NeuroImage **12,** 528–537 (2000)
doi:10.1006/nimg.2000.0626, available online at http://www.idealibrary.com on IDEAL®

The Effect of Switching between Sequential and Repetitive Movements on Cortical Activation

Lutz Jäncke,*,† Marc Himmelbach,*,† N. Jon Shah,† and Karl Zilles†

**Department of General Psychology, Otto-von-Guericke University, Magdeburg, Germany; and †Institute of Medicine, Research Centre Jülich, Jülich, Germany*

Received December 9, 1999

We used whole-head functional magnetic resonance imaging (fMRI) to investigate the effect of switching between different sequential and repetitive movements in the context of conditional and fixed tasks. Four different movement tasks were applied: (1) unpredictable switching between two movement sequences comprising six submovements each according to visual cues (SEQ-VC); (2) unpredictable switching between repetitive movement of one finger according to visual cues (REP-VC); (3) performance of the same sequential movements used for SEQ-VC but in a fixed mode triggered by a visual stimulus (SEQ-FIX); (4) performance of the repetitive movements used for REP-FIX but in a fixed mode by a visual stimulus (REP-FIX). The statistical group analysis of the hemodynamic responses revealed the following results: (1) the SEQ-VC compared to the SEQ-FIX condition (switching between movement sequences) engendered stronger activations in the left rostral supplementary motor area (pre-SMA), bilaterally in the posterior parietal lobule, the left ventral premotor area, and the visual cortices; (2) the REP-VC compared to the REP-FIX condition (switching between repetitive movements) only revealed stronger activation in extra-striate areas. We hypothesize that during switching of movement sequences higher motor control aspects are involved including movement selection, updating of motor plans, as well as recalling and restoring motor plans. The repetitive movements are too simple in order to evoke additional activations in the medial and lateral premotor areas, as well as in parietal areas.

Key Words: **fMRI; hand movement; motor program; motor control; movement sequences; premotor cortex; pre-SMA; SMA.**

INTRODUCTION

A major issue in the study of human motor behaviour is how we control the serial order of movements. Typically these kinds of motor behaviors are studied applying tasks requiring sequences of button presses. Such tasks have enabled researchers to develop detailed models of the memory representations underlying sequential behavior. One of these models assumes that manual response sequences are hierarchically controlled (Rosenbaum *et al.,* 1983; Povel *et al.,* 1982; Rosenbaum, 1985). Within these models it is assumed that motor programs are structured hierarchically and are "unpacked" during execution. These models are based on reaction time studies demonstrating that intervals between cross-hand key strokes are shorter than those for the same hand and keystrokes within one hand are a function of the number of fingers involved and the distance between keys. The different latencies were taken as evidence for the different hierarchy levels to be traversed between successive keystrokes. A further aspect, which is associated with serial keystrokes is that with increasing number of different keystrokes more and more motor memory capacity is required. From these findings and theoretical assumptions one can conclude that there is a fundamental difference in terms of computational demands between sequential keystrokes requiring different finger movements and repetitive keystrokes of the same finger. Sequential keystrokes will require more computational demands during preparation and execution because different hierarchy levels have to be traversed. In addition, more memory capacity will be necessary to store the commands for the different submovements.

Research in patients and monkeys, as well as human brain imaging have linked the control of sequential movements to a number of brain structures, including the lateral premotor cortex (dorsal and ventral: dPMC and vPMC), the supplementary motor areas (SMA proper and pre-SMA), and M1 (Catalan *et al.,* 1998; Jueptner *et al.,* 1997a, 1997b; Jenkins *et al.,* 1994; Grafton *et al.,* 1998a, 1998b; Deiber *et al.,* 1999; Van Oostende *et al.,* 1997; Shibasaki *et al.,* 1993; Karni *et al.,* 1995; Pascual-Leone *et al.,* 1995; Sadato *et al.,* 1996; Halsband *et al.,* 1993). In particular it was found that the SMA becomes more active as serial motor performances improve with practice (Grafton *et al.,*

1053-8119/00 $35.00

1992a). This is particularly evident when acquisition is made under implicit learning conditions. However, recent fMRI studies on humans revealed that the pre-SMA was activated during the explicit retrieval of sequential movements (Hikosaka *et al.*, 1996; Sakai *et al.*, 1999). A PET study by Catalan *et al.* (1998a) uncovered two groups of brain areas associated either with the executive role in running sequential movements (contralateral sensorimotor and premotor cortex, SMA, and ispsilateral cerebellar cortex) or which are selectively related to sequence performance, for example, in adjusting different sequence length (including the ipsilateral PMC, bilateral posterior parietal areas, and precuneus). In addition, single-cell recordings in monkeys revealed that the medial premotor areas (SMA, pre-SMA, and CMA) were particular prominent in retrieving the memorised information necessary for organising the temporal sequence of future movements and for updating a motor plan (Shima *et al.*, 1998a, 1998b, 1996; Matsuzaka *et al.*, 1996).

These studies were the starting point for the current study. In particular we were interested to delineate those brain areas which are specifically involved in shifting between well-learned movement sequences, a question that has not been investigated in humans until now. In order to examine this question, we utilized well-learned sequential button press tasks which were required to be performed in a fixed and predictable sequence while during a further condition the sequence of button presses was unpredictably changed on visual demand. These sequential tasks were also compared with repeated button-press tasks applying the same fingers, which were also performed in the context of fixed and conditional tasks. We hypothesized that during switching of movement sequences in contrast to switching of simple finger repetitions, subjects would have to eliminate or inhibit the previously used motor program and select the motor program for the next movement sequence. This switching of sequential movement patterns should impose additional motor control demands on the involved brain structures and should be reflected in changed cortical activation patterns. According to the aforementioned studies we hypothesized that these additional computations should be localized in those brain areas that have been shown to be involved in the control of sequential movements. However, it is not clear until now which of these areas are specifically involved in these processes. It might be that those areas which have been identified to be involved in adjusting sequence parameters (the ipsilateral PMC, bilateral posterior parietal areas, and precuneus) are stronger engaged during sequence switching (according to Catalan *et al.* (1998a)). In accordance with the single-cell recordings in monkeys (Shima *et al.*, 1996, 1998a, 1998b) it might also be that predominantly the medial premotor areas are candidate areas to control such processes.

MATERIALS AND METHODS

Subjects. Six healthy, right-handed adult volunteers (3 male, 3 female, age range 20 to 25 years) took part in this study. All were consistent right-handers as measured by standard handedness tests (Peters, 1998). Subjects were paid and gave informed consent according to institutional guidelines (Ethics Committee of the University of Düsseldorf).

Experimental protocol. Subjects lay supine on a MRI scanner bed with their right thumb and index finger on response keypads for each finger placed on the right tight. The two response keypads had an interkey distance of 3 cm. The wrist as well as all of the inactive fingers were taped so the latter could not directly participate in the button-press movement. Throughout the experiment a set of black code numbers on a white screen were used as instructional cues. Each number subtended a visual angle of 2° and was presented serially in the centre of the screen situated ~2 m in front of the subject's eyes to eliminate eye movements. Subjects saw the stimuli through a mirror inside the scanner. The interstimulus interval was randomized and ranged from 5 to 6 s. The code numbers of the stimuli (1 to 4) indicated which kind of movement type should be performed. There were two movement types (SEQ: sequential and REP: repetitive), each performed in two different ways to allow better comparison: (1) REP1; six alternated key tapings with the thumb (T) with a prelearned frequency of 2 Hz as accurately as possible using button 1; (2) REP2; six alternated key taping with the index finger (I) with a prelearned frequency of 2 Hz as accurately as possible using button 2; (3) SEQ1; six sequential key tapings applying the sequence T-I-T-T-I-T with a prelearned frequency of 2 Hz as accurately as possible; (4) SEQ2; six sequential key tapings applying the sequence I-T-I-I-T-I with a prelearned frequency of 2 Hz as accurately as possible. Both movement types were triggered by preceding visual stimuli. These stimuli were arranged in two different ways: each repetitive condition was performed block-wise during one session, thus using the visual stimulus as trigger stimulus. Thus, there was no uncertainty with respect to the upcoming movement. These movement conditions were denoted as fixed task (FIX). The sequential and repetitive movements were also conducted in the context of visual conditional tasks (VC). For these conditions there was considerable uncertainty for the next movement sequence to perform. In one further condition, the subjects were instructed to attentively view to the screen without any movements to perform while the cueing signals were randomly presented as for the unpredictable cueing conditions (V: visual). Thus, there were seven experimental conditions: (1) repetitive key tapping with the thumb (six times), each cluster of repe-

titions triggered by one preceding visual stimulus (REP1-FIX); (2) repetitive key tapping with the index finger (six times) each cluster of repetitions triggered by one preceding visual stimulus (REP2-FIX); (3) repetitive key tapping according to the visual stimulus, thus resulting in constantly changing the repetitive key tapping pattern (between REP1 and REP2) according to the preceding visual cue (REP-VC); (4) sequential key tapping 1 (T-I-T-T-I-T), each sequence triggered by one specific visual stimulus (SEQ1-FIX); (5) sequential key tapping 2 (I-T-I-I-T-I), each sequence triggered by one specific visual stimulus (SEQ1-FIX); (6) sequential key tapping according to visual stimuli, thus resulting in constantly changing the sequential key tapping patterns (between SEQ1 and SEQ2) according to the preceding visual cue (SEQ-VC); and (7) attentively looking at the screen and watching the visual stimuli but without performing any movement (V, visual).

The order of these conditions was randomised for each subject. Before each scanning session the subjects were informed about the nature of the forthcoming experimental conditions in order to avoid unnecessary attention effects. During a 1-week period before the actual scanning session, all subjects participated in seven training sessions each of 20-min duration. In these training sessions, subjects were intensively trained in order to perform each motor task with an accuracy of at least 95% throughout the training session. After each training session accuracy of tapping sequence was measured. Accuracy was measured in terms of percent of correctly performed movement sequences. Accuracy rates of 100% were quickly achieved for the fixed conditions (REP1-FIX, REP2-FIX, SEQ1-FIX, SEQ2-FIX), while the conditional movement tasks took a bit longer for the subjects to accomplish them with 100% accuracy. However, the sequential movements to unpredictable cues (SEQ-VC) was rather hard to learn and it took all subjects the seven training sessions to achieve 95% accuracy throughout the whole session. All six subjects reached the performance criterion and participated in the following functional magnetic resonance imaging study.

Magnetic resonance imaging. During magnetic resonance imaging, the same movement conditions were performed as in the training sessions except that an additional visual control condition was presented. All seven conditions were introduced in random order. Subjects were instructed to keep their eyes open throughout the scanning series in order to watch for the visual signals. During the scanning sessions room lights were dimmed. In each experimental condition a series of 120 images was acquired. Each series consisted of multiple periods of "baseline" (OFF, rest), during which subjects heard only the ambient machine noise and saw a fixation asterisk but did not perform the motor task, alternating with periods of "activation" (ON, task). Upon presentation of the visual signal, the subjects were asked to start the movement, while the asterisk indicated the start of the next rest condition, during which no movement was required. Tapping rate was monitored during scanning by use of a fibre optic system attached to a laboratory computer that counted the taps. Each scanning series began with five baseline images (15-s interval) allowing signal equilibrium to be reached and an initial baseline to be established, followed by 120 images during which "activation" alternated with "baseline" every 30 s (60 s/cycle, 20 images/cycle, 10 images/OFF, and 10 images/ON, 6 cycles). The total duration of each image series was about 4 min. Functional magnetic resonance (fMRI) imaging was performed on a 1.5 T MRI system (SIEMENS Magnetom VISION, Erlangen, FRG), equipped with echo planar imaging (EPI) capabilities using the standard head coil for radiofrequency (RF) transmission and signal reception. Sequences with the following parameters were employed: echoplanar imaging (EPI), repetition time (TR) = 3 s, echo time (TE) = 66 ms, field-of-view = 200×200 mm^2, $\alpha = 90°$, matrix size = 64×64, voxel size = $3.125 \times 3.125 \times 7.7$ mm^3. Using a midsagittal scout image, 16 axial slice positions (0.3-mm interslice gap) were oriented parallel to the bicommissural plane with the uppermost slice aligned 2 mm below the vertex, thus covering the whole brain. In addition, anatomical images of the entire brain were obtained by using a strongly T1-weighted, gradient-echo pulse sequence in 3-D (MP-RAGE, magnetization-prepared, rapid acquisition gradient echo) with the following parameters: TR = 11.4 ms, TE = 4.4 ms, 15° flip angle, FOV = 256×256 mm^2, matrix size = 256×256, 128 sagittal slices, with 1.33-mm thickness.

Image analysis. Image analysis was performed on an Ultra 4 workstation (Sun Microsystems) using MATLAB (Mathworks Inc., Natick, MA) and SPM96 software (http://www.fil.ion.ucl.ac.uk/spm). For analysis, all images were realigned to the first volume, corrected for motion artefacts, coregistered with the subject's corresponding anatomical (T1-weighted) images, resliced, and normalized (4 mm^3) into standard stereotaxic space (template provided by the Montreal Neurological Institute) (Evans *et al.*, 1993), and smoothed using an 8-mm full-width-at-half-maximum Gaussian kernel. The data were analyzed by statistical parametric mapping. The effect of global differences in scan intensity was removed by scaling each scan in proportion to its global intensity. Statistical analysis was performed for each condition in a general linear model, in which regionally specific activation is explored as to how well the reference waveform fits to the observed time series of the fMRI signal (i.e., hemodynamic responses) at each and every voxel (Friston *et al.*, 1995a, 1995b, 1994). The reference waveform was obtained by

smoothing a time-dependent sensorimotor parameter of interest (i.e., a box-car waveform with 0 s for rest epochs scans and 1 s for movement epoch scans) with a Gaussian kernel of a delay and dispersion of the square root of 8 s, modeling the hemodynamic response functions. The time-series fMRI data also were smoothed over observation (time) by use of the same Gaussian kernel as the hemodynamic response function. For further statistical analysis we also defined several sets of contrasts. The first set was used to identify significant hemodynamic responses relative to rest: (1) repetitive tapping during the fixed tasks vs. rest (REP-FIX vs rest [REP1-FIX + REP2-FIX]/2 vs rest); (2) repetitive tapping in the context of conditional visual cueing vs rest (REP-VC vs rest); (3) sequential movements during the fixed task vs rest (SEQ-FIX vs rest [SEQ1-FIX + SEQ2- FIX]/2 vs rest); (4) sequential movements in the context of conditional visual cueing vs rest (SEQ-VC vs rest); (5) visual control vs rest (V vs rest). The second set of contrasts was defined in order to identify significant differences between the fixed and conditional tasks for each movement type separately: (1) REP-VC vs REP-FIX (switching between repetitive movements); (2) SEQ-VC vs SEQ-FIX (switching between sequential movements). These contrasts are the critical contrasts which should uncover the additional activations during the switching processes. No further contrast will be discussed in the context of the present paper because we have focussed our hypothesis on the switching process. Voxels were defined as being significantly activated for each contrast if they passed the height threshold of $z = 4.5$ ($P = 0.05$ corrected for multiple nonindependent comparisons). The statistical analyses were performed for the entire group (group analysis) to account for the experimental paradigm (different experimental conditions which are randomised for each subject) and to compile mean activation "maps." These activation "maps" were superimposed on the spatially normalized brain averaged from the six individual normalised brains to identify activated brain regions.

RESULTS

Behavioral Data

The tapping frequencies (Table 1) for the four different movement sequences were subjected to a two-way ANOVA with repeated measurements applying the multivariate variant to account for possible inhomogeneities of variances (O'Brien *et al.,* 1985) (movement type: sequential vs repetitive movement; visual cueing: conditional vs fixed task). This ANOVA only revealed one significant effect for the difference between the movement types (sequential versus repetitive: $F(1,5) = 79.1$, $P < 0.001$, $\mathrm{ETA}^2 = 0.94$), qualified by faster tapping rates for the sequential movement sequences.

TABLE 1

Mean Tapping Frequencies (Taps/s) as Well as Reaction Times (in ms) and Standard Deviations Broken Down for the Movement Types and Visual Cueing Conditions as Measured during the Scanning Procedure

	Tapping frequency		Reaction times (ms)	
	FIX	VC	FIX	VC
Repetitive	2.0 ± 0.3	2.1 ± 0.4	492.5 ± 68.7	659.8 ± 65.7
Sequential	3.0 ± 0.6	2.8 ± 0.9	589.7 ± 30.3	547.5 ± 45.6

There was no further significant main effect nor interaction. In addition we also analyzed whether the intertap intervals especially for the sequential movements showed any peculiarities. Therefore, we calculated mean intertap intervals for each transition (1st to 2nd, 2nd to 3rd, 3rd to 4th, 4th to 5th, 5th to 6th) obtained for each movement type and each movement task. These measures were subjected to a three-way ANOVA with repeated measures on each factor with movement type, visual cueing, and intertap interval as factors. Again, there was only a significant main effect for movement type ($F(1,5) = 79.1$, $P < 0.001$, $\mathrm{ETA}^2 = 0.94$), but there was no effect of intertap interval, suggesting to us that there was no principle difference between the different intertap intervals. Although this motor task was not designed as a typical reaction time study and the subjects were not required to start their movements as fast as possible, we also calculated the mean reaction times for each subject and each condition. These data were subjected to a further ANOVA. This ANOVA revealed significant main effects (movement type: $F(1,5) = 8.3$, $P = 0.034$, $\mathrm{ETA}^2 = 0.63$; visual cueing: $F(1,5) = 45.3$, $P < 0.001$, $\mathrm{ETA}^2 = 0.90$). The main effect of movement type was qualified by longer reaction times for sequential movements (624.7 ms vs 520 ms) while the main effect of visual cueing was due to longer reaction times for the conditional task compared to the repetitive task (603.7 ms vs 541.0 ms), thus these measures are in line with data from the psychological literature (Woodworth, 1938; Rosenbaum, 1985).

Functional Imaging Findings

Comparison of the experimental conditions to rest. Comparing each experimental condition to rest revealed strong activations in extended cortical and subcortical areas (Fig. 1). However, activated regions were typically large expanses of cortex following gyral and sulcal topography rather than small foci and were thus more completely described by reference to anatomical structures than in terms of point coordinates. Activation areas were given anatomical labels only when the borders of the area followed borders of a gyral or sulcal

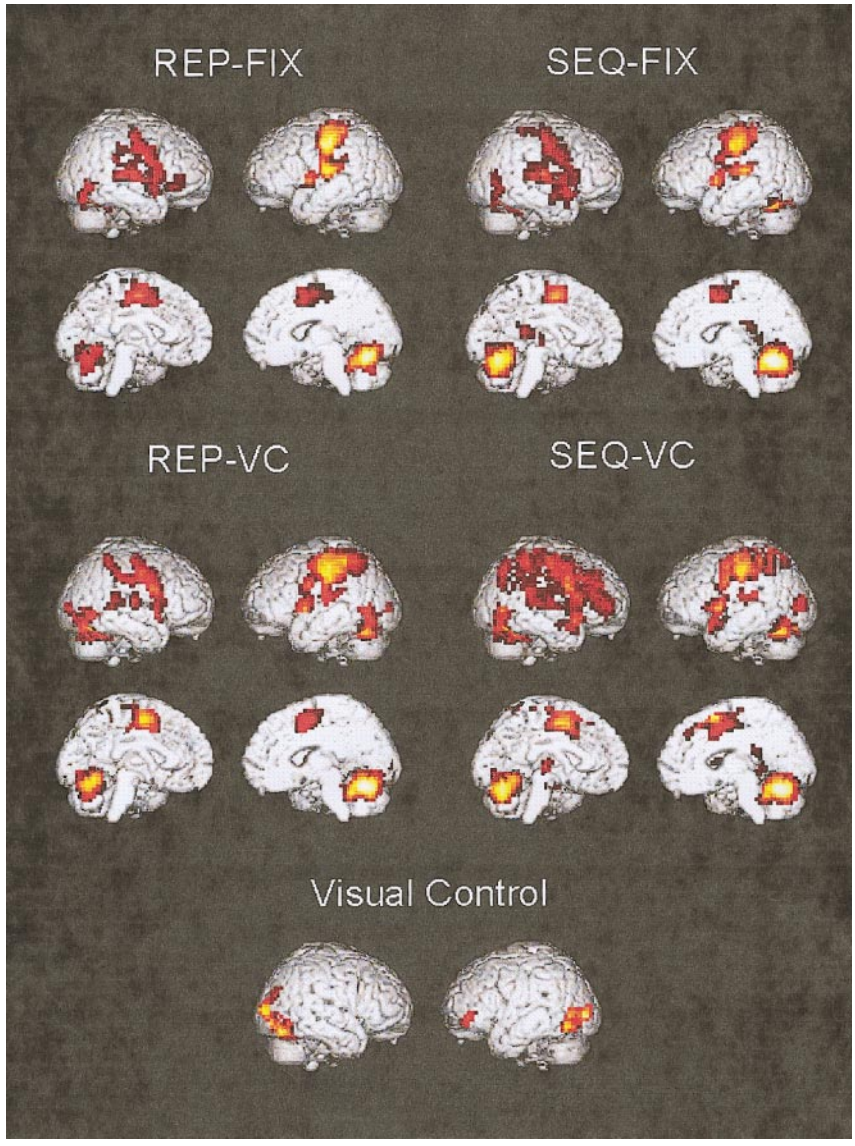

FIG. 1. Significant regions obtained for the group analysis for the contrasts comparing the four motor and the visual control conditions to rest. Significant increases in hemodynamic responses were overlayed onto a rendered standard brain.

structure in the Talairach and Tournoux atlas and the label was supported by three-dimensional inspection of the averaged anatomical data. All four motor conditions revealed strong mostly bilateral activations in lateral and mesial premotor areas including SMA-proper, pre-SMA, bilateral activations in the precentral and central gyrus area extending into the parietal lobe. There were also bilateral activations in the cerebellum, the superior temporal gyrus, and the occipital cortex. The visual control condition only revealed stronger activations in the middle and inferior occipital gyrus area.

Switching between movement sequences and repetitive movements. Comparing REP-VC with REP-FIX revealed increased hemodynamic responses within the right and left medial occipital gyrus. Table 2 and Fig. 2 show brain regions with significant activations during SEQ-VC compared to SEQ-FIX. This contrast uncovered increased hemodynamic responses in a frontoparietal network comprising the left and right superior parietal lobe, the precuneus, and a left-sided area on the dorsal frontal gyrus at a location anterior to VAC known to be the pre-SMA ($x = -8$, $y = 16$, $z = 48$). This activation focus as well as the anterior and inferior borders of the activation cluster corresponds well with the boundaries given by Picard and Strick (1996a), Roland and Zilles (1996b), and with the coordinates given by others for the pre-SMA (Petit *et al.*, 1998). There were also activations on the precentral gyrus located directly on the VAC ($x = -44$, $y = 0$, $z = 32$) located in an area, which most likely is the human homologue of the ventral premotor area (vPMC). In

TABLE 2

Regions of the Brain with Significant Increase in Hemodynamic Response during the Repetitive Movements (REP-VC) Compared to Sequential Movements (REP-TR) in the Context of the Conditional Tasks

Anatomical region	*x*	*y*	*z*	*Z* score
REP-VC > REP-FIX				
R Middle occipital gyrus	28	−92	0	6.33
R Middle occipital gyrus	36	−84	−8	5.08
L Middle occipital gyrus	−32	−92	0	6.05
SEQ-VC > SEQ-FIX				
R Superior parietal lobule	20	−76	56	6.98
M Precuneus	0	−60	64	6.79
L Superior parietal lobule	−20	−72	52	6.25
L Dorsal frontal gyrus (pre-SMA)	−8	16	48	5.82
L Precentral gyrus/L precentral sulcus (vPMC)	−44	0	32	5.73
L Middle occipital gyrus	−32	−92	4	5.30

Note. *x*, *y*, *z*, stereotaxic coordinates are in millimeters; *Z* scores are peak activations within the significant cluster of activated voxels; *Z* scores > 4.5, correspond to $P < 0.05$ (corrected for multiple comparison); peaks of activity are localised according to their position on the averaged MNI brain. The coordinates do not correspond to the Talairach and Tournoux atlas.

addition there was also an increased activation in the left medial occipital gyrus. Increased activation during the SEQ-FIX condition compared to the SEQ-VC condition were found for the cerebellum (left and right hemispheres, as well as in the vermis region), the left and right precentral gyrus region, the SMA, as well as the right and left superior temporal gyrus. The activations on the precentral gyrus were found in regions slightly anterior to the hand motor area ($x = -44$, $y = -16$, $z = 46$; $x = 52$, $y = -8$, $z = 44$; supposedly vPMC) as well as on the postcentral gyrus slightly behind the hand motor area ($x = -36$, $y = -36$, $z = 60$).

DISCUSSION

We identified distributed regions in the lateral and medial premotor cortex, the posterior parietal lobule, and the occipital cortex involved in switching between sequential movements. Interestingly, this differential pattern of activation was not seen for the simple repetitive movements, suggesting that these movements are merely too simple to evoke additional activations. For this task we found, however, increased activation in the visual cortices. Differential activation in pre-SMA has been demonstrated in various studies applying single cell recordings in nonhuman primates as well as human brain imaging studies. For example, it was shown that pre-SMA cells, but not SMA-proper cells, generated transient activity when shifting motor plans in response to the instruction signal (Matsuzaka *et al.*, 1996) and when different series of sequential motor tasks were updated (Shima *et al.*, 1996). Human brain imaging studies showed that, in the single Go/NoGo paradigm, the pre-SMA had an increased signal in association with both the Go and NoGo trials, and the area caudal to pre-SMA, the SMA-proper, was activated only with Go trials (Humberstone *et al.*, 1997). Further studies (Hikosaka *et al.*, 1996; Sakai *et al.*, 1999) applying fMRI found that the pre-SMA was particularly active for learning of new sequential movement procedures, not movements per se. The common denominator of these findings is that pre-SMA is critical for sequence retrieval or switching based on the context of task performance.

In contrast, the SMA proper was active for the performance of sequential movements, not learning. Finally, a recent study also applying fMRI in the context of various working memory tasks revealed pre-SMA activation during working memory delays suggesting that this area does not reflect simple motor preparation but rather a state of preparedness for selecting a motor response based on the information held on-line (Petit *et al.*, 1998). Taken together there is a functional difference between pre-SMA and SMA-proper, which is suggested by previous neurophysiological studies and is corroborated by our findings, showing that pre-SMA is involved in higher cognitive aspects of motor control

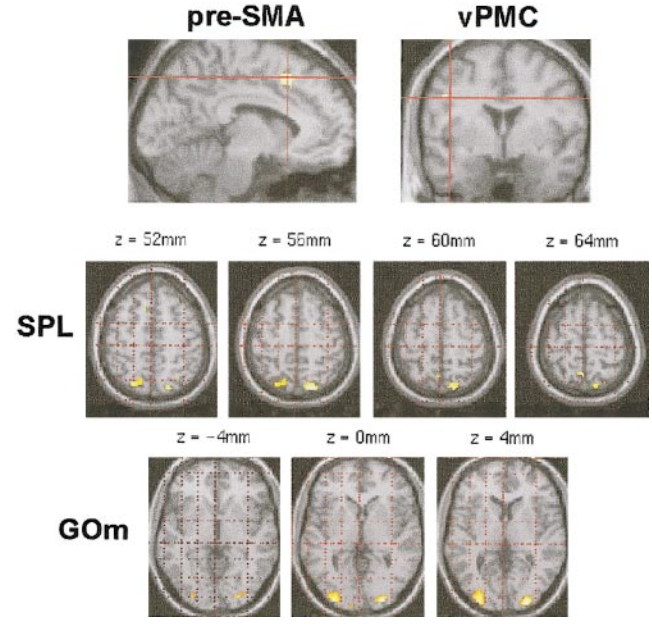

FIG. 2. Anatomical rendering of significant increases of hemodynamic responses for the "switching effects" obtained for the movement sequences (SEQ-VC > SEQ-FIX). The SPM(*Z*) for the relevant contrast has been thresholded at $P < 0.05$ (corrected for multiple comparisons) and superimposed on a representative brain used as template for the spatial normalization of the images. Top row, significant activations in the pre-SMA and vPMC areas; middle row, activations in the superior parietal lobule including the precuneus; lower row, bilateral activations in middle occipital cortex (GOm).

comprising movement preparation, updating of motor plans, motor memory processes while SMA-proper is more involved in motor control aspects comprising movement initiation and execution.

However, it is also possible that our findings relate to those studies, suggesting that the pre-SMA is strongly engaged when movements are self-initiated. A recent brain imaging study elegantly showed that the pre-SMA was more active during self-initiated fast movements (Deiber *et al.,* 1999). Our motor tasks comprised submovements which are self-initiated and relatively fast, too. For example, the visual trigger used in our study was applied to signal the initiation of a movement sequence comprising six finger movements. Whereas the sequence as a whole is triggered, the subjects initiate the sub-movements by themselves. Summarizing these observations, it appears that our task did involve all of these elements, but, of course, it is not at all obvious which of the elements is of cardinal importance. In view of the relatively circumscribed activation of the pre-SMA, our next goal will be to see how we can modify the task so that more substantial effects can be observed.

Switching between movement sequences also evoked activation located on the left vPMC in the vicinity of Broca's area. This activation focus is slightly higher but nevertheless within the variability range of Broca's area as indicated by a probability map computed for this area (Amunts *et al.,* 1999). Although there is no general consensus with respect to the differential roles of dPMC and vPMC in the visual guidance of movements, there are data available suggesting that the vPMC (especially the left) plays an important role in the recalibration of visual and motor coordinates (especially in body-part-centered coordinates), or in the explicit generation of motor programs (the blueprint for movements (Rijntjes *et al.,* 1999)). A more ventral and rostral part of the vPMC (predominantly on the left hemisphere) is also suggested to be involved in the imagination of complex movements (Stephan *et al.,* 1995), manipulation of complex objects (Binkofski *et al.,* 1999; Stephan *et al.,* 1999), preparation of imitated movements (Krams *et al.,* 1998), imitation of movements in general (Rizzolatti *et al.,* 1999, 1996a, 1996b), in the control of difficult pointing movements (Winstein *et al.,* 1997), or switching between cognitive tasks (Dove *et al.,* 2000). Thus, one may conclude that the vPMC area (especially on the left hemisphere) is specifically involved when higher-order cognitive processes like prediction, anticipation, imagination, or executive control are necessary which are applied in the context of movement control.

The bilateral activation within the posterior parietal lobe during the sequence switching relates to those studies demonstrating the involvement of the posterior parietal lobe in the selection and visual guidance of movements both in humans and monkeys (Passingham 1989; Wise *et al.,* 1996, 1997; Halsband *et al.,* 1982; Snyder *et al.,* 1998; Pantano *et al.,* 1996; Perenin *et al.,* 1988). However, although our findings emphasise the classical role of the posterior parietal lobe in the control of visually guided movements at least for movement sequences it is worth noting that the posterior parietal lobe may also be involved in higher cognitive processes which may interact with motor control processes. Here we would like to address two possible cognitive functions, which may be active during complex movements as used here namely visual imagery and spatial working memory.

First, it might be that the subjects learned the movement sequences by encoding them as visual patterns of finger movements in the sense of imagining the index finger and thumb moving in a specific sequence. If one follows this line of argumentation, one might assume that during the SEQ-VC condition the subjects have recalled a visual pattern of the movement sequence and then transferred that pattern to the lateral and mesial premotor areas. Such a view is consistent with findings showing activations in superior parietal lobe areas while subjects recalled learned visual patterns (Roland *et al.,* 1994) and when subjects recalled scenes of familiar surroundings (Roland *et al.,* 1987). The storage sites for these visuospatial representations in subject's brains would probably be reactivated when they are trying to retrieve the relevant visual information. Beside the bilateral activation in the superior parietal lobe found in our SEQ-VC task we also found activation in the superior part of the precuneus. In previous human motor studies using brain imaging techniques, precuneus activity was found when subjects performed movements guided by an internal trajectorial map (Deiber *et al.,* 1991) or during visually guided finger movements (Grafton *et al.,* 1992b). Precuneus activity was also found in studies during learning and retrieval of visual patterns or imaginable material (Fletcher *et al.,* 1995). Thus, it might be that during SEQ-VC the movements are visually coded and that this mental representation is maintained during the movement process.

Second, the operation of some kind of "cognitive intermediates" in parietal areas is partly corroborated by recent PET findings published by Coull and Frith (1998a) and Coull and Nobre (1998b). These authors found increased activity on the right posterior parietal cortex during tests of attention and working memory. Interestingly, that increase was not only evident during spatial attention tasks, for which the posterior parietal cortex has been shown to be especially involved, but also for nonspatial attention tasks. These findings led the authors to hypothesize that the right posterior parietal cortex, and in particularly the intraparietal sulcus, may be involved in fundamental low-level attentional processes that "act as lowest common denominator for many types of cognitive pro-

cesses." Although the posterior parietal cortex was activated both by spatial and nonspatial attentional conditions the activation was stronger for the spatial tasks suggesting some functional specialisation for spatial processing in the right parietal cortex in addition to its role in attention.

Beside the activations in this frontoparietal network there were also additional activations in the striate and extrastriate cortices during both the sequential and repetitive switching tasks. These activations are most likely due to increased attention placed on the switching task. The differences in attention between tasks relate to the significance of, or the information conveyed by, the visual stimulus. In the VC conditions the subjects relied on the visual stimulus for information about both the movement sequence to perform (movement selection signal) and the timing of the upcoming sequence. Thus, the stimulus served both as a movement selection signal and a GO signal. In the FIX tasks, the subject did not need to attend to the specifics of the visual stimulus and could have used the visual stimulus merely as a GO signal. There were no controls for attention in the behavioural tasks because it is virtually impossible to adequately control for this factor when the tasks themselves involve different levels of predictability which is the case for the VC compared to the FIX tasks. By definition, the unpredictable behavior requires more attention. Different levels of attention have been shown to affect the activity of cells in motor and nonmotor areas of the frontal cortex during visuomotor tasks (di Pellegrino *et al.*, 1993). However, these findings have not been substantiated in human brain imaging studies. Therefore, we refrain from discussing the influence of attention on motor control processes in order to avoid too much speculations. Although we are reluctant to speculate about attentional influences on motor control processes there are a couple of studies showing attentional influences on activations in the striate and extrastriate cortices in the context of visual stimulation thus corroborating our own findings (Jancke *et al.*, 1999; Watanabe *et al.*, 1998; Heinze *et al.*, 1994).

Concluding Remarks

In this fMRI study we identified several regions involved in switching between movement sequences, including the left pre-SMA, the left vPMC, bilaterally the SPL, and bilaterally visual cortices. These activations are comparable to activations reported in several neuroimaging studies and single-cell studies in nonhuman primates. These studies revealed that this distributed network is activated during higher order cognitive processes (updating of motor plans, motor memory processes, imagination of complex movements, manipulation of complex objects, preparation of imitated movements, imitation of movements in general, or switching between cognitive tasks) applied to motor control processes.

ACKNOWLEDGMENTS

This study was financed by the Deutsche Forschungsgemeinschaft (DFG JA 737/7-1 and JA 737/7-2). We thank two anonymous reviewers and Kai Lutz for valuable comments on an earlier version of this manuscript.

REFERENCES

Amunts, K., Schleicher, A., Burgel, U., Mohlberg, H., Uylings, H. B., and Zilles, K. 1999. Broca's region revisited: Cytoarchitecture and intersubject variability. *J. Comp. Neurol.* **412:** 319–341.

Binkofski, F., Buccino, G., Posse, S., Seitz, R. J., Rizzolatti, G., and Freund, H. 1999. A fronto-parietal circuit for object manipulation in man: Evidence from an fMRI-study. *Eur. J. Neurosci.* **11:** 3276–3286.

Catalan, M. J., Honda, M., Weeks, R. A., Cohen, L. G., and Hallett, M. 1998. The functional neuroanatomy of simple and complex sequential finger movements: A PET study. *Brain* **121**(Pt 2): 253–264.

Coull, J. T., and Frith, C. D. 1998a. Differential activation of right superior parietal cortex and intraparietal sulcus by spatial and nonspatial attention. *Neuroimage* **8:** 176–187.

Coull, J. T., and Nobre, A. C. 1998b. Where and when to pay attention: The neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI. *J. Neurosci.* **18:** 7426–7435.

Deiber, M. P., Honda, M., Ibanez, V., Sadato, N., and Hallett, M. 1999. Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: Effect of movement type and rate. *J. Neurophysiol.* **81:** 3065–3077.

Deiber, M. P., Passingham, R. E., Colebatch, J. G., Friston, K. J., Nixon, P. D., and Frackowiak, R. S. 1991. Cortical areas and the selection of movement: A study with positron emission tomography. *Exp. Brain Res.* **84:** 393–402.

di Pellegrino, G., and Wise, S. P. 1993. Effects of attention on visuomotor activity in the premotor and prefrontal cortex of a primate. *Somatosens. Mot. Res.* **10:** 245–262.

Dove, A., Pollmann, S., Schubert, T., Wiggins, C. J., and von Cramon, D. Y. 2000. Prefrontal cortex activation in task switching: An event-related fMRI study [In Process Citation]. *Brain Res. Cogn. Brain Res.* **9:** 103–109.

Evans, A. C., Collins, D. L., Mills, S. R., Brown, E. D., Kelly, R. L., and Peters, T. M. 1993. 3D statistical neuroanatomical models from 305 MRI volumes. *Proc. IEEE Nucl. Sci. Symp. Med. Imag.* 1813–1817.

Fletcher, P. C., Frith, C. D., Baker, S. C., Shallice, T., Frackowiak, R. S., and Dolan, R. J. 1995. The mind's eye—precuneus activation in memory-related imagery. *Neuroimage* **2:** 195–200.

Friston, K. J., Holmes, A. P., Poline, J. B., Grasby, P. J., Williman, S. C. R., Frackowiak, R. S. J., and Turner, R. 1995a. Analysis of fMRI time-series revisited. *Neuroimage* **2:** 45–53.

Friston, K. J., Holmes, A. P., Worsley, K. P., Poline, J.-B., Frith, C. D., and Frackowiak, R. S. J. 1995b. Statistical parametric maps in functional imaging: A general linear approach. *Hum. Brain Mapp.* **2:** 189–210.

Friston, K. J., Jezzard, P., and Turner, R. 1994. Analysis of functional MRI time-series. *Hum. Brain Mapp.* **1:** 153–171.

Grafton, S. T., Fagg, A. H., and Arbib, M. A. 1998a. Dorsal premotor cortex and conditional movement selection: A PET functional mapping study [In Process Citation]. *J. Neurophysiol.* **79:** 1092–1097.

Grafton, S. T., Hazeltine, E., and Ivry, R. B. 1998b. Abstract and effector-specific representations of motor sequences identified with PET. *J. Neurosci.* **18:** 9420–9428.

Grafton, S. T., Mazziotta, J. C., Presty, S., Friston, K. J., Frackowiak, R. S., and Phelps, M. E. 1992b. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. *J. Neurosci.* **12:** 2542–2548.

Grafton, S. T., Mazziotta, J. C., Woods, R. P., and Phelps, M. E. 1992a. Human functional anatomy of visually guided finger movements. *Brain* **115**(Pt 2): 565–587.

Halsband, U., Ito, N., Tanji, J., and Freund, H. J. 1993. The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. *Brain* **116**(Pt 1): 243–266.

Halsband, U., and Passingham, R. E. 1982. The role of premotor and parietal cortex in the direction if action. *Brain Res.* **240:** 368–372.

Heinze, H. J., Mangun, G. R., Burchert, W., Hinrichs, H., Scholz, M., Munte, T. F., Gos, A., Scherg, M., Johannes, S., Hundeshagen, H., and et al 1994. Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature* **372:** 543–546.

Hikosaka, O., Sakai, K., Miyauchi, S., Takino, R., Sasaki, Y., and Putz, B. 1996. Activation of human presupplementary motor area in learning of sequential procedures: A functional MRI study. *J. Neurophysiol.* **76:** 617–621.

Humberstone, M., Sawle, G. V., Clare, S., Hykin, J., Coxon, R., Bowtell, R., Macdonald, I. A., and Morris, P. G. 1997. Functional magnetic resonance imaging of single motor events reveals human presupplementary motor area. *Ann. Neurol.* **42:** 632–637.

Jancke, L., Mirzazade, S., and Shah, N. J. 1999. Attention modulates the blood oxygen level dependent response in the primary visual cortex measured with functional magnetic resonance imaging. *Naturwissenschaften* **86:** 79–81.

Jenkins, I. H., Brooks, D. J., Nixon, P. D., Frackowiak, R. S., and Passingham, R. E. 1994. Motor sequence learning: A study with positron emission tomography. *J. Neurosci.* **14:** 3775–3790.

Jueptner, M., Frith, C. D., Brooks, D. J., Frackowiak, R. S., and Passingham, R. E. 1997a. Anatomy of motor learning. II. Subcortical structures and learning by trial and error. *J. Neurophysiol.* **77:** 1325–1337.

Jueptner, M., Stephan, K. M., Frith, C. D., Brooks, D. J., Frackowiak, R. S., and Passingham, R. E. 1997b. Anatomy of motor learning. I. Frontal cortex and attention to action. *J. Neurophysiol.* **77:** 1313–1324.

Karni, A., Meyer, G., Jezzard, P., Adams, M. M., Turner, R., and Ungerleider, L. G. 1995. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature* **377:** 155–158.

Krams, M., Rushworth, M. F., Deiber, M. P., Frackowiak, R. S., and Passingham, R. E. 1998. The preparation, execution and suppression of copied movements in the human brain. *Exp. Brain Res.* **120:** 386–398.

Matsuzaka, Y., and Tanji, J. 1996. Changing directions of forthcoming arm movements: Neuronal activity in the presupplementary and supplementary motor area of monkey cerebral cortex. *J. Neurophysiol.* **76:** 2327–2342.

O'Brien, R. G., and Kaiser, M. K. 1985. MANOVA method for analyzing repeated measures designs: An extensive primer. *Psychol. Bull.* **97:** 316–333.

Pantano, P., Formisano, R., Ricci, M., Di Piero, V., Sabatini, U., Di Pofi, B., Rossi, R., Bozzao, L., and Lenzi, G. L. 1996. Motor recovery after stroke. Morphological and functional brain alterations. *Brain* **119:** 1849–1857.

Pascual-Leone, A., Nguyet, D., Cohen, L. G., Brasil-Neto, J. P., Cammarota, A., and Hallett, M. 1995. Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *J. Neurophysiol.* **74:** 1037–1045.

Passingham, R. E. 1989. Premotor cortex and the retrieval of movement. *Brain Behav. Evol.* **33:** 189–192.

Perenin, M. T., and Vighetto, A. 1988. Optic ataxia: A specific disruption in visuomotor mechanisms. I. Different aspects of the deficit in reaching for objects. *Brain* **111:** 643–674.

Peters, M. 1998. Description and validation of a flexible and broadly usable hand preference questionnaire. *Laterality* **3:** 77–96.

Petit, L., Courtney, S. M., Ungerleider, L. G., and Haxby, J. V. 1998. Sustained activity in the medial wall during working memory delays. *J. Neurosci.* **18:** 9429–9437.

Picard, N., and Strick, P. L. 1996a. Motor areas of the medial wall: A review of their location and functional activation. *Cereb. Cortex.* **6:** 342–353.

Povel, D. J., and Collard, R. 1982. Structural factors in patterned finger tapping. *Acta Psychol. (Amst)* **52:** 107–123.

Rijntjes, M., Dettmers, C., Buchel, C., Kiebel, S., Frackowiak, R. S., and Weiller, C. 1999. A blueprint for movement: Functional and anatomical representations in the human motor system. *J. Neurosci.* **19:** 8043–8048.

Rizzolatti, G., and Arbib, M. A. 1999. From grasping to speech: Imitation might provide a missing link: Reply. *Trends. Neurosci.* **22:** 152.

Rizzolatti, G., Fadiga, L., Gallese, V., and Fogassi, L. 1996a. Premotor cortex and the recognition of motor actions. *Brain Res. Cogn. Brain Res.* **3:** 131–141.

Rizzolatti, G., Fadiga, L., Matelli, M., Bettinardi, V., Paulesu, E., Perani, D., and Fazio, F. 1996b. Localization of grasp representations in humans by PET: 1. Observation versus execution. *Exp. Brain Res.* **111:** 246–252.

Roland, P. E., Eriksson, L., Stone-Elander, S., and Widen, L. 1987. Does mental activity change the oxidative metabolism of the brain? *J. Neurosci.* **7:** 2373–2389.

Roland, P. E., and Gulyas, B. 1994. Visual imagery and visual representation [see Comments]. *Trends. Neurosci.* **17:** 281–287.

Roland, P. E., and Zilles, K. 1996b. Functions and structures of the motor cortices in humans. *Curr. Opin. Neurobiol.* **6:** 773–781.

Rosenbaum, D. A. 1985. Motor programming: A review and scheduling theory. In *Motor Behavior: Programming, Control, and Acquisition* (H. Heuer, U. Kleinbeck, and K. M. Schmidt, Eds.), pp. 1–33. Springer-Verlag, Berlin.

Rosenbaum, D. A., Kenny, S. B., and Derr, M. A. 1983. Hierarchical control of rapid movement sequences. *J. Exp. Psychol. Hum. Percept. Perform.* **9:** 86–102.

Sadato, N., Campbell, G., Ibanez, V., Deiber, M., and Hallett, M. 1996. Complexity affects regional cerebral blood flow change during sequential finger movements. *J. Neurosci.* **16:** 2691–2700.

Sakai, K., Hikosaka, O., Miyauchi, S., Sasaki, Y., Fujimaki, N., and Putz, B. 1999. Presupplementary motor area activation during sequence learning reflects visuo-motor association. *J. Neurosci.* **19:** RC1.

Shibasaki, H., Sadato, N., Lyshkow, H., Yonekura, Y., Honda, M., Nagamine, T., Suwazono, S., Magata, Y., Ikeda, A., and Miyazaki, M. 1993. Both primary motor cortex and supplementary motor area play an important role in complex finger movement. *Brain* **116:** 1387–1398.

Shima, K., Mushiake, H., Saito, N., and Tanji, J. 1996. Role for cells in the presupplementary motor area in updating motor plans. *Proc. Natl. Acad. Sci. USA* **93:** 8694–8698.

Shima, K., and Tanji, J. 1998. Both supplementary and presupplementary motor areas are crucial for the temporal organization of multiple movements. *J. Neurophysiol.* **80:** 3247–3260.

Shima, K., and Tanji, J. 1998b. Role for cingulate motor area cells in voluntary movement selection based on reward. *Science* **282:** 1335–1338.

Snyder, L. H., Batista, A. P., and Andersen, R. A. 1998. Change in motor plan, without a change in the spatial locus of attention, modulates activity in posterior parietal cortex. *J. Neurophysiol.* **79:** 2814–2819.

Stephan, K. M., Binkofski, F., Halsband, U., Dohle, C., Wunderlich, G., Schnitzler, A., Tass, P., Posse, S., Herzog, H., Sturm, V., Zilles, K., Seitz, R. J., and Freund, H. J. 1999. The role of ventral medial wall motor areas in bimanual co-ordination. A combined lesion and activation study. *Brain* **122**(Pt 2): 351–368.

Stephan, K. M., Fink, G. R., Passingham, R. E., Silbersweig, D., Ceballos-Baumann, A. O., Frith, C. D., and Frackowiak, R. S. 1995. Functional anatomy of the mental representation of upper extremity movements in healthy subjects. *J. Neurophysiol.* **73:** 373–386.

Van Oostende, S., Van Hecke, P., Sunaert, S., Nuttin, B., and Marchal, G. 1997. FMRI studies of the supplementary motor area and the premotor cortex. *Neuroimage.* **6:** 181–190.

Watanabe, T., Harner, A. M., Miyauchi, S., Sasaki, Y., Nielsen, M., Palomo, D., and Mukai, I. 1998. Task-dependent influences of attention on the activation of human primary visual cortex. *Proc. Natl. Acad. Sci. USA* **95:** 11489–11492.

Winstein, C. J., Grafton, S. T., and Pohl, P. S. 1997. Motor task difficulty and brain activity: Investigation of goal-directed reciprocal aiming using positron emission tomography. *J. Neurophysiol.* **77:** 1581–1594.

Wise, S. P., Boussaoud, D., Johnson, P. B., and Caminiti, R. 1997. Premotor and parietal cortex: Corticocortical connectivity and combinatorial computations. *Annu. Rev. Neurosci.* **20:** 25–42.

Wise, S. P., Fried, I., Olivier, A., Paus, T., Rizzolatti, G., and Zilles, K. J. 1996. Workshop on the anatomic definition and boundaries of the supplementary sensorimotor area. *Adv. Neurol.* **70:** 489–495.

Woodworth, R. S. (1938). *Experimental Psychology*. Holt, New York.