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A MRI-COMPATIBLE SYSTEM FOR WHISKER STIMULATION

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Abstract

We describe here a system for whisker stimulation designed for functional studies in high-field magnetic resonance imaging (MRI) environments. This system, which incorporates real-time optical monitoring of the vibration stimulus, can generate well-controlled and reproducible whisker deflections with amplitudes up to 2 mm and frequencies up to 75 Hz, suitable for functional magnetic resonance imaging (fMRI) studies of animals. Whiskers on either or both sides of the head can be stimulated selectively during fMRI experiments without removing the subject from the magnet. With a user-friendly graphical interface of a computer, a user can conveniently control both the whisker vibration and gating of the MR imager, and synchronize the stimulation with the fMRI acquisition to ensure precise timing of the stimulus presentation. This whisker stimulation system should facilitate a wide variety of fMRI investigations of the neural systems mediating sensory information from the whiskers.

Keywords

barrel cortex; fMRI; imaging; rabbit; somatosensory; vibration; vibrissae; whisker

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1. Introduction

The mystacial whiskers provide an easily accessible and tractable system to study sensory processing in the mammalian brain. Each whisker forms the receptive field for groups of neurons in the brainstem (barrelettes), thalamus (barelloids) and cortex (barrels). The anatomical and functional properties of the mystacial vibrissae have been extensively examined (Brecht, Preilowski & Merzenich, 1996; Rice, Mance & Munger, 1986) and the barrel-field organization of the rabbit and rat has been mapped in detail (Gould, 1986; Hoeflinger, Bennett-Clarke, Chiaia, Killackey & Rhoades, 1995). The physiologic properties of the somatosensory barrel cortex have also been well described in rabbits (Swadlow, 1989; Swadlow & Hicks, 1996). These properties of the whisker-barrel system, plus the tolerance of rabbits for restraint, make the whisker system in rabbits an ideal system to study with fMRI provided that the whiskers can be stimulated with precise timing and amplitude in the magnetic environment.

A wide variety of techniques have been previously used to stimulate the whiskers of immobilized animals. The coarsest technique typically uses a fine brush to stroke the whiskers manually and repeatedly (Siucinska & Kossutt, 1966). This technique lacks temporal and spatial precision. Electrical stimulation of the nerve endings has also been used (Berwick, et al., 2005), but is invasive and generates electrical artifacts. Another technique uses a piezoelectric strip that is attached to the whiskers (Das et al., 2001; Galvez et al, 2006). However, the currents used to power the device can produce distortion in MR images. More sophisticated stimulators typically use solenoids to move a device that couples to one or more whiskers (Gerrits, Stein & Greene, 1998; Krupa; Brisben, Nicolelis, 2001; Lu, Soltysik, Ward, Hyde, 2005). However, implementing such a device in the presence of high-strength magnetic fields (3T or higher) would require a non-ferrous motor, or a motor outside of the magnet with a long non-magnetic actuator arm (Gerrits, Stein & Greene, 1998). Adapting any of these techniques to high-field MRI systems presents a challenge because of limited space inside the magnet bore and potential image artifacts due to the interference of the stimulating device with the MRI signals. Airpuff delivery has been used as an alternative method to produce a whisker deflection within a MRI environment (Sachdev et al., 2003), but does not readily allow precise tuning or monitoring of the stimulus waveform over a range of frequencies and amplitudes.

A device proposed by Yang et al. (1996) takes advantage of the strong static magnetic field of MRI systems to oscillate a simple coil of wire. When placed within the static field, the coil experiences alternating magnetic force when driven with an alternating current, causing it to oscillate perpendicular to the axis of the static field. This coil can be coupled to the whiskers to produce a well-controlled vibration stimulus. Electromagnetic interference can be reduced to a negligible level by positioning the oscillating coil at a distance from the MR imaging coil and coupling the oscillation to the whiskers using a long arm or band. However, the original design lacks the capability to measure the waveform of the whisker deflection in real time. The ability to monitor the stimulus waveform in real time is critical in order to control accurately the frequency and amplitude of the whisker deflection for consistent and reproducible stimulation.

Here we describe a MRI-compatible whisker stimulator which expands upon the design of Yang et al (1996). Our system represents a significant advancement over the original design, and incorporates several features essential for reproducible, artifact-free whisker-stimulation fMRI experiments on small animals in high-field MRI systems. These features include a fiber band for coupling the deflection generated by the oscillating coil to the whiskers in order to avoid MR artifacts, as well as an optical reflectance sensor for monitoring the amplitude and frequency of the deflection in real time. Our results demonstrate that we can

reliably vibrate selected whiskers at frequencies up to 75Hz and amplitudes up to 2mm (corresponding to a maximum deflection velocity of 940 mm/s) while collecting artifact-free fMRI data from the somatosensory whisker barrel cortex of awake rabbits.

2. Design and Materials

The key requirements of this whisker stimulation system were that it must establish a source of mechanical vibration compatible with the strong magnetic field of MRI systems and must couple the vibration in a consistent and well-controlled manner to the animal whiskers. Figure 1 shows the whisker stimulator that is incorporated into our standard rabbit imaging cradle (Wyrwicz et al., 2000). The stimulator consists of two 15mm-diameter vibrating coils (A) made of six-turns of copper wire (AWG: 30). Each coil is taped to a straight fiber band (B) with the coil plane parallel to the direction of the static magnetic field B_0 within the MRI system. At one end the fiber bands are attached to nylon machine screws (J) at the front of the cradle using round, non-magnetic beaded chain (I). The other ends are securely fixed at points below the crossbar that is used to secure the animal head. This setup allows the tension in each fiber band to be adjusted independently without rotating the plane of the band or the vibrating coils and without removing the cradle from the scanner. Fine adjustments of the fiber band tension enable a stable waveform of the vibration at the desired frequency and amplitude, which can be monitored with an optical reflectance sensor (D), as described below. The optical sensor is attached to the cradle using a custom-built holder (E) and aimed at a reflective surface (F) on the band.

When driven by the alternating current, the coil, coupled to the attached whiskers by the fiber band, oscillates due to the magnetic forces induced by the current in the static magnet field. The coil is connected in series with the output loop of a current amplifier. The current amplifier was built on a single NPN-type transistor (NTE270, NTE Electronics, Inc., Bloomfield, NJ 07003, USA). The current is controlled by the input voltage to the transistor, which serves as a driving voltage for the stimulation system and is provided by a sinusoidal signal from a function generator (Model 4040A, BK Precision Corp., Yorba Linda, CA, USA) which is operated in burst mode (gate mode) so that the stimulus starts and stops in response to a TTL gate from a computer. The frequency and amplitude of the coil vibration can thus be tuned by adjusting the driving voltage. Figure 2 illustrates the interconnections between the vibrating coil, the current amplifier and the function generator.

The mechanical vibration is monitored in real-time using a system that incorporates a fiber optic-based infrared (IR) reflectance sensor (Miller et al., 2005) calibrated specifically to quantify the whisker deflection. This sensor transduces the movement of the fiber band into a voltage waveform, which enables the mechanical vibration to be monitored visually by an oscilloscope (Tektronix, Model TDS 3004, Tektronix, Inc., Beaverton, OR, USA) or digitized and recorded. The optical reflectance sensor system consists of an IR light emitting diode (LED) and a photosensor which are integrated into an amplifier circuit. The amplifier box is placed behind the shielding wall of the magnet to avoid possible interference. A fiber-optic cable is used to transmit the light from the LED to the fiber band and transmit the reflected light to the photosensor. This cable consists of 19 multimode optical fibers (200 μ m core diameter) bifurcated into 9- and 10-fiber partitions. The 10-fiber segment transmits light from the LED to the fiber band, and the remaining 9 fibers transmit the reflected light from the fiber band to the photosensor. As shown in Figure 1, the 19-fiber probe end of the cable is encased in a rigid plastic housing which is easily fixed to the cradle to monitor the fiber band. A small (5mm diameter) hole was drilled through the horizontal bar that holds the probe head to avoid additional reflection or scattering. A small (10mm $\times$ 10mm) square of paper, which provides a consistent reflective surface identical to that used in the calibration described below, is attached to the fiber band directly below the probe head. Vibration of the

fiber band produces a change in the magnitude of reflected light that corresponds to the displacement of the fiber band. The amplified output voltage of the photosensor is digitized and stored in a personal computer (Dell Computer, Austin, TX, USA) via a data acquisition board (model: PCI-MIO-16E-4, National Instruments, Austin, Texas, USA) with a program written in LabView (Version 6, National Instruments, Austin, Texas, USA) programming platform (Li, et. al., 2003). The output waveform is also displayed on the oscilloscope during an experiment. Thus, this system can monitor both the driving and stimulus waveforms, ensuring that the whisker deflection occurs at the desired amplitude and frequency.

3. Setup and Calibration

For each experiment the selected whiskers are secured to a strip of card-stock paper coated with a mild adhesive from a glue stick. This paper is then attached to the fiber band using masking tape. The coil is secured to the fiber band using stronger adhesive tape. The vibrating coil is placed approximately 27 cm from the MR imaging coil, which we have observed is sufficient to avoid electromagnetic interference. At the end of each experiment, the masking tape and card-stock paper are brushed with a mild adhesive remover to allow them to be removed without damaging the whiskers.

The amplitude of whisker deflection can be calculated from the measured deflection of the fiber band at the location directly below the probe head. In the simplest case the whisker deflection could be monitored directly at point of whiskers attachment. However, this situation may not always be possible due to spatial limitations of the magnet or other experimental constraints. Thus, we describe below a more generalized method that allows for measurement of the whisker deflection at an arbitrary point on the fiber band.

Figure 3 shows a schematic of the fiber band and the locations of the vibrating coil (C), whisker attachment point (B) and the probe head (D) where IR light is reflected. When the fiber band oscillates, points B, C and D move in the same direction simultaneously but experience different deflection amplitudes. The deflections of the fiber band at points B, C and D are represented by Y_1 , Y_3 and Y_2 , respectively. It is straightforward to express the relationship between the deflection amplitudes Y_1 and Y_2 . Let us assume that at a given moment the fiber band deflects away from its equilibrium position, as indicated by a dash line on Figure 3. When the vibrating coil deflects from C to C_1 , the attached whiskers deflect from B to B_1 and the reflective surface on the fiber band deflects from D to D_1 simultaneously. By connecting the peaks of the deflections at points B, C and D with the dash and solid lines, we can define two pairs of similar triangles. The first pair is defined by ABB_1 and ACC_1 , and the second pair is defined by EDD_1 and ECC_1 . The first pair of similar triangles gives the relationship,

$$\frac{Y_3}{Y_1} = \frac{X_0 + X_1}{X_0} \quad [1]$$

Similarly, the second pair gives the relationship,

$$\frac{Y_3}{Y_2} = \frac{X_2 + X_3}{X_3} \quad [2]$$

where X_0 is the distance between A and B, X_1 is the distance between B and C, X_2 is the distance between C and D, X_3 is the distance between D and E, as illustrated in Figure 3. Combining these two equations gives a general relation of Y_1 and Y_2 :

$$Y_1 = \frac{X_0(X_2 + X_3)}{X_3(X_0 + X_1)} Y_2 \quad [3]$$

In our whisker stimulation system, $X_0=80\text{mm}$, $X_1=200\text{mm}$, $X_2=700\text{mm}$ and $X_3=100\text{mm}$. With these values, equation [3] is simplified to

$$Y_1 = 0.486 Y_2 \quad [4]$$

Thus, for our case the whisker deflection Y_1 is simply proportional to Y_2 , the deflection amplitude of the fiber band directly beneath the probe head, with a proportion constant of 0.486.

The deflection amplitude Y_2 is determined based on the relationship between the deflection amplitude and the magnitude of the reflected light. The relationship can be established by constructing a calibration curve to describe quantitatively the amplified output voltage from the photosensor as a function of the displacement of the fiber band relative to the surface of the probe head. We implemented this calibration using a Kopf stereotaxic (Model KOPF 1730, David KOPF Instruments, Tujunga, CA, USA). A 10mm-by-10mm square reflective surface, identical to that attached to the fiber band during experiments, is positioned at known distances above the optical probe head. The probe was fixed to the base of the stereotaxic device with the arm holding the reflective surface positioned vertically above. It was found that at distances below 8.4 mm the output voltage of the reflectance sensor was saturated for the reflective surface used in these experiments. The initial distance between the fiber-optic probe head and the reflective surface was 8.4mm. The arm was then moved vertically upward in increments of 100 μm and the output voltage was recorded after each step using the digital oscilloscope. We continued this process until the voltage reading was below the resolution of the oscilloscope. This calibration curve for our system is shown in Figure 4.

As expected, the change in sensitivity visible in the calibration curve over large distances reflects the inverse-square falloff in light emitted from the fiber. However, as shown by the linear regression in the inset of Figure 4 ($R^2=.996$) the response is linear to a good approximation over the relatively small distances (<2 mm) typically used for whisker deflection. The deflection characteristics of the vibrating fiber band can be described by both the peak-to-peak voltage, which corresponds to the deflection range of the band, and the mean voltage, which corresponds to the mean distance of the band from the probe head (i.e., the resting position around which the band oscillates). In practice, the mean distance can be chosen, as dictated by the choice of materials and other potential experimental constraints, to provide a suitable level of sensitivity without saturating the photosensor.

Figure 5 shows examples of waveforms recorded from the fiber band vibrating at 45 Hz and 65 Hz. The input waveforms from the function generator are also shown for reference. The vibration waveform reached a stable amplitude after approximately three cycles (Fig. 5A). After changing the frequency of the driving voltage from the function generator to 65 Hz, a distorted vibration waveform of the fiber band was observed (Fig. 5B). A stable deflection of the selected whiskers at the desired frequency and amplitude can be achieved by finely tuning the tension of the fiber band with the assistance of the real-time monitoring system. The deflection amplitude corresponding to output voltage from the photosensor can be calculated from the calibration curve and Equation [4]. By turning the nylon screw (Fig. 1), the tension in the band can be changed until the voltage waveform displayed on the oscilloscope stabilizes at the correct frequency and amplitude. For our system, we generally found that changing the driving frequency by 20 Hz or more resulted in a distorted output

which required adjustment of the fiber band tension. After this adjustment a stable waveform was restored (Figure 5C).

We have observed that this system can reliably and reproducibly vibrate selected whiskers at frequencies up to 75Hz and amplitudes up to 2mm. In general, the waveform of the whisker deflection follows the sinusoidal waveform of the driving voltage. The delay in the onset of the driven whisker deflection is less than one cycle of the driving waveform. The rise time of the vibration waveform to a stable maximum level is less than 250ms. A flatness of a non-perfect sinusoidal waveform can be estimated by a relative standard deviation (standard deviation/mean) of the peaks over a period of time during which the waveform is stable. The relative standard deviation for the driven whisker deflection waveform is 5% or less, although, as described above, fine tuning of the fiber band can be necessary to achieve a stable waveform. Outside of the frequency and amplitude range given above, fine tuning for a stable waveform of the whisker deflection becomes more time-consuming, and may be less practical for in-vivo animal experiments.

4. fMRI of the Whisker Stimulation

We have used this whisker stimulation system extensively for fMRI studies on awake rabbits, where it has demonstrated its ability to produce reliable and effective whisker stimulation and robust functional activation without inducing image artifacts related to electromagnetic interference. Below, we provide an example of fMRI data acquired during the stimulation of two adjacent whiskers to demonstrate the ability of our stimulation system to induce robust functional activation in the whisker barrel cortex.

4.1 Animal preparation

Female adult Dutch Belted rabbits (2–4kg) were implanted stereotactically with restraining headbolts as described previously (Wyrwicz et al., 2000). The headbolt enables consistent positioning of the radio-frequency (RF) surface coil on the animal's head, and allows us to achieve a consistent imaging angle and slice position. After recovering from surgery, the rabbits were habituated to the MRI environment before MR imaging. For this study we selected two whiskers (A1 and A2) on the left side of the face for stimulation.

4.2 fMRI data acquisition

All MRI experiments were performed on a Bruker Biospec 94/30 imaging spectrometer (Bruker Biospin MRI, Ettlingen, Germany) operating at ^1H frequency of 400MHz. The spectrometer is equipped with actively-shielded gradient coils which are capable of generating a maximum gradient field of 40 G/cm in each of three axes. A single-turn, 40mm-dia., circular RF surface coil was used for both transmission and reception. A multi-slice gradient-recalled echo (GRE) imaging sequence was used to obtain high-resolution anatomical images for localization of the whisker barrel cortex. fMRI data were acquired from four consecutive, 1mm-thick slices of brain in the axial plane using a single-shot, gradientecho multi-slice echo-planar imaging (EPI) pulse sequence with a repetition time (TR) of 2s, an echo time (TE) of 11ms, a 30mm×30mm field of view (FOV), and a data matrix of 80×80, corresponding to an in-plane resolution of 375μm×375μm.

4.3 Stimulus Presentation

Each set of fMRI data contained ten trials, where each trial consisted of a baseline period (20 images), a stimulation period (20 images), and a recovery period (20 images). The total imaging time for each set of data was approximately 20 minutes.

fMRI data sets were collected using a whisker stimulation frequencies of 40 Hz. We ensured that the whisker deflection was stable prior to fMRI data acquisition. Using the calibration curve and Equation [4], the whisker deflection amplitude was adjusted to 0.2mm, corresponding to a 100mV peak-to-peak output measured by the photodetector and a maximum deflection velocity of 50 mm/s. The mean voltage was measured to be -1.20V.

4.4 Data Analysis

All images were processed off-line using software developed in-house for Matlab (The Mathworks, Natick, MA). The data matrix was zero-filled to 128×128 and images were then reconstructed. The first five images were removed from each trial to ensure that the MR signal reached steady state. All images were examined for global motion artifacts, and any trial showing significant global motions was excluded. The remaining trials were averaged. Activated regions were detected by cross-correlation of the averaged data on a pixel-by-pixel basis with a boxcar reference function. Pixels with a cross-correlation coefficient (CCC) greater than 0.4 were further evaluated with a *t*-test. Only pixels with a *P* < 0.001 were considered to be activated. Activation maps were generated by superimposing color-coded CCCs of the activated pixels on EPI images.

5. Results

Subtraction of GRE and EPI images obtained with and without coil vibration revealed no difference in terms of image intensity or shape, indicating that the coil producing the vibration had no detectable interference with MR imaging.

Figure 6 shows the BOLD response in the whisker barrel cortex produced by stimulating whiskers A1 and A2 on the left side of the face. As expected, BOLD activation (Fig. 6a) appears contralateral to the stimulated whiskers as a focused cluster extending through the depth of the cortex, and no ipsilateral response is observed. This response is consistent with our previous fMRI study of the whisker barrel cortex (Song et al., 2010), and corresponds well to previous histological analysis of the rabbit somatosensory cortex (Gould, 1986). The averaged BOLD time courses of activated voxels in this cluster (Fig. 6b) illustrate the temporal behavior of the BOLD response, which shows a consistent plateau of activation after the initial peak following stimulus onset.

6. Discussion

We have described in detail our design, construction and application of a whisker stimulation system for use in high-field MRI environments. By incorporating an optical sensor that enables real-time monitoring of the vibration waveform, this system can produce a stimulus waveform that is stable throughout an entire experiment and well-controlled in frequency and amplitude. Our fMRI results demonstrate that this system can reliably generate activation in the whisker barrel cortex without inducing image artifacts from RF interference. A user can easily and accurately select the vibration frequency and amplitude with the guidance of the real-time display on either or both sides of the animal without removing the cradle from the scanner.

Although we employ the same vibrating coil design proposed by Yang et al. (1996), our system incorporates a number of features that facilitate the generation of a well-controlled stimulus. The fiber band provides an easier surface for attachment of the whiskers, as compared to a thin wire, and allows experimenters to selectively stimulate specific whiskers without the need to trim neighboring whiskers. Furthermore, the flat surface of the band and its attachment to the cradle with a small beaded chain ensures that the reflective surface remains perpendicular to the reflectance sensor even after tuning. Although, as described

previously, fine-tuning of the tension in the fiber band is necessary to ensure a stable vibration waveform, this process is quickly accomplished (typically in less than five minutes), and can be done prior to imaging. Despite these additional features, the components involved are simple and the material cost for constructing the stimulator remains low. A minor shortcoming that we observed with this design is that the vibration of the fiber band generates a faint but perceptible sound. However we have not detected any activation of the auditory cortex, and have not observed that the awake rabbits respond to the sound at the vibration amplitude used during fMRI experiments. In our current design, we made use of an existing rabbit cradle and the off-the-shelf materials in order to reduce the construction costs and time.

The ease of manipulation and clearly-organized representation that characterize the whisker system make it an ideal basis for fMRI studies seeking to measure detailed changes in activation area or temporal response. Quantifying these changes during modulation by such factors as anesthetics, local or systemic drug delivery, or learning-related plasticity provides deeper insight into the neurophysiological mechanisms that underlie the detected activation. This information is important for building more sophisticated models of hemodynamic response in the brain and for refining our ability to interpret fMRI data for both research and clinical applications. The ability of our system to deliver a stable, repeatable stimulus that is well-controlled in frequency and amplitude is crucial for advancing such quantitative studies in high-field MRI environments.

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Highlights

- > We designed, constructed and tested a whisker stimulator for high-field MRI systems.
- > Mechanical vibration of a coil of wire is coupled to whiskers.
- > The whisker deflection is monitored in real time with an optical system.
- > The stimulator deflects whiskers at frequencies up to 75Hz and amplitudes up to 2mm.
- > The whisker deflection can be synchronized with fMRI data acquisitions.

Figure 1.

Key components of the whisker stimulation system. The stimulator consists of two 15mm-diameter vibrating coils (A) of copper wire. Each coil is taped to a straight fiber band (B). At one end the fiber bands are attached to nylon machine screws at the front of the cradle using round, non-magnetic beaded chain (I) that is attached to a nylon machine screw (J). The coils are driven by an alternating current via BNC connectors (C). The deflection of the fiber band is measured by detecting the changes in the reflecting light from a 10mm×10mm surface attached to the fiber band directly below the probe head. The reflecting light is captured with an optical probe head (D), which is snapped on a holder (E) and aims at the fiber band.

Figure 2.

Interconnections between the vibrating coil, the current amplifier and the function generator. The current amplifier was built on a single NPN-type transistor (NTE270). The gate signal controls the stimulation with synchronization with data acquisition during an fMRI experiment.

Figure 3.

Schematic of the fiber band. At a given moment, the fiber band deflects from its equilibrium position (solid line) to a position indicated by the dashed line. The fiber band is fixed at both ends (A and E). When the vibrating coil deflects from C to C_1 , the attached whiskers deflect from B to B_1 and the light-reflection point on the fiber band deflects from D to D_1 , simultaneously. The deflections of the fiber band at points B, C and D are represented by Y_1 , Y_3 and Y_2 , respectively.

Figure 4.

Calibration curve for the output voltage of the reflectance sensor as a function of distance. The distance is measured from the light-detection probe head relative to a reflective surface identical to that attached to the fiber band for our experiments. The inset shows the response over a range of 2mm at a distance from the fiber band comparable to that used for our experiments. A linear regression of the calibration data within this 2mm range demonstrates that the response is linear to a good approximation ($R^2=0.996$). Note that the output voltage of the reflectance sensor saturated at distances below 8.4 mm (black bar).

Figure 5.

Optical measurement of whisker stimulation waveform. For all figures, the top trace shows the deflection waveform of attached whiskers and the lower trace shows the waveform of the driving voltage. A: A stable waveform of the attached whiskers with desired frequency (45Hz) and amplitude after the tension was initially adjusted. B: A waveform of the whiskers after the frequency of the driving voltage was changed from 45Hz to 65Hz. The waveform of the whiskers was seen distorted as compared with the waveform of the driving voltage from the function generator, as shown on Figure 5B. The waveform of the attached whiskers was restored to a stable state with desired frequency and amplitude after small adjustments of the tension of the fiber band (Figure 5C). For clear comparison, the traces of

the driving and whisker-deflection-induced waveforms are displayed together with artificially-shifted baselines and different voltage scales. The top traces are 50mV in amplitude and the lower traces are 2–2.5V in amplitude.

Figure 6.

Functional activation in the whisker barrel cortex in response to sinusoidal whisker stimulation. Robust BOLD activation (a) was observed in the whisker barrel cortex during 40 Hz stimulation of whiskers A1 and A2 on the left side of the face. As expected, activation appeared contralateral to the stimulated whiskers, with no response on the ipsilateral side. The color scale indicates the magnitude of the cross-correlation coefficient. The averaged time course of BOLD activation (b) in this activated region demonstrates the temporal behavior of the signal, which shows a consistent plateau of activation after an initial peak following stimulus onset. The gray bar indicates the timing of the stimulus presentation.