

Both primary motor cortex and supplementary motor area play an important role in complex finger movement

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SUMMARY

In order to clarify the roles played by the primary motor cortex and the supplementary motor area in the execution of complex sequential and simple repetitive finger movements, regional cerebral blood flow (rCBF) was measured with PET using ¹⁵O-labelled water in five normal subjects. The PET data of each individual subject co-registered to his own MRI, was analysed. Compared with the resting condition, the mean rCBF was markedly increased in the contralateral sensorimotor cortex (M1-S1) and moderately increased in the contralateral cingulate gyrus and putamen in both the simple and complex motor tasks. During the complex motor task, in addition to the above, the mean rCBF was markedly increased in the supplementary motor area and the contralateral premotor area, and moderately increased in the ipsilateral M1-S1 and cerebellum. In the supplementary motor area, there was a moderate rCBF increase also during the simple task. However, comparison of the mean rCBF increase against the resting condition between the two tasks revealed a greater increase during the complex task than in the other only in the supplementary motor area and the ipsilateral M1-S1. Thus, in agreement with our previous electrophysiological findings, not only the supplementary motor area but also the M1-S1 seems to play an important role in the execution of complex sequential finger movements.

INTRODUCTION

Different mechanisms underlying the execution of simple and complex motor tasks have drawn the attention of many investigators. An important role of the supplementary motor area in the planning and/or execution of complex finger movements was first reported in around 1980 by using the ¹³³Xe method and a planar gamma-camera for measurement of cortical surface regional cerebral blood flow (rCBF) (Orgogozo and Larsen, 1979; Roland *et al.*, 1980*a,b*). Recent investigations using PET with the ¹⁵O-labelled water tissue activity technique (Deiber *et al.*, 1991; Grafton *et al.*, 1992) and the recording of cortical DC potential shifts (Lang *et al.*, 1990, 1992) have also shown the significant

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role of the supplementary motor area in the execution of complex finger movements. Other rCBF studies, however, have not disclosed any difference between the execution of simple and complex hand movements (Fox *et al.*, 1985a; Colebatch *et al.*, 1991). These discrepancies probably result from the type of tasks employed for the complex movements as well as from the techniques used in the quantitative analysis of rCBF.

Investigations of rCBF within the primary motor and sensory cortex (M1-S1) have not shown any change dependent on the movement complexity (Orgogozo and Larsen, 1979; Roland *et al.*, 1980a; Mazziotta and Phelps, 1984; Colebatch *et al.*, 1991; Grafton *et al.*, 1992). However, our recent comparison of the scalp-recorded electrical potentials preceding complex and simple finger movements demonstrated an increased amplitude of the negative slow activity preceding the complex movement as compared with the simple one at both the midline vertex and the precentral areas bilaterally, which, based on the results of subdural recording in humans (Neshige *et al.*, 1988; Ikeda *et al.*, 1992), corresponds to the supplementary motor area and the M1-S1, respectively (Kitamura *et al.*, 1993). In order to resolve the discrepancies between the results of the electrophysiological and rCBF studies, an investigation of rCBF changes associated with complex versus simple finger movements was carried out, using a new analysis method for quantifying the relative rCBF changes in specific regions on the PET data superimposed on the MRI of each individual subject.

METHODS

Subjects

Five healthy male volunteers (age 21–26 years) participated in the present study. All were right-handed, and none of them had a prior history of neurological or psychiatric disorders. All gave informed written consent after the study had been fully explained to them. The study was approved by the Ethics Committee of Kyoto University School of Medicine. No medication was given before the PET study.

Magnetic resonance imaging of the head

Before the PET study, MRI data of head were obtained in each subject using a 1.5-T Signa Imager (GE Medical Systems, Milwaukee, USA) with a head coil, so that the MRIs were available at the time of PET study. T₁-weighted sagittal images were obtained by using the following parameters; 400 ms repetition time and 20 ms echo time, two excitations, 240 mm field of view, 256×256 imaging matrix, and 3 mm slice thickness without gap. T₁-weighted axial and coronal images were then obtained with 3 mm slice thickness with a 1.5 mm slice gap and the remaining parameters as given above. The axial and coronal planes were collected parallel and perpendicular to the anterior commissure (AC)–posterior commissure (PC) line, respectively, which was determined from the sagittal sequence. None of the MRIs showed any structural abnormalities.

Movement task

The subject was laid supine on the PET scanner bed in a quiet, dimly lit room with eyes gently closed. Eyes were not covered in order to avoid any uncomfortable sensation caused by a mask around the eyes. Earplugs were used which increased the hearing threshold to a certain degree, but the subject was still able to hear the verbal instructions given loudly by the experimenter. The head was fixed in an individually molded helmet-shaped head-holder. The left brachial artery and the right cubital vein were cannulated.

The movement paradigms used by Roland *et al.* (1980a) in their original experiment were modified and employed as the simple and complex tasks. For the simple motor task, the right thumb was repeatedly touched against the tips of all other fingers of the right hand at a self-paced repetition rate of ~2 Hz. For the complex task, the right thumb was touched against each of the other fingers a different number of times, also at a self-paced rate of ~2 Hz; namely twice against the index finger, once against the middle finger, three times

against the ring finger and twice against the little finger, then repeating in a reversed order. This sequence was repeated back and forth for 2 min. Since the subject inevitably counted the number of movements for each finger for executing the complex sequential movement, he was also instructed to count silently in blocks of 10 during the simple motor task so that the effect of counting could be counterbalanced between the two motor tasks. However, special caution was given to each subject not to move the tongue or mouth for counting, and actually no movements of the lips, jaw and neck were detected in any of the subjects. In order to study purely self-paced voluntary movements, no cue signals were given for making the pace. Instead, the subject's task performance was closely observed by at least two experimenters, and if the repetition rate of movements was judged inappropriate, that session was excluded from the later analysis and repeated. The magnitude and speed of muscle contractions were not monitored by electromyogram because the firm attachment of the surface electrodes onto the skin caused a very uncomfortable sensation in that arm which was especially noticed when moving the hand. Instead the actual movements were inspected visually by the experimenter, and when those were found inappropriate, they were corrected by verbal instructions.

Before the experiment, each subject had short training sessions for each of the complex and simple movements until he could carry out both tasks correctly at the same pace and speed of muscle contraction. Six sessions in total were given to each subject. The first session was always done in the resting condition with the eyes gently closed and with no finger movement, and was followed by the simple task and then the complex task. The same sequence was then repeated in three subjects, and in the remaining two subjects, the first sequence was followed by the simple task and the complex task, and then finally the resting condition. Each session continued for 2 min starting 30 s before the intravenous injection of the ^{15}O -labelled water (*see below*), with an intermission of ~ 15 min between each sessions.

Measurement of rCBF

For both the simple and complex motor tasks, ~ 30 mCi of ^{15}O -labelled water was injected into the right cubital vein 30 s after the beginning of each movement session. Then the head was scanned for the radioactivity with a multi-slice PET scanner (PCT 3600W, Hitachi Medical Co., Tokyo) for 90 s after the injection. The scanner acquired 15 slices with a centre-to-centre distance of 7 mm and the axial resolution of 6.5 mm full width at half maximum at centre (Mukai *et al.*, 1989; Endo *et al.*, 1991). The in-plane spatial resolution with stationary mode acquisition used in this protocol was 6.7 mm full width at half maximum, which was blurred to ~ 9 mm in the reconstructed PET images. The field of view and pixel size was 256 mm and 2 mm, respectively. Prior to the emission measurements, transmission data were obtained using $^{68}\text{Ge}/^{68}\text{Ga}$ standard plate source for attenuation correction. The tissue activity concentration in the PET images was cross calibrated against the scintillation counter using a cylindrical phantom filled with ^{18}F solution.

In each session for all the subjects, 2 ml of arterial blood was sampled from the left brachial artery every 5 s for the first minute and then every 10 s for the remaining portion of the scan. The blood samples thus obtained were immediately processed for measurement of the whole blood radiotracer concentration by a scintillation counter, and the data served as the basis for calculating the absolute rCBF value with the autoradiographic method on a pixel-by-pixel basis (Raichle *et al.*, 1983). For the control session in the resting condition, exactly the same method was applied except for movement task.

Analysis of data

Cerebral blood flow images of each subject were first globally normalized to a laboratory standard of 50 ml/min/100 g whole brain mean blood flow to correct fluctuations of the global CBF among successive scans (Fox and Raichle, 1984). The original 15 slice data set (7 mm interplane distance) was interpolated to an isotropic volume through a linear interpolation, giving a 50 slice data set with $2 \times 2 \times 2$ mm voxel size. Using the midsagittal and two parasagittal (+10 mm, +20 mm) slices of MRI data set which had been previously rotated into the Talairach proportional stereotactic system (Talairach and Tournoux, 1988), contours of the corpus callosum, brainstem, cerebellum, thalamus and medially visible cortical boundaries such as the orbitofrontal and ventral occipital surface were identified. These outlines were transferred to the similarly cut parasagittal slices of the resting PET data which had been rescaled to the same pixel size as the MRI data set ($0.9 \times 0.9 \times 0.9$ mm). The PET volume data were then rotated and translated to fit the outlines. The necessary rotation was then applied to all scans within the same subject. This method of the co-registration of MRI and PET data consists of a combined set of the direct PET based landmark method introduced by Friston *et al.* (1989) and the MRI/PET landmark matching method employed by Evans *et al.* (1992). The former method (Friston *et al.*, 1989) used four landmarks for identifying the AC-PC line employed with

the Talairach coordinate space localization method (Talairach and Tournoux, 1988), and the latter method (Evans *et al.*, 1992) used landmarks which were mutually identifiable on both the MRI and PET mid-sagittal aspects.

In order to determine the region of interest for further analysis, the data were averaged across subjects (intersubject averaging). After identification of AC and PC based on MRI for each subject, all data were linearly scaled to adjust the inter-commissural distance of each individual subject to that of Talairach (25 mm), and the scaling factor was applied in all directions. All subject data within each specific condition (e.g. 'resting') were then averaged on a pixel-by-pixel basis using the co-registered AC as the standard (Friston *et al.*, 1989).

The PET data of two identical sessions within each subject were averaged, and the result was superimposed on each co-registered level of the head MRI of each individual subject. For both the inter-subject average and the individual subject data, the data of the resting condition was subtracted from that of the simple and the complex motor task, respectively, and then the subtracted PET images (complex versus resting and simple versus resting) of each individual subject were visually inspected at all available slice levels in the axial and coronal planes. Then the template of the region of interest was determined for each subject by four authors (N.S., H.L., Y.Y. and M.H.) on the axial image of the MRI, by taking into account the areas of increased rCBF on the subtracted images of the inter-subject averaged PET data. Those regions of interest included the hand area of the precentral and postcentral gyrus, mesial frontal cortex corresponding to the supplementary motor area, premotor area, prefrontal cortex, anterior cingulate gyrus, thalamus, putamen and cerebellar hemispheres, all bilaterally. The same regions of interest, of size ranging from 1.1 to 3.3 cm², were used for different conditions within each subject. Then the mean relative rCBF value among all the pixels within each region of interest was measured for each condition (resting, simple and complex motor task) for each individual subject, and a group comparison of the mean rCBF values thus obtained within each region of interest among the three different conditions was done by analysis of variance (ANOVA). In addition, the mean relative rCBF increase in the complex task (complex versus resting) was compared with that in the simple task (simple versus resting) within each region of interest also using ANOVA. Statistical significance was evaluated by Scheffe's *F*-test.

RESULTS

Observation of rCBF changes in simple and complex movements in each subject

On visual inspection of the subtracted PET images (complex task versus resting, simple task versus resting) at different slice levels in both axial and coronal planes for each individual subject, increased rCBF was seen at a larger number of slice levels in the contralateral (left) M1-S1 in the complex task than in the simple one in four of the five subjects (Figs 1, 2). In a remaining subject, the area showing an increased rCBF within the contralateral M1-S1 appeared almost the same in both tasks. As for the ipsilateral (right) M1-S1, the rCBF increase was recognized to a greater extent in the complex task than in the simple one in two subjects (Figs 1, 2). In the supplementary motor area, the rCBF increase was greater and more widespread in the complex task than in the simple one in all five subjects (Figs 1, 2). There was no special tendency for more anterior spread in the complex task relative to the simple one. In the contralateral premotor area, the rCBF increase was more clearly recognized in the complex task than in the simple one in two subjects (Fig. 1). In the contralateral putamen, the rCBF increase was seen more clearly in the complex task than in the simple one in four subjects (Fig. 2). In a remaining subject, there was no recognizable rCBF increase in putamen during either task. In the cerebellar hemispheres, at the slice level which was included in four subjects, the rCBF was more clearly increased on the right in the complex task than in the simple one in two subjects, and there was no difference in the remaining two subjects.

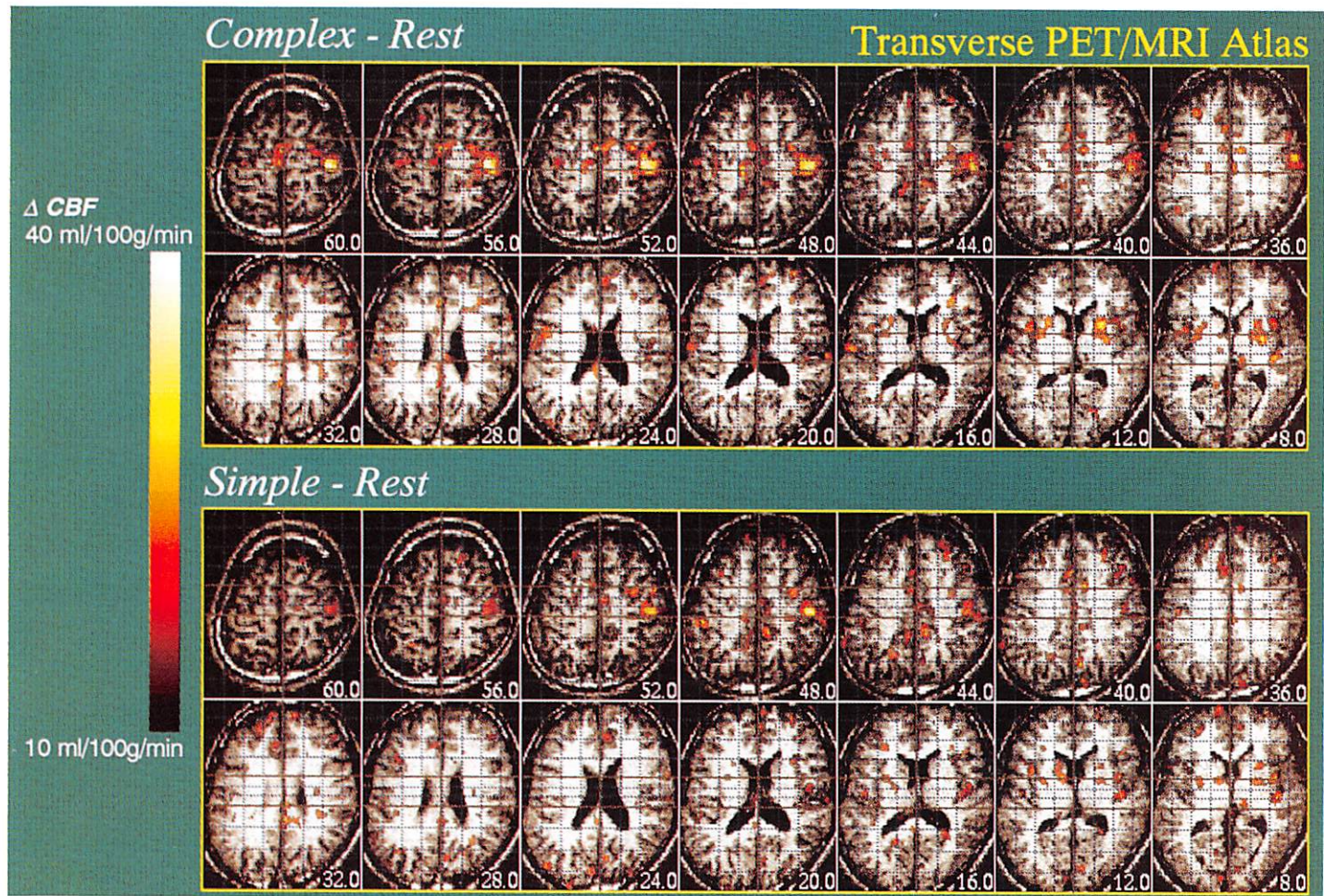


FIG. 1. Subtracted PET images of a subject (Y.T.) superimposed on his own MRI at various axial slice levels during complex sequential movement (Complex-Rest) and during simple repetitive movement (Simple-Rest) of the right fingers. The right side of the brain is shown on the left side of the image. The number at each slice level is the distance (millimetres) from the AC-PC line. Note increased rCBF at a larger number of slice levels of the left precentral and postcentral gyrus, and basal ganglia and the supplementary motor area in the complex motor task than in the simple task.

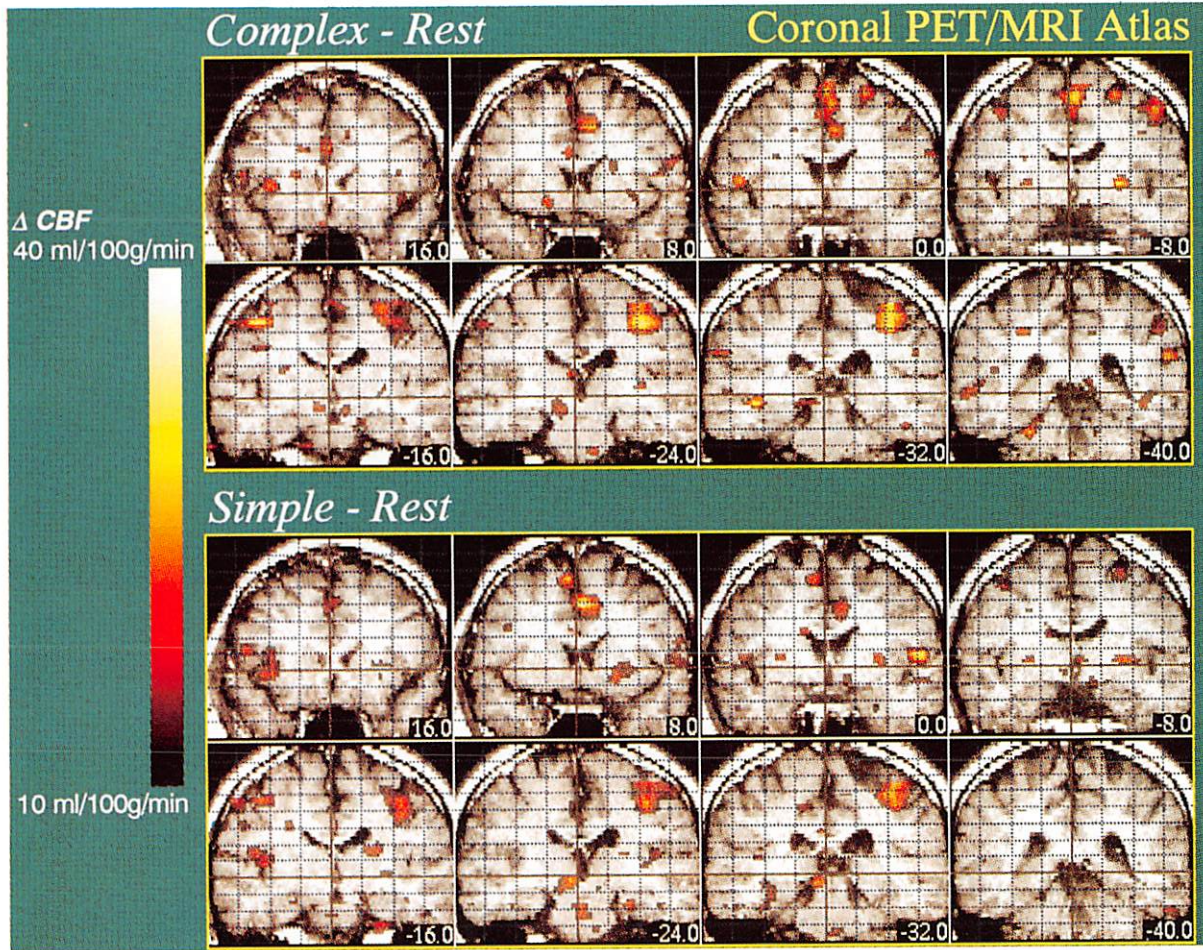


FIG. 2. Subtracted PET images of a subject (H.K.) superimposed on his own MRI at various coronal slice levels during complex sequential movement (Complex-Rest) and during simple repetitive movement (Simple-Rest) of the right fingers. The right side of the brain is shown on the left side of the image. The number at each slice level is the distance (millimetres) from the AC (+ = forward, - = backward). Note increased rCBF more extensively in the left precentral gyrus, supplementary motor area and putamen, and in the right precentral gyrus during the complex motor task than during the simple task.

Comparison of the mean rCBF values among three different conditions (Table 1)

In the hand area of the contralateral (left) precentral and postcentral gyrus, the mean rCBF was significantly larger during both the simple and complex movements than in the resting condition ($P < 0.001$). In the hand area of the ipsilateral (right) precentral and postcentral gyrus, the mean rCBF in the complex motor task was moderately larger compared with the resting condition ($P < 0.05$). In the bilateral supplementary motor areas and the contralateral premotor area, the mean rCBF was significantly larger only during the complex motor task ($P < 0.01$). In the ipsilateral supplementary motor area, the mean rCBF was moderately larger also during the simple task compared with the resting condition ($P < 0.05$). In addition, in the contralateral anterior cingulate gyrus and putamen, the mean rCBF was moderately larger in both the simple and complex tasks than in the resting condition ($P < 0.05$). The mean rCBF during the complex movement was also moderately increased in the ipsilateral cerebellar hemisphere ($P < 0.05$). In the prefrontal cortex and the thalamus, no significant difference in the mean rCBF values was observed among the different conditions. No significant reduction in rCBF was found in any of the regions of interest evaluated.

When the mean rCBF was compared between the complex and simple tasks, the only region of interest where the mean rCBF values were significantly different was the contralateral supplementary motor area (77.4 ± 4.8 ml/min/100 g for the complex task and 66.9 ± 8.8 ml/min/100 g for the simple task) ($P < 0.05$).

Comparison of the mean rCBF increase between simple and complex movements

When the mean rCBF increase (against the resting condition) in the complex motor task was compared with the corresponding rCBF increase in the simple task, the former was significantly greater in the contralateral supplementary motor area ($P < 0.01$) and moderately greater in the hand area of the ipsilateral precentral and postcentral gyrus ($P < 0.05$) than the latter (Fig. 3). In addition, although the mean rCBF increase appeared

TABLE 1

Region of interest	Contralateral			Ipsilateral		
	Resting	Simple	Complex	Resting	Simple	Complex
Precentral	58.0 ± 4.7	71.0 ± 7.4***	74.3 ± 6.0***	60.6 ± 4.0	63.4 ± 7.3	66.9 ± 7.2*
Postcentral	57.2 ± 4.8	68.7 ± 1.9***	70.8 ± 2.0***	58.6 ± 4.0	59.6 ± 4.2	62.4 ± 3.6*
Supplementary motor	60.2 ± 3.8	66.9 ± 8.8	77.4 ± 4.8***†	62.8 ± 2.9	69.9 ± 5.5*	71.9 ± 2.1**
Premotor	60.2 ± 4.5	65.5 ± 5.5	70.7 ± 7.7**	61.1 ± 8.3	60.9 ± 9.3	63.7 ± 12.6
Prefrontal	61.1 ± 4.5	59.6 ± 4.6	61.8 ± 8.4	56.9 ± 4.1	61.3 ± 5.0	58.5 ± 6.1
Anterior cingulate	65.9 ± 3.7	74.8 ± 4.7*	75.0 ± 1.0*	71.5 ± 8.8	72.9 ± 8.5	72.3 ± 9.3
Thalamus	60.6 ± 5.1	61.4 ± 5.3	63.7 ± 3.6	65.5 ± 5.0	62.4 ± 4.9	62.2 ± 2.4
Putamen	63.7 ± 5.2	68.7 ± 5.4*	69.2 ± 4.4*	65.4 ± 2.1	66.5 ± 4.8	67.5 ± 3.3
Cerebellum	51.7 ± 11.8	53.9 ± 12.0	57.4 ± 13.4	52.4 ± 12.4	56.6 ± 9.9	61.6 ± 16.3*

Regional cerebral blood flow values in the contralateral and ipsilateral region of interest in the resting condition and in the simple and complex movement tasks of the right fingers (ml/min/100 g) (mean ± SD, $n = 5$ for all regions of interest except for the cerebellum whose $n = 4$). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (each against the resting condition); † $P < 0.05$ (against the simple task).

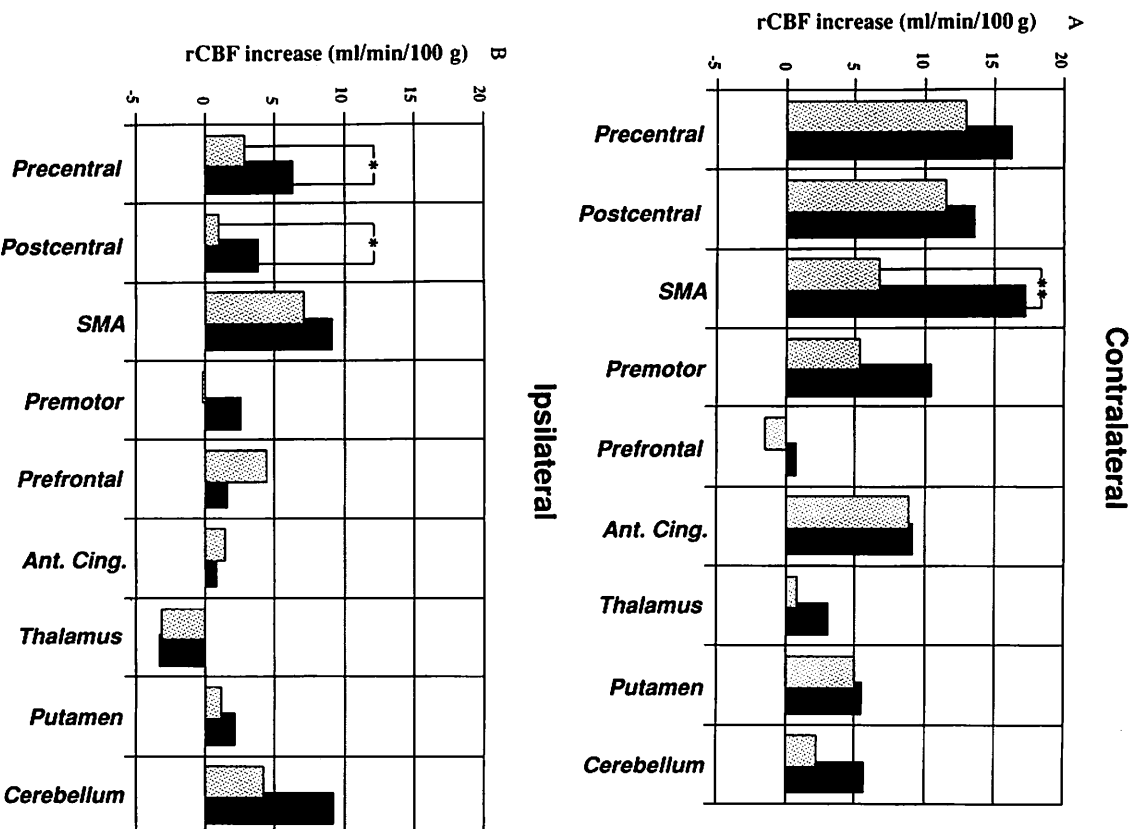


Fig. 3. Comparison of the mean rCBF increases (differences from the resting condition) in each region of interest contralateral (A) and ipsilateral (B) to the movement between the simple repetitive and complex sequential movements of the right fingers. The rCBF is increased more in the complex motor task than in the simple task in the contralateral (A) supplementary motor area (SMA) (** $P < 0.01$) and in the ipsilateral (B) precentral and postcentral gyrus (* $P < 0.05$).

to be greater in the complex task than in the simple task in the contralateral precentral and postcentral gyrus, the ipsilateral supplementary motor area, the bilateral premotor areas and the bilateral cerebellar hemispheres, the differences did not reach statistical significance.

DISCUSSION

In most of the previous studies on rCBF in relation to human voluntary movements (Roland *et al.*, 1980a, 1982; Fox *et al.*, 1985a,b; Chollet *et al.*, 1991; Colebatch *et al.*, 1991; Deiber *et al.*, 1991; Friston *et al.*, 1992; Playford *et al.*, 1992), localization of the activated brain areas was estimated from rCBF images which had been translated into the standardized plane of Talairach (Talairach and Tournoux, 1988). Moreover, some of the rCBF analysis was actually done on the group averaged data across all the subjects studied (Chollet *et al.*, 1991). However, it is reasonable to assume that, especially when higher brain functions are involved, the strategies adopted by each individual subject for dealing with the task may differ among subjects even if they are requested to carry out the same task. Thus the data obtained by the inter-subject averaging may not necessarily be ideal, and might even obscure the characteristics of each individual subject. In this regard, the present technique enabled us to analyse the rCBF data of each individual subject which was co-registered to the same slice level of his own MRI, thus providing a satisfactorily high spatial resolution. Although the number of subjects was relatively small in the present study, findings of individual data often supported the results obtained by statistical analysis across the subjects.

Studies of rCBF using a gamma camera (Orgogozo and Larsen, 1979; Roland *et al.*, 1980a) and PET (Deiber *et al.*, 1991; Grafton *et al.*, 1992) suggested an especially important role of the supplementary motor area in the planning and/or execution of complex voluntary movements in the human. Deiber *et al.* (1991) found an increased rCBF in the supplementary motor area when the subject had to select directions of a joystick movement but not when he moved it to a fixed direction. Grafton *et al.* (1992) reported that the temporal complexity of voluntary movements increased rCBF in the supplementary motor area, while spatial complexity did so in the medial and dorsal parietal cortex. However, other studies using PET did not find any difference in rCBF between simple and complex movements (Fox *et al.*, 1985a; Colebatch *et al.*, 1991). Thus the question as to whether the supplementary motor area is actually superior to or in parallel with the primary motor cortex in the planning and execution of voluntary movements has remained still controversial. The present findings add further evidence to support the importance of the supplementary motor area in complex sequential movement. Those discrepancies in the results of rCBF studies related to voluntary movements among different laboratories are most likely due to the different motor paradigms employed for complex movements and to the different methods of quantitative rCBF analysis.

The important role played by the primary motor cortex in the planning and/or execution of complex sequential movement has drawn little attention in the past. With special reference to the different degrees of the rCBF increase in M1-S1 between the complex and simple tasks observed in the present study, they cannot simply be explained by a different number of muscles involved in the two kinds of movement tasks, because in the present paradigm the same fingers participated in both movements. In fact, the overall number of muscles actually involved was even greater during the simple repetitive movement than during the complex sequential movement, because all fingers simultaneously participated in each of the repetitive movements during the simple task, whereas during the complex task only the thumb and one of the other fingers participated in each movement.

Furthermore, the present rCBF study demonstrated bilateral participation of M1-S1

in the complex sequential unilateral finger movement. This finding is in agreement with the recent report in which functional high speed MRI was used (Kim *et al.*, 1993), and suggests an important role of bilateral M1-S1, in addition to the supplementary motor area, in the preparation and/or execution of complex sequential movements.

The idea for the present rCBF study was based on our previous electrophysiological observation. Namely, the slow negative potential shift starting ~400 ms before the movement onset [Negative Slope; NS' (Shibasaki *et al.*, 1980)] was found to be larger over the midline vertex as well as at the bilateral precentral areas in the sequential compared with the simultaneous movement (Kitamura *et al.*, 1993). Based on the results of subdural recording (Neshige *et al.*, 1988; Ikeda *et al.*, 1992), we interpreted the above finding as indicating that not only the supplementary motor area but also the M1-S1 might play an active role in the preparation of the complex sequential movement. In the present PET study, the above hypothesis was partly supported by demonstrating the greater rCBF increase in the hand area of the ipsilateral M1-S1 in the complex movement compared with the simple movement. The same tendency was also observed in the contralateral M1-S1 upon visual inspection of each individual set of data, but the difference did not reach statistical significance in a group comparison. This may be due to a strong and selective activation of the contralateral M1-S1 by the steps directly related to the movement as well as the movement feedback itself to an equal degree in both simple and complex tasks (regardless of the complexity of the movement), thus masking the much smaller difference which might exist in relation to the motor complexity. In contrast to this, since the ipsilateral M1-S1 is not involved in the steps directly related to the movement, even a small difference could be demonstrated to be statistically significant. This is obviously due, at least in part, to the lack of temporal resolution in PET.

Cortical electric potentials associated with voluntary movements are recorded by back averaging the electroencephalograms time-locked to the onset of each of the movements which are repeated at a self-paced rate of once every 3 s or even longer (Shibasaki *et al.*, 1980; Neshige *et al.*, 1988; Ikeda *et al.*, 1992; Kitamura *et al.*, 1993). Therefore, this technique can provide us with the information about the time sequence of cortical activation with respect to the movement, but accurate localization of the activated cortical areas is difficult because of the attenuation, distortion and spread of cortical potential over the scalp due to the inhomogeneous electrical conductivity of various tissues surrounding the cortical surface (Nunez, 1981). On the other hand, the rCBF study with PET provides us with the spatial information with relatively high resolution, but it is lacking in information regarding the time sequence. In the present study, the movement paradigms employed a much faster repetition rate compared with the previous electrophysiological studies, in order to activate the relevant cortical regions sufficiently to increase the rCBF. Thus simultaneous studies of rCBF and electrical potentials in the same experimental paradigm will be useful for the correlative interpretation of the findings.

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