neuroReport

NeuroReport 8, 1257–1261 (1997)

Sequential activity in human motor areas during a delayed cued finger movement task studied by time-resolved fMRI

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ACTIVITY in the human primary motor cortex, the premotor cortex and the supplementary motor area during a delayed cued finger movement task was measured by time-resolved functional magnetic resonance imaging. Activity during movement preparation can be resolved from activity during movement execution in a single trial. All three areas were active during both movement preparation and movement execution. Activity in the primary motor cortex was considerably weaker during movement preparation than during movement execution; in the premotor cortex and the supplementary motor area, activity was of similar intensity during both periods. These observations are consistent with results from single neuronal recording studies in primates.

Key words: Functional magnetic resonance imaging; Functional mapping; Sequential neural processing; Voluntary movement

Introduction

The neural mechanisms resulting in voluntary movement are the subject of intense study in humans as well as in subhuman primates. Of particular interest are the relative roles of the primary motor area (MI), the premotor area (PM) and the supplementary motor area (SMA) during movement preparation and execution. Until recently, MI was thought to be involved exclusively in the execution of muscle contractions. However, this conventional view was challenged by the discovery of higher-order motor components in MI (for review see Ref. 1). Single-neuron recording studies in monkeys have examined the involvement of MI, SMA and PM during motor preparation and visuomotor transformation.[2–6] In the period preceding the execution of movements, neurons in MI as well as in the dorsal PM and the SMA are usually active. In one study, ~15% of the neurons in MI that were active during the task were also active during movement preparation (21% in PM, 27% in SMA).[6] These animal studies provide extremely valuable information about motor function in general; however, inferences about humans can only be drawn cautiously from them.

The subject of activity in the human brain during motor preparation and imaginary movements is controversial. In one of the earliest and most influential studies,[7] cerebral blood flow was measured by tracing ^{133}Xe uptake; the SMA was shown to be involved in both the imagination and the execution of sequential finger movements, but not in simple finger flexions. This suggested that the SMA is the center of higher-order motor functions. Later, PET and fMRI studies showed consistently that SMA and PM are involved in motor imagination.[8,9] However, in a previous study, this group found significant and reproducible activation in MI as well as in SMA and PM during imagination of complex movements.[10] In that study, activity was found to be located in the sensorimotor hand area; the activity was less intense than that during actual movements. Recently, activity in motor cortical areas was measured by PET during visually instructed, delayed, cued reaching experiments.[11] No activation was seen in motor areas during the motor preparation period. On the contrary, another group studied functional activation by PET, using a motor preparation period of 90 s.[12] That study showed activation in the contralateral MI and PM areas. The discrepancy in these findings may be explained by a dependence of cortical activation upon the testing paradigm employed, or by lack of sensitivity in some of the experiments.

To elucidate the relative roles of MI, PM, and SMA in humans during preparation and execution, fMRI

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was applied here in a delayed cued four-finger movement task. It was possible to resolve activation during movement preparation from activation during movement execution in a single subject in a single trial.

Materials and Methods

MRI experiments were carried out with a 4 Tesla whole body imaging system (Varian, Palo Alto, CA/Siemens AG, Erlangen, Germany) with a head gradient insert. For radio frequency transmission and detection, a homogeneous birdcage coil was used. Before each functional imaging study, sagittal, axial and coronal anatomic images were acquired by a conventional imaging technique. From these images, axial slices for functional imaging were identified of the basis of known brain anatomy. In each case, three contiguous 10 mm slices containing the regions of interest (ROIs) were chosen. For functional imaging, 183 single-shot blipped echo planar images were acquired (TE = 25 ms, TR = 196 ms, matrix size = 64 × 64, field of view = 24 × 24 cm^2).[13,14] The first baseline period consisted of 53 images, followed by a variable task period, and a variable second baseline period.

Normal volunteers (eight right handed, one left handed; five male, four female, mean age 24.2 ± 4.0 years) were studied according to guidelines set forth by the institutional review board of the University of Minnesota; informed consent was obtained from all subjects. While lying in the bore of the magnet, subjects viewed a rear-projection screen on which the computer-generated paradigms were displayed. The task used here was a delayed cued finger movement task (Fig. 1).[6,15,16] During the control period of the experiment (Fig 1: Baseline) outlines of five white circles on a black background were shown; four of these were arranged in a row, and the fifth was located in the center above this row. The four circles corresponded to four buttons on a key pad, one for each finger, and the fifth circle served as a GO signal to prompt the subject to execute the task. The four circles were sequentially filled with white color at random (Fig. 1: Presentation). They remained filled during the subsequent delay period (0–7 s; the actual length of this delay period was unknown to the subject; Fig 1: Preparation). After the delay period, the fifth circle was filled (Fig 1: GO), and the subject executed the task by pressing the buttons in the prescribed order, using the dominant hand (Fig 1: Execution). Upon pressing each button, the corresponding circle on the screen blinked once. After the last button was pressed, the screen went blank and remained blank for the duration of the second control period. Execution times were recorded by a personal computer (PC); the execution time for the first finger

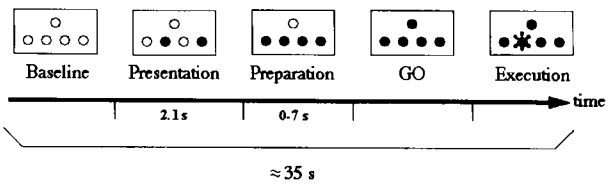

FIG. 1. Schematic depiction of the experiment.

movement was defined as the time between the GO signal and the execution, and for subsequent finger movements it was defined as the time elapsed since the preceding finger movement. Each experiment lasted ~35 s. Finger movement was monitored by electromyography (EMG) on the extensor digitorum with surface electrodes; the EMG signal was filtered, amplified and recorded by a PC. Whenever the EMG signal showed movement before the GO signal, the corresponding trial was discarded.

Functional MRI data were processed using the in-house software package STIMULATE.[18] The initial 33 images were excluded from data analysis to allow the magnetization to reach a steady state. For each subject, the relative intensity change from baseline was integrated over three different activation periods, using the trial with the delay time of 7 s. The whole task period was defined as the period from the commencement of the task display until 13 s after the GO signal; this period also served to define areas for time course analysis. The preparation period was the period from the commencement of the task display until display of the GO signal, and the execution period was the period beginning 3 s after the GO signal and lasting for 10 s. The gap of 3 s between preparation and execution period ensured that hemodynamically delayed signal originating in the preparation period but manifest in the execution period was excluded.

ROIs were chosen based on both brain anatomy and functional maps. MI (Brodmann's area 4) was defined here as the area bordered caudally by the anterior wall of the central sulcus and rostrally by the midline of the precentral gyrus. The dorsal PM (Brodmann's area 6) was defined as the area bordered caudally by the midline of the precentral gyrus, rostally by the anterior wall of the precentral sulcus, and medially by the lateral part of the superior frontal 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. Multiple medial motor areas exist;[17] for the purpose of this study, however, no further distinction was made. It is recognized that this ROI may contain contributions from cingulate motor areas; in order to reduce these contributions, only the superior two slices were used for time course generation.

Time courses were generated using only pixels with the largest average activation within each ROI. In order to exclude effects from large vessels, only pixels with a time course s.d. < 3% were used. To allow comparison between subjects, the number of pixels in each area was held constant.

Results

The activation map for one subject is shown in Fig 2, overlaid on to an anatomic image. The colors designate activation during the preparation period, the execution period, or both periods, respectively. Foci of activation are in the bilateral MI, the primary somatosensory cortex (Brodmann's areas 1, 2, 3), PM, SMA and several other areas of the parietal and frontal lobes. Parietal and frontal areas were not covered uniformly, and activation in the somatosensory area is not consistent among subjects. Activation of contralateral MI, bilateral PM and the SMA are seen consistently in all nine subjects; thus these areas were analyzed further. All areas that are activated during the preparation period show even more activation during the execution period, with the exception of the SMA, where some regions show more activation in the preparation period than in the execution period in three of nine subjects.

Figure 3 shows single-trial time courses (7 s delay) for one subject together with the trace of the EMG recording. There is no discernible movement during the preparation period; in this subject there is activation in all three areas during the preparation period. In this subject, the s.d. of the time courses during the baseline periods was < 0.5%, and signal changes during motor preparation and execution were statistically significant. Similar standard deviations were observed in the other subjects. The corresponding time courses, averaged over nine subjects, are shown in Fig 4. The average execution time was (564 ± 113) ms (average ± s.d.) for each finger movement (the average time to complete the four-finger movement was thus 2260 ms). All subjects showed activation in the SMA and the PM during both the preparation period and the execution period. The

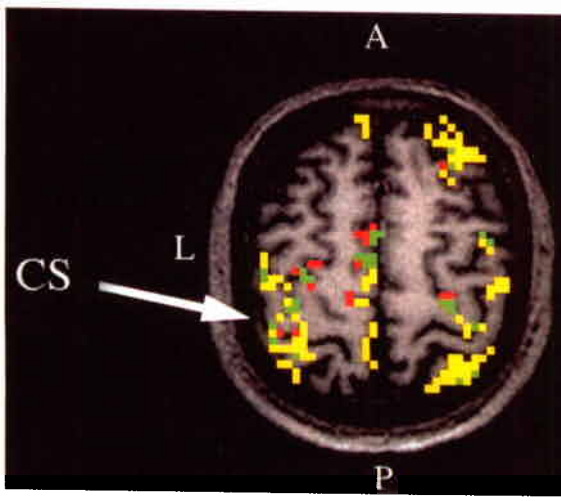

Fig 2. Activation map for one subject (middle slice) showing pixels activated during task preparation (red), task execution (yellow), and during both periods (green), overlaid on to an axial anatomic image The arrow marks the central sulcus (CS); right (R), left (L), posterior (P) and anterior (A) directions also marked.

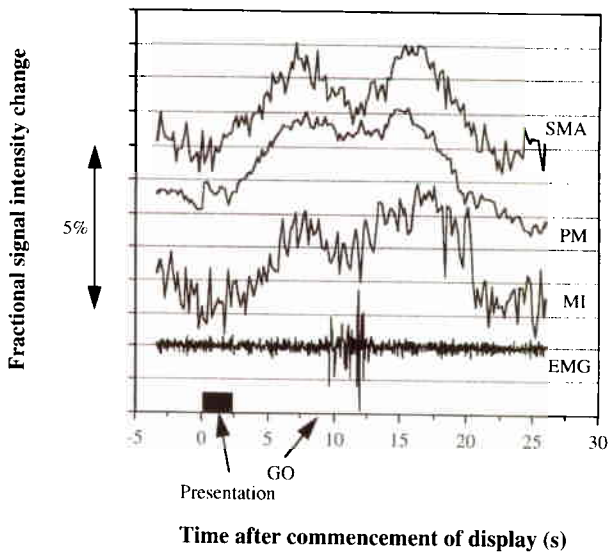

FIG. 3. Single-trial timecourse for a single subject (contralateral primary motor area (MI), bilateral premotor area (PM), and bilateral supplementary motor area (SMA) for the experiment with 7 s delay. The presentation starts at $t = 0$ and lasts for 2.1 s. The GO signal for task execution is displayed at $t = 9.1$ s in this trial. The scale of the y-axis indicates fractional change relative to baseline for each individual time course shown. The EMG recording shows absence of motion during the preparation period.

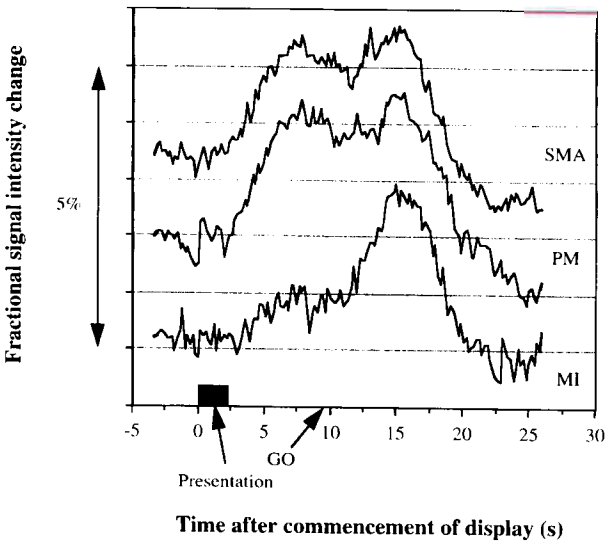

FIG. 4. As Fig. 3, but averaged over nine subjects.

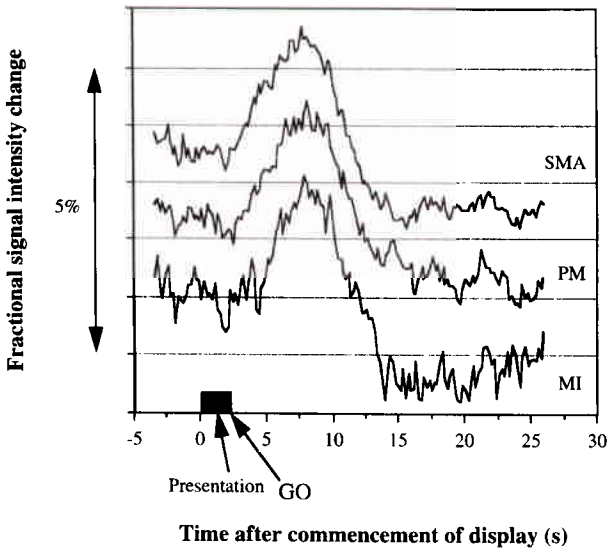

FIG. 5. As Fig. 4, but for the immediate execution experiment. The GO signal for task execution is given at $t = 2.1$ s in this trial.

peak intensity change in the SMA was 2.3 ± 0.8% ($n = 9$) during preparation and 2.8 ± 0.6% during execution. In the PM it was 2.7 ± 0.5% during preparation and 3.3 ± 0.5% during execution. Seven of nine subjects showed activation in the MI during the preparation period; the peak fractional intensity change during this period was 1.2 ± 1.1% ($n = 9$), while all nine subjects showed activation during the execution period (3.1 ± 1.2%).

Figure 5 shows average time courses for the trial with no delay (immediate execution). Both intensity and width of the peaks in the time courses are comparable to those of the later peaks in Fig. 4. The onsets and maxima of all three peaks occur at the same time, suggesting similar hemodynamic response characteristics. The average execution time was 732 ± 259 ms in each movement (the average time to complete the four-finger movement was thus 2930 ms). This time was significantly longer than that for the trial with 7 s delay time.

Discussion

In this experiment, fMRI provided temporal information about neural processing and the relative roles of MI, PM and SMA during movement preparation and execution. It was possible to measure activation in a single trial without averaging. By comparing time courses with variable experimental parameters, such as a delay time, the effects of different hemodynamic responses in different regions can be assessed. To the authors' knowledge, this experiment is the first time-resolved observation of activity in multiple regions in a single trial; it serves as a model to investigate neural processing during cognitive tasks with temporal resolution in the seconds range.

Activity was present in MI during movement preparation, suggesting that this area is involved in preparatory aspects of motor control such as movement planning. This observation agrees with neuronal recording studies in monkeys,[1–6] MEG/EEG studies in humans,[19] and this group's previously published data.[15] However, there is a large variability of signal intensity during movement preparation among subjects; two subjects showed no significant activation at all in MI during movement preparation. This suggests physiological or neuropsychological differences between subjects; different subjects may use different strategies to prepare for movement execution.

The signal intensities in SMA and PM were only slightly lower during movement preparation than during movement execution. This result cannot be quantitatively compared to results from single neuronal recording studies because the spatial resolution of the two methods is different. However, it is clear that both areas are significantly involved during both periods, and that MI is less involved than SMA and PM in motor preparation. These observations agree qualitatively with previous single neuronal recording in monkeys. Further studies are needed to investigate the exact roles, (such as the contribution of motor *vs* non-motor components) of SMA and PM during the delay period. The time courses generated for the SMA may also be contaminated by contributions from the pre-SMA and the cingulate motor areas; the relative roles of these areas can be studied in the future by high-resolution fMRI.

Conclusion

Activation during different processing stages of a delayed task can be resolved in a single trial for a single subject by high temporal resolution fMRI (200 ms per image). MI, PM and SMA are active during both movement preparation and movement execution in a delayed, cued complex finger movement task. Activity in MI was weaker during movement preparation than during movement execution; in PM and SMA, the activity was similar during both periods. These obervations are consistent with results from single neuronal recordings in monkeys.

ACKNOWLEDGEMENTS: The authors thank Kamil Ugurbil, Jim Ashe and Peter Strick for their insightful comments, John Strupp for his data processing software (STIMULATE), and Gregor Adriany for hardware support. This project was supported by NIH grants MH57180, RR08079, NS32919, and a Grant-in-Aid from the University of Minnesota.

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Received 18 November 1996; accepted 17 January 1997

General Summary

The neural mechanisms of movement preparation and execution by humans are subject of intense study. Functional magnetic resonance imaging (fMRI) is ideally suited for such studies because it is non-invasive and does not require administration of radioactive agents. In the past, fMRI has been hampered by relatively low temporal resolution on the order of tens of seconds. The experimental results presented here demonstrated for the first time that different stages of a delayed task can be observed in real time with a temporal resolution in the seconds range. As a result of the experiment, it was shown that three motor areas, the primary motor area, the supplementary motor area, and the premotor area are involved in both movement preparation and movement execution.