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Complexity Affects Regional Cerebral Blood Flow Change during Sequential Finger Movements

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Brain regions activated with complex sequential finger movements were localized by measuring regional cerebral blood flow (rCBF) with positron emission tomography. Whereas the total number and frequency of finger movements were kept constant, the complexity of auditory cued sequential finger movements of the right hand varied, with sequence length as the independent variable. In four conditions of differing complexity, the bilateral primary sensorimotor area, left ventral premotor cortex, posterior supplementary motor area, right superior part of the cerebellum, and left putamen were consistently and equally activated. This finding suggests an executive role in running sequences, regardless of their length. The right dorsal premotor cortex (Brodmann area 6) and the right precuneus (Brodmann area 7) showed a linear increase of rCBF as sequence complexity increased. This finding is consistent with the hypothesis that these areas function in the storage of motor sequences in spatial working memory and the production of ongoing sequential movement with reference to that of buffered memory. A similar increase in the cerebellar vermis and the left thalamus likewise suggests a role of these subcortical structures in complexity of sequential finger movements. Conversely, the left inferior parietal lobule showed a decrease of rCBF as complexity increased. Because short-term phonological storage is localized to this area, we suggest that the visuospatial working memory system may suppress other systems not in use. Our findings suggest that complex sequential finger movements recruit a discrete set of brain areas, in addition to areas underlying the execution of simple movement sequences.

Key words: regional cerebral blood flow; sequential finger movements; positron emission tomography; sensorimotor cortex; premotor cortex; supplementary motor area

The performance of complex movement requires the execution of preprogrammed temporal and spatial movement patterns. Our goal was to attain a better understanding of the brain mechanisms underlying complex sequential movements. Many reports concern the regions related to the complexity of movement (Orgogozo and Larsen, 1979; Roland et al., 1980; Grafton et al., 1992; Halsband et al., 1993; Rao et al., 1993; Shibasaki et al., 1993). Both the supplementary motor area (SMA) and the premotor cortex (PMC) appear to have an important role in the generation of sequences from memory that fit into a precise timing plan. SMA and PMC lesions resulted in impairment of programming of sequential and rhythmic patterns from memory (Halsband et al., 1993). Positron emission tomography (PET) showed that the left PMC was recruited for patterning of the motor sequences required for the right-handed manual execution of piano playing (Sergent et al., 1992). In addition to increased involvement of the ipsilateral primary sensorimotor cortex (SM1) in the execution of complex finger movements, Shibasaki et al. (1993) found a greater increase in regional cerebral blood flow (rCBF) in the SMA during self-paced complex finger movements than during the simple, simultaneous movement of all of the fingers. However, several other studies failed to show any difference between the execution of simple and complex hand movements (Fox et al., 1985a; Colebatch et al., 1991). As Shibasaki et al. (1993) pointed out, these discrepancies might result from the types of tasks used.

In the present study, we used acoustically paced sequential opponent finger movements. As an index of complexity, we varied the length of unit sequences while controlling the rate, rhythm, and total number of movements. The subjects were overtrained before the PET scan to minimize any learning effect during the scan.

SUBJECTS AND METHODS

We studied 10 normal volunteers (7 men, 3 women), aged 20 to 59 years (mean 34.4 years). The subjects were all right-handed by self-report. The protocol was approved by the Institutional Review Board, and all subjects gave their written informed consent for the study. A small plastic catheter was placed in the left cubital vein for injection of the radioisotope. The subjects lay in a supine position with their eyes closed and patched and their heads immobilized with an individually fitted thermoplastic face mask.

The PET scans were performed with a Scanditronix PC 2048–15B tomograph (Uppsala, Sweden), which collected 15 contiguous planes with an in-plane resolution of 6.5 mm [full-width at half-maximum (FWHM) after reconstruction, and a center-to-center distance of 6.5 mm]. Each slice was 6.5 mm thick. Field of view and pixel size of the reconstructed images were 256 mm and 2 mm, respectively. A transmission scan was obtained with a rotating germanium-68/gallium-68 source. Based on the reconstructed transmission images, the position of the head was set to cover SM1, sacrificing views of the lower cerebellum.

Images of CBF were obtained by summing the activity during the 60 sec period after the first detection of an increase in cerebral radioactivity after the intravenous bolus injection of 30 mCi of ^{15}O-labeled water. No arterial blood sampling was performed and, thus, the images collected are

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Table 1. Sequences of opponent finger movements

Complexity	Sequence[a]
1	1,2,3,4
2	1,2,3,4,1,3,2,4
3	1,2,3,4,1,3,2,4,4,2,3,1
4	1,2,3,4,1,3,2,4,4,2,3,1,4,3,2,1

[a]Sequence: 1, index finger; 2, middle finger; 3, ring finger; 4, little finger.

those of tissue activity. Tissue activity recorded by this method is nearly linearly related to rCBF (Fox et al., 1984; Fox and Mintun, 1989).

Each subject had 10 consecutive scans at 10 min intervals. A complete session consisted of two rest scans and eight scans with acoustically paced opponent movements of the right fingers with different sequences of different lengths (Table 1). Subjects were trained before the PET scan to perform these sequences without difficulty. The first and last scans were performed under resting conditions, and the second to ninth scans under movement conditions. For the rest scans, subjects lay quietly, listening to a metronome sounding at a frequency of 2 Hz. No attempt was made to control the subjects' thought content or attention during rest. For the movement scans, subjects briskly and precisely touched the tip of the thumb with the fingers of the right hand at a frequency of 2 Hz. The opponent finger movements were paced to the beat of the metronome, which began sounding 50 sec before the isotope injection and continued for the duration of the scan. The entire sequence was started 20 sec before the injection and was performed repeatedly in each condition until the end of the scan. The order of the different movement tasks was randomized across all subjects. The finger movements were monitored by an electrically equipped glove, which recorded the timing and the finger that tapped the thumb. Performance of the sequence was assessed by calculating the percentage of correct taps. No omission of taps was observed. Each complexity condition (Table 1) was tested twice in each subject, the tests being designated trial 1 and trial 2.

The data were analyzed with SPM software (MRC Cyclotron Unit, London, UK) in PROMATLAB (Mathworks) using ANALYZE image display software (BRU, Mayo Foundation, Rochester, MN). The data from each subject were first standardized for brain size and shape and reconstructed parallel to the intercommissural line (Talairach and Tournoux, 1988; Friston et al., 1989). Each image was smoothed to account for the variation in normal gyral anatomy using a Gaussian filter (FWHM = $10 \times 10 \times 6$ mm^3). In the standard space, each voxel was $2 \times 2 \times 4$ mm^3. The effect of global differences in rCBF between scans was removed by using an analysis of covariance (ANCOVA) (Friston et al., 1990).

Planned linear comparisons of the adjusted mean images followed. All image analyses were performed on a pixel-by-pixel basis. The t test was applied pixel-by-pixel to compare the difference in mean rCBF for each condition, using the adjusted pixel error variances estimated from the ANCOVA. The value of t for each pixel in each comparison was then transformed to a normal standard distribution (Z values), which was independent of the degree of freedom of the error. The resulting set of Z values constituted a statistical parametric map (SPM).

To identify the cortical areas activated with different lengths of the unit sequence, comparisons were performed over 10 different conditions: 1–0, 2–0, 3–0, 4–0, 2–1, 3–1, 4–1, 3–2, 4–2, and 4–3, where 0 stands for the rest condition and the other numbers stand for the complexity conditions shown in Table 1. All regions reported as being significantly activated exceeded the $p < 0.05$ level of significance with a Bonferroni-type correction for repeated measurements (Friston et al., 1991). This correction was made for the number of comparisons and the effective number of independent pixels in each plane to set a significance threshold strict enough to keep the false positive rate at the defined level per plane. Three-dimensional searches for local maximal and local minimal foci followed. Statistical evaluation focused on a total of 73 local maximal and minimal foci to determine whether the change in rCBF in these foci occurred linearly as complexity increased. Here, complexities 0, 1, 2, 3, and 4 were treated as continuous variables, not as discrete categories.

First, the feasibility of the linear model was evaluated with the "lack of fit" test (Draper and Smith, 1981). Let Y_{ijk} denote the actual rCBF for subject i, complexity j, and trial k, where $k = 1$ or 2, and μ_{ij} is the modeled rCBF for subject i and complexity j. The model is of the form:

$$\mu ij = \alpha i + \beta c_j, \tag{1}$$

where the subjects are from $i = 1$–10, $j = 1$–5, and $c_j = j - 1$. β is a common slope, and α_i is a different constant term for each subject for the linear relationship between complexity and rCBF. Denote by m_{ij} the value estimated by the linear model (Eq. 1) for subject i at complexity level j from the data. In the ANOVA formulation, the residual or error sum of squares (SSE) can be decomposed into two sums of squares as follows:

$$\begin{aligned} \mathrm{SSE} &= \Sigma\Sigma\Sigma\ (Yijk - mij)^2 \\ &= \Sigma\Sigma\Sigma\ (Yijk - Yijo)^2 + \Sigma\Sigma\Sigma(Yijo - mij)^2, \end{aligned} \tag{2}$$

where the sums are on $i = 1$–10, $j = 1$–5, and $k = 1$–2. Y_{ijo} denotes the mean of the Y_{ijk} over $k = 1$–2. The first term of the right side of Equation 2 is a within-repeat sum of squares. This term is pure error component (SSPE), because only the random variation can influence the results if the setting of the complexity is identical for two observations. Hence, the second term of the right side of Equation 2 is a lack of fit component (SSLF):

$$\mathrm{SSPE} = \Sigma\Sigma\Sigma = (Y_{ijk} - Y_{ijo})^2$$

$$\mathrm{SSLF} = \Sigma\Sigma\Sigma(Y_{ijo} - m_{ij})^2.$$

The degrees of freedom for SSE are 88 (100 − 10 − 1 − 1; 100 for 10 subjects × 10 conditions, 10 for subjects, 1 for ANCOVA slope for global CBF, and 1 for complexity slope); these are partitioned into degrees of freedom for pure error (50) and for lack of fit (38). Then, lack of fit is tested with the statistic:

$$\mathrm{F} = (\mathrm{SSLF}/38)/(\mathrm{SSPE}/50) \tag{3}$$

which has an F distribution with 38 and 50 degrees of freedom (Draper and Smith, 1981).

Second, for the foci in which the linear model was shown to be feasible, the lack of fit and pure error sums of squares were pooled and the significance of the linear regression was examined with the F test with 1 and 88 degrees of freedom. In this test, p values were adjusted with the Bonferroni correction for 58,650 voxels in the brain of Talairach's space. Both increases and decreases are reported.

Finally, the question of whether the linear model should include an additional term for the value of complexity at rest was addressed. The rest condition ($c0$) may not be the same "distance" from complexity 1 ($c1$) as $c1$ is from $c2$, because the difference between $c1$ and $c2$ is only the difference of the length of the sequence, whereas the difference between rest and $c1$ is the sequential finger movement itself. Hence, the reasonableness of including the rest condition as 0 in the linear model was determined by adding a term for the value of complexity at rest and testing whether it differed from 0 or not, using an F distribution with 1 and 87 degrees of freedom. When the estimated complexity value for rest was significantly ($p < 0.05$) different from 0, the foci were determined not to be linearly related to the change of complexity.

The effect of performance of correct tapping in the four complexity conditions and two trials was investigated. The proportion of correct taps per person in each trial and at each complexity was transformed by the angular transformation; this transform corrects the proportion P to the arcsine of the square root of P. The transformed data were analyzed by a general linear model that incorporated effects attributable to subjects, complexity conditions, and trials. The effect of trials was tested with an F test with 1 and 59 degrees of freedom (59 = 72 − 9 − 3 − 1; 72 for number of observations, 9 for subjects, 3 for complexity conditions, and 1 for trial effect).

RESULTS

There was no difference in the performance of trial 1 and trial 2 in each complexity condition ($p > 0.05$, F test). The nonparametric test of Page (Hollander and Wolfe, 1973) showed evidence of a monotonic decline in performance from complexity 1 to 4 ($p < 0.001$). However, the mean percent of correct taps was >90% in all complexity conditions (Table 2).

Increases in rCBF (activation) in all conditions, compared with rest, were observed in the SM1 bilaterally, right superior cerebellum, left ventral PMC, SMA, and left putamen (Fig. 1, Table 3). The left SM1 (Talairach's coordinates, −34, −24, 52) corre-

Table 2. Performance of sequential finger movements

Complexity	Trial 1 (n = 9)	Trial 2 (n = 9)
1	95.9 ± 7.0	96.9 ± 4.9
2	93.3 ± 9.2	95.6 ± 6.2
3	90.7 ± 11.0	93.4 ± 8.8
4	92.6 ± 7.6	94.7 ± 5.1

Values are mean ± SD for percentage of correct taps (% = correct taps/total taps ×100).

The difference in the percentage of correct taps between the first and second trials was not significant on the angular transform of the proportion of correct taps ($p > 0.05$, F test in general linear model with nine subjects, four complexity conditions, and two trials).

sponded to the hand area reported previously (Colebatch et al., 1991; Grafton et al., 1993). The right SM1 (28, −14, 52), which is located slightly anterior to the contralateral SM1, showed less activation. The activated focus in the left ventral PMC (−48, −8, 28) is close to the ventral SM1. The local maximal focus of SMA (−6, −8, 56) was located posterior to the anterior commissural line (Vac).

As complexity increased from 0 to 4, a linear increase of rCBF occurred in the right PMC, cerebellar vermis, right precuneus (Brodmann area 7), and left thalamus. In the left inferior parietal lobule (LPi), rCBF decreased linearly as complexity increased from 0 to 4 (Fig. 1, Table 4).

DISCUSSION

Task performance

Complex motor tasks require motor learning, and their execution is characterized by a preprogrammed process that takes advantage of that learning (Halsband et al., 1993). In this study, extensive practice before the PET scan avoided a learning effect during the scan. No significant differences in performance were observed between trial 1 and trial 2, and the percentage of correct taps was high for all complexity conditions, suggesting that subjects had reached an overtrained condition at the time of the PET scan. The activated foci, therefore, were unlikely to reflect learning. The decline in performance with increased length of the sequence confirmed that task complexity does indeed increase with sequence length.

Distinct sets of activated areas

In the present study, we tried to dissect the motor system by changing one parameter (i.e., complexity) to detect different responses, which presumably correspond to different functions. This correlative approach, as a means of identifying the function of areas, relies on the assumption that rCBF change is parallel to the electrical or neuronal activity. A direct relation between neuronal electrical activity and the metabolic rate of glucose utilization has been established in the peripheral nervous system (Yarowsky et al., 1983) and, for subcortical structures, in the CNS (Toga and Collins, 1981). In humans, this relation has been reported for the primary visual (Fox and Raichle, 1984) and primary auditory (Price et al., 1992) cortices. In the primary sensory cortex activated by median nerve stimulation at the wrist, there was an increase of rCBF up to 4 Hz and then a plateau (Ibáñez et al., 1995). These studies used rCBF changes as an indirect index of brain work and assumed a direct relation between the rate of a stimulus and the neuronal electrical response, although this may not hold in certain ranges of frequencies. The CBF response of the nonprimary cortices to the frequency of the stimulus may differ from that of the primary sensory cortices. During the presentation of heard words, the rCBF response in an area of the left posterior superior temporal gyrus (Wernicke's area) was primarily dependent on the occurrence of words regardless of their rate of presentation, whereas the primary auditory cortices showed a linear increase of rCBF response as the rate of presentation of heard words increased (Price et al., 1992). They speculated that the primary auditory cortices were associated with the early processing of complex acoustic signals, whereas Wernicke's area was associated with the comprehension of heard words. They concluded that time-dependent sensory signals detected in the primary auditory cortices were transformed into a time-invariant output that was channeled to a functionally specialized region (Wernicke's area). In the motor system, Sadato et al. (1996) found a rapid increase of rCBF in the SM1 and cerebellum during auditory cued, repetitive opponent finger tapping at a frequency of up to 2 Hz, with saturation of the rCBF at higher frequencies. On the other hand, the rCBF changes were largest in the SMA, anterior cingulate gyrus, and right prefrontal regions during very slow movements (0.25 and 0.5 Hz) and then declined at higher frequencies. The authors speculated that this was the result of a change in the character of the movement from reactive to predictive.

The present study showed that complex sequential finger movements activated two sets of brain areas with different patterns. One pattern was constant "step" activation, and the other pattern was a linear increase or decrease of activation as complexity increased. Although we base the following discussion on the assumption that these changes are directly reflective of neuronal activity, such an assumption may not always be correct, as the previous review attests.

Step activation

The bilateral SM1, right cerebellum, posterior SMA, and left putamen were activated with the simplest finger sequence and did not continue to increase as complexity increased. This kind of step increase of rCBF suggests that it is caused by the common characteristic among the four conditions, that is, execution of sequential movements of the fingers.

Primary sensorimotor cortex

The SM1 has a significant executive function linked to the movements themselves. Electrophysiological studies in nonhuman primates have shown that the movement-related activity of the primary motor cortex (M1) is similar to that of muscle activity during either visually triggered or internally triggered sequential movements (Mushiake et al., 1991) or during flexion/extension of the wrist (Butler et al., 1992). Step activation in the present study is consistent with these findings, confirming that the M1 activity is closely related to the spinal motor apparatus or movement itself.

Ipsilateral activation of the SM1 corresponding to the hand area confirms the previous rCBF report by Shibasaki et al. (1993). They found that, compared with simultaneous opponent finger tap movements, sequential opponent finger movements caused significant activation in the ipsilateral SM1. A functional magnetic resonance imaging study demonstrated ipsilateral activation with finger movements, which was greater for left-hand movement of right-handed subjects than for right-hand movement of left-handed subjects (Kim et al., 1993). Activation of the ipsilateral SM1 is more anterior than activation of the contralateral SM1, probably because sensory feedback is absent on the ipsilateral side. With limited spatial resolution, it is impossible to separate

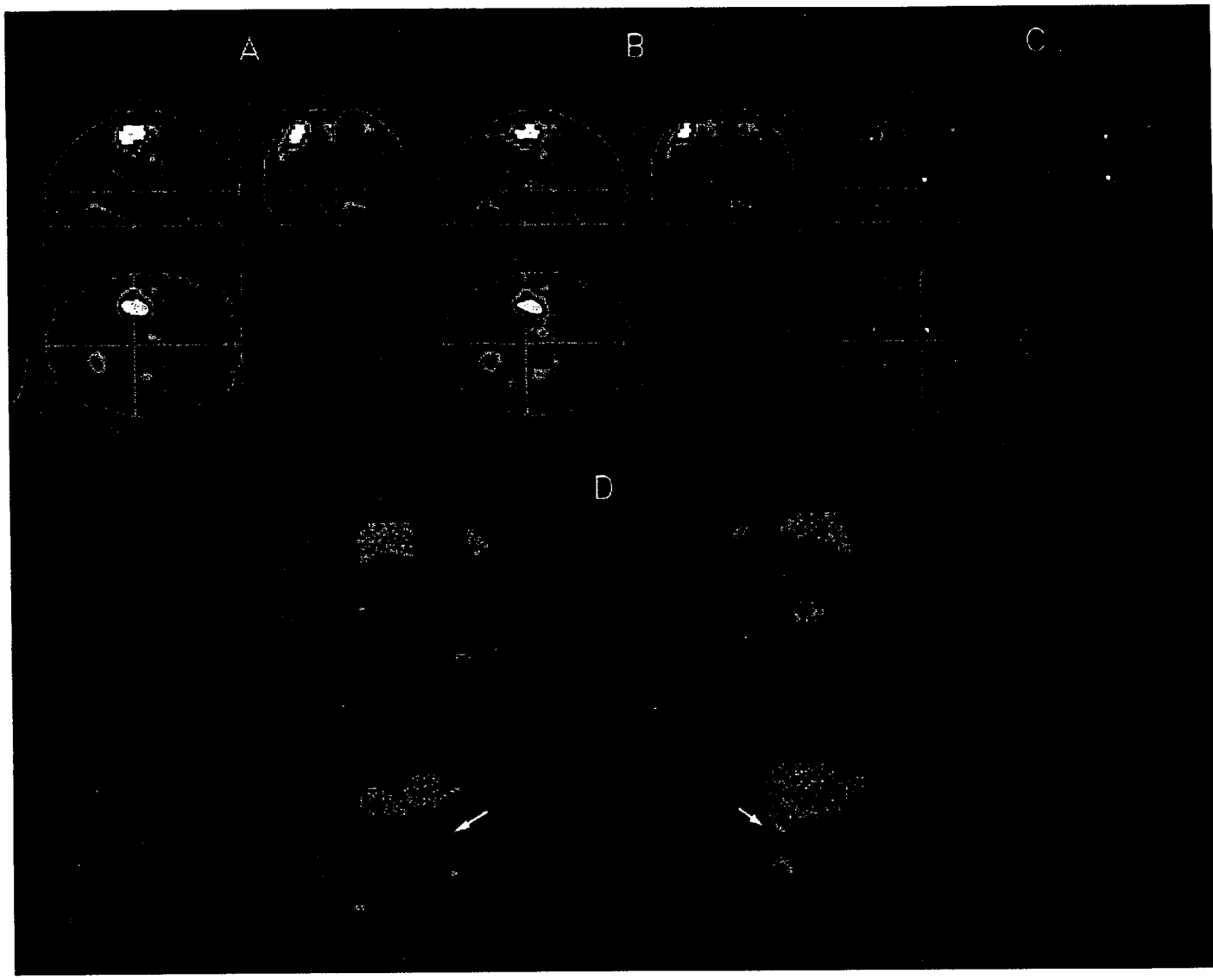

Figure 1. Activation of the brain (adjusted mean rCBF) by opponent movements of the fingers of the right hand. *A*, Comparison between rest and the simplest sequence (complexity 1 − rest). *B, D*, Comparison between rest and the most complex sequence (complexity 4 − rest). *C*, Comparison between the simplest and the most complex sequence (complexity 4 − complexity 1). *A–C* are SPM in three projections with the maximal pixel value displayed along each "line of sight." The grid is the standard proportional, stereotaxic grid of Talairach and Tournoux (1988), which defines the three-dimensional space into which all of the subjects' PET scans of the brain were normalized. The anteroposterior commissural line is set at zero on the sagittal and coronal projections. Vertical projections of the anterior commissure (*VAC*) and the posterior commissure (*VPC*) are depicted on the transverse and sagittal projections. Only pixels that are significantly different between conditions ($p < 0.05$, with a Bonferroni-type correction) are displayed and scaled to indicate threshold (*green*) and maximal Z values (*white*) for each comparison. *D*, Significant voxels within a rim 2 cm from the lateral and medial surfaces of the SPM are projected onto lateral and medial cortical views of the brain. Views of the brain are, from left to right: right medial hemisphere; left medial hemisphere; right lateral hemisphere; and left lateral hemisphere. The *arrows* indicate the central sulcus. In *A, B*, and *D*, activation is present in the bilateral primary sensorimotor cortex, right superior cerebellum, left ventral premotor cortex, SMA, and left putamen. In *C*, the comparison between complexity 4 and complexity 1, there is greater activation in the right premotor area, bilateral superior parietal lobule, and left thalamus.

precentral and postcentral foci (Colebatch et al., 1991), and increases in neuronal activity in either region could contribute to the activation observed. With source analysis of movement-related cortical potentials, Toro et al. (1994) found that, associated with finger movements, potentials in the contralateral SM1 most likely originated from both precentral and postcentral regions, whereas potentials in the ipsilateral SM1 originated from the precentral region only. This suggests that activation of the ipsilateral SM1 originates from the precentral region, causing the center of activation to be more anterior than in the contralateral SM1. Another possibility is that the ipsilateral representation of a hand is truly anterior to the representation of the contralateral hand. A study using transcranial magnetic stimulation indicates that this may be true (Wassermann et al., 1994).

Left ventral PMC

An activated focus with Talairach's coordinates of −48, −8, and 28 is on the precentral gyrus according to Talrairach's atlas, close to the ventral SM1. Because this focus is far ventral with respect to the main focus of hand activity in SM1, it likely represents the left ventral PMC. Stephan et al. (1995) found activation in the left ventral PMC during imagined movement and during execution of

Table 3. Activation of different brain regions by complex finger movements in sequences of various lengths

	Coordinates			Adjusted mean rCBF ± SD (ml/min/100 ml)						
Location[a]	*x*	*y*	*z*	Rest	*c*1	*c*2	*c*3	*c*4	*Z*	%ΔCBF
lt SM1	−34	−24	52	59.1 ± 2.5	70.2 ± 2.6	69.5 ± 2.0	69.2 ± 2.0	68.6 ± 1.8	10.8	18.8
cerebellum	14	−58	−16	59.5 ± 4.0	68.7 ± 4.2	68.6 ± 2.7	70.5 ± 3.6	70.2 ± 3.0	6.8	15.5
SMA	−6	−8	56	60.3 ± 4.3	66.8 ± 2.2	67.4 ± 1.9	68.2 ± 2.3	66.7 ± 2.9	6.0	10.8
rt SM1	28	−14	52	58.1 ± 2.3	63.2 ± 2.2	63.7 ± 2.3	63.2 ± 2.0	63.7 ± 1.8	6.1	8.8
lt putamen	−30	−6	4	64.6 ± 2.9	69.1 ± 2.3	67.3 ± 2.6	69.1 ± 2.1	69.2 ± 2.4	5.0	7.0
lt premotor	−48	−8	28	54.8 ± 2.2	58.9 ± 1.6	58.6 ± 2.2	57.7 ± 1.7	59.2 ± 1.7	5.7	7.5

Values are adjusted mean ± SD (n = 10 subjects × 2 conditions). Coordinates of local maximal points, Z scores, and %Δ in rCBF were calculated for comparison of the complexity 1 (*c*1) condition versus the rest condition. Adjusted mean rCBF values are also shown for complexity 2 (*c*2), complexity 3 (*c*3), and complexity 4 (*c*4) conditions. Activation was constant regardless of the sequence length.

[a]SM1, Primary sensorimotor cortex; SMA, supplementary motor area; premotor, premotor cortex; lt, left; rt, right.

upper limb movements. These findings suggest that activation in the left ventral PMC may constitute part of normal physiological processes during finger movement.

Posterior SMA

Activation of the SMA is associated with a wide range of functions, such as motor programming (Roland et al., 1980), motor planning (Orgogozo and Larsen, 1979; Grafton et al., 1992; Rao et al., 1992), readiness to move (Fox et al., 1985a), motor learning (Roland et al., 1989; Seitz et al., 1990; Grafton et al., 1992), complexity of movement (Shibasaki et al., 1993), and responsiveness to internal cueing of movements (Halsband et al., 1993) or to the selection of the movement (Deiber et al., 1991). The SMA is argued to have two distinct areas with different functions, that is, the anterior SMA, or pre-SMA, and the posterior SMA, or SMA proper (Matsuzaka et al., 1992; Luppino et al., 1993). They are roughly divided by the Vac line (Deiber et al., 1991). Whereas the anterior SMA is activated by the preparation for or selection of the movement ("what to do" or "when to do") (Deiber et al., 1991), the posterior SMA is more "executive," because it is activated during repetitive movement of the hand, foot, or elbow (Colebatch et al., 1991; Matteli et al., 1993; Sadato et al., 1995).

Sequential movements are generally considered to be performed as a unit and, therefore, require programming (previous determination of individual components) before their execution (Sternberg et al., 1983). The SMA might take part in the preparation of internally referenced or remembered motor acts. Tanji and Shima (1994) provided strong evidence for the involvement of the SMA in the programming, as well as the execution of sequential movements. Shibasaki et al. (1993), in an $H_2{}^{15}O$ PET study comparing self-paced sequential complex finger movements with self-paced simultaneous finger movements, found more activation in the SMA during the sequential complex finger movements. The difference between these tasks is the presence or absence of the sequence. In contrast, our present study modified the length of the sequence, and the SMA was consistently activated regardless of the sequence length, showing step activation. Hence, complexity of sequential finger movements has two components: presence or absence of the sequence, and length of the sequence. Sequential finger movements are more complex than simultaneous finger movements in that the forthcoming sequence has to be programmed based on memorized information (Mushiake et al., 1991) and then executed. A longer sequence should be more complex than a shorter one. As the predetermined sequence was performed repeatedly throughout the scan time in the present study, programming of the sequence might have occurred once at the beginning of the performance; hence, our finding of step activation in the SMA reflects the executive component of the SMA activity. On the other hand, a longer sequence "loaded" in the right PMC has to be retained during the entire performance; therefore, it is related to greater activation. We conclude that activation of the SMA is related to the execution of the sequence regardless of its length or complexity.

Table 4. Regions of the brain with a linear increase or decrease in rCBF as complexity increased

		Coordinates			Adjusted mean rCBF ± SD (ml/min/100 ml)							
Location[a]	Comp[b]	*x*	*y*	*z*	Rest	*c*1	*c*2	*c*3	*c*4	$F_{(88,1)}$	Slope	p[c]
rCBF increase												
rt premotor (6)	4–0	16	2	56	59.0 ± 2.7	60.7 ± 1.6	62.1 ± 2.2	62.4 ± 1.7	63.6 ± 2.1	50.5	1.1	<0.001
Cerebell. ver.	4–0	−4	−56	−12	55.8 ± 3.6	59.5 ± 2.8	60.5 ± 2.6	61.3 ± 2.7	62.6 ± 4.0	41.3	1.5	<0.001
lt thalamus	4–0	−12	−20	4	61.4 ± 3.6	63.7 ±2.9	65.9 ± 1.7	64.6 ± 2.7	67.3 ± 2.5	36.7	1.3	<0.01
rt PCu (7)	4–0	18	−56	48	54.4 ± 2.5	55.9 ± 2.2	56.8 ± 1.4	56.8 ± 1.6	58.4 ± 1.7	40.1	0.9	<0.001
rCBF decrease												
lt LPi (40)	1–4	−48	−56	24	57.8 ± 1.8	56.5 ± 2.0	54.5 ± 2.1	54.7 ± 2.4	53.3 ± 1.6	54.9	−1.1	<0.001

All foci had rest complexity values that were not significantly different from 0, indicating that the linear model was reasonable.

[a]Premotor, Premotor cortex; Cerebell. ver., cerebellar vermis; PCu, precuneus; LPi, inferior parietal lobule; rt, right; lt, left; numbers in parentheses are Brodmann areas, according to atlas of Talairach and Tournoux (1988).

[b]Comparison by which the focus was detected.

[c]With Bonferroni correction for 58,650 voxels in the brain of Talairach space.

Cerebellar hemisphere

Step activation was observed in the anterior cerebellar hemisphere ipsilateral to the movements, which appears to correspond to the intermediate zone of the anterior cerebellar cortex. The intermediate cerebellar cortex has been proposed to serve as a "comparator" in the execution of movement (Stein, 1986) because of the coincidence of signals from the motor cortex and spinal cord there. The major afferents are from the frontal and parietal cortex through corticopontocerebellar tracts (Glickstein et al., 1985), and the extrinsic spinocerebellar afferents with proprioceptive information are from the periphery (Tsukahara et al., 1968). Limb position commanded by motor cortical areas is compared with actual limb position through proprioceptive afferents. Other investigators (Fox et al., 1985b; Seitz et al., 1990; Shibasaki et al., 1993) have reported PET activation in the anterior cerebellar hemisphere during sequential finger movements. Grafton et al. (1992), who found no differences as the spatial or temporal complexity was altered during a finger-tracking task, concluded that the anterior cerebellar cortical response is related to the execution of motor tasks driven by external or internal cues. These results support our notion that step activation in the ipsilateral anterior cerebellar cortex represents an executive component of the tasks imposed in the present study.

Linear activation

As the complexity of the finger movements increased, there was a linear increase in activation of the right PMC, right precuneus, left thalamus, and cerebellum, and a linear decrease in activation of the left LPi. These findings suggest that these areas are involved in sequence processing rather than merely execution of the movements.

Right PMC

The "premotor cortex," a term originally applied to the lateral portion of the frontal agranular cortex rostral to the primary motor cortex, was considered to be the center of complex skilled movements (Dum and Strick, 1991). The PMC in the primate is heterogeneous and composed of multiple, discrete premotor areas (Dum and Strick, 1991), including PMd and PMv. PMd is located more caudodorsally around the precentral dimple of the monkey, and PMv is in the postarcuate region. Each premotor area is a nodal point for a distinct set of afferent inputs from subcortical nuclei and from cortical areas comprising a distinct system of movement control; hence, each premotor area is different physiologically as well as anatomically (Dum and Strick, 1991; He et al., 1993). The PMd of the monkey exhibited prominent motor set-related activity (Kurata et al., 1989; Mushiake et al., 1991). Sequence-specific neurons were also more numerous in the PMd (Dum and Strick, 1991; Mushiake et al., 1991). On the other hand, neuronal activity during a visually triggered task was more prominent in the PMv (Mushiake et al., 1991). The right PMC, which showed linear activation in the present study, may be equivalent to PMd because of its dorsal location.

There is clinical evidence for a critical role of the PMC in the temporal organization of sequential movements. A loss of hand skill, such as smooth typewriting or piano playing, is a typical dysfunction after PMC damage (Kleist, 1907, 1911). Deficits after unilateral PMC lesions affect both arms (Halsband and Freund, 1990). PMC lesions could be characterized by the disintegration of the dynamics of the motor act and skilled movements (Luria, 1966). Although some types of apraxia have been mainly related to left premotor lesions, a role for the right PMC has occasionally been described (Halsband et al., 1993).

In the present study, premotor activation progressively increased on the side ipsilateral to the movement as the length of the unit sequence increased, whereas activation of the contralateral PMC occurred not as a discrete focus but as part of a larger activation centered in the contralateral SM1. This finding is consistent with those of previous studies in nonhuman primates. In monkeys, simple limb movements activate the contralateral nonprimary motor area. With complex motor performance, a considerable portion of cells in the nonprimary motor cortex is active before and during bilateral limb movement (Tanji et al., 1988). Mushiake et al. (1991) showed that the motor set-related activity to perform a remembered sequential movement was more frequent in the PMd than in the PMv. In addition, sequence-specific neurons were more numerous in the PMd. In contrast, neuronal activity during visually triggered movement and transition-specific activity (activity during the transition between visually guided and internally guided tasks) was more prominent in the PMv. These findings suggest that the PMC, particularly the PMd, may have a role in preprogrammed processes linked to sequential motor actions. A PET study in humans (Jonides et al., 1993) showed that the right PMC is activated during functioning of visuospatial working memory. Jenkins et al. (1994) found that the learning of a new sequence of finger taps, compared with the performance of an overlearned sequence of finger taps, activated the PMC bilaterally. Activation was more prominent on the right side (%ΔCBF = 8.4%) than on the left side (%ΔCBF = 4.4%), although statistical significance was not assessed. This finding suggests that the right PMC has a role in working memory, because greater access to the buffer should be necessary for manipulation of sequences during learning, and the right PMC should be related to spatial tasks more than the left PMC. Sternberg et al. (1983) also suggested the existence of a movement sequence buffer, which was rapidly unloaded as soon as an imperative signal was given. Our findings, and those of the other PET studies cited, suggest that the right PMC may be part of the mechanism for storing motor sequences in a working memory buffer.

The absence of changes in various regions of prefrontal cortex is somewhat surprising given the evidence that various parts of this cortical region are involved in aspects of working memory (Goldman-Rakic, 1987). Jenkins et al. (1994) found that the prefrontal cortices were activated during trial-and-error learning of new sequences of finger tapping (NEW), whereas there was no activation during practice of the sequences that had been learned before scanning (PRE). They argued that although subjects had to rehearse the sequences in working memory in both conditions, the NEW condition required the subjects to generate (freely select) finger movements to discover the correct sequence. In their PRE condition and our present study, as subjects had mastered the sequences, they no longer had to select movements to try out, but simply executed the sequences that they had learned; hence, the prefrontal cortices were not activated.

Right precuneus

The right precuneus is designated as Brodmann area 7, and area 7 of macaque monkeys is said to be homologous to Brodmann area 7 of humans (Haxby et al., 1991). However, this view remains controversial, and the location of Brodmann area 7 in the superior parietal lobule makes a homology with area 5 in macaque monkeys at least a possibility. There are several lines of evidence that Brodmann area 7 is involved in multimodal integration of external

information and that it provides a sensory representation of extrapersonal space. Brodmann area 7 appears to function in spatial control of arm movement, and its cells are responsive to both visual and somatosensory input. They are mainly activated by stimuli moving in a certain direction (Leinonen et al., 1979; Savaki et al., 1993). Leinonen et al. (1979) suggested that Brodmann area 7 is an integrative system, analyzing the direction of the stimulus in one sensory system by using another sensory system as a reference. PET studies in humans have shown that Brodmann area 7 is related to motor selection with auditory cues as well as with visual cues, based on the integration of spatial information (Deiber et al., 1991; Grafton et al., 1992), and that the dorsal parietal cortex and precuneus respond to an increment of the spatial complexity of the task (Grafton et al., 1992). These findings are compatible with our results, because increased complexity implies an increase in the number of possible choices and, hence, increases the difficulty of selecting the correct finger for each movement within the given sequence.

The concomitant rCBF changes in Brodmann area 7 and the PMC support the previously reported findings of a functional–anatomical connection between them. In nonhuman primates, those areas are strongly interconnected by corticocortical fibers (Pandya and Kuypers, 1969). Areas 5 is also connected with the PMC, although to a different region. In nonhuman primates, the PMC and posterior parietal lobe, especially area 7b, appear to form a system for the coding of near-extrapersonal space for guidance of movement within that space (Graziano et al., 1994). Considering these functional connectivities, the similarity of rCBF changes with increased complexity suggests that Brodmann area 7 may have a role in selecting and monitoring the sequence with on-line reference to a working memory in the right PMC.

Another issue relating to Brodmann area 7 is attention. Jenkins et al. (1994) found activation of Brodmann area 7 bilaterally in auditory cued, complex sequential finger tapping. Activation of that area was also more prominent during learning of the new sequence, which they speculated might be related to spatial attention to the fingers, because subjects had to pay more attention to their fingers during learning than during the well learned phase. In the present study, subjects might have had to pay more attention to their fingers when performing more complex sequences.

Cerebellar vermis

Although the vermis of the cerebellum, together with the flocculonodular lobe, is related to the control of posture and reflex eye movements (Stein, 986), PET activation by nonmotor tasks such as visual vigilance has been reported (Pardo et al., 1991). The vermis is often activated in visual tasks that require visual working memory (Roland, 1993). These findings suggest that linear activation in the cerebellar vermis in the present study might represent a nonexecutive component of the task, such as attention or spatial working memory.

Thalamus

The thalamus is a component of the parallel basal ganglia–thalamocortical circuits (Alexander et al., 1986). The thalamocortical drive to the motor areas is modulated by striatopallidal pathways as a part of the basal ganglia–thalamocortical circuits, functioning perhaps to reinforce the desired movement and suppress unwanted movement (Hallett and Khoshbin, 1980; Mink and Thach, 1993). As sequence length increases, the number of possible choices also increases. Increased activity of the left thalamus might reflect pallidal inputs because of the increased workload for filtering and gating the sequence of the movement.

Left inferior parietal lobule

A linear decrease of rCBF with an increase of complexity was found only in the LPi. The left LPi, which is close to the angular gyrus, is related to phonological storage (Shallice et al., 1994), another "slave" system of working memory (Raichle, 1993). The decrease of rCBF suggests the reallocation of the brain's attentional resources. Cross-modal suppression of neural activity with selective attention has been described. Haxby et al. (1994) reported a decrease of rCBF in the auditory and somatosensory cortices during visual face matching and location matching tasks compared with sensorimotor control tasks. They suggested that selective attention to one sensory modality is associated with a decrease of activity in areas dedicated to processing input from other sensory modalities. Likewise, a reciprocal change of rCBF in the left LPi and right PMC suggests that attending to one slave system (the visuospatial scratch pad) of working memory suppresses another (the phonological loop) that is not in use (Baddeley, 1992).

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