Improved Auditory Cortex Imaging Using Clustered Volume Acquisitions

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Abstract: The effects of the noise of echo-planar functional magnetic resonance imaging on auditory cortex responses were compared for two methods of acquiring functional MR data. Responses observed with a distributed volume acquisition sequence were compared to those obtained with a clustered volume acquisition sequence. In the former case, slices from the volume were acquired at equal intervals within the repetition time, whereas the latter acquired all slices in rapid succession at the end of the imaging period. The clustered volume acquisition provides a period of quiet during which a stimulus may be presented uninterrupted and uncontaminated by the noise of echo-planar imaging. Both sequences were implemented on a General Electric Signa imager retrofitted for echo-planar imaging by Advanced NMR Systems, Inc. The sequences were used to acquire 60 images per slice of a fixed volume of cerebral cortex while subjects were presented an instrumental music stimulus in an On vs. Off paradigm. Data were acquired for both sequences using TR values of 2, 3, 4, 6 and 8 sec. The clustered volume acquisition sequence was found to yield greater measures of dynamic range (percent signal change, mean statistical power per unit imaging time) across the tested range of TR values. Observations of more consistent spatial extent of responses, greater mean signal changes, and higher and more consistent values of mean *t*-statistic per unit imaging time demonstrate the efficacy of using a clustered volume acquisition for fMRI of auditory cortex. *Hum. Brain Mapping* 7:89–97, 1999. © 1999 Wiley-Liss, Inc.

Key words: fMRI; pulse sequence; brain mapping; EPI

INTRODUCTION

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Acoustic contamination of functional MRI (fMRI) data is of great concern to those members of the scientific community attempting to elucidate the function of the auditory pathway (brainstem and cortex). The acoustic noise inherent in the process of echo-planar fMRI is a short duration (32–50 msec) burst of a tone complex (a “beep”) that is certain to generate

responses throughout the auditory pathway. The presence of a cortical fMRI response was demonstrated by Bandettini et al. [1998], highlighting the possibility that the response will limit the dynamic range of responses to the desired stimuli, reducing the sensitivity of the fMRI technique. The cortical response to the beeps may also change the spatial distribution of the stimulus-induced fMRI response, reducing the accuracy of traditional stimulus vs. no stimulus paradigms. This accuracy may be further degraded by the changed perception of the stimulus due to acoustic masking and a reduction in the ability of the subject to attend to the desired stimulus. The latter could yield a changed cortical response in both sensory [Woodruff et al., 1996; Scheich et al., 1997] and higher order cortical areas. This work was undertaken to assess the experimental effect of the fMRI measurement process on the activation observed in response to a stimulus known to yield strong activation in auditory cortex, instrumental music.

Peak noise levels generated by the echo-planar imaging (EPI) beep at our facility range from 117 dB Sound Pressure Level (SPL) on a 1.5 T machine to 133 dB SPL on a 3.0 T imager [Ravicz and Melcher, 1998]. These values are consistent with other measurements on similar machines [Counter et al., 1997]. Noise levels are typically reduced through the use of passive attenuation measures such as earmuffs and earplugs. These reductions are generally on the order of 30–35 dB, bringing the beep level down to 85–90 dB SPL at 1.5 T [Ravicz and Melcher, 1998]. This level is still loud enough to mask a desired auditory stimulus both simultaneous with and immediately following the imaging beep. Such simultaneous and non-simultaneous masking will be most evident under fMRI echo-planar sequences in which the beeps are present throughout auditory stimulation.

In most conventional and echo-planar techniques on General Electric/Advanced NMR Systems, Inc. (GE/ANMR) systems, slices are acquired at equal intervals within the repetition time (TR) of the imaging experiment (distributed volume acquisition, DVA). This is in contrast to the typical imaging sequence on other fMRI systems (e.g., Siemens) in which the volume is acquired at the end of the TR, with one slice acquired approximately every 100–200 msec (clustered volume acquisition, CVA).

The regular pulsing of the echo-planar gradients on the GE/ANMR system can lead to a consistent pattern of masking of the desired stimulus. Under typical functional imaging conditions, eight to 16 slices are imaged every 2 sec, producing four to eight beeps per second (one per slice acquisition). For the GE/ANMR

system, each gradient readout sequence is 32 msec in duration. The beep associated with each readout sequence lasts for approximately 50 msec, including reverberation [Ravicz and Melcher, 1998]. With less than 250 msec between beeps, a significant fraction of the auditory stimulus is being masked by the imaging noise. Such masking is likely to have an effect on the functional response dependent upon the measures taken to compensate for the imager noise background. Measurements at our facility indicate approximately 30 dB of masking of continuous, amplitude modulated noise (0.3 octave bandwidth) centered at the 1 kHz fundamental switching frequency of the 1.5 T machine EPI gradients. This masking drops to less than 5 dB for center frequencies more than two octaves from 1 kHz.

While the investigator can compensate for masking produced by the imaging noise, the effects of the beeps are not readily eliminated through modification of experimental parameters. For example, a simple measurement of the subject's behavioral hearing thresholds in the presence of imaging noise may be used to present stimuli at a fixed level above hearing threshold, but this will not eliminate the auditory cortex response induced by the beeps. The net fMRI response in cortex is probably a non-linear combination of responses to the background noise and the auditory stimulus. A related effect is that the stimulus being perceived by the subject is certainly different from the stimulus which would be perceived under the quiet conditions typical of other functional imaging modalities such as positron emission tomography (PET) and magnetoencephalography (MEG), making direct comparisons of results across these modalities difficult. Therefore, it is desirable that functional MRI is performed in an environment as free of imaging noise as is possible.

In CVA sequences the stimulus may be presented, uninterrupted, for most of the TR with the beeps occurring as rapidly as possible at the end of the TR. If the total duration of a volume acquisition is shorter than the onset of the fMRI-observable blood-oxygenation level dependent (BOLD) response to the beeps associated with that volume acquisition, the inclusion of cortical responses to the beeps is avoided. With selection of a long TR it should be possible for the cortical response to the beeps to decay prior to the next volume acquisition, providing volumetric fMRI data with greater dynamic range. In the case of TRs greater than 10 sec, and perhaps at shorter TR values in conjunction with small imaging volumes, this data should be free of the responses induced by the imaging noise. Accordingly, it becomes possible to use typical TR values to obtain data more consistent with a

Figure 1.

Comparison of temporal acquisition of eight slices with $TR = 4$ sec for (a) distributed volume acquisition (DVA) sequence and (b) clustered volume acquisition (CVA) sequence. Each slice acquisition (open box) is 117 msec in duration, producing a burst of imager noise (black box) that is 50 msec in duration, including

reverberation. A typical axial slice ordering, inferior (slice 1) to superior (slice 8), is shown at left. Note that in the interleaved DVA sequence, adjacent slices are imaged much further apart in time than in the centric CVA sequence.

stimulus-only response than obtained using a distributed volume acquisition (DVA) imaging sequence.

In this paper we use fMRI equivalent CVA and DVA sequences, both implemented on a 1.5 T GE/ANMR EPI system, to compare auditory cortex responses to complex acoustic stimuli, and discuss the advantages inherent in the use of CVA sequences in this and other fMRI applications.

METHODS

Imaging sequence

The CVA pulse sequence was implemented on a General Electric (Milwaukee, WI) 1.5 T Signa imager, retrofitted for echo-planar imaging (EPI) by Advanced NMR Systems, Inc. (Wilmington, MA). An asymmetric spin-echo (ASE) echo-planar sequence with slice acquisitions distributed equally throughout the repetition time (TR) was modified to perform the clustered multi-slice imaging. Both the DVA and CVA sequences are illustrated, with their accompanying beeps, in Figure 1 for the example of eight slices acquired with $TR = 4$ sec. Observe that the CVA sequence provides a block of time when no slices are acquired and during

which the stimulus may be presented without significant distraction.

Due to slice profile imperfections, acquisition of all slices within one TR can lead to significant crosstalk between adjacent slices. Assume that we are acquiring a volume of eight slices clustered at the end of each TR. Further assume that the slice acquisitions are interleaved such that the odd slices (1, 3, 5 and 7) are acquired in the first half of the cluster and the even slices (2, 4, 6 and 8) in the second half. Overlapping of the slice profiles results in the acquisition of one slice perturbing some fraction of the spins in the neighboring slices (e.g., acquisition of slice 4 perturbs the spins in slices 3 and 5). In a clustered volume acquisition with normal interleaving the odd slices are imaged almost a full TR after being perturbed and signal levels for these slices are comparable to those obtained in a single-slice acquisition. The acquisition of the odd slices perturbs some of the spins in the even slices (2, 4, 6 and 8) that are imaged just 500 msec later, resulting in signal levels that may be significantly reduced from those obtained in a single-slice acquisition. The multi-slice signal-to-noise ratio (SNR) in the even slices was reduced by as much as 60% from the single-slice acquisition SNR when using the default GE/ANMR

slice excitation pulses. The SNR loss was reduced to below 5% by sharpening the profile of the acquired slices by the following modifications. First, the Hamming-windowed 90- and 180-degree sinc pulses were widened from 3.2 msec with a single side lobe to 6.4 msec with two side lobes. Then the corresponding slice-select gradient amplitudes and transmit frequencies were rescaled to maximize slice width with minimal crosstalk between adjacent slices. This optimization was performed using a phantom containing a wide range of T1 values, including those of fat, white matter and gray matter. The 90- and 180-degree pulses of the DVA sequence were modified to use slice profiles identical to the CVA sequence.

Imaging parameters

Data acquisition for all experiments described in this paper was performed on the 1.5 T system using asymmetric spin-echo (ASE) echo-planar imaging (TE = 70 msec, $\tau = -25$ msec, 128×64 collection matrix, $40 \text{ cm} \times 20 \text{ cm}$ FOV). Slices were 4 mm thick and contiguous. The in-plane resolution for all studies described was $3.1 \text{ mm} \times 3.1 \text{ mm}$. A surface receive coil positioned around the left ear was used to maximize signal from Heschl's gyrus (site of primary auditory cortex) and the rest of the auditory cortex. This coil is integrated into a passive attenuation system used to reduce the level of the EPI noise by 30 dB to approximately 85–90 dB SPL [Ravicz and Melcher, 1998]. The body coils of the magnet were used for transmit. Functional images were acquired with the coolant compressor turned off to eliminate the dominant, periodic component of the non-EPI background noise, effectively producing a condition of quiet for periods which required no auditory stimulation.

Experiments

Four subjects (ages 22–26 years; three male, one female) were imaged using both the CVA (clustered volume acquisition) and the DVA (distributed volume acquisition) sequences for TR values of 2, 3, 4, 6 and 8 sec to acquire 60 images of eight (axial) oblique slices. Images of the left auditory cortex were acquired during right monaural presentation of an instrumental music stimulus in an On vs. Off paradigm with 24 sec epochs. Music stimulation was continuous for the entire 24 sec period. The TR values were chosen to cover the typical experimental usage at our facility, and range from the shortest to longest TRs that are experimentally practical due to duty cycle requirements and total imaging time limitations. Two subjects

were exposed to the five TR values in an increasing order, and two in a random order. Multiple presentation orders were used to prevent bias resulting from habituation.

The primary goal of this study was to plot percent signal change against TR for both CVA and DVA sequences to determine if the auditory cortex response to a consistent paradigm would be dependent upon the volume acquisition sequence. Therefore, runs of the paradigm obtaining equal numbers of images, rather than utilizing equal imaging time, were chosen so that the percent signal changes, *t*-statistics, and activation maps could be directly compared across TR values and volume acquisition sequences with consistent error bars. As a consequence of this decision, the duration of each imaging session remained less than 2 hr because runs using shorter TR values required less time than runs using longer TR values. The 2 hr imaging session duration was desired to prevent boredom or discomfort from distracting the subjects from the presented stimuli.

Data analysis

Prior to statistical analysis, images were motion corrected using SPM95 [Friston et al., 1995], spatially smoothed by a three-point Hamming filter and drift corrected using a minimum mean square error fit for each individual voxel. Computation of percent signal change and Student's *t*-statistic for all voxels meeting a minimum signal threshold requirement was performed using in-house software. A boxcar paradigm waveform was shifted by one (TR = 3 and 4 sec) or two images (TR = 2 sec) to account for the approximately 3 sec onset delay of the BOLD response. The waveform was not shifted for the cases of TR = 6 and 8 sec.

Indicators of the dynamic range of auditory cortex, percent signal change and Student's *t*-statistic, were computed to determine the optimal TR that minimizes the stimulation of auditory cortex by the beeps while maximizing the number of images per unit time. Auditory cortex was defined for this study as a volume including Heschl's gyrus, the planum temporale and extending inferiorly to the superior temporal sulcus. Areas of functional activation were defined as regions achieving statistical significance of $P < 0.01$ (uncorrected *t*-statistic, $t > 2.66$ for 30 time points in each condition) in at least three of the 10 runs of the music paradigm. The three in 10 criterion was selected to reduce the false positive rate to approximately one in 1 million. For each subject, all voxels that met the three in 10 criterion were combined to form a single region of interest (ROI).

To assess variations in dynamic range as the TR was changed for each sequence, mean values of both percent signal change and t -statistic were computed using each subject's ROI. Ninety-five percent confidence intervals were computed for both mean quantities. Statistical power per unit imaging time was computed for each run by dividing the mean t -statistic in the ROI by the square root of the TR. Assuming that the image noise (non-acoustic) is stationary and uncorrelated across runs, this quotient weights the mean t -statistic by the number of points that are acquired per unit imaging time. Comparison of values of statistical power per unit imaging time indicates at which TR the strongest responses would be observed given a fixed total imaging time, rather than a fixed number of image acquisitions. A fixed total imaging time is a more common constraint when planning fMRI experiments.

RESULTS

Activation maps obtained with the CVA sequence were directly compared to DVA sequence maps obtained under identical conditions. Measures of dynamic range (percent signal change) and statistical power were compared for the two sequences. Increases in both dynamic range and statistical power were found to occur when using the CVA sequence with long TR values, with improvement over the DVA sequence maintained at shorter TRs.

Spatial extent of responses

Figure 2 compares, for all subjects, the spatial extent of activation for the CVA and DVA sequences during auditory functional studies. In these images, the color-coded P -value is overlaid on a T1-weighted anatomic image (grayscale), with P -value magnitudes indicated on the colorbar. The slices presented for both the CVA and DVA sequences contained the sites of strongest responses over the range of TR values. These slices include Heschl's gyrus, much of the planum temporale and other secondary auditory areas. The left side of the figures depicts the responses obtained with the CVA sequence while the right side presents those obtained using DVA. For each subject, the images in the top row are results for TR = 8 sec and the bottom row consists of the maps for TR = 3 sec. Because each run consisted of a constant number of images, the low-level cutoff for statistical significance was fixed, at $P < 0.01$ (uncorrected t -statistic, $t > 2.66$). For both displayed TR values, the CVA responses were always greater in both spatial extent and statistical significance than the DVA

results. This was generally true across the set of TRs (Table I).

Strength of responses

In Figure 3, the averages of all activated voxels in the four subjects for a) percent signal change and b) statistical power per unit imaging time are plotted as a function of TR for both sequences. The results for mean t -statistic paralleled those of percent signal change. The statistical power per unit imaging time, achieved by dividing by the square root of TR, provides an assessment of the mean statistical power achieved for each TR under the more practical assumption of constant imaging time, rather than constant number of images. Statistically significant differences ($P < 0.05$, t -test) between CVA and DVA percent signal changes were observed at each TR value. The mean statistical power per unit imaging time exhibited a statistically significant difference ($P < 0.05$, t -test) between CVA and DVA sequences for TR values of 2, 3, 6 and 8 sec. At a TR of 4 sec, the improvement in statistical power for the CVA sequence over the DVA sequence did not achieve significance.

DISCUSSION

The BOLD response due to neuronal activation in auditory cortex has both a time constant for activation and a time constant for recovery to the initial baseline. In visual cortex, the rise time from stimulus onset to 90% maximum activation and the recovery time from stimulus cessation to 10% above baseline have been observed to be 4–10 sec [Buckner et al., 1996; Savoy et al., 1994; Bandettini et al., 1993; Kwong et al., 1992]. These values suggest rise and recovery time constants on the order of 3–4 sec, but such values may be different for auditory cortex.

If a DVA sequence is used with a TR longer than the rise time, the beep associated with the initial slice acquisition for the volume may produce an observable fMRI response in the latter slices acquired. After the initial BOLD response develops, because the time between slice acquisitions is shorter than the duration of the response to the imaging noise, all subsequent slice acquisitions are contaminated by responses to imager noise. Elimination of this effect would require the use of very long (e.g., 10 sec per slice) and experimentally impractical TR values.

A CVA sequence simplifies this problem by allowing the separation of within-acquisition responses from between-acquisition responses due to the quiet period between volume acquisitions. The music activation

Figure 2.

Comparison of the spatial extent and statistical significance of auditory cortex activation, in response to instrumental music, as a function of imaging sequence (CVA left, DVA right) and TR. Activation (t -test, $P < 0.01$) is displayed as a colormap overlaid on T1-weighted images (grayscale). For each subject, a single anatomic slice containing the majority of auditory cortex is shown. Re-

sponses obtained using TR = 8 sec are displayed in the top row and responses obtained using TR = 3 sec are displayed in the bottom row. The CVA sequence responses are consistent across TR in both location and spatial extent while the DVA results vary in both of these respects, sometimes considerably.

maps generated using a CVA sequence with TR = 8 sec for eight slices should be largely free from imager noise contamination. The CVA sequence should, in general, be free of direct, slice acquisition-to-slice acquisition contamination because the readout time for up to eight slices is less than 1 sec in duration. There will be a long-term BOLD response to the noise of the CVA volume acquisition, but the use of a long TR (e.g., 8 sec) will permit this response to decay prior to the subsequent volume acquisition. At shorter TR values, the response to previous acquisitions does not achieve full recovery to baseline, thereby limiting the dynamic range of responses to auditory stimuli. This will lead to partial saturation of the signal in auditory cortex, with saturation increasing with decreasing TR. It is unknown if this is saturation of the neuronal response, the BOLD response, or due to a limitation of the sensitivity of the fMRI technique to hemodynamic changes.

Analysis of functional effect

Both CVA and DVA sequences yield similar areas of cortical activation for TR = 3 sec, but the CVA activation appears to be more robust in spatial extent across TR values (Fig. 2 and Table I). At shorter TR values, e.g., 2–4 sec, the DVA maps differ from longer TR data in both the spatial extent and location of foci of greatest statistical significance. The changes in DVA activation at long TRs, though consistent across the four subjects, were particularly large for Subjects 1 and 2. Both subjects reported difficulty attending to the stimulus at TR = 8 sec due to interaction of the music tempo with the 1 Hz rate of the beeps. The reduction of such stimulus-specific interactions by the introduction of a quiet period into the TR interval is an advantage of CVA sequences.

TABLE I. Spatial extent (number of voxels) of activation ($P < 0.01$) in auditory cortex

Subject (ROI points)	Imaging sequence	TR (sec)				
		2	3	4	6	8
1 (223 points)	CVA	96	186	144	144	164
	DVA	130	142	108	130	66
2 (356 points)	CVA	195	283	301	200	328
	DVA	193	281	285	160	33
3 (506 points)	CVA	281	436	445	346	348
	DVA	63	287	362	165	148
4 (280 points)	CVA	158	190	152	143	272
	DVA	130	175	167	157	203

Figure 3.

Graphs of (a) mean percent signal change and (b) mean statistical power per unit imaging time. Values were computed by pooling data of all subjects from ROIs of those voxels achieving $P < 0.01$ (uncorrected t -statistic, $t > 2.66$) in at least three of the 10 runs of the instrumental music paradigm. Error bars indicate 95 percent confidence intervals. Mean percent signal changes were significantly higher ($P < 0.05$, t -test) for the CVA sequence at all TR values. Power per unit imaging time was also significantly higher ($P < 0.05$, t -test) for the CVA sequence than for the DVA sequence (TR = 2, 3, 6 and 8 sec).

The response strength differences between CVA and DVA seen in the activation maps of Figure 2 are reflected in the graph of percent signal change in Figure 3a. The mean percent signal change for the CVA sequence was reasonably constant from 3–6 sec. The increase in percent signal change at TR = 8 sec may be a consequence of our reduced sampling of the onset of the response to the stimulus and thus may be artificially high. The increase in percent signal change when the TR was increased from 6 sec to 8 sec could also indicate that, for at least some portions of auditory cortex, the beep-induced response may persist longer than our maximum measured TR of 8 sec. The percent signal change for the DVA sequence remained relatively constant, and lower than for the CVA sequence, across all TR values.

The statistical power per unit imaging time (Fig. 3b) was higher across TR values for the CVA sequence

than the DVA sequence. The relatively constant percent signal changes observed between 3 and 6 sec for both sequences imply that there should be no statistical gain from using a longer TR value. This is confirmed by the linear decrease observed in power per unit imaging time over this range. The large drop in percent signal change at TR = 2 sec is not compensated for by the increased number of images for a given experimental duration. As previously stated, this analysis assumes that all non-acoustic noise across experiments is uncorrelated and stationary. Because some sources of physiologic noise in the fMRI experiments are correlated (e.g., cardiac, respiratory), this analysis leads to a small bias in favor of the lower-TR experiments.

For these experiments in which eight slices were acquired (1 sec duration of 8 Hz beeps for CVA) the optimal TR for the use of the clustered volume acquisition sequence was 3 sec. A TR value of 3 sec selects the peak statistical power per unit time (Fig. 3b) and results in a statistically significant improvement in percent signal change over the DVA sequence at all TRs (Fig. 3a). This value strikes a good balance between temporal resolution and experimental duration along with the subject's ability to track and respond to the stimulus prior to image acquisition. Subjectively, for TR values greater than 2 sec, subjects expressed a preference for the CVA sequence over the DVA sequence. Subjects reported that it was easier to concentrate on the stimulus during the CVA quiet periods and to block out the periodic trains of beeps than to concentrate on a stimulus which is "constantly" being masked.

We wish to emphasize that the optimal TR will vary with the duration of the volume acquisition. Changes in the duration of the volume acquisition will need to be offset by changes in the inter-acquisition delay. This delay appears to serve three purposes. First, the subject is permitted a period of time to recover from masking effects from the beeps. Second, the BOLD response to the imager beeps is allowed to rise and decay during these non-imaging periods. Finally, the subject is able to attend to the stimulus alone rather than the stimulus plus beeps. All of these changes in the perception of the stimulus are believed to contribute to the greater percent signal changes observed for the CVA sequence over the DVA sequence.

Benefits of clustered volume acquisition

Clustered volume acquisition sequences have a number of advantages over distributed volume acquisition sequences when used for auditory experiments. CVA

does not require prolonged continuous presentation of stimuli in order for all slices in the volume to exhibit a functional response in the short-term. By triggering the stimulus to the beginning of the TR, not only is the time between stimulus and slice readout precisely known for all slices, but the BOLD response in each slice may have time to evolve to detectable levels prior to the first acquisition in a stimulus epoch. This may not occur in a DVA sequence due to the acquisition of slices throughout the TR period, during the onset delay of the BOLD response.

The effect on response latencies is a more general benefit of the imaging sequence, as these will become more uniform across the slices imaged. Under the DVA sequence, adjacent slices are often collected at widely spaced intervals, potentially leading to response onsets occurring within different volume acquisitions for any two slices in the volume of interest. The clustered, rapid readout of the slices in the CVA sequence reduces this temporal spread and makes it easier to precisely localize the imaging time of a slice relative to the onset of the stimulus.

Use of the CVA sequence should also improve the effectiveness of standard image registration routines. With slices in the volume of interest being acquired as rapidly as possible rather than being interleaved throughout the TR as in the DVA sequence, motion is more likely to occur between, rather than within, volume acquisitions. Therefore, the standard rigid body approximation used in most motion correction algorithms should be more accurate.

Extension of paradigms

The CVA sequence permits many complex functional paradigms to be explored to a greater degree than the DVA sequence. For example, experiments involving language stimuli, such as word presentation or vocalization, are straightforward to implement and analyze on a trial-by-trial basis, perhaps even separating the perception of the word from the execution of the required activity (e.g., verb generation, repetition). Paradigms that require significant time locking of the stimulus to the imaging, such as an "oddball" paradigm used to elicit the P300 EEG response, should be more easily implemented using a CVA sequence. Event-related fMRI experiments, including those utilizing random order of stimulus presentation, are a logical application of CVA imaging sequences. Utilization of a flow-compensated gradient-echo sequence rather than the current asymmetric spin-echo technique should permit even more rapid imaging of the cortex, potentially further reducing the acquisition-to-

acquisition effect of the imaging noise. This will also permit a greater volume of cortex to be imaged for a given duration of acquisition. Clustered volume acquisitions could also be applied to auditory fMRI using conventional sequences (e.g., FLASH) to realize similar benefits.

CONCLUSIONS

The changes in fMRI activation maps across TR values provide evidence that the imaging noise (a beep) does not combine additively with acoustic stimuli, but interferes with the stimulus and partially saturates the response of auditory cortex. Under the continuous imaging of a DVA sequence, the stimulus perceived by the auditory system may be quite different from the stimulus presented in quiet. The CVA sequence provides this quiet period in which the subject may attend and respond to an uncontaminated stimulus.

When conducting auditory fMRI experiments, a CVA sequence is less affected by beep-induced responses than a DVA sequence. The improved dynamic range of the CVA responses is demonstrated by the observation of greater signal changes at all tested TR values. There also appears to be an optimal ratio between imaging time (acquisition duration) and TR. For a 1 sec duration volume acquisition, a TR value of 3 sec yielded the highest statistical power per unit imaging time. Use of this sequence for auditory fMRI should improve the ability to observe dynamic signal changes for a minimum amount of imaging time and yield activation maps that are largely free of auditory responses to the noise of the imaging process.

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REFERENCES

- Bandettini PA, Jesmanowicz A, Wong EC, Hyde JS. 1993. Processing strategies for functional MRI of the human brain. *Magn Reson Med* 30:161-173.
- Bandettini PA, Jesmanowicz A, Van Kylen J, Birn RM, Hyde JS. 1998. Functional MRI of imager acoustic noise induced brain activation. *Magn Reson Med* 39:410-416.
- Buckner RL, Bandettini PA, O'Craven KM, Savoy RL, Petersen SE, Raichle ME, Rosen BR. 1996. Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. *Proc Nat Acad Sci USA* 93:14878-14883.
- Counter SA, Olofsson A, Grahn HF, Borg E. 1997. MRI acoustic noise: sound pressure and frequency analysis. *J Magn Reson Imaging* 7:606-611.
- Friston KJ, Ashburner J, Frith CD, Poline JB, Heather JD, Frackowiak RSJ. 1995. Spatial registration and normalization of images. *Hum Brain Map* 2:165-189.
- Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, Cheng H-M, Brady TJ, Rosen BR. 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci USA* 89:5675-5679.
- Ravicz ME, Melcher JR. 1998. Reducing imager-generated acoustic noise at the ear during functional magnetic resonance imaging: passive attenuation. In: Abstracts of the Twenty-First Midwinter Research Meeting, Association for Research in Otolaryngology, 1998, p 208.
- Savoy RL, O'Craven KM, Kwong KK, Weisskoff RM. 1994. Enhancing the effective temporal resolution of functional neuroimaging: measuring fMRI responses to very brief (100 msec) visual stimuli using computer synchronized stimulus generation and signal averaging. In: Proceedings of the Society of Magnetic Resonance, Second Meeting, San Francisco, 1994, p 667.
- Scheich H, Baumgart F, Gaschler B, Tempelmann C, Tegeler C, Stiller D, Heinze HJ. 1997. Masking of acoustic stimuli produces fMRI activation in a particular human auditory cortex field. In: Abstracts of the Twentieth Midwinter Research Meeting, Association for Research in Otolaryngology, 1997, p 26.
- Woodruff PWR, Benson RR, Kwong KK, Howard RJ, Talavage T, Belliveau J, Rosen BR. 1996. Modulation of auditory and visual cortex by selective attention is modality-dependent. *Neuroreport* 7:1909-1913.