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Utilizing Hemodynamic Delay and Dispersion to Detect fMRI Signal Change Without Auditory Interference: The Behavior Interleaved Gradients Technique

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A major problem associated with the use of functional magnetic resonance imaging (fMRI) is the attendant gradient noise, which causes undesirable auditory system stimulation. A method is presented here that delays data acquisition to a period immediately after task completion, utilizing the physiological delay and dispersion between neuronal activity and its resulting hemodynamic lag. Subjects performed finger movements with the gradients off, followed by a rest period with the gradients on. This resulted in task-related signals comparable to those obtained with concurrent task performance and image data acquisition. This behavior interleaved gradients technique may be particularly useful for the studies involving auditory stimulation or overt verbal responses. Magn Reson Med 41:13–20, 1999.

Key words: neuroimaging; motor cortex; auditory; behavior interleaved gradients; single-trial fMRI

Even though the efficacy of functional magnetic resonance imaging in detecting task-related signal change reflecting sensory and cognitive processing has been demonstrated, fMRI data acquisition involves high levels of potentially contaminating acoustic noise. Language or auditory processing studies are particularly susceptible to interference from this source. Gradient noise can adversely affect detection of task-related signal change in numerous ways. First, the background noise generated by the scanner may alter difficulty levels in tasks involving acoustically presented stimuli such as tone discrimination or verbal processing. This acoustic interference may not be consistent across conditions. Second, gradient noise may also induce hemodynamic changes in regions involved in auditory processing. Third, when using non-auditory stimuli in visual, motor, or tactile tasks, acoustic noise may distract the subject from the task at hand.

Some of these potentially contaminating effects might be mitigated if the signal changes induced by the gradient noise were linearly additive with task-related signal changes. For example, many sensory and cognitive studies using fMRI are based on a subtraction analysis technique. This approach assumes that the physiological changes induced by the gradient noise are similar in both the control and task conditions and therefore cancel. Should this ‘‘subtraction’’ assumption be incorrect, noise-induced signal change might be misidentified as task-related signal change. Furthermore, the range of modulation between the resting and activation states may be artificially decreased due to saturation of auditory cortical activity by the relatively loud gradient noise (1,2).

In auditory experiments, attempts have been made to reduce the effects of the gradient noise by acoustically insulating the subject. To date there exist no wholly successful methods for noise reduction, with partial success resulting from the use of earplugs and acoustic shielding. This poses a serious problem for fMRI compared with other neuroimaging techniques, such as positron emission tomography (PET), that acquire image data in a comparatively quiet environment. As noise abatement does not seem technically feasible at present, an alternative approach involves confining gradient noise to a time in which it will have minimal contaminating effects on task-related signal change (3,4). This is accomplished by utilizing the hemodynamic delay between neural activity and its resulting hemodynamic response. In response to neural activity, there is an increase of blood flow and oxygen delivery (5,6). Because the oxygen utilization is far less than the amount delivered during blood volume changes, there is a net deoxyhemoglobin concentration decrease, resulting in the blood oxygenation-level dependent (BOLD) contrast response. This response is delayed in time by 4–8 sec and lasts far longer than its antecedent neural activity (7–9). However, as the delay and dispersion times are approximately known, this phenomenon may be used to advantage to capture the task-related signal long after task completion.

In the present method, the gradients were off during periods of task execution and then immediately switched on for image acquisition, effectively interleaving task performance and its detection with echo planar imaging (EPI). We call this the behavior interleaved gradients technique. In addition to this delay, the response is also temporally dispersed, with a brief burst of neuronal activity resulting in a hemodynamic response with a longer time scale. This delay and dispersion allows detection of task-related activity after its corresponding neural activity has ceased. In this study, we used a simple motor task, known to produce robust signal changes, to compare the interleaved data acquisition approach with more conventional techniques in which image data acquisition and task performance are concurrent.

MATERIALS AND METHODS

Six right-handed control subjects (five females and one male; mean age 28 years, range 24–33 years) participated in this study. Hand dominance was determined with the

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Edinburgh Handedness Inventory (10). Exclusion criteria included any significant medical or neurological illness, history of drug abuse, or any first-degree relatives with significant neurological disease. Women participating in this study were not pregnant, and subject screening included exclusion for susceptibility to claustrophobia, presence of a cardiac pacemaker, surgical clips, or other metallic implants. Written informed consent was obtained following procedures approved by the Georgetown University Medical Center Institutional Review Board. Subjects lay supine in the bore of the magnet. A right-angled mirror mounted on the head coil provided a clear view of a rear projection screen suspended in the magnet opening. Each individual performed an externally paced finger movement task known to induce large signal changes in motor areas. This task involved moving the index finger of the dominant hand at a rate paced by the presentation of a large flashing green star. Finger movement alternated with periods of rest, during which the subject viewed a red star, flashing at the same rate.

Data Acquisition

We employed multi-slice EPI acquisition on a 1.5 T Siemens Vision System. EPI acquisition parameters were as follows: 43 msec echo time (TE), 12 sec repetition time (TR), 64 × 64 matrix, 256 mm field of view (FOV) with 40 interleaved slices of 4 mm thickness. These parameters allowed coverage of the entire brain with 4 mm cubic voxels. Each of the four task conditions is described in Fig. 1.

Fifty-one time points (brain volumes) were obtained per run (one task condition per run), and the first time point was discarded. All four runs lasted 10 min, and each run was repeated in a second scanning session on another day. The task order was counterbalanced within and between subjects.

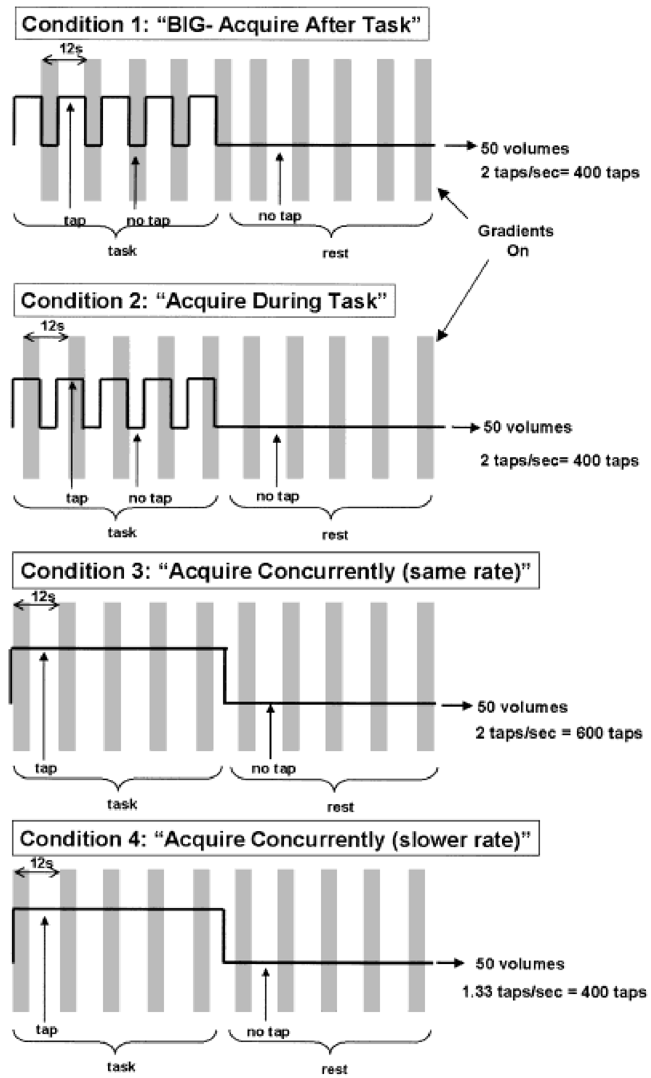

FIG. 1. Task descriptions.

Condition 1: Acquire After Task

This is the *behavior interleaved gradients* condition. Data acquisition occurred after completion of the task. Subjects made finger movements at 2 Hz for an 8-sec period during which no data was acquired, followed by a 4-sec interval of no movement during which one whole-head volume was acquired. This condition resulted in data acquisition after the initiation and maximization of the hemodynamic response. Subjects performed the task over a silent 8-sec period and only heard gradient noise after completing the requested task, in this case finger movement. In each task block, this 12-sec trial was repeated 5 times, yielding 5 data points per minute. Next, a 1-min rest period would occur during which subjects would only see the flashing red star. Again, one brain volume was acquired every 12 sec until 5 rest volumes were collected. These 1-min blocks of rest and task were alternated until 50 volumes (25 in each condition) had been acquired. The delay of 8 sec between finger movement initiation and data acquisition initiation allowed data collection during the hemodynamic response peak.

Condition 2: Acquire During Task

Subjects alternated between movement and rest as in Condition 1, but image data acquisition began during the 2nd half of the movement period (i.e., as in Condition 1 but with the data acquisition shifted forward by 4 sec). This condition was employed as a control for Condition 1, with data acquisition beginning sooner after movement initiation (Fig. 1). Task-related activation in this condition was anticipated to be less strong, because the hemodynamic response peak was not yet reached when data acquisition began.

Condition 3: Concurrent Acquisition With Same Movement Rate

In this condition, data acquisition was concurrent with task performance. The same data acquisition parameters were used, including a 12-sec TR period. In contrast to the first two conditions, a traditional block design of alternating task and rest epochs was used. Subjects would generate finger movements continuously over the entire minute of the task period, followed by a 1-min rest period. Comparison of these results with the behavior interleaved gradients technique (Condition 1) revealed whether this latter, quieter method would produce the same task-related change. Even though the movement rate was the same in Conditions 1 and 3, a larger total number of movements (600 vs 400) occurred in Condition 3 because the subjects paused for one-third of the time during image acquisition in the behavior interleaved gradients condition. To control for this difference in the overall number of movements produced at this rate, a slower rate condition was introduced.

Condition 4: Concurrent Acquisition With Slower Movement Rate

This condition was similar to Condition 3, except that the finger movement rate was reduced to 1.33 Hz to yield the same total number of movements per run as in Conditions 1 and 2 (400 movements over 10 min).

Data Analysis

All eight runs per subject underwent the processing described below using MEDx (Sensor Systems, Sterling, VA), resulting in eight statistical maps for each subject.

Head Motion Detection and Correction

Head motion was estimated by computing the motion of the center-of-intensity of each image volume and corrected in all subjects using the re-registration algorithms developed by Woods et al (11,12).

Volume Intensity Normalization

Global intensity variations were corrected with global image intensity rescaling, performed by computing the ratio relating the mean image intensity in a particular volume to the mean intensity of a reference volume. Voxel intensities were rescaled by multiplication such that the mean of the newly created volume matched that of the reference volume.

Baseline Correction

Signal fluctuations may arise from slow, head translations that are incompletely corrected by the head motion re-registration step. They were removed by linear detrending, a process that removes the linear component of the signal intensity time series of each voxel.

Spatial Filtering

Next, a three-dimensional Gaussian filter (full-width at half-maximum 12 mm in all dimensions) was applied to each volume in the time series. This has the effect of reducing image noise and optimizing the detection of task-related activations to areas 12 mm in diameter, such as the hand area of primary motor cortex.

Statistical Map Construction

Task-related changes in signal were detected by comparing scans acquired under each of the four different task conditions with their respective rest condition. T-statistic and percent-difference maps were computed for each of the four experimental conditions contrasted with the common-baseline control task (rest). Next, the resulting statistical volume was converted to a probability volume by estimating the correct number of degrees-of-freedom for that time series and then computing the corresponding probability for that location. The estimation of degrees-of-freedom is strongly influenced by the temporal auto-correlation in the time series, which increases with decreasing TR (13). In the present case, with a relatively long TR of 12 sec, the resulting correction was negligibly small and was neglected. For comparison with other statistical tests, the resulting probability volume was converted to a Z-score volume, by determining that probability's location on a Gaussian distribution. From these statistical maps the following derivative response measures were generated: a) the mean Z-score in the MI (primary motor cortex) cluster, b) the spatial extent of the MI cluster, c) the peak Z-score in MI, and d) the corresponding percent signal change at this local maximum in MI.

Local Maxima Detection

Local maxima and their corresponding clusters were determined by searching each statistical volume for local maxima. The constraint on distance between adjacent maxima was that there must be at least 3 voxel-widths between maxima. The spatial extent of each cerebral activation was determined by allowing a cluster to ‘‘grow’’ around each maximum to a predetermined critical threshold ($P < 0.001$). The probability that the cluster arose by chance alone was reported if it exceeded a threshold of $P < 0.10$ (14). The procedure allowed hypothesis testing accounting for the spatial extent of a task-related activation.

Visualization of Structure/Function Correlation

We spatially registered the statistical maps to a high-resolution structural volume from the same subject, to identify the neuroanatomical localization of the observed activations. The time course of significant voxels was examined for confirmation of the task-related nature of the activity identified by the statistical techniques.

RESULTS

All subjects were able to complete the task in all conditions. Examination of the structure/function maps in all subjects revealed task-related changes in primary motor cortex and anterior cerebellum. Signal changes in all subjects were highest in primary motor cortex (MI) in the left hemisphere. For comparison of the four conditions with one another, only the task-related signal changes in MI were examined, as they were easily quantified in all runs from all subjects.

Repeated measures ANOVAs using the multivariate approach (15) were conducted for the four dependent variables (mean Z-score, peak Z-score, percent change, and cluster size), and the peak-to-peak head motion in X, Y, and Z dimensions. The two repeated factors were CONDITION [1, behavior interleaved gradients; 2, acquisition during task; 3, acquisition concurrently at 2 finger movements/sec (same rate); 4, acquisition concurrently at 1.33 movements/sec (slower rate); and REPETITION (scan, rescan)]. As

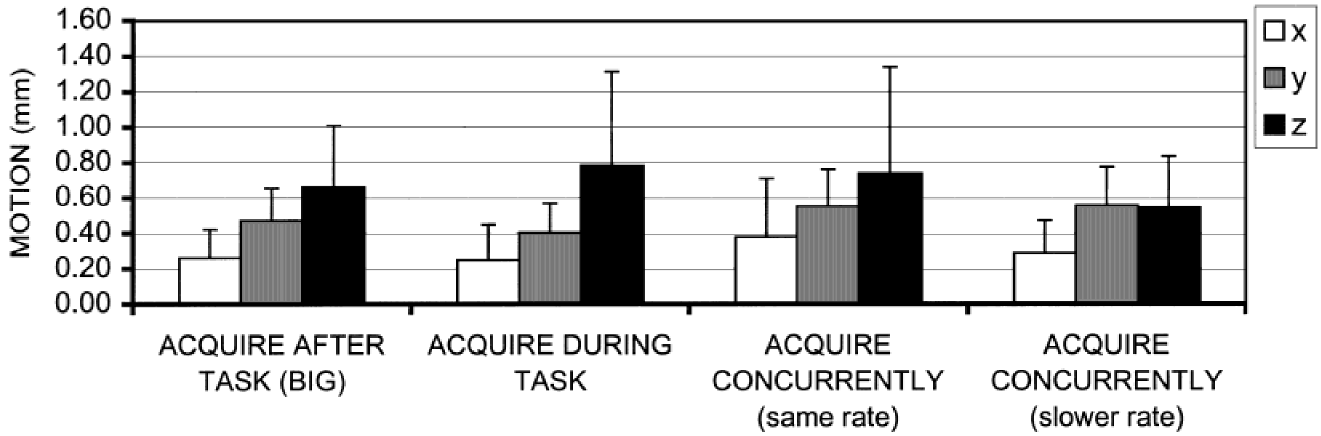

FIG. 2. Head motion in X,Y, and Z across the different experimental conditions. Each bar represents the mean peak-to-peak estimated head motion for all subjects in mm + 1 standard deviation.

suggested by Hertzog and Rovine (16), we used the adjusted degrees of freedom univariate tests rather than the multivariate tests because we had a small sample size ($n = 6$) and two estimates of epsilon were greater than 0.49. Planned contrasts comparing all conditions with the silent condition were conducted in all analyses.

Effect of Task on Head Motion

Variation in head motion could directly affect the significance values of task-related changes measured, and this would confound any differences observed between the acquisition conditions. Specifically, increased head motion in one condition could lead to apparently lower task-related change in that condition compared with conditions with less motion. Figure 2 illustrates the mean peak-to-peak head motion in the horizontal (X), anterior-posterior (Y), and inferior-superior (Z) direction for each of the tasks. In all tasks, head motion was confined predominantly to the Y and Z plane, a result typical for experiments conducted with minimal head restraint (17). No main effects or interactions were significant for head motion in the X- or Z-plane. In the Y-plane, although the main effect of condition was significant, $F(3, 15) = 5.4$, $P = 0$ .01, comparisons of Conditions 3 and 4 with 1 were not. The main effect of REPETITION and the CONDITION × REPETITION interaction were not significant, indicating that there were no differences between scan and rescan. Of relevance for the interpretation of results comparing the four conditions, it is important to note that there was not significantly less head movement in the behavior interleaved gradients task compared with its controls. Therefore, reduced head motion cannot be invoked as an explanation for the higher Z-scores observed in this condition.

Effect of Condition on Task-Related Signal Changes

As there is still debate concerning the optimal quantitative measure of cerebral activation in functional neuroimaging studies, we examined four different measures of task-related activity: a) the mean Z-score in the MI cluster, b) the spatial extent of the MI cluster, c) the peak Z-score in MI, and d) the corresponding percent signal change at this local maximum in MI. The *mean Z-score* for the cluster of activity in MI for the group in each condition is shown in Fig. 3.

The main effect of CONDITION was significant, $F(3, 15) = 6.2$, $P = 0.006$, with Condition 1 (behavior interleaved gradients technique) producing higher mean Z-scores than Condition 3, $F(1, 5) = 12.9$, $P = 0.0156$, and Condition 4, $F(1, 5) = 10.6$, $P = 0.0226$. The slightly higher Z-score for Condition 1 compared with Condition 2 was only marginally significant, $F(1, 5) = 5.4$, $P = 0.0681$. The main

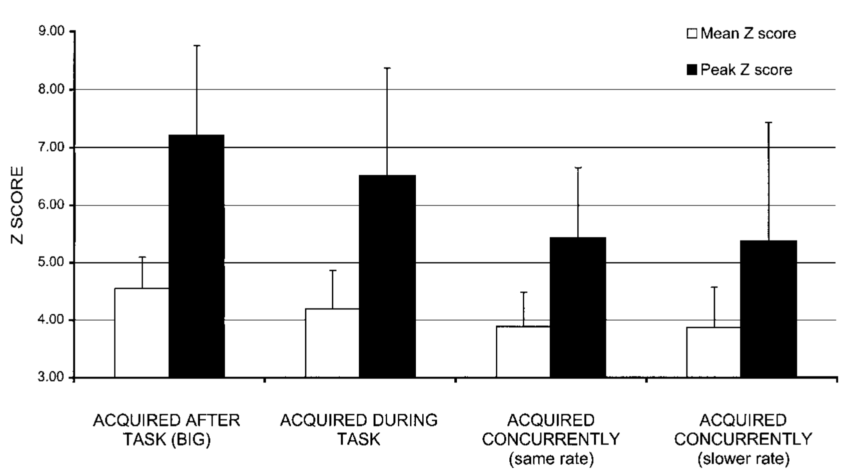

FIG. 3. Peak and mean Z-score values for MI cluster across the four experimental conditions.

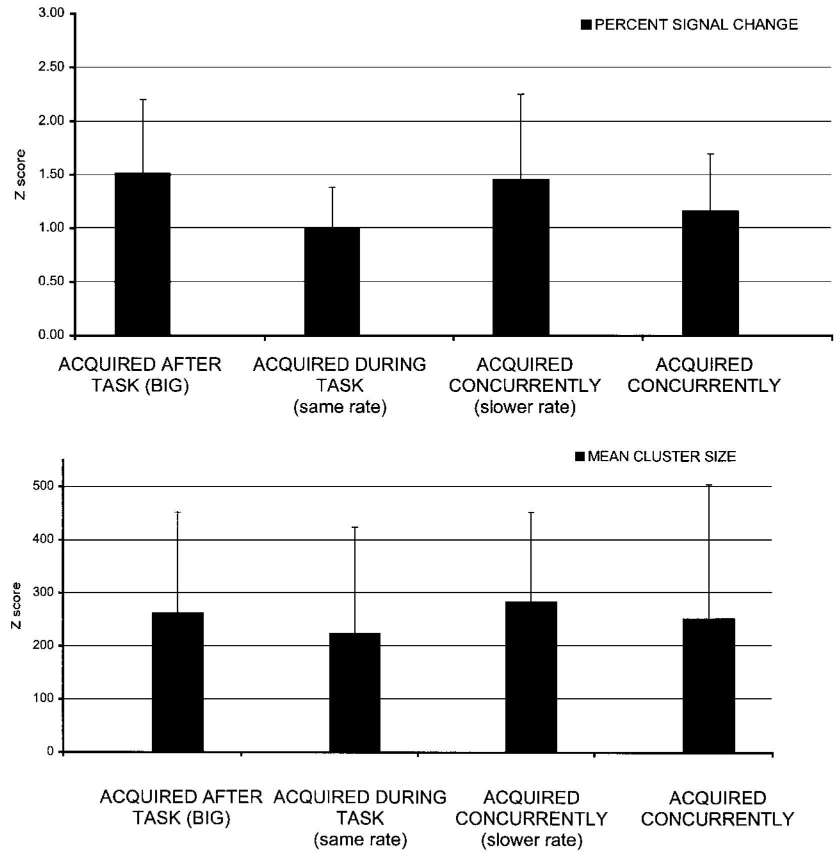

FIG. 4. Percent-change in single voxel (top) and cluster size (bottom) for MI across the four experimental conditions.

effect of REPETITION was not significant, nor was the CONDITION × REPETITION interaction. For *cluster size*, no main effects or interactions were significant (Fig. 4). Therefore, there was no effect on the spatial extent of voxels with values above the critical threshold. For *peak Z-score* (single voxel significance, Fig. 3) the main effect of CONDITION was significant, $F(3, 15) = 6.7$, $P = 0.004$. Condition 1 (behavior interleaved gradients) produced higher peak Z-scores than Condition 2, $F(1, 5) = 15.4$, $P = 0.0111$, Condition 3, $F(1, 5) = 12.3$, $P = 0.0171$, and Condition 4, $F(1, 5) = 10.9$, $P = 0.0214$. Neither the main effect of REPETITION nor the CONDITION × REPETITION interaction were significant. For *percent signal change* (in a single voxel Fig. 4) the main effect of CONDITION was not significant. Again, neither the main effect of REPETITION nor the CONDITION × REPETITION interaction were significant.

In summary, the results revealed higher Z-score values in the behavior interleaved gradients condition compared with the other conditions when examining single voxels or voxel clusters. Task-related signal changes in primary motor cortex were similar or higher when data acquisition occurred after the task completed. This is illustrated in Fig. 5, which depicts signal-change from a single voxel in the same individual across the four acquisition conditions.

DISCUSSION

Although the existence of hemodynamic delay and dispersion is usually said to limit temporal resolution in functional neuroimaging studies, these phenomena allow the interleaving of data acquisition and behavior, as described in this paper. This interleaved arrangement permits task performance under relatively quiet experimental conditions with little acoustic interference. Because the hemodynamic response builds as the neuronal activity associated with task performance continues, 8-sec task performance periods were sufficiently long to yield excellent statistical results. By limiting data acquisition to a period 8 sec after task performance initiation, we were likely to detect maximal task-related hemodynamic responses.

There is no clear consensus concerning the optimal dependent measure for detection of task-related activity. For this reason we examined the effects of different acquisition procedures on task-related activity in MI using four different measures of response. The behavior interleaved gradients image acquisition procedure yielded significantly larger task-related signal changes in peak and mean Z-score compared with concurrent data acquisition conditions. This result might be expected, as the acquisition timing coincided with the temporal peak of the hemodynamic response. As the different acquisition procedures were not likely to recruit different volumes of cortex, the spatial extent of activated cortex in MI was not significantly different.

Rate Dependence

Using behavior interleaved gradients, the time spent in performance of the task of interest is reduced, raising the possibility that the difference between results in this condition and others is due to a rate dependence. There were no significant differences in fMRI signal when the frequency of tapping was reduced from 2 to 1.33 Hz,

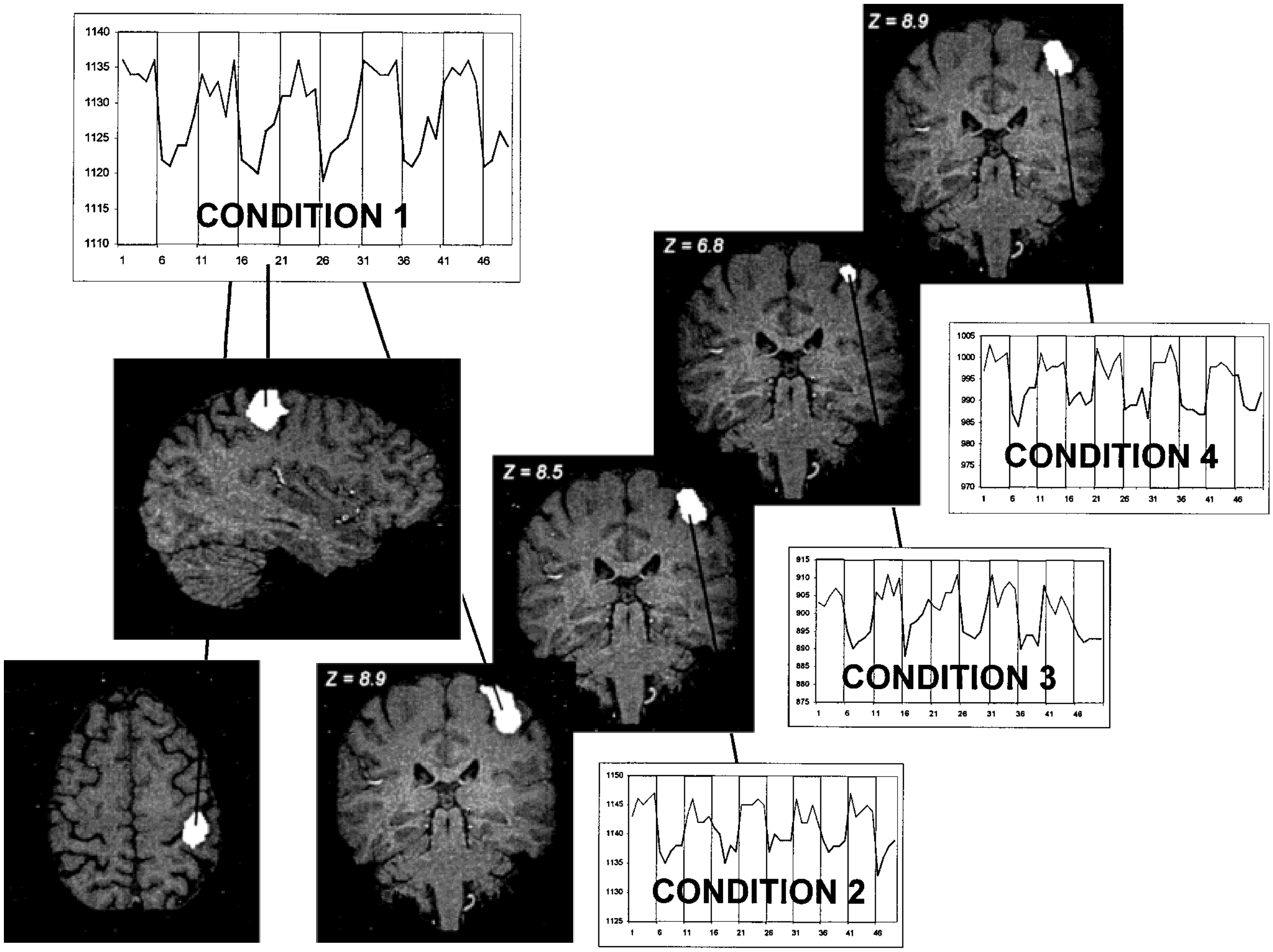

FIG. 5. Signal change in MI in all task conditions in one individual. Task-related signal change is presented in the maximally activated single voxel.

demonstrating that any differences observed between interleaved and concurrent data acquisition could not be explained by rate variation. It may be surprising that there was no noticeable difference between the two concurrent acquisition methods that varied in rate (Conditions 3 and 4). Parametric variation of movement rate has been shown to result in a linear increase in regional cerebral blood flow or BOLD signal in contralateral primary motor cortex (18,19). This linear modulation has been examined in movements that occurred between 0.5 and 5 Hz. It is plausible that the range of rates employed in the present study (between 2.00 and 1.33 Hz) were too small to cause detectable change. It is also possible that there was response habituation with concurrent acquisition (Conditions 3 and 4). When using interleaved gradients, subjects alternate more frequently between rest and task. This may result in less response habituation and therefore greater task-related signal changes.

Origins of Greater Sensitivity

While the interleaved technique produces excellent statistical maps, which are comparable to or better than those derived using conventional methods, it is important to consider the basis of this result. One might expect that reduced head motion would result in less misregistration of images from different points in the time series and therefore higher resulting Z-scores. In our estimates of head motion there was no difference in displacement across the four conditions. Therefore, variation in motion artifact is unlikely to explain the relatively larger signal changes seen in the interleaved condition. As discussed previously, the present technique employs a longer TR, which results in increased sensitivity to small signal changes due to the improved contrast-to-noise ratio that occurs with longer TR intervals. Since all four conditions employed the same acquisition parameters, the effect of the longer TR cannot explain the better results seen with interleaved gradients. However, frequent alternation of task and rest in the interleaved technique could account for the excellent quality of the data. By interleaving breaks at every third portion of the cycle (8 sec of task alternated with 4 sec of acquisition during which the task-performance ceased), the possibility of task habituation is reduced.

Motion-Induced Susceptibility Artifacts

Another major advantage of the interleaved technique is that susceptibility artifacts from jaw motion can be reduced. Experimental designs requiring verbal responses are necessarily associated with jaw movements that can induce noticeable susceptibility artifacts in medial and inferior temporal cortical regions. As these areas are involved in language, it is obvious that jaw motion can generate potentially serious image artifacts in regions that would be expected to show task-related signal change. Speech responses are also likely to cause head motion. This results from the mechanical coupling of the jaw and skull such that relatively small jaw movements can result in large translational movements of the skull. Since even small amounts of interscan motion in a time series can result in large artifacts in statistical maps derived from that series, it is best to take precautions to minimize head motion (17). Failing that, there are a number of post-hoc image processing approaches that can partially reduce the effects of interscan motion in a time series of EPI volumes (11,12,20). Using the behavior interleaved gradients technique, the subject's speech response occurs prior to image data acquisition, minimizing this source of artifact.

To illustrate a direct practical application of this method, Fig. 6 shows our implementation of the behavior interleaved gradients technique in a reading study. The goal in this case is to reduce the problem of induced susceptibility artifacts due to head and jaw movements. The use of verbal responses is an important issue in understanding language processing, because evidence from PET studies indicates that covert and overt responses engage different neural processing systems (21,22). Results from a single subject are shown for the comparison of reading words silently versus fixation (bottom) and reading words aloud versus fixation (top). The interleaved acquisition mechanism ensures that jaw movement does not occur during data acquisition and results in reduced susceptibility artifact in the resulting statistical maps. The data show that overt and covert reading not only make different demands on the inferior frontal gyrus, as might be predicted, but there are also noticeable differences in visual cortex and temporal lobes between these two tasks.

Relationship to Other Single-Trial Techniques

Behavior interleaved gradients acquisition techniques are members of the larger class of evoked hemodynamic response techniques, also referred to as single-trial fMRI techniques (23). In comparison with other single-trial approaches, the behavior interleaved gradients technique uses a longer TR and therefore has greater signal contrast and potentially greater sensitivity to small task-related signal changes. For similar reasons, the interleaved technique has limited temporal resolution and is optimal for experimental designs requiring imaging of the entire brain at a relatively low sampling rate of 5/min or less. Three to four seconds are required to image the entire brain utilizing EPI. As the hemodynamic response to a brief movement takes 10 sec to complete (24), it is possible to image the entire cerebrum during the peak hemodynamic response period. An additional advantage of single-trial techniques not explored in the present study is the ability to avoid subject expectation effects by randomizing the order of different trial types.

CONCLUSIONS

These results demonstrate that the behavior interleaved gradients technique may be used to acquire functional neuroimaging data in a relatively quiet environment, with no compromise in sensitivity to task-related signal changes. Implementation of interleaved gradients is cost effective, as it requires no additional hardware or other equipment.

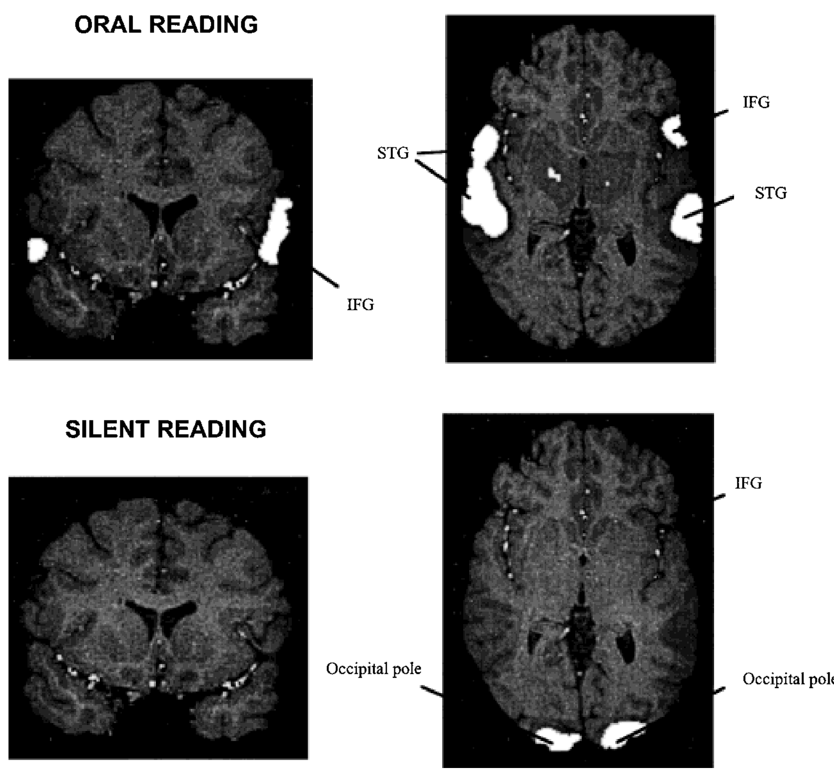

FIG. 6. Activation in one of the subjects acquired with the behavior interleaved gradients technique. The task in this case is (bottom) silent word reading and (top) reading aloud. Resulting Z-maps and task-related signal change illustrate the feasibility of utilizing BIG in overt language studies. IFG, inferior frontal gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus.

We expect this technique to be very useful when the experiment requires maximal acoustic isolation of the subject. It also promises to be advantageous when speech is required, given that articulation (and its attendant motion artifacts) will not occur during periods of data acquisition. The behavior interleaved gradients technique will allow study of language mechanisms that have not been investigated due to constraints imposed by the MR environment. Improved sensitivity is possible with tasks associated with rapid habituation. The more frequent alternation between task and rest may reduce response habituation and thereby maximize the neuronal activity associated with task performance.

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REFERENCES

1. Cho ZH, Chun SC, Lim DW, Wong EK. Effects of the acoustic noise of the gradient systems of fMRI: a study on auditory, motor, and visual cortices. Magn Reson Med 1998;39:331–336.
2. Bandettini PA, Jesmanowicz A, Van Kylen J, Birn RM, Hyde JS. FMRI of scanner-induced auditory cortex activation. In: International Conference on Functional Mapping of the Human Brain. 1997. p 193.
3. Scheffler K, Bilecen D, Seelig J. In: Proceedings of the International Society of Magnetic Resonance in Medicine. 1997. p. 1689.
4. Scheffler K, Bilecen D, Schmid N, Tschopp K, Seelig J. Auditory cortical responses in hearing subjects and unilateral deaf patients as detected by functional magnetic resonance imaging. Cereb Cortex. 1998;39:156–163.
5. 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. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci USA 1992;80:5675–5679.
6. Ogawa S, Tank DW, Menon R, Ellerman JM, Kim S-G, Merkle H, Urgubil K. Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping using MRI. Proc Natl Acad Sci USA 1992; 89:5951–5955.
7. Belliveau JW, Kennedy DN, McKinstry RC, Buchbinder BR, Weisskoff RM, Cohen MS, Vevea JM, Brady TJ, Rosen BR. Functional mapping of the human cortex by magnetic resonance imaging. Science 1991;254: 716–719.
8. Blamire AM, McCarthy G, Gruetter R, Rottman DL, Rattner Z, Hyder F, Shulman RG. Echo planar imaging of the left inferior frontal lobe during word generation. In: Proceedings of the Eleventh Annual Meeting of the Society of Magnetic Resonance in Medicine, p. 1834.
9. Frahm, J, Bruhn H, Merboldt K-D, Hanicke W. Dynamic MRI of human brain oxygenation during rest and photic stimulation. Magn Reson Imaging 1992;2:501–505.
10. Oldfield RC. The assesment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia 1971;9:97–113.
11. Woods RP, Grafton ST, Holmes CJ, Cherry SR, Mazziotta JC. Automated image registration: I. J Comput Assist Tomogr 1998;22:139–152.
12. Woods RP, Grafton ST, Watson JD, Sicotte NL, Mazziotta JC. Automated image registration: II. J Comput Assist Tomogr 1998;22:153–165.
13. Friston KJ, Jezzard P, Turner R. Analysis of functional MRI time-series. Hum Brain Map. 1994;1:153–171.
14. Poline JB, Worsley KJ, Evans AC, Friston KJ. Combining spatial extent and peak intensity to test for activations in functional imaging. Neuroimage 1997;5:83–96.
15. O'Brien R, Kaiser M. MANOVA method for analyzing repeated measures designs: an extensive primer. Psychol Bull 1985;97:316–333.
16. Hertzog C, Rovine M. Repeated-measures analysis of variance in development research: selected issues. Child Dev 1985;56:787–809.
17. Green MV, Seidel J, Stein SD, Tedder TE, Kempner KM, Kertzman C, Zeffiro TA. Head movement in normal subjects during simulated PET brain imaging with and without head restraint. J Nucl Med 1994;35: 1538–1546.
18. VanMeter JW, Maisog JM, Zeffiro TA, Hallett M, Herscovich P, Rapaport SI. Parametric analysis of functional neuroimaging: application to a variable-rate motor task. Neuroimage 1995;2:273–283.
19. Rao SM, Bandettini PA, Binder JR, Bobholz JA, Hammeke TA, Stein EA, Hyde JS. Relationship between finger movement rate and functional magnetic signal change in human primary motor cortex. J Cereb Blood Flow Metab 1996;16:1250–1254.
20. Zeffiro TA, Eden GF, Woods RP, VanMeter JW. Intersubject analysis of fMRI data using spatial normalization. Adv Exp Med Biol 1997;413:235–240.
21. Bookheimer SY, Zeffiro TA, Blaxton T, Gaillard W, Theodore W. Regional cerebral blood flow during object naming and word reading. Hum Brain Map 1995;3:93–106.
22. Price CJ, Wise RJS, Watson JDG, Patterson K, Howard D, Frackowiak RSJ. Brain activity during reading: the effects of exposure duration and task. Brain 1994;117:1255–1269.
23. Buckner RL, Bandettini PA, O'Craven KM, Savoy RL, Peterson SE, Raichle ME, Rosen BR. Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. Proc Natl Acad Sci USA 1996;93:14878–14883.
24. Kim SG, Ashe J, Hendrich K, Ellermann JM, Merkle H, Ugurbil K, Georgopoulos AP. Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. Science 1993;261:615–617.