

Cortical activity in multiple motor areas during sequential finger movements: An application of independent component analysis

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Multiple cortical regions such as the supplementary motor area (SMA), premotor cortex (PM), and primary motor cortex (M1) are involved in the sequential execution of hand movements, but it is unclear how these areas collaborate in the preparation and execution of ipsilateral and contralateral hand movements. In this study, we used right-handed subjects to examine the spatial distribution and temporal profiles of motor-related activity during visually cued sequential finger movements by applying independent component analysis (ICA) to event-related functional magnetic resonance imaging (fMRI) signals. The particular merit of the ICA method is that it allows brain activity in individual subjects to be elucidated without making a priori assumptions about the anatomical areas that are activated or the temporal profile of activity. By applying ICA, we found that (1) the SMA contributed to both the preparation and execution of movements of the right and left hand; (2) the left M1 and dorsal premotor cortex (PMd) contributed to both the preparation and execution of movements of the right and left hand, whereas the right M1 and PMd contributed mainly to the execution of movements of the left hand; (3) pre-SMA areas were activated in some subjects in concert with the posterior parietal and prefrontal cortex; and (4) fMRI signals over superficial cortical draining veins could be distinguished from cortical activation. We suggest that ICA is useful for categorizing distributed task-related activities in individual subjects into several spatially independent activities that represent functional units in motor control.

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Introduction

Much of our daily behavior depends on the sequential execution of multiple movements in an appropriate temporal order. Among the various cortical regions that are involved in planning and executing sequential movements, studies in humans (Dick et al., 1986; Halsband et al., 1993; Laplane et al., 1977) have highlighted the importance of the supplementary motor area (SMA). In agreement with the aforementioned studies, monkeys were reportedly unable to carry out a sequence of three movements in a predetermined order after a bilateral injection of muscimol into the SMA (Shima and Tanji, 1998). In another study, neurons in the SMA of monkeys were active during both premovement and movement periods, at which time the animals recalled and pressed three touch-pads in a predetermined sequence in the absence of any external guidance (Mushiake et al., 1991). These observations illustrate the importance of the SMA not only during the execution of sequential movements, but also during the preparation of such movements.

In contrast to the SMA, the primary motor cortex (M1) was conventionally thought to be involved primarily in the execution of movements. However, this traditional view was challenged by single-neuron recording studies in monkeys, which revealed that M1 neurons were active not only during the execution of movements, but also during the period of preparation of visually guided movements (Alexander and Crutcher, 1990; Georgopoulos et al., 1993; Weinrich and Wise, 1982). Mushiake et al. (1991) showed that ~15% of M1 neurons were active during the period that preceded the execution of sequential movements. In addition, neurons in the dorsal premotor cortex (PMd) have also been reported to be active during the premovement periods of not only single (Kurata, 1993) but also sequential movements (Mushiake et al., 1991).

In accordance with these single-neuron studies in monkeys, Richter et al. (1997) used time-resolved functional magnetic

resonance imaging (fMRI) in humans to show that the SMA, M1, and PMd were active during both the preparation and execution phases of sequential movements. However, preparation-related activity in M1 has not been detected in other studies (Lee et al., 1999; Toni et al., 1999), although preparation-related activity in M1 was apparently detected in a more recent study (Zang et al., 2003). These reports illustrate the controversy concerning which areas of motor cortex are activated in human subjects during the preparation and execution of motor activity to achieve a sequence of multiple movements.

In some previous imaging studies (Richter et al., 1997; Zang et al., 2003), regions of interest were defined anatomically over a limited number (one to three) of motor areas. However, the variation of functional borders in individual subjects might have been overlooked by using the anatomical approach. In other studies (Lee et al., 1999; Toni et al., 1999), hypothesized temporal patterns of activation have been used to identify voxels in fMRI signals that exhibit changes that concur with the hypothesized models. In such hypothesis-driven approaches, it is possible to fail to identify activity that is not captured in the hypothesized model.

To overcome these shortcomings, we applied independent component analysis (ICA) to sequential blood oxygen level-dependent (BOLD) contrast image volumes (Ogawa et al., 1993) that were acquired during visually cued sequential finger movements to evaluate the cortical distribution and temporal profiles of activation in each individual subject. Even though the theoretical development of ICA occurred relatively recently (Bell and Sejnowski, 1995; Karhunen et al., 1997; Yang and Amari, 1997), this method has already been used as a data-driven approach for fMRI (Berns et al., 1999; Duann et al., 2002; Esposito et al., 2003; Kansaku et al., 2000a; McKeown et al., 1998; Seifritz et al., 2002; Zeki and Bartels, 1999). In the application of ICA, no a priori assumption is required as to the extent of activation or the temporal profiles of fMRI signal changes; the only assumption is that each BOLD contrast image volume is a weighted sum of a certain number of independent components (image volumes) that are statistically independent of one another. By applying ICA in the present study, we succeeded in identifying cooperative and independent combinations of activity across different areas of motor cortex during the preparation and execution phases of visually cued sequential finger movements.

Materials and methods

Subjects

Healthy males ($n = 3$, age 22–30 years) and females ($n = 2$, age 22–23 years) participated in the experiments. All subjects were neurologically normal and strongly right-handed according to the Edinburgh Inventory (Oldfield, 1971). The studies were approved by the appropriate institutional review committee. All subjects provided written informed consent in accordance with the institutional guidelines.

Behavioral task

The subjects were laid supine on the bed of an fMRI scanner. Two custom-made keyboards that comprised four keys each were

placed on the right and left thigh of the subject. The second through fifth fingers of the right and left hands were placed onto the appropriate keyboard keys (key pitch = 20 mm). The subjects were required to make a pretrained sequence of key-presses (fifth–third–fourth–second fingers, in order) three times (i.e., a total of twelve key-presses consisting of a sequence of four three times). In one experiment, the subjects made the sequential movement three times with each hand (i.e., each session comprised six movements). The subjects were instructed about the order in which to move their fingers 1 day before the experiment. Visual cues (blue and red rectangles) were presented on a tangent screen to instruct the subjects to prepare for movement of the right (blue rectangle) or the left (red rectangle) hand (preparation phase; Fig. 1). The disappearance of the visual cue was the signal for the execution of the movement (execution phase). To uncorrelate the timing of the preparation and execution phases, the interval between the appearance and disappearance of the visual cue was selected randomly from among six intervals (9, 11, 13, 15, 17, and 19 s; Fig. 1). The order of the cues for the right and left hand (right, right, left, left, right, and left) and the order of the cue appearance/disappearance intervals (19, 9, 13, 11, 17, and 15 s) were fixed for each of the five subjects. Each experiment lasted 240 s. Each subject participated in one experiment.

The performance of each subject was recorded by a PC system with infrared photosensors (Keyence, Co., Osaka, Japan). None of the subjects made any errors in six sequences of movements. The mean reaction time from the disappearance of the cue was 390 ± 160 ms (mean \pm SD). The mean duration of movement was 1700 ± 550 ms (mean \pm SD). There were no significant differences between the right- and left-hand finger movements ($P > 0.5$, Wilcoxon signed rank test) for either the mean reaction time (right, 360 ± 98 ms; left, 420 ± 210 ms) or the movement duration (right, 1700 ± 500 ms; left, 1700 ± 620 ms).

Imaging

Two-hundred and fifty sequential BOLD contrast image volumes (Ogawa et al., 1993) were acquired at 3.0 T for each experiment (Signa, GE Medical Systems, Milwaukee, WI) using gradient-echo echo-planar imaging (TR/TE = 1000 ms/30 ms, FA =

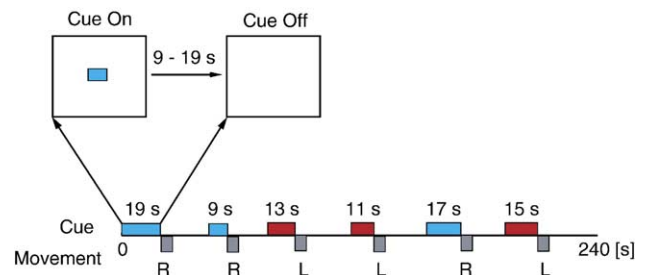


Fig. 1. Behavioral task used to examine activity in the motor cortex during the preparation and execution of visually cued sequential finger movements. Blue and red rectangles were used as visual cues. The blue and red cues were assigned to a sequential finger movement of the right (R) and left (L) hand, respectively. The appearance of a cue was used as a signal for the subject to prepare for finger movement, while the disappearance of the cue was used as a signal for the subject to execute the finger movement. The length of time for which the cue was presented was selected randomly from among six intervals (9, 11, 13, 15, 17, and 19 s).

30°, slice thickness/gap = 6/3 mm, field of view (FOV) = 20 × 20 cm², matrix size = 64 × 64). One image volume comprised five slices that were obtained in sequence, starting at the top of the brain. The regions of interest included the SMA, M1, and PMd in all subjects. We improved the homogeneity of the magnetic field by using both linear and second-order shims; this method was developed for spectroscopic imaging at 1.5 T (Spielman et al., 1998), and the effectiveness of this method for gradient-echo echo-planar imaging has been evaluated at 3.0 T (Kansaku et al., 2000b). Anatomical template images of the BOLD contrast image slices were acquired using a conventional technique (T2-weighted images; TR/TE = 6000 ms/180 ms).

Data analysis

For the ICA, we used software that was developed at the National Institute of Advanced Industrial Science and Technology (AIST, Japan). We modified the algorithms that were proposed by Bell and Sejnowski (1995) and Karhunen et al. (1997), and we included an additional algorithm with which we could assess the validity of convergence (Nishimori, 1999). The number of independent components was assumed to be 48 for the standard ICA. The data dimension was reduced first with the principal component analysis. Forty-eight independent components were calculated from 240 of 250 BOLD contrast image volumes (we excluded the first ten image volumes) that were acquired with a

repetition time of 1 s during each experiment. Each of the 48 independent components was expressed as an image volume of 5 contiguous axial images (Fig. 2). Voxel values of each independent component were thresholded at two times of the standard deviation, and superimposed on the T2-weighted images according to a pseudocolor scale (e.g., Fig. 2). Each independent component was associated with a corresponding row in a mixing matrix that consisted of 240 coefficients; the resultant data are referred to as the temporal profile of activity for the independent component (Fig. 2). We normalized the variance of each temporal profile to 1 by adjusting the scaling factor for each independent component and sorted the independent components in descending order according to the variance of each component. Note that the temporal profile of activity for each independent component was obtained without any a priori assumption about the temporal profile of brain activity; the temporal profiles were calculated assuming only that each independent component (image volume) was statistically independent of all other independent components.

To select physiologically relevant components from among the 48 independent components in the standard ICA, we cropped the temporal activity profile of each independent component into six fragments that were aligned with the presentation of either the preparation or execution cue. We calculated the correlation between each pair of the six fragments (${}_6C_2 = 15$), calculated the *P* value for each correlation, and finally selected the smallest *P* value among the 15 values. If the *P* value for the cropped data is small (i.e., the correlation is large), the independent component is

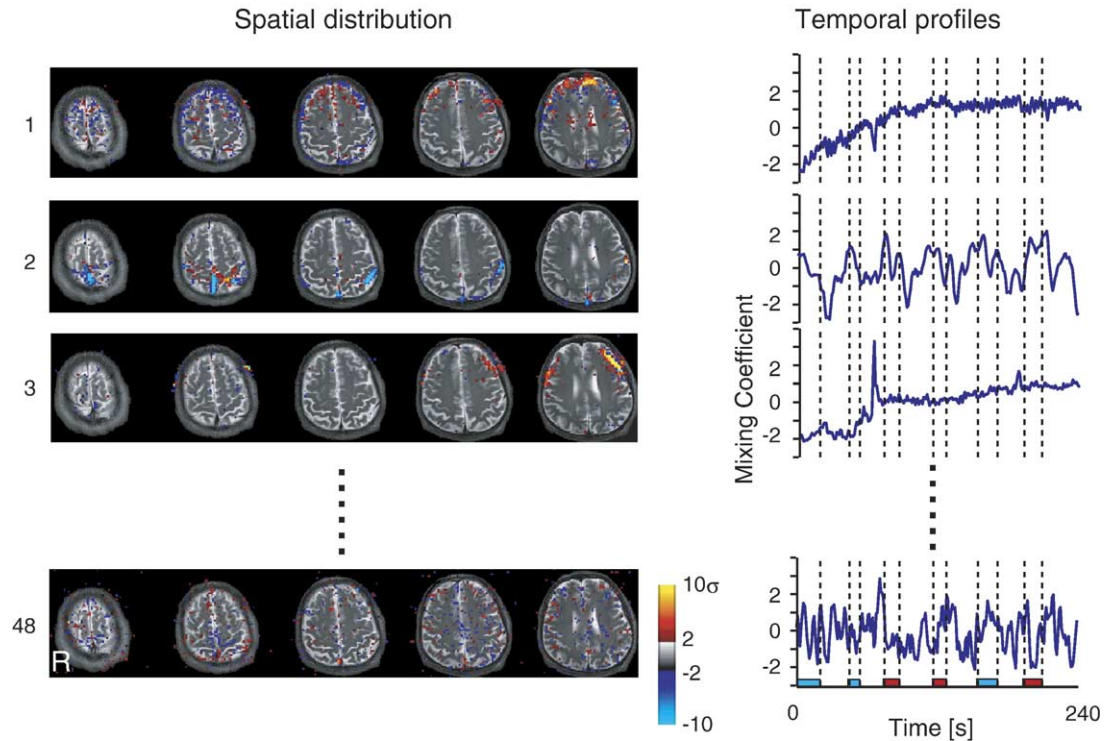


Fig. 2. Examples of independent components that were extracted from subject KK. The components were sorted according to the variance of each component, and independent components 1–3 and 48 are shown. The spatial distribution of the functional magnetic resonance imaging (fMRI) signals of each of the independent components is shown in the left panel. T2-weighted images were used as anatomical templates. Voxels that deviated from the mean by more than two times of the standard deviation are shown in color. The colored bar is a pseudocolor scale. Temporal profiles of activity for each of the independent components are shown in the right panel. It is noteworthy that the temporal profile for component 1 exhibited a sharp downward peak at the same time as the sharp peak in the temporal activity profile of component 3.

likely to be related to either the preparation (cue appearance) or the execution (cue disappearance) of finger movement. We selected all independent components for which the minimum P value was smaller than 0.00001 after Bonferroni correction for further examination. Between three and seven independent components were selected for each subject. To test the consistency of this method of selecting components, we repeated the ICA, but assumed a different number of components (specifically 8, 16, 32, 96, and 144 components).

We named some of these physiologically relevant components by evaluating if signals above the threshold (two times of the standard deviation) fell within anatomical ROIs that were defined over the SMA, M1, and PMd. The M1 was anatomically defined as the area bordered caudally by the anterior wall of the central sulcus and rostrally by the midline of the precentral gyrus. The SMA was defined as the area bordered caudally by the anterior lip of the precentral gyrus, and laterally by the medial part of the superior frontal gyrus. The PMd was defined as the area bordered caudally by the midline of the precentral gyrus, rostrally by the anterior wall of the precentral sulcus, and medially by the lateral part of the superior frontal gyrus (Richter et al., 1997). Using the vertical anterior commissure line as a landmark, the premotor cortices were additionally divided into two subdivisions (pre-PMd and PMd; pre-SMA and SMA) (Picard and Strick, 2001). When the signals in one independent component distributed over multiple ROIs, we named the component in the following order of priority: the SMA, right M1, left M1, and PMd. Thus, a component that showed major activation over the SMA was named as an “SMA component” even if supra-threshold signals were distributed over the other ROIs (Fig. 5).

For comparison, the data were further analyzed by using the general linear model implemented in Statistical Parametric Mapping 2 (SPM2, <http://www.fil.ion.ucl.ac.uk/spm/>) to estimate the finite impulse response (FIR) associated with the preparation and execution of finger movements. FIR model, which is sometimes referred to as the selective averaging, also allows us to model any forms of task-induced hemodynamic response (Burock and Dale, 2000; Ollinger et al., 2001). An FIR model comprised series of delta functions at each TR following stimulus onset. In our study, each task-induced response was modeled with N FIR bin, where N was different between the preparation and execution phase for right or left finger and corresponded to maximum trial length of each task phase, i.e., 19 s or 15 s for the preparation phase of right or left finger, and 25 s or 31 s for the execution phase of right or left finger, respectively. The design matrix contained total 90 FIR bins and one constant term. We also used the high pass filter that was composed of the discrete cosine basis function with a cut-off period of 128, to eliminate artifactual low frequency trends. Serial autocorrelation assuming a first-order autoregressive model was estimated with ReML (restricted maximum likelihood) procedure and used to whiten the data and design matrix (Friston et al., 2002a,b). The least-square estimation was performed on the high pass filtered and pre-whitened data and design matrix, giving the 90 estimated FIR parameters. Task-related effect was evaluated through F contrast. F contrast of the identity matrix of size 90 (the 90×90 square matrix with ones on the main diagonal and zeros elsewhere) is appropriate for detecting any response to the four task phases, i.e., the preparation and execution of right or left finger movement. For this analyses, significantly activated voxels were identified if they reached the height threshold of $P < 0.05$ (uncorrected).

Results

Fig. 2 shows the independent components that were extracted for a representative subject (KK). The fMRI signal of independent component 1 was distributed over the edge of the brain and ventricles. The temporal profile for independent component 1 revealed a gradual increase without any apparent correlation with the timing of the task events. Consequently, component 1 is likely an artifact. The fMRI signal of independent component 2 was distributed over the superficial cortical veins, and the temporal profile for this component revealed a sharp decrease in activity after the disappearance of the visual cues. The fMRI signal of independent component 3 was distributed over the edge of the brain, and the temporal profile for this component became relatively constant following a single sharp peak between the presentation of the second and third visual cues. As in the case of component 1, component 3 is likely an artifact. The fMRI signal of independent component 48 was distributed randomly inside and outside the brain, and the associated temporal profile was not correlated with the timing of the task events; therefore, component 48 was considered also to be an artifact. Observation of each of the 48 extracted independent components revealed a small number of components that were considered to be physiologically relevant. Consequently, we attempted to select physiologically relevant components objectively by determining whether the temporal profile for each component was associated with the events of the behavioral task, i.e., whether the temporal profile for each component changed after the appearance or disappearance of the visual cues.

Fig. 3A shows the temporal profile for independent component 16 from subject KK. The temporal profile was cropped into six 10-s fragments that corresponded to the appearance (arrowheads in Figs. 3A and B) and six 14-s fragments that corresponded to the disappearance (arrows in Figs. 3A and B) of the visual cues. It is apparent that activity associated with the disappearance of the visual cue (right panel in Fig. 3B) increased in a similar manner for each of the six disappearance episodes. The cross-correlation between activity associated with the disappearance and appearance of the visual cue was calculated for each pair of the six episodes (15 pairs each for disappearance- and appearance-related activities), after which the smallest (i.e., the most highly significant) P values for each of the 48 independent components were plotted (Fig. 3C). For further examination, we selected six independent components for which the smallest cross-correlation P value was less than 10^{-5} (red dots in Fig. 3C); this stringent selection criterion was used so that approximately five components were selected on average without losing the ability to select physiologically relevant components that were distributed over motor-related cortical areas.

Fig. 4 shows six statistically significant extracted independent components. Independent component 16 was distributed mainly over the SMA (Fig. 4A). The other components were distributed mainly over the right primary sensorimotor cortex (M1–S1, component 30; Fig. 4B), the pre-dorsal premotor cortex (pre-PMd) (component 20; Fig. 4C), the anterior cingulate cortex (component 25; Fig. 4D), and the cortical draining veins (component 2; Fig. 4E). Independent component 9 was distributed over the presupplementary motor area (pre-SMA), prefrontal cortex, and posterior parietal cortex (Fig. 4F).

The selection analysis described above was applied to the independent components that were extracted from each of the five

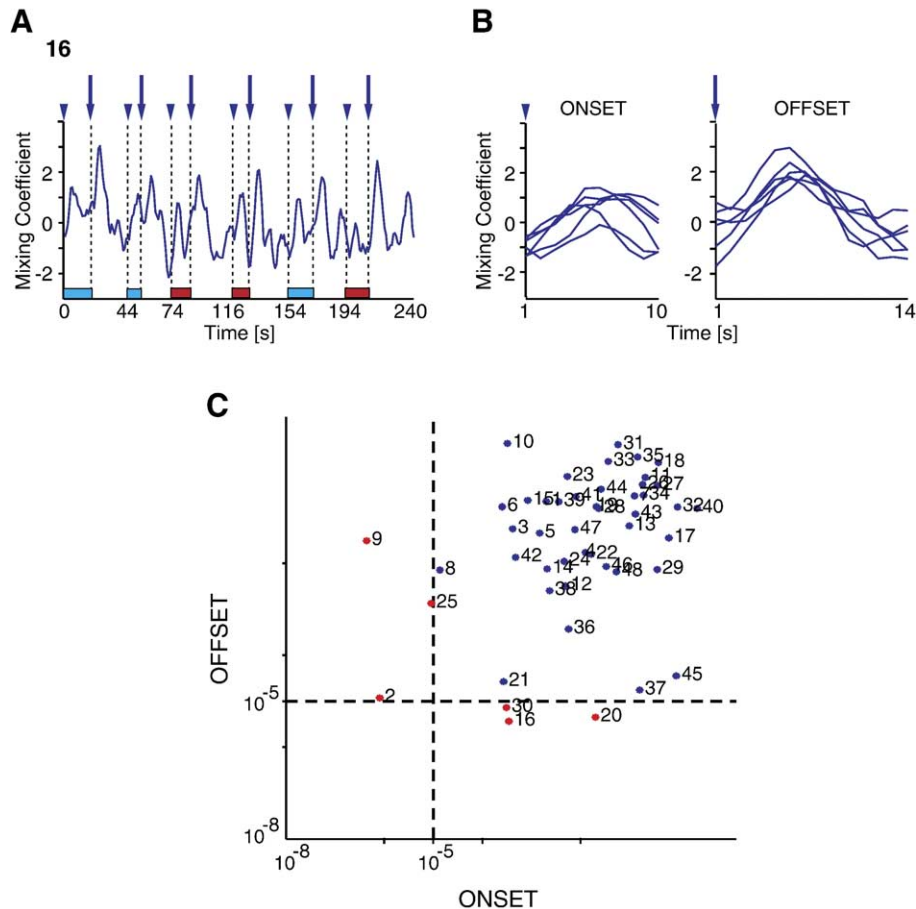


Fig. 3. Temporal profile associated with independent component 16 in a representative subject (KK). (A and B) Data were cropped at the time of the appearance (arrowheads in panels A and B) and disappearance (arrows in panels A and B) of the visual cues. (C) P values for the cross-correlation of the temporal profile corresponding to the appearance and disappearance of the cues. For the data that are presented, 6 of 48 independent components were significantly correlated ($P = 10^{-5}$) with the timing of the task paradigm.

subjects (Table 1). Between three and seven statistically significant independent components were identified for each subject. One independent component with a strong fMRI signal that was distributed over the SMA was isolated in each of the five subjects (Table 1), and a different independent component with a strong fMRI signal that was distributed over the right M1–S1 was detected also in all subjects (Table 1). An independent component with a strong fMRI signal that was distributed over the left M1–S1 was identified in two of the five subjects, and this component was extracted together with the SMA-associated component in the remaining three subjects. Signals that were distributed over the PMd appeared to be located within the precentral gyrus and the adjacent region (e.g., component 30 for subject KK; Fig. 4B), and these components were extracted together with the M1–S1 component (Table 1). An independent component over the pre-PMd was observed in one subject (KK). In addition, an independent component with activity distributed over the pre-SMA was observed in two of the five subjects. The pre-SMA component was extracted together with the components that were associated with the prefrontal cortex and posterior parietal cortex in both subjects. An independent component with activity distributed over the prefrontal cortex (TM) and anterior cingulate cortex was extracted in two subjects (KK and HS), and an independent component with activity distributed over the superficial cortical draining veins was observed

in four of the five subjects. The subject from whom the component was not extracted (TM) exhibited a component with activity distributed randomly, which was likely an artifact. These observations indicate that activity associated with most of the components that were selected as physiologically relevant was distributed over multiple areas of the motor cortex.

Independent components over the supplementary motor area

Fig. 5A shows the independent components that were distributed over the SMA for each of the five subjects. The mean temporal activity profiles of the independent components (Fig. 5B) consisted of six repetitions of a successive small and large peak in activity. The latency between these two peaks was highly correlated with the interval between the appearance and disappearance of the visual cue (Fig. 5C; $r = 0.91$, $r^2 = 0.82$, $P < 0.0001$, $n = 30$). The second peaks were significantly larger than the first peaks ($P = 0.0000031$, Wilcoxon signed rank test, 30 pairs). These results indicate that the first (smaller) peak occurred in response to the appearance of the visual cue (preparation cue), while the second (larger) peak occurred in response to the disappearance of the visual cue (execution cue). It is worth noting that (1) the sizes of the peaks were constant irrespective of which hand was used in

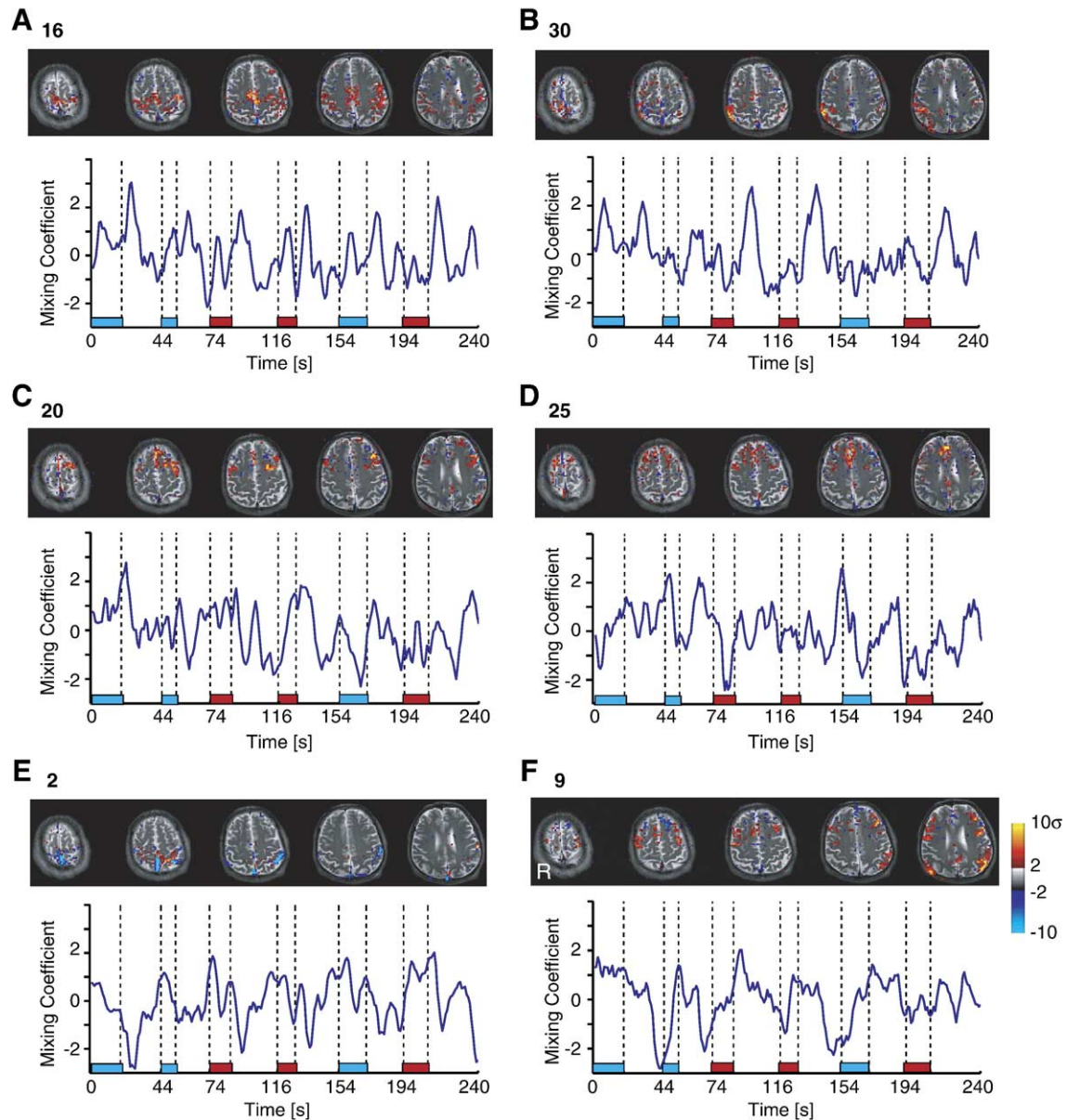


Fig. 4. Spatial and temporal distributions of six independent components reflecting physiologically relevant cortical activity. Panels A–F demonstrate independent components 16, 30, 20, 25, 2, and 9, respectively. For each component, the temporal profile corresponded to the timing of the behavioral task, and the spatial distributions corresponded to the location of anatomical structures within the cortex.

the behavioral task; (2) the fMRI signals were distributed bilaterally over the SMA; and (3) the fMRI signals were distributed over the left M1 in addition to the SMA in three of the five subjects (KK, MN, and HS). These findings suggest that the bilateral SMA contributed to the preparation and execution of sequential movements of either hand and that this occurred in collaboration with the left M1 in some subjects.

Independent components over the dorsal premotor cortex and primary sensorimotor cortex

An independent component distributed over the right M1–S1 was extracted for each subject (Fig. 6A). A relatively stronger fMRI signal was located spatially on the knob structure along the central

sulcus (Yousry et al., 1997). Additional fMRI signals were located along the post-central sulcus, the precentral sulcus, and adjacent areas (specifically, the PMd). It is also noteworthy that an independent component that was extracted in four of the five subjects (MN, HS, KM, and TM) was associated with fMRI signals over the posteromedial portion of the right SMA in addition to the fMRI signal that was distributed over the right M1–S1 (Fig. 6A). The mean temporal activity profile contained marked increases that were time locked to the disappearance of the execution cue for left-hand finger movement (red cues; Fig. 6B). The peaks after the execution cue for left-hand finger movement were significantly larger than those after the cue for right-hand finger movement ($P = 0.000061$, Wilcoxon signed rank test, 15 pairs). Therefore, the right PMd–M1–S1 (together with the right SMA) would appear to be mainly associated with the control of the left hand.

Table 1

Spatial distribution of independent components

KK	MN	HS	KM	TM
SMA + lt M1–S1 + lt PMd(16) rt M1–S1 + PMd(30)	SMA + lt M1–S1 + lt PMd(18) rt M1–S1 + PMd(19)	SMA + lt M1–S1 + lt PMd(8) rt M1–S1 + PMd(6) lt M1–S1 + PMd(18)	SMA(15) rt M1–S1 + PMd(20) lt M1–S1 + PMd(10)	SMA(7) rt M1–S1 + PMd(12)
pre-PMd(20) pre-SMA, PF, PPC(9)			pre-SMA, PF, PPC(21)	PF(25) PF(26)
AC(25) Vein(2)	Vein(6)	AC(10) Vein(20)	Vein(10) Vein(19)	Noise(23) Noise(29)

SMA, supplementary motor area; M1–S1, primary sensorimotor cortex; PMd, dorsal premotor cortex; pre-PMd, pre-dorsal premotor cortex; pre-SMA, pre-supplementary motor area; PF, prefrontal cortex; PPC, posterior parietal cortex; AC, anterior cingulate cortex; rt, right; lt, left. The numbers in parentheses indicate the number of independent components, which were sorted according to the magnitude of variance.

In two of the five subjects (KM and TM), an independent component that was distributed over the left PMd–M1–S1 (Fig. 7A) was associated with a strong fMRI signal that was distributed over the posteromedial portion of the left SMA (Fig. 7A). The largest peaks in the mean temporal activity profile (Fig. 7B) occurred after the disappearance of the execution cue for right-handed movement (blue cue), but large peaks also occurred after the execution cue for movement of the left hand. These observations suggest that the left PMd–M1–S1 might be involved in the execution of left-handed movements in addition to right-handed movements and that this occurred often in collaboration with the left SMA. In the remaining subjects (KK, MN, and HS), the left PMd–M1–S1 component was extracted together with the bilateral SMA component, as described above (see Fig. 5).

Stability of independent components

We assumed that there were 48 independent components without knowing precisely how many independent components actually existed in the fMRI signals. Consequently, we tested whether independent components similar to the physiologically relevant components would be identified irrespective of how many independent components were assumed to exist. For this purpose, we repeated the ICA under the assumption that there were 8, 16, 24, 32, 96, or 144 independent components. We selected three physiologically relevant independent components from the standard ICA, in which we assumed that there were 48 independent components, to be used as templates; specifically, we used the components associated with increased activity in (1) the SMA (five subjects; Fig. 5A), (2) the right PMd–M1–S1 (five subjects; Fig.

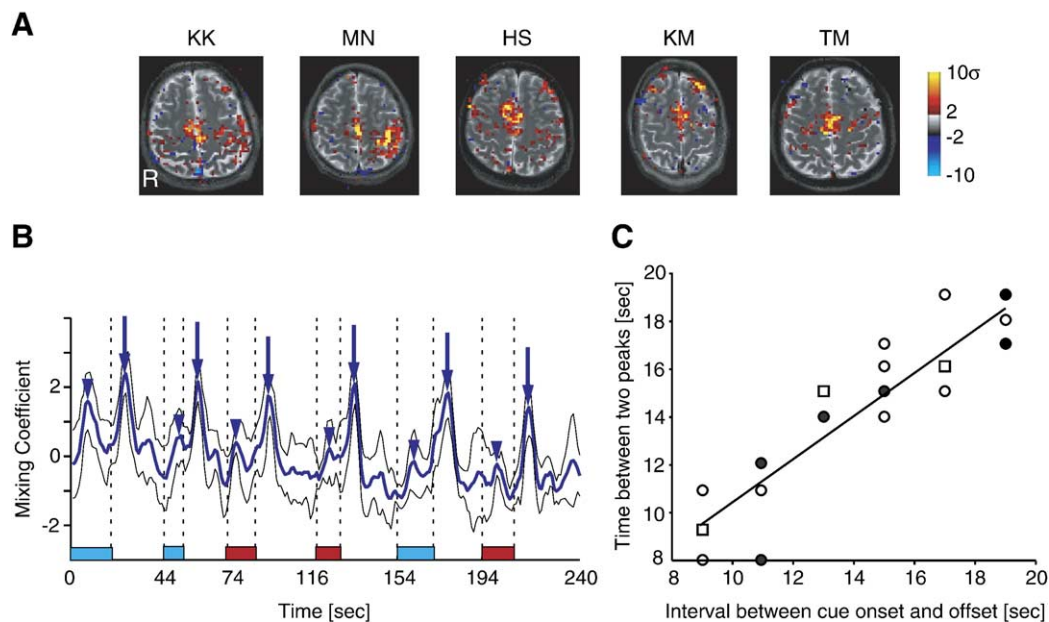


Fig. 5. Independent component distributed over the supplementary motor area (SMA). (A) Data from each of the five subjects are shown (KK, MN, HS, KM, and TM). (B) Mean temporal activity profile for the SMA component. The mean temporal profile of the SMA component (thick line) consisted of six repetitions of a successive small and large peak in activity. (C) The latency between the two peaks was highly correlated with the randomized delay between the appearance and disappearance of the visual cue ($r = 0.91$, $r^2 = 0.82$, $P < 0.0001$, $n = 30$). The filled circle and open square represent overlapping data points from two and three different subjects, respectively.

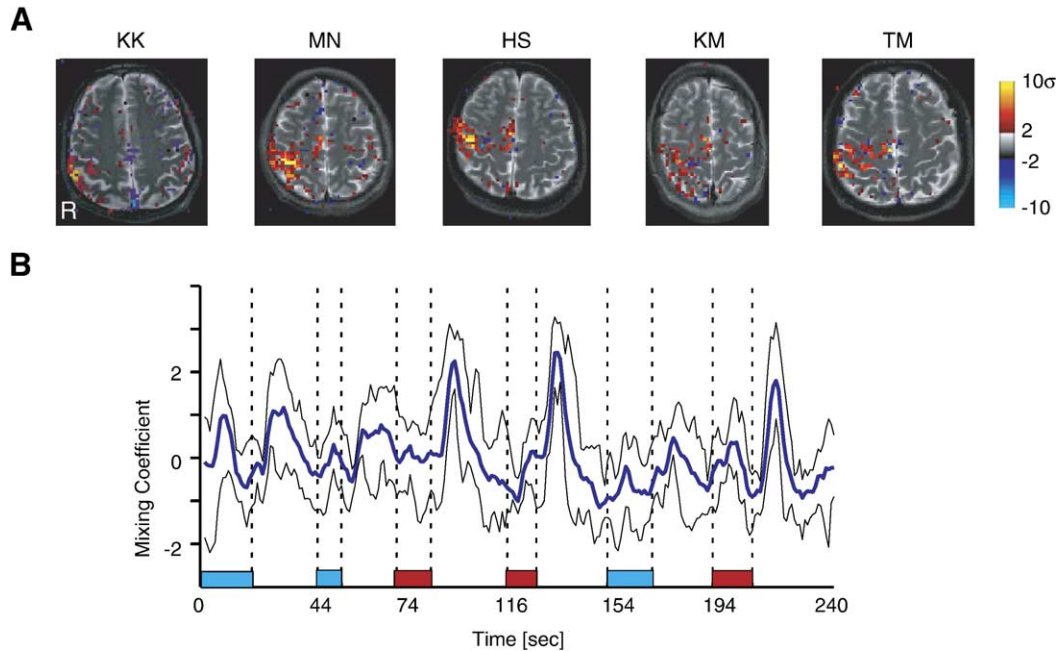


Fig. 6. The right dorsal premotor cortex and primary sensorimotor cortex (PMd–M1–S1) component. (A) An independent component with activity distributed mainly over the right M1–S1 was identified in all of the subjects. (B) Marked increases in the temporal profile were time locked to the disappearance of the red cue. In addition, small increases in the temporal profile were time locked to the appearance of the blue and red cues and the disappearance of the blue cue.

6A), and (3) the left PMd–M1–S1 (two subjects; Fig. 7A). We calculated the correlation between each of the physiologically relevant spatial templates ($n = 12$) and each of the independent components that were extracted based on a different assumption regarding the number of independent components (8, 16, 24, 32, 96, and 144; Fig. 8). A correlation of 1 indicates that a corresponding extracted component is identical to the template. The highest correlation coefficients between the template and the

extracted components were larger than 0.8 for all 12 templates at the assumed numbers of 96 and 144 components, and for 11 of the 12 templates at the number of 32 (Fig. 8). These results indicate that the physiologically relevant components were highly stable over a wide range (32–144) of assumed numbers of independent components.

We additionally examined the stability of the first independent component of each subject (e.g., Fig. 2, left panel, component 1) as an example of the independent component other than the physiologically relevant ones. The highest correlation coefficients were larger than 0.75 in 4 of 5 subjects over a range of number from 32 to 144, and at the number of 8. Although the non-relevant components were generally stable, they seemed to be less stable than the physiologically relevant components.

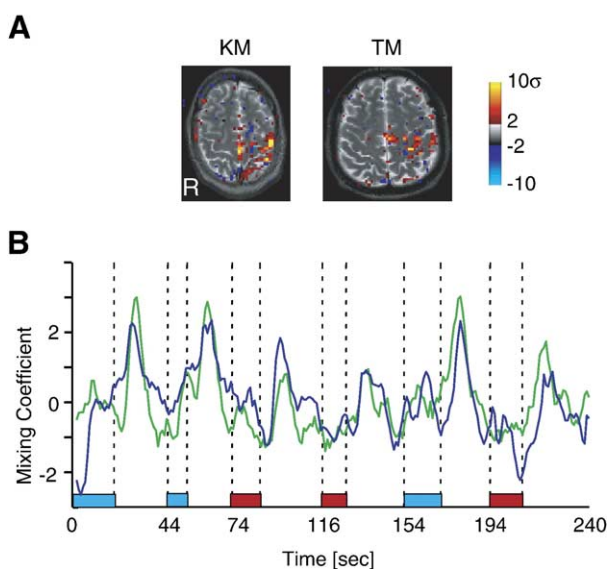


Fig. 7. The left PMd–M1–S1 component. (A) An independent component with activity distributed mainly over the left M1–S1 was identified in two of five subjects (KM and TM). (B) Temporal profiles for the independent components in subjects KM (blue) and TM (green).

Comparison with the finite impulse response model

After applying the ICA, we selected physiologically relevant components by hypothesizing that the temporal profile for each relevant component changed after the appearance or disappearance of the visual cues. The conventional finite impulse response model (FIR), on the other hand, starts from the same assumption that relevant voxels show changes of signals that were time locked to the task offset and onset. Thus, the distribution of physiologically relevant components selected from the independent components should agree with that of activation yielded by the FIR. Fig. 9 shows the results of FIR that were applied to the data from a typical subject (subject KK), whose physiologically relevant components are shown in Fig. 4. Areas of activation time locked to target onsets or offsets revealed by FIR (Fig. 9A) approximately agreed with the combination of independent components over the SMA + left M1 + left PMd (Fig. 4A), right M1 (Fig. 4B), and the

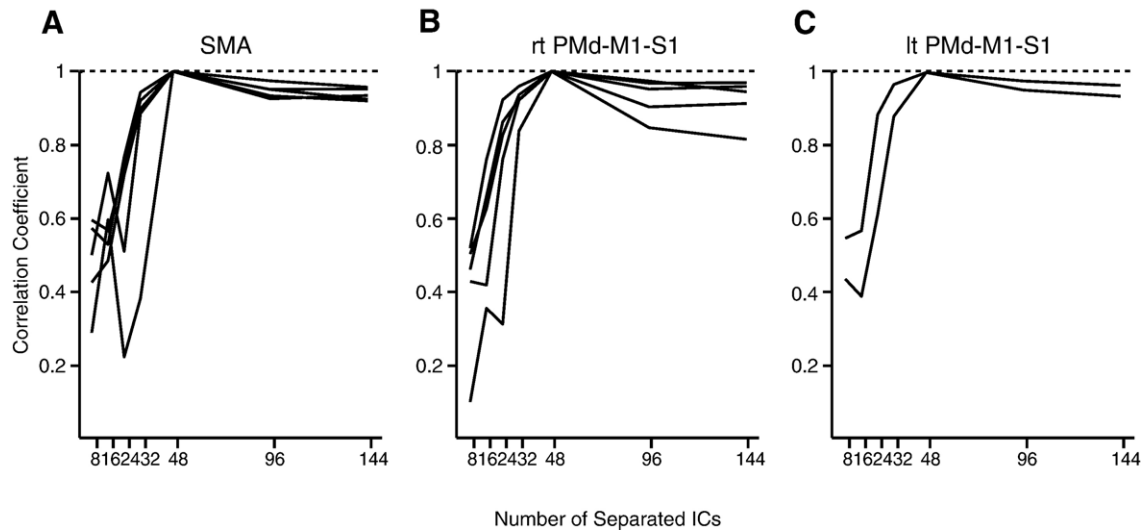


Fig. 8. Analysis of the stability of the method for selecting physiologically relevant components. An independent component analysis was carried out using different numbers of assumed independent components ($n = 8, 16, 24, 32, 48, 96,$ and 144). In the initial analysis, independent components were extracted under the assumption of 48 independent components. Following this, three physiologically relevant independent components were selected for which activity was distributed over the (1) SMA, (2) right PMd–M1–S1, and (3) left PMd–M1–S1. Each component was used as a template for cross-correlation with the components selected using different numbers of assumed independent components. The template with the maximal correlation with the components identified using different numbers of independent components was identified. The highest correlation coefficient extracted for each of the different numbers of independent components is shown. The analysis revealed that the method used to identify physiologically relevant independent components was consistent across a range of assumed components.

draining vein (Fig. 4E). In addition, temporal profiles associated with each independent component agreed in general with fitted responses yielded by the FIR in the corresponding voxels. For example, the temporal profile associated with the SMA + left M1 component in ICA (Fig. 4A, bottom panel) agreed well with the fitted responses yielded by the FIR in the SMA (Fig. 9C) and the left M1 (Fig. 9B). These temporal profile and fitted responses consisted of a smaller response to the preparation cue and a larger response to the execution cue in movements of not only the right but also the left hand. In a similar manner, both ICA (Fig. 4B) and FIR (Fig. 9D at an arrowhead d in 9A) yielded large responses in the right M1 after the go signals of left-hand movement (offsets of the red target).

We also applied the FIR to all the other subjects, and significant voxels ($P < 0.05$) were detected within the anatomical ROIs for bilateral M1, PMd, and SMA in all of them. In the FIR analysis, voxels that showed lowest P value tended to distribute over the draining veins. This may be because signal increase is often smaller in the cortical area than in its draining vein (Kansaku et al., 1998).

Discussion

In the present study, we used ICA to examine the spatial extent and temporal profiles of motor-related activity in the brain during visually cued sequential finger movements. An advantage of ICA is that it allows for the elucidation of brain activity in individual subjects without having to assume any anatomical areas of activation or temporal profiles of activity prior to the analysis. By applying ICA, we identified combinations of activity over the SMA, M1, and PMd during both the preparation and execution phases of visually triggered sequential finger movements in individual subjects.

Methodological considerations on the ICA

We assumed that the series of 240 image volumes that were acquired in each experiment could be decomposed into a certain number of components (images) that were statistically independent of one another. Thus, the results of the ICA might depend on the number of independent components. In addition, not all of the extracted components necessarily have biological significance because the components are extracted based only on the statistical assumption that each component is independent. In applying ICA, it is therefore important to address two questions. First, how can we select physiologically relevant components from among the numerous independent components that are extracted during the analysis? Second, how many independent components should we assume for each analysis?

To select physiologically relevant components, we analyzed the temporal activity profile (a column of the mixing matrix) of each independent component that had been extracted simultaneously in the ICA. We defined physiologically relevant components as those for which the temporal profiles were time locked either to the appearance or disappearance of the color cue, which indicated which hand to use (preparation cue) or acted as a signal for movement (execution cue), respectively. It is worth emphasizing that we did not make any a priori assumptions about the form of the temporal activity profile. The definition of physiologically relevant component was applied objectively to the temporal profiles of each of the independent components ($n = 48$); between three and seven independent components were selected in this manner as being physiologically relevant for each subject. We set the significance level (P value) of the cross-correlation of the temporal profiles at 10^{-5} (Bonferroni corrected P). Therefore, we are confident that the selected components were related to the visual cues that were used in the behavioral task. It is possible that our stringent selection criterion might have resulted in a failure to

select components that were either less physiologically relevant (i.e., less statistically significant) or related to other aspects of the task.

With regard to the number of independent components, we tested whether the results of the analysis depended on the number of independent components that were assumed. We assumed that there were 48 components for our initial (standard) ICA. We repeated the analysis after assuming a different number of components (ranging from 8 to 144) and found that 11 of 12 components that had been extracted and identified as physiologically relevant under the initial assumption were highly correlated ($r > 0.8$) with the components that were extracted under the assumption of 32, 96, or 144 components. Therefore, our method of selecting physiologically relevant components is highly consistent, and the selected components are likely to reflect physiologically relevant activity.

Finally, it is also possible to apply the independent component analysis to the data in the time domain so that independent temporal activities are extracted (Calhoun et al., 2001). However, we chose spatial ICA because our main goal was to characterize multiple motor areas that reportedly contribute to both preparation and execution of movements but with different amplitudes. Temporal profiles with the mere difference in peak amplitudes cannot be yielded by the temporal ICA, because they are not independent of one another.

Comparison of ICA and FIR

For comparison, we applied the finite impulse response model (FIR) to the data from the subjects. The results, shown for one subject in Fig. 9, basically agreed with those yielded by the ICA (Fig. 4) in two respects. First, areas of activation time locked to target onsets or offsets revealed by FIR (Fig. 9A) approximately agreed with the union of three independent components: those over the SMA + left M1 + left PMd (Fig. 4A), right M1 (Fig. 4B), and the draining vein (Fig. 4E). Second, temporal profiles associated with each independent component agreed with fitted responses in FIR in the corresponding voxels.

If both analyses yielded similar results, then what was the merit of using ICA? The largest merit was that ICA “automatically” categorized distributed activities into several spatially independent activities: activities over the SMA + left M1 + left PMd (Fig. 4A), over the right M1 (Fig. 4B), and over the draining veins (Fig. 4E). After the categorization, it was easy to biologically characterize activation in each area with the help of temporal profiles associated with each component. The SMA, left M1, and left PMd contributed to both the preparation and execution of movements of the right and left hand, whereas the right M1 contributed mainly to the execution of movements of the left hand.

The FIR method has an advantage over the ICA in that it demonstrates quantitative F values for each voxel. However, it does not further discriminate or categorize activations over the SMA, M1, PMd, and that over the draining veins, unless we assume additional hypotheses or impose borders just by depending on the anatomical structures that may vary among subjects. ICA was able to accomplish categorization automatically by discriminating between activation patterns that were spatially independent of one another.

Independent component associated with the supplementary motor area, left dorsal premotor cortex, and primary sensorimotor cortex

We identified an independent component for which the fMRI signal was strong over the bilateral SMA in all subjects. The temporal profiles that were associated with the SMA component were time locked not only to the appearance of the visual cue (the signal for movement preparation phase), but also to the disappearance of the cue (the signal for the movement execution phase). Moreover, this increase in activity in the SMA occurred in response to the movement of either hand. The SMA may participate in both the preparation and execution of hand movements. The marked increase in the fMRI signal intensity of the SMA component in association with the execution phase concurs with the results of previous studies of humans (Dick et al., 1986; Halsband et al., 1993; Laplane et al., 1977; Richter et al., 1997) and monkeys (Mushiake et al., 1991). In addition, the relatively smaller level of activation that occurred in the SMA during the preparation phase concurs with the results of a previous study (Richter et al., 1997).

In three of the five subjects, the SMA component was also spatially distributed over the left M1–S1 and left PMd. The region of the PMd over which the SMA component was distributed was adjacent to the M1 anteriorly but did not extend to the pre-PMd (Picard and Strick, 2001). In the two remaining subjects, the left PMd–M1–S1 component was extracted as a separate independent component, which was again associated with a temporal activity profile in which a relatively small and large peak in activity characterized the movement preparation and execution phases, respectively, for either hand (Fig. 7). These results suggested that the left PMd–M1–S1 contributed to the preparation and execution of the movement of both the right and left hands, although the degree of collaboration between the PMd–M1–S1 and the SMA might vary from subject to subject. Our results favor the view that the M1 contributes to both the preparation and execution of hand movements (Lee et al., 1999; Richter et al., 1997; Toni et al., 1999; Zang et al., 2003). In addition, this finding agrees with previous reports that the left M1 contributes to contralateral and ipsilateral hand movements (Cisek et al., 2003; Salmelin et al., 1995; Schluter et al., 2001; Shibasaki et al., 1993).

Independent component associated with right dorsal premotor cortex and primary sensorimotor cortex

We identified an independent component for which the fMRI signal over the right PMd–M1–S1 was strong in each of the five subjects. This right PMd–M1–S1 component was associated with a temporal activity profile with a marked increase in activity during the movement of the left hand. There was also a relatively smaller increase in activity during the preparation for movement of either hand and during the execution of movement of the right hand. These observations suggested that the right PMd and M1 were involved primarily in the execution of left-handed movements, although these areas might also have contributed to some extent to both the execution of ipsilateral hand movements and the preparation of movements of either hand.

The results of the present study suggest that the right PMd–M1–S1 was associated primarily with the execution of movements of the left hand, whereas the left PMd–M1–S1 was active during both the preparation and execution of movements of either hand. This type of

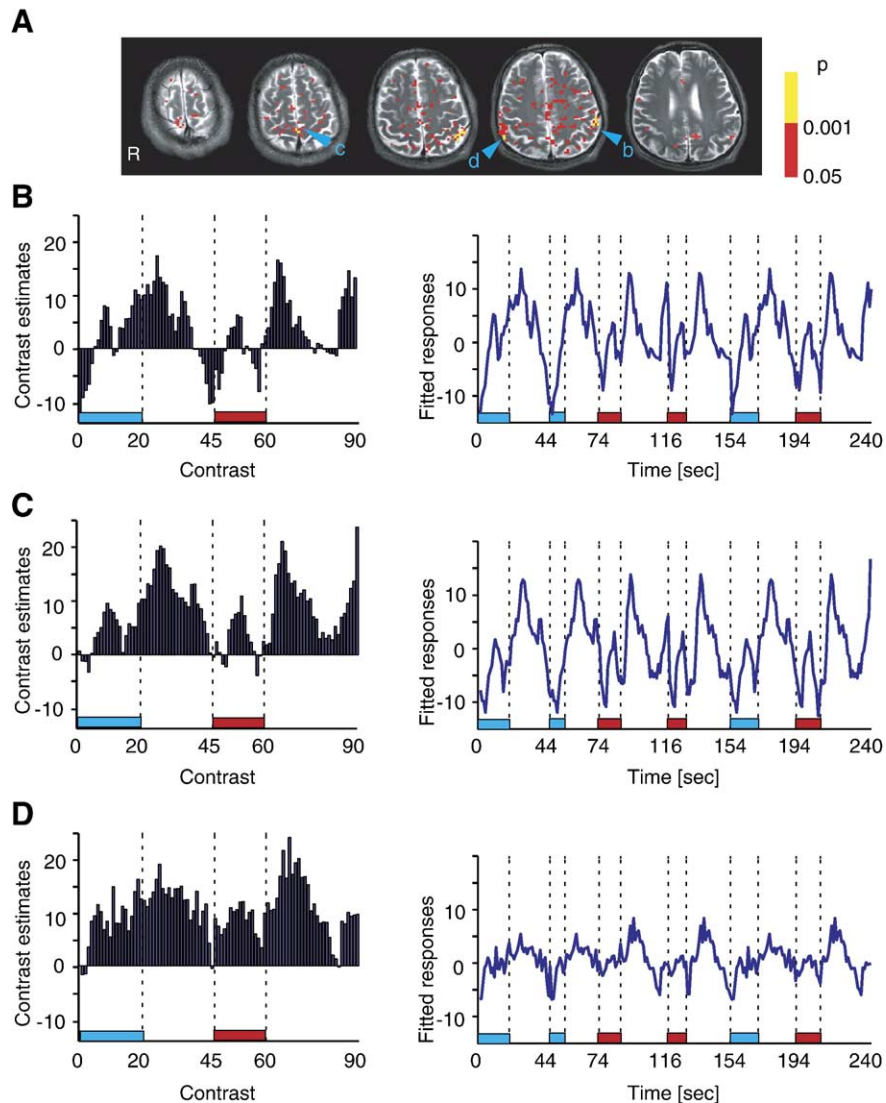


Fig. 9. Spatial and temporal activation patterns derived from the finite impulse response model (FIR). The FIR was applied to the same data from a typical subject shown in Fig. 4. (A) Spatial distribution of voxels with signals that were time locked to the task offset and/or onset for the right and/or left finger movements (red voxels, uncorrected $P < 0.05$; yellow voxels, $P < 0.001$; extend threshold 2 voxels). Arrowheads (b–d) show three voxels with the largest F values in the left M1 (b, $F = 2.53$), SMA/drainage vein (c, $F = 2.30$), and right M1 (d, $F = 2.14$). (B–D) Temporal profiles of the three voxels (b–d) in panel A. Left panels show a series of unconstrained explanatory variables that were time locked to the cue onset and offset for both right (blue rectangle) and left (red rectangle) finger movements (1 s time bins). Fitted responses are shown in the right panels.

left/right asymmetry has been found commonly in the M1 of right-handed subjects (Dassonville et al., 1997) and more recently has been found in the SMA (Babiloni et al., 2003). Our results suggest in addition that a left/right asymmetry also exists in the PMd.

It is worth noting that the PMd–M1–S1 components were accompanied by fMRI signals that were located over the posterior and ipsilateral portion of the SMA (Figs. 6 and 7). The portion of the SMA component that was extracted together with the ipsilateral PMd–M1–S1 component was located posterior to the bilateral SMA component.

Independent components associated with other cortical areas

The posterior parietal cortex (Catalan et al., 1998; Grafton et al., 1998), prefrontal cortex (Kolb and Milner, 1981), anterior

cingulate cortex (Deiber et al., 1999), and pre-SMA (Lu and Ashe, 2002) have been reported to participate in sequential hand movements. In the present study, we found an increased level of activation in the pre-SMA, pre-PMd, prefrontal cortex, posterior parietal cortex, and anterior cingulate cortex in some subjects. A component that corresponded to activity in the pre-SMA, which is anterior to the SMA (Luppino et al., 1993; Matsuzaka et al., 1992; Tanji, 1996), was extracted in two subjects (KK and KM) together with components that were associated with activity in the posterior parietal and prefrontal cortex (e.g., Fig. 4F). The pre-SMA has been proposed to participate in motor learning (Hikosaka et al., 1999; Shima et al., 1996; Shima and Tanji, 1998), preparation of finger movements (Lee et al., 1999), and the ordering of sequential finger movements (Lu and Ashe, 2002). The temporal activity profile associated with the pre-SMA component in the present study (Fig. 4F) appeared to increase continuously during the

preparation phase up to the point at which the execution phase commenced. This profile was distinct from the temporal profile of the SMA component but might be explained in terms of the preparation of the sequence of movements prior to their execution. The results of the present study also suggest that the pre-SMA works in concert with the posterior parietal and prefrontal cortex. The combination of activities in the pre-SMA, posterior parietal cortex, and prefrontal cortex is not unexpected in light of the fact that the prefrontal cortex is anatomically connected with both the pre-SMA (Bates and Goldman-Rakic, 1993) and posterior parietal cortex (Cavada and Goldman-Rakic, 1989). The pre-SMA, posterior parietal cortex, and prefrontal cortex might also participate in working memory or goal-directed behavior (Fuster, 1997; Selemon and Goldman-Rakic, 1988). However, the pre-SMA component was not detected in three of the five subjects in the present study, which suggests that activity in these areas might be related to the different strategies used by different individuals to complete the same task.

In addition to the independent components that were distributed over the motor areas, we identified an independent component that was associated with increased activity in the region of the superficial cortical draining veins. It was reported that increases in the fMRI signal in the cortical draining veins are delayed by 0.5–1.0 s relative to increases in fMRI signals in the cerebral cortex (Kansaku et al., 1998). The results of the present study illustrate that ICA is sufficiently sensitive to discriminate signal changes in the superficial cortical veins from signal changes in the underlying cortical regions.

The spatiotemporal patterns of the independent components that we identified allowed us to infer not only the functional roles of each combination of cortical activity, but also the anatomical location of the cortical draining veins in individual brains.

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