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Presence of Strong Harmonics During Visual Entrainment: A Magnetoencephalography Study

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Abstract

Visual neurons are known to synchronize their firing with stimuli that flicker at a constant rate (e.g., 12 Hz). These so-called visual steady-state responses (VSSR) are a well-studied phenomenon, yet the underlying mechanisms are widely disagreed upon. Furthermore, there is limited evidence that visual neurons may simultaneously synchronize at harmonics of the stimulation frequency. We utilized magnetoencephalography (MEG) to examine synchronization at harmonics of the visual stimulation frequency (18 Hz). MEG data were analyzed for event-related-synchronization (ERS) at the fundamental frequency, 36, 54, and 72 Hz. We found strong ERS in all bands. Only 31% of participants showed maximum entrainment at the fundamental; others showed stronger entrainment at either 36 or 54 Hz. The cortical foci of these responses indicated that the harmonics involved cortices that were partially distinct from the fundamental. These findings suggest that spatially-overlapping subpopulations of neurons are simultaneously entrained at different harmonics of the stimulus frequency.

Keywords

steady-state response; SSR; event-related synchronization; ERS; occipital; cortex

1. Introduction

The visual steady-state response (VSSR) occurs when visual neurons entrain to the specific frequency of a continuous repetitive stimulus, such as a flickering light. This response is distinct from a transient response, in which populations of neurons fire transiently at the onset of stimulation (Regan, 1989). Clinically, the VSSR, or photic driving, is used as an indicator of normal cognitive function, and is used in the diagnosis of disorders such as epilepsy and depression (Jin, Potkin, Sandman, & Bunney, 1997). While the VSSR is a well-studied phenomenon (Fox & Raichle, 1985; Herrmann, 2001; Müller, Teder, & Hillyard,

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1997; Pastor, Artieda, Arbizu, Valencia, & Masdau, 2003; Pastor, Valencia, Artieda, Alegre, & Masdau, 2007; Schwab et al., 2006), there is little agreement across studies in regards to actual findings or interpretations. As an example, the optimal driving frequency for the VSSR is widely disagreed upon. Some studies have reported that 8–10 Hz elicits the strongest response, whereas other studies have suggested 15 Hz. Using electroencephalography (EEG), Herrmann (2001) investigated the response to flicker stimuli ranging from 1–100 Hz and found that the strongest responses on average were elicited in the teens, especially 14 and 16 Hz. Interestingly, Herrmann (2001) also observed responses at sub-harmonics of the fundamental frequency (i.e. the stimulus frequency). For example, participants produced strong 10 Hz and 15 Hz responses to the driving 30 Hz stimulus. Lazarev and colleagues (2001) reported that the strongest entrainment occurred at frequencies closest to the alpha peak of individual subjects, with other group-wise responses being strongest at 4 Hz, 15 Hz, and 24 Hz. Finally, Pastor and colleagues (2003, 2007) observed maximum response amplitudes at 15 Hz, with amplitudes decreasing progressively at higher frequencies.

It has also been reported that the VSSR produces synchronization at harmonics of the stimulus frequency (Fawcett, Barnes, Hillebrand, & Singh, 2004; Herrmann, 2001; Kim, Grabowecky, Paller, & Suzuki, 2011). Herrmann (2001) found entrainment at harmonics of the fundamental stimulus frequency, and speculated that these harmonics were a result of the square-wave nature of their LED stimulus. Square wave stimuli are complex waves comprised of multiple sine waves of various frequencies. While harmonics of the fundamental are certainly present in square wave stimuli, the fundamental is by far the strongest and most dominant frequency in such a square wave. Additionally, Fawcett et al. (2004) found entrainment at harmonics of multiple stimulus frequencies using both square and sinusoidal wave stimuli.

Pastor and colleagues (2003, 2007) not only demonstrated second-order harmonic entrainment to visual stimulation, but they also provided evidence that this harmonic was localized independently of the fundamental, using both EEG and positron emission topography (PET). While the fundamental frequency was localized to the primary visual cortex, the second harmonic was localized in the rostral portion of the calcarine sulcus and the inferior half of the parieto-occipital sulcus. These locations were confirmed using two different imaging methods in two different participant populations (Pastor et al., 2003, 2007). Clear entrainment at the third and fourth harmonics of their stimulation frequency were also observed (see Pastor et al., 2007, Figure 1B), but these results were given little attention and were not acknowledged or discussed. Kim and colleagues (2011) showed that the second harmonic is a spatially-distinct response and suggested that it may be modulated by attention. Despite evidence of neuronal entrainment at harmonics of visual stimuli and growing questions about how such responses may contribute to the visual experience, the presence of higher (i.e., third and fourth) harmonics of stimulation frequency have not been directly investigated. In this study, we used MEG to examine entrainment at multiple higher level harmonics of the visual stimulation frequency. Our primary hypotheses were that visual cortical neurons would entrain to the fundamental frequency of the visual flicker stimulus, as well as multiple higher harmonics of the fundamental. We also hypothesized that these multiple harmonics would be spatially distinct from the fundamental, providing evidence for spatially-distinct subpopulations of neurons entraining simultaneously at different harmonics of the stimulation frequency. In line with Pastor and colleagues (2007), we expected to see the localization of one or more harmonic responses outside the calcarine fissure, potentially within the parieto-occipital sulcus.

2. Methods and Materials

2.1 Subject Selection

We studied 16 healthy right-handed adults (8 females), all of whom were recruited from the local community (Oldfield, 1971). Three participants were excluded from analysis, as distinct responses within any of the four frequency bins of interest were unable to be distinguished from the baseline (see Section 2.5 in Methods). The mean age of the remaining 13 participants (6 females) at the time of scan was 28.2 years-old (range: 24–46 years). Exclusionary criteria included any medical illness affecting CNS function, psychiatric or neurological disorder, history of head trauma, and current substance abuse. Informed consent was obtained in accord with guidelines of the Wake Forest University Institutional Review Board.

2.2 MEG Paradigm

During each MEG session, participants were seated within the magnetically-shielded room (MSR) with both arms resting on cushions attached to the chair body. Ambient lighting in the MSR was equal throughout and slightly dimmed. Participants were instructed to remain still and fixate on an amber LED presented centrally on a 2.0 m distant visual display with a dull gray background. In the lower left and right visual field quadrants (~4 cm from the amber LED), two green 12-volt super bright LEDs (Alpena Hyper LED, Marklyn Group Inc., Brampton, Canada) were positioned and these were driven to flicker in-phase at a rate of 18 Hz using square wave pulses. The duration of a single flicker-train was 1.5 s and the interval between trains was 1.5–2 s, making the average trial duration 3.25 s. Each participant performed approximately 90 trials.

2.3 MEG Data Acquisition

With an acquisition bandwidth of 0.25–150 Hz, neuromagnetic responses were sampled continuously at 600 Hz using a whole-cortex CTF 2005 neuromagnetometer system equipped with 275 first-order axial-gradiometer coils (CTF Systems Inc., Vancouver, BC, Canada). All MEG data were subjected to synthetic third-gradient balancing, which removed or strongly attenuated external non-biological noise sensed by the 29 MEG reference sensors located distant to the cortex.

2.4 Anatomic MRI Acquisition & MEG Coregistration

High resolution neuroanatomic images were acquired using a 1.5T GE TwinSpeed scanner with Excite HDx. The T1-weighted axial images were obtained using a 3D spoiled gradient echo (3D-SPGR) sequence with the following parameters: matrix, 256×256 ; field of view, 20 cm; slice thickness, 1.5 mm with no gap between slices; number of slices, 124; in-plane resolution, 0.78×0.78 mm. The structural scans were aligned parallel to the anterior and posterior commissures and used for MEG coregistration. MRI-visible markers were placed on the three fiducial locations prior to image acquisition.

Prior to MEG, three coils were attached to the participant following a conventional three-point fiducial system (nasion and left/right periauricles). Once positioned for MEG, these coils were energized to induce a magnetic field and thereby allow the coils to be localized in reference to the sensors. The electric current applied to the MEG coils was maintained throughout the recording, which enabled head position to be continuously monitored during each session. Since the coil locations were known in head coordinates, all MEG measurements could be transformed into a common coordinate system based on the spatial relationship of the fiducials to each gradiometer coil. Using this coordinate system, the raw MEG data was coregistered with the participant's structural MRI volume before source analyses. All structural MRI data were transformed into the Talairach coordinate system

(Talairach & Tournoux, 1988) using BrainVoyager QX (Brain Innovations, The Netherlands).

2.5 MEG Pre-Processing

Artifact rejection was based on a fixed threshold method, supplemented with visual inspection. Epochs were of 2500 ms duration (−1000 to 1500 ms), with 0 ms defined as stimulus onset and the baseline being the −750 to 0 ms window. Artifact-free epochs were transformed into the time-frequency domain using complex demodulation (resolution: 0.5 Hz, 100 ms; Paap and Ktonas, 1977; Hoechstetter et al., 2004), and the resulting spectral power estimations per sensor were averaged over trials to generate time-frequency plots of mean spectral density. These data were normalized by dividing the power value of each post-stimulus time-frequency bin by the respective frequency's baseline power, calculated as the mean power during the period preceding stimulus onset, averaged across all trials. This normalization procedure allowed task-related power fluctuations to be readily visualized in sensor space and once identified, the neural regions generating these event-related synchronizations (ERS; power increases) could be imaged by subjecting the data to a beamformer.

Based on our hypotheses, four frequency bins that were equivalent to the frequency of stimulation and the first three harmonics were chosen for analysis. The twelve sensors that were the most entrained at all frequencies of interest ± 2 Hz were identified. To account for individual variation in peak frequency of entrainment, the most entrained 2 Hz band at 200 ms–1400 ms in each frequency bin was identified for each subject in their most active sensor for that bin and used for analysis. The baseline for this analysis was −700 ms to −100 ms.

2.6 MEG Source Imaging

Cortical networks were imaged through an extension of the linearly constrained minimum variance vector beamformer (Gross et al., 2001), which employs spatial filters in the frequency domain to calculate source power for the entire brain volume. The single images are derived from the cross spectral densities of all combinations of MEG sensors averaged over the time-frequency range of interest, and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, the source power in these images was normalized per condition and subject using a separately averaged pre-stimulus noise period of equal duration and bandwidth (van Veen, van Drongelen, Yuchtman, & Suzuki, 1997). In principle, the beamformer operator generates a spatial filter for each grid point, which passes signals without attenuation from the given neural region while minimizing interference from activity in all other brain areas. The properties of these filters are entirely determined from the MEG covariance matrix and the forward solution for each grid point in the image space, which are used to allocate sensitivity weights to each sensor in the array for each voxel in the brain (for a review, see Hillebrand, Singh, Holliday, Furlong, & Barnes, 2005).

Normalized source power was computed for the selected frequency bands over the entire brain volume per participant at $4.0 \times 4.0 \times 4.0$ mm resolution. Each subject's functional images, which were co-registered to their anatomical images prior to beamforming, were transformed into standardized space (Talairach & Tournoux, 1988) using the transform previously applied to their structural MRI volume (see Section 2.4).

3. Results

3.1 Sensor Space Analyses

All participants were able to complete the task. A log transform was applied prior to analysis, as data distribution approached non-normalcy. However, it should be noted that this transform did not change the overall results as the same comparisons were significant regardless of whether the input data was transformed. Thus, we report results from the non-transformed data below to facilitate interpretation.

Paired-sample t-tests indicated that entrainment in the 18 Hz ($t(12) = 4.16$, $p < 0.01$), 36 Hz ($t(12) = 2.99$, $p < 0.01$), 54 Hz ($t(12) = 2.67$; $p < 0.02$) and 72 Hz ($t(12) = 3.08$; $p < 0.01$) bands all increased following visual stimulation (see Figures 1 and 2). A within-subjects ANOVA was completed to determine whether there was a pattern of stronger entrainment among the four frequencies, but this analysis yielded no significant results. There was large between subject variability as to which harmonic was entrained at the highest amplitude during stimulation. It is important to note, however, that of the thirteen subjects only four (less than $1/3^{\text{rd}}$) had peak activation at the fundamental frequency (Table 1). Furthermore, as can be discerned from Figure 1, the 72 Hz band had significantly less activation than the 36 Hz band ($p = .001$), and had marginally less activation than the 18 Hz ($p = .055$) and 54 Hz ($p = .064$) bands.

3.2 Source Space Analyses

We probed activation patterns for the fundamental frequency and the first three harmonics using a random effects analysis for each frequency bin. All resulting statistical parametric maps (SPMs) were thresholded at a family-wise error (FWE) rate of $p < 0.05$ and inspected for regions of significant ERS. For the 18 Hz fundamental response, no voxels were activated at the conservative FWE-corrected ($p < 0.05$) threshold, but follow-up exploratory analyses indicated 18 Hz entrainment in superior aspects of the left calcarine fissure using a much more liberal statistical threshold ($p < 0.005$, uncorrected). Entrainment at 36 Hz was found directly lateral to the calcarine fissure ($p < 0.05$, FWE-corrected), with strong right hemispheric dominance. Entrainment at 54 Hz also had a right hemispheric bias, with maximum responses superior and slightly lateral to the calcarine fissure ($p < 0.05$, FWE-corrected; see Figure 3 and Table 2). Finally, entrainment at 72 Hz localized to the parieto-occipital sulcus near the midline ($p < 0.05$, FWE-corrected).

We also evaluated activation differences between each of the frequency bins using paired-samples t-tests. None of these comparisons survived the FWE-corrected significance testing. However, using a more liberal statistical criteria ($p < 0.00001$, uncorrected), greater entrainment in the right superior and lateral occipital lobe was detected at both 36 Hz and 54 Hz compared to entrainment at the fundamental 18 Hz frequency (see Figure 4 and Table 3). Additionally, there was stronger 72 Hz entrainment relative to 18 Hz in the right inferior and posterior parietal lobes. While each of the harmonic responses differed from the fundamental response, none of the harmonic responses differed from each other.

4. Discussion

Using MEG, we found that visual entrainment to a flickering stimulus occurs at the fundamental frequency, as well as at 36 Hz (2nd harmonic), 54 Hz (3rd harmonic), and 72 Hz (4th harmonic). There was no clear pattern of maximum entrainment between frequencies. Four participants had their strongest response at 18 Hz, five participants at 36 Hz, and four participants at 54 Hz; thus, overall, the maximum entrainment frequency was almost perfectly split amongst our participants. Furthermore, our source space analyses indicated that entrainment at the fundamental frequency (i.e., 18 Hz) is the least reliable of the four

frequency bins of interest. Below, we discuss the implications of these findings for current theories of the VSSR, as well as further understanding of the mechanisms involved in VSSR generation.

The neural mechanism underlying the VSSR is not agreed upon, and in general is poorly understood. Some have suggested the VSSR reflects locally synchronized neural populations that spatially localize to cortices corresponding to the location of the stimulus in the visual field (i.e., retinotopically mapped areas; Di Russo et. al. 2007). Still others suggest that the VSSR is not really a steady-state response, but rather the superposition of transient responses (Capilla, Pazo-Alvarez, Darriba, Campo, & Gross, 2011). Capilla and colleagues recorded responses from both a single transient stimulation and continuous stimulation. They were able to successfully superimpose continuous responses on synthetic responses made up of a repetition of recorded transient responses. They also found no continuation of response after the termination of stimulation, another potential indicator that the steady-state response can be explained by the superposition of transient responses. Capilla et al. (2011) also found harmonics in their participant's responses, but no explanation was given as to how or why transient response might include the harmonics of the fundamental frequency of the driving stimulus. Herrmann's (2001) view that explains the presence of harmonics as a result of the square-wave nature of the stimulus has some explanatory power in regards to why harmonics could appear in the steady-state response, but it fails to explain many dimensions of our findings. For example, the complex nature of square wave stimuli does not clarify why neurons would more strongly entrain to a relatively weak harmonic component rather than the much stronger fundamental, which was exhibited in 69% of our participants, or why these harmonic responses have different cortical foci than the fundamental response. These larger harmonic responses could potentially indicate that the activated circuits have greater efficiency at these particular resonant frequencies (i.e., 36 Hz and 54Hz) compared with that at the fundamental (i.e., 18 Hz), which could reflect individual differences in local GABA neurotransmitter concentrations (e.g., see Muthukumaraswamy, Edden, Jones, Swettenham, & Singh, 2009). Likewise, the spatial segregation of the harmonic and fundamental responses may indicate regional differences in the circuit, in regards to wiring and/or chemistry, that favors one resonant frequency over another regardless of the amplitude of the particular sine wave in the driving stimulus. In addition, at least one study observed higher harmonics of the driving frequency when the visual stimulus was following a sine wave pattern (Fawcett et al., 2004). Lastly, a number of studies investigating the auditory steady-state response have used square-wave (i.e., click) stimuli and demonstrated that the most robust response is clearly at the fundamental (driving) frequency (Wilson, Rojas, Reite, Teale, & Rogers, 2007; Wilson et al., 2008). These auditory results, while worth noting, should be equated with caution as they pertain to completely different populations of neurons which would likely have disparate response parameters. Our findings suggest that spatially-overlapping subpopulations of neurons are entraining simultaneously at different harmonics of the stimulus frequency, and that this entrainment responds like a steady-state response, as it continues well after the end of visual stimulation. The slight spatial location differences we observed between each of the harmonics and the fundamental response supports this viewpoint, although some caution is warranted as these differences were at the more liberal statistical ($p < 0.0001$, uncorrected) threshold. Finally, it should be noted that these results corresponded closely to the results of Pastor and colleagues (2007), who found second harmonic entrainment superior and lateral to the calcarine fissure, as well as in the parieto-occipital sulcus.

Recent work has suggested that the second-harmonic response is dependent upon the level of attention that the participant devotes to the stimulus (Kim et al., 2011). Kim and colleagues asked participants to voluntarily attend to one of two grating stimuli that were presented simultaneously in separate visual fields. Their results showed clear entrainment at

the second harmonic of the stimulus where attention was focused, but not for the stimulus that was ignored. Our current results likely support the findings of Kim and colleagues. Though we did not manipulate attention, our subjects were told to focus their attention on a fixation point (i.e., amber LED) that was between the flickering LED stimulus lights, and we did observe activation at the second harmonic (i.e., 36Hz). All participants in the current study were very high functioning and although speculative were likely to be paying close attention. However, it should also be noted that the frequency of maximum responsivity in the visual system is partially dependent on luminance of the stimuli. To our knowledge, no VSSR study has yet varied luminance in a control method to evaluate whether response amplitudes to the fundamental and harmonics vary accordingly. This should also be considered a limitation of the current study.

Finally, our findings indicate that there are substantial individual differences in the brain's response at the fundamental and harmonic frequencies. The fundamental (18 Hz) response was likely the most inconsistent among participants, and had the weakest task effect in our beamforming analyses. Essentially, some participants showed little to no entrainment at the fundamental frequency, and of those that showed entrainment, it was not reliably localized to one area. Some participants also entrained better at the third and fourth harmonic than others. As stated earlier, about 31% of the sample showed a maximum response at 54 Hz, 38% at 36 Hz, and about 31% at 18 Hz. In addition, a few participants exhibited strong responses at multiple harmonics, including one with more than 100% increases in the fundamental and all three harmonics, and another showing over 90% increases in all harmonics but not in the fundamental. Pastor et al. (2007) also reported substantial inter-subject variability in entrainment at the fundamental frequency and associated harmonics. In their study, entrainment at the fundamental was more variable when 15 Hz and 25 Hz were used as the stimulation frequency compared with 5 Hz and 10 Hz. Interestingly, entrainment at higher harmonics was least variable at 15 and 25 Hz and most variable when the stimulation frequency was very low or high (e.g., 5 Hz and 40 Hz; Pastor et al., 2007). Thus, at least some inter-subject variability may potentially be related to the specific visual stimulation frequency employed by the investigators. Future studies should examine possible demographic (e.g., sex, age, education level) or task-dependent (e.g., stimuli or task effects) effects on the third and fourth harmonic responses to gain a fuller understanding of the benefit of this type of brain response pattern. Since behavioral data was not collected in our study, it is difficult to predict which cognitive/performance factors might be linked to these higher harmonic responses. Kim and colleagues (2011) suggest differential top-down and bottom-up processing effects, such as attention, could be the cause of multiple harmonics entraining simultaneously. Since attention was shown to affect second-harmonic entrainment in their study, it is possible that other top-down processes, such as presence of novel stimuli or stimuli recognition, could affect responses in the third and fourth harmonic. Finally, the presence of higher harmonic responses could be linked to other situational variables such as time of day (e.g., whether MEG was collected early or late in the day), various medications, or even food or beverage consumption (e.g., caffeine effects). However, at this point, we can only speculate about the role that such situational variables might play in the nature of individual VSSR generation and maintenance.

In conclusion, using MEG we examined the VSSR at the fundamental frequency, as well as the 2nd, 3rd, and 4th harmonics. We found high amplitude responses at each of the harmonics, which were sometimes stronger than the VSSR at the fundamental frequency. In addition, we observed a substantial degree of individual variability in regards to the strength of responses at the fundamental and higher-level harmonics. For example, 31% of subjects showed maximum entrainment at the fundamental, 38% at the second harmonic, and 31% at the third harmonic. No subjects showed the largest VSSR at 72 Hz, though entrainment in this frequency band was significantly stronger than baseline. Finally, we found differences

in the cortical focus of entrainment between the harmonics and the fundamental frequency. This implies at least partially independent subpopulations of neurons entraining to each frequency. Further studies are necessary to identify the mechanism underlying these responses.

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Highlights

- Participants viewed a visual stimulus that flickered at 18 Hz during MEG
- Synchronization was examined at the fundamental, 2nd, 3rd, and 4th harmonic frequencies
- Strong event-related synchronization (ERS) was found in all frequency bins
- There was large individual variation in participants' strongest harmonic response
- Higher harmonic responses had partially distinct cortical loci from the fundamental

Figure 1.

Average Amplitude of Sensor-Space Event-Related Synchronization (ERS) Responses. Using the pre-stimulus baseline period, ERS per frequency band (4 total) was computed for each participant and averaged across their twelve most active occipital sensors. The average percentage increase (ERS) during stimulation (from the baseline) is shown on the Y axis, while the four frequency bands of interest are shown on the X axis. There was significant ERS activity in all four frequency bands (all p 's < 0.02), and similar activation in the 18 Hz (fundamental frequency of stimulation), 36 Hz, and 54 Hz bands. Error bars represent one standard error of the mean (SEM).

Figure 2.

Time-Frequency Spectra of a Representative Subject during Stimulation. Spectra are representative of the percent amplitude increase in entrainment from baseline in a single axial-gradiometer located in the right medial occipital lobe. The percentage increase is shown as a color gradient. Blue indicates no increase from baseline, while red indicates up to a 325% increase from baseline (see color scale-bar on right). Time is shown on the X axis in ms, with onset of stimulation (defined as 0 ms) demarcated with a red line. Frequency is shown on the Y axis. In this participant, the strongest entrainment occurred at 36 Hz and 54 Hz, with the smallest entrainment occurring at the fundamental frequency.

Figure 3. Statistical Map of ERS Activation in the 18 Hz, 36 Hz, 54 Hz, and 72 Hz bands during stimulation. Map for 18 Hz is shown at $t = 3.43$ ($p < .005$, uncorrected), while maps for the harmonics are shown at $t = 8.07$ ($p < 0.05$, FWE-corrected) threshold. Maximum ERS responses for the fundamental were in the primary visual cortex, with a left hemispheric bias. Maximum ERS responses for the harmonics were superior and slightly lateral to the calcarine fissure, with a right hemispheric bias.

Figure 4.

Statistical Map of ERS Difference between Fundamental and Harmonic Responses. Map is shown at $t = 5.26$ ($p = .00001$, uncorrected) threshold. There was preferential activation at 36 Hz and 54 Hz over the 18 Hz band in the right superior and lateral occipital lobe above and below the calcarine fissure, as well as preferential activation at 72 Hz over the 18 Hz band in the right superior occipital lobe.

Table 1

Participant's average percentage change in activity from baseline in the fundamental and harmonic frequency bins.

Participant	18 Hz	36 Hz	54 Hz	72 Hz
1	132.44 *	46.55	11.56	--
2	27.52	179.42	261.10 *	--
3	118.71 *	38.67	5.17	8.44
4	84.98	93.30 *	31.61	4.57
5	109.59	427.63 *	24.39	14.83
6	1.65	201.41 *	192.65	18.48
7	8.97	54.45 *	41.36	22.52
8	44.80	44.54	139.77 *	95.66
9	62.91	22.74	98.75 *	20.99
10	152.60	108.06	841.26 *	104.73
11	55.76	186.94 *	157.27	90.03
12	100.82 *	85.87	43.80	16.45
13	450.01 *	95.07	52.53	22.55

* Strongest response of the four frequency bins.

Table 2

Task Effects: Peak Activation Coordinates

Frequency	Anatomical Label	Talairach Coordinates (x,y,z)	T-value
18 Hz (Fundamental)	L superior calcarine fissure	-6 -101 -4	3.77
36 Hz (2 nd Harmonic)	R lateral calcarine fissure	29 -76 -8	8.47
54 Hz (3 rd Harmonic)	R superior calcarine fissure	22 -74 12	9.186
	R lateral calcarine fissure	30 -76 -8	8.902
72 Hz (4 th Harmonic)	R parieto-occipital sulcus	23 -64 26	11.13

Note: Maximum for 18 Hz (T value) is significant at $p < 0.005$ (uncorrected); maxima for 36 Hz, 54 Hz, and 72 Hz (T-value) are significant at $p < .05$ (FWE-corrected)

Table 3

Frequency Effects: Peak Activation Coordinates

Frequency	Direction of Significant Effect	Anatomical Label	Talairach Coordinates (x,y,z)	T-value
18 Hz vs. 36 Hz	36 Hz > 18 Hz	R lateral occipital lobe	39 -79 10	6.05
	36 Hz > 18 Hz	R superior occipital lobe	39 -65 36	5.72
18 Hz vs. 54 Hz	54 Hz > 18 Hz	R lateral occipital lobe	39 -79 14	7.32
	54 Hz > 18 Hz	R superior occipital lobe	39 -68 35	5.59
18 Hz vs. 72 Hz	72 Hz > 18 Hz	R posterior parietal lobe	26 -62 48	6.43
36 Hz vs. 54 Hz	<i>n.s.</i>			<i>n.s.</i>
36 Hz vs. 72 Hz	<i>n.s.</i>			<i>n.s.</i>
54 Hz vs. 72 Hz	<i>n.s.</i>			<i>n.s.</i>

Note: All maxima significant at $p < .00001$ (uncorrected).