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Temporal pattern of acoustic imaging noise asymmetrically modulates activation in the auditory cortex

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Abstract

This study investigated the hemisphere-specific effects of the temporal pattern of imaging related acoustic noise on auditory cortex activation. Hemodynamic responses (HDRs) to five temporal patterns of imaging noise corresponding to noise generated by unique combinations of imaging volume and effective repetition time (TR), were obtained using a stroboscopic event-related paradigm with extra-long (27.5s) TR to minimize inter-acquisition effects. In addition to confirmation that fMRI responses in auditory cortex do not behave in a linear manner, temporal patterns of imaging noise were found to modulate both the shape and spatial extent of hemodynamic responses, with classically non-auditory areas exhibiting responses to longer duration noise conditions. Hemispheric analysis revealed the right primary auditory cortex to be more sensitive than the left to the presence of imaging related acoustic noise. Right primary auditory cortex responses were significantly larger during all the conditions. This asymmetry of response to imaging related acoustic noise could lead to different baseline activation levels during acquisition schemes using short TR, inducing an observed asymmetry in the responses to an intended acoustic stimulus through limitations of dynamic range, rather than due to differences in neuronal processing of the stimulus. These results emphasize the importance of accounting for the temporal pattern of the acoustic noise when comparing findings across different fMRI studies, especially those involving acoustic stimulation.

Keywords

Imaging related acoustic noise; Primary Auditory Cortex; Acoustic Noise induced Hemodynamic Response; Auditory fMRI; Asymmetric Auditory Response

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1. Introduction

A challenge that exists in the application of functional magnetic resonance imaging (fMRI) to neuroscience is the adverse acoustic environment generated during imaging (Ravicz et al., 2000). Every time an image is acquired, loud acoustic noise is generated by the MRI system. This imaging-related acoustic noise confound can be as loud as 130 dB sound pressure level (SPL) (Ravicz et al., 2000), though continuous levels are more typically around 110 dB SPL (More et al., 2006; Amaro et al., 2002). Even at this lower level, extended exposure without hearing protection could cause damage to hearing of the subject/patient (Brammer, 1998). Many passive and active noise reduction techniques have been developed to reduce the perceived noise below a safe and comfortable level (Ravicz et al., 2000; Chambers et al., 2001; Hall et al., 2009). However, even with such noise reduction techniques, the acoustic noise remains audible throughout the imaging session, largely due to bone conduction of sound through the head and body (Berger et al., 2003; Ravicz and Melcher, 2001). The acoustic noise alters the acoustic environment from the ideal condition of a quiet background, and can alter the response of the brain. This is a particular confound for auditory fMRI since the acoustic noise acts as a secondary auditory stimulus that can mask or distort the primary (intended) stimulus, and can activate areas of the brain related both to auditory sensation and perception, reducing the dynamic range available for the stimulus of interest to evoke a response (Shah et al., 1999; Talavage and Edmister, 2004; Schmidt et al., 2008).

Overcoming the confound of imaging-related acoustic noise in auditory fMRI is complicated by the dependence of this noise on factors such as pulse sequence parameters, the shape and materials present in the MRI system, and the physical properties of the scan room. Therefore, direct comparison of observations with published data can be problematic. For example, the localization and extent of detected activation can depend on the level of the noise (Talavage and Edmister, 2004; Schmidt et al., 2008). As technologies for attenuation and prevention of imaging-related acoustic noise have developed, it has become more likely that recent auditory fMRI data will exhibit disagreement with the early fMRI literature, necessitating either re-collection of numerous studies, or computational compensation for the variable acoustic noise environment. In this latter, arguably more attractive alternative, a marked complication is that the central auditory pathway – and the brain, in general – does not behave as a linear system (Talavage and Edmister, 2004; Hu et al., 2010). It is therefore non-trivial to predict how changes to the acoustic noise environment will affect the magnitude (and thus detection or characterization) of signal changes associated with a desired auditory task.

One possible method to address the above issue is the use of a model based correction algorithm to compensate for the variable effects of imaging-related acoustic noise, arising from differences in imaging parameters. Such an algorithm could potentially remove some of the effects due to differences between experimental conditions across different studies. However, to develop such an algorithm, measurement of the auditory response under multiple conditions with different imaging parameters and hardware is warranted.

As a first step toward modeling and potential compensation for interaction of noise-induced responses with desired responses, this study characterizes the behavior of primary auditory cortex in response to a variety of temporal patterns of imaging-related acoustic noise. Near ideal hemodynamic responses (HDRs) were obtained in response to five temporal patterns of acquisition-related noise in the absence of a traditionally-presented stimulus, permitting characterization of noise-induced responses as a function of acoustic history (Ranaweera et al., 2011).

2. Methods

2.1. Subjects

Twelve subjects (6M/6F; average age = 22.8 ± 2.1 years) participated in this study. All subjects reported normal hearing with no history of hearing deficit, and gave written informed consent prior to participation in this study. Collection of data for each subject extended over three imaging sessions, conducted on three different days. 11 of 12 subjects participated in all three sessions.

All work described in this paper was conducted in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and used methods approved by the Human Research Protection Committee at Purdue University.

2.2. Stimulus

Subjects were exposed to variable histories of acoustic noise associated with the acquisition of 5 and 15 slice imaging volumes. The use of the actual acoustic noise associated with scanning (e.g., Bilecen et al., 1998; Tamer et al., 2009) is preferable to recorded noise (e.g., Hall et al., 2000; Seifritz et al., 2006) as conduction of sound occurs not only through the ears, but also through the skull and remainder of the body (Ravicz and Melcher, 2001). Therefore, all imaging-related acoustic noise was generated using actual imaging sequences, with the radiofrequency transmit disabled (i.e., RF-disabled) to avoid perturbation of the longitudinal magnetization (Hu et al. 2010).

The fundamental acoustic stimulus used in this work corresponds to the noise generated (a “ping” sound) during RF-disabled acquisition (“dummy” image acquisition) of a single slice. Each ping generated for this experiment is 46 ms in duration and has a fundamental frequency of 738 Hz, with its spectral maximum at 2.2 kHz (Figure 1A). The peak sound level generated by the ping was 106 dB SPL. These “dummy” image acquisitions produce the same noise as actual image acquisitions, minus the low intensity “click” sound associated with RF excitation, assumed to be a minimal contribution (Hu et al., 2010). This noise replicates the level, direction, and tactile sensations (e.g., vibration of the patient bed) associated with true image acquisitions. All stimuli comprised multiple such slices grouped to mimic a volume as if acquired using a clustered volume acquisition (CVA) (Edmister et al., 1999).

The actual perceived stimulus was the imaging-related acoustic noise after passive attenuation. In this study, a combination of earplugs and earmuffs was used to provide passive attenuation, with the resulting peak sound level at the ear canal measured to be about

75 dB SPL during scanning. The sound attenuation introduced by the combination of earplugs and earmuffs at different frequencies was explicitly measured during a separate experiment and was used to estimate the sound level at the ear canal during this experiment. Note that the low intensity sounds of RF clicks and the coolant pump were expected to fall below noticeable levels with this auditory setup (Tamer et al., 2009).

2.3. Stimulus Paradigm

Five temporal patterns of simulated volume acquisitions were used to generate imaging-related acoustic noise stimuli, as shown in Figure 1B. Two patterns represent acquisitions of a single volume comprising 5 or 15 slices (hereafter referred to as 5ping and 15ping), and three patterns seek to simulate the effects of multiple volume acquisitions within the expected duration of the positive lobe of the HDR, specifically corresponding to acquisition of two consecutive volumes (each of five slices) with a repetition time (TR) of 1, 2, or 4 s (hereafter referred to as 5-5(1s)ping, 5-5(2s)ping, and 5-5(4s)ping). The three imaging sessions comprised collection of responses to the (a) 5ping and 5-5(4s)ping, (b) 5-5(1s)ping and 5-5(2s)ping, and (c) 15ping stimuli.

To control attention and divert subjects from focusing on the acoustic noise, a movie (randomly selected from a set of five, without replacement, for each of the three sessions for the given subject) was shown during each experimental session, via a pair of MRI compatible goggles [NordicNeuroLab; Bergen, Norway]. The sound associated with the movie was not provided to the subject. Subjects were instructed to lie still and pay attention to the movie during the experiments.

To further control for common experimental conditions, subjects were given ear plugs with probe tubes to which rubber tubing was attached, connecting the plugs to an MR-compatible pneumatic sound delivery system. No acoustic stimulus was presented with this system to the subjects during this experiment.

2.4. Imaging protocol

All imaging took place at the Purdue MRI Facility (InnerVision West, West Lafayette, IN), using an eight-channel brain array (InVivo) on a General Electric (Waukesha, WI) 3 T Signa HDx imager. After acquisition of a 3-plane localizer, local high-resolution images (0.9375 mm $\times$ 0.9375 mm; FOV = 24 cm $\times$ 24 cm) of 15 axial slices (3.8 mm thick) were collected, such that the center slice passed through left and right Heschl's gyri and the volume encompassed all of the superior temporal plane and auditory cortex (Galaburda and Sanides, 1980). In the first session for a given subject, after completion of the functional runs (see below), a T1-weighted, full-brain, high-resolution anatomical volume (sagittal 3D FSPGR: 24 cm FOV, 256 $\times$ 256 acquisition matrix, 1mm slice thickness) was collected for each subject. The 15 slices of local high-resolution volume collected during each session had the same slices as the functional images, but at a higher resolution. These were used to facilitate better realignment of the functional images with the full-brain, high-resolution anatomical volumes, which were collected only during the first session.

Functional imaging (blipped gradient echo-echo planar imaging; flip angle = 90°) runs were subsequently acquired using the same volume prescription as the local high-resolution

images, but with each slice now having an in-plane resolution of $3.75 \text{ mm} \times 3.75 \text{ mm}$. Note that a double acquisition was performed in each repetition time (TR) period, one using an echo time (TE) of 26 ms, and the second a TE of 28 ms. This double acquisition enabled correction of image distortions introduced by B_0 magnetic field inhomogeneities (Jezzard & Balaban 1995).

A stroboscopic imaging paradigm (Belin et al., 1999) was used to acquire images at a fixed set of post-stimulus offsets ranging from 1.5 s to 15 s (see Table 1) after stimulus delivery with a fixed TR in a CVA scheme as shown in Figure 1C. A null condition was also included, in which no stimulus was presented during the TR period (denoted as a post-stimulus offset of $t_{\text{off}} = 0 \text{ s}$, hereafter). Images collected during this null condition provided a baseline for subsequent calculation of percent signal change.

To minimize imaging session durations, the TR value used in all functional runs associated with each of the five stimuli (see Table 1) was chosen to allow at least 15s of quiet time following the true volume acquisition before stimulus presentation took place (see Figure 1C), a gap intended to allow the hemodynamic response to return approximately to baseline after each true volume acquisition.

Either six (5ping, 5-5(1s)ping, 5-5(2s)ping, 5-5(4s)ping) or twelve (15ping) functional runs were conducted for a given stimulus, with 12 measurements made of the response at each t_{off} listed in Table 1. The order of runs was randomized across subjects, but was held fixed across stimuli for a given subject. Acquisition of t_{off} values was counter-balanced across the 6 or 12 runs. These post-stimulus offsets were chosen to sample the HDR with temporal resolution as high as 0.5 s during the expected peak and more sparsely during the prolonged post-stimulus undershoot (Le et al., 2001; Hua et al., 2011).

2.5. Pre-processing of fMRI data

Data were preprocessed for artifact removal and to facilitate inter-subject analysis. Functional images were first corrected for B_0 inhomogeneities using in-house software based on Jezzard & Balaban (1995). B_0 corrected functional images were subsequently corrected for subject motion by realignment to the 3rd image of the first functional run of each experimental session using AFNI (Cox, 1996). No data were excluded on the basis of motion, as all runs exhibited maximum movement of less than half the voxel size (1.8 mm). All images were registered to the corresponding subject's anatomical image to permit identification of anatomical structures. First, the local high-resolution slices acquired during each session were aligned to the full-brain anatomical for each subject using the *align_epi_anat.py* script (Saad et al., 2009). After visual verification of the alignment, the full-brain anatomical was spatially transformed into Talairach space (Talairach and Tournoux, 1988), with the same transformation applied to the functional images. These normalized functional images were then spatially smoothed with a 4 mm full width at half maximum (FWHM) Gaussian kernel and re-sliced to produce $4 \times 4 \times 4 \text{ mm}^3$ isotropic voxels. For subsequent analysis, the acquired volumes (and corresponding motion parameters) for each run were sorted in increasing order of t_{off} .

2.6. Region of Interest Analysis and Hemodynamic Response Modeling

All fMRI data were analyzed for activation as a function of imaging parameters on a region of interest (ROI) basis, focused on left and right primary auditory cortices. ROIs were defined on an individual basis, identified in each subject's high-resolution data as the medial two-thirds of Heschl's gyrus (Hu et al., 2010). Average volumes for the left and right primary auditory cortex ROIs were, respectively, $1122 \pm 370 \text{ mm}^3$ (17.5 ± 5.8 voxels) and $797 \pm 170 \text{ mm}^3$ (12.5 ± 2.7 voxels) consistent with previous findings (Rademacher et al., 2001; Hu et al., 2010; Olulade et al., 2011).

Estimates of the HDRs in each voxel of each ROI were calculated by computing the percent signal change (PSC) induced by the stimulus at each t_{off} , with respect to the null ($t_{\text{off}} = 0\text{s}$) condition (Belin et al., 1999; Hu et al., 2010). These signal change values were first averaged across all voxels in the ROI, then across runs (of each experimental condition) for each subject to obtain subject-specific average HDRs (aHDRs). These subject-specific aHDRs were then averaged across all subjects to obtain group aHDRs corresponding to each experimental condition for the left and right primary auditory cortices. Each of the five different experimental conditions produced two aHDRs per subject or group, corresponding to responses from each of the left and right primary auditory cortices.

The primary auditory cortex hemodynamic responses due to different temporal patterns of imaging related acoustic noise were compared across conditions and hemispheres. A peak PSC analysis was performed in each ROI to identify significant differences between peak responses under different stimulus conditions. In this analysis, the peak values of subject specific aHDRs, across all time points, under different conditions were pair-wise compared across subjects using a set of paired t-tests to identify conditions with significantly different peak response values. In addition, statistical tests (two-way ANOVA and single sided paired t-tests) were performed to check if the primary auditory cortex hemodynamic response due to imaging acoustic noise in one hemisphere was significantly different compared to the other under each experimental condition.

For further analysis, each obtained aHDR was fitted with a double gamma-variate (DGV) modeled hemodynamic response function (HRF) (Glover, 1999) using a nonlinear least squared algorithm (as implemented in *lsqcurvefit* function in MATLAB®). To ensure reasonable morphology in the modeled HRFs, the fitting process was constrained to avoid double positive or double negative lobes, and to exhibit only a single post-undershoot (that occurred after the initial positive response). Note that fitted responses were necessary for cross-condition comparisons, given that the sampled time points were not identical across the different stimuli (see Table 1).

Comparison of responses arising from the longer stimuli (e.g., 5-5(2s)ping and 5-5(4s)ping) required augmentation of the early portion of the responses. Because the durations of the 5-5(2s)ping and 5-5(4s)ping stimuli were 2.5s and 4.5s, respectively, and the smallest non-zero value for t_{off} in the experiment was 1.5s, the first non-zero sample point was at 4 or 6s post-onset, respectively, for the two conditions. Due to the acoustic equivalency of the onset of these stimuli with the onset of the 5ping stimulus, the (missing) response to the first dummy volume acquisition is expected to likewise be equivalent. Therefore, the 5-5(2s)ping

and 5-5(4s)ping aHDRs were augmented by appending the initial portion of aHDR of the 5ping prior to the first acquired data point (i.e., 4 or 6s post-onset), with a smooth combination achieved using a 3rd order polynomial fit. These augmented, fitted responses for 5-5(2s)ping and 5-5(4s)ping stimuli and the simple DGV-model fitted hemodynamic responses for other stimuli (5ping, 15ping, and 5-5(1s)ping) are referred to hereafter as fitted hemodynamic responses (fHDRs). All fHDRs are shown in Figure 2A.

2.7. Linearity Analysis

Prior either to comparison across conditions or analysis of linearity of superposition, the quality of both the average and fitted HDRs was assessed for goodness-of-fit using the coefficient of determination (R^2 value). A value of this coefficient close to one would indicate that a fHDR is appropriate for use in place of a limited-resolution aHDR. After confirmation of the quality of fHDRs, assessment was made of the linearity of the responses in the primary auditory cortex arising from the various temporal patterns of imaging-related acoustic noise.

The level of (non-)linearity exhibited by each of the primary auditory cortices was quantified by comparing the observed aHDR and the predicted response, constructed using a linear-time-invariant (LTI) system model for which the 5ping fHDR served as the basis function. The LTI-predicted HDR was calculated by a composite waveform constructed through superposition of appropriately time-shifted DGV-modeled 5ping fHDRs (referred to as D^n model). The R^2 value when this LTI-predicted response was compared to the corresponding aHDR was computed, with values near unity indicating a good fit, and thereby consistency with the assumption of linearity.

In initial investigations, it was observed that the peak post-stimulus undershoot of the aHDRs did not significantly differ across stimulus conditions despite differences in delay in time to the peak post-stimulus undershoot (see Figure 2A). This observation is intuitively inconsistent with LTI superposition of modeled responses (e.g., DGV-modeled 5ping fHDR) that each contain an undershoot. Therefore, an additional combination of models (i.e., a mixed-model HDR approach) was evaluated as reference functions for repeated 5ping presentations. In this case ($S^{(n-1)}D$ model) a single gamma-variate (SGV) model was used to represent responses to the initial $n-1$ sets of pings (assuming a train of n sets) and a DGV model to represent the response to the final set of pings. This mixed HDR model was only used for analyzing linearity of superposition of successive responses when predicting the total response to multiple stimuli. It was not used for detection of activation.

2.8. Detection of Activation

Detection and quantification of activation in the cortex, arising in response to the variable histories of stimulations, were performed using the general linear model (GLM) (Worsley and Friston, 1995). A k-cross validated (Kearns and Ron, 1999) model of the HDR was used as the reference function while using motion parameters and a constant term as covariates of no interest in the GLM matrix. The k-cross validated model was calculated by fitting the DGV-modeled response (created above) to the mean percent signal change of response across left and right hemispheres, due to the stimulus condition being used, from all the

subjects *except* the subject being tested. This approach was reportedly more effective in detecting the activation than using a canonical HRF model as demonstrated by Hu et al. (2010). A mask with 2738 voxels (175,232 mm²) was applied to individual subject statistical maps to incorporate only the voxels common to all conditions and subjects, and to eliminate regions of partial-volume averaging. A single-factor, across-subject, random-effects analysis was then performed on the data to generate *t*-statistic maps corresponding to each of the five stimulus conditions. A Bonferroni correction (Curtin and Schulz, 1998) was used to correct for effects due to multiple comparisons across number of voxels, treating them as independent measurements. The resulting statistical maps were displayed at significance level of $p_{\text{Bonferroni}} < 0.01$.

3. Results

3.1. fMRI Response Dependence on Temporal Pattern of Acoustic Noise

The fitted HDRs for the whole group of subjects in the left and right primary auditory cortices, as observed for each of the five temporal patterns of acoustic noise, are shown in Figure 2A. The error bars in the figure correspond to the standard error of mean percent signal change at each time point, across subjects. Table 2 lists estimated response parameters for the average (aHDR) and fitted responses (fHDR): peak PSC, time-to-peak, peak post-stimulus undershoot and, for fHDR, FWHM and “goodness-of-fit” coefficient (R^2). Note that R^2 values for the model fits are all near 1.0, indicating that the modeled fitted responses are representative of the observations.

The analysis of peak PSC across subjects revealed some significant differences in responses across the temporal patterns of noise presentation (see Figure 2B). The peak PSC due to the 15ping stimulus is significantly larger than all the other types except for 5-5(1s)ping response in the left primary auditory cortex, and significantly larger in the right primary auditory cortex than the 5ping and 5-5(2s)ping conditions. The responses to 15ping and 5-5(1s)ping stimuli appeared to have similar peak PSC values in both hemispheres.

A three-way ANOVA across subjects, hemispheres, and time points in the positive lobe of the HDR revealed a statistically significantly ($p < 0.05$) greater response in the right auditory cortex compared to the left under all conditions except for the 5-5(4s)ping condition ($p = 0.076$). In addition, a single sided *t*-test was used to assess the differential (right-left) response across subjects, treating the time index (except 0) as the repeated measure. This test revealed a statistically significantly ($p < 0.01$) greater response in the right primary auditory cortex compared to the left, during all conditions as indicated in Figure 3.

3.2. Linearity Analysis

The first and third columns (marked Dⁿ) of Figure 4 present aHDRs (thick blue continuous line), and fitted responses (thick red dotted line) from the LTI assumption using as a basis the DGV-modeled 5ping aHDR (references presented as thin green continuous lines). A comparison of measures and similarity assessments for these curves are listed in Table 3.

The results from modeling the observed nonlinearity using the mixed HDR approach are presented in the second and fourth columns in Figure 4. The mixed HDR model ($S^{(n-1)}D$)

improved the fit to the responses during the post-stimulus undershoot, as is reflected in the increased R^2 values (Table 3), and is evident from visual inspection.

3.3. Extent of Activation

A summary of results from the analysis of areas of activation is presented in Table 4. The extent of activation maps under each of the stimulus conditions is illustrated in Figure 5.

Under all conditions, the primary auditory cortex was strongly activated, while parts of secondary auditory cortex and other auditory related areas were also activated, especially as the stimulus duration increased. In almost all cases (except during the 5-5(1s)ping condition), the peak activation was observed in left Heschl's gyrus, the site of left primary auditory cortex. As the duration between two ping sets (effective TR) increased, the activation extent decreased. The least activation was observed during the 5-5(4s)ping condition, while the greatest activation was seen during the 15ping condition. During this last condition widespread activation was observed bilaterally, in auditory and related areas as well as non-auditory brain regions.

4. Discussion

The objective of the current study was to characterize the primary auditory cortex hemodynamic responses to different imaging-related acoustic noise history patterns, allowing the study of the effect of the acoustic history on auditory cortical response. Modeling of responses using combinations of traditional hemodynamic response functions indicates that the auditory cortical response, in both amplitude and spatial extent, is modulated by the history of the imaging noise. While the nonlinearity was greatest during the post-stimulus undershoot phase of the hemodynamic response, the peak amplitude also failed to exhibit linearity with increased exposure to imaging-related acoustic noise. A greater response to imaging-related acoustic noise was observed in the right primary auditory cortex compared to the left under all experimental conditions used in the current study, warning of potential bias effects in auditory fMRI experimentation due to differentially limited dynamic range in the primary auditory cortices.

4.1. Hemodynamic Responses Due to Imaging-Related Acoustic Noise

As has been noted in the literature, imaging-related acoustic noise is a significant confound for auditory-related fMRI because the induced HDRs are generally consistent with the shape and amplitude of responses to presented stimuli (Shah et al., 1999; Hall et al., 2000; Moelker and Pattynama 2003; Tamer et al., 2009; Hu et al., 2010). The variable duration stimuli in this study serve as references to illustrate this key point. Glover et al. (1999) used 1s long tone pulses in an auditory and finger tapping experiment and observed a time-to-peak (T_p) of 5 s, FWHM of 3.5 s, and a peak post-stimulus undershoot of about 25% of the peak response, with the signal returning to baseline after about 20 s. In a separate study, Harms et al. (2002) used trains of noise bursts with varying repetition rates and durations with a rapid ER experiment and observed peak PSC of about 1%, T_p of about 4–6 s, and comparable post-stimulus undershoots to this study (the reported values correspond to the responses due to 5 noise bursts at 35/s and 2 noise bursts at 2/s). However, in contrast to the current study,

Harms et al. observed a return to baseline within 8 to 10 s of stimulus onset, whereas the responses observed in this work did not return to baseline until 12–15 s following stimulus onset. In a study analogous to the present evaluation, Inan et al. (2004) used single or paired pure tone pulses (1 kHz, 100 ms) with 1, 4, or 6 s inter-pulse-intervals interleaved with a visual experiment to study the effect of stimulus repetition in auditory and visual cortices and observed peak percent signal change of about 0.6% with peak times of 4.7 to 5.7 s for 1 s inter-pulse-interval—a slightly smaller peak percent signal change and a similar T_p relative to the most comparable condition, 5-5(1s)ping, in this study. Therefore, excepting some variations in post-stimulus undershoot duration, the stimulus responses observed here are consistent with expectations from previous work, with differing experimental setups (e.g., noise/tone busts vs. imaging-related acoustic noise; variations in TE and TR; field strengths of 1.5T vs. 3T) likely being the primary source of differences in response amplitude and duration.

4.2. Nonlinearity of Response in Primary Auditory Cortex

The linearity analysis conducted in this work revealed that in addition to the response magnitude, the extent of activation also showed a nonlinear modulation effect with the acoustic noise pattern (See Figure 5). While the extent of activation generally increased with increasing acoustic history (i.e., more acoustic energy in the temporal proximity), there was a reduction in activation extent during the 5-5(4s)ping condition. The activation extent during 5ping condition was greater compared to the 5-5(4)ping condition, contrary to predictions of a linear model based on activation maps generated using the random effects analysis.

The results of this study confirm that the primary auditory cortex responds nonlinearly to stimuli presented in (close) temporal proximity, especially when the presentation duration is long (see Figure 4). Several investigators have studied the nonlinearity of the auditory cortex using different methods as a function of stimulus presentation rate (Buxton et al., 1998; Friston et al., 1998; Vazquez and Noll, 1998), evaluating how reduced stimulus separation affects response amplitude and duration. Superposition of responses has been examined using imaging-related acoustic noise (Talavage and Edmister, 2004) or using paired stimuli (Glover, 1999; Inan et al., 2004).

Previous attempts to model these nonlinearities have been successful, but most have not been physiologically-based, a key concern when extension to disordered populations is desirable. The earliest attempts to model these non-linearities included use of a broadening function in series with a linear system model to absorb the nonlinearities of the observed responses (Vazquez and Noll, 1998) and use of estimated Volterra kernel basis functions (Friston et al., 1998). Though these methods have been extremely effective in modeling the nonlinearities, they are purely theoretical and do not have a clear physiologic basis. Physiologically-based modeling is best exemplified by the Balloon model proposed by Buxton et al. (1998) and further developed by Uludag and colleagues (Uludag et al., 2004; Sadaghiani et al., 2009; Havlicek et al., 2015). However, while also effective, this method requires estimation of various difficult-to-obtain parameters that characterize the hemodynamics in the cortex (venous volume, deoxyhemoglobin content, oxygen extraction

fraction, etc.). Such approaches have been combined (Friston et al., 2000) in an effort to reduce the number of estimated physiological parameters.

In the current study, a relatively simple combination of SGV and DGV models was used to model the nonlinearity, attempting to bypass the ensemble of parameters required for the Balloon model, and requiring no estimation of basis functions (e.g., Volterra kernels). Such an approach was motivated by the observation that most of the nonlinearity observed during the current study involves the disproportionate increase in post-stimulus undershoot, relative to the predicted responses, with increased duration of acoustic stimulation. Therefore, it seemed that a simpler model (i.e., having fewer parameters to estimate) could account for the time-limited observed nonlinearity, especially during the post-stimulus undershoot phase of the response. Though the combined model was also not physiologically inspired, a physiologically relevant derivative of the balloon model, presented by Havlicek et al. (2015), provides some basis for the physiological validity of such a combined approach. Havlicek et al. (2015) considered the conditions of stimulus and lack-of-stimulus as two modulating inputs in the model. Therefore, the post-stimulus undershoot could be modulated by the response to cessation of the stimulus. In the combined $S^{(n-1)}D$ model presented herein, the undershoot is only present in the response to the final set of pings, for which the DGV which could be considered as a composite of two SGV responses, one to the pings and one to the cessation of acoustic stimulation.

4.3. The BOLD Post-Stimulus Undershoot

The typical segment of response observed to be most deviant from linearity was the undershoot period that follows the primary response to the imaging-related acoustic noise stimulus. The post-stimulus undershoot predicted in this work using a LTI system model (5ping response as basis) was always larger than the observed, even when the positive lobe was well predicted (See Figure 4 columns 1 and 3). This is unlikely to be an artifact of imaging, for while Zhao et al. (2007) observed a linear dependence of post-stimulus undershoot on the echo time (TE), all of these data were collected using a fixed TE. Therefore, one must examine physiological sources.

The BOLD post-stimulus undershoot is believed to reflect a post-response transient increase of deoxy-hemoglobin brought about by one or more of many possible causes (Chen and Pike, 2009; Buxton et al., 2004). These causes could include (1) the temporal mismatch between the cerebral blood flow (CBF) and venous cerebral blood volume (CBV) changes (Mandeville et al., 1999; 2001; Friston et al., 2000; Obata, 2004) as incorporated into biomechanical models (Buxton et al., 1998; Mandeville et al., 1999), (2) transient post-stimulus decoupling of cerebral metabolic rate of oxygen ($CMRO_2$) from CBF and CBV (Lu et al., 2004; Donahue et al., 2009), and (3) a combination of post-stimulus undershoot in CBF (Uludag et al., 2004; Huppert et al., 2006; Chen and Pike, 2009) and slow CBV response (Chen and Pike, 2009). In addition to these, the work by Krekelberg et al. (2006) and Sadaghiani et al. (2009) suggest that the BOLD post-stimulus undershoot may also reflect the number of active voxels or the activation and deactivation pattern of the neurons in addition to blood volume effects. These however may in fact be related to $CMRO_2$, CBV, and CBF effects brought about by neuronal activations.

While this study did not investigate the neurophysiology at a level that may directly address the physical causes of the post-stimulus undershoot, it is of note that the post-stimulus undershoot could be better predicted using combinations of both SGV and DGV functions than by sole use of DGV modeling (See Figure 4 columns 2 and 4). The inclusion of a SGV model, which lacks an undershoot component, seems to have served to bound the post-stimulus undershoot amplitude, suggesting that the growth of the post-stimulus undershoot period may have an underlying physiologic limit related to the temporal or spatial extent of the transient deoxy-hemoglobin increase, noted above. Recent findings by Mullinger et al. (2013) suggest that, contrary to the current consensus, the post stimulus response could be an independent response not directly coupled to the primary positive BOLD response. The lack of correlation in the peak amplitude of post-stimulus undershoot phase to the positive response in this study can also be explained using the above finding.

4.4. Hemispheric Asymmetry in Primary Auditory Cortex Response to Imaging Related Acoustic Noise

A comparison of measured HDR in left and right primary auditory cortices across subjects revealed a statistically significantly greater response in the right auditory cortex during all conditions as shown in Figure 3. Schmidt et al. (2008) observed such rightward bias in auditory cortex response when measured with sparse temporal acquisition scheme (clustered sparse temporal acquisition) similar to current study, but not with continuous acquisition. This implies that the right auditory cortex simply is “more sensitive” to the presence of a sustained input, resulting in greater sensitivity to imaging-related acoustic noise. Such greater sensitivity in the right primary auditory cortex to acoustic noise was also observed during a combined fMRI and MEG study by Mathiak et al. (2002).

As a consequence of the observed noise-related asymmetry, fMRI experiments utilizing either distributed volume acquisition (DVA) schemes or clustered volume acquisitions (CVA) with short TR values, could exhibit asymmetric responses to intended acoustic stimuli in left and right primary auditory cortices. These asymmetries could be observed even in the absence of any differences in neuronal processing of the stimulus, rather being related to differing baseline activation levels between the cortices. The hemodynamic response of the brain, and the auditory cortex in particular, is known to behave nonlinearly with a limited dynamic range for the response (Talavage and Edmister, 2004; Schmidt et al., 2008). Because of its greater noise-related HDR, the right primary auditory cortex may have a lesser available dynamic range with which to respond to the external stimulus. Therefore, it is possible to observe a smaller stimulus-induced response magnitude in the right auditory cortex, when such a difference might not be present with a quiet background.

The greater sensitivity of the right primary auditory cortex observed in this study is likely due to a greater inherent sensitivity to the dynamic structure of the imaging-related acoustic noise stimulus, which has a complex spectral structure and dynamic pitch—features for which a right hemispheric bias (Schmidt et al., 2008), especially in non-primary auditory cortex have previously been documented (Zatorre and Belin, 2001; Harms and Melcher, 2002; Jamison et al., 2006; Hyde et al., 2008). Though it is possible that differences in neural mechanisms and vascular structures in the left and right primary auditory cortices

could have played a role in the observed asymmetry in HDR magnitude, the data from the current experiment are not sufficient to ascertain their contribution. Therefore, a closer look at the reasons behind this greater sensitivity is warranted in light of the observations of the current study in order to minimize the effects of this asymmetric sensitivity to imaging-related-acoustic noise in left and right primary auditory cortices.

4.5. Effect of Temporal Pattern on Activation Extent

Results suggest that activation detection, in addition to response estimation, can be negatively influenced by the presence of imaging-related acoustic noise, in both auditory- and non-auditory-related areas of the brain. Under the implemented model of multiple volume acquisitions, the extent of activation due to imaging-related acoustic noise was generally observed to increase as with duration and density of such noise (i.e., from 5-5(4s)ping to 5-5(2s)ping to 5-5(1s)ping). While the extent of activation increased during two imaging-related acoustic noise segments separated by 1 and 2 s compared to a single segment, when the separation was 4 s, the activation extent decreased. The least extent of activation was observed during the 5-5(4s)ping condition, encompassing only the “core” auditory areas, as presumed to be located along Heschl’s gyrus (Langers and van Dijk, 2011). As the temporal density was increased, the extent of activation spread from cortical sensory areas to include additional auditory-related areas (Harms and Melcher, 2002) such as the insula, auditory thalamus (medial geniculate body), and the MTG. When the noise was constructed to be continuous and extended from 500 ms (5ping condition) to 1500 ms (15ping condition), activation also included non-auditory areas such as the visual cortex, prefrontal cortex, and the hippocampus.

While it is possible that the increase in extent of activation is related to recruitment of novel and additional neural pools during multiple temporally close stimulus presentations, as suggested by Inan et al. (2004), the observation that the 5-5(4s)ping condition had a lesser extent of activation than the 5ping condition suggests the exact temporal pattern of the acoustic history plays a role in modulating extent of activation. Also, while the 5-5(1s) and 15ping conditions had similar HDRs, the activation extents detected under the two conditions differed greatly, indicating a difference in the mechanism of recruiting neural pools to respond to the corresponding acoustic conditions. This further suggests that the phase (e.g., increasing, peak, decreasing, or post-stimulus undershoot) of the HDR due to the first stimulus at the time the second stimulus is delivered can have an effect on not only the size of the response, but also the areas in which activation may be detected due to the second stimulus (Talavage and Edmister, 2004).

The variable time experienced by the subject between acoustic noise segments, either due to the actual acquisitions or due to experimental stimuli (range: 15–32 s) is not believed to have affected results due to a startle-like effect. Though possible, it is expected that this effect would be relatively small relative to the forced response arising from the actual stimulus, and would likely be evidenced in responses from non-auditory areas such as the thalamus, caudate nucleus, left angular gyrus, anterior cingulate, and transitional medial cortex (Hazlett et al. 2001, Kumari et al. 2005, Campbell et al. 2007). Conversely, the extent of activation in this study encompasses primary and secondary auditory cortices (Bandettini

et al., 1998; Ulmer et al., 1998; Shah et al., 1999; Talavage et al., 1999), and additional areas that have also been reported to be active under noisy conditions, such as operculum, insula, thalamus, hippocampus, putamen, and the visual cortex (Cho et al., 1998; Mazard et al., 2002; Zhang et al., 2005; Tomasi et al., 2005; Schonwiesner et al., 2007; Hu et al., 2010; Olulade et al., 2011). Therefore, the general extent of non-auditory area activation is consistent with other studies that have not used a stroboscopic design, indicating that it is unlikely that a startle-like effect is playing a predominant role.

Although this study did not specifically analyze the differences between responses to imaging-related-acoustic noise in cortical areas other than left and right primary auditory cortices, it is possible that asymmetric responses may exist in other locations. If true, baseline levels of other brain areas could also be affected due to imaging-related acoustic noise, and inferences regarding stimulus laterality/preference must take such response biases into account.

4.6. Conjecture on Compensation for Effects of Imaging Related Acoustic Noise

This body of non-auditory area activation suggests that the influence of imaging related acoustic noise be considered for the broader array of non-auditory fMRI experiments. Because the extent of activation as well as the HDR due to a stimulus is modulated by the exact temporal pattern of imaging-related acoustic noise, it is important to account for parameters that affect imaging-related acoustic noise when comparing results across different fMRI studies. Failure to do so could result in inaccurate inferences when combining results from different studies. As demonstrated in this work, the modulation effect not only applies to the auditory cortex, but also to higher-order auditory and non-auditory brain regions that may also be influenced by the presence of imaging-related acoustic noise.

One approach to compensate for the variable effects of imaging-related acoustic noise, arising from differences in imaging parameters is to use a model based correction algorithm. While this approach will likely be impractical, in a large-scale sense, it remains probable that through the use of L1-norm regularization (or similar) approaches, a reasonable degree of compensation may be generated (e.g., Tamer et al. 2010). The lack of studies looking into methods to account for the variable effects of imaging-related acoustic noise is an indication that there is ample opportunity in research to find solutions to this problem.

5. Conclusions

Imaging related acoustic noise produces asymmetric responses in the right and left primary auditory cortices, does not exhibit post-response undershoot growth with increasing noise duration, but does modulate the extent of activation in non-auditory areas of the brain as duration increases. The hemispheric bias in primary auditory cortex activation, coupled with limitations in the dynamic range available for fMRI responses, could lead to observation of asymmetric amplitudes for external (non-imaging-related acoustic noise) auditory stimuli that could be (incorrectly) interpreted as asymmetric neurophysiologic responses to the stimulus. Experiments using DVA or CVA approaches with short TR values could be more prone to these asymmetric noise-induced responses. The limited post-response undershoot

may indicate a physiologic limit to the transient increase of deoxy-hemoglobin levels, supporting the idea of a limited dynamic range. The results of the current study emphasize the importance of considering the effects of imaging-related acoustic noise in auditory as well as non-auditory fMRI experiments used for estimation of the response as well as for detection of activation, and when comparing results across fMRI studies.

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References

- Amaro E, Williams SC, Shergill SS, Fu CH, MacSweeney M, Picchioni MM, Brammer MJ, McGuire PK. Acoustic noise and functional magnetic resonance imaging: current strategies and future prospects. *J Magn Reson Imaging*. 2002; 16:497–510. [PubMed: 12412026]
- Bandettini PA, Jesmanowicz A, Van Kylen J, Birn RM, Hyde JS. Functional MRI of brain activation induced by scanner acoustic noise. *Magn Reson Med*. 1998; 39:410–416. [PubMed: 9498597]
- Belin P, Zatorre RJ, Hoge R, Evans AC, Pike B. Event-related fMRI of the auditory cortex. *Neuroimage*. 1999; 10:417–429. [PubMed: 10493900]
- Berger EH, Kieper RW, Gauger D. Hearing protection: surpassing the limits to attenuation imposed by the bone-conduction pathways. *J. Acoust. Soc. Am*. 2003; 114:1955–1967. [PubMed: 14587596]
- Bilecen D, Radü EW, Scheffler K. The MR tomograph as a sound generator: fMRI tool for the investigation of the auditory cortex. *Magn Reson Med*. 1998; 4(0):934–937. [PubMed: 9840840]
- Brammer MJ. Multidimensional wavelet analysis of functional magnetic resonance images. *Human Brain Mapping*. 1998; 6(5-6):378–382. [PubMed: 9788076]
- Buxton RB, Uludag K, Dubowitz DJ, Liu TT. Modeling the hemodynamic response to brain activation. *Neuroimage*. 2004; 23:S220–S233. [PubMed: 15501093]
- Buxton RB, Wong EC, Frank LR. Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. *Magn Reson Med*. 1998; 39:855–864. [PubMed: 9621908]
- Campbell LE, Hughes M, Budd TW, Cooper G, Fulham WR, Karayanidis F, Schall U. Primary and secondary neural networks of auditory prepulse inhibition: a functional magnetic resonance imaging study of sensorimotor gating of the human acoustic startle response. *European Journal of Neuroscience*. 2007; 26(8):2327–2333. [PubMed: 17908169]
- Chambers J, Akeroyd MA, Summerfield AQ, Palmer AR. Active control of the volume acquisition noise in functional magnetic resonance imaging: method and psychoacoustical evaluation. *J. Acoust. Soc. Am*. 2001; 11(0):3041–3054. [PubMed: 11785805]
- Chen JJ, Pike GB. Origins of the BOLD post-stimulus undershoot. *Neuroimage*. 2009; 46(3):559–568. [PubMed: 19303450]
- Cho ZH, Chung SC, Lim DW, Wong EK. Effects of the acoustic noise of the gradient systems on fMRI: a study on auditory, motor, and visual cortices. *Magn Reson Med*. 1998; 39:331–335. [PubMed: 9469720]
- Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*. 1996; 29(3):162–173. [PubMed: 8812068]
- Curtin F, Schulz P. Multiple correlations and Bonferroni's correction. *Biological psychiatry*. 1998; 44(8):775–777. [PubMed: 9798082]
- Donahue MJ, Stevens RD, De Boorder MJJ. Hemodynamic changes after visual stimulation and breath holding provide evidence for an uncoupling of cerebral blood flow and volume from oxygen metabolism. *Journal of Cerebral Blood Flow & Metabolism*. 2009; 29(1):176–185. [PubMed: 18797471]
- Edmister WB, Talavage TM, Ledden PJ, Weisskoff RM. Improved auditory cortex imaging using clustered volume acquisitions. *Hum Brain Mapp*. 1999; 7:89–97. [PubMed: 9950066]

- Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R. Event-related fMRI: characterizing differential responses. *Neuroimage*. 1998; 7:30–40. [PubMed: 9500830]
- Friston KJ, Mechelli A, Turner R, Price CJ. Nonlinear responses in fMRI: the Balloon model, Volterra kernels, and other hemodynamics. *NeuroImage*. 2000; 12(4):466–477. [PubMed: 10988040]
- Galaburda A, Sanides F. Cytoarchitectonic organization of the human auditory cortex. *J. Comp. Neurol.* 1980; 19(0):597–610. [PubMed: 6771305]
- Glover GH. Deconvolution of impulse response in event-related BOLD fMRI. *Neuroimage*. 1999; 9:416–429. [PubMed: 10191170]
- Hall DA, Chambers J, Akeroyd MA, Foster JR, Coxon R, Palmer AR. Acoustic, psychophysical, and neuroimaging measurements of the effectiveness of active cancellation during auditory functional magnetic resonance imaging. *J. Acoust. Soc. Am.* 2009; 12(5):347–359. [PubMed: 19173422]
- Hall DA, Haggard MP, Akeroyd MAAR. “sparse” temporal sampling in auditory fMRI. *Human brain mapping*. 1999; 7(3):213–223. [PubMed: 10194620]
- Hall DA, Summerfield AQ, Gonçalves MS, Foster JR, Palmer AR, Bowtell RW. Time-course of the auditory BOLD response to scanner noise. *Magn Reson Med*. 2000; 43:601–606. [PubMed: 10748437]
- Harms. Sound temporal envelope and time-patterns of activity in the human auditory pathway- an fMRI study. (Doctoral dissertation, Massachusetts Institute of Technology). 2002
- Harms MP, Melcher JR. Sound repetition rate in the human auditory pathway: representations in the waveshape and amplitude of fMRI activation. *J. Neurophysiol.* 2002; 88:1433–1450. [PubMed: 12205164]
- Havlicek M, Roebroeck A, Friston K, Gardumi A, Ivanov D, Uludag K. Physiologically informed dynamic causal modeling of fMRI data. *NeuroImage*. 2015; 122:355–372. [PubMed: 26254113]
- Hazlett EA, Buchsbaum MS, Tang CY, Fleischman MB, Wei TC, Byne W, Haznedar MM. Thalamic activation during an attention-to-prepulse startle modification paradigm: a functional MRI study. *Biological psychiatry*. 2001; 50(4):281–291. [PubMed: 11522263]
- Hu S, Olulade O, Castillo JG, Santos J, Kim S, Tamer GG, Luh WM, Talavage TM. Modeling hemodynamic responses in auditory cortex at 1.5 T using variable duration imaging acoustic noise. *Neuroimage*. 2010; 49:3027–3038. [PubMed: 19948232]
- Hua J, Stevens RD, Huang AJ, Pekar JJ, van Zijl PC. Physiological origin for the BOLD poststimulus undershoot in human brain: vascular compliance versus oxygen metabolism. *J. Cereb. Blood Flow Metab.* 2011; 31:1599–1611. [PubMed: 21468090]
- Huppert TJ, Hoge RD, Diamond SG, Franceschini MA, Boas DA. A temporal comparison of BOLD, ASL, and NIRS hemodynamic responses to motor stimuli in adult humans. *Neuroimage*. 2006; 29:368–382. [PubMed: 16303317]
- Hyde KL, Peretz I, Zatorre RJ. Evidence for the role of the right auditory cortex in fine pitch resolution. *Neuropsychologia*. 2008; 46:632–639. [PubMed: 17959204]
- Inan S, Mitchell T, Song A, Bizzell J, Belger A. Hemodynamic correlates of stimulus repetition in the visual and auditory cortices: an fMRI study. *Neuroimage*. 2004; 21(3):886–893. [PubMed: 15006655]
- Jamison HL, Watkins KE, Bishop DVMPM. Hemispheric specialization for processing auditory nonspeech stimuli. *Cerebral cortex*. 2006; 16(9):1266–1275. [PubMed: 16280465]
- Jezzard P, Balaban RS. Correction for geometric distortion in echo planar images from B0 field variations. *Magnetic resonance in medicine*. 1995; 34(1):65–73. [PubMed: 7674900]
- Kearns M, Ron D. Algorithmic stability and sanity-check bounds for leave-one-out cross-validation. *Neural Comput.* 1999; 11:1427–1453. [PubMed: 10423502]
- Krekelberg B, Boynton GM, van Wezel RJA. Adaptation: from single cells to BOLD signals. *Trends in neurosciences*. 2006; 29(5):250–256. [PubMed: 16529826]
- Kumari V, Antonova E, Zachariah E, Galea A, Aasen I, Ettinger U, Sharma T. Structural brain correlates of prepulse inhibition of the acoustic startle response in healthy humans. *Neuroimage*. 2005; 26(4):1052–1058. [PubMed: 15961045]
- Langers DR, van Dijk P. Mapping the Tonotopic Organization in Human Auditory Cortex with Minimally Salient Acoustic Stimulation. *Cerebral Cortex*. 2011 bhr282.

- Le TH, Patel S, Roberts TP. Functional MRI of human auditory cortex using block and event-related designs. *Magn Reson Med*. 2001; 45:254–260. [PubMed: 11180433]
- Lu H, Golay X, Pekar JJ, van Zijl PCM. Sustained poststimulus elevation in cerebral oxygen utilization after vascular recovery. *Journal of Cerebral Blood Flow & Metabolism*. 2004; 24(7): 764–770. [PubMed: 15241184]
- Mandeville JB, Jenkins BG, Kosofsky BE, Moskowitz MA, Rosen BR, Marota JJ. Regional sensitivity and coupling of BOLD and CBV changes during stimulation of rat brain. *Magn Reson Med*. 2001; 45:443–447. [PubMed: 11241702]
- Mandeville JB, Marota JJ, Ayata C, Moskowitz MA, Weisskoff RM, Rosen BR. MRI measurement of the temporal evolution of relative CMRO(2) during rat forepaw stimulation. *Magn Reson Med*. 1999; 42:944–951. [PubMed: 10542354]
- Mathiak K, Rapp A, Kircher TT, Grodd W, Hertrich I, Weiskopf N, Lutzenberger W, Ackermann H. Mismatch responses to randomized gradient switching noise as reflected by fMRI and whole-head magnetoencephalography. *Hum Brain Mapp*. 2002; 16:190–195. [PubMed: 12112773]
- Mazard A, Mazoyer B, Etard O, Tzourio- N. Impact of fMRI acoustic noise on the functional anatomy of visual mental imagery. *Journal of Cognitive Neuroscience*. 2002; 14(2):172–186. [PubMed: 11970784]
- Moelker A, Pattynama PM. Acoustic noise concerns in functional magnetic resonance imaging. *Human brain mapping*. 2003; 20(3):123–141. [PubMed: 14601139]
- More SR, Lim TC, Li M, Holland CK, Boyce SE, Lee JH. Acoustic noise characteristics of a 4 Telsa MRI scanner. *J Magn Reson Imaging*. 2006; 23:388–397. [PubMed: 16463341]
- Mullinger KJ, Mayhew SD, Bagshaw AP, Bowtell R, Francis ST. Poststimulus undershoots in cerebral blood flow and BOLD fMRI responses are modulated by poststimulus neuronal activity. *Proc. Natl. Acad. Sci. U.S.A.* 2013; 110:13636–13641. [PubMed: 23898206]
- Obata. Discrepancies between BOLD and flow dynamics in primary and supplementary motor areas: application of the balloon model to the interpretation of BOLD transients. *NeuroImage*. 2004; 21(1):144–153. [PubMed: 14741651]
- Olulade O, Hu S, Gonzalez-Castillo J, Tamer GG, Luh WM, Ulmer JL, Talavage TM. Assessment of temporal state-dependent interactions between auditory fMRI responses to desired and undesired acoustic sources. *Hear. Res.* 2011; 277:67–77. [PubMed: 21426929]
- Rademacher J, Morosan P, Schormann T, Schleicher A, Werner C, Freund HJ, Zilles K. Probabilistic mapping and volume measurement of human primary auditory cortex. *Neuroimage*. 2001; 13:669–683. [PubMed: 11305896]
- Ranaweera, RD.; Kwon, M.; Hu, S.; Tamer, GG.; Talavage, TM. Measurement of auditory hemodynamic response function due to different temporal patterns of imaging acoustic noise using functional magnetic resonance imaging. *Industrial and Information Systems (ICIIS); 2011 6th IEEE International Conference on; 2011. p. 239-243.*
- Ravicz ME, Melcher JR, Kiang NY. Acoustic noise during functional magnetic resonance imaging. *J. Acoust. Soc. Am.* 2000; 108:1683–1696. [PubMed: 11051496]
- Ravicz ME, Melcher JR. Isolating the auditory system from acoustic noise during functional magnetic resonance imaging: examination of noise conduction through the ear canal, head, and body. *J. Acoust. Soc. Am.* 2001; 109:216–231. [PubMed: 11206150]
- Saad ZS, Glen DR, Chen G, Beauchamp MS, Desai R. A new method for improving functional-to-structural MRI alignment using local Pearson correlation. *Neuroimage*. 2009; 44(3):839–848. [PubMed: 18976717]
- Sadaghiani S, Ugurbil K, Uludag K. Neural activity-induced modulation of BOLD poststimulus undershoot independent of the positive signal. *Magn Reson Imaging*. 2009; 27:1030–1038. [PubMed: 19761930]
- Schmidt CF, Zaehle T, Meyer M, Geiser E, Boesiger P, Jancke L. Silent and continuous fMRI scanning differentially modulate activation in an auditory language comprehension task. *Hum Brain Mapp*. 2008; 29:46–56. [PubMed: 17318832]
- Schonwiesner M, Krumbholz K, Rubsamen R. Hemispheric asymmetry for auditory processing in the human auditory brain stem, thalamus, and cortex. *Cerebral Cortex*. 2007; 17(2):492–499. [PubMed: 16565292]

- Seifritz E, Di Salle F, Esposito F, Herdener M, Neuhoﬀ JG, Scheﬄer K. Enhancing BOLD response in the auditory system by neurophysiologically tuned fMRI sequence. *Neuroimage*. 2006; 29:1013–1022. [PubMed: 16253522]
- Shah NJ, Jäncke L, Grosse- ML. Influence of acoustic masking noise in fMRI of the auditory cortex during phonetic discrimination. *Journal of Magnetic Resonance Imaging*. 1999; 9(1):19–25. [PubMed: 10030646]
- Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain (Thieme Medical Publishers). 1988
- Talavage TM, Edmister WB, Ledden PJ. Quantitative assessment of auditory cortex responses induced by imager acoustic noise. *Human brain mapping*. 1999; 7(2):79–88. [PubMed: 9950065]
- Talavage TM, Edmister WB. Nonlinearity of FMRI responses in human auditory cortex. *Hum Brain Mapp*. 2004; 22:216–228. [PubMed: 15195288]
- Tamer GG, Luh WM, Talavage TM. Characterizing response to elemental unit of acoustic imaging noise: an FMRI study. *IEEE Trans Biomed Eng*. 2009; 56:1919–1928. [PubMed: 19304477]
- Tamer G, Guo Y, Bauman C, Hu S, Talavage T. A Correction Algorithm with Lasso Regression to Account for Imaging Acoustic Noise in Auditory fMRI. *OHBM*. 2010
- Tomasi D, Caparelli EC, Chang L, Ernst T. fMRI-acoustic noise alters brain activation during working memory tasks. *Neuroimage*. 2005; 27(2):377–386. [PubMed: 15893942]
- Ulmer JL, Biswal BB, Yetkin FZ, Mark LP. Cortical activation response to acoustic echo planar scanner noise. *Journal of computer assisted tomography*. 1998; 22(1):111–119. [PubMed: 9448773]
- Uludag K, Dubowitz DJ, Yoder EJ, Restom K, Liu TT, Buxton RB. Coupling of cerebral blood flow and oxygen consumption during physiological activation and deactivation measured with fMRI. *Neuroimage*. 2004; 23:148–155. [PubMed: 15325361]
- Vazquez AL, Noll DC. Nonlinear aspects of the BOLD response in functional MRI. *Neuroimage*. 1998; 7:108–118. [PubMed: 9558643]
- Worsley KJ, Friston KJ. Analysis of fMRI time-series revisited--again. *Neuroimage*. 1995; 2:173–181. [PubMed: 9343600]
- Zatorre RJ, Belin P. Spectral and temporal processing in human auditory cortex. *Cereb. Cortex*. 2001; 11:946–953. [PubMed: 11549617]
- Zhang N, Zhu XH, Chen W. Influence of gradient acoustic noise on fMRI response in the human visual cortex. *Magnetic resonance in medicine*. 2005; 54(2):258–263. [PubMed: 16032671]
- Zhao F, Jin T, Wang P, Kim SG. Improved spatial localization of post-stimulus BOLD undershoot relative to positive BOLD. *Neuroimage*. 2007; 34(3):1084–1092. [PubMed: 17161623]

Highlights

Effect of acoustic noise pattern during fMRI on auditory cortex activation studied
Right primary auditory cortex more sensitive to imaging acoustic noise than left
Different left/right auditory cortex baseline activations from imaging noise possible
Response shape and activation extent depends on imaging acoustic noise pattern
Longer acoustic imaging noise segments activate even some non auditory areas

Figure 1.

Summary of experimental stimuli. (A.) Acoustic spectrum of basic imaging-related acoustic noise stimulus (5ping). Dotted lines indicate peaks above 100 dB SPL at 738 Hz (102 dB SPL), 1.48 kHz (101 dB SPL), and 2.21 kHz (106 dB SPL). (B.) Temporal schematics of stimuli, illustrating timing of “pings” (46 ms duration) in the mock volume acquisitions. Stimuli with multiple groupings of pings produce an effective TR (TR_{eff}) based on the timing between group onsets—e.g., 2 s for the 5–5(2)ping case. (C.) Schematic of experimental paradigm. Tall dark rectangles indicate actual volume acquisitions, occurring at a repetition time of TR, and during which data were acquired. The imaging noise associated with actual acquisitions is expected to induce an HDR (dotted waveform). Shorter grey rectangles indicate the time during which the stimulus in part B would be presented as the primary acoustic stimulus, inducing an expected HDR (solid waveform). The light gray circles within dark gray rectangles show the signal level sampled by the volume acquisition. The gap between the end of the stimulus pings (part B) and the onset of the actual volume acquisition defines the post-stimulus offset time (t_{off}).

Figure 2.

Evaluation of hemisphere-specific responses to stimuli in Figure 1, part B. (A) Model-fitted hemodynamic responses (fHDRs; thick lines) in left and right hemispheres, depicted for each stimulus. Error bars indicate standard error across subjects at each observed data point, representing the average hemodynamic response (aHDR). Responses are aligned at stimulus offset (i.e., at $t_{off} = 0$ s). Open rectangles indicate presentation of imaging-related acoustic noise (ping) stimuli. Symbols and line types are specific to a given temporal pattern of “ping” presentations: (circles and solid lines) 5ping (triangles and dotted lines) 5-5(1s)ping, (squares and dash-dotted lines) 5-5(2s)ping, (stars and dashed lines) 5-5(4s)ping, (crosses and dotted lines) 15ping, and. (B) Pair-wise assessment of significant ($p < 0.05$; single-tailed t -test) differences in fHDR peak percent signal changes, within left (lower left of chart) and right (upper right) auditory cortex. Cells indicating statistically significant differences ($p < 0.05$; single-tailed t -test) are marked with an asterisk (*).

Figure 3.

Comparison of left and right primary auditory cortex (PAC) responses to acoustic stimuli associated with fMRI volume acquisition. Squares (Blue) and triangles (Red) indicate average hemodynamic response values at the indicated sampling times (aHDR) in left and right PAC, respectively. Continuous (Blue) line and dotted (Red) line represent the DGV fitted hemodynamic responses (fHDR) for left and right PAC, respectively. Error bars indicate standard error of the aHDR measures across subjects at each observed data point. Dark groupings of vertical lines represent the temporal extent of the acoustic stimulation. For each set of measurements, the coefficient of determination (R^2) between the aHDR and the fHDR is indicated, and the significance of a test to determine if the right aHDR is significantly greater than the left aHDR is also presented (p -value associated with a single sided t-test across subjects treating the non-zero time index as the repeated measure).

Figure 4.

Evaluation of linearity of superposition for modeled responses to imaging-related acoustic noise stimuli in left and right primary auditory cortex (PAC). The first column (D^n) presents linear superposition models (thin, green line) constructed using the DGV-modeled response to the 5ping stimulus for each of the n 5ping “presentations”. The second column ($S^{(n-1)}D$) presents linear superposition models (thin, red dotted line) constructed using SGV modeled response for the initial $n-1$ 5ping “presentations” and DGV modeled response for the final. In both cases, the thick red dotted lines indicate LTI-predicted responses obtained by time-shifting and adding modeled 5ping responses. Error bars indicate standard error of the average hemodynamic response (aHDR) across subjects at each observed data point. Thick blue lines indicate the fitted hemodynamic responses (fHDR) obtained by fitting DGV functions to the observed data points.

Figure 5.
Schematic comparing extent of activation ($t > 5.7$) for the acoustic stimuli depicted in Figure 1, part B.

Table 1

Functional MRI data acquisition parameters associated with each stimulus condition. See Figure 1, part C, for schematic of volume acquisition.

Stimulus Condition	Stimulus duration (s)	TR (s)	Quiet period (s)	Post-stimulus Offsets (t_{off} , s)
5ping	0.5	27.5	15.0	1.5, 3, 3.5, 4, 5, 6.5, 8.5, 12
15ping	1.5	33.5	17.0	1.5, 2, 2.5, 3, 3.5, 4, 5, 7, 9, 10, 11, 12.5, 14, 15
5-5(1s)ping	1.5	28.5	15.0	1.5, 3, 3.5, 4, 5, 6.5, 8.5, 12
5-5(2s)ping	2.5	29.5	15.0	1.5, 3, 3.5, 4, 5, 6.5, 8.5, 12
5-5(4s)ping	4.5	31.4	15.0	1.5, 3, 3.5, 4, 5, 6.5, 8.5, 12

Table 2

Estimated waveform parameters for the average (aHDR) and DGV fitted (fHDR) hemodynamic response associated with fMRI responses due to the different temporal patterns of acoustic noise associated with imaging.

Parameter	5Ping		55(1s)Ping		55(2s)Ping		55(4s)Ping		15Ping		
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	
aHDR	Peak PSC (%)	0.49	0.59	0.86	1.01	0.69	0.81	0.49	0.67	0.94	1.08
	Time to Peak (s)	3.50	3.50	5.00	4.50	5.50	5.50	3.50	7.50	5.00	4.50
	Undershoot (%)	-0.27	-0.26	-0.25	-0.18	-0.31	-0.19	-0.25	-0.21	-0.36	-0.35
fHDR	Peak PSC (%)	0.48	0.57	0.83	1.06	0.74	0.89	0.52	0.72	0.91	1.07
	Time to Peak (s)	3.60	3.70	4.80	4.20	4.80	4.70	6.80	6.80	4.40	4.70
	Undershoot (%)	-0.30	-0.28	-0.27	-0.24	-0.36	-0.22	-0.20	-0.15	-0.38	-0.36
	FWHM (s)	2.80	3.50	3.50	3.50	3.30	3.60	6.10	6.30	3.50	3.80
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R ² between fHDR and aHDR		0.99	1.00	1.00	1.00	0.99	0.99	0.98	0.98	0.98	0.99

Table 3

Comparison of LTI-predicted responses for concatenated DGV (D^n) and concatenated SGV/DGV ($S^{(n-l)D}$) models with a single DGV model fit to the measured portion of the fitted response (fHDR) in the primary auditory cortex to imaging related acoustic noise stimuli. Predicted response waveforms were evaluated for peak PSC and R^2 relative to the reference fHDR (see Table 2).

Model	Parameter	Auditory cortex	5ping	5-5(1s)ping	5-5(2s)ping	5-5(4s)ping	15ping
fHDR	Peak PSC (%)	Left	0.48	0.83	0.74	0.52	0.91
		Right	0.57	1.06	0.89	0.72	1.07
D^n	LTI-predicted peak PSC (%)	Left	0.48	0.89	0.73	0.48	1.37
		Right	0.57	1.08	0.94	0.57	1.65
	R^2 value between prediction and fHDR	Left	1.00	0.58	0.71	0.34	0.36
		Right	1.00	0.78	0.72	0.71	0.57
$S^{(n-l)D}$	LTI-predicted peak PSC (%)	Left	0.48	0.91	0.67	0.50	1.40
		Right	0.57	1.05	0.85	0.62	1.67
	R^2 value between prediction and fHDR	Left	1.00	0.87	0.93	0.69	0.86
		Right	1.00	0.94	0.84	0.84	0.74

Table 4

Extent of activation in left and right hemisphere and auditory cortex regions of interest (ROIs) in response to acoustic stimuli associated with volume acquisition. For each stimulus those regions exhibiting activation ($p < 0.01$, corrected t) are indicated along with the number of voxels exceeding this threshold in the left/right hemisphere and auditory cortex ROIs, and the peak observed t -statistical value. Anatomical areas are abbreviated using the automated anatomical labeling (AAL).

Stimulus Condition	Left Hemisphere			Right Hemisphere		
	Auditory Cortex ROI (183 max)	Hemisphere ROI (1293 max)	Activated Areas (AAL system)	$t_{\max}$	Auditory Cortex ROI (179 max)	Hemisphere ROI (1445 max)
5ping	15.7	87	HES,STG,ROL,MTG,INS	14.3	101	213
5-5(1s)ping	21.1	102	HES,STG,ROL,INS,THA,CAL,LING	16.7	114	255
5-5(2s)ping	13.6	102	HES,STG,ROL,MTG,INS	13.2	99	210
5-5(4s)ping	8.7	51	HES,STG,THA	7.9	42	74
15ping	32.7	110	HES,STG,ROL,MTG(BA19),INS,THA,CAL,LING,PUT,IFG,HIP,PCUN	32.7	123	558

The following anatomical areas, identified using the automated anatomical labeling (AAL) system are abbreviated in the table: Heschl's gyrus (HES), superior temporal gyrus (STG), Rolandic operculum (ROL), middle temporal gyrus (MTG), Insula (INS), Thalamus (THA), Calcarine gyrus (CAL), Lingual gyrus (LING), inferior frontal gyrus (IFG), Hippocampus (HIP), Putamen (PUT), Precuneus (PCUN), temporal pole (TPO).