Visual cortex responds to transient sound changes without encoding complex auditory dynamics

Abbreviated Title: Visual cortex is sensitive to sound transients

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Conflict of Interest Statement

The authors declare no competing financial interests.

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Data and Code Availability

Data and code used in analyses will be made available at the time of publication.

ABSTRACT

Sounds enhance visual cortical sensitivity for co-occurring visual signals. Previous research has demonstrated that this facilitation occurs through crossmodal modulations of cortical oscillatory activity. However, the neural origin of these signals and auditory information conveyed by this mechanism remain poorly understood. Using intracranial electroencephalography (iEEG) in humans, we examined the sensitivity of visual cortex to three different forms of auditory information: rhythmic entrainment to sounds, auditory onset responses, and auditory offset responses. Subcortical auditory neurons exhibit frequency following behaviors in response to amplitude-modulated sounds, with oscillatory activity entrained at the rhythmic rate of the auditory signal. This auditory response is paralleled in the visual system by the entrainment of visual neurons to the rhythmic rate of flashing strobe lights. In contrast, ~20% of neurons in auditory cortex do not entrain to amplitude modulations but respond only to the onsets and/or offsets of auditory stimuli. In visual cortex, amplitude-modulated sounds elicited transient onset and offset responses in multiple areas, but no entrainment to the sounds' modulations frequencies. These results suggest that auditory information conveyed to visual cortex does not include temporally fine-grained stimulus dynamics encoded by the auditory midbrain and thalamus but, rather, a temporally segmented representation of auditory events that emerges only in auditory cortex. Crossmodal responses were maximal in low-level visual cortex, potentially implicating a direct pathway for rapid interactions between low-to-mid-level auditory and visual cortices. This mechanism may facilitate perception by time-locking visual computations to environmental events marked by discontinuities in auditory input.

HIGHLIGHTS

- Sounds modulate visual processing and can enhance visual cortical excitability
- The information transmitted from auditory to visual regions is poorly understood
- We used electrodes implanted in humans to test what auditory signals are relayed
- Sounds transferred an event-segmented representation of auditory events (on/offset)
- Sounds did not transfer fine-grained auditory information (e.g., entrainment)

Keywords: Multisensory; Audiovisual; Amplitude Modulation; ECoG; Intracranial, Phase-reset

1. INTRODUCTION

Co-occurring sounds can facilitate the detection and identification of visual stimuli (Lippert et al., 2007; Jaekl and Soto-Faraco, 2010; Chen et al., 2011), but the neural pathways and mechanisms underlying these multisensory interactions are poorly understood. At subcortical levels, signals from the inferior colliculus or auditory thalamus could be transmitted to visual cortex via the tecto-pulvinar system (Lyon et al., 2010) or other thalamocortical connections conveying modulatory signals (Cappe et al., 2012). Cortically, auditory signals could instead be relayed to visual cortex via direct cortico-cortical pathways connecting low-level auditory and visual cortex (Falchier et al., 2002; Rockland and Ojima, 2003; Clavagnier et al., 2004) or feedback connections from multisensory association cortex (Falchier et al., 2002; Noesselt et al., 2007; Borra and Rockland, 2011; Leitão et al., 2012).

While early investigations focused on multisensory convergence in the superior colliculus and higher-order association cortices (Stein and Meredith, 1993; Ghazanfar and Schroeder, 2006), recent research has demonstrated the importance of crossmodal modulations of oscillatory activity in nominally “unisensory” cortical areas (Kayser and Logothetis, 2007; Thorne and Debener, 2014; van Atteveldt et al., 2014; Murray et al., 2016) such as sounds evoking early responses in primary visual cortex (Brang et al., 2015; Plass et al., 2019). By crossmodally entraining or resetting the phase of oscillations in visual cortex, simple transient sounds can enhance cortical sensitivity for temporally coupled visual input (Lakatos et al., 2009; Naue et al., 2011; Romei et al., 2012; Mercier et al., 2013, 2015). However, because the signals driving these crossmodal modulations may originate from many levels of the auditory processing hierarchy (Schroeder and Foxe, 2005; Driver and Noesselt, 2008; Cappe et al., 2009, 2012), the content and representational complexity of the information conveyed by this mechanism are unknown.

The auditory system encodes a large number of perceptually relevant dimensions from auditory signals, including pitch, spatial location, sound onset and offset, and rhythmic responses, among others (for a review see Wang, 2018). While it is well-documented that sounds can bias visual perception and modulate visual activity, the information encoded in this auditory-visual transmission has received much less

attention. The strongest evidence to date demonstrates that sounds can bias visual cortex onset timing and visual spatial processing (e.g., Romei et al., 2007, 2009, 2012; McDonald et al., 2013). However, it is unclear what other forms of auditory information is transmitted to visual areas and show relevance to behavior. To better understand the content present in auditory-visual transmissions, we used intracranially implanted electrodes in humans (intracranial electroencephalography; iEEG) to measure the sensitivity of visual cortex to three different forms of auditory information: rhythmic entrainment to sounds, auditory onset responses, and auditory offset responses.

In general, auditory neurons exhibit frequency following behaviors in response to amplitude modulated (AM) sounds (Figure 1), with oscillatory activity entrained at the rhythmic rate of the auditory signal (Joris et al., 2004). This auditory response is paralleled in the visual system by the entrainment of visual neurons at the rhythmic rate of flashing strobe lights (Foster et al., 1985; Norcia et al., 2015). The fidelity at which neurons entrain to higher frequency AM sounds decreases along the auditory processing hierarchy (Steinschneider et al., 1998; Giraud et al., 2000; Harms and Melcher, 2002; Joris et al., 2004), with preferred modulation frequencies decreasing from approximately 32-64 Hz in the inferior colliculus (Müller-Preuss et al., 1994), to 16-32 Hz in the medial geniculate nucleus (Preuss and Müller-Preuss, 1990), to less than 16 Hz in auditory cortex (Bieser and Müller-Preuss, 1996). Moreover, auditory cortical neurons exhibit transient responses to the onsets and offsets of AM sounds that are not observed in auditory subcortical regions or thalamocortical fibers, indicating a transition toward event-segmented stimulus coding that emerges in primary auditory cortex and is subsequently passed onto higher auditory regions (Chatrian et al., 1960; Steinschneider et al., 1998; Giraud et al., 2000; Harms and Melcher, 2002; Harms et al., 2005). By characterizing the temporal response properties of crossmodal modulations, it can be inferred whether auditory information conveyed to visual cortex primarily reflects this event-segmented cortical representation of auditory stimuli, or the temporally

Figure 1. Schematic of Experiment 1 auditory task, showing three example amplitude modulated (AM) sounds at different AM frequencies.

fine-grained representation of stimulus dynamics observed in auditory subcortical and, to a lesser extent, cortical neurons.

2. MATERIAL AND METHODS

2.1 Participants

Data were acquired from patients with epilepsy during invasive work-up for medically intractable seizures using intracranial electroencephalography (iEEG) monitoring from chronically implanted depth electrodes (5 mm center-to-center spacing, 2 mm diameter) and/or subdural electrodes (10 mm center-to-center spacing, 3 mm diameter). 16 patients participated in Experiment 1. Patients ranged in age from 17-50 (mean = 37.5, mean absolute deviation = 7.9) and included 8 females. 13 patients with epilepsy (7 of whom were included in Experiment 1) participated in Experiment 2. Patients ranged in age from 21-49 (mean = 36.8, mean absolute deviation = 9.1) and included 5 females. For both experiments, electrodes were placed according to the clinical needs of the patients. Written consent was obtained from each patient according to the direction of the institutional review boards at the University of Michigan, University of Chicago, and Henry Ford Hospital.

2.2 Method Details

2.2.1 Amplitude-modulated Sound Paradigm

Patients were seated in a hospital bed. Auditory stimuli (approximately 65 db-SPLA) were delivered via a laptop using PsychToolbox (Brainard, 1997; Pelli, 1997) through a pair of free-field speakers placed approximately 15 degrees to the right and left of participants' midline. A central fixation cross against a blank background was presented on the laptop display throughout the duration of the experiment. Patients were instructed to maintain central fixation and passively listen to presented sounds.

In Experiment 1, participants were presented with 1- or 2-second in duration auditory stimuli consisting of sinusoidally amplitude-modulated white noise with different rates of modulation (100%

modulation depth). For three participants, trials included nine different AM rates, ranging from 10 Hz to 50 Hz in 5 Hz intervals (2 seconds in duration), with 10 trials of each condition, resulting in 90 total trials. For the remaining 13 participants, trials included 10 different AM rates, ranging from 5 Hz to 50 Hz in 5 Hz intervals (1 second in duration), with 20 trials of each condition, resulting in 200 total trials. The sounds were presented in a randomized order for each participant, and the inter-sound interval was randomly varied between 1.25 - 1.75 seconds (uniform distribution) for variant A of the task, and 2.25 - 2.75 seconds (uniform distribution) for variant B of the task. The paradigm was updated across participants with an increase in the number of trials to increase the signal-to-noise ratio in detecting transient onset responses while maintaining sensitivity to entrainment (if it was present).

In Experiment 2, participants were presented with 10-second in duration AM sounds. Patients 1-4 were presented with 36 trials of 10-second sounds consisting of amplitude-modulated white noise differing in the rate and depth of modulation. The sounds were presented in a randomized order for each participant, and the inter-sound interval was randomly varied between 4 and 6 seconds (uniform distribution). Patients 5-13 were presented with 8 trials of 10 second sounds consisting of white noise amplitude-modulated at 40 Hz at 100% depth with an inter-sound interval randomly varying between 12 and 14 seconds (uniform distribution). The present study reports neural activity evoked by sounds amplitude-modulated at 40 Hz at 100% depth (a subset of the amplitude-modulated sounds presented for participants 1-4 totaling 40 seconds per participants, and all of the amplitude-modulated sounds presented for participants 5-13 totaling 80 seconds). 40 Hz AM sounds were selected for Experiment 2 to increase the chances that a maximally robust auditory entrainment signal would be transmitted and isolated visual cortex if it exists, given the sensitivity of auditory regions to this rate and as 40 Hz is above the range of activity modulated by transient onset/offset responses.

2.2.2 MRI and CT Acquisition and Processing

A preoperative T1-weighted MRI and a postoperative CT scan were acquired for each participant

to aid in localization of electrodes. Cortical reconstruction and volumetric segmentation of each participant's MRI was performed with the Freesurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>) (Dale et al., 1999; Fischl et al., 1999). Postoperative CT scans were registered to the T1-weighted MRI through SPM and electrodes were localized along the Freesurfer cortical surface using customized open-source software developed in our laboratories (Brang et al., 2016) (available for download online <https://github.com/towle-lab/electrode-registration-app/>). This software segments electrodes from the CT by intensity values and projects the normal tangent of each electrode to the dura surface, avoiding sulcal placements and correcting for post-implantation brain deformation present in CT images.

2.2.3 Intracranial Electroencephalography (iEEG) Data Acquisition and Pre-processing

For Experiment 1, iEEG recordings were made at either 1024 Hz (10 participants), 4096 Hz (4 participants), or 1000 Hz (2 participants) due to differences in the clinical amplifiers used. For Experiment 2, recordings were made at either 1024 Hz (7 participants), 4096 Hz (3 participants), or 1000 Hz (3 participants). Data recorded at 4096 Hz were down-sampled to 1024 Hz for the initial stages of processing, and all participants' data were resampled to 1024 Hz for group-level time-frequency analyses. The onset of each trial was denoted online by a voltage isolated TTL pulse. In order to ensure that electrodes reflected maximally local and independent activity, we used bipolar referencing. Noisy channels were identified by first calculating the standard deviation across time for each channel (resulting in one value per channel) and then by comparing this value across channels: those with a value exceeding 5 standard deviations above or below the mean were excluded. Noisy trials were identified by first calculating the standard deviation across time for each trial (resulting in one value per trial) and then by comparing this value across trials: those with a value exceeding 3 standard deviations above or below the mean were excluded. Following the rejection of artifactual channels and trials, data were high-pass filtered at .01 Hz to remove slow drift artifacts, and notch-filtered at 60 Hz and its harmonics to remove line-noise.

2.2.4 Electrode Selection

Auditory and visual electrodes included for analyses were selected on the basis of their functional responses and anatomical locations. Spatial selection of the auditory electrodes was limited to those located proximal to the superior temporal gyrus or neighboring white matter based on the Desikan-Killiany-Tourville atlas calculated on individual-participant Freesurfer cortical parcellations. Functional selection of the auditory electrodes was limited to those that showed significant early event-related potential (ERP) responses to sounds (AM sounds for Experiment 1, tones and noise-bursts obtained from separate tasks for Experiment 2). Spatial selection of the visual electrodes was limited to those located in occipital, parietal, or inferior temporal areas or neighboring white matter. Functional selection of the visual electrodes was limited to those that showed significant early ERP responses to salient visual stimuli (including faces, houses, and other objects, obtained from separate tasks for both Experiments 1 and 2). A significant functional response across both auditory and visual areas was defined as any significant deviation from baseline between 0-120 ms: statistics were calculated using one-sample *t*-tests separately at each timepoint, with random effect = trial, and corrected for multiple comparisons across time-points using FDR. ERPs were used for functional localization because our analyses focus on low-frequency oscillations that are reflected in the ERP waveform. Locations for each participant's electrodes are given in Supplemental Table 1 and participant-specific maps are shown in Supplemental Figures 1 and 2.

2.3 Quantification and Statistical Analyses

After pre-processing, iEEG data were segmented into 6-second epochs (-3 to 3 seconds around the onset of the sound) for Experiment 1 and 24-second epochs (-12 to 12 seconds around the onset of the sound) for Experiment 2. For all analyses, the resultant epochs were convolved with wavelets of varying center frequencies (either 1-20 Hz or 1-50 Hz depending on the analysis) and durations (number of cycles equal to the center frequency, with a minimum of 3) before calculating instantaneous phase-angles for each

time-point, frequency bin, and trial. At each timepoint for each convolved frequency, inter-trial phase coherence (ITPC) was calculated as the magnitude of the complex average of the phase-angle vectors across trials. For all analyses except the time-frequency analyses, these values were averaged over the duration of each analysis period of interest, yielding a single value for each condition/electrode indexing average phase alignment across each period. ITPC values are bound between 0 (uniform phase angle distribution) and 1 (identical phase angles across epochs). Throughout all analyses, only increases in ITPC values were considered significant because both phase-reset and entrainment are expected to produce increases, and not decreases, in ITPC. Results for electrode-specific analyses of transient onset, transient offset, and entrainment responses are tabulated according to participant and electrode location in Supplemental Figure 1.

2.3.1 Analysis of Transient Phase Coherence

For group-level analyses of transient ITPC, each epoch was convolved with 20 wavelets with center frequencies ranging from 1-20 Hz in 1 Hz intervals, with the number of cycles varying across this frequency range (3 cycles for the frequencies 1-3 Hz and 4-20 cycles varied linearly for the frequencies 4-20 Hz). For group-level comparisons against baseline, ITPC was calculated separately for each frequency band and each electrode during the pre-stimulus baseline period (-1000 to -500 ms) and the 200 ms stimulus onset or offsets period (0 to 200 ms); additional time was included in the baseline period to ensure stable 'null' ITPC values. Frequency-specific ITPC values for each period were subtracted and Fisher's Z-transformed before averaging across frequencies to produce electrode-specific difference scores. These difference scores were then averaged across each participant's auditory or visual electrodes, and these participant-level difference scores were compared to 0 using a one-tailed, one-sample *t*-test. Because 3/7 participants with auditory electrodes were not tested on the 5 Hz AM sound condition, this condition was omitted from group-level analyses of auditory electrodes.

For group-level time-frequency analyses, ITPC values for each time-point (-1 to 1 second) and

frequency band were first averaged across electrodes within each participant and then averaged across participants. Significant time-points were identified in the 0 to 1 second range relative to the pre-stimulus baseline period (-1 to -.5 seconds) using one-tailed one-sample *t*-tests at each time-point and frequency. Multiple comparison corrections were applied using cluster statistics, in which the time-frequency map of *t*-value statistics is permuted 10,000 times in order to identify clusters of significant contiguous pixels (at $p < .05$) that are larger than those in 95% of the permuted data (Cohen, 2014).

For single-electrode analyses of transient ITPC, phase-shuffling was used to generate a null distribution of ITPC values for the 200 ms onset period in each electrode. For 10,000 iterations, a random value ranging from $-\pi$ to $+\pi$ (uniformly sampled) was added to each trial prior to calculation of ITPC. The distribution of ITPC values produced by this procedure is designed to reflect the expected distribution of values observed under purely spurious phase coherence. *P*-values were determined by identifying the proportion of values from this distribution that equaled or exceeded observed ITPC values, and then were corrected for multiple comparisons using FDR correction ($q = .05$).

The proportions of electrodes exhibiting transient onset responses near area V5/hMT+ versus other visual areas were compared using a permutation test with restricted exchangeability (Winkler et al., 2015). For each of 10,000 permutations, labels indicating electrode location were permuted so that the relationship between electrode location and ITPC significance was obliterated, and the number of significant electrodes with a V5/hMT+ label was recorded for each permutation to generate a null distribution. Permutations were restricted so that labels were only exchanged between electrodes belonging to the same participant, producing an exchangeability restriction reflecting the dependency structure of the data. All participants with at least one electrode within the V5/hMT+ label also had at least one electrode outside of the label. The *p*-value was determined by identifying the proportion of values from the resultant null distribution that equaled or exceeded the observed number of significant electrodes with a V5/hMT+ label (i.e., those within 1 cm of the Freesurfer V5/hMT+ probabilistic label). Statistical results were comparable when using unrestricted permutations or a parametric chi-squared test for equality of proportions.

2.3.2 Analysis of Entrainment

For group-level time-spectral analyses of entrainment, the epoched data were convolved with 10 wavelets (center frequencies ranging from 5-50 Hz in 5 Hz intervals) with the number of cycles varying linearly across this frequency range (5-50 cycles in 5 Hz intervals). ITPC values for each time-point and frequency were calculated separately for each participant, Fisher's Z-transformed, and then averaged across participants, with a group-level t-tests conducted at each time-point and frequency. Multiple comparison corrections were applied using cluster statistics, in which the time-frequency map of t -value statistics is permuted 10,000 times in order to identify clusters of significant contiguous pixels (at $p < .05$) that are larger than those in 95% of the permuted data (Cohen, 2014).

For frequency-specific analyses, data from each condition were convolved with a single wavelet: center frequency and the number of cycles included were equal to the condition AM frequency (e.g., data from the 40 Hz condition were

convolved with a 40-cycle long wavelet with a center frequency of 40 Hz). ITPC values were then calculated separately at each time-point, Fisher's Z-transformed, and averaged across time to yield two ITPC values for each

electrode and condition: one for data in the pre-stimulus baseline period (Experiment 1: -1.5 to -.5; Experiment 2: -11

Figure 2. (Top) Intracranial electrodes from 16 patients, displayed on an average brain (all electrodes projected into the left hemisphere). Each colored sphere reflects a single electrode contact included in analyses, localized in auditory areas (red, 55 electrodes) or visual areas (blue, 178 electrodes). Auditory electrodes were limited to those located proximal to the superior temporal gyrus or neighboring white matter and showing a significant event-related potential (ERP) to sounds beginning at less than 120 ms. Visual electrodes were limited to those located in occipital, parietal, or inferior temporal areas and showing a significant ERP to visual stimuli beginning at less than 120 ms. (Bottom) ERP responses at all auditory electrodes (red) evoked during an auditory task, and at all visual electrodes (blue) evoked during a visual task; the time zero indicates stimulus onset in each task.

to -1 seconds) and another during the full stimulus period. Difference scores were then taken from these values to yield a single ITPC value (relative to baseline) per condition, electrode, and participant. For single-electrode analyses of entrainment, frequency-averaged ITPC values for the full stimulus period were compared to null distributions generated through phase shuffling. *P*-values were determined by identifying the proportion of observed ITPC values that exceed values from this distribution, and then corrected for multiple comparisons using FDR correction ($q = .05$). For group-level analyses of entrainment, data were averaged across electrodes before statistics (one-sample *t*-tests) were conducted separately at each condition (with multiple corrections applied using FDR).

3. RESULTS

3.1 Sound Onsets Produce Transient Phase Reset in Visual Cortex

To test whether AM sounds produce transient modulations of oscillatory activity in visual cortex, we first examined whether auditory onsets produced transient inter-trial phase coherence (ITPC) in visually responsive electrodes (see Figure 2, Supplemental Figures 1 and 2, and Methods for electrode selection criteria). ITPC is quantified across trials and is therefore sensitive to the consistency of oscillatory phase-angles produced by both stimulus-evoked phase-resetting and oscillatory entrainment. To isolate phase coherence evoked by auditory onsets (regardless of AM frequency), we combined data across stimulus conditions so that the frequencies of potential entrainment responses were inconsistent across trials and, therefore, would not produce reliable frequency specific ITPC. We restricted our analysis of transient responses to the 1-20 Hz range based on previous reports indicating that brief auditory stimuli reset visual oscillations in the delta, theta, and alpha frequency bands (Lakatos et al., 2009; Fiebelkorn et al., 2011; Romei et al., 2012). At the group level (data were averaged across electrodes and frequency bands (1-20 Hz) for each participant before group comparison), we found significantly more phase coherence in both auditory ($t(6) = 6.212, p = .0004, d = 2.3478$; Figure 3a) and visual electrodes ($t(12) = 3.573, p = .0019, d = .9908$, Figure 3b) during the 200 ms period following stimulus onset than the pre-stimulus baseline period,

suggesting that auditory onsets produced transient phase coherence in both auditory and visual cortex. Note that the degrees of freedom vary according to the number of participants contributing to each group-level analysis (Auditory: $n = 7$; Visual: $n = 13$).

To characterize the spectro-temporal profile of these effects, we identified time-points and frequency bands in which significant ITPC was observed at the group level (auditory and visual electrodes were

Figure 3. (a-b) Group inter-trial phase coherence (ITPC) time-spectral plots for auditory (a) and visual (b) electrodes during the average of all AM sound conditions. Dotted lines denote analyzed time-frequency range. Relative to the pre-stimulus baseline period, significantly larger ITPC values were present at low frequencies for both auditory and visual electrodes, highlighting the presence of an auditory-driven transient phase-reset to the onset of AM sounds at auditory and visual areas. Black polygon shapes highlight significant times and frequencies using cluster-corrected statistics ($p < .05$). (c) Auditory and visual electrodes from all patients showing either significant (red to yellow) or non-significant (black) ITPC values during the average of all AM sound conditions. Significant electrodes cluster around the central superior temporal gyrus, proximal to auditory cortex, and are additionally broadly distributed throughout visual areas, most strongly at pericalcarine and occipitotemporal areas (potentially V5/hMT+). The bottom row of images reflects the same data on partially transparent brains to show statistics from electrodes not visible at the surface.

separately averaged within each participant before being averaged across participants). After correcting for multiple comparisons using cluster-based statistics (see Methods), significant clusters were observed in the 1-20 Hz range for auditory electrodes (Figure 3a; black polygon shapes surround significant clusters) and the 1-9 Hz range for visual electrodes (Figure 3b). Although stimuli were 1 second or longer in duration, significant phase coherence persisted for only approximately 500 ms in frequency bands over 3 Hz, indicating the transient nature of these responses. While more prolonged phase coherence is apparent in the 1-3 Hz range, this likely reflects temporal smoothing inherent to frequency-resolved analysis of slower

oscillations due to the temporal widths of the wavelets and does not appear to indicate a genuine sustained response. These group-level results suggest that the onsets of AM sounds produce transient phase coherence in both auditory and visual cortex.

To examine the regional specificity of these effects, we identified individual electrodes showing significant phase coherence using a similar, but electrode-specific, analysis (Figure 3C). For each electrode, we computed the average ITPC across the 1-20 Hz frequency range (ITPC calculated independently at each 1 Hz band) during the initial 200 ms following stimulus onset. To assess statistical significance, ITPC values averaged for each electrode were compared to the distribution of values produced by phase-shuffled data, and the resulting p -values were FDR-corrected ($q = .05$) for multiple comparisons across electrodes. Based on this analysis, 55/55 (100%) of auditory electrodes and 41/178 (23.0%) of visual electrodes showed significant phase coherence (Figure 3C). Significant visual electrodes were broadly distributed across sampled regions, with multiple electrodes clustered in pericalcarine, posterior parietal, and inferior temporal cortex, and many significant electrodes observed in lateral occipito-temporal cortex. The location of this region, situated inferior to the angular gyrus at the juncture between inferior/middle temporal cortex and lateral occipital cortex, corresponds closely to the expected anatomical location of area V5/hMT+ (Watson et al., 1993). To examine more closely whether significant electrodes preferentially clustered near area V5/hMT+, we compared the proportions of visual electrodes within 1 cm of the estimated anatomical location of area V5/hMT (Freesurfer probabilistic atlas) (Malikovic et al., 2007) that showed significant transient ITPC to the proportion of visual electrodes in other areas that showed significant transient ITPC. 16 out of 30 (53.3%) electrodes in the V5/hMT+ region showed significant ITPC, while only 25 out of 148 (16.9%) of remaining electrodes showed significant ITPC, with a significant difference across these proportions ($p = .0001$; restricted permutation test). These results suggest that electrodes exhibiting transient onset responses cluster preferentially near area putative V5/hMT+, while also occurring in multiple regions of visual cortex. Indeed, electrodes exhibiting significant onset responses in the V5/hMT+ region came from 4 out of 6 participants with electrodes in this region, indicating the generalizability of

these findings.

Altogether, these results suggest that the onsets of AM sounds produce transient phase coherence in both auditory and visual cortices. Importantly, because both evoked responses that are independent of oscillatory activity and phase-resetting of oscillatory activity can produce the appearance of transient phase coherence, event-related ITPC must be interpreted with care (Sauseng et al., 2007). In auditory cortex, sounds are known to evoke changes in both spectral power and oscillatory phase-reset, suggesting that phase coherence in auditory cortex likely reflects both mechanisms (Fuentemilla et al., 2006). In contrast, converging evidence from TMS, EEG, psychophysics, and intracranial electrophysiology in human and non-human primates (Lakatos et al., 2009; Fiebelkorn et al., 2011; Romei et al., 2012) suggests that sounds influence visual cortex by modulating sub-threshold oscillatory activity, rather than driving event-related evoked responses, suggesting that transient phase coherence in visual cortex most likely reflects crossmodal phase-resetting to auditory onsets. Because transient responses to the onsets of AM sounds only emerge at the cortical level of the auditory processing hierarchy, these results provide initial evidence that crossmodal phase-resetting in visual cortex may be driven by auditory cortical activity.

3.2 Sound Offsets Produce Transient Phase Reset in Visual Cortex

In addition to auditory onsets, cortical auditory neurons also display transient responses to the offsets of AM sounds that are not observed in subcortical auditory neurons (Chatrian et al., 1960; Bieser and Müller-Preuss, 1996; Steinschneider et al., 1998; Harms and Melcher, 2002; Harms et al., 2005). To rule out the possibility that the transient onset responses observed in visual cortex simply reflect rapidly adapting or highly damped entrainment responses, we tested whether cortical offset responses were also reflected in visual oscillations. To examine whether auditory offsets produce transient phase-resetting in visual cortex, we applied the same analyses to the 200 ms window following auditory offsets as we did to the 200 ms window following auditory onsets (Figure 4). In group-level analyses averaging ITPC values for auditory or visual electrodes within each participant, both auditory ($t(6) = 2.746, p = .0167, d = 1.0377$)

Figure 4. (a) Representative electrodes (auditory electrodes are red, visual electrodes are blue) from six participants that showed significant ITPC responses (after correcting for multiple comparisons) at the offset of sounds. Auditory electrodes (left) and visual (right) electrodes during the average of all AM sound conditions. Dotted lines denote analyzed time-frequency range. (b-c) Individual participant ITPC plots at selected auditory (b) and visual (c) electrodes. AM sound onset occurred at 0 seconds, and offset at 1 second. Each electrode shows both onset and offset responses.

and visual ($t(12) = 2.560, p = .0125, d = .7100$) regions showed significant phase coherence in response to auditory offsets (compared to pre-stimulus baseline), suggesting that auditory offsets do indeed produce transient phase coherence in visual cortex. Analyzing electrodes individually, 39/55 of auditory electrodes (70.9%; representative electrodes/responses: Figure 4A-B) and 7/178 of visual electrodes (3.9%; Figure 4A,C) showed significant phase coherence following auditory offsets, suggesting that both auditory and visual cortex showed reliable, but comparatively weaker, responses to auditory offsets. This weakened response is consistent with previous human iEEG research showing weaker offset than onset responses in auditory cortex (Chatrian et al., 1960).

In visual cortex, although only a small number of electrodes showed significant offset responses, these responses were statistically robust, suggesting that they are unlikely to be spurious (all $p < .005$ after FDR-based multiple comparison correction; Figure 4C). Of the 7 visual electrodes that showed significant

offset responses, 6 showed significant onset responses, suggesting that onset and offset responses occurred at similar sites in visual cortex. Restricting our offset analysis to the 41 visual electrodes that showed significant responses to auditory onsets, 10/41 (24.4%) of visually selective electrodes showed significant offset responses. The greater number of significant electrodes observed here is due to the smaller number of electrodes tested, reducing the severity of the multiple comparison corrections applied. These results suggest that crossmodal responses to auditory offsets tend to occur in the same neural populations that display crossmodal responses to auditory onsets. Electrodes showing both responses tended to cluster around pericalcarine and occipito-temporal (putative V5/hMT+) cortex, suggesting that these regions may be particularly responsive to modulatory input originating from auditory cortex.

3.3 Visual Neurons Do Not Entrain to Auditory Amplitude Modulations: 1-2 Second Stimuli

Previous research indicates that while approximately 20% of neurons in auditory cortex show transient onset and/or offset responses to AM sounds, the remaining neurons show primarily band-pass or low-pass frequency-following responses maximally tuned to AM frequencies below 16 Hz (Bieser and Müller-Preuss, 1996). If visual neurons are sensitive to neural dynamics in auditory cortex in general, then they should also exhibit entrainment to these AM frequencies. However, if visual cortex primarily receives input from auditory neurons that display transient responses, then no crossmodal entrainment should be apparent. Finally, if some visual neurons receive input from other, subcortical auditory areas, then they should exhibit entrainment to higher frequencies.

To determine whether visual cortex exhibits entrainment to AM sounds, we tested whether visual electrodes displayed ITPC in the frequency bands of auditory amplitude modulations. Individual modulation frequencies were analyzed separately for frequency-specific analyses and averaged together to gauge overall entrainment. Group and individual-electrode level analyses were analogous to analyses of transient responses, except that ITPC was taken across full stimulus durations using only the AM frequency of each stimulus.

In group-level comparisons to the pre-stimulus baseline, auditory electrodes (Figure 5A, left) showed significant entrainment in the frequency-averaged analysis ($t(6) = 3.9327$, $p = .0038$, $d = 1.4864$), and for 10/10 modulation frequencies in frequency-specific analyses (all $p < .05$, corrected for multiple comparisons), suggesting that auditory neurons exhibited the expected reliable entrainment to amplitude modulations. No clear frequency tuning was evident, potentially indicating an influence of higher frequency thalamocortical signals on auditory electrodes. In contrast, visual electrodes (Figure 5A, right) showed no significant entrainment in either the frequency-averaged ($t(12) = 1.30511$, $p = .1082$, $d = .3620$) or frequency-specific analyses (all $p > .2949$), suggesting that neurons in visual cortex do not exhibit entrainment to auditory amplitude modulations. As an illustrative example, group-level entrainment responses to 40 Hz AM sounds are shown for auditory and visual electrodes in Figure 5B. While entrainment is clearly visible in the 40 Hz frequency band in auditory electrodes, it is notably absent in visual electrodes.

Figure 5. Experiment 1. (a) Group-level analysis of inter-trial phase coherence (ITPC) at auditory (left) and visual (right) electrodes in response to amplitude modulated (AM) sounds relative to ITPC values in the pre-stimulus baseline period. Individual bars reflect auditory AM rate and matched analysis frequency. Center line indicates median; box limits, upper and lower quartiles; whiskers, 1.5x interquartile range; points, outliers. * $p < .05$ ** $p < .005$ (corrected for multiple comparisons). Error bars reflect SEM. (b) Group ITPC time-spectral plots for auditory (left) and visual (right) electrodes during a representative AM sound condition (40-Hz). Black polygon denotes $p < .05$ significance (corrected for multiple comparisons). Significant entrainment is present at 40-Hz only for auditory electrodes. (c) Auditory and visual electrodes from all patients showing either significant (red to white) or non-significant (black) ITPC values during the presentation of AM sounds relative to phase-shuffled data, reflecting neural entrainment to the auditory stimulus. Significant electrodes cluster around the central superior temporal gyrus, proximal to auditory cortex, and are noticeably absent from visual areas.

Electrode-specific analyses using frequency-averaged ITPC values yielded similar results. Relative to phase-shuffled data, 41/55 (74.5%) of auditory electrodes showed significant ($p < .05$ FDR-corrected) entrainment (Figure 5C). By contrast, only 1/178 visual electrodes (0.56%) showed significant entrainment when compared to either phase-shuffled data. Because only a single visual electrode was significant in this analysis, we inspected its response profile in detail to determine whether it genuinely exhibited entrainment or was merely a false positive. This analysis was of particular interest because the electrode in question was located in the anterior portion of the calcarine sulcus (Figure 6, left; also Electrode 6 in Figure 4), where direct crossmodal connections from auditory cortex have been shown to terminate in non-human primates (Falchier et al., 2002; Rockland and Ojima, 2003). Closer examination of frequency-resolved ITPC in this electrode indicated that it did not exhibit sustained entrainment to AM frequencies but, rather, showed pronounced transient onset responses in the 2-12 Hz range regardless of AM frequency. This large transient response may have produced the appearance of entrainment by introducing exceptionally large ITPC values from the low-frequency conditions into the frequency-averaged analysis. Consistent with this interpretation, transient ITPC at stimulus onset was greater in amplitude at this electrode than any other visual electrode and, indeed, 87% of auditory electrodes. Taken together, these results suggest that visual cortex does not

Figure 6. (left) Sole visually-selective intracranial electrode (represented by white disk on patients' post-operative MRI) showing significant ITPC values (following correction for multiple comparisons) in neural entrainment analyses. Electrode was localized to the anterior portion of the calcarine sulcus in the right hemisphere, probabilistically mapped to either V1 or V2. (right) Spectral-temporal plots showing ITPC values evoked at this electrode in each of the 10 AM sound conditions. Black polygons denote $p < .005$ significance (corrected for multiple comparisons using cluster statistics). Significant ITPC values were evoked transiently in the alpha frequency range regardless of AM sound, highlighting the presence of a transient phase-reset, and absence of AM sound entrainment of visual areas.

exhibit any reliable entrainment to AM sounds and, therefore, is crossmodally modulated primarily by event-segmented auditory signals, potentially originating from auditory cortex.

3.4 Visual Areas Do Not Entrain to Auditory Amplitude Modulations: 10 Second Stimuli

To further verify this interpretation, we considered the possibility that the stimuli used in our first experiment could have been too short to allow for reliable crossmodal entrainment to emerge. To test whether entrainment would become apparent with longer stimulus durations, we conducted a second experiment in which we presented 40 Hz AM sounds lasting 10 seconds in duration to 13 participants with similar electrode coverage (7 participants of whom were included in Experiment 1 as well; see Figure 7 and Extended Data Figure 7-1 for electrode selection). Using this modulation frequency provided a rigorous test for subcortically-driven crossmodal entrainment because it is near the preferred modulation frequencies for neurons in both the inferior colliculus and auditory thalamus (Preuss and Müller-Preuss, 1990; Müller-

Preuss et al., 1994). Moreover, studies using non-human primates suggest that brief sounds can produce transient phase-resetting near the 40 Hz frequency band in low-level visual cortex (Lakatos et al., 2009). Therefore, if any subcortically-driven crossmodal entrainment was present in visual cortex, it would likely be evident in this frequency band.

Figure 7. Experiment 2. (Top) Intracranial electrodes from 13 patients, displayed on an average brain (all electrodes projected into the left hemisphere). Each colored sphere reflects a single electrode contact included in analyses, localized in auditory areas (red, 73 electrodes) or visual areas (blue, 151 electrodes). Auditory electrodes were limited to those located proximal to the superior temporal gyrus or neighboring white matter and showing a significant event-related potential (ERP) to sounds beginning at less than 120 ms. Visual electrodes were limited to those located in occipital, parietal, or inferior temporal areas and showing a significant ERP to visual stimuli beginning at less than 120 ms. (Bottom) ERP responses at all auditory electrodes (red) evoked during an auditory task, and at all visual electrodes (blue) evoked during a visual task; the time zero indicates stimulus onset in each task.

To test for entrainment, we divided the duration of each stimulus (from 0 to 10 seconds) and each pre-stimulus baseline period (from -11 to -1 seconds) into 1-second epochs, producing a total of 10 stimulus and 10 baseline epochs per trial. We then used all stimulus or all baseline epochs to estimate ITPC in each frequency band from 5-50 Hz (in 5 Hz intervals) and averaged these values across each participant's electrodes for our group-level analysis.

Comparing ITPC values between stimulus and baseline periods at the group level, we found significant entrainment in only the 40 Hz frequency band in auditory electrodes ($t(7) = 2.998$, $p = .0100$, $d = 1.0599$), indicating selective entrainment to the modulation frequency of the auditory stimulus (Figure 8A, left). In contrast, no significant entrainment was observed at the group level in the 40 Hz frequency band for visual electrodes ($t(10) = 1.099$, $p = .1487$, $d = .3314$; Figure 8A, right), providing additional evidence that AM sounds do not produce entrainment in visual cortex. In electrode-specific analyses comparing ITPC values in the 40 Hz frequency band to those produced using phase-shuffled data, 43/73 (58.9%) of auditory electrodes showed significant ($p < .05$ FDR-corrected) entrainment (Figure 8B). In

contrast, 0/151 (0%) of visual electrodes showed significant entrainment, providing further evidence that even prolonged AM sounds do not produce entrainment in visual cortex. These results provide additional support for the conclusion that visual cortex receives event-segmented auditory information,

Figure 8. Experiment 2. (a) Group-level analysis of inter-trial phase coherence (ITPC) at auditory (left) and visual (right) electrodes in response to 40-Hz AM sounds relative to ITPC values in the pre-stimulus baseline period. Individual bars reflect ITPC values at various frequencies, highlighting the specificity of auditory entrainment at 40-Hz. Center line indicates median; box limits, upper and lower quartiles; whiskers, 1.5x interquartile range; points, outliers. ** $p < .01$ (non-40-Hz frequencies corrected for multiple comparisons), Error bars reflect SEM. (b) Auditory and visual electrodes from all patients showing either significant (red to yellow) or non-significant (black) inter trial phase coherence (ITPC) values during the presentation of amplitude modulated (AM) sounds relative to phase-shuffled data, reflecting neural entrainment to the auditory stimulus. Significant electrodes cluster around the central superior temporal gyrus, proximal to auditory cortex, and are noticeably absent from visual areas.

potentially transmitted from cortical, as opposed to subcortical, auditory regions.

4. DISCUSSION

In this study we used iEEG to identify what information from an auditory signal is transmitted to visual cortex. While we found clear evidence of transient phase-resetting to the onsets and offsets of AM sounds, we found no reliable evidence of crossmodal entrainment to AM frequencies. These transient cortical responses are thought to reflect temporal parsing of fine-grained stimulus dynamics into a segmented representation of auditory events (Harms and Melcher, 2002), indicating that crossmodal phase-resetting primarily conveys the timing of individuated auditory events, rather than relatively “raw” auditory stimulus dynamics, to visual cortex. Furthermore, these results put an upper limit to the question of which auditory information is made available to the visual system as neurons in visual cortex failed to demonstrate entrainment to AM sounds.

These results validate and extend prior studies demonstrating the forms of information relayed from auditory to visual areas, including auditory timing and spatial location (e.g., Romei et al., 2009; McDonald et al., 2013). Here, we demonstrate the novel result that auditory onsets and offsets elicit transient responses in visual cortex which show similar temporal dynamics to transient responses in the auditory system. These onset/offset potentials may have perceptual effects on the visual system, enabling better sensitivity to visual motion tracking and temporal duration estimation. These potentials may also contribute to the sound-induced illusory flash experience, in which a single visual flash paired with two auditory beeps is perceived as two distinct visual events (Shams et al., 2000), or the audiovisual stream-bounce illusion, in which transient auditory onsets/offsets promote the perception of visual objects bouncing off of, rather than passing by each other (Meyerhoff and Suzuki, 2018).

Moreover, the topography and dynamics of these crossmodal responses may also provide information about the likely sources of crossmodal modulatory signals that influence visual cortex. While we found significant transient responses throughout visual cortex, onset responses were most pronounced

in pericalcarine (putative V1/V2) and lateral occipito-temporal (putative V5/hMT+) sites where significant offset responses were also observed. One possibility is that modulatory signals from auditory cortex are transmitted directly to V1/V2 and V5/hMT+ through direct “lateral” cortico-cortical pathways from auditory cortex. Anatomical tracer studies in non-human primates have revealed direct connections from auditory cortex to V1/V2 (Falchier et al., 2002; Rockland and Ojima, 2003; Clavagnier et al., 2004), and recent diffusion MRI findings suggests a similar connection to area V5/hMT+ in humans (Gurtubay-Antolin et al., 2020). Consistent with this interpretation, we observed the strongest crossmodal response in the anterior portion of the calcarine sulcus, where direct connections from auditory cortex have been shown to terminate in non-human primates (Falchier et al., 2002). This area is also densely connected with V5/hMT by projections from magnocellular-pathway neurons in V1 (Born and Bradley, 2005), which are characterized by their rapid transient responses to visual dynamics (Nassi and Callaway, 2009). One plausible hypothesis is that this set of connections could facilitate rapid detection of and behavioral responses to multisensory stimuli by connecting auditory and visual cortical neurons that are tuned to sudden changes in the sensory environment. Indeed, psychophysical studies suggest that temporally correspondent sounds primarily enhance the perception of transient low-spatial-frequency or peripheral visual stimuli that are preferentially encoded by magnocellular neurons (Jaekl and Soto-Faraco, 2010). Direct connections between low-level auditory and visual cortices may also contribute to the facilitative effects of spatialized sounds on visual perception and spatial orienting by modulating visual activity in a hemispatially biased manner (e.g., Brang et al., 2015; Plass et al., 2019).

This interpretation is further supported by the observed temporal dynamics of auditory responses in visual cortex. Because neurons at different levels of the auditory processing hierarchy exhibit unique responses to AM sounds, the likely sources of crossmodal modulatory signals may be able to be inferred from characteristic response patterns reflected in visual oscillations. Importantly, while subcortical auditory neurons reliably exhibit entrainment to AM sounds, approximately 20% of neurons in auditory cortex do not exhibit entrainment and respond only to the onsets and/or offsets of auditory stimuli (e.g., Bieser and

Müller-Preuss, 1996). Similarly, in human iEEG, neural populations in posterior superior temporal cortex have been found to respond preferentially to sentence onsets, rather than the extended amplitude dynamics of speech (Hamilton et al., 2018).

Mirroring the expected response of these auditory cortical neurons, we observed reliable phase coherence to the onsets of AM sounds, weaker coherence to sound offsets, and no evidence of extended entrainment in visual cortex. These results appear to suggest a cortical auditory source for the crossmodal modulations observed in visual cortex. Indeed, onset-sensitive auditory neurons in the posterior temporal cortex are a plausible candidate source given their proximity to white-matter pathways connecting auditory cortex to V1/V2 and V5/hMT+ (Falchier et al., 2002; Clavagnier et al., 2004; Borra and Rockland, 2011; Gurtubay-Antolin et al., 2020). Thus, both anatomical and functional considerations point to direct “lateral” connections from auditory cortex as a plausible source for the observed crossmodal responses. Alternatively, cortical auditory signals could be transmitted to visual cortex via feedback connections from multisensory association cortex, including the posterior superior temporal sulcus and intraparietal sulcus (Brang et al., 2013; Schepers et al., 2015). In non-human primates, feedback connections from the superior temporal polysensory (STP) region also target low-level visual cortex (Falchier et al., 2002; Clavagnier et al., 2004), leaving open the possibility that cortical auditory signals could be conveyed to visual cortex via this pathway. However, the speed with which sounds modulate activity in low-level visual cortex leads us to disfavor this explanation. Specifically, reliable auditory effects on V1/V2 activity have been observed as early as 28 ms after stimulus onset, only 2 ms after the earliest responses observed in (non-primary) auditory cortex in the same participant (Brang et al., 2015) and 15 ms after the earliest responses to clicks recorded from primary auditory cortex in earlier reports (Celesia, 1976), leaving little time for polysynaptic delays along the crossmodal pathway from polysensory cortex. Indeed, in the present dataset, a significant auditory-evoked potential was observed in the calcarine sulcus (the electrode highlighted in Figure 6) beginning at 39 ms, replicating prior reports of fast auditory-driven modulation of visual activity.

Finally, the pulvinar nucleus of the thalamus is another potential source of crossmodal modulations in visual cortex through its connections with the V1/V2, and V5/hMT+ (Purushothaman et al., 2012; Kinoshita et al., 2019), regions we observed as showing auditory onset- and offset modulations, and as recent research suggests that the pulvinar may exhibit temporal parsing of auditory patterns (Barczak et al., 2018). Alternatively, these effects could in principle through interactions between the pulvinar and the superior colliculus (i.e., the tecto-pulvinar system). Both the pulvinar nucleus and tecto-pulvinar connections have been implicated in “blindsight” phenomena, in which cortically blind patients exhibit visually-guided behavior despite substantial damage to visual cortex, including V1 (e.g., Kinoshita et al., 2019). One possibility is that similar thalamocortical connections could contribute to auditorily driven visual behaviors (e.g., saccades) or attention-like processes in the visual system, potentially through the mechanism of phase-resetting.

However, contrary to these alternatives, the functional properties of pulvinar neurons and their cortical connections are largely inconsistent with the iEEG responses observed in our experiments using lateralized sounds (Plass et al., 2019). For example, consistent with lateralized blindsight phenomena in humans, inactivation of the pulvinar in non-human primates with V1 lesions selectively impaired visually-guided saccades in the contralesional hemifield, while completely sparing the ipsilateral hemifield (Kinoshita et al., 2019). Moreover, pulvinar neural populations tend to have receptive fields of roughly 1 to 10 degrees (DeSimone et al., 2015), and output to cortical neurons with spatially matched receptive fields (Kinoshita et al., 2019). Thus, pulvinar outputs to visual cortex would be expected to exhibit at least hemifield-specific spatial tuning.

By contrast, in our iEEG experiments, sounds lateralized at approximately 45 degrees away from the midline produced bilateral responses throughout visual cortex, with only a modest contralateral bias (Plass et al., 2019). Thus, the topography of crossmodal responses to lateralized sounds is not consistent with the expected strictly-hemispheric response pattern predicted by a pulvinar source. Rather, the pattern of responses is more consistent with a source which exhibits only partial hemispheric response bias, such

as the auditory cortex (Celesia, 1976; Kaiser and Lutzenberger, 2001). Thus, the current results, taken in conjunction with the previous literature, lead us to favor a cortico-cortical explanation for the observed crossmodal modulations.

Importantly, these inferences rest on the premise that responses observed in visual cortex primarily reflect the response properties of upstream neurons in the auditory system, and not transformations generated within visual cortex itself. We believe this assumption is likely justified for two reasons. First, the types of transformations or response non-linearities required to produce the observed responses are unlikely to occur in V1 given the properties of relevant neural populations in V1. Second, even if the observed onset/offset responses were the result of a transformation in visual cortex, input from auditory subcortical regions would be expected to produce detectible pre-synaptic activity entrained to stimulus modulation frequencies in visual cortex.

For example, one potential alternative explanation of our results is that the observed pattern of visual responses reflects low-pass filtering or non-linear transformations of subcortical auditory input in visual cortex (i.e., visual neurons filter out irrelevant auditory information locally). However, this interpretation is largely inconsistent with the known properties of visual cortex and the biophysical basis of the iEEG signals studied here. In non-human primates, V1 neurons exhibit entrainment to visual dynamics up to 100 Hz (Krolak-Salmon et al., 2003; Williams et al., 2004), with typical high-frequency cut-offs ranging from 12-48 Hz (Hawken et al., 1996), providing sufficient temporal resolution for robust entrainment to high-frequency inputs from auditory subcortical sites.

Moreover, the likely generator of crossmodal responses observed in pericalcarine cortex is unlikely to produce the types of transformations or non-linearities required to generate the observed response profiles. Previous research in non-human primates suggests that crossmodal influences on oscillatory activity, including auditory effects on primary visual cortex, occur through modulatory phase-resetting of sub-threshold oscillations in the supragranular layers (layers 2/3) of nominally unisensory cortex (Lakatos et al., 2009; Schroeder and Lakatos, 2009; Kajikawa et al., 2012). Population responses in these layers of

V1, as assessed using voltage-sensitive dye imaging, do not exhibit transient onset and offset responses to visual stimuli, and produce only negligible response nonlinearities associated with gain control (Sit et al., 2009). Moreover, because sub-threshold modulations generally do not produce spiking activity, response nonlinearities associated with spiking are unlikely to have contributed to the crossmodal responses observed in the current study. Additionally, while some V1 neurons exhibit transient offset responses to static visual stimuli (Macknik and Livingstone, 1998), to our knowledge, there are no previous reports demonstrating transient offset responses to the terminations of temporally modulated stimuli (e.g., flicker) in visual cortex, despite the substantial literature exploring sustained entrainment responses to such stimuli. Rather, flickering stimuli tend to produce repeated offset responses at the frequency of stimulation, without especially pronounced offset responses or afterdischarges at stimulus offset (Norcia et al., 2015). Therefore, the response profiles observed in pericalcarine visual cortex are unlikely to have originated from transformations of subcortical inputs that occur in visual cortex.

Finally, because the extracellular potentials measured by iEEG partially reflect synaptic potentials associated with subthreshold synaptic inputs (Haider et al., 2016), temporally organized synaptic potentials produced by AM entrained inputs from auditory subcortex would have likely been observable even if substantial transformations of subcortical inputs occurred in visual cortex. For example, these synaptic potentials may have contributed to the apparently flat AM frequency tuning observed in auditory cortex entrainment responses, despite the well-documented low-pass tuning of auditory cortex neurons (Bieser and Müller-Preuss, 1996). However, similar entrainment responses were not observed in visual cortex, suggesting a lack of auditory subcortical input.

Nevertheless, as this study did not measure activity along a specific white matter pathway or functional connectivity between cortical auditory and visual sites, it remains possible that some of the observed effects are subcortical in origin, with the pulvinar as one reasonable candidate. Additional data will be required to resolve this question conclusively, including functional connectivity analyses between auditory and visual sites in humans, supplemented by recordings of the pulvinar. One possibility is that, as

hypothesized in studies on unimodal attention, the pulvinar may play a role in coordinating functional connectivity across cortico-cortical anatomical connections (e.g. Arcaro et al., 2015).

The present study represents one of the largest iEEG studies of multisensory processing to date. Invasive recordings were necessary to address the question because scalp-recorded EEG lacks the required spatial resolution and as fMRI is insensitive to phase-encoded oscillatory information (Hermes et al., 2017). One potential concern in the interpretation of these data is that they were acquired from patients with epilepsy who may exhibit altered network topology or neural activity. However, this concern is tempered by the fact that electrodes exhibiting epileptic activity were not included in any analyses, data were collected from a large number of patients with different seizure etiologies, and as electrodes were selected on the basis of their functional responses to visual stimuli and anatomical locations.

In summary, the present data demonstrate that sounds elicit robust phase-resetting responses in visual cortex in the absence of entrained responses. This response pattern stands in contrast to more extended modulations produced by dynamic visual signals (e.g., visual speech; Luo et al., 2010; Golumbic et al., 2013) in auditory cortex. As the present studies used AM sounds as opposed to auditory speech stimuli, we cannot exclude the possibility that visual cortex may encode complex auditory dynamics in some contexts. Alternatively, we believe it more likely that differences in modulatory dynamics may reflect the distinct functional roles that low-frequency oscillations play in perceptual computations in each modality. While nested oscillations in auditory cortex track the extended dynamics of vocalizations at multiple (e.g., phonemic, syllabic, phrasal) time-scales (Giraud and Poeppel, 2012; Gross et al., 2013), indicating their role in the integrative encoding of temporally extended auditory information, slow oscillations in visual cortex are thought to reflect temporally discretized sampling of visual signals (VanRullen and Koch, 2003; Dugué et al., 2011; Wutz et al., 2014; Samaha and Postle, 2015). Crossmodal modulations may facilitate perception in a modality-dependent manner by modulating oscillatory dynamics in ways that support their primary functional role in the recipient cortical region. In visual cortex, this would entail temporally aligning periodic sampling to important visual events to maximize the information content

of encoded visual signals (Romei et al., 2012). Crossmodal phase-resetting to the onsets and offsets of sounds could facilitate this process by time-locking visual computations to multisensory events marked by auditory discontinuities, thereby optimizing visual sampling in the temporal domain.

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Supplemental Table 1

Locations for each participant's electrodes within visual areas. Numbers reflect significant hits out of possible electrodes for transient onset (On), transient offset (Off), and entrainment responses (Ent).

[illegible][illegible]

Supplemental Figure 1. Experiment 1. Individual electrode maps for each patient. Red spheres reflect auditory electrodes, blue spheres visual electrodes, and black spheres other electrodes excluded from analyses (due to artifacts or for not meeting the required anatomical or functional inclusion criteria).

Supplemental Figure 2. Experiment 2. Individual electrode maps for each patient. Red spheres reflect auditory electrodes, blue spheres visual electrodes, and black spheres other electrodes excluded from analyses (due to artifacts or for not meeting the required anatomical or functional inclusion criteria).