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Event-Related fMRI of Tasks Involving Brief Motion

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Abstract: The assessment of brain function by blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) for tasks involving motion near the field of view is compromised by artifacts arising from the motion. The aim of this study is to demonstrate that these artifacts can be reduced by acquiring the average response from a brief stimulus (a ''single-trial,'' or ''event-related,'' paradigm) as opposed to alternating blocks of repeated task with rest (a ''block-trial'' paradigm). The basis of this technique is that the NMR signal changes from neuronal activation are delayed relative to the motion due to a slow hemodynamic response. By acquiring the average response from a brief stimulus, motion-induced signal changes occur prior to neuronal activation-induced signal changes, and the two can thus be distinguished. This technique is applied to the tasks of speaking out loud, swallowing, jaw clenching, and tongue movement. Functional activation maps derived from the single-trial paradigm contain significantly less artifact than functional activation maps derived from a more traditional block-trial paradigm. *Hum. Brain Mapping 7:106–114, 1999.* © 1999 Wiley-Liss, Inc.

Key words: magnetic resonance imaging; artifacts; brain function; human brain mapping; image processing; speech; deglutition

INTRODUCTION

Blood oxygenation level dependent functional magnetic resonance imaging (BOLD-fMRI) has become an important tool in recent years in the study of the neuronal control of a variety of tasks from motor, auditory, and visual processing to cognitive tasks [Binder, 1995; Cohen and Bookheimer, 1994; Schulmanet al., 1993]. Certain tasks, however, have eluded study by fMRI due to large image artifacts caused by motion associated with the tasks. Overt word production, for example, has been shown to lead to gross artifacts, forcing the study of language systems to focus on silent word generation and semantic processing tasks. This inability to speak aloud during an fMRI scan has also imposed restrictions on the subject feedback required for many neuropsychological tests. Similar difficulties have been encountered in functional magnetic resonance imaging of swallowing or movement of the jaw, facial muscles, or eyes [Binder, 1995; Kern et al., 1995; Lang et al., 1994; Yetkin et al., 1996]. In this paper, we present a technique that partially overcomes this limitation and enables the acquisition of functional magnetic resonance images and subsequent determination of functional activation

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maps from tasks requiring brief movement, such as overt responses.

Motion presents a difficulty for functional magnetic resonance imaging in that it leads to signal intensity changes that can either mask or mimic the signal changes due to neuronal activation. These signal changes can result either directly from motion of the subject's head in the field of view (FOV), or indirectly, through image warping resulting from magnetic field changes induced by motion outside the FOV, such as the jaw, tongue, or facial muscles. This magnetic field artifact can be significant, especially in slices in the inferior region of the brain close to the motion outside the field of view leading to signal changes of anywhere from 5 to 100% [Birn et al., 1998; Yetkin et al., 1996]. Thus even perfect immobilization of the subject's head does not eliminate all motion artifacts. Typically regions of neuronal activation are detected by alternating periods of repeated task performance with periods of rest, and identifying pixels where the signal changes in this ''on-off'' pattern [Bandettini et al., 1993]. This has often been referred to as a ''blocked-trial'' paradigm, since the tasks are performed in blocks. If the task is necessarily associated with motion, commonly referred to as stimulus correlated motion, then the signal changes resulting from motion exhibit this same ''on-off'' response and can be mistaken for the BOLD signal changes characterizing neuronal activation.

Since the motion induced signal changes result from quite different mechanisms than the BOLD signal changes, the two types of signal variations exhibit considerable differences in their temporal dynamics. Early studies of the BOLD effect noted that the hemodynamic response is delayed in onset by several seconds relative to the performance of the task, or the presentation of the stimulus [Kwong et al., 1992]. Subsequent studies using brief stimuli, from 2 sec down as low as 34 msec, not only demonstrated that BOLD signal changes could be measured from brief events, but also showed that the BOLD response is prolonged in duration and that it was consistent between repeated task performances. Blamire et al. [1992], for example, noted signal changes following only 2 sec of visual stimulation, while Bandettini et al. [1995] demonstrated signal changes following a motor task of only 0.5 sec duration. These experiments were followed by similar studies of motor and visual systems [Boulanouar et al., 1996; Friston et al., 1994; Humberstone et al., 1995; Konishi et al., 1997; Savoy et al., 1994, 1995]. In all cases the observed hemodynamic response to even such brief stimuli was delayed in onset by 2–5 sec, reached a peak at approximately 5–6 sec, and returned to baseline at about 10–12 sec after the stimulus presentation.

The demonstration of the two principles mentioned above—that the BOLD signal is detectable even from brief stimuli and that the response is consistent—led to the application of these techniques to cognitive paradigms in what became known as a ''single-trial,'' or ''event-related,'' imaging paradigm [Buckner et al., 1996; Hickock et al., 1997; Josephs et al., 1997; McCarthy et al., 1997; Schacter et al., 1997; Zarahn et al., 1997]. In this event-related imaging paradigm, a task is performed briefly, typically once every 15 sec. The resulting epochs can then be averaged to produce the average response to a brief stimulus.

In contrast to the delayed and prolonged hemodynamic response characterizing the BOLD signal changes, 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. This difference in the temporal delay and shape can be exploited either by ignoring the images occurring during the motion or by removing the rapid signal changes resulting from motion from each signal intensity time-course prior to correlating with the ideal BOLD response. It should be noted that even if there is some overlap between the motion induced signal changes and the BOLD signal changes, the shape of the signal responses is quite different, allowing removal of the motion induced signal intensity changes and subsequent determination of functionally active areas.

METHODS

The power of the single trial paradigm to overcome artifacts resulting from motion associated with the task, such as speech, was demonstrated by acquiring a series of images from six subjects using both a block-trial and a single-trial paradigm during tasks involving significant subject motion: 1) speaking out loud, 2) swallowing, 3) jaw clenching, and 4) tongue movement. In all studies, a series of eight axial T2* weighted echo-planar images through the motor cortex was acquired. For the speaking task, the eight slices were acquired slightly inferior in order to include the auditory and language areas associated with speech production. For comparison of the location of activated regions, a finger tapping task was also performed. All scans were performed on a Bruker Biospec 3T/60

magnet with a home-built local gradient and radio-frequency head coils [Wong et al., 1992]. Head motion was reduced by tight foam padding around the subject's head. Both paradigms used echo planar imaging, with a TR (for the entire volume) of 1000 msec, TE of 27.2 msec, 10 mm slice thickness, and a FOV of 24 cm with a matrix size of 64 × 64, giving an in-plane resolution of 3.75 × 3.75 mm. All volunteers gave proper consent and FDA safety guidelines were strictly followed.

Block trial paradigm

To compare the functional activation maps acquired with the single trial paradigm with a more traditional imaging approach, functional images were first acquired using a block-trial paradigm. In this paradigm, each task followed an "on-off" pattern of activity interleaving five 15-sec periods of task with five 15-sec periods of rest, for a total of 150 images in the imaging run. The specific tasks were repeatedly speaking a single word out loud, swallowing repeatedly, or continuous motion of the jaw or tongue. Functional activation maps were derived from these image time-series by correlating the signal intensity time-course of each pixel with a time-delayed square wave reference function [Bandettini et al., 1993]. The first five images of the image time series occur during the initial relaxation of the longitudinal magnetization to equilibrium and were thus ignored in the correlation analysis. In addition, any linear trend in time was removed from each voxel prior to the correlation.

Single trial paradigm

The tasks of speaking, swallowing, jaw clenching, and tongue movement were each repeated using a single-trial paradigm. In this paradigm, the subject was cued by a flash of light to perform the task briefly once every 15 sec, repeated 20 times for a total of 300 images. The tasks consisted of speaking out loud a single word chosen by the investigator, swallowing once, one jaw clench, or a brief movement of the tongue to the roof of the mouth. The images from the twenty 15-sec epochs were then averaged together to produce one 15-sec averaged image response time-course. Longer image series were used for these experiments than for the block trial experiments because the functional contrast is lower in the single trial paradigm. This is simply due to the fact that fewer events are sampled in the single trial paradigm.

A difficulty arises in applying the single trial paradigm to swallowing in that the swallowing process is not under complete voluntary control. A subject instructed to swallow at a particular instant will actually swallow some variable time later, the delay of which is not under the voluntary control of the subject. The timing of the instructions thus cannot be used to align the swallowing epochs in time prior to averaging to obtain the average response time-course. Instead, the swallowing epochs are aligned in time by using an internal temporal marker of the swallow, or "navigator"—the NMR phase. As previously demonstrated, the process of swallowing is accompanied by large changes in the NMR phase as a result of the magnetic field changes induced by the motion of the pharyngeal muscles, jaw, and tongue outside the field of view [Birn et al., 1998]. These phase changes are consistent and have been shown to be coincident with the largest EMG change during swallowing [Martin et al., 1998]. Therefore, these phase changes can be used to synchronize the image time-series to the swallowing motion. Time points in the image series where the images containing large phase changes were identified and used to temporally align the swallowing epochs prior to signal averaging (see Fig. 1).

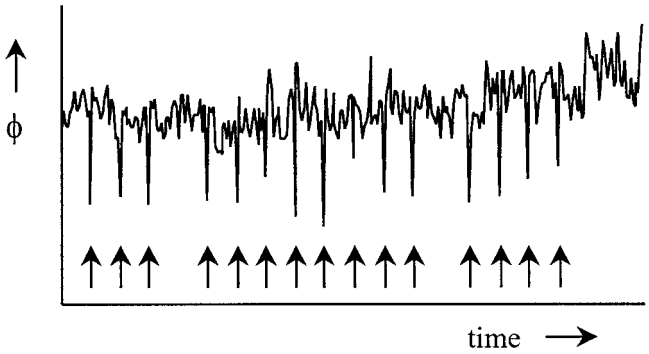

Figure 1.
Time course of the MR signal phase from a pixel while the subject swallowed every 15 sec. Times coinciding with a swallow are indicated by the arrows. Note the large (negative) phase changes accompanying each swallow. Swallows that were not detected in this fashion were excluded from further analysis.

Areas corresponding to regions of neuronal activation were determined by correlating each pixel time-course with an ideal reference waveform embodying the characteristics of the hemodynamic impulse response. This ideal waveform chosen to represent the hemodynamic response was the convolution of a 1 sec duration pulse with a three-parameter gamma variate function,

$$S(t) = At^{8.60}e^{-t/0.547} \quad [1]$$

where *A* is varied according to the amplitude of the response [Cohen, 1997].

The effect of motion related signal changes on the image time series can be reduced in two ways. The simplest method is to ignore the first few images in the time series, which are acquired during the motion, when performing the correlation, thus searching only for those regions with a similar delayed BOLD response. An alternative technique which offers some improvement is to remove signal changes related to motion from each voxel's time-series prior to the final correlation analysis. This process is identical to that used to remove any linear trend from the voxel time-courses. Both techniques were applied to the averaged time courses.

To further illustrate the temporal dynamics of the signal changes, a series of difference images was computed by subtracting the first averaged image from all other images in the averaged response time series. Note that for all tasks except swallowing, the motion occurred just after the first image, and thus the first image can justifiably be used as a reference image for subtraction.

RESULTS

For each of the tasks studied, both the block-trial and the single-trial paradigms indicated regions of activation. The block trial paradigm, however, contained significant artifacts, especially near the edges of the brain, making the precise localization of the functional response difficult. Functional activation maps generated from the single trial approach by ignoring the timepoints occurring during the motion had reduced motion artifacts. This approach, however, failed when the motion overlapped with the onset of the hemodynamic response, such as in the case of swallowing. Subtracting out the motion time-course from each pixel's signal intensity time-course led to an improved reduction of motion artifacts in the functional activation maps, allowing clearer visualization of functionally active regions. This latter method was therefore used to produce the functional images from the single trial paradigm depicted in Figure 4.

An example of the signal response from a pixel near the edge of the brain (most likely the result of motion), and the response in a region exhibiting a more characteristic BOLD response are shown in Figures 2 and 3 for the block-trial and single-trial paradigms respectively, together with the timing of the stimulus and ideal reference function used for detection of functionally active areas. The signal changes resulting from motion occur exactly in synchrony with the task, in contrast to the BOLD signal response, which is slightly delayed relative to the stimulus. Motion related signal changes in the single-trial paradigm appear as large spikes in the signal intensity in first few images. These spikes can be either positive or negative depending on the precise motion involved and the location of the edge. Functional activation maps and signal intensity time courses of representative pixels, one near an edge and another in a region of neuronal activity, are shown in Figure 4 for each of the four tasks for both single-trial and block-trial paradigms. Figure 4 shows the result for one representative subject. Each subject showed similar signal changes with a reduction of motion artifact in the single trial paradigm. The exact location, magnitude, and signal intensity time-course of the motion artifact, however, varied between the subjects, as it is highly dependent on the exact movement performed.

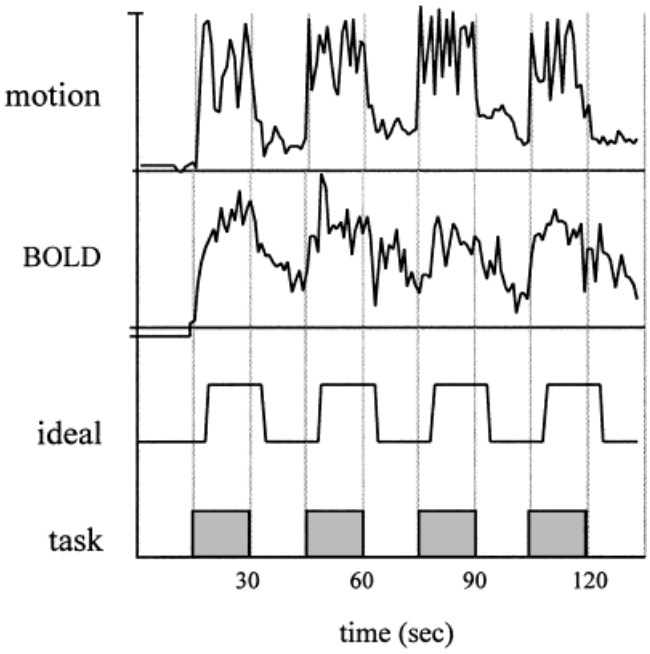

Figure 2.
Signal intensity time-courses, for the task of jaw clenching with the block-trial paradigm, of a pixel near an edge showing signal changes due to motion, and a pixel in a region of the motor cortex demonstrating signal changes typical of the BOLD response. The time course for the ideal reference function used for the correlation, as well as the time during which the task was performed are also indicated. The motion induced signal changes occur in synchrony with the task.

Speaking

For the task of speaking out loud, activated regions were identified in motor and auditory regions. The

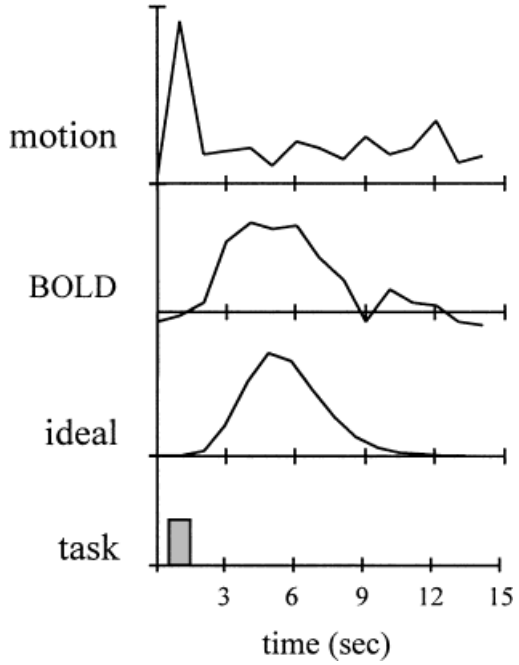

Figure 3.

Signal intensity time-courses for the task of jaw clenching with the single-trial paradigm, of a pixel near an edge showing large signal changes in the first few images due to motion, and a pixel in a region of the motor cortex demonstrating a slower, delayed signal change, more typical of the BOLD response. The ideal reference function used for correlation is the gamma variate function described in Eq. [1] convolved with a 1 sec duration pulse. The large motion induced signal changes occur before the BOLD signal changes, allowing the separation of motion and functional related signal changes.

averaged signal response from speaking a single word indicates large signal changes in the first two or three images appearing predominantly at the edges of the brain or near the ventricles. These signal changes are most likely the result of motion or motion associated magnetic field changes. A delayed and slower signal change starting its rise 1–2 sec after the motion related signal changes and reaching its peak after 4–5 sec is observed in regions of the motor and auditory cortexes.

Swallowing

For the task of swallowing, significant signal changes were detected in the motor cortex inferior to the region associated with finger tapping using both the block trial and the single trial paradigms. As with the speaking task, the block trial paradigm contained significant artifactual signal changes, especially near edges, making reliable detection of regions of neuronal activation difficult. In the averaged time-courses from the single-trial paradigm these regions near the edge of the brain exhibit large spikes in the signal intensity in the first one to two images (see Fig. 4a). Since the phase changes associated with the swallowing motion were used to align the epochs, any motion related signal changes will occur primarily in the first two images. Hence the spikes in the averaged time-series appear much earlier for this task than they do in the average signal response from the speaking, jaw, or tongue movement tasks. Pixels in the motor cortex exhibited a much slower response more characteristic of the hemodynamic signal changes associated with neuronal activation. Since the single-trial technique described here localizes primarily those pixels exhibiting this slower response, functional maps derived from the single trial paradigm show considerably less stimulus correlated motion.

Jaw clenching, tongue movement

A similar pattern of response is seen for the tasks of jaw clenching and tongue movement. Large signal changes occur in the first few images, predominantly at edges in the image, and a much slower response is present in the motor cortex. In each of these tasks, the single trial paradigm showed considerably less artifactual signal changes compared to the block-trial paradigm (see Fig. 4c,d). This is seen especially on the right side of the brain (left side of the image) where the function is obscured by the artifact in the block-trial paradigm.

Difference images

A time series of difference images obtained by subtracting the first image from all other images of the averaged image response time-course for the overt word production task shows large signal changes at the edge of the brain in the third image of the averaged image time-course. Signal changes resulting from functional activation occur 3–5 sec later (see Fig. 5).

DISCUSSION

The single trial paradigm offers a method to obtain functional MR images in the presence of a specific class of motions–those that involve brief subject movement associated with the task. Such brief movements induce signal changes with markedly different temporal characteristics than the delayed and prolonged BOLD signal changes associated with neuronal activation,

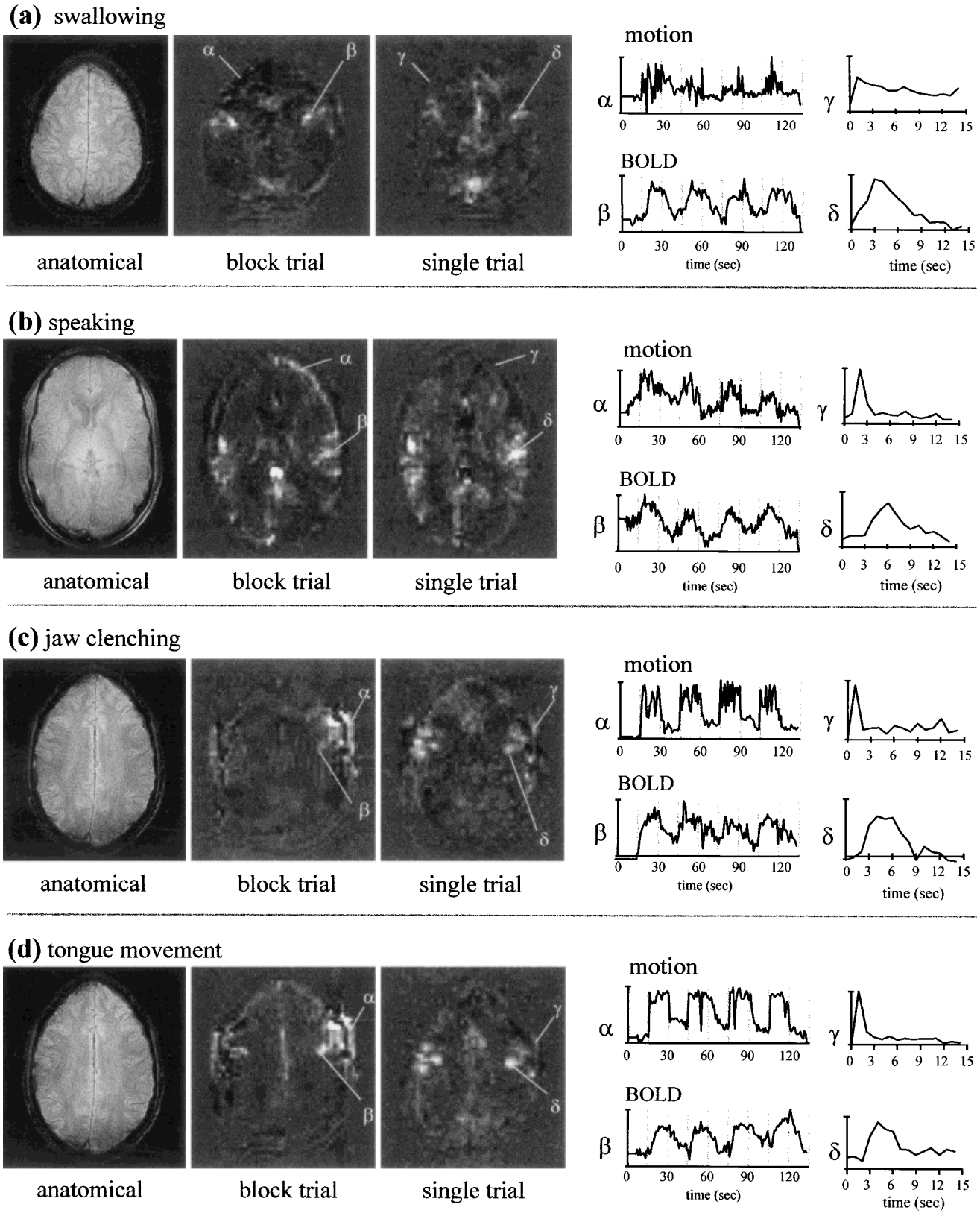

Figure 4.

Functional activation maps for the tasks of **(a)** swallowing, **(b)** speaking, **(c)** jaw clenching, and **(d)** tongue movement obtained using either the single-trial or the block-trial paradigm. A gradient echo magnitude image is shown to the left of the activation maps to aid in localizing the slice being imaged. The graphs on the right show signal intensity time courses of a pixel at an edge (α) and in a region showing functional activation (β) for the block trial paradigm, and at an edge (γ) and in a region of functional activation for the single-trial paradigm (δ) demonstrating characteristic BOLD signal changes. The BOLD signal changes (γ) are slower and delayed relative to the motion-related signal changes (δ).

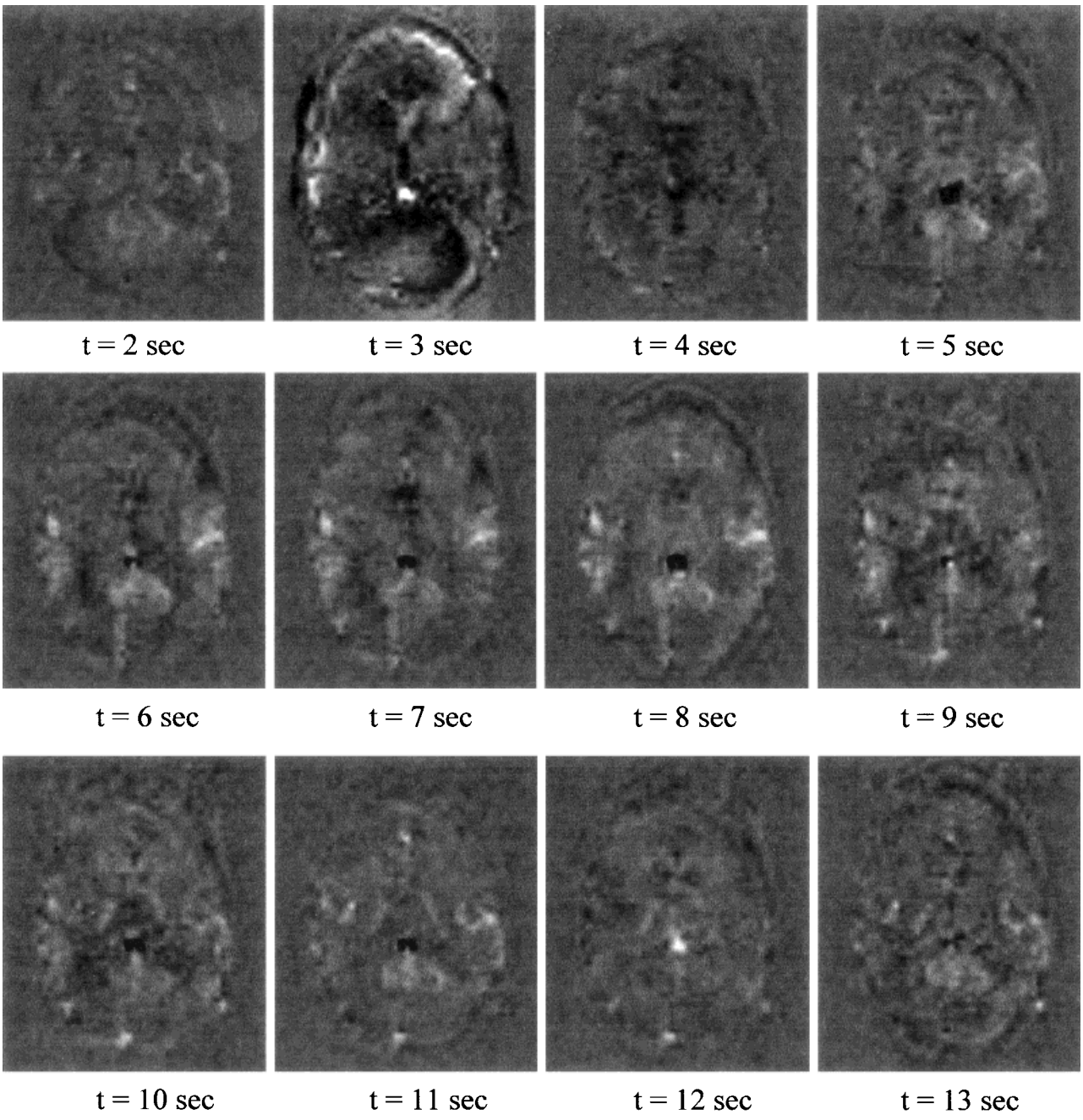

Figure 5.
A series of difference images obtained by subtracting the first image from each image in the averaged time series from the single trial study of speaking. The motion related signal changes are seen at the edges of the brain at t = 3 sec, whereas the functional signal changes peak at t = 8 sec.

allowing motion artifacts to be distinguished from regions of brain activation. An implicit assumption of this technique is that the brain image returns to its original state between task performances. While this seems quite restrictive, there are several cases when the assumption is valid. In the case that the signal changes are due to magnetic field changes resulting from motion outside the FOV, such as during tasks involving movement of only the jaw, tongue, or facial muscles, the image returns to its original state since the

jaw, tongue, and facial muscles easily return to their original position between tasks. Additionally, with proper restraints, the head can relax back to its original position between tasks. In cases where significant head motion does occur between task performances, image registration routines can be applied [Friston et al., 1995; Hajnal et al., 1995; Woods et al., 1993].

In the present study, motion artifacts were reduced by removing the signal changes proportional to motion from each pixel's signal intensity time-course. Since the slices are acquired successively, the time-course of the signal changes due to motion vary between the slices. The correction must therefore be performed on a slice-by-slice basis. An alternate method for motion correction is to ignore the images occurring during the motion. This was found to reduce the motion artifacts, but not as well as orthogonalizing with respect to the motion, especially in cases where the motion induced signal changes overlap slightly with the BOLD response.

A potential drawback of the technique presented here is that neural activity occurring prior to the overt motion may be much harder to detect. For example, motor sequencing before a swallow might occur several seconds before the actual action, so that the BOLD response and the motion artifact could overlap. If the motion is brief, however, then the motion induced signal changes occur only for a short duration, unlike the prolonged BOLD response associated with neuronal activity.

As expected, the signal responses to brief stimuli (less than 2 sec) are much smaller than those for longer stimulations found in a blocked trial design. Experiments have shown that a stimulation of 2 sec results in a functional contrast-to-noise (fCNR) 35% lower than that encountered in blocked trial paradigms [Bandettini and Cox, 1998] (Bandettini et al., submitted). This reduction in fCNR, however, may be acceptable in a number of cases. Certain cognitive paradigms, such as the ability to randomize task types or to analyze fMRI responses based on measured subject responses, lend themselves more to an event-related imaging approach. In the context of this work, the employment of event-related imaging paradigms allows substantial reduction of motion artifacts.

Repeated dry swallowing, which is required for the block style paradigm, becomes precipitously difficult due to drying of the mouth and throat and may thus involve additional areas responsible for anxiety. The difficulty of the task has also been shown to be related to the amount of signal change, and therefore the magnitude and extent of activation may not accurately reflect the control of swallowing under more normal circumstances. Using a single trial paradigm enables the neuronal control of both voluntary and reflexive swallowing to be studied under more natural conditions. The imaging paradigm should therefore be chosen according to the task being studied, the hypothesis being tested, and the analytical techniques to be applied to the data.

Since the functional contrast between single trial and block trial paradigms are not the same, a comparison of the functional activation maps between the two techniques can be performed by either keeping the imaging time constant, or by recording a similar number of events. In the current study, shorter imaging time-series were used for the single trial paradigm in order to offset the lower functional contrast in the single trial paradigm resulting from sampling fewer events. The difference in the timing and shape of the two types of signal responses (BOLD and motion), however, has been demonstrated and is unlikely to be changed by longer acquisitions.

Motion artifacts are a significant concern in the successful determination of functional activation maps. The single-trial paradigm presented here offers a way to overcome stimulus correlated motions, allowing for new neuropsychological tests to be performed with fMRI and increases the flexibility of current protocols.

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