Neuroscience Letters 477 (2010) 109–114

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

# Auditory enhancement of visual phosphene perception: The effect of temporal and spatial factors and of stimulus intensity

Nadia Bolognini[a,*], Irene Senna[a], Angelo Maravita[a], Alvaro Pascual-Leone[b], Lotfi B. Merabet[b]

[a] Department of Psychology, University of Milano-Bicocca, Milano, Italy
[b] Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

*Article history:*
Received 11 February 2010
Received in revised form 31 March 2010
Accepted 21 April 2010

*Keywords:*
Phosphenes
Multisensory
Subthreshold
Auditory
Visual cortex
TMS

ABSTRACT

Multisensory integration of information from different sensory modalities is an essential component of perception. Neurophysiological studies have revealed that audiovisual interactions occur early in time and even within sensory cortical areas believed to be modality-specific. Here we investigated the effect of auditory stimuli on visual perception of phosphenes induced by transcranial magnetic stimulation (TMS) delivered to the occipital visual cortex. TMS applied at subthreshold intensity led to the perception of phosphenes when coupled with an auditory stimulus presented within close spatiotemporal congruency at the expected retinotopic location of the phosphene percept. The effect was maximal when the auditory stimulus preceded the occipital TMS pulse by 40 ms. Follow-up experiments confirmed a high degree of temporal and spatial specificity of this facilitatory effect. Furthermore, audiovisual facilitation was only present at subthreshold TMS intensity for the phosphenes, suggesting that suboptimal levels of excitability within unisensory cortices may be better suited for enhanced crossmodal interactions. Overall, our findings reveal early auditory–visual interactions due to the enhancement of visual cortical excitability by auditory stimuli. These interactions may reflect an underlying anatomical connectivity between unisensory cortices.



Information regarding external events typically reaches our brain through independent sensory systems that integrate these multisensory inputs into a unified percept.

The frontal, parietal and temporal lobes of the primate brain contain neurons that respond to more than one sensory modality and consequently have been identified as sites of multimodal integration [12]. According to a hierarchical model, sensory information converges in these higher level areas through feedforward pathways arising from unimodal areas [17]. Recently, the notion that multisensory interactions occur only at the level of these high-order areas has been challenged by anatomical, neuroimaging and electrophysiological data suggesting that crossmodal structures also exert relevant feedback modulation within early, modality-specific areas [22,34].

It is noteworthy that a variety of constraints regarding multisensory interactions in low-level unisensory cortices have been identified including spatial, temporal, as well as semantic and associative [3,8,22,34,36]. The characterization of such functional features is crucial in order to understand the causal interplay between different senses that affect brain areas and responses. Indeed, different types of constraints on multisensory interactions might likely arise at different points in time during sensory processing (in accord with different temporal windows for extracting relevant stimulus features) and may therefore reflect distinct functional mechanisms subserved by specific networks [12,19,20].

Based on these considerations, the present study aimed at exploring the effects of spatial (i.e. stimulus congruency) and temporal (i.e. time window) factors as well as stimulus intensity on crossmodal interactions in early visual areas. We have taken advantage of the fact that the perception of visual phosphenes can be induced by Trancranial Magnetic Stimulation (TMS). TMS delivered over the occipital cortex induces transient visual sensations (i.e. phosphenes) that occur at a precise spatial location in visual space. The TMS intensity threshold that is needed to generate phosphene is believed to provide a measure of the excitability of the visual cortex [2,11,18]. Using this approach we aimed to investigate crossmodal interactions directly by studying the effect of auditory stimuli on the perception of TMS-induced visual phosphenes [2,28,30,31].

Eight participants took part in each of the four experiments (Experiment 1: 8 females, mean age 22; Experiment 2: 7 females, mean age 26; Experiment 3: 6 females, mean age 25; Experiment 4: 8 females, mean age 21).

All participants were right-handed (except one in Experiment 4) according to the Oldfield handedness questionnaire [27] and

* Corresponding author at: Department of Psychology, University of Milano-Bicocca, viale dell'Innovazione 10, Ed. U9, 20126 Milan, Italy. Tel.: +39 0264483822.
*E-mail address:* nadia.bolognini@unimib.it (N. Bolognini).

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doi:10.1016/j.neulet.2010.04.044

reported normal hearing and normal or corrected-to-normal vision. None of the participants had any contraindication to TMS. All were naïve to both the experimental procedure and the purpose of the study and gave written informed consent prior to participating. The experiment was carried out in accordance with the ethical standards of the Declaration of Helsinki (BMJ 1991; 302:1194) and was approved by the ethical committee of the University of Milano-Bicocca. All the accepted recommendations for the use and safety of TMS were applied [32].

Given the subjective nature of phosphene perception, an initial screening session was carried out in order to ascertain if subjects could reliably report phosphenes following single TMS pulses delivered to the occipital cortex. Only subjects who reported robust, reliable and stable phosphenes were enrolled in the study [11]. Approximately 60% of the screened subjects fulfilled these criteria, allowing for four groups of 8 participants described above.

Participants sat in an armchair wearing an elastic swimming cap. The cap was used to mark the site of stimulation and ensure reliable and reproducible coil placement throughout the experiment. Participants also wore a specially designed blindfold to prevent the possibility of any ambient light perception. Participants adapted to darkness for 15 min to stabilize the level of visual cortex excitability prior to performing the TMS experiment [11]. Single-pulse TMS was delivered using a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim, Whitland, UK) connected with a figure-of-eight coil (70 mm diameter). The optimal site of occipital stimulation for inducing phosphenes in the peripheral visual field was initially determined for each participant using a mapping procedure (for details, see [11]). In Experiments 1, 2 and 4, phosphenes were perceived in every participant at an eccentricity of at least 30° within in the periphery of the contralateral visual hemifield. In Experiment 3, phosphenes were perceived at an eccentricity of less then 10° (see below). The optimal scalp position was then marked on the elastic swimming cap. This site was located in the left hemispheres for 38% of the participants in Experiment 1, for 63% of the participants in Experiment 2, for 25% of the participants in Experiment 3, for 63% of the participants in Experiment 4.

The spatial location of the perceived phosphenes was marked by the experimenter on a board placed in front of the participant. This was done in order to position the speaker delivering the auditory stimuli at exactly the location of the reported phosphene in Experiments 1, 3 and 4 (see Fig. 1).

Finally, after identifying the optimal scalp position for the induction of reliable and robust phosphenes, the individual's phosphene threshold (PT, defined as the stimulator output intensity inducing phosphenes in half of the trials) was determined [11]. The PT corresponded to a mean TMS intensity of 64% (±12% SD) of the maximal stimulator output across all participants.

*Experiment 1*. Subjects remained blindfolded throughout the experiment and TMS was applied over the occipital pole at constant subthreshold TMS intensity (80% of individually defined PTs). Auditory stimuli consisted of a 20-ms burst of white noise (intensity 60 dB), delivered from two external piezoelectric loudspeakers (0.4 W, 8 Ω). The loudspeakers were placed on a plastic semicircular perimeter device (height 40 cm, length 200 cm) that was fixed on to the surface of a table at a distance of 40 cm from the participant. One loudspeaker was placed exactly at the same spatial location as the perceived phosphene in both the vertical and the horizontal meridians (Same Side: auditory stimulus ipsilateral to phosphenes), while the other was placed at the corresponding position in the opposite hemifield (Opposite Side: auditory stimulus contralateral to phosphenes).

During the experimental session, TMS pulses were delivered alone (Unimodal condition), or paired with the auditory stimulus presented in the right or left hemifield (crossmodal condition). In the crossmodal conditions, the auditory stimulus could precede (−80, −60, −40 or −20 ms), follow (+20 or +40 ms) or be synchronous to the TMS pulse. These interstimulus intervals (ISIs) were chosen in light of previous work investigating the temporal profile of crossmodal interactions in nonhuman primates [35]. Catch trials, i.e. left or right unimodal auditory stimuli without TMS, were also randomly presented. The participant's task was to press the space bar of the keyboard to indicate the perception of a phosphene.

Stimuli were delivered with an inter-trial interval that was randomly varied between 5 and 7 s to minimize the potential of any carry-over effect of TMS on visual cortical excitability. In total, there were 306 trials, equally distributed in three blocks (each lasting approximately 9 min): 210 Crossmodal Stimuli (i.e. 15 trials for each of the 14 possible crossmodal combinations); 66 Unimodal Stimuli (corresponding to the 20% of trials) and 30 Catch Trials (10%). Sequence and timing of the stimuli and responses recording were all under computer control (E-Prime Software, Psychology Software Tools, Inc.).

*Experiment 2*. A second experiment was conducted to further explore the effect of spatial correspondence of auditory stimuli on phosphene perception and as a function of perceived phosphene location. Here, the same procedure of the Experiment 1 was adopted with the exception that now the auditory stimuli could appear in either the same or opposite visual hemifield (Same vs. Opposite Sides), but without an exact spatial correspondence to the perceived phosphene location. The auditory stimulus was delivered from two loudspeakers located horizontally at ear level and at an eccentricity of 40° to the left and right of midline. This setting was used for every participant regardless of the perceived location of the phosphene (located on average at 30° in the contralateral visual field).

*Experiment 3*. This experiment further investigated the spatial constraints of any crossmodal interaction by inducing phosphenes in the central visual field, rather than in the visual periphery. Again, the same procedure of Experiment 1 was used but now phosphenes were induced at an eccentricity of less than 10°. Given the central location of phosphenes, only one auditory stimulus was presented from a single loudspeaker placed exactly at the perceived phosphene location (i.e. Same Side).

*Experiment 4*. Here we investigated the effect of stimulus intensity. Following the procedure of Experiment 1, we now set the intensity of the TMS pulse at a suprathreshold level (i.e. 120% of individual PT).

The effect of Auditory Stimulation on Phosphenes Perception was determined by analyzing the difference in the percentage of phosphene detections between Crossmodal (i.e. occipital TMS plus Auditory Stimulus) and Unimodal (i.e. TMS alone) trials (trials, Δ Accuracy = Perceived Phosphenes in Crossmodal Trials − Perceived Phosphenes in Unimodal Trials). To normalize the data distribution, the percentage of phosphene detection was then converted to the arcsin of the square root of the raw values [40].

In Experiments 1, 2 and 4, the mean change in Phosphenes Detection in Crossmodal Trials from the Unimodal Trials condition was subjected to a 2-way repeated measures ANOVA, including factors of Spatial Congruency and ISI. In Experiment 3 the ANOVA included only the Factor ISI. Pairwise comparisons were run using the Newman–Keuls test. Finally, the effect size of the ANOVA was measured by calculating the partial Eta Squared ($p\eta^2$) to quantify the degree of association between an effect and the dependent variable, i.e. the proportion of the total variance that is attributable to the main factor or interaction [7].

In every experiment, all subjects reliably reported phosphenes within the contralateral visual field at a constant location and with a stable PT as assessed by *t*-tests carried out on the mean PT for the first half vs. the second half of trials (Experiment 1: first half = 36% vs. second half = 40%, $p = 0.36$; Experiment 2: 41% vs. 37%, $p = 0.32$; Experiment 3: 39% vs. 41%, $p = 0.46$; Experiment 4: 68% vs. 64%,