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Assessment of Temporal State-Dependent Interactions between Auditory fMRI Responses to Desired and Undesired Acoustic Sources

O. Olulade^{a,b}, S. Hu^c, J. Gonzalez-Castillo^d, G.G Tamer Jr^d, W-M Luh^e, J.L. Ulmer^f, and T.M. Talavage^{a,d}

O. Olulade: oao24@georgetown.edu; S. Hu: shuowen.hu@us.army.mil; J. Gonzalez-Castillo: javier.gonzalez-castillo@nih.gov; G.G Tamer: gtamer@purdue.edu; W-M Luh: luh@mail.nih.gov; J.L. Ulmer: julmer@mcw.edu; T.M. Talavage: tmt@ecn.purdue.edu

^aSchool of Electrical and Computer Engineering, Purdue University, West Lafayette, Indiana, USA

^bCenter for the Study of Learning, Georgetown University Medical Center, Washington, D.C., USA

^cU.S. Army Research Laboratory, Adelphi, MD, USA

^dWeldon School of Biomedical Engineering, Purdue University, West Lafayette, Indiana, USA

^eNational Institutes of Health, Bethesda, Maryland, USA

^fDepartment of Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

Abstract

A confounding factor in auditory functional magnetic resonance imaging (fMRI) experiments is the presence of the acoustic noise inherently associated with the echo planar imaging acquisition technique. Previous studies have demonstrated that this noise can induce unwanted neuronal responses that can mask stimulus-induced responses. Similarly, activation accumulated over multiple stimuli has been demonstrated to elevate the baseline, thus reducing the dynamic range available for subsequent responses. To best evaluate responses to auditory stimuli, it is necessary to account for the presence of all recent acoustic stimulation, beginning with an understanding of the attenuating effects brought about by interaction between and among induced unwanted neuronal responses, and responses to desired auditory stimuli. This study focuses on the characterization of the duration of this temporal memory and qualitative assessment of the associated response attenuation. Two experimental parameters — inter-stimulus interval (ISI) and repetition time (TR) — were varied during an fMRI experiment in which participants were asked to passively attend to an auditory stimulus. Results present evidence of a state-dependent interaction between induced responses. As expected, attenuating effects of these interactions become less significant as TR and ISI increase and in contrast to previous work, persist up to 18s after a stimulus presentation.

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Corresponding Author: Olumide A. Olulade, oao24@georgetown.edu, EE Building, 465 Northwestern Avenue, West Lafayette, IN 47907-2035, Tel.: (813) 486-4474, Fax: (765) 494-3358.

¹Permanent Address: 4226 Trumpworth Court, Valrico, FL 33596

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Keywords

fMRI; human auditory processing; neuroimaging; BOLD response; response suppression; EPI

Introduction

The acoustic noise associated with the acquisition of functional magnetic resonance imaging (fMRI) data has long been of concern to the experimental community, particularly when perception of auditory stimuli is of interest. Imaging-related acoustic noise is demonstrated to produce fMRI-observable responses in auditory cortex, potentially competing with responses to desired stimuli (Bandettini et al., 1998; Talavage et al., 1999; Elliot et al., 1999; Novitski et al., 2001; Moelker et al., 2003; Talavage and Edmister, 2004; Scarff et al., 2004). Obviation of imaging-related acoustic noise responses has been sought both through efforts to minimize their interaction with responses induced by the intended stimulus (e.g., Edmister et al., 1999; Hall et al., 1999; Eden et al., 1999; Belin et al., 1999; Schmithorst et al.), and through hardware modifications to mitigate the acoustic intensity of the imaging-related noise at the ear (e.g., Chambers et al., 2001; Ravicz et al., 2000; Edelstein et al., 2002; Edelstein et al., 2005; Hall et al., 2009). In spite of these many efforts, this acoustic noise source remains a critical consideration during the design, execution and analysis of auditory-related fMRI experiments.

Given the limited potential to prevent interaction between imaging-related acoustic noise-induced responses and responses to desired stimuli, characterization of this interaction, which is dependent on the state of the hemodynamic system (from which all fMRI responses are derived), would seem one of the best options for enhancing auditory-related fMRI. This state-dependence refers to the expectation that the observed hemodynamic response (HDR) to a presented stimulus will vary as a function of the regional cerebral blood flow, blood volume and oxygenation levels at the time of onset of the response. This is particularly expected to hold true given known limits on the dynamic range of the hemodynamic system, or in cases where the hemodynamic system exhibits hysteresis (e.g., as per the Balloon model (Buxton et al., 1998)). Specific to this study, it would be ideal to understand how the fMRI-observable response to the desired stimulus may be altered by this state-dependence, as well as probable non-linear time-invariant (non-LTI) behavior (e.g. Hu et al., 2010) of the hemodynamic system in the auditory cortex. For example, at the time of a desired stimulus presentation, saturation of the hemodynamic system due to presence of an already ongoing HDR could produce distortion and/or attenuation of the desired response relative to that observed in the absence of the competing response. Such seemingly non-LTI superposition of responses (e.g., Talavage and Edmister, 2004) is likely the result of a state-dependent effect. Note that we state ‘seemingly’ given that while the observed response may not represent ideal superposition of the individual responses as observed in isolation, the distorted response will, in fact, be reproducible.

For the purpose of generalization, it is advantageous to extend the characterization of this state-dependent behavior of auditory cortex response to interactions between responses to multiple desired acoustic stimulus presentation events. Given that temporal overlap of responses to desired and undesired acoustic events can produce distortion of a desired response, it is logical to conclude that the overlap of responses to multiple desired stimulus presentations may also produce such distortions. Present auditory-related fMRI experimentation frequently involves presentation of multiple categories of acoustic stimuli, potentially creating such a situation — e.g., see Garcia et al. (2010) where separate paradigms involved presentation of pitch stimuli interspersed with either noise stimuli or

with gaps of silence, with results suggesting non-linear addition of responses to multiple stimuli.

Results by Langers et al. (2005) indicate that the degree of non-linear superposition is state dependent, and that the greatest reduction in dynamic range may be observed for presentation of a stimulus when the accumulated response to previous stimulations (desired and undesired) is maximal. The authors investigated how the first-order stimulus-to-scan interval (Δt : interval between a presented tone stimulus and the subsequent volume acquisition) and the repetition time (TR; time between successive volume acquisitions, controlling the number of slice/volume acquisitions within any given time interval) affect the amplitude of the response to a given stimulus presentation. Their study utilized a variable TR clustered volume acquisition (CVA; Edmister et al. (1999)) paradigm to examine a range of both TR (2 – 10s) and Δt (2 – 8s). They observed that the response to the stimulus presentation of interest was most attenuated for small values of TR and Δt (2 – 4s), and when stimulus presentation coincided with (the acoustic noise of) image acquisition. They also found that these maximally negative interaction effects were observed (for stimuli with frequency components similar to that of the imaging-related acoustic noise) when the TR corresponded to a Δt value for which the response to the stimulus was at a maximum (TR = 4s, Δt = 8s).

To better predict the state-dependence of HDRs, it is necessary to measure effects over the entire window of the response. Non-LTI response superposition might be expected whenever HDRs to two or more stimuli overlap, especially when the interval between successive stimuli (i.e. the inter-stimulus interval – ISI) is shorter than the duration of the HDR to the first stimulus. The results of Langers et al. (2005) provide valuable information for auditory-related fMRI experiments, but primarily address only the level of effect likely to arise from overlap of the early portion of responses, concluding that stimuli presented more than 10s prior to a given stimulus will not adversely affect the resulting response. However, given that the HDR is well-documented to exhibit an undershoot after a return to baseline (approximately 8–10s post-stimulus offset) until 20–30s after the stimulus offset (Kwong et al., 1992; Buxton et al., 1998; Mandeville et al., 1999), it is reasonable to expect that the state-dependence will extend beyond 10s, and that acoustic events presented during this interval could affect responses to the stimulus through deviation of the auditory cortex vasculature from the “rest” state. In particular, it is critical to assess whether the HDR to a stimulus, presented during a period of undershoot, is equivalent to that presented when the system is more truly “at rest,” when the system is experiencing neither a positive response nor its subsequent undershoot.

An additional (albeit lesser) issue regarding application of the findings of Langers et al. (2005) is that the T_1 intensity correction applied to compensate for the variable TR experiment may lead to time-dependent errors, possibly altering the ability to predict the signal reduction associated with the preceding events. T_1 compensation for variable TR, as applied to cardiac gating, has been found to increase the noise level in fMRI data (Birn et al., 2001a). Hu et al. (2009) also observed non- T_1 -related signal fluctuations in images of a phantom when using a variable TR paradigm, and attributed these fluctuations to the varying eddy current and gradient coil heating characteristics associated with a (temporally) non-uniform acquisition scheme. Thus, a variable TR acquisition scheme may yield sub-optimal evaluations of the interaction of responses in auditory fMRI.

This study sought to more completely assess the temporal window critical to the quantification and potential prediction of responses to a desired acoustic stimulus presentation event given state-dependencies associated with the presence of previously presented desired and/or undesired stimuli. This assessment was effected through

investigation of interaction of a desired stimulus presentation with both temporally distant presentations of the same stimulus, and the acoustic noise associated with CVAs. First-order ISI values up to 24s were investigated, allowing assessment of the effect on the HDR to a given stimulus presentation event arising from the post-stimulus undershoot associated with HDR to a temporally-distant stimulus presentation. Additionally, this study avoided issues associated with use of a T_1 recovery model by maintaining a constant TR during each run. It was expected that the degree of apparent non-LTI behavior arising from state-dependent effects would increase for shorter TR and ISI values, and that this would manifest as a decrease in the percent signal change and the spatial extent of the detected response with each of TR and ISI.

2. Materials and Methods

2.1 Subjects

10 subjects (6 male, 4 female, ages 21 – 35) participated in the study. All subjects reported no history of hearing disorder, and gave written informed consent prior to participation.

2.2 Acoustic Stimulus Presentation

The stimulus was a single 0.75s segment of jazz music, having limited spectral roll-off over the range 500-8000Hz – though it is likely that the upper half of this range was appreciably attenuated by roll-off associated with the plastic tubing used for pneumatic stimulus delivery, occurring around 3000Hz (Airas et al., 1999). The stimulus was delivered binaurally into the ear canals at a volume set to a comfortable level by each subject prior to the start of the experiment (range: 65-85 dB SPL over all the sessions). Subjects were instructed to passively attend to the music stimulus. Alertness was assessed after each run, via verbal interaction with the subject.

2.3 Imaging Protocol

Imaging was performed on a 1.5T GE Signa CVi imager, located at Froedtert Memorial Lutheran Hospital, a part of the Medical College of Wisconsin (Milwaukee, WI). Functional images were acquired using a blipped EPI pulse sequence (TA = 500ms, TE = 40ms, flip angle = 70° for TR = 1.5s, and 90° for TR = 3s and 6s), with custom bilateral auditory surface coils as described in Talavage et al. (2000). The sound intensity of the EPI acquisition was previously measured as 105 dB SPL, with the employed attenuation techniques providing approximately 40dB noise reduction at the subjects' ears (Ravicz et al., 2001; Tseng et al., 2004). For each subject, five axial slices, (field of view = 20cm, acquisition matrix = 64 × 64, slice thickness = 5mm) were approximately centered on the transverse temporal (Heschl's) gyrus to acquire functional data from both left and right primary auditory cortex. In a separate acquisition within each session, a birdcage head coil was used to obtain a 3D volumetric image of the brain (124 slices, field of view = 24cm) to facilitate subject registration and selection of regions of interest (ROIs).

2.4 Experimental Paradigm

Each session lasted approximately 90 minutes and included 14 functional runs, each comprising 36 periods of constant length. To minimize the duration of the scanning session (and avoid subject fatigue), the stimulus presentation paradigm was designed such that two ISIs were used in each run. Therefore, the stimulus was not presented in all of the 36 trial periods, rather being skipped during certain periods to double the actual ISI for the next trial (Fig. 1). Approximately 36% of trial periods did not involve stimulus presentation. Using period lengths of 6, 9 and 12s, actual ISIs of 6, 9, 12, 18 and 24s were obtained. While the TR was held constant within each run, different values of TR were utilized over the course

of the session. Overall, the TR/ISI combination pairs obtained in each session were TR = 1.5 and 3s for all ISI values, and TR = 6s for ISI = 12 and 24s. Two runs were conducted for each TR/period-length combination: 1.5/6, 3/6, 1.5/9, 3/9, 1.5/12, 3/12 and 6/12). Presentation of these combinations was performed in a pseudo-random order, and counter-balanced across subjects.

All stimulus presentations commenced 0.5s after the beginning of an ISI period, coinciding with 0.5s after onset of the immediately preceding volume acquisition. Due to the lack of preceding acoustic stimulation (by stimulus or the imaging-related acoustic noise), the first ISI period in each run was not included in the analysis. Over all subjects, a total of 230 trials were conducted for TR/ISI = 1.5/6, 1.5/9, 3/6 and 3/9; 370 trials for 1.5/12 and 3/12; and 140 trials for TR/ISI = 1.5/18, 1.5/24, 3/18, 3/24, 6/24 and 6/12.

2.5 Analysis

Preliminary data analysis was performed on an individual subject basis using AFNI (Cox et al., 1996). For each session, functional datasets were motion corrected and aligned to the subjects' anatomical images for identification of anatomical structures of interest.

Regions of Interest (ROIs)—Two ROIs, one focused on primary auditory cortex and one more generally encompassing auditory-related cortex in the superior temporal plane, are defined within this study for specific analyses, as described below.

Primary Auditory Cortex (pAC): Voxels within this individually-based ROI were selected from each subject's anatomical dataset after motion-correction and alignment, but prior to normalization. Specifically, the postero-medial two-thirds of the most anterior Heschl's gyrus (Hackett et al., 2001, Wallace et al., 2002) was chosen as the pAC ROI. This region is most consistent with the primary auditory area of Galaburda and Sanides (1980), and overlaps with primary auditory regions defined in Rademacher et al. (2003). The medial end of the first transverse sulcus was defined as the medial boundary of Heschl's gyrus, while the anterior temporal gyrus was selected as the lateral boundary based on Penhume et al., (1996). In all axial slices containing Heschl's gyrus, voxels within the medial two-thirds portion of the defined area, in each of the left and right hemispheres, were selected from each subject. The average size of pAC for subjects in this study was (left) 1240 mm³ and (right) 850 mm³.

Auditory Cortex (AC): Areas selected within this group-level ROI included the whole of Heschl's gyrus (thus encompassing the pAC ROI), as well as the superior temporal gyrus, defined as the region between the sylvian fissure and the superior temporal sulcus (Taylor et al., 2004). This region encompasses areas which most reliably exhibit auditory activity (Arnott et al., 2004, Talavage et al., 2004). The volume of the ROI was (left) 9779 mm³ and (right) 9565 mm³. The AC region was defined using the standardized TT_N27 (AFNI – Talairach) template.

Percent Signal Change—HDR estimates were generated within the individual-based pAC ROI by means of percent signal change calculation. The pAC voxel time-series were extracted from the full brain data, individually corrected for signal drift, and normalized to a mean of 10,000 (providing signal change sensitivity of 0.01%) prior to averaging across runs.

For each stimulus presentation trial within each run, HDR estimates were generated for each voxel in the left and right pAC ROI by calculating the percent signal change at each post-onset measurement time, relative to the mean value of the signal averaged over all time-

points immediately preceding stimulus presentation. This reference time-point was interpreted as the post-stimulus onset response time of $t = -0.5s$. HDR estimates were obtained for each subject by averaging trials over all voxels in the pAC ROIs. Group-average HDR estimates were obtained by averaging all single-subject estimates. Responses were evaluated as a function of TR and ISI.

Model Fitting—Quantitative evaluation of the amplitude of response for each TR/ISI condition was performed using model fitting to a reference waveform. Left and right hemisphere reference waveforms were generated by non-linear regression of the double gamma variate HDR model (Glover, 1999) to the ten subject-based HDR estimates (from the corresponding hemisphere) for the TR/ISI = 1.5s/24s response. This particular TR/ISI pair was chosen since it represented the largest number of post-onset sample points, and is expected to generate the most accurate fit.

Changes in amplitude (particularly peak amplitude) of the response for varying conditions of TR and ISI were assessed by amplitude scaling the obtained HDR estimates based on the equation: $[s = A f]$. In the equation, the parameter f represents the double gamma variate fitted response for TR/ISI = 1.5s/24s in either the left or right ROI, while s represents the amplitude scaled response for a particular TR/ISI condition in the corresponding ROI. The parameter (**A**) – the amplitude scaling factor – was obtained by means of a linear regression comparing the HDR estimates for a given TR/ISI pair to the fitted response f . Since the peak amplitude of the response, rather than the undershoot, is the characteristic of interest, only those available sample points occurring prior to 8.5s post-onset (i.e., the peak) and the last measured time-point (i.e., theoretically representing the return to baseline) for each TR/ISI condition were used in the regression analysis to obtain **A**.

Validation of the amplitude fitting procedure was effected by calculating the residuals for each TR/ISI condition, for each time-point used in the fitting process. These residuals were found to be randomly distributed around zero. In addition, standardized residuals were obtained to probe for outliers in the datasets (Ryan, 1998). As none of the resulting values exceeded 2.5, it was determined that there were no outliers present in the fitting dataset.

To facilitate statistical analysis, amplitude scaling factors (**A**) were separately generated for each subject and hemisphere, by applying the above fitting procedure to the corresponding HDR estimate for each TR/ISI condition. Resulting values were entered into a linear mixed effects model using the R statistical software package (<http://www.r-project.org>), to probe for main effects and interactions between the two parameters (TR and ISI), on a hemisphere basis. Post-hoc analysis involved the use of pair-wise t -tests to compare TR conditions (collapsed across all ISI values – e.g. TR = 1.5s vs. TR = 3s) and ISI conditions (collapsed across TR values). This method was used because generating pair-wise t -tests to compare individual TR/ISI conditions separately would significantly increase the potential for type I error (12 TR/ISI conditions * 2 ROIs = 132 tests). While collapsing across TR and ISI values does not represent an optimal solution – any interactions between the two parameters will be ignored – it represented the most feasible method for obtaining an overview of the effect of varying each parameter, while reducing the potential for type I error. The resulting values were also false discovery rate (FDR) corrected for multiple comparisons.

Assessment of Linear Time-Invariance—In fMRI experiments involving multiple presentations of a stimulus, traditional GLM analyses using canonical HDR models assume linear time-invariant (LTI) superposition of (temporally) overlapping responses. Convolution of the stimulus presentation paradigm with a canonical HDR is used to estimate the time-series obtained from a series of impulse responses (HDRs) elicited by multiple presentations of a brief stimulus. However, many studies have demonstrated the non-LTI

behavior of the BOLD response, and conveyed implications for addition of superimposed responses (Vasquez et al., 1997; Mechelli et al., 2001; Soltis et al., 2004; Hu et al., 2009b). Based on known non-LTI behavior, it is reasonable to expect that, for conditions under which overlapping responses are highly probable (i.e., shorter values of TR and/or ISI), the potential ‘non-linearity’ in the system will lead to the greatest difference between the observed response waveform and that predicted by the LTI assumption. This non-LTI behavior is expected to be a result of the state-dependent nature of the hemodynamic system, with the degree of ‘non-linearity’ being greater for conditions in which the response to a presented stimulus occurs when the system is not fully “at rest.” To test this non-LTI assumption under different conditions of TR/ISI, a ‘pristine’ LTI response was generated for each ISI for comparison to the measurements. Percent signal change was used to obtain an estimated HDR using only trials in the TR/ISI = 1.5s/24s condition for which no stimulus had been delivered in the previous 36s window. This was subsequently convolved with the stimulus presentation paradigm to obtain the pristine LTI response.

Quantitative assessment of the observed ‘non-linearity’ was made by calculating the coefficient of determination (R^2) for all TR/ISI conditions. While the coefficient of determination lacks an associated p -value, it provides a good metric for determining how well an observed result matches the predicted value. Here it assesses how well the amplitude-fitted estimates (observed result) resemble the responses predicted by the LTI assumption, lending insight into the extent to which overlapping responses exhibit superposition. In conditions where R^2 approaches the ‘best-fit’ value of 1, it is less probable that adverse (state-dependent) effects of overlapping responses will be manifested.

Analysis of Response Spatial Extent—Following motion correction and registration to the anatomical image, functional datasets from each subject were converted to standardized Talairach stereotaxic co-ordinates, enabling group analysis. Normalized datasets were spatially smoothed with a 6mm FWHM Gaussian kernel and merged into a single trial time-series for each TR/ISI condition pair by averaging over all appropriate trials in each run. For each subject, multiple linear regression was used to compare the resulting datasets with a reference waveform.

Detection of auditory cortex activation was enhanced through use of a k-cross method (e.g., Kearns et al., 1996) to estimate responses for each subject. In traditional fMRI analysis, a canonical reference waveform (such as the default gamma variate function provided in AFNI) is used in regression analysis to detect fMRI activation. However, the characteristics of the HDR vary across brain regions (Lange and Zeger, 1997; Birn et al., 2001b; Handwerker et al., 2004), and as the canonical waveform further deviates from the true response, detection sensitivity decreases dramatically (Lindquist et al., 2009). Use of customized HDR waveforms, tailored to specific regions, has been suggested to improve detection of the underlying neuronal activation. Here, reference waveforms were estimated for each subject using only data acquired for the other nine subjects (to avoid over-fitting). Averaged HDR estimates (TR/ISI = 1.5s/24s) for the other nine subjects were fitted to the double gamma variate model, and then input to the linear regression analysis to obtain each subject's activation map. Activation maps were subjected to a single factor (subjects) analysis of variance (ANOVA) to generate random effect t -statistic maps, which were FDR-corrected for multiple comparisons.

Because the 12 TR/ISI pairs represent variable sampling rates (and consequently variable numbers of samples per event), fair comparison of the statistical power per unit sample required scaling of t -statistic display thresholds. Threshold scaling was based on the number of post-onset time-points per ISI in a given pair (as above, limited to 8.5s post-onset). The scaling factor for a particular TR/ISI pair was the square root of the ratio of the number of

time-points for the given pair to the minimum number of post-onset time-points acquired (two; for TR/ISI = 6s/12s and 3s/6s). The threshold for a given TR/ISI condition was computed as the product of this scaling factor with the t -statistic threshold corresponding to an FDR corrected $p < 0.05$ for the TR/ISI = 6s/12s map. Note that this scaling factor may bias the activation maps in favor of conditions with long ISI and short TR (e.g., TR/ISI = 1.5s/24s) due to serial correlation between samples, so this procedure represents the idealized scenario, in the absence of a practical method to estimate the actual serial correlation.

The spatial extent of activation in auditory cortex was quantified for each TR/ISI condition by determining the percentage of active (above threshold) voxels in the stereotactically-defined AC ROI for each hemisphere (see *Regions of Interest* above).

All experiments conducted on human subjects were approved by the Institutional Review Boards of Purdue University and the Medical College of Wisconsin.

3. Results

3.1 Hemodynamic Response Estimates

Group-averaged HDR estimates are shown in Figs. 2 (left pAC) and 3 (right pAC). In each figure, ISI increases from left to right, while TR increases from top to bottom. Each sub-plot within the figure – corresponding to a different TR/ISI condition – contains the HDR estimate (bars: standard error, $N = 10$), the amplitude-fitted response, the value of the mean amplitude scaling factor (**A**), and the predicted response under the assumption of linearity (with corresponding R^2 value). Note that for TR/ISI = 3s/6s, the shape of the curves were too different for the coefficient of determination to provide a meaningful comparison.

Results from the mixed effects model varied slightly in the left and right hemisphere ROIs. In the left hemisphere, the main effect of TR and ISI achieved trend-level significance ($p = 0.052$ and 0.061 respectively). However, no significant main effect of either TR ($p = 0.290$) or ISI ($p = 0.152$) was observed in the right hemisphere. Neither left nor right hemisphere interactions achieved significance ($p = 0.280$ and 0.453 respectively). Results of the pair-wise t -tests (depicted in Table 1 (ISI) and Table 2 (TR)) provide more information about the direction of observed effects. The amplitude of response was significantly lower for ISI = 6s relative to all the other ISI values (Table 1), in both hemispheres. Pair-wise comparison of other ISI conditions did not achieve significance. In the left hemisphere only, the TR = 6s condition yielded significantly greater amplitude than all other TR values. No significant gain in amplitude for TR = 3s over TR = 1.5s was observed in either hemisphere.

While statistical results highlighted effects of TR and ISI on amplitude changes at the extreme ends of the spectrum (i.e. short ISI, long TR), the observed trend was for an increase in response amplitude with increasing ISI and TR. Of note, however, while in both hemispheres the conditions with the lowest amplitude occur at the short ISI (6s), the amplitude was unexpectedly greater for TR = 1.5s than for TR = 3s (see *Section 4.1*), and was unexpectedly large for TR/ISI = 1.5s/9s (see *Section 4.4*).

Assessment of Linear Time-Invariance—For both left and right pAC ROIs at TR = 1.5s, ISI values of 9s or higher led to minimal HDR distortion from LTI superposition of responses, as indicated by the high R^2 values — mean R^2 value for ISI ≥ 9 s is (left cortex) 0.76 ± 0.03 and (right cortex) 0.85 ± 0.05 . In both hemispheres, ISI = 6s proved to be associated with poor representation of the predicted linear response, suggesting that LTI superposition was not well-exhibited in this condition. A similar trend was observed at TR = 3s. For this condition, both ISI = 6 (severely distorted response) and ISI = 9s exhibited

strong deviation from the LTI predicted response in both hemispheres. However, large R^2 values for ISI = 12s and 18s in both hemispheres, and for ISI = 24s in the right hemisphere, suggest minimal HDR distortion for these conditions. Low peak amplitude of response for ISI = 24s in the left hemisphere resulted in a low R^2 value, but see *Section 4.1* for a possible explanation of this unexpected behavior. Finally, when TR increased to 6s, both hemispheres exhibited appreciably large R^2 values for ISI = 12s and 24s, suggesting a benefit for this longer TR condition.

3.2 Spatial Extent of Activation

Fig. 4 presents random effects t -statistic maps of activation for all TR/ISI conditions. As in Fig.2 and Fig.3, ISI increases from left to right, while TR increases from top to bottom. Each map also shows the percentage of voxels exceeding threshold within the AC ROIs. Using radiologic coordinates, the numbers represent the percentage of active voxels in the right and left ROIs.

With increasing ISI, the observed changes in extent of activation (as a function of TR) are largely consistent across TR = 1.5s and 3s, while almost no change in extent is observed with increasing ISI for TR = 6s. Maps for TR = 1.5s exhibit a steady increase in extent of activation as ISI increases from 6s to 12s, decreases slightly at 18s, and holds approximately constant at this level for ISI = 24s. The trend at TR = 3s is comparable to that at TR = 1.5s with two exceptions. First, no meaningful activation is detected at ISI = 6s, and the activation detection at 24s is appreciably less than that observed at 18s. Critically, the observed decrease in response for ISI = 18 and 24s for both TR values suggests some non-linear perturbation of the system still exists for these long ISI conditions (see *section 4.1*). Finally, for TR = 6s the extent of activation is similar across the two assessed ISI values (12s and 24s).

For all ISI conditions, the extent of activation was mostly consistent across TR values of 1.5s to 3s, with the most notable exception again being at ISI = 24s where the activation is lower for TR = 3s than for TR = 1.5s. This trend is also observed for TR = 6s with almost no change in the extent of activation between all TR values for ISI = 12s, and the observed increase for ISI = 24s most probably being due to the reduced activation at TR = 3s.

4. Discussion

This study investigated state-dependence of auditory cortex HDRs as a function of both imaging-related acoustic noise and prior presentations of a desired acoustic stimulus. Changes in both amplitude and shape were examined as a function of the recent history of overall acoustic stimulation. Results indicate that when ISIs of 18s or less are used, sound-induced responses can become attenuated, with the potential for saturation of the BOLD response. Use of higher sampling rates (i.e., short TR values) can also produce attenuation, potentially becoming the dominant factor over a wide range of ISI values. These findings emphasize the importance of considering all events producing acoustic stimulation within a window extending up to 18s prior to the presentation of a given desired stimulus.

4.1 Evaluation of Fitting Procedure

The amplitude-scaled fitting procedure implemented in this study is based on the prior expectation of compression/attenuation of response resulting from multiple desired and undesired stimuli within a given time window. The trial-based averaging procedure used to obtain post-presentation measurements reveals that the observed response can deviate appreciably from the LTI assumption, resulting in poor fitting when using a classic canonical reference waveform. Such cases include all data acquired at ISI = 6s, and those

obtained with a high sampling rate (e.g., TR = 3s; Figs.2 and Fig.3). The resulting poor fits can adversely affect detection of activation (e.g., Fig.4, TR/ISI = 3s/6s) using the chosen long-ISI reference waveform (constructed from TR/ISI = 1.5s/24s). Therefore, we must consider the effects of this fitting procedure on the interpretation of changes in amplitude and extent of activation.

The sub-optimal fitting likely arises from two physiological factors. First, visual inspection of the trial-based average for the ISI = 6s condition reveals that the HDR did not exhibit a positive lobe consistent with a gamma variate shape. Rather, these data suggest a substantial negative initial response followed by a rise approaching the estimated baseline. The implemented procedure cannot effectively model this response given the non-negative early component of the reference waveform. Second, the positive lobe post-onset sampling times associated with TR = 3s (2.5s and 5.5s) appear to frame the peak of the auditory cortex HDR, estimated to be near 4s post-onset (within the expected range from previous literature: Hall et al., 2000; Le et al., 2001). Therefore, for TR = 3s (and possibly also 6s) the obtained sample points have missed the peak, and the fitting procedure will readily mis-estimate the true response. This hypothesis was evaluated for TR = 3s by constructing waveform fits (and corresponding **A**) for downsampled versions of the TR = 1.5s data that matched the measurement times at TR = 3s. These fits consistently resulted in decreased amplitude estimates for the short ISI condition (6s). As is noted below, more information regarding the direction of this error can be obtained for longer ISI conditions, for which more measurements have been obtained. The effects of sub-optimal fitting were further quantified for TR/ISI = 3s/6s by generation (per Section 2.5) of trial-based estimated responses and use of these waveforms (by means of a k-cross scheme; Fig. 5, parts A and B) as the reference in detection of spatial extent of activation. When contrasted with sampled versions of the individual-subject fitted responses for TR/ISI = 1.5s/24s previously used to obtain the activation maps of Fig. 4, this alternate fitting procedure reveals greatly altered HDRs from the linear expectation. Use of these new data-driven waveforms in a random effects analysis produces statistically significant responses for TR/ISI = 3s/6s (Fig.5C), but still at a lesser extent than higher ISIs with TR = 3s (see Fig.4). These results suggest that obtained values for R^2 and **A** in Fig.2 and Fig.3 overstate the response attenuation as the ISI decreases to 6s, but still suggest that greater acoustic stimulation has appreciably reduced the amplitude and detection of stimulus-driven responses.

For other TR/ISI conditions assessed in this study, the two factors noted above are expected to have a greater impact on amplitude estimation than activation detection. As the samples per trial increases with ISI, detection of responses should become less problematic. Additionally, once temporal density of presentation of acoustic stimulation decreases (through increased TR, ISI or both), the HDR is not expected to be appreciably distorted, as it is unlikely that the BOLD effect will saturate (e.g., Davis et al., 1998). Rather, the fact that the peak has been missed for TR = 3s and 6s is the more likely confound to persist as ISI increases.

The characteristics of the response undershoot influence the accuracy of fitted responses. Given a lack of a prior hypothesis about how the undershoot varies with TR/ISI, we did not account for this variability in the modeling procedure and subsequent analysis, and this has likely contributed to less accurate fitting. As noted above a typical HDR returns to baseline 8-10s post-stimulus offset, and is followed by an undershoot persisting to 30s post-offset. While the overall response for shorter ISIs (6s, 9s and 12s) consists mostly of the positive signal, the undershoot comprises an increasing portion of the measurements obtained for longer ISI conditions (18s and 24s). As can be observed in the HDR estimates (Fig.2 and Fig.3), the shape and duration of the positive portion of the signal remains fairly consistent for all TR/ISI values. Conversely, the shape and apparent duration of the response

undershoot exhibits appreciable variability across TR values for both ISI = 18s and 24s. Therefore, while the waveform used to probe for activation is effective at modeling the positive portion of the response, variability in undershoot, coupled with the increasing percentage of the dataset it represents, could reduce overall activation detected for ISI = 18s and 24s. Given that it has been demonstrated (Zhao et al., 2007) that the magnitude of the undershoot and the positive BOLD response are correlated, underestimation of Δ may reasonably be assumed for measurements in which a longer or greater magnitude undershoot is observed (e.g. for TR/ISI = 3s/24s in the left pAC).

4.2 Hemodynamic Response Estimates

The dynamics of interaction between sampling rate (TR) and ISI provide implications for estimation of HDRs in auditory fMRI studies. Post-hoc *t*-tests revealed significant attenuation of response for short ISI (6s), and significant gain in amplitude for longer TR (6s). These results fit prior expectations. However for ISI = 9s, an unexpected response amplification, rather than moderate attenuation, was observed for TR = 1.5s, with a decrease observed at TR = 3s contrary to prior observations of the effects of imaging-related acoustic noise (e.g., Edmister et al., 1999; Langers et al., 2005). Deviations from expectations may arise from multiple sources. First, the unexpected gain may arise from interaction of the stimulus-induced HDR having an onset during the undershoot from the previous stimulus-induced HDR (see Section 4.4). Second, the decrease in amplitude scaling factor at TR = 3s (also observed for ISI = 6s) is conjectured to be a consequence of samples that miss the peak of the response. Some of these deviations may also be due to the small sample size and relatively poor signal-to-noise ratio afforded by 1.5T fMRI.

Assessment of Linear Time-Invariance—Results from the linearity assessment correlate strongly with TR/ISI interaction effects, suggesting state-dependence is greatest for high sampling rates (TR = 1.5s and 3s) and low ISI values (ISI = 6s). Hence, auditory fMRI studies should use TR values of at least 6s combined with ISIs of 18s to 24s when HDR estimation is of paramount interest. The benefits of reduced temporal density of acoustic stimulation appear to occur up to an ISI of at least 18s. The observed increase in R^2 for the longest ISI values suggest that some level of state-dependent, non-LTI response overlap still occurs at ISI = 12s, and likely 18s. This conjecture of state-dependent interaction even at long ISI is supported by observation that fitted responses for TR = 6s exhibit larger amplitudes than the LTI predictions.

Shape of Response—Differences in response shape were observed between amplitude-fitted HDR estimates and LTI-predicted responses. The amplitude-fitted response peak lags the LTI-predicted response peak (Fig.2-Fig.3). This lag is likely due to non-linear properties of the HDR, including effects of elevated baseline and limitations on regional cerebral blood flow, blood volume and rates of oxygen replenishment. This non-linearity has previously been shown to lead to prolonged responses (Cohen et al., 2002; Vazquez et al., 2006), consistent with the present data. Given that parameterization of this effect as a function of TR and ISI was not conducted in the current study, future investigation may reveal additional response differences under varying acquisition conditions.

4.3 Analysis of Spatial Extent of Activation

Results from the group-level activation maps provide additional evidence of state-dependence of the HDR as a function of the composite stimulation from imaging-related acoustic noise (influenced by TR) and the desired acoustic stimuli (influenced by ISI). Results demonstrate that use of low ISI values (such as 6s) can result in responses that are not detected using typical HDR models under GLM analysis. Fig.4 and Fig.5C indicate that sensitivity to the response is lowest at short ISIs, where (as expected) only a small

percentage of voxels in the AC ROIs were deemed active. Increasing ISI improved detection, with a slight peak at 12s. As noted above, it is suspected that the observed decrease in detection for longer ISIs is a consequence of a sub-optimal fitting of the undershoot with the reference waveform. The lack of observed activation for TR/ISI = 3s/6s, is proposed to be the consequence of underestimation of the HDR peak and the corresponding poorly estimated waveform.

4.4 Interaction with Response Undershoot

The undershoot observed in the HDR associated with the desired stimulus may, like the peak of the HDR, play a critical role in the nature of response amplitude interactions between successive stimulus presentations and/or the acoustic noise associated with the image acquisitions. Specifically, behavior of the amplitude of the undershoot period in the HDR may provide critical information about the state-dependent behavior of the vascular response underlying BOLD fMRI. HDR estimates obtained using more finely sampled data clearly depict an undershoot period between 7s and 11.5s post-stimulus onset (see Fig.2 and Fig.3 TR = 1.5s, ISI > 9s; but note that this undershoot is observed to extend beyond 11.5s post-onset under certain TR/ISI conditions—e.g., 1.5s/18s). This undershoot overlaps with subsequent stimulus presentations for ISI = 9s (and possibly ISI = 12s). These succeeding stimulus presentations, occurring when the system is arguably suppressed, could induce a driven vascular response back to the same peak level observed where the BOLD effect had returned to baseline (see Buxton et al., 1998). Should this response achieve the same maximal signal, the appearance of a larger amplitude trial-based response is produced. Thus, even though the vascular system may not be truly “at rest,” a comparable activated state (requiring a larger change from the suppressed baseline) may be achieved for some subset of portion of the undershoot and subsequent recovery periods.

5. Implications and Further Considerations

The expected benefit gained by using longer TR and ISI values when detecting desired responses may be enhanced through incorporation of a better model for the response undershoot as a function of TR and ISI. The increased response amplitude observed in some conditions suggests it may be beneficial to use ISI values that fall within the range of the undershoot portion of the HDR in auditory cortex. However, variability within and across hemispheres of the post-stimulus undershoot (shape and duration) exhibited for different TR/ISI conditions in this study, highlights the potential for undesirable variability in observed responses. Given that the spatial characteristics of the undershoot response (Zhao et al., 2007) under different experimental conditions are yet to be fully understood, parameterization of the amplitude, duration and shape of the undershoot portion of the response as a function of TR and ISI will provide insight into the characteristics of the underlying neural and vascular mechanisms. Ultimately, the presence of a period of response undershoot and recovery that may, as a function of time or level, differentially alter the estimated response amplitude demonstrates that the 10s post-stimulus return to baseline signal does not represent a return to “rest” for the auditory cortex, as previously assumed by Langers et al. (2005). Rather, acoustic stimulations within this time window are presented during the trough of the response to the preceding stimulus (or stimuli), creating the potential for inaccuracies in estimating the HDR, given that the system may not behave as it would if it were in a state of ‘rest’.

Demonstrated effects of short ISI may also have implications for rapid-event related fMRI techniques (Dale and Buckner, 1997; Burock et al., 1998) which utilize short ISI values and assume some linearity of the BOLD response (Heckman et al., 2007). The expected effect due to such paradigms will be a reduction in magnitude of response, and potentially greater variance. Both of these changes will reduce detection power, producing more false negatives

than would otherwise be expected. Further, while the authors attribute the observed differences in activation between ISI conditions to hemodynamic state effects, the possible role of neural adaptation to frequently presented stimuli (e.g. Harms and Melcher, 2000) is worth noting and is worthy of further investigation.

Finally, it is important to recognize the trade-off between the suggested use of longer TR/ISI values and other experimental considerations. For example, longer TR/ISI will increase the overall length of an experimental session (assuming a fixed target number of samples and statistical power), bringing into play concerns about subject fatigue and attention. This study has provided insight into the potential attenuating effects from interaction of responses due to the selection of TR and ISI, and also indicated TR and ISI values that may best mitigate these effects. Ultimately, it is likely better for the complex interaction between temporal sampling rate and stimulus presentation rate to be incorporated into models of auditory cortex activity to assess whether “ideal” values of TR and ISI may be identified, the shorter of which are more conducive to practical experimentation. Given that no single set of experimental parameters will be optimal for all studies, researchers may now make better informed assessment of the experimental parameters to be employed in their studies to obtain the desired statistical power from alert and effectively behaving subjects.

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Abbreviations

HDR	Hemodynamic Response
CVA	Clustered Volume Acquisition
ISI	Inter-stimulus Interval
TR	Repetition Time
LTI	Linear Time-Invariant
pAC	Primary Auditory Cortex
AC	Auditory Cortex

Fig.1.

Example of the experimental paradigm. In this illustration, $ISI = 12s$ and $24s$, $TR = 3s$. The stimulus was not presented during some trial blocks in order to create an ISI of $24s$. Italicized boldface post-onset times indicate values that were included in the HDR estimate for the particular trial.

Hemodynamic Response Time Courses - Left Auditory Cortex

Fig.2.

Group averaged hemodynamic response estimates in **left** primary auditory cortex region of interest (pAC). In the figure, ISI increases from left to right, while TR increases from top to bottom. Each subplot corresponds to a specific TR/ISI condition and contains the averaged hemodynamic response estimate (with error bars – N = 10), the amplitude-fitted response (with the corresponding value of 'A' – solid) and the predicted response under the assumption of linear time-invariance (with the corresponding R² value – dashed).

Fig.3.

Group averaged hemodynamic response estimates in **right** primary auditory cortex region of interest (pAC). In the figure, ISI increases from left to right, while TR increases from top to bottom. Each subplot corresponds to a specific TR/ISI condition and contains the averaged hemodynamic response estimate (with error bars – $N = 10$), the amplitude-fitted response (with the corresponding value of 'A' – solid) and the predicted response under the assumption of linear time-invariance (with the corresponding R^2 value – dashed).

GROUP RANDOM EFFECTS ACTIVATION MAPS

Fig.4.

Group random effects maps of activation. In each map, threshold scaling was performed in order to account for differences in the sampling rate between the various TR/ISI conditions. The lowest t -threshold (3.106) corresponds to $p < 0.05$ (FDR-corrected) for TR/ISI = 6s/12s, the condition with the least number of time-points. The percentage of active voxels within the auditory cortex (AC) region of interest (containing Heschl's gyrus, Heschl's sulcus and the superior temporal gyrus – an outline of this region is shown in blue for the TR/ISI = 1.5s/6s map) is displayed below each t -statistic map for both left and right hemispheres.

Fig.5.

Random effects activation map for $TR/ISI = 3s/6s$ using the HDR estimates as the input to non-linear regression. Parts A (subject 1 to subject 5) and B (subject 6 to subject 10) illustrate the differences between the fitted reference response waveforms for $TR/ISI = 1.5s/24s$ (sampled – dashed) and HDR estimates for $TR/ISI = 3s/6s$ (solid) used in the k-cross scheme to generate the random effects maps of activation (for $TR/ISI = 3s/6s$) shown in Part C. The short TR/ISI condition produces a distorted response that does not resemble a typical hemodynamic response. Part C depicts the random effects map ($p < 0.05$; FDR-corrected) generated using the HDR estimates (for comparison with Fig. 4). While the use of the HDR estimate generated by the k-cross scheme leads to an increase in number of active voxels from $TR = 1.5s$ in both left and right auditory cortex (AC) regions of interest, the total activation remains appreciably reduced relative to longer ISIs (Fig.4), demonstrating the effects of response saturation.

Table 1

Results of the paired t-tests comparing the amplitude of responses across ISI conditions in left and right primary auditory cortex. Boldface values are significant at FDR corrected $p < 0.05$

Left pAC					Right pAC				
ISI	9	12	18	24	ISI	9	12	18	24
6	0.017	0.018	0.019	0.011	6	0.004	0.031	0.045	0.047
9	•	0.850	0.560	0.717	9	•	1.000	1.000	1.000
12	•	•	0.729	0.800	12	•	•	1.000	1.000
18	•	•	•	0.740	18	•	•	•	0.940

Table 2

Results of the paired t-tests comparing the amplitude of responses across TR conditions in left and right primary auditory cortex. Boldface values are significant at FDR corrected $p < 0.05$

Left pAC			Right pAC		
TR	3	6	TR	3	6
1.5	0.46	0.042	1.5	0.520	0.092
3	•	0.027	3	•	0.126