, tactile, and audiotactile stimuli on the

participants' ability to detect phosphenes and to judge their brightness. We observed a significant enhancement of subthreshold phosphenes in every cross-modal condition. This finding is in line with previous evidence showing that the stimulation of the somatosensory (Bolognini & Maravita, 2007; Ramos-Estebanez et al., 2007) and auditory (Romei et al., 2007, 2009, 2012; Bolognini, Senna, et al., 2010) modalities can boost visual cortical excitability, as measured by phosphenes induction. There is evidence, based on a psychophysical approach, that the cross-modal modulation of phosphene perception is associated to changes in perceptual sensitivity, rather than in the response criterion (Bolognini & Maravita, 2007), and it is dependent on strict temporal and spatial constraints (Bolognini, Senna, et al., 2010; Romei et al., 2007, 2009; Bolognini & Maravita, 2007; Ramos-Estebanez et al., 2007). Moreover, the short onset of effects of looming sounds (80 msec) on phosphene perception, which is below psychophysical discrimination threshold, strongly suggests a mechanism that allows for a crossmodally driven modulation of the visual cortex at preperceptual processing stages (Romei et al., 2009). Finally, Romei and coworkers (2012) have recently shown that a salient sound can phase-align oscillatory alpha activity over occipital areas (typically around 8–14 Hz), with direct consequences on phosphene perception. Taken together, these pieces of evidence concur to indicate that the cross-modal enhancement of phosphene perception reflects the consequence of cross-modal interactions on early stages of visual processing, rather than a strategic sensory encoding process, or a more general warning effect.

Our study further shows that delivering a trimodal stimulation, occipital sTMS with an audiotactile stimulus, maximizes the cross-modal benefit, further enhancing the likelihood of detecting a phosphene. This finding is in agreement with evidence related to the redundant signal effect for cross-modal stimuli (Diederich & Colonius, 2004; Todd, 1912), showing that a trimodal (visual–auditory–tactile) stimulus combination yields reduced latencies not only to unimodal stimuli but also to combinations of bimodal stimuli. The effect of adding a third-modality stimulus may be related to a coactivation mechanism (Miller, 1982, 1986) that may combine inputs from the different modalities to jointly trigger a response. This, in turn, suggests a possible contribution from trimodal multisensory neurons, sensitive to simultaneous visual, auditory, and somatosensory stimulation (Stein & Meredith, 1993).

Moreover, we observed that providing redundant auditory and/or tactile information not only facilitates the detection of subthreshold phosphenes, but it also increases their level of brightness, with the maximal enhancement occurring again for trimodal stimuli. Previous evidence indicates that extraneous cues from one modality can substantially alter perceptual judgments in another modality. In particular, Stein, London, Wilkinson, and Price (1996) have demonstrated an enhancement of the perceived intensity of a visual target by an auditory cue; this

effect was most pronounced at the lowest intensities of the visual stimulus (Stein et al., 1996). Because judgments of the intensity of a stimulus are assumed to depend on the population of neurons activated along a modality-specific pathway and the frequency with which they discharge (Orban, 1984; Barlow, Snodderly, & Swadlow, 1978; Papaioannou & White, 1972), the physiological correlates of increased phosphene brightness may likely represent a cross-modal amplification of signal intensity in the visual cortex. In line with this proposal, a recent study shows that auditory spatial cueing can influence visual contrast appearance by enlarging an early neural response in the visual cortex contralateral to the cued target (Stormer, McDonald, & Hillyard, 2009). Hence, cross-modal interactions can alter the probability of detecting visual stimuli, likely by amplifying the apparent intensity of the signal in modality-specific visual areas.

Our subsequent experiments show that the depolarization of cortical tissue by anodal tDCS can facilitate phosphene perception in both unisensory and cross-modal conditions, but in a pretty selective manner. First, anodal tDCS of the occipital cortex enhances phosphene detection, when phosphenes are probed by sTMS given alone (unimodal condition). This result is in agreement with previous evidence concerning effects of anodal tDCS on the excitability of the visual cortex, as measured by either phosphene induction (Antal et al., 2003a, 2003b), and the modulation of visual-evoked potentials (Antal et al., 2004). Here, the novel result is that the benefit induced by occipital tDCS on phosphene perception becomes comparable to that induced by cross-modal stimuli. This finding nicely demonstrates that we can effectively up-regulate visual cortical excitability either by polarizing it through the application of low currents to the occipital pole or by presenting an external, nonvisual stimulus.

Another new finding from Experiment 2 is that an improvement of unimodal phosphenes emerges also after stimulation of the PPC. Indeed, occipital and parietal tDCS yield a similar facilitation of phosphene perception under sensory-specific visual conditions. The involvement of the parietal cortex is not entirely unexpected, as phosphene perception is not a strictly local phenomenon; rather, it involves an extensive recurrent processing within a wide array of posterior areas (Taylor, Walsh, & Eimer, 2010). Additionally, the PPC exerts perceptually significant top–down influences on the primary visual cortex, which, in turn, can affect visual processing (Corbetta, Patel, & Shulman, 2008). In broad agreement with our findings, there is evidence that PT can be reduced if TMS is first applied to the PPC unilaterally (Silvanto et al., 2009; but see also Marzi, Mancini, & Savazzi, 2009). Conversely, TMS over the right, but not the left, PPC (at the level of the intraparietal sulcus) increases activity (i.e., the BOLD signal) in the occipital cortex, in line with a right-hemisphere predominance for frontoparietal causal influences upon processing in the human visual cortex (Ruff et al., 2009). Interestingly, the effects of right-parietal TMS

occur especially when no visual stimuli are presented, so that the visual cortex is not preactivated by an external input (Ruff et al., 2009), as in the case of phosphenes perception. Therefore, one may speculate that the enhancement of unimodal phosphenes by anodal tDCS of the right PPC may be because of an increase of parietal influences upon processing in the visual cortex, which, in turn, may induce a perceptual–attentional facilitation of visual processing.

Furthermore, subthreshold phosphene perception in cross-modal conditions can be selectively facilitated by tDCS of the temporal and parietal cortices: in particular, it is temporal tDCS to increase phosphene detection when the paired stimulus is auditory and parietal tDCS when the paired stimulus is tactile (Experiments 3-A and 3-B, respectively).

Within the PPC and the superior temporal cortex, there are heteromodal regions (namely, the inferior parietal lobule and the STG), where inputs from the different senses converge and integrate (Driver & Noesselt, 2008; Stein & Stanford, 2008; Macaluso, 2006; Teder-Sälejärvi, Di Russo, McDonald, & Hillyard, 2005; Andersen, 1997). Posterior parietal areas are mainly involved in updating the relative position of extrapersonal visual and somatosensory bodily stimuli for visuotactile interactions, which are typical of the peripersonal space (Vallar & Maravita, 2009; Bolognini & Maravita, 2007; Macaluso, 2006; Maravita, Spence, & Driver, 2003). The STG is primarily involved in audiovisual integration of both speech and nonspeech stimuli (Bolognini et al., 2011; Beauchamp, Argall, Bodurka, Duyn, & Martin, 2004; Calvert, 2001), as well as in the multisensory enhancement of detection sensitivity for low-contrast visual stimuli by co-occurring sounds (Noesselt et al., 2010; Beauchamp et al., 2004; Calvert, 2001).

Behaviorally, there is also a large body of evidence showing that cross-modal links in spatial attention can facilitate modality-specific perceptual processing (Spence & Driver, 2004). For instance, orienting attention involuntarily to the location of a sudden sound improves perception of subsequent visual stimuli that appear nearby (e.g., Bolognini, Olgiati, et al., 2010; Bolognini, Frassinetti, Serino, & Làdavas, 2005; Frassinetti, Bolognini, & Làdavas, 2002). Cross-modal orienting of spatial attention toward unisensory and cross-modal visual-tactile events are subtended by discrete subregions of the parietal lobe (Chambers, Stokes, & Mattingley, 2004; Macaluso, Frith, & Driver, 2000), which send feedback projections to occipital areas, whereas enhanced visual perception by spatially nonpredictive auditory cues results from neural feedback from the superior temporal cortex to the visual cortex (McDonald, Teder-Salejarvi, Di Russo, & Hillyard, 2003). Hence, anodal tDCS of the STG and the PPC might have targeted such cross-modal (by sound and touch, respectively) spatial mechanisms, facilitating a cross-modal shift of attention toward the sector of the visual field where phosphenes had appeared.

However, considering the low spatial resolution of tDCS (Brunoni et al., 2012; Vallar & Bolognini, 2011; Nitsche et al., 2008)—although computer-based modeling studies indicate that direct functional effects of tDCS are restricted to the area under the active electrode (Wagner et al., 2007; Miranda, Lomarev, & Hallett, 2006)—it is possible that the parietal and temporal stimulation may have affected activity also in primary somatosensory and auditory areas, respectively, hence modulating cross-modal interactions mediated by direct, feed-forward connections between these sensory regions and the primary visual areas where phosphenes originate.

On the other hand, sub-threshold phosphene perception in cross-modal conditions was not modulated by occipital tDCS. In a previous study, we have shown that anodal tDCS of the occipital cortex decreases the sound-induced flash illusion, an illusory multisensory effect associated with increased activation of V1 (Watkins, Shams, Tanaka, Haynes, & Rees, 2006), whereas anodal tDCS of the superior temporal cortex increases the illusory effects (Bolognini et al., 2011). Hence, for modulating the cross-modal influences on visual cortical excitability, the best approach seems to be the enhancement of cortical excitability in areas where the cross-modal influences originate (namely, parietal and temporal areas), rather than in areas where these influences terminate (namely, the visual cortex). Conversely, the increased visual activity by occipital tDCS could counteract and thus reduce the cross-modal effects on visual perception. This is also broadly in line with the "inverse effectiveness rule" for multisensory integration: In multisensory neurons within the superior colliculus of the cat, the salience of the unimodal signals represents a major determinant of the advantage resulting from their integration (Holmes & Spence, 2005; Meredith & Stein, 1983). In this perspective, the level of excitability in visual areas might predict the extent of cross-modal interactions, with higher multisensory gains for low-level visual activity (Bolognini, Senna, et al., 2010).

In conclusion, this study shows that cross-modal stimuli, presented at roughly the same spatial location of sTMS-induced phosphenes, increase their rate, likely by enhancing cortical excitability in low-level visual areas. The more sensory inputs are combined (i.e., trimodal versus bimodal), the greater is the increase of phosphene perception. These multisensory interactions take place in temporal and parietal brain regions, which can send a cross-modal feedback input to the primary visual areas. In particular, the temporal areas are involved in the auditory enhancement of visual cortical excitability, whereas the parietal areas mediate the tactile enhancement of it. tDCS can be used to up-regulate cortical excitability in these areas to reinforce auditory and tactile influences on sensory-specific visual processing (see also Bolognini, Fregni, et al., 2010; Bolognini, Olgiati, et al., 2010; Bolognini, Senna, et al., 2010; Bolognini & Maravita, 2007; Ramos-Estebanez et al., 2007; Macaluso, 2006; Macaluso & Driver, 2005). The selectivity of the target areas with respect to the type of cross-modal effect (i.e., tactile vs. auditory enhancement of visual cortical responses) may reflect a regional preference of the PPC and the temporal areas for one modality more than others or for specific pairings of two modalities (Driver & Noesselt, 2008).

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