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Experimental designs and processing strategies for fMRI studies involving overt verbal responses

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Event-related paradigms have been used increasingly in the past few years for the localization of function in tasks involving overt speech. These designs exploit the differences in the temporal characteristics between the rapid motion-induced and the slower hemodynamic signal changes. The optimization of these designs and the best way to analyze the acquired data has not yet been fully explored. The purpose of this study is to investigate various design and analysis strategies for maximizing the detection of function while minimizing task-induced motion artifacts. Both event-related and blocked paradigms can be specifically designed to meet these goals. Various event-related and blocked designs were compared both in simulation and in experiments involving overt word reading in their ability to detect function and to avoid speech-induced motion artifact. A blocked design with task and control durations of 10 s and an event-related design with a minimum stimulus duration (SD) of 5 s and an average interstimulus interval (ISI) of 10 s were found to optimally detect blood oxygenation level-dependent signal changes without significant motion artifact. Ignoring images acquired during the speech can help recover function in areas particularly affected by motion but substantially reduces the detection power in other regions. Using the stimulus timing as an additional regressor to model the motion offers little benefit in practice due to the variability of the motion-induced signal change.
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Introduction

The ability for a subject to speak out loud during fMRI time series collection is of significant utility in the study of brain function. In addition to the study of brain systems subserving the production of speech and processing of language, many studies would benefit from having the subject vocalize a response since vocalization can provide substantially more precise and information-rich feedback than button box responses in the context of language tasks. Since there is no animal model that can adequately represent the complex task of language production, the need for a noninvasive imaging method, such as functional MRI, to assess language production is clear. The difficulty with speaking in the MR scanner in these tasks is that the repositioning of the head, jaw, tongue, and facial muscles during speech lead to distortions and misregistration in the time series MR images (Barch et al., 1999; Binder, 1995; Birn et al., 1998, 1999a,b). These artifactual signal changes can both mask and mimic the blood oxygenation level-dependent (BOLD) signal changes associated with neuronal activity, making detection and localization of speech-related brain activation difficult.

A number of solutions have been proposed to overcome this problem. The most common approach has been to eliminate the motor component of speech in the tasks, relying instead on silent word production (Binder, 1995; Buckner et al., 2000). Huang et al. (2002) have found reduction of motion artifacts when subjects are trained to reduce speech associated head movements prior to the actual scan, and Small et al. (1996) have obtained reasonable results when head movement was severely restricted by using a bite bar.

Each of these techniques has its limitations in studies involving overt speech. While silent word production certainly reduces the occurrence of motion artifacts, overt word production could certainly involve the activation of additional brain regions not active during silent word processing (Barch et al., 1999; Huang et al., 2002; Palmer et al., 2001). Additionally, the restriction on speaking out loud may not be psychologically or behaviorally appropriate for the particular task being studied, for example, if the task requires the subject to receive feedback from the vocalization of the words or when it is necessary to record the subject's verbal response. Postprocessing of images using rigid-body image registration techniques cannot remove all of the image distortions arising from speaking since the movement of the subject's head, jaw, tongue, and facial muscles also causes changes in the magnetic field. These magnetic field changes cause a warping of

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the image in the phase encode direction (for echo-planar acquisitions) or a blurring of the image (for spiral acquisitions). This distortion can be significant, especially in slices in the inferior region of the brain, leading to signal changes of anywhere from 5% to 100% (Birn et al., 1998; Yetkin et al., 1996). Since this warping is not necessarily uniform across the image, the 'apparent' motion cannot be corrected using rigid-body image registration routines. Dynamic correction of magnetic field changes would require continuous acquisition of magnetic field maps throughout the imaging run. This requires a modification of existing imaging sequences and is susceptible to physiologically induced phase variations. Training of subjects prior to the scan can reduce, but not completely eliminate, speech-related movement artifacts since the movement of the jaw, tongue, and facial muscles are inherent to word production.

More recently, studies have begun to use event-related fMRI designs to separate the effects of motion from the neuronal-induced BOLD signal changes (Barch et al., 1999; Birn et al., 1999a,b; Burgund et al., 2003; Huang et al., 2002; Palmer et al., 2001; Preibisch et al., 2003). The key to these methods is the difference in the temporal dynamics of motion-induced and hemodynamic signal changes arising from the difference in the physical mechanisms producing these changes. The BOLD response is delayed in onset by several seconds and increases to a peak value 5–6 s after the initiation of a task. In contrast, motion-induced signal changes for tasks such as overt word production, jaw clenching, tongue movement, or swallowing occur primarily during the task performance. If the task is performed only briefly, such as in an event-related paradigm, then the signal changes resulting from motion occur prior to and have a much different temporal shape than the delayed BOLD signal changes.

In the simplest case, overt speech can be performed for brief periods, separated by periods of time sufficiently long to allow for the full evolution of the hemodynamic response (Birn et al., 1999a,b). The motion-induced signal changes appears as a rapid increase or decrease in the MR signal, concomitant with the speech production. These artifactual signal changes usually occur in less than a second, much more rapidly than the slower hemodynamic response. This difference in the temporal delay and shape between the motion-induced and BOLD signal changes can then be exploited either by ignoring the images occurring during the motion or by modeling the signal as a sum of the stimulus timing (representing the motion-induced changes) and the slower ideal hemodynamic response. A predominant drawback with event-related techniques using constant interstimulus intervals is that tasks are limited to brief periods of word production, separated by long rest periods, which may not be appropriate for all psychological studies. Since the signals from brief stimuli are so small, the task must be repeated numerous times to reach sufficient functional contrast to noise, leading to long acquisition times if long interstimulus intervals are required. The hemodynamic response must also be sampled quickly enough to allow discrimination against motion-induced signal changes, limiting the TR and hence the number of slices that can be acquired.

Successful functional imaging during more rapid speech is possible by employing an event-related design with a varying interstimulus interval (ISI) (Birn et al., 1999a,b). The success of this type of design was recently demonstrated by Palmer et al. (2001) in a word stem completion task. In this study, localization of function without significant motion artifacts was achieved without explicitly modeling the motion in their analysis. The effectiveness of this strategy is based on the fact that the model hemodynamic responses of these designs have a low intrinsic correlation with the motion-induced signal changes. As a result, a linear fit of the model hemodynamic response to voxel time series will contain only a very small component of the motion-induced signal.

A key principle is that stimulus time courses can be specifically designed to minimize the correlation between anticipated motion-induced and BOLD signal changes. This minimization can also be employed for a block design, where the duration of the task and control periods can be designed such that the correlation between the stimulus timing (which is quite similar in character to the expected motion-induced signal change) is orthogonal to the expected hemodynamic response. A question that therefore arises is which stimulus design is optimal in the sense of reducing sensitivity to task-related motion and maximizing detection of BOLD signal changes. The purpose of this paper is to develop a framework for designing optimal stimulus paradigms and evaluate different analysis strategies to provide motion artifact-free functional activation maps during task-induced motion, such as overt speaking. Several different stimulus designs and analysis strategies are presented and compared in terms of their sensitivity to motion and detection power, first in simulation, and finally in experiments involving overt word production.

In the first section of this paper, the effects of motion-induced signal changes in fMRI using both blocked and event-related stimulus designs with both constant and varied ISI are simulated. Two quantities of interest are computed: (1) the correlation between motion-induced and BOLD signal changes (leading to false-positives in signal detection), and (2) the efficiency of the design to detect BOLD signal changes both in the presence and in the absence of motion-induced signal changes (an assessment of the true-positives and false-negatives). The efficiency of the design optimal for minimizing the detection of motion-induced signal changes will be compared to the efficiency of the design optimal for detection of function in the absence of motion artifacts; the latter has been the subject of several recent studies (Birn et al., 2002; Dale, 1999; Friston et al., 1999; Liu et al., 2001). In the second part of this paper, experiments involving an overt word generation task are performed using a blocked design and an event-related design with either a constant or a varying ISI, and the sensitivity to motion and detection power of BOLD activation are compared.

Methods

Simulations

The effectiveness of various stimulus timing designs in reducing the false-positives and increasing the correct detection of BOLD signal changes was first tested by a series of simulations. Three types of paradigms were assessed: (1) a blocked design with equal task and control periods; (2) an event-related design with a constant interstimulus interval (ISI) and stimulus duration (SD); and (3) an event-related design with varying ISIs and varying SDs. A task block was considered to consist of repeated task performances (one at each imaging repetition time; TR), analogous to speaking several words. Task events always occurred at even multiples of the TR. A TR of 1 s and a time course duration of 300 s was used for all simulations.

A range of stimulus timing parameters (ISI and SD) were tested for each paradigm, spanning values that would realistically be used in an experimental design. In the blocked design, task and control conditions (of equal durations) were varied between 2 and 63 s. In the event-related design with a constant ISI, the ISI (defined as the duration from the beginning of one stimulus to the beginning of the next stimulus) was varied between 2 and 33 s. In the event-related design with a varying ISI, stimuli were generated with exactly half of the time points being in the task state and the other half in the control state. This ratio of task-to-control has been shown to be optimal for detecting functional signal changes (Birn et al., 2002; Friston et al., 1999; Liu et al., 2001). The order of the task and control states was completely randomized, resulting in a geometric distribution for the interstimulus interval. As an additional parameter, five different minimum stimulus durations were tested (1, 3, 5, 7, and 9 s). The longer minimum stimulus durations cause the random event-related designs to consist of longer blocks of task and control, more closely resembling a blocked design. It has been shown that these more blocked designs are more efficient at detecting functional activation than more rapidly varying designs, if a slow hemodynamic response is assumed in the detection (Birn et al., 2002; Friston et al., 1999; Liu et al., 2001). Thirty-two stimulus time courses were generated for each minimum stimulus duration. The range of parameter values tested was found to be sufficient to illustrate the dependence of the detection power and motion sensitivity on the minimum stimulus duration. Minimum stimulus durations longer than 9 s were not tested since these are expected to be even more sensitive to motion-induced signal changes.

Three types of signal changes are considered: (1) motion-induced signal changes in the absence of BOLD signal changes; (2) BOLD signal changes in the absence of motion-induced signal changes; and (3) a combination of motion-induced and BOLD signal changes. The first (purely motion-induced signal changes) allows testing of the likelihood of false-positives, the second (purely BOLD changes) can provide a measure of detection efficiency, and the third (combined BOLD and motion-induced signal changes) can provide an estimate of how much the detection power is reduced by the presence of motion.

Time courses representing motion were simulated as large spikes in the signal intensity at times coincident with the performance of the task. The amplitude of this motion-induced signal spike was a Gaussian random variable with a mean of 30% and a standard deviation of 10% of the baseline signal intensity. In other words, the motion-induced signal change varied for each task performance, with an average deviation from baseline of 30% (six times the maximal BOLD response in a blocked design). This level and variability of the motion-induced signal change used in the simulation was obtained in a separate experiment in one subject who was instructed to speak a monosyllabic word every 5 s (see Fig. 1). These values were used in the simulation as approximate levels of motion that might be expected in a task involving overt speech. The actual amount of movement observed is likely to be subject and scanning session dependent. The motion-induced signal change could therefore vary for each task performance during the block, as it would if a series of different words were spoken (see Fig. 2). One hundred and twenty-eight instances of motion-induced signal changes were simulated for each time course. Ideal BOLD signal changes were generated by convolving the task timing with a gamma variate function, with parameters according to Cohen (1997). This gamma variate rises to a peak of 5 s after a brief stimulus and returns to baseline after a further 6 s. These functions were scaled to 5% of the baseline signal. Gaussian white noise with a standard deviation equal to 0.5% of the baseline signal was added to each time course.

The possibility for motion to be classified incorrectly as functional activation in the different paradigms was tested by fitting the ideal BOLD response for each task timing to time courses representing signal changes purely due to motion. A high t statistic indicates that the motion-induced signal change can easily be mistaken as a BOLD signal change if no methods for dealing with the motion are employed. The t statistic of (falsely) detecting this simulated motion as functional activation (false-positive) was computed as

$$t = \alpha / \sigma_\alpha \tag{1}$$

where α is the amplitude of the fit of the ideal BOLD signal to the simulated time series, and σ_α is the standard deviation of this estimate. This standard deviation was computed as

$$\sigma_\alpha = \sqrt{\left(\mathbf{R}^T\mathbf{R}\right)^{-1}}\ \sigma_\eta \tag{2}$$

where $\mathbf{R}$ is a matrix whose columns are the regressors in the analysis, $(\mathbf{R}^\mathrm{T}\mathbf{R})^{-1}$ is the covariance matrix of the design, and σ_η is the standard deviation of the residual signal after the fitted BOLD response has been subtracted out. Since in this simulation no ideal BOLD response was present, a large t statistic signals a large false-positive rate.

It is also desirable to reduce the number of false-negatives in the analysis technique. These can occur when the efficiency of the design is low compared to the noise in the signal. In regions of the brain where there are both motion-induced and BOLD signal changes, detection is affected not only by the stimulus design, but also by the presence of motion-induced signal changes. The likelihood of false-negatives for the various paradigms was assessed by generating ideal BOLD responses in either the absence or presence of motion-induced signal changes and computing their detection efficiencies according to Eq. 1. The motion-induced and BOLD signal changes were generated as described above. For pure BOLD signal changes in the absence of motion, this detection efficiency is identical to that described in Birn et al. (2002). Designs with higher t statistics are better able to distinguish BOLD signal changes from noise; that is, a small t statistic in these simulations indicates a large false-negative rate. In the presence of motion, a low t statistic would indicate that the BOLD signals are easily corrupted by motion and would be more difficult to detect. Multiple instances of motion-induced signal changes were generated at each level of motion and the resulting correlation coefficients were averaged.

The detection of BOLD signal changes in the presence of motion can be improved by accounting for the motion in the detection process. One of the simplest methods to accomplish this is to ignore data at time points occurring during the motion. This works particularly well for event-related designs where the slower hemodynamic response is separated in time from the motion-induced signal changes. In a blocked design, all the images during the block are ignored, and the detection of function is based solely on the return of the signal to baseline following cessation of the task, a period of about 12 s. Detection efficiencies for the various designs were recomputed with this additional correction. A second approach is to incorporate a model of the motion-induced signal changes in the detection. The simplest model for motion-induced

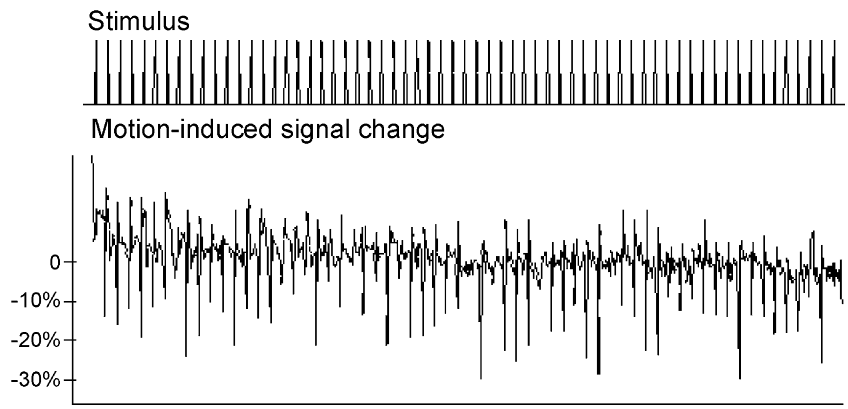

Fig. 1. Variability of motion-induced signal changes taken from a voxel near the edge of the brain in one subject when speaking one of the words "red," "yellow," "green," and "blue" every 5 s.

changes is the stimulus timing itself since movement-induced signal changes occur primarily during the task. This model is not exact since the amplitude of the motion-induced signal change can vary for each task performance.

Experiments

In the second part of the study, a set of experiments were performed to compare the various designs during an overt word production task. A series of words were presented to the subject at various timings using an LCD projector and a backprojection screen viewed via a mirror. Each of the words was chosen from a list of frequently used mono- and bisyllabic English words. Subjects were instructed to speak the displayed word out loud immediately after it was presented. Five task timings were assessed: (1) a blocked-trial paradigm with 30 s periods of a word presented and spoken every second alternated with 30 s periods of rest (Fig. 3a); (2) a blocked-trial paradigm with 10 s periods of repeated speaking (one word per second) alternated with 10 s periods of rest (Fig. 3b); (3) an event-related paradigm with a single word spoken every 15 s (Fig. 3c); (4) an event-related paradigm with variable ISI (an average ISI of 2 s and an minimum stimulus duration of 1 s; see Fig. 3d); and (5) an event-related paradigm with a variable ISI and longer blocks of activation and rest (an average ISI of 10 s and an minimum stimulus duration of 5 s; see Fig. 3e). The latter two paradigms were specifically designed to minimize sensitivity to motion and maximize the detection power of BOLD signal changes within the constraints of the stimulus generation parameters (ISI and minimum stimulus duration). This was done by selecting the stimulus time course in the simulation with a t statistic of falsely detecting motion less than 0.5 and the highest detection efficiency for a 1-s minimum stimulus duration (Fig. 3d) or for all minimum stimulus durations (Fig. 3e).

During these tasks, a series of 310 axial T2*-weighted echo planar images (EPI) was acquired on a 3-T GE Signa MR scanner (Waukesha, WI, USA) (TR: 1 s; TE: 30 ms; field of view: 24 cm; slice thickness: 5 mm; matrix size: 64 × 64). A brain-specific quadrature Medical Advances RF coil was used (Wauwautosa, WI, USA). A limited coverage of 8–12 slices was used, allowing a TR of 1 s in order to improve sampling of the hemodynamic response.

Data were analyzed by fitting the ideal hemodynamic BOLD response to each pixel's entire signal intensity time course. This multiple linear regression analysis was performed using Analysis of Functional NeuroImages (AFNI) software, including a regressor to model linear trends, or drifts, in the data (Cox, 1996). Rigid-body registration was performed to provide a measure of the amount of rigid-body motion, but the analysis was done primarily on the unregistered data in order to compare the effectiveness of different paradigm designs in reducing task-related motion. Signal time courses in the event-related paradigms were additionally deconvolved to estimate each voxel's impulse response function. These impulse response functions served as an

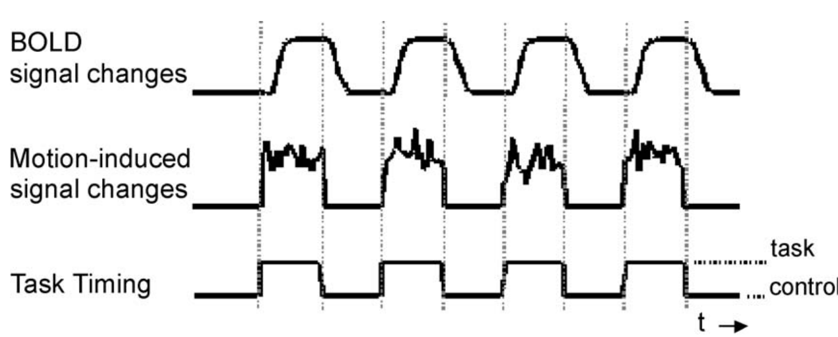

Fig. 2. Simulated BOLD signal changes and task-related motion-induced signal changes for a blocked design. A task block consists of repeated task performances, each of which produces the same BOLD response but different amounts of motion.

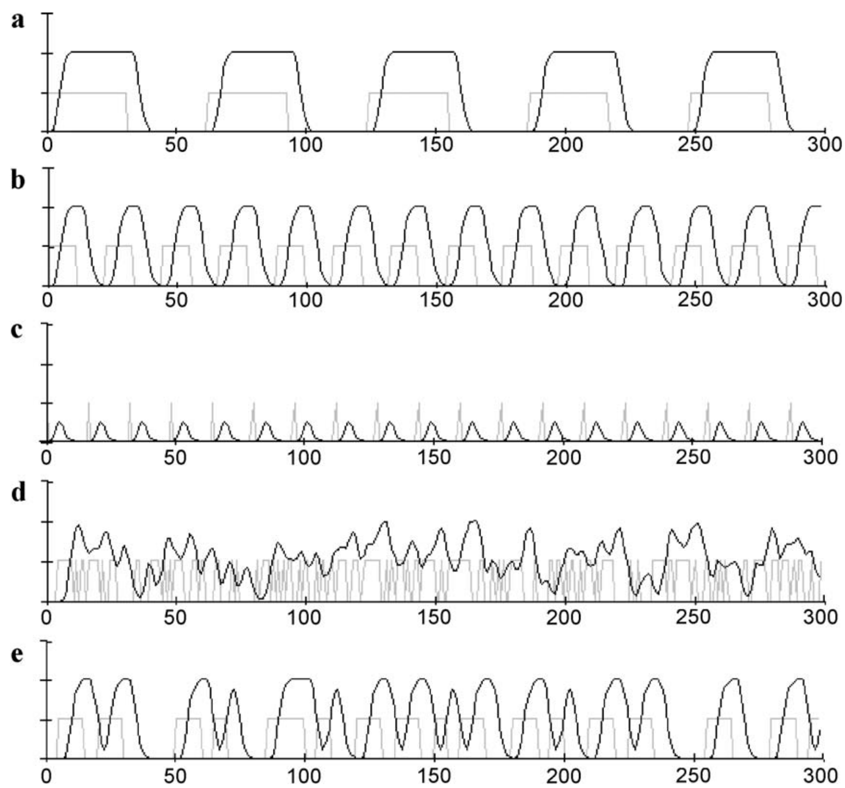

Fig. 3. Simulated task time courses (gray) and ideal BOLD responses (black) for various task timings: (a) blocked design with 30 s task periods; (b) blocked design with 10 s task periods; (c) event-related design with a constant interstimulus interval (ISI) of 15 s (one word spoken every 15 s); (d) event-related design with a varying ISI, a minimum stimulus duration (SD) of 1 s, and an average ISI of 2 s; and (e) an event-related design with a varying ISI, a minimum SD of 5 s, and an average ISI of 10 s. Stimuli d and e were designed such that motion-induced and BOLD signal changes were minimally correlated.

additional aid to visually discern motion-induced and BOLD signal changes and to validate the choice for the ideal BOLD response.

A quantitative measure of each paradigm's sensitivity to motion was obtained by computing the average of the absolute value of the t statistic of signals correlated with the ideal hemodynamic response at the edge and outside the brain. More specifically, a mask was created by thresholding the baseline signal intensity at 45% of the maximum signal (see Fig. 4). In order to avoid the possibility of Nyquist-ghosted activation contributing to a measure of task-related motion artifact, signal changes in the Nyquist ghost regions of the brain image (anterior and posterior to the brain) were also ignored. Voxels outside this "brain + ghost" mask that are correlated with the ideal hemodynamic response are considered to be purely the consequence of motion. The mean t statistic in this region can therefore be used to compare the amount of artifact between the various paradigms. The efficiency of each design to detect BOLD signal changes was obtained by computing the average t statistic in regions in the brain significantly correlated with the ideal response ($t > 2.5$) in all five paradigms. The assumption made here is that the area of activation stays constant across stimulus paradigms whereas the location of the artifact

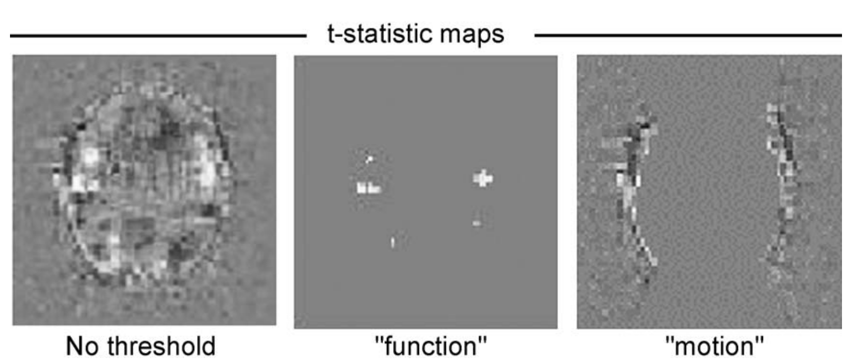

Fig. 4. An example of image masks used to quantify the detection of function vs. the false detection of motion. Regions where signal changes are considered to represent "function" consisted of areas inside the brain correlated with the ideal BOLD response (as measured by a t statistic) across all paradigms in a subject. Areas outside the brain that were correlated with the ideal BOLD response were considered the results of task-related "motion." For quantitation, the absolute value of the t statistics was averaged over the defined regions.

(inside the brain) varies. Visual inspection of the functional masks for all subjects confirmed that the regions primarily encompassed motor, visual, and language areas.

Results

Simulations

Of particular interest is the minimization of false-positives while maximizing the detection efficiency. Fig. 5 shows the detection efficiency of various designs in the absence of motion on the horizontal axis plotted against the t statistic of detecting purely motion-induced signal changes as BOLD signal changes. Blocked designs with long task and control periods have a high detection efficiency but also show the greatest likelihood of false-positives, as indicated by the high t statistic of detecting purely motion-induced signal changes. The likelihood of false-positives depends on the duration of the stimulus (task) and control periods. At a stimulus duration of 10 s (an on–off cycle duration of 20 s), the hemodynamic response is delayed by the amount for it to be approximately orthogonal to the motion-induced signal changes (see Fig. 3b). At an on–off cycle duration of 10 s (a stimulus duration of 5 s), the hemodynamic response is anticorrelated with the motion-induced signal change, with peaks in the response occurring during the control periods, and troughs of the response occurring during the task period. This results in a negative t statistic, and again a larger likelihood of being falsely classified as functional activation, if negative activations are included.

An event-related fMRI design with a constant ISI shows a slight negative t statistic in the (false) detection of purely motion-induced signal changes. This is due to the fact that spikes in the signal caused by motion occurred during the trough of the functional response. Event-related designs with a varying ISI offer a greater detection efficiency, in agreement with earlier studies (Birn et al., 2002; Burock and Dale, 2000; Burock et al., 1998; Dale, 1999; Liu et al., 2001). The response to stimulus designs with short block durations (<5 s), parameterized in this simulation by the minimum stimulus duration, generally have a low correlation with expected motion-induced signal changes. At greater minimum stimulus durations, the detection of BOLD signal changes in the absence of motion is improved but the likelihood of false-positives increases rapidly. An event-related design with a varying ISI (all varying in a geometric distribution) and a minimum stimulus duration of 5 s offers the best tradeoff in detection efficiency and reduction of false-positives. An example of such a design is shown in (Fig. 3e).

In the case that both task-related motion-induced and BOLD signal changes are present in a voxel, the rate of false-negatives depends on the sign of the motion-induced signal change. If the motion-induced signal change is positive, then the detection of BOLD signal changes with a blocked design is least affected. In this case, the motion-induced signal changes closely resemble the expected BOLD signal changes. If the motion-induced signal changes are negative, then the detection of BOLD signal changes in a blocked design depends on the extent to which the motion-induced signal change cancels out the positive BOLD signal. Due to their lower functional contrast, event-related designs are slightly more sensitive to task-related motion, the presence of which decreases the ability to detect function. Event-related designs with a varying ISI are generally less susceptible to motion than designs with a constant ISI (see Fig. 5).

Fig. 6 also examines the detection efficiency when time points during the motion are ignored. The loss of several data points results in a loss of detection efficiency for signals not contaminated by motion (Fig. 6b) but can improve the detection of BOLD signal changes in the presence of motion and reduce the number of false-positive detections of purely motion-induced signal changes (Fig. 6a). In all cases, false-positive detection of motion was minimal when time points during which the motion occurred were ignored. This is not surprising since no motion-induced signal changes remain in these simulated signal time courses. The efficiency of event-related designs with a constant ISI at detecting purely BOLD signal changes is least affected. The detection efficiency of event-related designs with a varying ISI was reduced more significantly

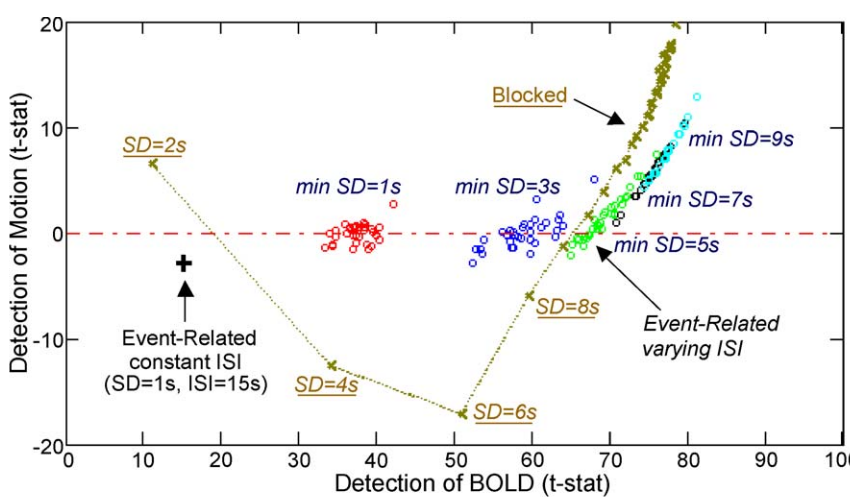

Fig. 5. The detection power of BOLD activation (true-positives) compared to the detection of motion (false-positives) for various designs as computed by simulations. Circles (○) represent event-related designs with varying ISI and different minimum stimulus durations (min SD); the plus (+) represents an event-related design with a constant ISI of 15 s; and the crosses (×) represent blocked designs with different block durations (2, 4, 6,. . ., 64 s). Detection powers were computed by correlating either the BOLD response + noise or simulated motion + noise with the ideal BOLD response, expressed here using a t statistic (300 time points, TR = 1 s, 5% maximum BOLD activation, 0.5% white Gaussian noise). The optimal design has a detection of motion near zero and a maximal detection of BOLD.

(since more data points were ignored), but it was still higher than the efficiency of designs with a constant ISI. Similarly for blocked designs, the efficiency of detecting function in the absence of task-related motion is substantially reduced due to the large number of ignored data points. Note that detection of activation is still possible even when all the data during the performance of the task is ignored since the hemodynamic BOLD response is delayed and slowly returns to baseline over a period of 10–14 s after cessation of the stimulus. Fig. 6 also examines the detection efficiency when the stimulus timing is used as an additional regressor to model the motion-induced signal changes. The detection of BOLD signal changes in the absence of motion is less affected than ignoring the data points during the motion, as described above, since the addition of one regressor results in the loss of only one degree of freedom. The success of this approach in improving the detection of BOLD signal changes in the presence of task-related motion, however, depends on the variation of the motion-induced signal, that is, how well the additional regressor (the stimulus timing) fits the motion-induced changes. If the motion associated with speaking the words out loud varies during the run, then the stimulus timing does not accurately model the motion-induced signal changes, and using this as an additional regressor is less effective. The t statistic of the BOLD fit can also be lower after including an additional regressor to model the motion, even though the combined fit (motion and BOLD) is improved. This is because the high similarity of motion and BOLD signals can result in an erroneous overprediction of the BOLD amplitude if the motion is not modeled. Since the t statistic is equal to the amplitude divided by the standard deviation of the amplitude estimate ($t = \alpha / \sigma_\alpha$), the presence of motion could increase the t statistic. This explains the decrease in t statistic for the blocked design in the combined motion and BOLD signal when both motion and BOLD signal changes are modeled.

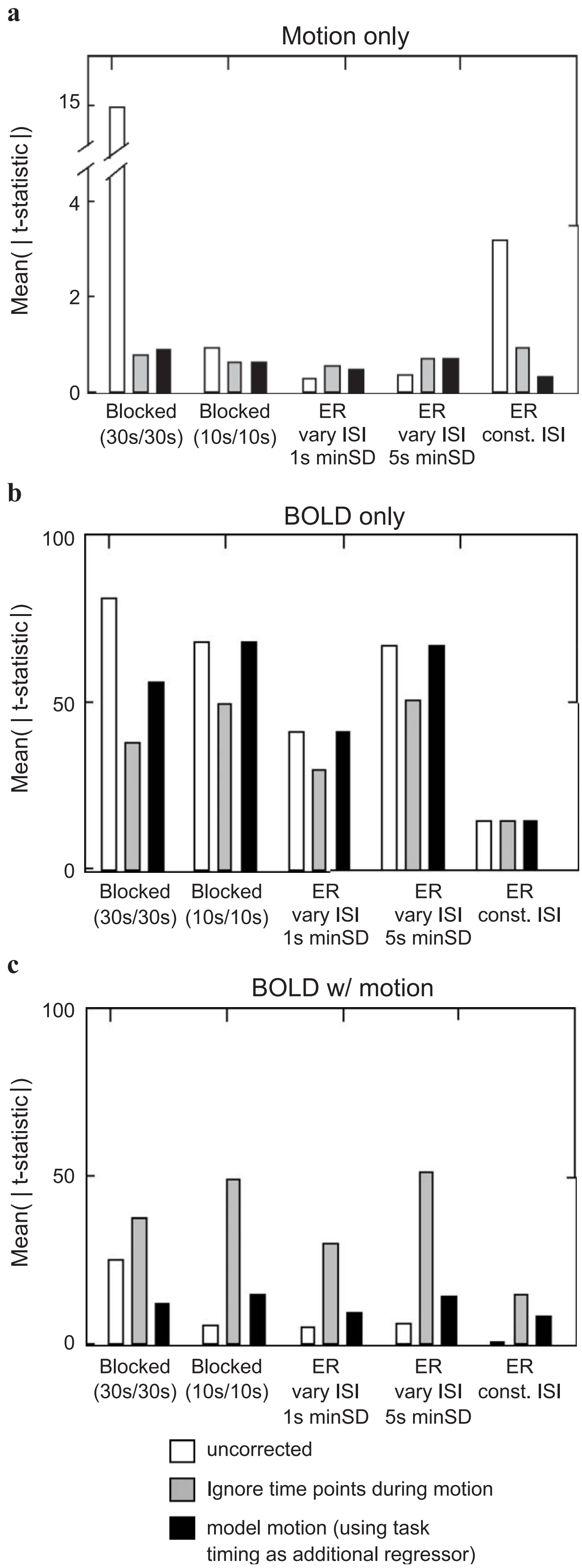

Fig. 6. Simulation results showing (a) the (false) detection of task-related motion, and (b and c) the detection of BOLD activation in the presence and in the absence of task-related motion, respectively, as computed by simulation (300 time points, TR = 1 s, 5% maximum BOLD activation, 0.5% white Gaussian noise). Detection power is measured by the mean of the absolute value of the t statistic when an ideal BOLD response is fit to the BOLD + noise + motion, or BOLD + noise. Three analysis strategies are compared: no corrections for motion (white), ignoring time points during the motion (gray), or modeling the motion using the task timing as an additional regressor (black). The likelihood of falsely classifying task-related motion as function is reduced when the motion is modeled or time points during the motion are ignores, particularly in the blocked design. In the absence of task-related motion, detection power is substantially reduced, particularly in blocked designs, when time points during motion are ignored. In contrast, ignoring time points during the motion improves detection of true function when the signal time course is a sum of both BOLD signal changes and task-related motion changes.

Experiments

Functional images obtained from the blocked-trial paradigm with 30 s task and rest periods contained significant artifacts, most prominently at the edge of the brain. These artifacts were reduced substantially when the block duration was shortened to 10 s. Artifacts were also reduced for all three event-related techniques. In the blocked-trial paradigm with 30 s task and rest periods, the signal intensity time course of a pixel near an edge is similar to the signal time course of a pixel in the motor cortex (see Fig. 7). These two time courses appear quite different in the

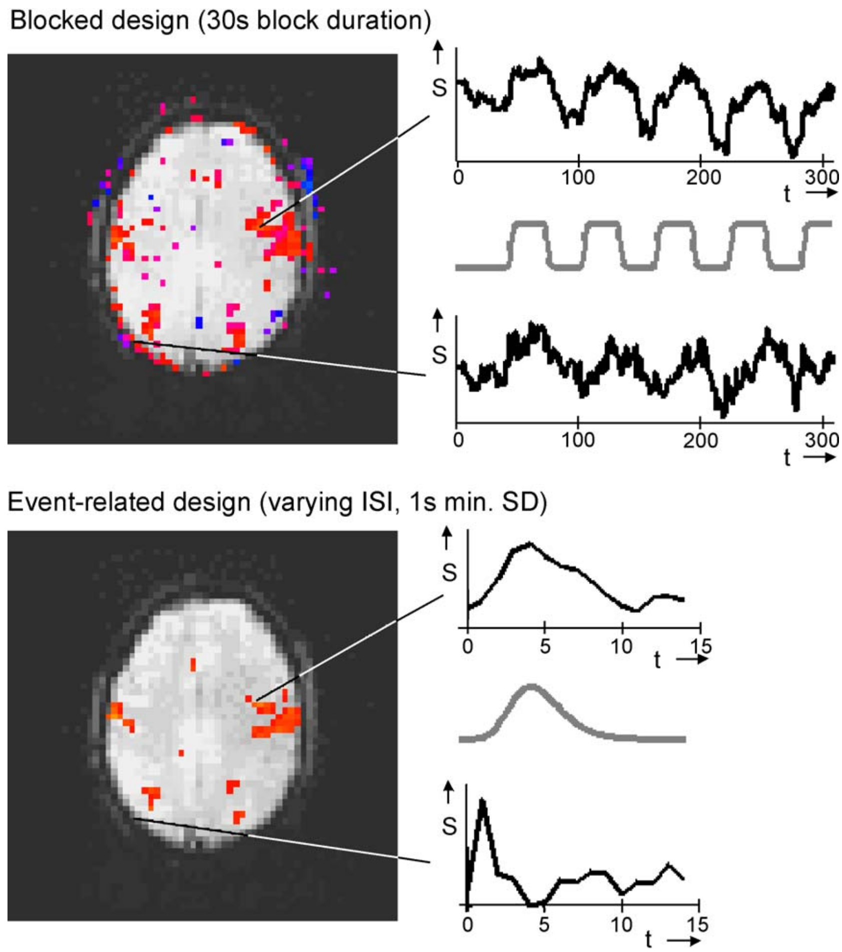

Fig. 7. Activation maps (left) and time courses (right) for speaking words out loud either in blocks of 30 s (top) or at varying intervals in an event-related paradigm (on average one word every 2 s). Blocked designs lead to significant motion artifacts evident at the edge of the brain image. A voxel at the edge of the brain shows signal intensity changes correlated with the expected BOLD response (indicated in gray). In contrast, in the event-related paradigm, a voxel at the edge shows a large spike in the signal at the time coincident with the spoken word, while a voxel in the motor cortex shows the expected hemodynamic response.

event-related paradigms, as can visually be easily appreciated from the average time courses in the event-related paradigm with a varying ISI (Fig. 7).

In regions significantly activated for all paradigms, the blocked design with long task and rest periods showed the greatest detection power of function, as evidenced by its high mean t statistic (t = 15.2) (see Fig. 8b). The blocked design with a 10-s block duration had a slightly smaller detection power (t = 14.4). This is similar to the reduction seen for the more blocked event-related technique (with varying ISI and a minimum stimulus duration of 5 s). Event-related designs with a varying ISI had a slightly lower detection power, on average by a factor of 1.8 compared to the blocked design, and an event-related design with a constant ISI resulted in the lowest detection power. Rigid-body registration indicated movements typically less than 1 mm and 1° rotation, which did not significantly affect these t statistic values.

Ignoring the time points during the overt speaking task resulted the greatest reduction of motion-induced signal changes at the edge of the brain for the blocked design. The average t statistic of false detections of motion (averaged over the entire region outside the brain and its Nyquist ghost) was reduced from 0.83 to 0.56 (see Fig. 8a). Less improvement is seen in the event-related designs since these designs are already minimally sensitive to motion artifacts. This analysis, however, decreased statistical power to detect function by a factor of 1.9 in the blocked design with 30 s task periods (see Fig. 8b).

When the stimulus timing was used as an additional regressor in order to approximate the motion-induced signal changes, motion-induced signal changes at the edge of the brain were reduced slightly but not eliminated. This is likely due to the fact that the motion-induced signal change varied for different words that were spoken, or for different parts of the run, and was therefore not accurately modeled by the stimulus timing. The greatest improvement is again seen in the blocked design.

Discussion

As demonstrated by both simulations and experimental results, the sensitivity to motion caused by overt speech can be significantly reduced by properly designing the stimulus paradigm. All of these designs work by exploiting the difference in the temporal properties (i.e., the delay and duration) of rapid motion-induced signal changes and the more sluggish hemodynamic

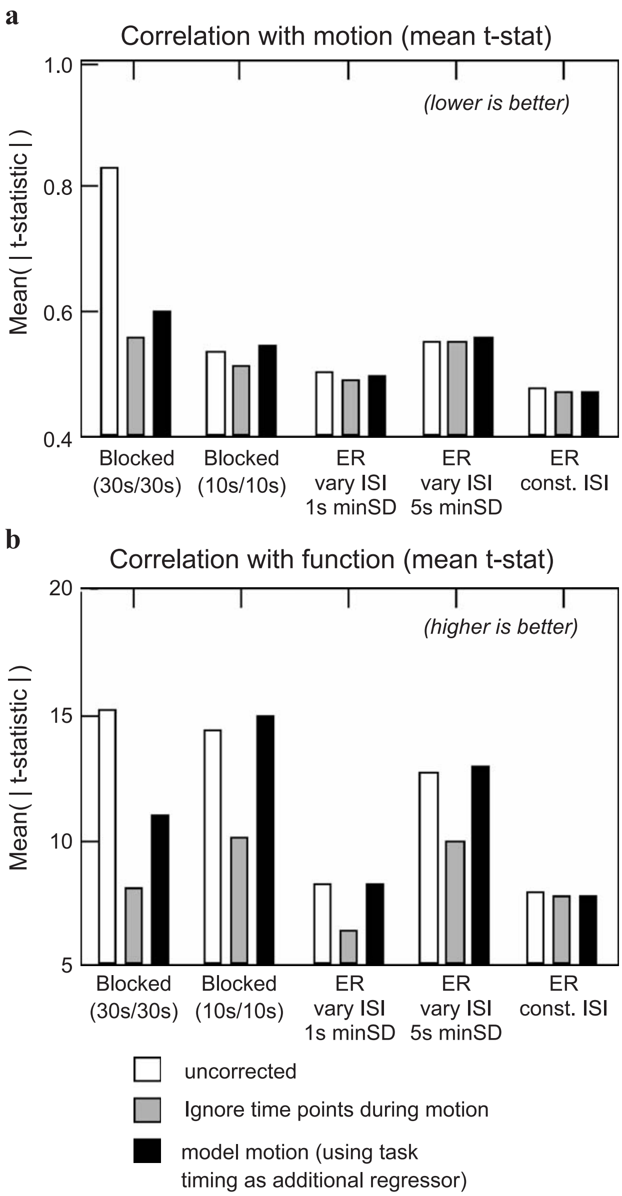

Fig. 8. Correlation of the ideal BOLD response (a) in regions outside the brain (likely the result of task-related motion) and (b) in regions commonly activated by all task paradigms, as measured by the mean of the absolute value of the t statistic in the respective areas. Three analysis strategies are compared: no corrections for motion (white), ignoring time points during the motion (gray), or modeling the motion using the task timing as an additional regressor (black). While false detection of task-related motion is reduced when time points during the motion are ignored, the efficiency of detecting function is also reduced, particularly in blocked designs. Using the task timing to model the motion offers some benefit in reducing task-induced motion artifacts in the blocked design, but little benefit in other designs. Blocked designs with a short block duration of 10 s and an event-related design with longer blocks (5 s minimum block size) offer the best detection of BOLD activation while keeping false detection of motion at a minimum.

BOLD response. In previous studies, this strategy was implemented in an event-related paradigm with long constant ISIs (Barch et al., 1999; Birn et al., 1999a,b; Preibisch et al., 2003) or varying ISIs (Palmer et al., 2001). As seen from the simulations performed here, the BOLD response of most rapidly varying event-related paradigms (with minimum stimulus durations below 3 s) is orthogonal to motion-induced signal changes, explaining the success of previous studies using these designs (Palmer et al., 2001). Furthermore, the simulations and experiments presented here show that there are large range of designs that meet the criterion of reduced sensitivity to task-related motion. We can therefore start to ask which of these designs is optimal in detecting BOLD activation while still maintaining a low sensitivity to task-related motion. Our simulations showed, for example, that a design with a varying ISI but longer block durations (of 5 s) would still provide low correlation with task-induced motion while improving detection power substantially (see Figs. 5 and 6). Our experiments confirmed this prediction (see Fig. 8). Reduction of task-related motion artifact can also be achieved simply by reducing the stimulus and control durations of a conventional blocked design. This large range of available designs can help investigators choose a design that is maximally sensitive to BOLD signal changes, minimally sensitive to task-induced motion, and appropriate for their particular neuropsychological test.

Most of the observed motion-induced signal changes, resulting from either bulkhead motion or image warping from associated magnetic field changes, occur at the edges of the brain and therefore do not overlap significantly with BOLD signal changes. This is confirmed by the deconvolved responses from the event-related designs that show a large spike in the signal intensity at the edge of the brain compared to a slower response in regions of the motor cortex (see Fig. 7). Since task-related motion-induced signal changes are minimally correlated with the BOLD signal changes in event-related paradigms with varying ISIs, functional activation maps free from task-induced motion artifacts can be obtained by simply correlating each pixel time course with the ideal BOLD response.

In cases where motion-induced signal changes do occur in the same voxel as the BOLD signal change, the detection of the BOLD signal change is slightly reduced if this motion is not taken into account in the detection procedure. Ignoring the time points occurring during the motion or modeling the motion by an additional regressor, such as the stimulus timing, can improve the detection of these BOLD signal changes obscured by task-related motion. Ignoring time points during a task that contains motion is particularly simple and reduces the number of false-positives by not including any time points that might be corrupted by task-related motion. As seen from Fig. 9, activation is still detectable in a blocked design, even when all the images during the task block are ignored. This may at first seem surprising, but it relies on the delay of the BOLD response; the detection is based purely on the decrease of the response to baseline after the task block. This return of the BOLD signal to baseline from the activated state takes approximately 10–14 s. For a 10-s block (20 s on–off cycle duration), the signal closely resembles a sine wave, and entire control period is used for the signal to return to baseline. This entire transition period is used in the regression analysis. For block durations longer than 12 s, the detection efficiency is slightly reduced since the design is unbalanced with more time spent sampling the control (baseline) state. At block durations shorter than 10 s, the signal does not fully return to baseline, and the detection efficiency is significantly reduced. The detection efficiency of event-related designs with a constant ISI is least affected since only one out of every 15 points is ignored.

There is an inherent tradeoff when data points acquired during the task are ignored in the analysis. The possible influence of task-

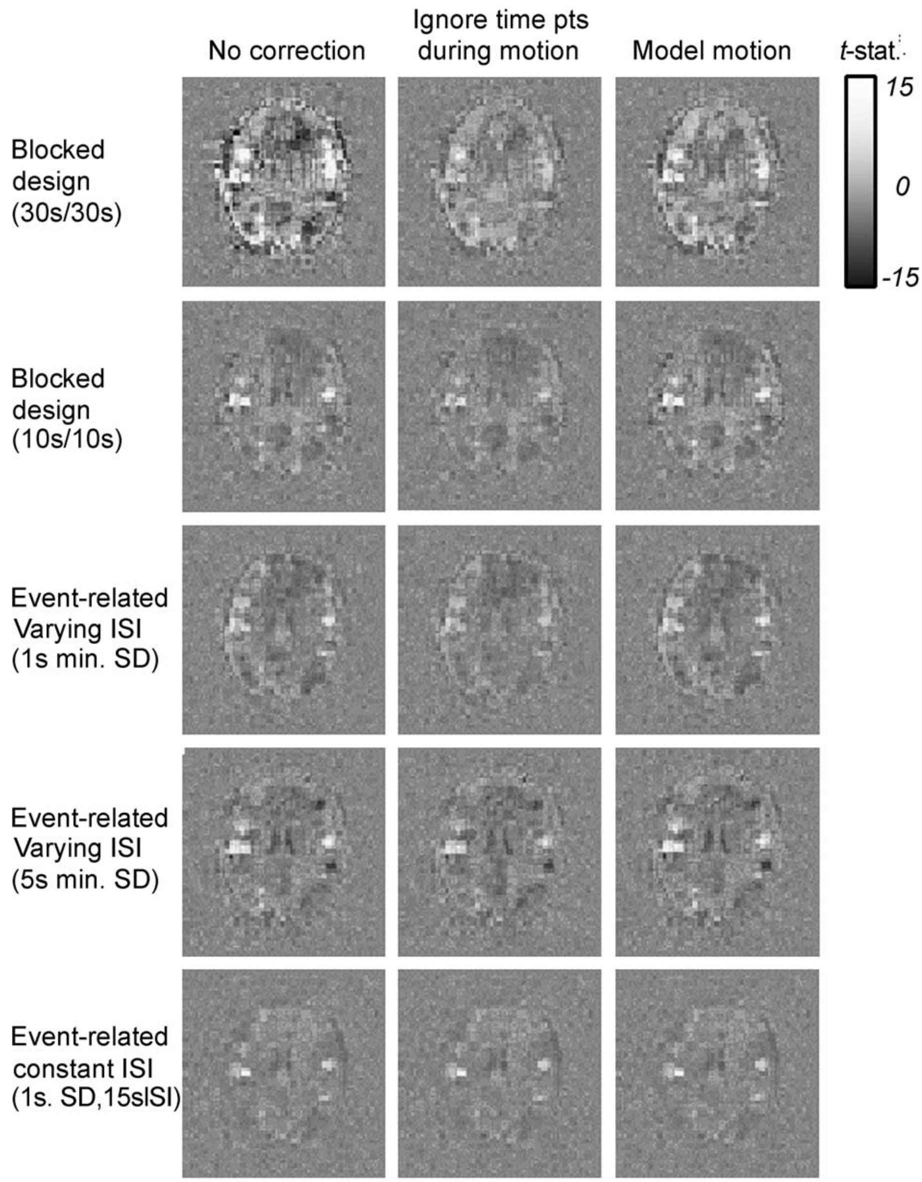

Fig. 9. One axial brain slice at the level of the motor cortex in a representative volunteer showing the t statistic maps of correlating an ideal BOLD response for five different designs. Three analysis strategies are shown: left: no explicit correction for task-related motion (aside from rigid-body registration); middle: ignoring time points during the task; right: using the task timing to model the motion-induced signal change. The blocked design with long block durations (30 s) shows the most artifact. Blocked designs with shorter block durations (10 s) and more blocked event-related designs (5 s minimum stimulus duration; min. SD) show the clearest activation with little motion artifact.

related movement is removed, reducing the number of false-positives, but the detection power of true function (for voxels not corrupted by motion) is reduced. The point at which ignoring these time points hinders rather than aids the detection of function depends on the amplitude of the motion-induced signal change relative to the expected BOLD signal change, the contrast-to-noise of the BOLD signal, the total number of time points in the imaging run, the number of time points during the task, and the stimulus design. For example, the simulations presented here (Fig. 6) show that for a blocked design with a 30-s block duration, ignoring data points during the task block reduces the t value of artifactual task-correlated motion from 15 to 0.9, but also reduces the t value for true functional changes from 82 (with 300 degrees of freedom) to 37 (with 150 degrees of freedom). For robust activation, such as the 5% signal changes considered in the simulation or for the visual stimulation studied here, this loss of detection power may not be a problem. If smaller signal changes are expected, a power analysis should be performed to judge whether this reduction in detection power is acceptable. For example, in this simulation the smallest BOLD signal change detectable at $P < 10^{-7}$ (uncorrected) (i.e., where the mean t value for purely BOLD signal changes corresponds to a $P < 10^{-7}$) is increased from 0.35% to 0.75% when the data are ignored. The factor by which the detection power is reduced varies for different stimulus designs, as indicated in Fig. 6. Note that while false-positives resulting from task-correlated motion can be reduced by raising the statistical threshold (e.g., to a value greater than 15 in the above example), smaller activations are more likely to be missed. From the experimental results for the blocked design (with 30 s block duration), it was found that simply raising the statistical threshold was not the most effective strategy of eliminating the effects of task-correlated motion since the number of "activated" voxels (in the motor cortex region) was reduced while large signal changes near the edge of the brain remained.

Modeling the task-related motion-induced signal changes can be more advantageous in designs with a large number of task periods since ignoring time points during the motion results in a large amount of data being discarded. Modeling the motion with an additional regressor would only result in the loss of one degree of freedom. The accuracy of this technique is of course limited to the accuracy to which the motion-induced signal change can be modeled. Motion artifacts during overt speech generally manifest themselves as increases or decreases in signal intensity near the edges of the brain during the task performance. For a brief movement occurring within a TR, the stimulus timing can therefore be used as a first approximation to the movement time course. It is only approximate because it makes the assumption that an equal deviation in the signal occurred for each movement. An additional complicating factor is that if the movement is very brief, then a signal change may only occur during the acquisition of one slice in the volume. In a particular slice, therefore, a motion-induced signal change may not appear for each task performance. This signal time course will thus only partially resemble the stimulus timing used as a model for the motion. This likely explains the lack of significant improvement in the reduction of artifact when the stimulus timing was used as an additional regressor to model the motion.

As an alternative, the time course representing the task-related motion may be obtained from voxels at the edge of the brain or by observing the NMR phase of the signal. The latter is possible since both head movement and motion-induced magnetic field changes cause changes in the NMR phase. Combining multiple voxels showing motionlike behavior is not trivial since signal changes from motion often show increases in one part of the brain and decreases in another, confounding simple averaging. A principle component or independent component analysis of these voxels influenced by motion may extract the characteristics of interest.

Data were analyzed in this study using multiple linear regression assuming a specific shape for the expected hemodynamic response. Deconvolution is an alternative analysis commonly used in event-related designs. This analysis considers regions of the brain as 'active' when the signal changes are time-locked to the stimulus regardless of the shape of the impulse response function. The results of such an analysis performed on tasks with associated motion, such as overt speech, must be interpreted with caution since the motion-induced signal changes are also time-locked to the task. Motion-induced and BOLD signal changes must therefore be subsequently distinguished based on their different temporal shape. An added difficulty with deconvolution is that the motion-induced signal change is not necessarily the same for each task performance. This variability leads to increased noise in the estimate of the impulse response function. An alternative analysis strategy that may provide separation of BOLD and motion-induced signal changes is independent component analysis (ICA), although again a subsequent discrimination of which component is considered to be BOLD activation and which is related to motion is necessary (Moritz et al., 2003; Quigley et al., 2002).

An alternative method that has been used successfully in the study of overt speech incorporates the use of "sparse sampling" or "clustered volume acquisition" (Edmister et al., 1999; Hall et al., 1999). In this technique, slices within a volume are acquired as rapidly as possible rather than evenly spaced throughout the TR interval. A primary motivation for this method is that it allows for silent periods (if the TR is longer than the acquisition time of a single volume), which can improve the presentation of sounds and monitoring of subject responses. Motion artifacts can be reduced by having overt speech occur in the silent period after the volume is acquired. When duration of the silent interval is equal to the time required for the acquisition of one volume, then this method is similar to acquiring the data continuously as rapidly as possible and discarding the images during the motion. The key difference is that the longer TR of the clustered acquisition will allow for more recovery of longitudinal magnetization and therefore greater signal, particularly at TRs of 1 s or less. This advantage will likely be less pronounced compared to continuous imaging at longer TRs. Conversely, at rapid scan rates (short TRs), a continuous design where only volumes during speech are ignored allows for finer sampling of the signal dynamics during periods not affected by motion, such as the falling edge of the response in a blocked design following the cessation of the speech task.

Recently developed algorithms, based on adaptive filtering, can remove the gradient acoustic noise from audio recordings of subject responses, allowing for clearer intelligibility and extraction of reaction times (Nelles et al., 2003). At present, these algorithms still take too long for real-time feedback, and therefore clustered acquisitions are preferred when auditory feedback or a clear perception of sounds is required.

The clustered acquisition design also suggests a variation on the blocked design presented in these simulations and experiments. Brief periods of speech could be blocked together, similar to a blocked design, but with gaps where data uncorrupted by motion artifacts can be obtained. A clustered design would scan only during these periods, while a continuous design would scan continuously and ignore the time points during the motion. If the duration of the speech task and control periods are equal during the block, this would result in a BOLD response one half the amplitude of a blocked design where the speech is performed continuously throughout the block. The detection power of this design is therefore lower if no motion exists and no images are ignored, but it can be comparable or better than a blocked design when images during the motion are ignored.

While a blocked design with a stimulus duration of 10 s was found to be minimally sensitive to task-induced motion artifacts if the ideal hemodynamic response is used as a regressor, this strategy of minimizing the motion artifact relies solely on the difference in latency between the motion-induced and BOLD signal changes. Because of this, the design may not be optimal for experiments focused on estimating delays or where the response latency is an additional variable in the regression analysis. In contrast, event-related designs with a varying ISI rely on the difference in both delay and shape of the signal to discriminate motion and BOLD signals and may therefore be more appropriate.

Another confound of blocked designs with shorter block durations is that the stimulation frequency may overlap more with frequencies of physiological noise, particularly respiration. In the robust motor activation studies illustrated here, the effect of respiration is likely minimal, but it may become significant when attempting to detect smaller activations. Using a variable ISI distributes the power of the design across multiple frequencies and is therefore less susceptible to these effects.

The minimum stimulus duration is only one of many ways to parameterize a stimulus with a varying ISI but generally larger blocks. The key to the increased detection power of these designs lies in the fact that these designs have more energy at low temporal frequencies, which is less affected by the smoothing of the hemodynamic response (Birn et al., 2002). Desirable stimulus timings can be obtained by generating multiple random stimuli and selecting the one with maximum detection efficiency and minimum correlation with motion as the experimental timing design. Two underlying assumptions to this method are that the head returns to its original position between brief movements, and that the image distortions are small if the motion-induced signal changes are not removed or modeled in the analysis. If movements are large enough to displace or distort the region of activation imaged significantly during the task, then the signal acquired during this time becomes unusable. If the latter is a significant problem in a study, then designs with longer rest periods can be implemented, allowing for more samples of the hemodynamic response uncorrupted by motion.

A significant motion in the slice direction can also change the effective TR that an area of the brain experiences. This can potentially corrupt the image time points both during and immediately after the motion when the brain has returned to its original position. A design with a longer ISI will also allow for more uncorrupted data not during or immediately after a task. The effect of varying TRs should also be reduced at a longer TR. Care should also be taken to secure the head in order to restrict bulk motion, particularly in the slice direction. Even perfect immobilization of the subject's head does not prevent all speech-related motion artifacts due to the contraction of muscles at the side of the head during jaw clenching, and changes in the magnetic field as the jaw, tongue, and facial muscles are moved (Birn et al., 1998). This may in fact be the dominant source of the observed task-induced motion artifacts as suggested by the lack of any significant bulk head motion detected by image registration. In addition, most of the motion artifact was found at the edge of the brain rather than in regions with long T1s, such as CSF, suggesting that the varying T1 saturation caused by varying effective TRs may play a minimal role, at least in our study.

This technique is not limited to the study of speech but can in principle be used in any experiment that involves movement correlated with the task. The studies that to date have benefited the most from this design are those that involve motion of the head itself or motion of tissues near the head, such as in studies of swallowing, or facial muscle movement (Birn et al., 1999a,b; Gosain et al., 2001; Kern et al., 2001; Martin et al., 2001). It could also be used for studies with other task-related movements, for example, the motion of a stimulation device that might cause field distortions and resultant signal changes during the task. The key of this method is the delay and slow rise and fall of the BOLD response compared to the more rapid task-related motion-induced signal changes.

A repetition time (TR) of 1 s was used to obtain a good sampling of the hemodynamic response function. At a longer TR, the hemodynamic response is nonzero at only a few points and may therefore appear more similar to motion-induced signal changes. Ignoring time points during the motion results in a substantial amount of the sampled signal being discarded. The analysis could in principle be modified to ignore only the slices corrupted by motion. Including regressors to model the effects of motion in this case also requires each slice to be modeled separately since brief motion is likely to occur during the acquisition of only a few slices in a volume. A shorter TR, which improves the distinction between BOLD and motion-induced signal changes, limits the number of slices that can be acquired and may preclude whole-brain imaging on many scanners. As shown by Preibisch et al. (2003), a TR of 3 s is still sufficient to obtain artifact-free images during speech production. Measurement of the hemodynamic response and separating it from motion could also be improved at long TRs by incrementing the offset between the stimulus and the acquisition (e.g., performing the task every 14 s for a TR of 3 s). Each point in the resulting (averaged) response function is sampled less frequently, but at finer intervals.

Nonlinearities of the BOLD response would change these results slightly. If the response from a brief stimulus is larger than would be expected given the response from a longer stimulus, event-related paradigms may have higher functional contrast-to-noise ratios than indicated by this linear model. This rather simple description of nonlinearities in the BOLD response may not necessarily hold in more rapid event-related designs with a varying ISI, where the dynamics are governed by both adaptation during stimulation and a refractory period during stimulus 'off' periods (Birn and Bandettini, 2001).

Ultimately, the limit of this technique is the knowledge of neuronal activity being investigated. For example, the movements involved in continuous speech production can be thought of as a rapid event-related design with a varying ISI. What is relevant to BOLD-fMRI is the timing of the neuronal activity underlying this movement, not the task or stimulus timing. Therefore, while the motor cortex activity may very well be detected during continuous speech using this technique by using the task timing, other areas may be active more continuously during the entire speaking process, or vary in rate of neuronal firing different from the rate of actual production of words, and may therefore be unknown. The BOLD activity resulting from the neuronal activity of interest may therefore not be perfectly orthogonal to the stimulus timing. The general robustness of rapid event-related designs with a range of interstimulus intervals and stimulus durations, however, suggests that these designs may be favorable in these instances.

Conclusions

There are a number of paradigm design strategies for reducing the influence of task-induced motion. For blocked designs with equal task and control period durations, a block duration of 10 s offsets the hemodynamic response by precisely a quarter cycle relative to the task timing. While this strategy exploits primarily the temporal delay of the BOLD response and is therefore susceptible to variations in the onset delay, it is a simple modification for many fMRI studies. Across all subjects studied, consistently the best activation maps were obtained using event-related designs with a varying ISI. These paradigms were specifically designed such that the correlation between the rapid motion-induced signal changes and the slower BOLD signal changes are uncorrelated. Because of this, a simple regression analysis without explicitly accounting for the motion is generally sufficient. If movement artifacts remain, or if activation is expected near an edge where the motion artifact could potentially mask true function, the artifacts can be reduced either by ignoring the time points during the motion or modeling the motion using an additional regressor. Ignoring the time points is best at removing the motion but can result in a significant loss of detection power, whereas modeling the movement relies on the accuracy with which the motion-induced signal change can be modeled.

Following the introduction of rapid event-related designs to fMRI (Burock et al., 1998), recent efforts have focused on optimizing these designs for the detection of BOLD activation or the estimation of the hemodynamic response function. In a similar manner, by understanding the underlying properties and differences of artifactual and BOLD signal changes resulting from overt speech, stimuli can be specifically optimized to minimize the sensitivity to motion while maximizing the sensitivity to BOLD activation.

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