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RESEARCH ARTICLE

Retinal and visual cortex distance from transcranial magnetic stimulation of the vertex affects phosphene perception

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Abstract Recent studies claim that the perception of flashes of light (i.e., phosphenes) can be induced by stimulation of higher visual areas, including parietal cortex, suggesting a critical role of these regions in generating visual percepts. In this study, we show that transcranial magnetic stimulation (TMS) of even the vertex can induce phosphenes, but that their neural origins are likely to be a consequence of current spread into visual areas (e.g., retina or visual cortex). After vertex stimulation, subjects with smaller head circumferences—for whom the distances from the coil to retina and visual cortex are smaller—report a two-fold increase in perceiving phosphenes. In contrast, both smaller and larger headed individuals perceived phosphenes equivalently and on nearly all trials following TMS of early visual cortex. These results demonstrate a critical role of early visual areas but not higher ones in generating visual perceptions. These findings further suggest that phosphenes perceived from TMS of the vertex or parietal cortex arise from induced activity in the retina or nearby early visual cortex and warn against the use of the vertex as a control site for TMS experiments of visual perception.

Keywords Visual perception · Vertex · Parietal cortex · Transcranial magnetic stimulation

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Introduction

Stimulation studies of the cerebral cortex have provided important insights into the functional organization of the brain (Penfield and Rasmussen 1950). In the visual system, transcranial magnetic stimulation (TMS), a non-invasive brain stimulation technique, has been used with great success to study the role of different brain areas in visual perception by inducing visual percepts (i.e., phosphenes) (Meyer et al. 1991; Marg and Rodiak 1994; Kammer 1999) or interrupting the processing of visual information (Amassian et al. 1989, 1994; Kamitani and Shimojo 1999; Kammer 1999). Curiously, several groups have recently reported the induction of phosphenes from TMS over regions beyond the visual cortex, including the intraparietal sulcus (IPS) in parietal cortex (Marzi et al. 2009; Fried et al. 2011; Mazzi et al. 2014; Bagattini et al. 2015; Samaha et al. 2017). However, the effects of TMS are not focal; it non-invasively induces currents into the brain through a magnetic flux produced through a relatively large stimulating coil. Although TMS has been an invaluable tool in the study of the visual system, the nature of perceived phosphenes after parietal TMS is highly suspect given the spread of current and spatial proximity of the IPS to the visual cortex. Therefore, phosphenes produced by TMS over parietal regions may in fact be the result of stimulation of early visual cortex or even the retina.

Indeed, phosphenes elicited by activation of tissue distal to the stimulation site have been noted in studies using transcranial alternating current stimulation (tACS). Although phosphenes have been reported from tACS over visual cortex (Kanai et al. 2008), similar but more intense phosphenes can be induced with tACS by placing the stimulating electrodes over the frontal and vertex regions.

Furthermore, voltage-related potentials can be detected around the eye with electrodes positioned over the occipital and vertex regions (Schutter and Hortensius 2010), suggesting that the locus of these visual effects is not visual cortex, but rather the retina. This has been corroborated by a study demonstrating that tACS phosphene thresholds decrease as the stimulating electrode is brought farther from visual cortex and closer to the retina (Kar and Krekelberg 2012). There is also no difference in phosphene perception latency from stimulation over visual cortex and stimulation near the eye (Kar and Krekelberg 2012) and a small percentage of the current produced by occipital-vertex tACS likely flows through the highly conductive eyes (Laakso and Hirata 2013). These results raise the question of whether phosphene perception from TMS over parietal cortex may also be generated from current spread to or indirect stimulation of visual areas such as nearby visual cortex or the retina. This is especially a concern when considering that the qualities of phosphenes induced by stimulation of parietal cortex seem to reflect features of early visual areas rather than later ones, an idea that was also suggested by Fried et al. (2011).

To determine whether TMS can generate perceptual effects from direct or indirect stimulation of regions distal to the stimulation site, we investigated whether stimulation of even a non-visual area could elicit phosphene perception. In the present study, we measured phosphene perception from TMS over the vertex in addition to visual cortex as a function of head circumference. Head circumference was chosen as our independent measure, because it is correlated with anatomy (e.g., occipital pole to vertex and retina distance) and, therefore, is a quick and efficient method of assessing whether vertex stimulation affects distal regions. We hypothesized that if current induced by TMS affects regions beyond those directly beneath the coil, vertex stimulation may also affect visual cortex as well as the retina and may be the underlying basis for phosphene perception, especially in subjects with smaller heads.

Methods

This research conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the City University of New York.

Subjects

Thirty-six subjects were recruited for participation. Of these, 17 subjects did not complete the study, because they could not reliably perceive phosphenes on greater than 75% of at least 20 prescreening trials and an additional subject did not complete the experiment due to discomfort from the experimental procedures. The remaining 18 subjects (nine females, mean age of 28.11 years, and range of 21–50 years) reported reliable perception of phosphenes produced by stimulation over the vertex and over visual cortex. All subjects gave written informed consent and had normal or corrected-to-normal vision.

TMS procedure

Single-pulse TMS was administered using a Magstim Rapid stimulator (Whitland, UK) connected to a figure-of-eight coil with 70 mm circular components. Initial screening for inclusion in the study involved functionally localizing a visual cortex stimulation site and determining a TMS intensity that produced phosphenes on >75% of trials using the following procedures.

For visual cortex stimulation, the coil was initially placed approximately 2 cm above the inion with the handle of the coil pointed upwards and parallel to the midline to minimize activation of the neck and shoulder muscles (see Figs. 1 and 2 for all coil positions and orientations). The intensity was initially set at 50% of maximum stimulator output. Subjects were instructed to close their eyes. The position along both the mediolateral and rostrocaudal axes and the intensity of the TMS were then adjusted as necessary until the subject reported perception of a phosphene or until maximum stimulator output was reached without perception of phosphenes.

Several criteria were used to confirm whether subjects perceived true phosphenes. First, a dependency of the location of the perceived phosphene on stimulation site was established, such that stimulation of the left hemisphere produced phosphenes in the right visual field and vice versa (Meyer et al. 1991). Furthermore, these phosphenes should be present both with eyes open and closed (Kammer and Beck 2002) and should shift correspondingly with shifts in fixation (Meyer et al. 1991). If these criteria could not be met, subjects were not included in the study.

If genuine phosphenes were reported, subjects were instructed to open their eyes, while TMS was administered. Optimal stimulation intensity was then determined using an adaptive staircase-like procedure to find the intensity that produced the brightest phosphene. This procedure was chosen, because investigations of TMS intensity on phosphene perception have yielded conflicting results. Several studies have suggested that phosphene perception increases with increasing intensity until it eventually saturates (Kammer et al. 2001; Kammer and Beck 2002; Mazzi et al. 2014; Salminen-Vaparanta et al. 2014; Bagattini et al. 2015), whereas others have suggested that phosphenes may become less visible at higher intensities (Kastner et al. 1998). To ensure that phosphenes were maximally visible in all subjects, intensity was

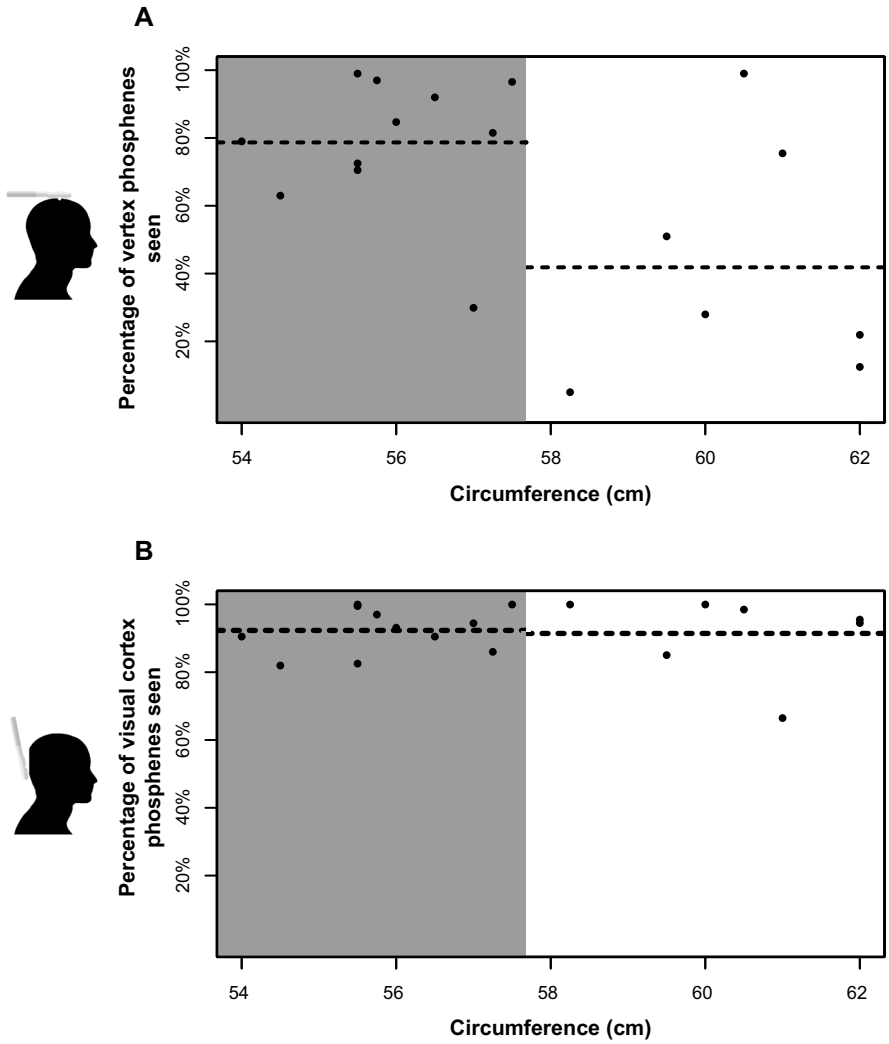

Fig. 1 Percentage of phosphenes seen for each TMS site as a function of head circumference. The percentage of phosphenes seen from stimulation over each site was compared between subjects with smaller head circumferences (*shaded regions*) and subjects with larger head circumferences (*white regions*). *Dashed lines* represent the mean percentage. **a** Percentage of phosphenes seen from TMS over vertex. **b** Percentage of phosphenes seen from TMS over V1

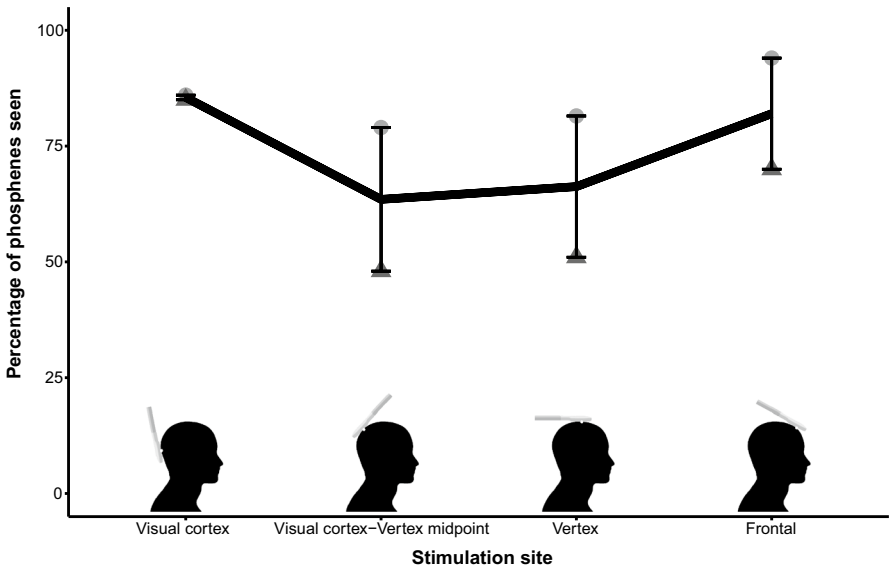

Fig. 2 Phosphene perception by TMS site for two subjects. *Circles* represent data from a subject with a small head circumference; *triangles* represent data from a subject with a large head. The *solid line* represents the mean across the two subjects. *Error bars* reflect SE of the mean

adjusted independently for each subject rather than using a fixed intensity increase above threshold.

Two separate and distinct TMS pulses, differing in intensity by 3% of maximum stimulator output, were delivered to subjects in both ascending and descending orders. Subjects were instructed to indicate which phosphene in each pair appeared brighter. If subjects could not reliably indicate which intensity produced a brighter phosphene, the pair was repeated and, if necessary, the difference in intensity between the two pulses was increased. Once the intensity that produced the brighter phosphene was determined, this intensity was used as the starting point in the next pair and was compared to an intensity that differed by 3% of maximum stimulator output. This process was repeated, increasing and decreasing the step size as necessary, until an optimal intensity was determined that produced a brighter phosphene than the intensities above or below it. This optimal intensity was then tested on a series of eight TMS pulses to ensure that it was sufficient to produce phosphene perception on >75% of trials. The mean intensity required to produce phosphenes on >75% of trials was 69% of maximum output (range 59–86%). This intensity was used for the remaining duration of the experiment.

For vertex stimulation, the center of the coil was positioned over Cz as measured by the international 10–20 system and oriented parallel to the axial plane with the handle pointed backwards. TMS intensity was set at the optimal intensity for producing phosphenes over visual cortex, as is common when the vertex is used as a control site.

Two of these 18 subjects underwent TMS to a total of four stimulation sites. The visual cortex and vertex conditions were localized in the same manner as the other subjects. However, for each of these two subjects, the distance between the visual cortex and vertex stimulation sites was measured, and then, the midpoint between these two locations was denoted as the occipital-vertex midpoint. A second stimulation site was placed an equal distance rostral to the vertex stimulation site and was denoted as the frontal site. Stimulation intensity for all four sites was set at the same intensity that produced phosphenes on greater than 75% of the visual cortex stimulation trials.

Electrooculogram (EOG) recordings

Blinks and eye movements were recorded to rule out the possibility that vertex stimulation was causing ocular artifacts that could be misinterpreted as phosphenes. A TMS-compatible EEG system (Brain Products GmbH, Munich, Germany) was used to record EOG signals (BrainVision Recorder) at a 1000 Hz sampling rate during the experiment. EOG data were minimally processed in MATLAB (Mathworks, Natick, MA) using EEGLAB (Delorme and Makeig 2004). Electrode AFz served as the ground and FCz served as the online reference electrode. Impedances were maintained below 10 kΩ. Subjects were instructed to minimize blinks and eye movements during each trial.

Stimuli and experimental procedure

Subjects were seated 57 cm from a CRT monitor running at a 100 Hz refresh rate. On each trial, a disk subtending 1° of visual angle in diameter was presented within 0–180 ms of the TMS. This disk was matched in brightness to the perceived brightness of the phosphene prior to the start of the experiment. The mean luminance of the disk was 8.21 cd/m^2 (range 0.01–39.98 cd/m^2). To further ensure that phosphenes were perceived as distinct events, subjects reported on each trial whether the phosphene or visual stimulus was perceived first or indicated that no phosphene was perceived. The range of SOAs between the onset of the visual stimulus and the TMS was chosen to ensure that subjects perceived the phosphene first on approximately 50% of visual cortex trials. The visual stimuli were presented against a black background. All stimuli, TMS triggers, and response collection were controlled using custom software written in Visual C++ with Microsoft DirectX libraries.

TMS was delivered over the course of 200 trials for each stimulation site. The order of the stimulation sites was counterbalanced between subjects. On each trial, subjects indicated the presence or absence of a phosphene using the mouse and keyboard.

Results

Temporal order judgements

For each subject and stimulation site, we calculated the percentage of trials in which the phosphene appeared first out of the total number of trials in which a phosphene was perceived. Across all subjects, the phosphene was perceived first on 50.89% (SD 16.79%) of visual cortex trials in which a phosphene was perceived. This did not differ significantly from the expected value of 50% given the range of SOAs used [$t(17) = 0.22$, $p = 0.82$, $d = 0.05$]. The phosphene was perceived first on 44.17% (SD 21.71%) of vertex trials in which a phosphene was perceived. This did not differ significantly from 50% [$t(17) = 1.14$, $p = 0.27$, $d = 0.27$]. Importantly, the difference in phosphene first reports for the visual cortex and vertex TMS conditions was not significantly different [$t(17) = 1.69$, $p = 0.11$]. These results indicate that subjects perceived phosphenes as discrete events, were able to make temporal order judgements about them, and perceived phosphene onsets similarly between the vertex and visual cortex stimulation conditions.

Phosphene descriptions

Qualitative descriptions of the phosphenes originating from visual cortex stimulation and vertex stimulation were collected. Phosphenes arising from stimulation over visual cortex were described as stationary and appearing contralateral to the stimulation site or close to the midline of the visual field. The shape of these percepts was described as either amorphous, "splotches", "dots", or a line. Descriptions of phosphenes arising from stimulation over the vertex were generally similar. One subject noted that the vertex phosphene shifted in location, two noted that it changed shape, one noted that it changed in both shape and location, three noted changes in brightness, and four noted changes in brightness and location.

Phosphene reports and head circumference

The mean head circumference of our sample was 57.68 cm (SD 2.57, 54–63 cm). Vertex stimulation produced phosphenes on 64.36% of trials across subjects. There was a significant negative correlation between head circumference and the percentage of perceived phosphenes after vertex stimulation, $r(16) = -0.50$, $p = 0.03$. The data were then split by mean head circumference, giving us a smaller head circumference group ($N = 11$) and a larger head circumference group ($N = 7$). The mean percentage of phosphenes perceived by the smaller head circumference group ($M = 78.69\%$) was significantly greater than the mean percentage of phosphenes perceived by the larger head circumference group ($M = 41.84\%$), $t(16) = 2.87$, $p = 0.01$ (see Fig. 1a). This effect size was large, $d = 1.39$ (Cohen 1988).

By contrast, visual cortex stimulation produced phosphenes on 91.97% of trials across subjects. There was no significant correlation between head circumference and the percentage of visual cortex phosphenes perceived, $r(16) = -0.04$, $p = 0.87$. Furthermore, splitting the data by mean head circumference did not reveal any differences between the mean percentage of visual cortex phosphenes perceived by the smaller head circumference group ($M = 92.32\%$) and the larger head circumference group ($M = 91.43\%$), $t(16) = 0.20$, $p = 0.84$, $d = 0.10$ (see Fig. 1b).

The differences in phosphene perception from vertex stimulation could not be explained by differences in TMS intensity between the two groups. There was no significant correlation between TMS intensity and head circumference, $r(16) = 0.37$, $p = 0.14$. Furthermore, there was no significant correlation between TMS intensity and perception of phosphenes from vertex stimulation, $r(16) = -0.17$, $p = 0.51$. Similarly, there was no significant correlation between TMS intensity and perception of phosphenes from visual cortex stimulation, $r(16) = 0.14$, $p = 0.58$.

Retinal and occipital cortex distance from TMS

Two subjects underwent TMS to two additional stimulation sites: the occipital-vertex midpoint and a frontal site. One of these subjects had a smaller head circumference of 57.25 cm. The other subject had a larger head circumference of 59.5 cm. The smaller headed subject's optimal phosphene intensity was 83% of maximal stimulator output, while the larger headed subject's optimal phosphene intensity was 59% of optimal stimulator output. The percentage of phosphenes perceived by stimulation site is shown in Fig. 2. Both subjects perceived phosphenes on the majority of visual cortex stimulations (smaller headed subject 86.00% and larger headed subject 85.00%). Furthermore, both subjects demonstrated the aforementioned correlation between head circumference and perception of vertex phosphenes, with the smaller headed subject perceiving phosphenes on 81.50% of vertex stimulations and the larger headed subject perceiving phosphenes on only 51.00% of vertex stimulations. The least effective stimulation site for producing phosphenes in both subjects was the occipital-vertex midpoint. For the smaller headed subject, this site still produced phosphenes on the majority (79.00%) of stimulations, but for the larger headed subject, this site produced phosphenes on only 48.00% of stimulations. The frontal cortex site produced a secondary peak in phosphene perception. This site produced phosphenes on 94.00% of stimulations for the smaller headed subject and on 70.00% of stimulations for the larger headed subject, suggesting that the origin of these frontal (and some vertex) phosphenes may have been retinal.

Blinks and eye movements

EOG activity was recorded to rule out the possibility that vertex TMS caused blinks or eye movements that could be interpreted as phosphenes. For each subject and stimulation site, EEG data were epoched around the onset of the TMS pulse from 0 to 300 ms and were visually inspected for ocular artifacts. This epoch window should be more than sufficient to capture any eye movements induced by the TMS (Ghezzi et al. 1992; Corthout et al. 2011). The proportion of trials in which an ocular artifact occurred within 300 ms of the onset of the TMS was noted for each subject and stimulation site. Across all subjects and stimulation sites, blinks and eye movements occurred on average on 1.52% of trials (SD 1.23%). The proportion of blinks and eye movements were then submitted to a paired-samples t test. There was no significant difference in the rate of blinks and eye movements occurring within 300 ms of the

TMS pulse during visual cortex stimulation ($M = 1.70\%$, SD 1.33%) compared to vertex stimulation ($M = 1.34\%$, SD 1.14%), $t(17) = 0.96$, $p = 0.35$, $d = 0.28$. Furthermore, there were no significant differences in the rate of blinks and eye movements occurring within 300 ms of the vertex TMS pulse in subjects with smaller heads ($M = 1.50\%$, SD 1.24%) compared to subjects with larger heads ($M = 1.09\%$, SD 1.00%), $t(16) = 0.75$, $p = 0.47$, $d = 0.34$. There were also no significant differences in the rate of blinks and eye movements occurring within 300 ms of the visual cortex TMS pulse in subjects with smaller heads ($M = 1.51\%$, SD 0.95%) compared to subjects with larger heads ($M = 2.00\%$, SD 1.83%), $t(16) = -0.75$, $p = 0.46$, $d = -0.35$.

Discussion

We show that perception of phosphenes from vertex stimulation is related to head circumference: there is a significant negative correlation between head circumference and phosphene perception following vertex TMS. Individuals with smaller heads, for whom the distances from the coil to retina and visual cortex are smaller, perceived more phosphenes after vertex stimulation than individuals with larger heads. Importantly, we did not find the same relationship when we stimulated visual cortex directly. Furthermore, this relationship between head circumference and perception of phosphenes from vertex stimulation cannot be explained by differences in TMS intensity. Our results suggest that phosphenes perceived from vertex stimulation are likely the result of current spread or indirect stimulation of visual areas.

Qualitative descriptions of the phosphenes suggest that subjects perceived phosphenes from vertex TMS in a similar manner to phosphenes perceived from visual cortex TMS. In both conditions, they were able to describe the general shape, location, and brightness of the percepts. Frequently, these percepts were described as being similar across stimulation sites, but changes in appearance followed what one would expect from changing stimulation sites (e.g., changes in brightness and location). This supports the idea that vertex TMS was inducing percepts similar to visual cortex TMS, rather than false alarms based on blinks, eye movements, or other factors. Indeed, blinks and eye movements occurring within the first 300 ms following the TMS pulse were rare across all subjects and stimulation sites—occurring on less than 2% of trials. This small effect is not sufficient to account for the nearly two-fold increase in phosphene perception from vertex stimulation in subjects with smaller heads compared to those with larger heads. Furthermore, there were no differences in the rates of blinks and eye movements produced by TMS over visual cortex or vertex. There were also no differences in the rates of blinks and eye movements produced in subjects with smaller heads compared to those with larger heads under either stimulation condition. Therefore, it is unlikely that vertex TMS produced false alarms in phosphene perception by inducing blinking or eye movements.

Origins of phosphenes from vertex TMS

While useful in informing us about the general nature of phosphene perception from vertex TMS, qualitative descriptions alone cannot be used to infer the origin of these percepts. For example, shifts in perceived phosphene location (to the lower visual field) occurring from stimulation over the vertex could be produced by current spread to either visual cortex or the retina, given the retinotopic organization of both structures. In addition, changes in brightness (dimmer phosphenes) would also be expected from distal stimulation, regardless of the origin. Although these qualitative descriptions are highly suggestive, other methods and converging data, such as visual cortical and retinal neuron recordings, are necessary to more precisely determine the origin and mechanism of phosphene perception from vertex stimulation. This is especially the case given that there may be several underlying mechanisms by which vertex TMS can produce phosphene perception.

In addition to polysynaptic neuronal changes, current spread alone can occur in a number of ways—for example, shunting across the scalp or through the cerebrospinal fluid (CSF). CSF has much greater conductivity than the surrounding brain tissue (Gabriel et al. 1996; Baumann et al. 1997), causing current to preferentially travel along this path of reduced resistance. This asymmetry in conductivity causes peaks in electric field intensity in grey matter adjacent to regions of lower CSF volume (Bijsterbosch et al. 2012). The short distances between the vertex and the occiput, as well as between the vertex and the eyes, through the CSF in the interhemispheric fissure, thus provide an avenue of low resistance to the early visual cortex and retina (Laakso and Hirata 2013), especially in subjects with smaller heads. All of these effects should have an early onset and brief duration.

Alternatively, the behavioral effects elicited from vertex TMS may arise from activation of visual areas through neuronal connectivity between these areas and the stimulated cortex (e.g., antidromic stimulation). Ilmoniemi et al. (1997) demonstrated that TMS over motor cortex causes contralateral activations emerging around 20 ms post-stimulation, which they suggest is the result of transmission via transcallosal connections. However, it is unlikely that the phosphenes elicited from vertex stimulation arise from orthodromic or antidromic stimulation of neuronally connected brain areas, since these connections should have also

been equally activated in subjects with larger heads and do not project directly to visual regions. Further research will be necessary to determine whether phosphenes from vertex stimulation are the result of direct stimulation of visual areas from current spread through the scalp or CSF.

Although phosphenes with a retinal origin have not been clearly demonstrated using modern TMS, Meyer et al. (1991) found that stimulation over the frontal convexity of the skull produced weak phosphenes that spanned both visual fields in 60% of subjects. However, because phosphenes could not be induced by stimulation above the eyeball, Meyer et al. concluded that the likely locus of frontal phosphenes was the optic nerve.[1] In contrast, Walsh et al. (1946) and Barlow et al. (1947) found that phosphenes could be evoked when the core of a magnet was placed within a few centimeters of the temple, with the location of the phosphenes corresponding to the part of the retina being stimulated. A retinal origin was supported by the finding that pressure ischemia of the eye rendered the eye insensitive to magnetic stimulation.

In addition, it has been shown that the eye is highly conductive (Gabriel et al. 1996; Lindenblatt and Silny 2001) and sensitive to stimulation by induced currents (Marg 1991). Furthermore, it has been demonstrated that the threshold for evoking phosphenes from magnetic stimulation of the retina is five times lower than that required from magnetic stimulation of visual cortex (Marg 1991). This suggests that even though the electric field drops off with distance from the point of stimulation, current density evoked at the retina from vertex stimulation may be sufficient to produce phosphenes, especially in subjects with smaller heads. These findings further suggest a retinal or visual cortex origin of phosphenes induced by TMS of the vertex, and likely also phosphenes from TMS of parietal areas. However, it should be noted that our speculation of the possible induction sites of these percepts focuses on the retina and visual cortex, because the literature on a variety of stimulation techniques has provided evidence that phosphenes can be produced with a locus in these regions. Nevertheless, other potential loci exist along the visual pathway (including the optic nerve, as suggested by Meyer et al. 1991), and these regions may also give rise to phosphene perception.

[1] We attempted to evoke retinal phosphenes in ourselves by applying TMS lateral to the outer canthus with the handle oriented posteriorly. Similar to Meyer et al. (1991), phosphenes were not perceived at this stimulation site. However, the effects of using TMS near the face—including discomfort, eye movements, and blinking—make it difficult to determine whether TMS near the eye is truly incapable of producing phosphenes with a retinal origin or whether the associated eye movements and other non-specific effects of TMS near the face make these phosphenes difficult to detect.

We employed a temporal order judgement task to verify that subjects perceived phosphenes as discrete events about which they could make judgements. Based on the range of visual stimulus-to-TMS SOAs used, we anticipated that true perception of phosphenes should result in the phosphene being perceived first on 50% of trials. Our results for both visual cortex and vertex stimulation are consistent with this prediction and suggest that these phosphene reports are genuine rather than a misattribution of perception to some other event coinciding with the TMS, such as blinks and/or eye movements. Although not statistically significant, the vertex stimulation condition resulted in a numerically lower proportion of phosphene first reports as compared to the visual cortex stimulation condition. One potential reason for this may be that vertex stimulation induces phosphene perception from a mixture of visual cortex and retinal stimulations. Notably, if vertex stimulation induces phosphene perception from stimulation of the retina, then we should expect to measure a lower proportion of phosphene first reports because of the retinal to cortical delay that is not present from visual cortex stimulation. A current follow-up study in our laboratory is attempting to further isolate these different potential contributions to phosphene perception by comparing temporal order judgements to visual cortex and more direct retinal stimulation.

Relationship to TMS Intensity

Although there were no relationships between TMS intensity and head circumference or between TMS intensity and perception of vertex phosphenes in this study, it has been demonstrated that higher TMS intensities yield less focal activations. Two studies of TMS over motor cortex showed that higher intensity TMS generally produces more functional magnetic resonance imaging (fMRI) activity both underneath the coil (Fox et al. 2006) and contralaterally, as measured by the extent and intensity of activation (Bohning et al. 1999; Nahas et al. 2001). In addition, Komssi et al. (2004) demonstrated that TMS was able to evoke clear cortical responses at intensities as low as 60% of motor threshold, and in one subject as low as 40% of motor threshold. While these intensities were insufficient to produce a behavioral response (i.e., a muscle twitch) through visual inspection, the clear pattern of cortical activation suggests that remote brain regions could be stimulated even with this "subthreshold" stimulation.

One might have expected a correlation between TMS intensity and vertex phosphene perception given that higher intensity TMS is less focal and might, therefore, more readily affect visual areas than lower intensity TMS. However, overall excitability of visual structures, including the retina, does not directly correlate with stimulation intensity, which is apparent from the large range of optimal stimulation

intensities for producing phosphenes across subjects. Although this may be a consequence of differences in cortex to stimulation coil distances between subjects for cortically induced phosphenes, differences in the size of the eye, optic nerve orientation, and other factors may introduce variability in the stimulation intensities required for retinal phosphenes. Future studies that assess the geometry of the eyes and other low-level factors may help to elucidate some of these susceptibility differences between individuals.

Parietal phosphenes?

Phosphene perception was assessed from two additional stimulation sites in two subjects. Stimulation over the visual cortex was effective in producing phosphenes in both subjects, and the smaller headed subject perceived phosphenes more frequently from vertex stimulation than the larger headed subject. Interestingly, the occipital-vertex midpoint stimulation site, which was over the parietal cortex, was the least effective site in producing phosphenes, but, nonetheless, produced a substantial proportion of phosphene perceptions in both subjects. The frontal site produced a secondary peak in phosphene perception, suggesting that vertex and frontal TMS may more easily elicit phosphenes with a retinal origin than a visual cortex origin.

Unlike previous parietal phosphene studies, we did not stimulate directly over lateral posterior parietal cortex. It is, therefore, possible that the IPS is a secondary and independent generator of phosphenes. However, given that percepts were elicited from stimulation of even non-visual areas, namely, the vertex, and phosphene perception was lowest at the midpoint between visual cortex and the vertex, it is likely that previous reports of phosphene perception from stimulation of the IPS are a result of stimulation of nearby visual areas.

Much of the perceptual influence of higher visual areas arises from feedback to early visual cortex (e.g., Pascual-Leone and Walsh 2001; Ro et al. 2003), and studies have shown that stimulation of posterior parietal cortex induces activity in visual cortex (Parks et al. 2015). Research beyond these parietal phosphene studies does suggest that the IPS plays an important role in visual perception, but this role seems to be largely related to the spatial deployment of attention (e.g., Silver and Kastner 2009) and control of saccades (Shibutani et al. 1984). In fact, there are no other examples in the literature besides these parietal TMS phosphene studies (to our knowledge) of IPS generating perception. Therefore, while IPS may indeed have been directly stimulated in these previous parietal phosphene studies, it is unclear whether there is sufficient evidence to support the claim that these percepts are actually generated in the IPS. At the very least, the results reported here call for reconsideration of the possible contributions of early visual areas to the percepts elicited by stimulation over the IPS.

The implications of these results may extend to a larger question of whether higher visual areas are sufficient for generating visual perception. Intracranial stimulation studies in non-human primates (Murphey and Maunsell 2007) and humans (Murphey et al. 2009) have shown that stimulation of higher visual regions alone can elicit visual percepts. From these results, the authors suggest that cortical areas beyond early visual cortex may be sufficient for visual perception. However, given that the frequency of elicited percepts decreases as stimulation moves from early to later visual areas and that the complexity of percepts is unaffected by stimulated region, it is possible that these percepts, too, arise from activity in early visual cortex. Our results suggest that the role of early visual areas in generating visual percepts from stimulation of higher visual areas, such as through orthodromic/antidromic stimulation or from current spread, should not be ruled out.

Implications for using the vertex as a control site

Interestingly, another recent study that mapped the regions of visual cortex capable of producing phosphene perception from TMS indirectly showed that phosphene perception can be elicited from vertex TMS (Schaeffner and Welchman 2017). In that study, a number of control stimulations (48–178, depending on the performance of the subject) were delivered over the vertex. Eight subjects perceived phosphenes on more than one vertex stimulation trial and were consequently excluded from their study. Given that subjects who perceived phosphenes from vertex stimulation were excluded from their study, it is unclear how frequently these subjects would have perceived phosphenes from vertex stimulation and whether this perception was related to head circumference. Furthermore, Schaeffner and Welchman's use of fixed intensity of 80% of maximum stimulator output along with fewer trials and a different coil orientation from our study may have resulted in an underestimation of the rate of phosphene perceptions from vertex TMS. Nevertheless, their results corroborate the findings presented here and demonstrate that vertex stimulation can produce perceptual effects in some subjects.

Given that many TMS studies use the vertex as a control TMS site, our demonstration of reliable phosphene perception from vertex TMS has implications for the selection of appropriate control sites for TMS studies. Structural MRI data would likely provide more details about the anatomical differences associated with phosphene perception from vertex stimulation. However, this information may not be any more informative than the results demonstrated here, given that these anatomical differences (e.g., distance between the scalp and the cortex, distance from the coil to

visual cortex, and distance from the coil to the retina) are likely to be highly correlated with head circumference.

Recently, neuronavigated TMS and modeling techniques have been used to estimate induced electric field and current spread from TMS. However, these methods are unable to definitively determine the mechanism by which activity is induced in distal areas, because they provide only estimates of current spread that do not reflect with certainty where current is actually induced. Furthermore, many of these modelling techniques are based on oversimplified models of the head and brain. This lends their use more toward assessing the general shape of the electric field or measuring correlations between the extent of current spread and stimulation parameters, but precludes the determination of the specific location(s) of stimulation. As a result, data on structure alone are likely insufficient to determine where and how vertex stimulation induces perception. To elucidate these distal effects more definitively, future studies employing neural recording methodologies that are not affected by the TMS artifact, such as optical imaging, may be far more useful. Regardless, the current results suggest that the vertex may not be a suitable "neutral" control site for many TMS studies.

Conclusions

We demonstrate that perception of phosphenes can be elicited from TMS over the vertex but that this perception is most likely due to current spread into the visual cortex and/or the retina. Future work in this area should aim to address the underlying neural mechanism, namely, whether the origin of these visual percepts is the retina or visual cortex. Nevertheless, the finding that effects on visual perception can be elicited from TMS over the vertex—a presumed visually-neutral region of cortex—calls into question the use of the vertex as a control site in studies of visual perception. Given that TMS over this region likely also stimulates visual areas, especially in subjects with smaller heads, it is important that future studies of visual perception carefully consider the characteristics of their sample before employing this region as a control site. Furthermore, determining whether the phosphenes reported from vertex stimulation arise from retinal or visual cortical stimulation, or both, will help to determine whether there might be better active control sites anterior or posterior to the vertex. Traditional control sites, such as the vertex, may also be acceptable under certain conditions (e.g., particular coil orientations/current directions that do not produce phosphenes). Alternative controls, such as the employment of various sham conditions, should also be considered (Bolognini and Ro 2010). Based on the results reported here, we recommend that control conditions are rigorously tested prior to their employment to ensure that stimulation does not elicit behavioral effects. More importantly, our findings also cast doubt on the ability of other higher cortical regions in independently generating percepts after stimulation and further demonstrate the importance of early visual areas in visual perception.

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Compliance with ethical standards

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The procedures performed here were approved by the Institutional Review Board of the City University of New York.

Informed consent Informed consent was obtained from all individual participants included in the study.

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