Supplementary Motor Area and Other Cortical Areas in Organization of Voluntary Movements in Man

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SUMMARY AND CONCLUSIONS

1. Previous studies in man have revealed a coupling between the regional cerebral blood flow (rCBF) and the regional cerebral metabolic rate for oxygen. In normal man, increases in the regional cerebral metabolic rate for oxygen leads to proportional increases in the rCBF (34). We have measured the rCBF as an expression of the level of cortical activity simultaneously from 254 cortical regions in 28 patients with no major neurological defects, during rest and during planning and execution of a few types of learned voluntary movements with the hand.

2. We found that the rCBF increases exclusively in the supplementary motor area while subjects were programming a sequence of fast isolated movements of individual fingers, without actually executing it.

3. During execution of the same motor sequence, there were equivalent increases of the rCBF in both supplementary motor areas, but only in the contralateral primary motor area. In addition, there were more modest rCBF increases in the contralateral sensory hand area, the convexity part of the premotor area, and bilaterally in the inferior frontal region.

4. Repetitive fast flexions of the same finger or a sustained isometric muscular contraction raise the blood flow in the contralateral primary motor and sensory hand area.

5. A pure somatosensory discrimination of the shapes of objects, without any concomitant voluntary movements, also leaves the supplementary motor areas silent.

6. We conclude that the primary motor area and the part of the motor system it projects to by itself can control ongoing simple ballistic movements with the self-same body part. A sequence of different isolated finger movements requires programming in the supplementary motor areas. We suggest that the supplementary motor areas are programming areas for motor subroutines and that these areas form a queue of time-ordered motor commands before voluntary movements are executed by way of the primary motor area.

INTRODUCTION

Roy and Sherrington’s (39) old hypothesis about a coupling between neuronal activity, cerebral oxygen consumption, and cerebral blood flow has, during the last decade, been confirmed both in animal experiments and by observations in man (7, 8, 11, 22, 34, 35, 40). In man, Olesen (25) showed that regional cerebral blood flow (rCBF) increases by about 50% in the motor cortex during vigorous repetitive movements with the contralateral hand. That this local increase of the blood flow was the result of an enhanced oxidative metabolism in the motor cortex was subsequently verified by Raichle et al. (34), who demonstrated that the increase in the cortical oxygen consumption in the human motor cortex during vigorous hand exercise was proportional to the increase in the rCBF.

Therefore, if one is ready to accept the hypothesis that any change in local cerebral oxidative metabolism is due to concomitant changes in neuronal and glial activity (transmembrane ion pumping, synaptic transmis-
sion, synthetic processes), then the regional cerebral blood flow (rCBF) is a reliable measure of integral neuroglial activity. We have used simultaneous rCBF measurements from 254 cortical regions in the human brain to evaluate the role of different cortical areas in the programming and control of a few types of voluntary hand movements with proprioceptive and cutaneous feedback. In two preliminary studies (21, 37) we noticed the activation of the supplementary motor area during voluntary finger movements and speech. This article presents a more systematic analysis of the role of the supplementary motor area and the primary motor area in the elaboration of voluntary movements.

METHODS

Subjects

This study included 28 subjects, aged from 15 to 65 yr, who had no major neurological deficits but on whom carotid arteriography was carried out to exclude an intracranial disease process. After informed consent had been given, arteriography was followed by measurement of rCBF at rest. When no abnormalities were found by carotid angiography, the rCBF at rest, and in most cases a computer-assisted axial tomography (CT) scan, the patient was accepted in the study. When an epileptic was included it was a prerequisite that the electroencephalogram made during the rCBF study showed no paroxysmal changes. Three subjects were left handed, the rest right handed according to the Edinburgh inventory (24).

Measurement of rCBF

The description of the equipment, its spatial resolving power, and details of the method of rCBF measurements have been published elsewhere (36, 41). Under local anesthesia with lignocaine, the common carotid artery was punctured with a needle. After arteriography a soft guide wire was introduced, through the needle, into the internal carotid artery. The needle was withdrawn, and a polyethylene catheter coated with heparin was introduced on the guide wire into the internal carotid artery. The catheter and the inlet stopcock were regularly perfused with a solution of 5,000 IU heparin in 1,000 ml 0.9 M NaCl.

\[^{133}\text{Xe}, 5 \text{ mCi}, \text{dissolved in } 3 \text{ ml } 0.9 \text{ M NaCl was injected in the internal carotid artery in } 1 \text{ s.}
\]

The clearance of the isotope from 254 regions of the cerebral hemisphere was then measured by a 254-channel dynamic \( \gamma \)-camera and the data processed on-line in a digital computer (Fig. 1). The computer was programmed to give a least-squares fit of the logarithmically transformed clearance curves. If \( C_t \) is the concentration of the isotope in the brain at time \( t \): \( C_0 \), the concentration of isotope in the brain at time zero (or the initial maximal counts per second); \( f \), the flow in milliliters per gram tissue per minute; \( \lambda \), the cortex-blood partition coefficient for an inert gas (ml/g); and \( t \), time (min)—then:

\[
C_t = C_0 \exp(-\lambda f t)
\]

or

\[
f = -\lambda \ln(C_t)/dt \text{ ml g}^{-1} \cdot \text{min}^{-1}
\]

provided that the clearance curve is monoexponential. For 100 g cortex we have

\[
rCBF = \lambda |\alpha| \cdot 100 \text{ ml per } 100 \text{ g per minute, in which } \alpha \text{ is the slope of the logarithmically transformed initial part of the clearance curve. This method of computation is the initial-slope method (26). All flow values reported in this communication are evaluated by the initial-slope method. In practice only the first part of the clearance curve from 15 to 60 s after the start of injection is monoexponential, so the determination of rCBF in this study only is based on this part of the curve. This implies that the rCBF value computed by equation 7 is an expression of the regional flow of the tissue compartment with the highest flow: the gray matter, and in particular, the cerebral cortex (13, 18). The computer program corrected automatically for background activity including possible residual isotope activity in the tissues.}

Immediately after the measurement the rCBF values from the 254 cortical regions were displayed in the TV screen in color codes together with the logarithmically transformed clearance curves (cf. Fig. 2).

Measurement of rCBF at rest

First a reference determination of rCBF was made with the subject at rest. The ears were plugged and the eyes were closed with cotton-wool pads that reduced eye movements. The subject was awake and relaxed. He was told not to move or tense the muscles and to “think of nothing,” in other words to behave as if he were going to sleep. Within the first minute after the injection of the isotope a blood sample was taken from the internal carotid artery for determination of arterial \( \text{P}CO_2 \). The \( \text{P}CO_2 \) of the rCBF determination during rest is a reference value and differences in blood flow in subsequent rCBF determination due to changes in arterial \( \text{P}CO_2 \) are corrected by 4%/mm Hg (26). The intra-arterial blood pressure and the pulse were recorded with an electromanometer. In about one-third of the
FIG. 1. Block diagram of the equipment and the principles of the method. The head is fixed to the collimator by a vacuum pillow. The 254 collimator tubes are arranged radially in a 50-mm-thick spherical lead segment. The spatial resolving power of the camera when used for rCBF measurements is one channel (36, 41). The center-to-center distance of two adjacent collimator tubes is 10 mm. Signals from the 254 cortical regions are processed on-line, the isotope clearance curves, the rCBF values, and background radioactivity can be recorded in the three different formats for further processing or displayed on the TV screen.

subjects we recorded the electromyogram with bipolar leads and two surface electrodes placed on the flexor digitorum superficialis. In all cases two researchers looked for movements of body parts during the rCBF determination. If EMG activity or movements occurred during the rCBF measurement, the subject was either excluded or a new determination was made with the patient at rest.

Twenty minutes after the injection practically all isotopes had disappeared from the brain, and then a new determination of rCBF was made. 

Tests of voluntary movements and programming of voluntary movements

The only difference between the rest and the test conditions was unilateral voluntary contractions of the muscles that move the fingers. Prior to these experimental rCBF determinations, the subjects were instructed and trained in the tests
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until they could perform within the set time limit. The test started 10 s before the injection and continued until 60 s after the start of injection. Thus the test consisted of learned, voluntary movements with cutaneous and proprioceptive feedback, but with no visual or auditory feedback.

LOW-FORCE FAST ISOLATED FINGER MOVEMENTS IN A SEQUENCE: MOTOR-SEQUENCE TEST. The subjects were trained first with eyes open and then with eyes closed to perform a quick sequence of opposing movements with the thumb and the ulnar fingers one by one (Fig. 3). The thumb must in quick succession briefly touch the index finger 2 times, the middle finger once, the ring finger 3 times, and the little finger 2 times, then with the thumb in this position the order of movement is reversed, as seen in Fig. 3. The criterion was that one run should be accomplished within 10 s. The subject should continue the test until the rCBF measurement was finished. The number of flexion-extensions during the 45 s the rCBF was measured was thus at least 32 \times 4.5 = 144 (one run is 32 flexion-extensions).

INTERNAL PROGRAMMING OF BALLISTIC MOVEMENTS IN A SEQUENCE. The motor-sequence test was now repeated but with the important distinction that the subject was not allowed to execute the movements. The subjects should simulate the motor sequence internally at the same speed as before and, as soon as they were asked, start to execute the test from the point they had reached in their internal performance. An electromyogram was recorded in five of the seven subjects during this test procedure to make sure that no muscular activity occurred (see also Fig. 6). This internal programming of movements is inevitably self-paced, but the subject was instructed to perform the test as quickly as possible—and without internal counting of the number of movements. Before each investigation we made sure that they could still perform the motor-sequence test within the time limit (10 s) as soon as they were asked to do so, but during the rCBF measurement this control procedure was delayed until the isotope-counting period was finished.

FORCEFUL REPETITIVE FINGER FLEXIONS. In this test the subject must flex the index finger against a spring-loaded movable cylinder (Fig. 4). The subjects hold the cylinder between the thumb and index finger with the three ulnar fingers flexed and compress the object the maximum possible (27.5 mm) with a brisk flexion. The subjects are trained to do one flexion per second. The actual test starts 10 s before the injection and continues until the rCBF measurement is finished. During the 45 s the rCBF is measured simultaneously with the test, the subjects thus have time to do 45 flexions.

The stiffness of the spring is 5.88 N/cm, thus the amount of work exerted during the rCBF measurement is about 7.5 J.

SUSTAINED ISOMETRIC CONTRACTION. The spring-loaded cylinder from the previous experiment is held fully compressed between the thumb and index finger on one hand from 10 s before the injection until the rCBF measurement is finished. The three ulnar fingers are flexed as before.

Data processing

The rCBF values from the 254 different brain regions from each experiment were stored as a matrix. The rCBF matrix from each test was thereafter compared to the rCBF matrix obtained during rest, with special reference to changes in the rCBF pattern and changes in the absolute rCBF values.

We define the rCBF-pattern as the matrix obtained by dividing each flow value by the mean blood flow of the hemisphere, i.e., as: \( \{ \Phi \} \); in which

\[
\Phi_i = \frac{rCBF_i}{FM} \quad (4)
\]

\( rCBF_i \) is the flow value of the cortical area monitored by channel \( i \); \( FM \) is the mean flow of the hemisphere:

\[
FM = \frac{1}{CH} \sum_{i=1}^{CH} rCBF_i \quad (5)
\]

\( CH \) is the number of channels in the matrix. Sometimes this is less than 254 (cf. Tables 2–7); namely, when some channels look outside the brain. These channels are therefore eliminated from the matrix.

Repeated measurements of the rCBF during rest have revealed that the rCBF pattern is relatively constant while the mean flow of the hemisphere is often not (20, 22). On the basis of the 95% confidence limits of the variations in the rCBF pattern and the absolute rCBF values from previous normative studies (14, 20, 36), we define a focal change in the rCBF pattern from rest to test as a change of more than 9% in one channel. An increase in an individual of more than 12% of the absolute rCBF values in a region monitored by one detector is a focal increase. Every subject was thus examined for focal changes in the rCBF pattern and for focal increases in the matrix of absolute rCBF values. Thereafter, the statistical reproducibility of the focal changes were evaluated in the whole group of patients by the method of paired comparisons.

The mean percent increase (\( \Delta F_{i,j} \)) in a given area is:

\[
\Delta F_{i,j} = \frac{100}{NC} \sum_{i=1}^{N} \sum_{j=1}^{C} \left( \frac{rCBF_{i,j,\text{rest}}}{rCBF_{i,j,\text{test}}} - 1 \right) - 100 \quad (6)
\]
FIG. 2. Upper left: the motor-sequence test. Two examples of focal increases of the blood flow in the hemisphere during the execution of contralateral low-force ballistic finger movements in sequences. The scale at right shows the increases of rCBF in percent + 100. In this section and the other sections the region lying in the penumbra of two adjacent channels is shown with a value of flow increase obtained by linear interpolation. The posterior part of the occipital lobe and the lower part of the temporal lobe is not supplied by the internal carotid artery and, therefore, not visible by carotid artery isotope injection. The projection of the cortical surface in these sections will, due to the converging collimator system, approach the true convex surface of the brain. The standard head position used will give a relative overrepresentation of the frontal lobe. Top: case 7, original data, right hemisphere monitored. Note the focal increases of rCBF in the supplementary motor area, the sensory and motor hand area, and inferior frontal region. In addition, this subject has a diffuse increase of the blood flow of 13%. Lower: case 19, original data, left hemisphere monitored, no diffuse increase of rCBF. Lower left: vertex view of the rCBF increases during execution of the motor-sequence test with the ipsilateral hand (top) and the contralateral hand (lower). Case 10, original data, right hemisphere monitored. Note that both supplementary motor areas are activated, whereas only the contralateral sensory and motor hand area is activated. No diffuse increase of rCBF in this subject. The apparent decrease of rCBF in the occipital region is an artifact due to the low isotope supply to this region. Upper right: increase of rCBF, in percent + 100, in the contralateral hemisphere during internal programming of the motor-sequence test. The concrete internal plan for motor action is the sequence depicted in Fig. 3. Top: case 25, original data, left hemisphere monitored. This subject had a diffuse increase of 9% in CBF. Lower: case 22, original data, left hemisphere monitored. No diffuse increase in CBF. Note that the supplementary motor area is exclusively activated. Lower right: simple repetitive flexions of the contralateral index finger against
in which N is the number of subjects, C is the number of channels monitoring the focus.

In some individuals a test may evoke a non-specific diffuse increase of the hemispheric blood flow, in addition to the focal increase. For the types of voluntary movements examined, this diffuse increase of the blood flow does not change the rCBF pattern and is, therefore, presumed to affect all parts of the cortex uniformly (cf. color plate 1). It was therefore necessary to find out whether any of the focal increases could be explained as a part of the nonspecific diffuse activation. We assume that the mean increase in all extrafocal regions (\(\Delta y\)) is a fair estimate of the diffuse increase of blood flow:

\[
\Delta y = \frac{1}{C_e} \sum \frac{C_e}{J} (rCBF_{j,\text{test}} - rCBF_{j,\text{rest}})
\]

where \(CE\) is the sum of all extrafocal channels minus detectors not looking at the brain. We furthermore assume that the rCBF increase in a focus is partly caused by a specific flow increase due to the specific test, and partly due to the diffuse increase. Let \(\Delta F\) be the mean absolute increase of rCBF in a focus:

\[
\Delta F = \frac{1}{C} \sum (rCBF_{j,\text{test}} - rCBF_{j,\text{rest}})
\]

then we calculate the focal rCBF increase corrected for the diffuse flow increase as:

\[
\Delta F_{\text{corr}} = \Delta F - \Delta y
\]

Figures 6–10 show the average focal increases of rCBF corrected for diffuse increases during the four motor tests.

No attempt was made to correlate the localization of individual foci with regional anatomical structures. The relation between different points in the rCBF matrix and the general topography of the brain was in each case established by a comparison of the rCBF display with the display of the initial maximal counting rates showing the general outline of the brain and the initial course of the ramifications of the internal carotid artery (36).

In Figs. 6–10 the individual foci of rCBF increases have been transferred to a brain of standard dimensions with the aid of a proportional system similar to that of Talairach et al. (42) and subsequently averaged such that the localization and size of a focus in the figure is the average of the group.

RESULTS

The main result was that both supplementary motor areas are activated during the internal programming and during the execution of unilateral fast sequential voluntary finger movements, whereas the mere repetition of isolated movements, such as repetitive flexions of one finger, or a sustained isometric contraction cause no statistically significant increases in the rCBF in these areas. The primary motor area apparently did not participate in the

![Fig. 3. Motor-sequence test. A whole run is shown. The second half of one run is the mirror image of the first half. The test consists of a sequence of flexion-extensions of the thumb and the corresponding ulnar finger, interrupted by oppositions of the thumb. The test goes on continuously run after run during the rCBF measurement.](https://jn.physiology.org/)

a spring-loaded moveable cylinder (cf. Fig. 4). Top: the rCBF increase in the left hemisphere of case 26, original data. This subject had a diffuse decrease of 7% in CBF during the test. Lower: case 19, original data, left hemisphere monitored. This subject had a diffuse increase of 1% during the test. Note that only the sensorimotor hand area is activated.
FIG. 4. Device used for the forceful repetitive flexions and the sustained isometric contractions.

programming, but only in the execution of the voluntary movements.

We observed no systematic changes in the arterial Pco2, mean blood pressure or the pulse rate when the values from the various tests are compared to those obtained during rest (P > 0.1 in all cases, paired t test). But the mean hemispheric flow increased during the motor-sequence test (11.8 ± 1.7%, means ± SE) and during the sustained isometric muscular contractions (8.6 ± 3.3%). We observed no systematic decreases of rCBF in any of the monitored cortical areas.

Figure 5 shows a survey of the terminology used in the text to describe the topographical relations.

Focal increases of rCBF during motor-sequence test

The greatest increases of the rCBF appeared in the supplementary motor area and in the primary sensorimotor hand area (Fig. 2, upper and lower left). These increases were present in every subject. The localization of the hyperemia marking the supplementary motor area is seen by a comparison of the lateral projections in the upper left with the vertical projection in the lower left. It appears that the active cortex is located on the mesial side and superolateral border of the hemisphere. In our record-

ings, the active cortex seems to cover most of the mesial part of the premotor region. This area is thus considerably greater than the small gigantopyramidal field on the mesial side of area 6 described by Braak (2).

When the motor-sequence test is performed with the hand ipsilateral to the monitored hemisphere, the ipsilateral supplementary motor area is also active (Fig. 2, lower left) but the primary motor area is not (Table 3 and Fig. 2, lower left). This means that these voluntary movements, performed with one hand, are controlled by both supplementary motor areas and one (contralateral) primary motor area. It appears from a comparison of Table 1 with Table 3 that the amounts of rCBF increase in both supplementary areas were the same (approximately 35%). However, in this study only ipsilateral movements with the left hand have been performed.

The hyperemia in the Rolandic hand region appeared as one focus in which the precentral motor component and the postcentral sensory component could not be separated. In Tables 1 and 2 this focus is arbitrarily divided in an anterior (motor) part, an intermediate (sensorimotor), and a posterior (sensory) part. The increase of rCBF in the anterior (motor) part of this focus was quantitatively the same as the increase of rCBF in the supplementary motor areas (roughly 35%). The increase of flow in the posterior part of the Rolandic hand area was more moderate (20%). We attribute the increase of the blood flow in the anterior part of the Rolandic hand area as due to the execution of the voluntary movements, whereas the increase in the posterior part is probably due to the exteroceptive and proprioceptive feedback during the movements.

In addition to these considerable focal increases of the rCBF, there were also minor rCBF increases in the inferior frontal region just at the beginning of the lateral fissure, in the premotor cortex on the convexity of the hemisphere just in front of the motor hand area, in the mesial part of the superior frontal region (viz. Fig. 2, lower left), and in the anterior part of the superior parietal region (Tables 2 and 3), when the movements were performed with the con-

1 The word programming in this report is used in its technical sense: the formation of a message that is a translation of an algorithm. When the message is decoded and executed the result (i.e., movement sequence) is a specific realization of the algorithm.
Many subjects had, in addition to the focal rCBF increases, blood flow increase in extrafocal regions (Tables 1 and 2). The flow increase in the extrafocal regions is a diffuse increase because the rCBF pattern (see METHODS section) remains unchanged here. The extrafocal increase of blood flow is not related to the specific task performed by the brain (15, 22, 36). We assume, therefore, that the extrafocal rCBF increase is a manifestation of a diffuse activation, provoked by the test situation per se, which probably affects all parts of the cortex uniformly. Because the statistical evaluation of the specific focal increases in rCBF due to the motor-sequence test is based on a comparison of the rest rCBF with the test rCBF, some of the observed increases in rCBF listed in Tables 1, 2, and 3 might not be true specific focal increases, but the result of the diffuse cortical activation. In the third column of Tables 1 and 2, we have subtracted the estimated contribution of the diffuse activation from the focal rCBF increases. It appears that there still are considerable and statistically significant increases of rCBF in the supplementary motor areas bilaterally and the contralateral primary motor and sensory area, and a modest increase in both inferior frontal regions (Tables 1, 2, and 3). A small but statistically significant increase remained in the mesial part of the superior frontal region in the left hemisphere and in the premotor area in the right hemisphere when the motor-sequence test was performed with the respective contralateral hand. These rCBF increases thus could not be explained as the result of a diffuse activation of the hemispheres during the motor-sequence test. The average size and relative position of the specific focal increases in rCBF during the motor-sequence test have been drawn in Figs. 7 and 8. Apart from the
TABLE 1. Reproducibility of regional increases in blood flow in right hemisphere during execution of low-force fast isolated finger movements in sequences with contralateral hand

<table>
<thead>
<tr>
<th>Area</th>
<th>Channels</th>
<th>Increase, ml·100 g⁻¹·min⁻¹</th>
<th>% Increase</th>
<th>% Increase Corrected for Diffuse Increase of rCBF</th>
<th>P, Test-Rest on Corrected Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementary motor</td>
<td>5</td>
<td>19.6 ± 1.4</td>
<td>36.9 ± 3.2</td>
<td>28.5 ± 2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Motor hand</td>
<td>4</td>
<td>20.8 ± 2.1</td>
<td>40.4 ± 3.5</td>
<td>31.5 ± 3.9</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Sensorimotor hand</td>
<td>3</td>
<td>13.2 ± 2.0</td>
<td>26.5 ± 4.4</td>
<td>18.9 ± 3.7</td>
<td>&lt;0.0025</td>
</tr>
<tr>
<td>Sensory hand</td>
<td>4</td>
<td>9.9 ± 1.6</td>
<td>21.2 ± 4.2</td>
<td>13.0 ± 3.7</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Superior parietal, anterior part</td>
<td>5</td>
<td>4.3 ± 2.0</td>
<td>11.1 ± 4.9</td>
<td>4.3 ± 6.7</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>6</td>
<td>9.7 ± 2.4</td>
<td>18.5 ± 4.4</td>
<td>7.8 ± 3.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Superior mesial frontal</td>
<td>9</td>
<td>4.0 ± 1.9</td>
<td>7.1 ± 3.4</td>
<td>-2.0 ± 2.5</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Premotor area</td>
<td>8</td>
<td>9.4 ± 1.9</td>
<td>17.8 ± 3.3</td>
<td>9.4 ± 2.5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Extrafocal</td>
<td>189</td>
<td>4.6 ± 1.1</td>
<td>9.1 ± 1.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE for 10 subjects. P values determined by Student's t test.

Focal increase of rCBF due to internal programming of sequences of individual finger movements

The subjects had to simulate the motor-sequence test with the contralateral hand.

activation of the superior frontal region in the left hemisphere and the lateral premotor area in the right hemisphere (Fig. 7), there was no difference between the activation of the right and the left hemispheres.

The motor-sequence test, like typing, is a job that requires a considerable speed in the succession of the isolated finger movements. It is likely that the subjects' actual skilled performance in the motor-sequence test would be impossible without some sort of motor program that determined the sequence of the movements in advance of their execution. In order to examine whether the activation of the supplementary motor areas was due to a direct control of ongoing voluntary movements or due to the cortical work of assembling a part of a central motor program, we made a modification of the motor-sequence test. The subjects should simulate the motor-sequence test internally, but not execute the movements (for control procedures see METHODS section).

TABLE 2. Reproducibility of regional increases in blood flow in left hemisphere during execution of low-force fast isolated finger movements in sequences with contralateral hand

<table>
<thead>
<tr>
<th>Area</th>
<th>Channels</th>
<th>Increase, ml·100 g⁻¹·min⁻¹</th>
<th>% Increase</th>
<th>% Increase Corrected for Diffuse Increase of rCBF</th>
<th>P, Test-Rest on Corrected Values</th>
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</thead>
<tbody>
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<td>19.8 ± 2.6</td>
<td>35.3 ± 4.0</td>
<td>28.8 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Motor hand</td>
<td>4</td>
<td>20.0 ± 2.2</td>
<td>36.3 ± 2.4</td>
<td>30.2 ± 1.5</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Sensorimotor hand</td>
<td>3</td>
<td>14.6 ± 2.2</td>
<td>28.4 ± 5.4</td>
<td>22.3 ± 5.9</td>
<td>&lt;0.0025</td>
</tr>
<tr>
<td>Sensory hand</td>
<td>4</td>
<td>10.2 ± 1.7</td>
<td>18.5 ± 2.8</td>
<td>12.4 ± 4.0</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Superior parietal, anterior part</td>
<td>5</td>
<td>7.7 ± 1.1</td>
<td>15.4 ± 2.7</td>
<td>9.1 ± 4.9</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>6</td>
<td>8.9 ± 3.0</td>
<td>17.2 ± 5.7</td>
<td>10.6 ± 4.1</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Superior mesial frontal</td>
<td>9</td>
<td>6.3 ± 2.3</td>
<td>10.8 ± 3.4</td>
<td>4.3 ± 1.9</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Premotor area</td>
<td>8</td>
<td>7.1 ± 3.0</td>
<td>13.1 ± 5.4</td>
<td>6.9 ± 3.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Extrafocal</td>
<td>188</td>
<td>3.4 ± 1.6</td>
<td>6.5 ± 3.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE for five subjects. P values determined by Student's t test.
TABLE 3. Reproducibility of regional increases in blood flow in ipsilateral hemisphere during execution of motor-sequence test

<table>
<thead>
<tr>
<th>Area</th>
<th>Channels</th>
<th>Increase, ml·100 g⁻¹·min⁻¹</th>
<th>% Increase</th>
<th>% Increase Corrected for Diffuse Increase of rCBF</th>
<th>P, Test-Rest on Corrected Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementary motor</td>
<td>5</td>
<td>16.4 ± 2.0</td>
<td>34.8 ± 2.5</td>
<td>27.3 ± 6.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Motor hand</td>
<td>4</td>
<td>1.4 ± 1.8</td>
<td>4.1 ± 4.9</td>
<td>-1.8 ± 0.8</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Sensorimotor hand and sensory hand</td>
<td>7</td>
<td>-0.3 ± 3.3</td>
<td>2.1 ± 7.8</td>
<td>-2.8 ± 6.3</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Superior parietal, anterior part</td>
<td>5</td>
<td>0.7 ± 4.9</td>
<td>5.1 ± 10.4</td>
<td>2.8 ± 6.9</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>6</td>
<td>6.1 ± 2.2</td>
<td>14.1 ± 6.1</td>
<td>5.3 ± 1.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Superior mesial frontal</td>
<td>9</td>
<td>5.6 ± 2.9</td>
<td>9.9 ± 5.3</td>
<td>3.0 ± 5.9</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Premotor area</td>
<td>8</td>
<td>0.3 ± 4.2</td>
<td>2.3 ± 8.6</td>
<td>-4.1 ± 5.2</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Extrafocal</td>
<td>186</td>
<td>3.3 ± 1.6</td>
<td>7.5 ± 4.3</td>
<td>7.5 ± 3.3</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE for four subjects. P values determined by Student’s t test.

The only consistent increase of the blood flow due to the internal programming was in the supplementary motor area (Fig. 2, upper right, and Table 4). There were no muscle potentials in the electromyogram (Fig. 6) and no movements of other body parts. The increase of flow in the supplementary motor area could not be explained as the result of

TABLE 4. Reproducibility of regional increases in blood flow in contralateral hemisphere during internal programming of low-force fast isolated finger movements in sequences

<table>
<thead>
<tr>
<th>Area</th>
<th>Channels</th>
<th>Increase, ml·100 g⁻¹·min⁻¹</th>
<th>% Increase</th>
<th>% Increase Corrected for Diffuse Increase of rCBF</th>
<th>P, Test-Rest on Corrected Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplementary motor</td>
<td>5</td>
<td>9.5 ± 2.0</td>
<td>19.4 ± 4.3</td>
<td>17.3 ± 4.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Motor hand</td>
<td>4</td>
<td>-1.4 ± 3.6</td>
<td>-2.2 ± 3.2</td>
<td>4.3 ± 6.0</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Sensorimotor and sensory hand</td>
<td>7</td>
<td>-1.7 ± 2.6</td>
<td>-2.8 ± 5.7</td>
<td>-4.4 ± 1.9</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>9</td>
<td>2.5 ± 1.8</td>
<td>5.7 ± 4.3</td>
<td>-0.1 ± 6.5</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>7</td>
<td>-2.3 ± 2.9</td>
<td>-3.2 ± 5.8</td>
<td>-3.5 ± 4.6</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Superior mesial frontal</td>
<td>9</td>
<td>-1.4 ± 3.2</td>
<td>-2.3 ± 6.5</td>
<td>-3.3 ± 1.0</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Premotor area</td>
<td>8</td>
<td>2.3 ± 3.9</td>
<td>6.4 ± 9.4</td>
<td>4.4 ± 3.7</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Extrafocal</td>
<td>189</td>
<td>0.8 ± 2.7</td>
<td>2.8 ± 6.5</td>
<td>2.8 ± 6.5</td>
<td></td>
</tr>
<tr>
<td>Left hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplementary motor</td>
<td>5</td>
<td>12.5 ± 1.3</td>
<td>25.1 ± 2.1</td>
<td>21.2 ± 4.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Motor hand</td>
<td>4</td>
<td>-1.6 ± 2.0</td>
<td>-2.9 ± 3.9</td>
<td>-0.7 ± 2.9</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Sensorimotor and sensory hand</td>
<td>7</td>
<td>-1.2 ± 1.7</td>
<td>-2.4 ± 3.5</td>
<td>-6.0 ± 5.4</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Superior parietal</td>
<td>9</td>
<td>2.4 ± 1.8</td>
<td>5.2 ± 3.5</td>
<td>-0.3 ± 0.7</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>7</td>
<td>2.8 ± 0.5</td>
<td>7.2 ± 1.3</td>
<td>5.9 ± 2.6</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Superior mesial frontal</td>
<td>9</td>
<td>4.6 ± 1.9</td>
<td>8.8 ± 3.1</td>
<td>5.1 ± 7.0</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Premotor area</td>
<td>8</td>
<td>3.4 ± 3.4</td>
<td>8.4 ± 8.5</td>
<td>4.5 ± 9.0</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Extrafocal</td>
<td>187</td>
<td>0.4 ± 2.7</td>
<td>2.1 ± 6.9</td>
<td>2.1 ± 6.9</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE for five subjects in right hemisphere and three subjects in left hemisphere. P values determined by Student’s t test.
Fig. 6. Electromyogram from the finger flexors in the forearm recorded by surface electrodes from case 9 (three upper records) and case 16 (last record). Top: repetitive fast flexions of the index finger against the spring-loaded cylinder (cf. Fig. 4). Second row: no activity during internal programming of the motor-sequence test. Third row: sustained isometric contraction. Last row: motor-sequence test executed.

a diffuse activation of the hemisphere (Table 4). However, the increase of rCBF in the supplementary motor area during the internal programming was only 60% of the increase seen during the actual execution of the motor-sequence test. The primary motor area was completely inactive during programming of these voluntary movements. There was obviously no sensory feedback in this modification of the test, so the sensory hand area was silent too (Fig. 8).

Focal increase of rCBF during forceful repetitive finger flexions

The flexion movements with the index finger against the spring-loaded cylinder (Fig. 4) was considerably greater work than the previous delicate individual finger movements. This test was only performed with the contralateral hand. Most strikingly, there was no activation of the supplementary motor area, but only activation of the contralateral Rolandic hand area (Fig. 2, lower right, and Table 5). Although the muscular work and the energy of the cutaneous stimulation were considerable in comparison to the motor-sequence test, the rCBF increase in the Rolandic hand area was of the same size (Fig. 7 compared to Fig. 10). In Table 5 the results from the right and the left hemisphere have been pooled because there were no differences in rCBF pattern and absolute rCBF increases among the test subjects. There were no increases in other brain regions.

Focal increase of rCBF during a sustained isometric contraction

In this test the subjects exert a constant force of at least 5.8 N against the spring-loaded cylinder. The cylinder is to be fully compressed. Thus the muscular work is greater during the 45 s the rCBF is measured than in any of the other tests. In contrast to the greater muscular work, the increase of rCBF in the motor hand area as well as the
TABLE 5. Reproducibility of regional increases in blood flow in contralateral hemisphere during forceful repetitive flexions of index finger

<table>
<thead>
<tr>
<th>Area</th>
<th>Channels</th>
<th>Increase, ml·100 g⁻¹·min⁻¹</th>
<th>% Increase</th>
<th>% Increase Corrected for Diffuse Increase of rCBF</th>
<th>P, Test-Rest on Corrected Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementary motor</td>
<td>5</td>
<td>3.6 ± 2.0</td>
<td>6.8 ± 3.5</td>
<td>2.0 ± 3.7</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Motor hand</td>
<td>4</td>
<td>17.0 ± 2.5</td>
<td>34.2 ± 9.9</td>
<td>29.9 ± 6.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Sensorimotor hand</td>
<td>3</td>
<td>15.4 ± 2.2</td>
<td>29.7 ± 6.0</td>
<td>25.9 ± 2.8</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Sensory hand</td>
<td>4</td>
<td>9.0 ± 2.3</td>
<td>22.3 ± 11.0</td>
<td>17.4 ± 7.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Superior parietal, anterior part</td>
<td>5</td>
<td>1.7 ± 2.4</td>
<td>6.7 ± 6.2</td>
<td>1.8 ± 2.3</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>6</td>
<td>−1.1 ± 2.5</td>
<td>−1.2 ± 3.8</td>
<td>−8.0 ± 6.5</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Superior mesial frontal</td>
<td>9</td>
<td>2.1 ± 3.5</td>
<td>5.1 ± 6.1</td>
<td>0.3 ± 3.2</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Premotor area</td>
<td>8</td>
<td>3.0 ± 2.0</td>
<td>7.6 ± 6.1</td>
<td>3.3 ± 1.8</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Extrafocal</td>
<td>188</td>
<td>2.2 ± 1.8</td>
<td>6.6 ± 5.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE for five subjects, two in the left hemisphere and three in the right hemisphere. P values determined by Student’s t test.

sensory hand area was less than before (Fig. 10, Table 7). There was, in addition, a moderate focal rCBF increase in the supplementary motor area (Table 6), but it was not possible to separate this increase from the diffuse increase of blood flow in the hemisphere during this test (Table 7). Thus, these last two tests elicited only the focus in the contralateral Rolandic hand area.

Supplementary motor area is not directly involved in analysis of somatosensory information

Finally we tried to see whether the supplementary motor area participated in the analysis of sensory information since direct electrical stimulation of this area in man has evoked somatosensory responses (33) and stimulation of peripheral nerves have elicited field potentials in this area (43). The rCBF was measured in four subjects who discriminated various shapes placed in the contralateral hand (for procedure see Roland and Larsen, Ref. 36). Their fingers were moved passively over the objects while their arms and hands were relaxed with no observable muscular contractions. The subjects were not allowed to report their judgments until the rCBF measurement was finished. There was no increase of the blood flow in the supplementary motor area (0.1 ± 2.4; mean increase in percent ± SE). There were also no changes in the blood flow in the supplementary motor area when the tendon of the contralateral flexor carpi radialis longus was forcibly vibrated in one subject. Thus, the supplementary motor area is not activated when a subject analyzes somatosensory information that is not utilized for the programming and control of movements.

DISCUSSION

The rCBF method has some limitations, which are necessary to point out before the results are interpreted. The most severe is that it is not possible to study the time relations between the different cortical activations. With the rCBF method one can measure the total change of metabolism in a small cortical area, but since it takes 45 s to measure the rCBF, it is likely that cortical regions with only a brief activation may be missed. Because rCBF is an expression of the total oxidative metabolism regionally and, therefore, the sum of neuronal and glial metabolism, one cannot infer that the observed rCBF increases are due to increased neuronal activity only. Another limitation is the lack of control of mental activity during the reference state, which we have termed the rest condition. Although the somatosensory input is constant and the subjects deprived of visual and auditory information, we cannot prevent them from thinking and perhaps even establishing motor programs for later use. However, the random and nonrandom cerebral activity in the rest condition follows a certain pattern,
FIG. 7. Mean increase of the rCBF in percent during the motor-sequence test performed with the contralateral hand, corrected for diffuse increases of the blood flow. The individual focuses of rCBF increases have been transferred to a brain map of standard proportional dimensions (42). The size and location of each focus shown is the geometrical average of the individual focuses. Cross-hatched areas have an increase of rCBF significant at the 0.0005 level (Student’s t test, one-sided significance level). Hatched areas have an increase of rCBF significant at the 0.005 level, for other areas shown the rCBF increase is significant at the 0.05 level. Left: left hemisphere, five subjects. The standard error of the mean is shown in Table 2 (third column). Right: right hemisphere, 10 subjects. For regions shown, the standard error of the mean is shown in Table 3 (third column). For further relations between the topography of the brain and the rCBF increases see METHODS section and Ref. 36.

which is reflected in the constancy and stability of the rCBF pattern in repeated measurements during rest (14, 20, 22).

The rCBF calculated as the slope of the logarithmically transformed initial part (15–60 s) of the $^{133}$Xe washout curve is a reliable measure of the blood flow of the gray matter (13, 18). Due to the absorption of the relatively soft $^{133}$Xe radiation in the cerebral tissue, the rCBF in the cortex on the supero-

TABLE 6. Reproducibility of regional blood flow increase in contralateral hemisphere during a sustained isometric contraction

<table>
<thead>
<tr>
<th>Area</th>
<th>Channels</th>
<th>Increase, ml·100 g$^{-1}$·min$^{-1}$</th>
<th>% Increase</th>
<th>% Increase Corrected for Diffuse Increase of rCBF</th>
<th>% Increase Corrected Test-Rest on Contralateral Hemisphere</th>
<th>P, Corrected Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementary motor</td>
<td>5</td>
<td>5.1 ± 1.1</td>
<td>10.8 ± 2.6</td>
<td>3.1 ± 3.6</td>
<td>&gt;0.1</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Motor hand</td>
<td>4</td>
<td>11.3 ± 2.4</td>
<td>24.6 ± 4.3</td>
<td>17.2 ± 3.8</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Sensorimotor hand</td>
<td>3</td>
<td>8.6 ± 3.4</td>
<td>20.2 ± 7.2</td>
<td>12.2 ± 5.3</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sensory hand</td>
<td>4</td>
<td>6.2 ± 2.7</td>
<td>14.0 ± 5.4</td>
<td>6.4 ± 3.5</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Superior parietal, anterior part</td>
<td>5</td>
<td>2.7 ± 3.6</td>
<td>7.7 ± 7.7</td>
<td>-0.7 ± 4.7</td>
<td>&gt;0.1</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Inferior frontal</td>
<td>6</td>
<td>4.7 ± 2.5</td>
<td>8.9 ± 3.7</td>
<td>-1.5 ± 1.6</td>
<td>&gt;0.1</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Superior mesial frontal</td>
<td>9</td>
<td>5.7 ± 1.7</td>
<td>11.5 ± 3.3</td>
<td>3.7 ± 2.0</td>
<td>&gt;0.1</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Premotor area</td>
<td>8</td>
<td>1.4 ± 1.8</td>
<td>2.8 ± 3.5</td>
<td>-4.2 ± 1.9</td>
<td>&gt;0.1</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Extrafocal</td>
<td>178</td>
<td>3.2 ± 1.7</td>
<td>7.7 ± 3.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE for seven subjects, two in the left hemisphere and five in the right hemisphere. P values determined by Student’s t test.
lateral surface of the brain will, with a few exceptions, be measured with the highest efficiency. Hence, the rCBF from each of the 254 channels is a weighted sum of local blood flows from the layers of gray matter in the tissue cone monitored by each detector. Theoretically, it should be possible to record very marked changes of the blood flow in deeper structures such as the basal ganglia in regions where these structures are closest to the brain surface and provided that the superjacent cortex is relatively inactive. For instance, we cannot exclude that the rCBF increase in the inferior frontal region during performance of the motor-sequence test originates from the anterior part of the basal ganglia.

From simple geometrical considerations it can be seen that the uppermost detectors, with the converging collimator system in lateral position mainly, will monitor the rCBF in the cortex on the mesial side of the superior frontal cortex and the supplementary motor area. This is why the rCBF changes in these areas are recorded so efficiently with lateral position of the collimator system (cf. Fig. 2, upper right). A change in the collimator position to vertex position makes it possible to locate the supplementary motor area on the mesial cortex and suprolateral border of the hemisphere when the recordings from the two collimator positions are compared. However, the efficiency with which rCBF
changes can be measured in the mesial frontal and parietal cortex decreases rapidly as one approaches the cingular region, so our method of recording clearly favors rCBF changes in the superior 2 or 3 cm of the mesial cortex.

The appearance of a focal hyperemia, and consequently increased metabolism in the motor hand region, is a physiological event that means that voluntary hand movements are executed. The motor hand region is a physiological concept, not an anatomical entity. Although we are able to localize this area fairly well in the individual, its position in the rCBF matrix may vary somewhat from subject to subject; just as attempts to localize the motor hand area by electrical stimulation of the precentral gyrus turn out differentially among individuals (32). Figures 8–11, showing the average size and location of the focal hyperemias, should therefore be regarded as no more than heuristic diagrams in which no true scientific accuracy is possible.

The supplementary motor area and the primary motor area are both activated during the execution of learned, sequential ballistic movements of individual fingers (the motor-sequence test); whereas the primary motor area, as apparently the only cortical motor region, can control repetitive ballistic flexions of the same finger. The primary motor area does not participate in the programming of motor sequences, but in their execution. The increased metabolism in the motor hand area is produced by cortical cells, which undoubtedly are close to the central sulcus, but whether the majority of these cells are pyramidal tract neurons is not clear from our observations. There is, consequently, no discrepancy between our observation that the rCBF in the motor hand region is most efficiently intensified by the execution of simple fast isolated movements, irrespective of their force or time derivative of force and of whether these movements occurred in sequences or not, and the observation that most pyramidal tract neurons have been found to discharge closely related to force and time derivative of force (10). A sustained isometric contraction caused only a

FIG. 10. Mean increase of the rCBF in percent during forceful repetitive flexions of the contralateral index finger, corrected for diffuse increases of the blood flow. Data from right and left hemispheres have been pooled and subsequently averaged, here the pattern of increases is shown on a left hemisphere. Five subjects; standard error of the mean shown in Table 5.

FIG. 11. Mean increase of rCBF in percent during a sustained isometric contraction of the contralateral index finger and thumb. Values corrected for diffuse increases of the blood flow. Data from the right hemisphere and the left hemisphere have been pooled and subsequently averaged. Here the pattern of increases have been shown on a left hemisphere. Seven subjects; standard error of the mean shown in Table 6 (third column).
moderate increase of the rCBF, probably because it costs less total neuronal activity to maintain a constant force and position, than to change the movement parameters repetitively. The type of movements that can be elicited after electrical stimulation of the primary motor area are simple flexions, extensions, supinations, etc., of a very localized body part (31, 32). This is in accordance with the present results: the control of ongoing, simple, repetitive, ballistic movements of the self-same body part is a job that the primary motor area, and those parts of the motor system it projects to, can manage without contributions from other cortical regions. This seems to hold for sustained isometric contractions as well, at least insofar as muscular fatigue does not cause any change in the position that must be maintained. More complex tasks require a programming from other cortical areas, although the elements in these tasks are also simple ballistic movements.

The supplementary motor area is active when a sequence of simple ballistic movements is planned. This area, consequently, participates in the assembly of a central motor program. In our experimental design we have left the learning phase out of account; all subjects were well trained and could execute the motor-sequence test with a minimum of errors prior to the rCBF measurements. The information about the type of movements (ballistic flexion-extensions and oppositions), the body parts to be moved, and the number of isolated finger movements must, therefore, have been stored in a memory before the rCBF measurements started. The cerebral events during internal programming of the motor-sequence test are formally a recall of this information and the formation of a queue of time-ordered commands. The formation of a motor subroutine, specifying the sequence of isolated ballistic flexion-extensions and oppositions of the fingers, seems to be the most important contribution of the supplementary motor areas during the planning and execution of the motor-sequence test.

The reason why repetitive ballistic flexions of the same finger do not activate the supplementary motor area, whereas a sequence of ballistic flexion-extensions of different fingers and thumb oppositions does, is probably due to the stochastic nature of the motor subroutine in the last case. In Fig. 12, the two tasks are depicted as Markov sources. When repetitive flexions are executed, the probability that a flexion succeeds an extension is 1.0. The source is deterministic: once started, the movement sequence is given. The motor-sequence test, on the contrary, needs a constant reprogramming subroutine to form the right queue of commands because the transition probabilities change once a single movement has been executed.

The increase of rCBF in the supplementary motor area was greater during the execution of the motor sequence test than during the internal programming. The supplementary motor area in the monkey receives its cortical afferents mainly from the contralateral supplementary motor area, from other parts of area 6, from the somato sensory areas 3, 1, 2, and 5, and from the
primary motor area (6, 16, 17, 28, 29). Of these the sensory and motor hand areas were clearly activated during execution of the motor sequence with the contralateral hand, whereas the activation of the convexity part of the premotor area was very modest and not statistically significant in the left hemisphere. It is possible that information from the sensory and primary motor areas even in man reach the supplementary motor area and the convexity part of the premotor area when the motor-sequence test is executed, and thus make their contribution to the blood flow increases here. Thus, the information from the sensory hand area would only be gated to the supplementary motor area during execution, as the supplementary motor area does not participate in the analysis of somatosensory information when the subjects do not move their hands. On the basis of the limited information about the role of the lateral part of the premotor area at present, the discussion of its functions is postponed to the next article (38).

Electrical stimulation of the supplementary motor area most often provokes an arrest of ongoing voluntary movements, but in a considerable number of such experiments it has been possible to elicit motor sequences. As in the present study, the responses have been a complicated time sequence of contractions of different muscles or muscle groups such as: the repetition of consonants (3), syllables (5) or words (32), longer series of movements of the extremities (1, 5, 32, 33), or even piano-playing movements with the fingers (5).

The supplementary motor areas are not supplementary, but they are motor in the sense that they are programming areas for motor subroutines. Human speech is another type of skilled voluntary movement that is composed of sequences of fast isolated muscular contractions. Recent observations from our laboratory indicate that the supplementary motor areas are active during speech (20). The functions of the supplementary motor areas are presumably not restricted to the programming of sequences of fast delicate movements of the fingers or articulatory muscles but, as will be shown in the next article (38), are probably more general. On this background it might seem paradoxical that there are so few permanent symptoms after ablation of the supplementary motor area in man (27, 32, 33). The only permanent symptoms hitherto reported have been an improvement of bilateral alternating hand movements (alternatively clench one fist and spread the contralateral fingers) (19), and reduction in typewriting speed (30). The cause of these sparse symptoms might be that all the reported ablations have been unilateral, and thus the impairment only arises in bimanual skills. The fact that both supplementary motor areas are active during unilateral sequential finger movements could indicate that the elaboration of motor subroutines is bilateral. Very recently Brinkman and Porter (4) showed that 80% of the cells in the supplementary motor area of conscious monkeys (Macaca fascicularis) modulated their activity during a stereotyped motor task with a similar pattern of discharging regardless of whether the movement sequence was made with the contralateral arm or the ipsilateral arm.

The increase in the inferior part of the frontal lobe is variable and perhaps due to internal counting; although we cannot exclude that the rCBF increase recorded in this region might originate from the underlying anterior part of the basal ganglia (12), which in this region lies approximately 3 cm below the cortical surface. Most subjects who perform the motor-sequence test admit afterward that they had difficulties in controlling the number of flexions unless they guided their performance by internal counting. In this way internal language might help to organize a motor activity. The inferior frontal region might then represent a higher step in the hierarchy of subroutines in the central motor program.

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