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Electrocorticography links human temporoparietal junction to visual perception

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Electrical stimulation of visual cortex can produce a visual percept (phosphene). We electrically stimulated visual cortex in humans implanted with subdural electrodes while recording from other brain sites. Phosphene perception occurred only if stimulation evoked high-frequency gamma oscillations in the temporoparietal junction (TPJ), a brain region associated with visual extinction and neglect. Electrical stimulation of TPJ modified the detectability of low-contrast visual stimuli.

Electrical stimulation of occipital lobe can produce the perception of phosphenes, bright spots in the visual field[1]. Phosphenes have been proposed to be a fundamental unit of visual perception and may provide the building blocks for cortical prosthetics for the treatment of blindness[2]. Previously, we electrically stimulated identified human visual areas and found that only some areas support phosphene perception[3]. To search for the neural correlates of perception, we stimulated or recorded from 214 electrodes in three subjects.

In an initial screening step, individual electrodes were electrically stimulated and subjects verbally reported whether they perceived a phosphene. Across three subjects, 16 electrodes produced a phosphene (percept electrodes) and 128 electrodes did not (non-percept electrodes). Percept electrodes were concentrated over early visual areas near the occipital pole[1,3] (**Fig. 1a**). Following screening, one percept electrode and the nearest non-percept electrode (both positioned on occipital cortex) in each subject were selected for experiment 1. Single 5-ms current pulses were repeatedly delivered at a constant current sufficient to always produce a phosphene in the percept electrodes. Subjects were instructed to remain alert, but did not perform a behavioral task. Time-locked to delivery of the electrical pulses, neurophysiological data were collected from all nonstimulated electrodes. Neural oscillations in the gamma range (~30–200 Hz) have been found to reflect neuronal spiking activity[4,5] and may serve as a general mechanism of information processing[6]. We compared the gamma activity evoked by percept and non-percept electrode stimulation and found a much greater response in and around the TPJ

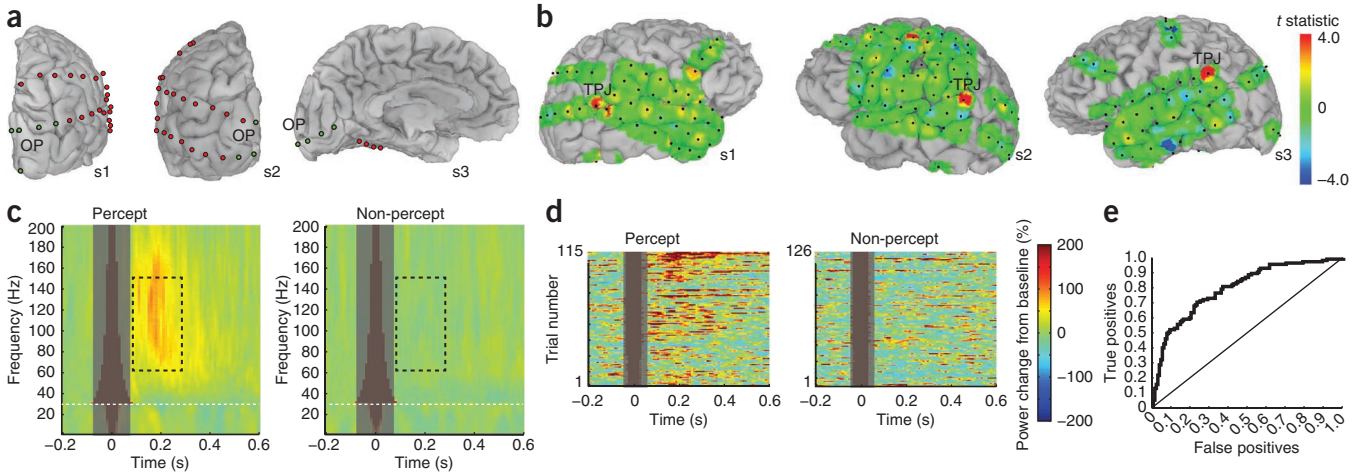

Figure 1 Gamma activity linked to visual perception. (**a**) Percept electrodes (green) that produced a phosphene following electrical stimulation and non-percept electrodes (red) that did not in three subjects. Electrodes were implanted only in a single hemisphere for each subject (right for subject 1, left for subjects 2 and 3). OP, occipital pole. (**b**) The difference in gamma power between percept electrode stimulation and non-percept electrode stimulation in the three subjects. For each subject, one percept electrode and the nearest non-percept electrode in the implanted hemisphere were repeatedly stimulated, and the significance of post-stimulation difference in gamma power at each electrode was calculated and mapped to the cortical surface. Black spheres show electrode locations. (**c**) TPJ response during electrical stimulation of occipital electrodes that did (left) or did not (right) produce a phosphene, averaged across subjects. Color scale indicates power at each frequency. Dark gray bar centered at time = 0 indicates stimulation artifact. Dashed white line indicates boundary between frequency estimate techniques. Dashed black line indicates frequency-time window used to estimate power for single-trial analysis. Color scale as in **d**. (**d**) TPJ gamma responses for every trial during stimulation of a percept (left) or non-percept (right) electrode. Each horizontal line (raster) shows the power in a single trial over time, collapsed across 60–150 Hz. (**e**) ROC analysis of single trial data.

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for percept versus non-percept stimulation (**Fig. 1b**). We selected the electrode closest to the TPJ in each subject for further analysis. When percept electrodes were electrically stimulated, a burst of high-frequency (60–150 Hz) gamma activity was observed in the TPJ (**Fig. 1c**) beginning within 100 ms of stimulation onset and continuing for 200 ms. Non-percept electrode stimulation at the same current produced no such TPJ activity. To quantify this effect, we performed a two-factor ANOVA with stimulation electrode type (percept versus non-percept) as the fixed factor, subject as the random factor and TPJ gamma response as the dependent measure. A significant effect of stimulation electrode type was observed ($F_{1,237} = 64$, $P = 10^{-13}$). Across subjects, the gamma power increased 54 ± 6% (mean ± s.e.m.) with percept electrode stimulation versus −3 ± 3% with non-percept electrode stimulation. To determine whether the effect was specific to high-frequency gamma power, we performed a similar ANOVA with low-frequency power (1–30 Hz) following stimulation as the dependent measure and found a small difference (percept, 8 ± 5%; non-percept, −7 ± 5%; $F_{1,237} = 4$, $P = 0.04$).

To examine the consistency of the TPJ gamma power change, we plotted the TPJ gamma response to single 5-ms pulses of occipital stimulation (**Fig. 1d**). Single pulses of percept electrode stimulation resulted in high TPJ gamma power, whereas single pulses of non-percept electrode stimulation did not. We constructed a receiver operating curve (ROC) to test whether it was possible to discriminate between percept and non-percept trials on the basis of the TPJ gamma response (**Fig. 1e**). A high degree of discriminability was observed (mean d' across subjects = 1.2). This suggests that the TPJ gamma activity carries information that an ideal observer could use in determining whether the subject perceived a phosphene.

The observation that TPJ gamma activity was present on percept trials but not on non-percept trials raises the possibility that TPJ gamma power might be causally related to visual perception. Another possibility is that TPJ gamma power was merely correlated with the location of electrical stimulation: high for stimulation of early visual areas (which tend to produce phosphenes) and low for late visual areas (which tend not to produce phosphenes)[3]. To distinguish these possibilities, we capitalized on the observation that electrical stimulation of percept electrodes over early visual areas does not always produce a phosphene: the likelihood of phosphene perception increases with the stimulation current[3]. Thus, in experiment 2, we stimulated individual percept electrodes in the occipital lobe of each subject, but varied the stimulation current from trial to trial. At low stimulation currents, low levels of gamma power were observed; as the stimulation current increased, so did TPJ gamma power (**Fig. 2a**). To quantify this effect, we carried out a two-factor ANOVA with stimulation current as the fixed factor, subjects as the random factor and the TPJ response as the dependent measure. A significant effect of stimulation current was observed ($F_{3,1236} = 47$, $P = 10^{-28}$). To measure phosphene perception, we asked the subjects to perform a two-interval forced-choice behavioral task that required them to report the interval containing electrical stimulation[7]. At high currents, performance was nearly perfect, indicating that a phosphene was always perceived; at low currents, performance was near chance, indicating no percept. The relationship with increasing stimulation currents was similar for TPJ gamma power (neurometric function) and for behavioral performance (psychometric function), with monotonic increases in both variables (**Fig. 2b**).

The similarity between the psychometric and neurometric functions supported the idea of a link between TPJ responses and perception. The null hypothesis is that while increasing currents led to both improved discrimination and increased TPJ gamma power, these were independent processes. To test this hypothesis we examined trials in the two-interval forced choice task in which the identical near-threshold current was delivered to a percept electrode. As expected, this level of current produced a mix of correct trials in which subjects correctly detected the stimulation interval, suggesting phosphene perception, and incorrect trials in which they did not, suggesting no phosphene perception. If TPJ gamma power was dependent on the amount of stimulation current but not related to perception, we would expect no power difference between correct and incorrect trials because the stimulation current was the same across trials. An ANOVA was performed with trial type as the random factor, subject as the fixed factor, and gamma power as the dependent measure. Across subjects, a significant effect of trial type was observed ($F_{1,465} = 26$, $P = 10^{-6}$) with greater power in correct than incorrect trials (99 ± 5% versus 42 ± 9%), demonstrating a relationship between TPJ gamma power and perception (**Fig. 2c**). It should be emphasized that the physical stimulation parameters in these two trial types were identical: the same electrode and stimulation current.

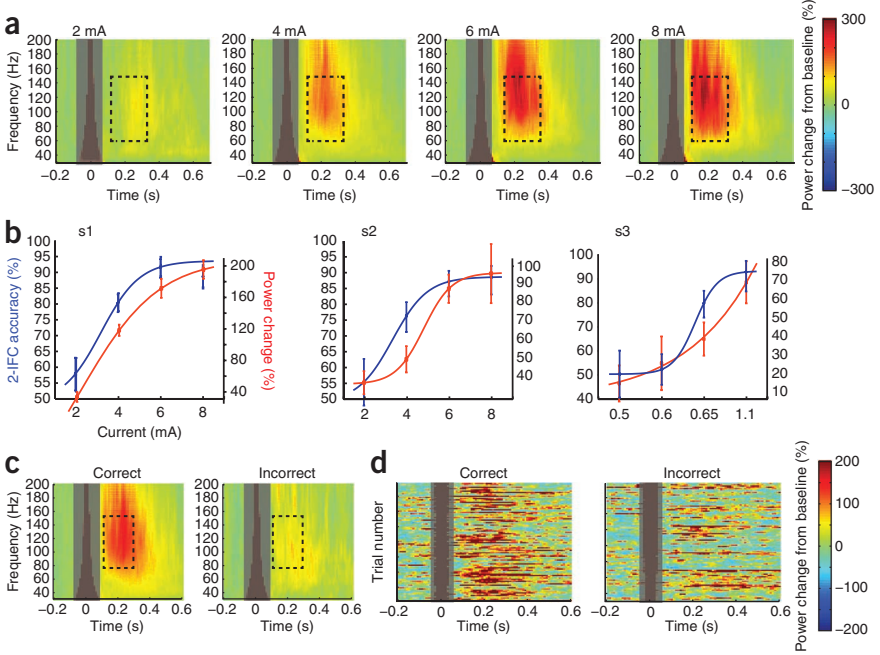

Figure 2 TPJ gamma changes with behavioral performance. (**a**) Average TPJ response during electrical stimulation of three percept electrodes in occipital lobe in subject 1 at varying stimulation currents (2–8 mA). (**b**) Psychometric (blue) and neurometric (red) functions for subjects 1, 2 and 3. Psychometric curve shows behavioral performance during the two-interval forced choice (2-IFC) task at different stimulation currents (error bars show 75% confidence interval from the binomial distribution). Neurometric curve shows TPJ gamma power at the same currents (error bars, s.e.m.) (**c**) TPJ response during percept electrode stimulation with near-threshold currents, averaged across subjects and trials in which subjects correctly or incorrectly performed 2-IFC at the same current. Color scale as in **d**. (**d**) TPJ response in the gamma band for single correct and incorrect trials at the same current.

To examine the reliability of this effect, we examined individual correct and incorrect trials (**Fig. 2d**). An ROC analysis of the individual trial data revealed a significant ability to discriminate correct from incorrect trials based on TPJ gamma power (mean d' across subjects, 0.74).

These results suggest that gamma oscillations in TPJ might be a neural signature of the phosphene percept. If this is the case, an ideal observer could perform the two-interval forced choice task by comparing the TPJ gamma power across the two intervals in a single trial. To test this idea, we compared the TPJ gamma activity between stimulation and nonstimulation intervals in individual trials. In correct trials, there was a very large power difference between the stimulated and nonstimulated intervals (99 ± 5% versus 19 ± 3%, $t_{374} = 14$, $P = 10^{-36}$). In incorrect trials, there was a much smaller power difference between the stimulated and nonstimulated intervals (42 ± 9% versus 20 ± 6%, $t_{93} = 2.2$, $P = 0.03$). An ROC analysis confirmed that an ideal observer could do very well at distinguishing the two intervals in correct trials ($d' = 1.1$), but not in incorrect trials ($d' = 0.3$). This suggests that electrical stimulation of visual cortex on incorrect trials does result in TPJ gamma oscillations, but that the amplitude of the oscillations is below the neural threshold for perception, leaving subjects unable to discriminate the two intervals.

If TPJ gamma oscillations are critical for visual perception, disrupting them should interfere with perception. Thus, in experiment 3, we electrically stimulated the TPJ while subjects detected visually presented sine-wave gratings in a Gaussian window (Gabor patches). A preliminary test examined whether TPJ stimulation in isolation produced a behavioral effect; for instance, if it produced a phosphene, this could hinder perception of gratings in an uninteresting way. In our initial screening, subjects did not report a phosphene following TPJ stimulation. We also performed a more sensitive two-interval forced choice task in which subjects attempted to detect TPJ stimulation; subjects performed at chance level on this task (49%; 95% confidence interval from the binomial distribution = 32–65%). Next, we tested subjects' ability to detect the location of a grating randomly presented in either the left or right hemifield on each trial. At high contrast, subjects easily detected the grating, performing at ceiling (99%, confidence interval = 95–100%). At threshold contrast, subjects detected the grating on 58% of trials (confidence interval = 50–66%). We then electrically stimulated the TPJ while the subjects performed the task; stimulation and nonstimulation trials were randomly intermixed. Subjects continued to perform at ceiling levels (99%, confidence interval = 95% to 100%) for high-contrast gratings, indicating that TPJ stimulation did not interfere with the ability to perform the task. However, for threshold contrast gratings, a significant effect of stimulation was observed. Detection was better for gratings presented ipsilateral to the stimulated TPJ than for gratings presented contralateral to the stimulated TPJ (76% versus 53%, $P = 0.03$, confidence intervals = 66–85% and 42–63%). Relative to no stimulation, performance improved when gratings were presented ipsilaterally (76% versus 58%, $P = 0.05$), but was not significantly different for gratings presented contralateral to the stimulated TPJ (53% versus 58%, $P = 0.6$).

Electrical stimulation of some sites in visual cortex, but not others, produces phosphenes[1,3]. We combined electrical stimulation with electrical recording and found that subjects perceived a phosphene during electrical stimulation only when high-gamma power was recorded in the TPJ. TPJ activity during phosphene perception was observed both during passive stimulation (experiment 1) and while subjects performed a behavioral task (experiment 2), making it difficult to attribute to task performance. Our observation of visual perception–related activity in the TPJ is notable, as converging evidence suggests that the TPJ is critical for detecting behaviorally relevant stimuli[8]. The TPJ has been proposed as a neural generator for the P300 event-related potential, which is linked to target detection across sensory modalities[9]. In particular, damage to ventral regions of parietal lobe, especially the TPJ, may cause difficulties in orienting to a meaningful stimulus presented contralesionally either alone (spatial neglect) or with a simultaneous ipsilesional stimulus (spatial extinction)[10–12]. This suggests a possible parallel with the results of experiments 1 and 2. When electrical stimulation does not produce a phosphene, neural activity is produced at the electrode site, but does not propagate through the cortical network to evoke TPJ activity, and therefore fails to enter conscious awareness just as with neglected/extinguished visual stimuli. In contrast, when neural activity at the stimulation site does propagate to the TPJ, the activity enters conscious awareness and a phosphene is produced. The results of our third experiment suggest that TPJ stimulation alters the ability to detect visual stimuli, with enhanced detection ipsilaterally and reduced detection contralaterally. These behavioral results are consistent with the hemispheric competition model of attentional control[13]. If the TPJ in one hemisphere is disrupted, it becomes less able to detect stimuli in the contralesional hemifield, but also decreases its transcallosal inhibition of the contralateral TPJ, producing an ipsilesional attentional bias that can actually improve detection performance for ipsilesional stimuli[14].

METHODS

Methods and any associated references are available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

M.S.B. and D.Y. designed and conducted the experiments and wrote the manuscript. P.S. conducted the experiments and analyzed the data. S.H.B. conducted the experiments. A.S.T. contributed to experiment 3.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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ONLINE METHODS

Informed consent was obtained and all procedures were approved by the Baylor College of Medicine Institutional Review Board or the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston. We studied three patients who had electrodes implanted for surgical treatment of epilepsy. Subject 1 was a 47-year-old female, subject 2 was an 18-year-old male and subject 3 was a 36-year-old female. Subject 1 had electrodes implanted in the right hemisphere only; subjects 2 and 3 had electrodes implanted in the left hemisphere only. Electrodes that were determined to be near the epileptogenic region of cortex were excluded from the experiment.

Electrical stimulation. For all experiments, the patient being studied was seated comfortably in their hospital bed. Because phosphenes are typically perceived as bright flashes, the patient sat with their eyes open looking at an LCD display showing a black screen to maximize the detectability of phosphenes. A Bak Electronics stimulator was used to deliver electrical stimulation under computer control[15].

Electrophysiological recording and data analysis. Electrophysiological data was recorded using a 128-channel NeuroPort System from Blackrock Microsystems. Stimuli were delivered using Objective C programs running on a Macintosh. Electrophysiological data was acquired at 2 kHz and analyzed using Matlab and the FieldTrip toolbox[16]. Responses were filtered with Savitzky-Golay polynomials[17]. For responses below 30 Hz, a Hanning taper with a fixed window length was used. For responses above 30 Hz, a multitaper filter was used. The ROC analysis was conducted using standard methods and the Matlab function perfcurve. Data from each subject were first analyzed independently. Time-frequency plots (**Fig. 1c**) were combined by simple averaging. To combine the percentage power change data across subjects, repeated-measures ANOVAs were performed using the Matlab function anovan. The dependent measure was the power in the electrode closest to the TPJ. Subject was used as a random factor and trial type (percept versus non-percept or stimulation current level) was used as a fixed factor. Behavioral data from the two-interval forced choice task was analyzed using the Matlab function binofit.

Neuroimaging. Before electrode implantation, structural magnetic resonance scans were obtained using an eight-channel parallel acquisition radio frequency coil on the whole-body 3 T scanner in the University of Texas Health Science Center at Houston Magnetic Resonance Imaging Center (Phillips Medical Systems). The structural scans included two repetitions of a magnetization-prepared 180° radio-frequency pulses and rapid gradient-echo (MP-RAGE) sequence optimized for gray-white matter contrast with 1-mm-thick sagittal slices and an in-plane resolution of 0.938 × 0.938 mm. Three-dimensional surface models of the subjects' brains were reconstructed using FreeSurfer[18,19].

Electrode implantation and localization. Following implantation surgery, the subject underwent whole-head computed tomography (CT). The electron-dense metal electrodes appeared as bright spheres in the CT. The center of each electrode in the ventral temporal strip was manually localized at the center of each sphere. Next, the CT scan was aligned to the pre-surgical structural magnetic resonance imagery using the mutual information algorithm in the 3dAllineate program in the AFNI package. Standard subdural recording electrodes were used (AdTech). Each electrode consisted of a disc of platinum alloy covered in insulating silastic, except for a central 2.2-mm diameter region on the brain side of the electrode. To visualize the location of the electrode in the MR volume, we created a mask volume that consisted of a sphere of diameter 2.2 mm (centered on the electrode) using the AFNI program 3dcalc. To visualize the location of the electrode on the cortical surface, we mapped this mask volume to the nearest nodes on the cortical surface using the AFNI program 3dVol2Surf.

Screening. Individual electrodes were electrically stimulated and subjects verbally reported whether or not they perceived a phosphene, defined as a localized, brief visual percept, commonly described as a flash of light.

Experiment 1. In experiment 1, a single percept electrode and a single non-percept electrode were selected for repeated stimulation. For subject 1, a single 5-ms biphasic pulse of electrical stimulation at 8 mA was delivered for 60 trials at 1.2-s intertrial intervals (ITIs; subject 2, 6 mA, 50 trials, 1-s ITI; subject 3, 2 mA, 50 trials, 1.5-s ITI). Data was collected from all electrodes that were not stimulated. The gamma power was calculated as the percent change in the window 60–150 Hz and 100–300 ms post-stimulation relative to a pre-stimulation baseline consisting of the period of 200–100 ms before stimulation. To create a map of the gamma power on the cortical surface (**Fig. 1b**), we calculated the *t* statistic of the difference in the gamma power following stimulation (compared with pre-stimulation baseline) between percept and non-percept electrode stimulation for each non-stimulated electrode. Then, this *t* statistic was applied to all cortical surface nodes in a sphere with radius of 5 mm centered on each electrode. Finally, spatially smoothing of the *t* values on the cortical surface was applied with a full-width at half maximum of 1 mm.

Experiment 2. In experiment 1, passive stimulation at a single current was used. In experiment 2, subjects made a judgment during each trial of electrical stimulation, and the stimulation current was varied from trial to trial. Each trial contained two intervals, during only one of which a single 5-ms biphasic pulse of electrical stimulation (with a current that varied from trial to trial) was delivered. Subjects performed a two-interval forced choice task, determining which of the two intervals contained the electrical stimulation. The intervals were marked by spoken auditory cues ("one" or "two"), separated by an inter-interval period of 500 ms. Following both intervals, a tone indicated that the subject should respond by pressing one of two mouse buttons to signal their choice, and auditory feedback (a voice saying "good job" for correct trials or "try again" for incorrect trials) was delivered. If no response was received during the 2,500-ms response window, other feedback ("please respond") was delivered. An intertrial interval elapsed (1,200 ms for subject 1, 1,000 ms for subject 2, 1,500 ms for subject 3) before the next trial began.

For experiment 2, a single TPJ electrode was analyzed for each subject. This electrode selection was based solely on anatomical criteria (and the results of experiment 1), meaning that the results of experiment 2 cannot be attributed to selection bias.

To increase trial numbers and to minimize stimulation at each individual site, we stimulated multiple percept electrodes for subject 1. Only one electrode was stimulated at a time, and comparisons between correct and incorrect trials were made only within a single electrode. For subject 1, three percept electrodes were stimulated. The stimulation currents were 2, 4, 6 and 8 mA and there were 130, 280, 130 and 130 trials at each current, respectively. For subject 2, one percept electrode were stimulated at 2, 4, 6 and 8 mA (60, 100, 80 and 59 trials, respectively). For subject 3, one percept electrode was stimulated at 0.5, 0.6, 0.65 and 1.1 mA with 45, 100, 89 and 39 trials, respectively. A near-threshold current was selected as the current that gave closest to 75% behavioral performance. 75% was selected to provide a sufficient number of both correct and incorrect trials for analysis because it is midway between chance level (50%, no phosphenes) and perfect performance (100%, phosphenes always present). This current was 4 mA for subject 1, 4 mA for subject 2 and 0.65 mA for subject 3. There were 226 correct and 54 incorrect trials at these currents for subject 1, 78/22 for subject 2, and 71/18 for subject 3.

Experiment 3. Two subjects were used in experiment 3. Electrical stimulation at 200 Hz was delivered to the TPJ. A control experiment was conducted for one subject. The subject attempted to detect the interval of TPJ stimulation using a two-interval forced choice task[15,20] at a stimulation current of 1 mA for subject 1 (39 trials). For the main experiment, subjects viewed windowed sine-wave gratings (Gabor patches) of varying contrast. Electrical stimulation was delivered beginning at the onset of the visual stimulus (50-ms duration and 1 mA for subject 1, 100 ms and 2.5 mA for subject 2). Gratings were presented at 5° eccentricity (50-ms duration for subject 1, 500 ms for subject 2). At high contrast, there were 114 trials without stimulation and 114 trials with stimulation. At threshold contrast, there were 170 trials without stimulation, 84 trials with ipsilateral stimulation and 89 trials with contralateral stimulation.

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