# tACS entrains neural activity while somatosensory input is blocked

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**Recent results suggest that transcranial alternating current stimulation (tACS) can non-invasively change humans' mental states, but the neural mechanisms behind these exciting results remain poorly understood. Although tACS is traditionally thought to produce electrical fields that directly affect neurons in the targeted area, much of the current never reaches the brain, and flows through the skin instead. Since the skin is packed with somatosensory afferents, this shunted current can produce tactile percepts that affect subjects' behavior, even if the targeted brain area is otherwise unaffected. These sensations are widely recognized as a potential confound in tACS experiments, but a recent *Nature Communications* article by Asamoah, et al. [1] argues that somatosensory input is the principal mechanism underlying the neural effects of tACS. Here, we directly test that hypothesis with neural recordings from non-human primates. We find that tACS entrains hippocampal neurons even when somatosensation is blocked or strongly suppressed, suggesting that peripheral input is not required for tACS to affect the brain.**

Asamoah, et al. [1] suggest that applying alternating current to the scalp (or other skin) produces rhythmic patterns of activity in somatosensory afferents, which then entrain cortical neurons. They argue that peripheral stimulation is necessary for this entrainment, as the skull is too thick and insulative for electric fields generated by tACS to reach the brain. Evidence in support of this hypothesis comes from three experiments in which tACS was applied to motor cortex to entrain physiological tremor in healthy subjects (Experiment 2A) or in essential tremor in patients (Experiment 2B). Tremors became synchronized with tACS when peripheral sensations were intact, even when the stimulation was applied to subjects' arms, rather than

heads (Experiment 3). Topical anesthetic, however, abolished tremor entrainment, even when sensations were only reduced, not completely blocked. These results are construed as showing that motor cortex entrainment requires somatosensory input.

Tremor, however, is a very indirect proxy for neural activity. Tremor is not produced just by activity in motor cortex, but arises from a cerebello-thalamocortical loop [2] that integrates somatosensory information [3]. More generally, the somatosensory and motor systems are closely linked, even in the periphery, which may make Asamoah et al.'s result[1] a special case rather than an example of a more general phenomenon. Indeed, the neurophysiological[4] and behavioral effects of tACS [4,5] are quite sensitive to the position of the stimulating electrodes on the scalp, even though such changes have little effect on the level of somatosensory stimulation.

The relationship between tACS entrainment and somatosensory input thus remains unclear. Since it has major implications for the design and use of tACS devices, this question is best answered by a direct, unambiguous test. The decisive experiment—a comparison of single-neuron entrainment with and without topical anesthesia of the skin—has not yet been performed. Here, we use a non-human primate model system that allows us to collect this data under conditions that closely match human tACS usage.

We first validated in monkeys the effectiveness of 5% EMLA cream, the topical anesthetic used by Asamoah, et al. [1]. In our previous studies [6,7], animals were initially distracted and agitated by the onset of tACS, but eventually learned to continue working despite the evoked percepts. If EMLA effectively blocks somatosensation, it should reduce distractions, increasing the time monkeys spend on-task. Since naive subjects would be most sensitive to these effects, a well-trained monkey that had never received tACS was used for this experiment. Two pairs of tACS electrodes were placed on its head, one on anesthetized skin over one hemisphere and the other at identical locations on the untreated contralateral side. The monkey performed a visual fixation task while bursts of tACS were sporadically applied through each pair of electrodes. As Figure 1 shows, time-on-task was significantly increased ($p < 0.05$) at all stimulation amplitudes when tACS was applied to the anesthetized skin, as compared to control sites. Furthermore, performance was not significantly different from ceiling (100%) during 0.5 and 1.0 mA tACS (0.5 mA: $p=0.07$, $t(10)=-2.01$; 1 mA: $p=0.12$; $t(10)=-1.72$; 1-sample t-test) with anesthesia, but was reduced during control conditions ($p=0.01$ $t(10)=-3.13$ and $p<0.001$ $t(10)=-5.04$, respectively). These data suggest that EMLA increases somatosensory thresholds to ~1 mA, and reduces—but does not eliminate—sensation at 2.0 mA, just as it does in humans (see Figure 6 in Asamoah, et al. [1]).

Next, we asked whether blocking somatosensation during tACS also blocks neuronal entrainment to tACS. Using a monkey that was already acclimatized to tACS (Monkey N), we

recorded the activity of individual neurons in left hippocampus while applying interleaved blocks of 20 Hz tACS and sham stimulation (see Figure 1B) during the fixation task. Every recording session used the same electrode montage, one generating a field strength at the recording site comparable to that found in human studies (~0.3 V/m during ±2 mA stimulation). During 14/22 sessions, the skin under and around each tACS electrode was pre-treated with 5% EMLA; the skin was left untreated for the remaining 8 control sessions.

For each neuron, we calculated two phase-locking values (PLVs), one summarizing its entrainment to the tACS waveform (during tACS) and another showing its entrainment to the corresponding frequency component of the local field potential (during sham). Subtracting these values provides a within-cell measurement of tACS entrainment. Comparing these changes between neurons recorded during EMLA and control sessions then provides an additional measurement of the effect of topical anesthesia.

Data collected during 2 mA stimulation are shown in Figure 2. Under control conditions (Figure 2B), tACS entrained 50 percent of the neurons (N=28/56; $p<0.05$ per-cell permutation tests). The median PLV during tACS was 0.054, significantly larger than that observed during sham blocks (~0, $p<0.001$; Wilcoxon sign-rank test). Similar results were obtained after applying topical anesthetic. As Figure 2C shows, 45 percent of the neurons (N=31/69) were entrained by tACS. PLVs significantly increased with stimulation compared to sham, reaching 0.038 ($p<0.001$; Wilcoxon sign-rank test). Critically, topical anesthesia did not significantly alter the strength of entrainment during tACS ($p=0.35$; Wilcoxon rank-sum test) or the proportion of neurons entrained ($p=0.72$, Odds Ratio=1.19; Fisher's Exact Test). These null results may reflect true equivalence between the control and anesthetic conditions, or a lack of statistical power. We therefore performed an equivalence test [8], which indicated that the difference between these proportions is significantly equivalent to zero (±20%; $p=0.047$, $Z=-1.67$; TOST). Additional analyses confirmed that these results were not affected by the anesthesia's effectiveness varying over time (SI Methods, "Topical Anesthesia").

These data were collected with supra-threshold stimulation, matching the HIGH condition in Asamoah, et al. [1]'s experiments. Similar results, shown in Figure S1, were obtained when stimulation was reduced to 1 mA to match their LOW condition. Neurons tested during EMLA anesthesia also showed significantly increased entrainment during tACS ($p<0.05$; N=12, randomization tests). As before, the strength of entrainment was not significantly different between EMLA and control sessions ($p>0.05$; Wilcoxon rank-sum test), demonstrating entrainment without any behaviorally-detectable somatosensory input.

These results suggest that neural entrainment during tACS, when measured directly, survives a topical blockade of somatosensation. Our data cannot rule out effects produced by any residual somatosensory input. However, Figure 2-3 of Asamoah, et al. [1] demonstrate that

tACS can entrain neurons even when it is applied to the bare skull, with the somatosensory afferents completely removed. Nevertheless, peripheral nerve stimulation has undeniable effects that may confound behavioral experiments and indirectly entrain neurons in brain regions receiving strong somatosensory input. It may be possible to combine these influences to produce more effective stimulation [9]. Additionally, scalp stimulation may affect the vagus or other cranial nerves [10]. These effects will necessarily vary across brain regions and stimulation protocols, frustrating any simplistic interpretation of the tACS literature. Nevertheless, our data are consistent with a role for direct neural entrainment by tACS.

## Data availability

Raw data and code is available by reasonable request.

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## AUTHOR CONTRIBUTIONS.

P.G.V and M.R.K collected and analyzed the data. P.G.V, M.R.K, and C.C.P wrote the paper.

## COMPETING INTERESTS.

The authors declare no competing interests.

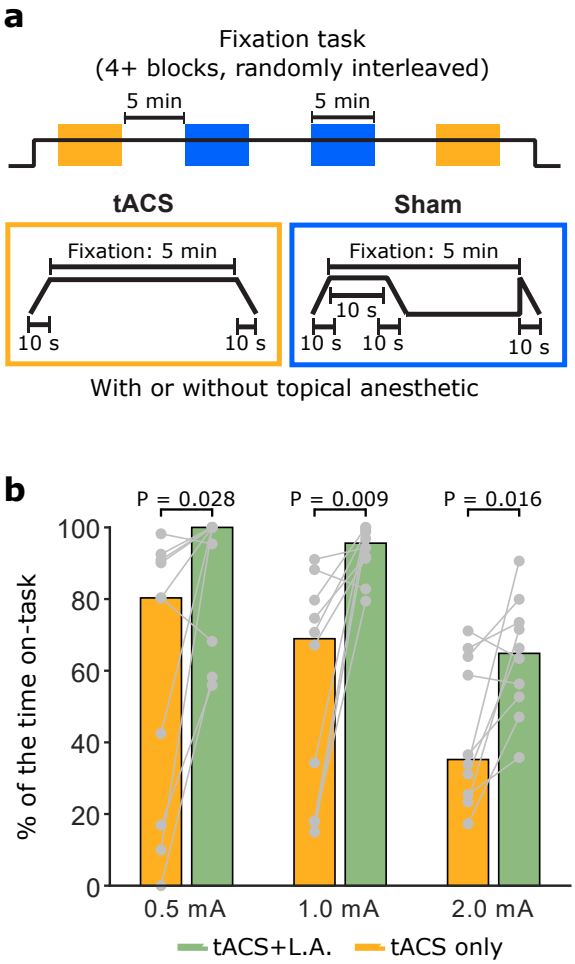



**Figure 1. Experimental Paradigm and Validation**. **a)** We applied 20 Hz tACS and sham stimulation in randomly interleaved 5 minute blocks, separated by a 5 minute interstimulus interval. Inset figures describe the envelope of each condition's waveform: 10 sec ramp-up/down and 5 minutes of full stimulation. Animals continuously performed the fixation task for the entire session. **b)** We adapted this paradigm to validate the effectiveness of topical anesthesia. Stimulation blocks were reduced to 15 seconds, with 3 second ramp-up/down to maximize the number and intensity of ramps, which typically disrupt this animal's behavior. To quantify this disruption, we recorded the proportion of time that the animal's gaze remained within 2 degrees of the fixation target. Topical anesthesia (TA, green bars) significantly reduced this disruption at all current levels (Wilcoxon sign-rank tests, 0.5mA: p=0.028; Z=-2.19, 1mA: p=0.009; Z=-2.60, p=0.016; Z=-2.39) when compared to stimulation applied over intact skin (yellow bars). Individual data points are shown in grey. These data suggest that EMLA effectively blocks or reduces tACS-related somatosensation.

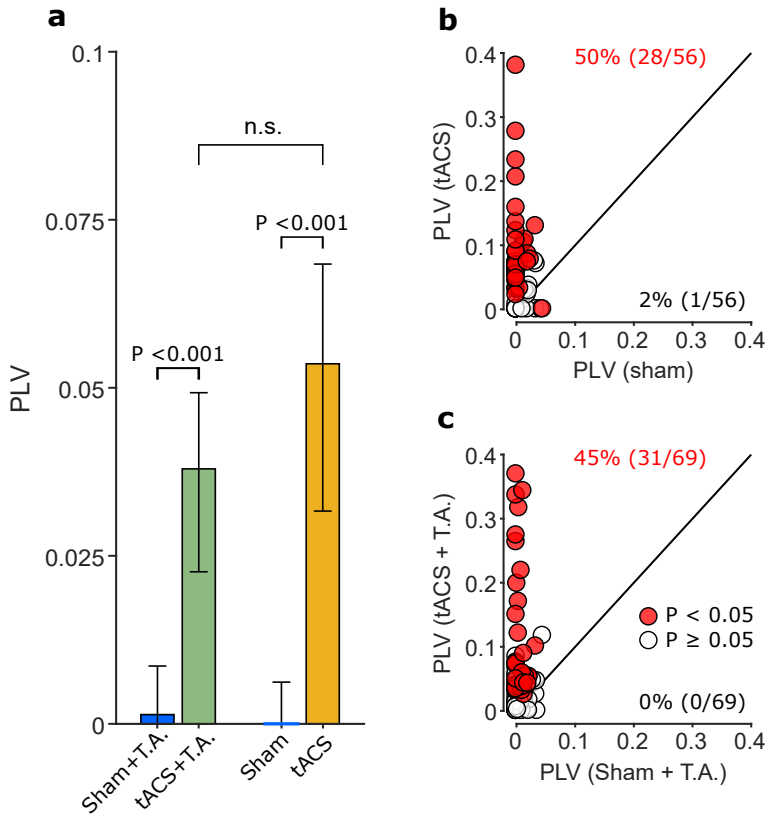
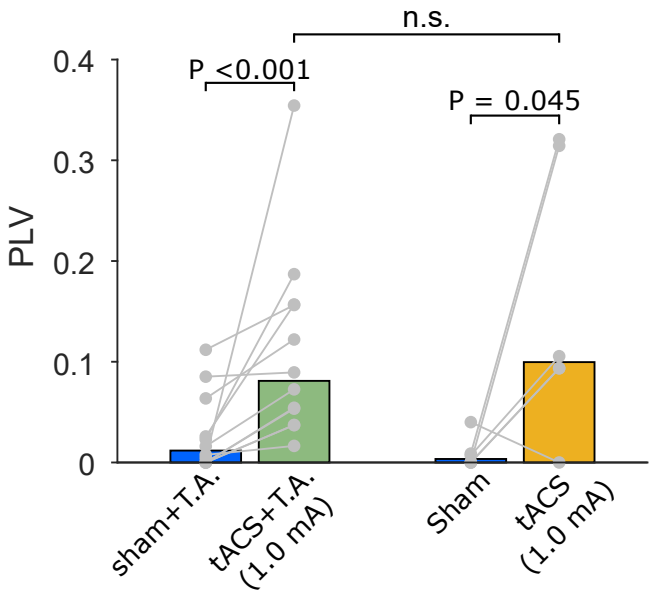



**Figure 2. Topical Anesthesia does not reduce neuronal entrainment.** Using the paradigm in Figure 1 (see also SI Methods), we measured neuronal entrainment during 2mA 20 Hz tACS and sham stimulation during 14 sessions with anesthesia (green bar) and 8 without (yellow bar). Phase-locking values were computed for each neuron in both conditions. **a)** Median and interquartile ranges, separated by anesthetic conditions. Applying tACS significantly increased entrainment vs. sham in both anesthesia and control conditions (TA: $p<0.001$; $Z=-5.93$; Control: $p<0.001$; $Z=-5.39$ Wilcoxon sign-rank test), but there was no statistically significant (n.s) effect of anesthetic ($p=0.35$ $Z=-0.92$; Wilcoxon rank-sum test). **b & c)** PLV values during sham (abscissa) and tACS (ordinate) for each neuron recorded during control (b) and anesthesia (c) sessions. Cells showing individually significant changes in PLV are shown in red ($p<0.05$, randomization tests). The proportion of cells exhibiting significantly increased or decreased entrainment is shown above/below the unity line. Values in red indicate proportions larger than would be expected by chance (i.e., outside the 95% binomial confidence interval for $p=0.05$).

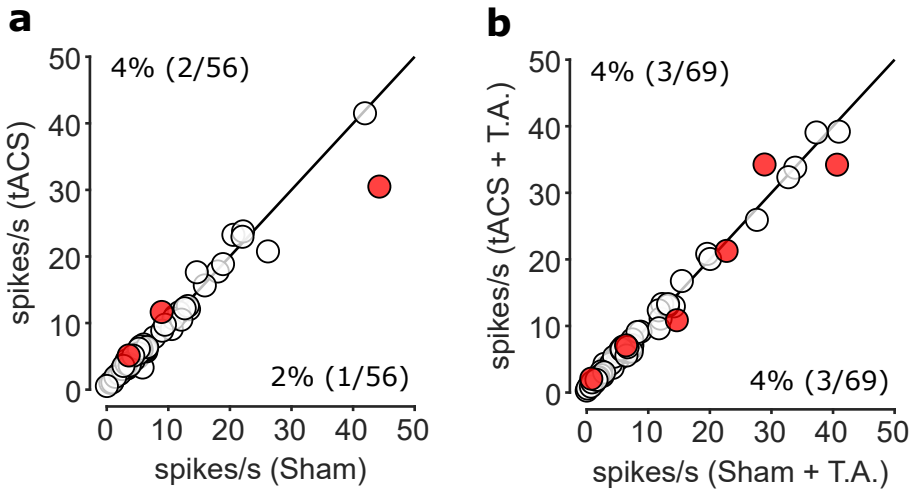
## Supplementary Information

# tACS does not require somatosensory input to entrain neurons

Pedro G. Vieira, Matthew R. Krause, and Christopher C. Pack (2019)




**Supplementary Figure 1.** Same as Figure 2a, but data were collected using 1 mA, rather 2 mA stimulation, corresponding to Asamoah et al.'s LOW conditions. As before, tACS increases entrainment during topical anesthesia (TA, green) and control conditions (yellow), but by indistinguishable amounts.




**Supplementary Figure 2.** Firing rates during 2 mA control (a) and topical anesthesia (TA) (b) sessions, plotted in the style of Figure 2b and 2c. Rates were distributed along the equality line, indicating the firing rates did not change across conditions. The few filled circles indicate neurons with individually significant changes at the p=0.05 level. However, the proportion of cells showing these changes in firing rate is consistent with our p=0.05 threshold for each cell.

# Supplementary Methods

This paper describes data collected from two adult male rhesus monkeys (*Macaca mulatta*), using techniques and experiments that, with the exception of the topical anesthesia, are virtually identical to those in our previous work[1,2]. Monkey N (7 year old male, 10 kg), from whom neurophysiological data was recorded, participated in the experiments described in Krause, et al. (2019)[1], while Monkey S (9 year old male, 20 kg), used to validate the topical anesthetic regime, was obtained specifically for these experiments. These procedures were approved by the Montreal Neurological Institute's Animal Care Committee and conformed to the guidelines of the Canadian Council on Animal Care.

## Transcranial Alternating Current Stimulation

Using the method described in our previous work[1,3], we built an individualized finite-element model from MRIs of Monkey N's head and neck, which was solved to find a montage that maximized field strength at the recording site. This montage corresponds to Fp1/O1 in 10-10 coordinates, and was predicted to produce a field of 0.26 V/m. We verified this prediction in [1], where we reported that the mean field strength was 0.19 ±0.02 V/m (mean ± standard error) with peak strengths of up to 0.35 V/m.

We applied stimulation using an unmodified StarStim8 system (Neuroelectrics, Barcelona, Spain), using 1 cm (radius) Ag/AgCl electrodes (PISTIM; Neuroelectrics; Barcelona) coated with conductive gel (SignaGel) and attached to the intact scalp with a thin layer of silicon elastomer (Kwik-Sil, World Precision Instruments). Electrode impedance was continuously monitored during the experiment and was typically between 1-2KΩ, and always below 10 KΩ.

Stimulation consisted of a 20 Hz sinusoidal waveform; its envelope is shown in Figure 1A. We did not optimize the stimulation frequency or phase for individual subjects, but our previous experiments[1] demonstrate that neurons readily entrain to this frequency. For the neurophysiology experiments, current was linearly ramped up from 0 to ±1 or ±2 mA over 10 seconds, held at full amplitude (±1 or ±2 mA) for five minutes, and then ramped back down to 0, again over 10 seconds. The sham stimulation contains the same ramp-up period, but current remained at at full amplitude (±1 or ±2 mA) for 10 seconds, before being ramped back down. Since steeper ramps produced stronger percepts, the ramp length was decreased to 3 seconds for the behavioral experiments.

## Topical Anesthesia

We used 5% EMLA cream, the same topical anesthetic used by Asamoah et al., to control somatosensory input. At the beginning of topical anesthesia experiments, a thick layer of EMLA cream (~3 grams) was applied to a 5 cm (diameter) region surrounding each electrode site. Following the manufacturer's recommendations, the cream was tightly covered with a plastic dressing and allowed to absorb for approximately one hour (median: 52 minutes, range: 46-72 minutes). The skin was then cleaned with soap and water, followed by alcohol, and allowed to air-dry before the tACS electrodes were attached. Recording typically began 15-20 minutes later, and were always completed within two hour anesthetic window recommended by the manufacturer (median: 68 minutes, range: 24-92 minutes). To ensure an accurate comparison, behavioral experiments in Figure 1 were delayed to match the setup time needed for recording.

To verify this window, we analyzed each block of data collected during anesthesia sessions separately, using a mixed-effects model with fixed effects of stimulation time (tACS or sham), EMLA 'dose' (the duration of EMLA pretreatment, in seconds), and the time elapsed between EMLA removal and midpoint of each block (in seconds). The model also included a random intercept for each block (to account for neurons recorded simultaneously) and a random intercept and slope for stimulation type (to account for cell-specific factors). As in the main text, we find that entrainment significantly increases during tACS ($p<0.001$, $t(267)=3.35$), but the model's anesthesia-related coefficients are both indistinguishable from zero (EMLA dose: $p=0.82$; $t(267) = 0.225$; time elapsed: $p=0.49$; $t(267)=-0.692$). These features had little impact on the model, and removing them increased its parsimony, as measured by AIC and BIC (**Δ**AIC = 3.5; **Δ**BIC = 10.7). A similar non-parametric analysis found no significant differences in entrainment between blocks that were recorded 30, 45, or 60+ minutes after EMLA removal ($p>0.05$; Kruskal–Wallis test).

## Behavioral Task

Since arousal and occulomotor activity can strongly affect neural oscillations, we used a simple fixation task to control the animal's behavioral state and minimize eye movements.

Animals sat in a standard primate chair (Crist Instruments; Hagerstown, Maryland), 57 centimeters from a computer monitor covering the central 30˚ x 60˚ of their visual field. We monitored eye position non-invasively, using an infrared eyetracker (Eyelink-1000; SR Research, Ontario Canada). Monkeys were trained to fixate a small

black target (~0.5°) presented against a neutral grey background. Whenever their gaze remained on this target for ~1-2 seconds, they received a liquid reward. Inter-reward intervals were drawn from an exponential distribution (with a flat hazard function) to prevent entrainment to rewards or expected rewards. Both animals had received extensive training before these experiments, and tended to maintain their gaze continuously on the fixation target.

Custom software written in Matlab (The Mathworks, Natick, MA, USA) controlled the behavioral task and coordinated the eye tracker, tES stimulator, and recording hardware.

## Neural Data Collection

Single-neuron data was obtained from the left hippocampus, an interesting test-bed for these experiments because it receives input from a wide range of areas, including sensory ones, yet is not tightly tied to any specific modality.

At the start of each recording session, we penetrated the dura with a sharpened 22 ga. stainless steel guide tube. A 32-channel V-Probe with 150 μm spacing (Plexon Inc; Dallas, Texas) was then inserted into the guidetube and positioned with a NaN Microdrive (NaN Instruments; Nazareth Illit, Israel). The target depth was determined from the animal's MRIs, and confirmed via CT. The electrode position for Monkey N is shown in Supplemental Figure 1 of Krause, et al. (2019)[1]

Wideband signals were recorded using a Neural Interface Processor (Ripple Neuro; Salt Lake City, Utah). Signals were referenced against the guidetube, bandpass filtered between 0.3 and 7500 Hz, and stored at 30,000 Hz with 16 bit/0.21 μV resolution for offline analysis.

The raw wideband signals were first preprocessed with PCA-based filtering algorithm adapted from [4] to attenuate stimulation artifacts. Next, single units were identified by bandpass filtering the signal between 500-7000 Hz with a 3rd order Butterworth filter and thresholding it at ±3 standard deviations. The 2 ms segments around each threshold crossing were then sorted using UltraMegaSort 2000, a *k*-means overclustering algorithm[5]. Its results were manually reviewed and refined to ensure that each unit had a clear refractory period, stable width and amplitude, and good separation in PCA space.

## Data Analysis

We quantified the neurons' entrainment to the electrical stimulation using pairwise phase consistency (PPC), a measure of the synchronization between a point process

(spikes) and a continuous signal (tACS or local field potential) with several statistical advantages over a direct calculation of the phase-locking value or spike-field coherence [6]. PPC scores are an unbiased estimate of the square of the phase-locking values (PLVs) used by Asamoah et al., so we reported values as PLVs to facilitate comparison with previous work.

Neurons may fire rhythmically even in the absence of stimulation. We therefore compared entrainment to the tACS waveform (during stimulation) with entrainment to the corresponding frequency component (20±1 Hz) of the local field potential (LFP), during sham stimulation. Only the middle four minutes of each block was analyzed, when no current whatsoever was being applied during the sham condition. In both cases, the continuous signal came from an adjacent channel to avoid spectral contamination by the spiking activity[7]. This approach also accounts for physiological distortions of the tACS waveform[8].

Data acquisition or signal processing artifacts could potentially produce the appearance of entrainment. If the tACS saturated the recording system, for example, spikes might not be detectable during certain phases of the stimulation cycle, which would decrease neurons' apparent firing rate. As Figure S2 shows, however, firing rates were not significantly different ($p>0.05$) between stimulation and sham conditions. Our previous work [1] describes a number of other analyses and controls addressing this issue, using data collected with the same equipment, monkey, and electrodes. We showed that entrainment is unrelated to firing rate or signal amplitude, and neurons' waveforms remain consistent between tACS and sham conditions, as well as across different phases of the tACS. These analyses suggest that the entrainment seen here is unlikely to be due to technical issues.

Our analyses combine all data collected in the same condition, though a block-by-block analysis (see Topical Anesthesia, above) yields the same conclusion. Where possible, non-parametric tests were used avoid distributional assumptions. Randomization tests were used to compare PPC values across tACS and sham conditions; population-level analyses were carried using Wilcoxon rank-sum and sign-rank tests, as appropriate. All statistical tests are two-tailed. Sample sizes were determined based on our previous work[1] and data was analyzed using Matlab (The Mathworks, Natick, MA).

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