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Activation of the Supplementary Motor Area During Voluntary Movement in Man Suggests It Works as a Supramotor Area

Abstract. *Measurements of cerebral blood flow in man revealed that complex voluntary movements are associated with a blood flow increase in the supplementary motor area of the brain. This increase is additional to and similar in magnitude to the Rolandic sensorimotor area activation that occurs during all kinds of movement. When subjects counted silently there was no activation of any focal cortical area in the brain; when they counted aloud there was a marked increase in activity in the supplementary motor area. These results are consistent with the hypothesis that the supplementary motor area plays a major role in the initiation and control of at least some kinds of voluntary movement in man and is, therefore, a motor center of a higher order than the primary Rolandic areas.*

Cortical stimulation studies (*1*) have located the supplementary motor area (SMA) in man and animals. It is immediately anterior to the primary sensorimotor area for the foot and leg on the medial aspect of both cerebral hemispheres. But its role in voluntary and other movements has still not been clarified some 30 years after its original description. Unilateral ablation of this area for intractable focal epilepsy in man results in a transient akinesia—global at first, with speechlessness, then contralateral to the ablation. Recovery is nearly complete after a few weeks, except for a permanent inability to perform rapid alternating movements with the hands (*2*). It was therefore hypothesized that the SMA might initiate and sustain voluntary motor activity and that other areas, particularly the contralateral SMA, could almost completely compensate for the effects of unilateral ablation (*2*).

In normal brain cortex, an increase in function in a given area produces an increase in the metabolism of its neuronal and glial cell populations, with a concomitant increase in the cerebral blood flow (CBF) to that area (*3*). Measurement of regional CBF thus permits investigation of regional cortical activation: The CBF of many discrete areas of one cerebral hemisphere can be mapped after a bolus injection of a small dose of ^{133}Xe into the internal carotid artery. The clearance of the isotope from the labeled hemisphere is measured externally by multiple scintillation detectors and the flow under each detector is computed by using the initial slope method (*4*). The use of a high-resolution multidetector scintillation camera with 254 detectors has demonstrated that specific patterns of increase in regional CBF can be elicited in normal subjects by various external stimuli or brain functions (*4*). In particular, CBF increases of up to 40 percent occur in the upper premotor region of both hemispheres during simple speech such as counting aloud (*5*) or complex (planned) sequential movements of the fingers (*6*). Simple saccadic eye movements in response to a rapidly moving target are associated with a small but definite increase of CBF in this area (*7*); more complex eye movements, such as occur in looking at pictures or reading silently, are accompanied by a slightly higher flow increase of about 15 percent (*8*). Conversely, during a sustained isometric contraction of the fingers there is only a moderate focal CBF increase in the mesial premotor region, an increase that cannot be distinguished from the diffuse increase of the hemispheric blood flow. Also, during forceful repetitive finger flexions (against a spring), no activation in the mesial premotor region occurs despite the more strenuous muscular work involved compared to the planned motor sequence test (*6*). In contrast, simple repetitive flexion of all fingers without external resistance usually elicits an obvious increase of CBF in this area (*9*).

Thus it was suggested (*6*) that the mesial premotor cortex helps control the motoric subroutines needed for skilled movements and, in view of the size of the area of activation and its localization at the upper border of the hemisphere, it was hypothesized (*6*) that the regions in which these CBF increases occur correspond to or at least include the SMA.

In this report we demonstrate that complex sequential voluntary movements activate the SMA and the appropriate sensorimotor (Rolandic) areas, without obvious somatotopy within the SMA.

We used a 254-detector gamma-ray camera to study the regional CBF correlates of the premotor activations associated with voluntary movements in five patients who were subjected to carotid angiography for focal epileptic seizures and shown to be free of brain lesion. With this camera, CBF can be recorded in 254 small adjacent cortical areas, each about 1 cm^2 (*4*).

The detectors were positioned above the head of the patient in a plane facing the vertex of the skull, with the midline of the collimator array in alignment with the midline of the brain. (Measurements made by the detectors positioned over the nonlabeled hemisphere in this position were excluded from the results.) Two to five consecutive regional CBF measurements were made in each patient (a total of 25 determinations). Measurements were made under a number of experimental conditions. Three patients lay motionless with eyes closed and ears plugged; four performed static foot contraction (pushing the foot contralateral to the labeled hemisphere against a continuous resistance); five performed sequential foot movements for 45 seconds (moving the toes once downward, twice upward, three times to the right, four times to the left, and then repeating this sequence); four performed complex sequential finger movements (*6*); one performed repetitive saccadic horizontal eye movements; three counted aloud from 1 to 20; two made sequential mouth movements (alternately baring the teeth and protruding the lips); and three counted silently from 1 to 20 several times, without moving the lips or tongue.

Contralateral sustained foot contraction resulted in all cases in an increase in CBF of 17 to 28 percent (mean, 24 percent) in an area 2 to 3 cm in diameter in the cortex close to the midline (Fig. 1A), an area that corresponds to the sensorimotor area for the foot. The complex foot movement sequence was accompanied by an even higher CBF increase of 22 to 38 percent (mean, 29.5 percent) in this region, with the appearance of a second small focus of increased CBF, about 2 cm in diameter, just anterior and slightly medial to the sensorimotor foot area (Fig. 1B)—corresponding exactly to

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the SMA. A CBF increase in the same area was also elicited by sequential finger movements and counting aloud (Fig. 1B) as well as (although less markedly) during eye movements and sequential mouth movements. For each test condition, an accompanying increase in CBF in the appropriate sensorimotor area along the Rolandic fissure was noted (Fig. 2). The individual CBF increases in the supplementary motor and Rolandic areas are shown in Table 1.

To evaluate the possible contribution of "internal language" to these SMA activations, since it is probably involved in the memorization of complex motor sequences and in counting, we asked three patients (two whose left hemisphere and one whose right had been studied) to count silently during the CBF measurements. Silent counting caused no activa-

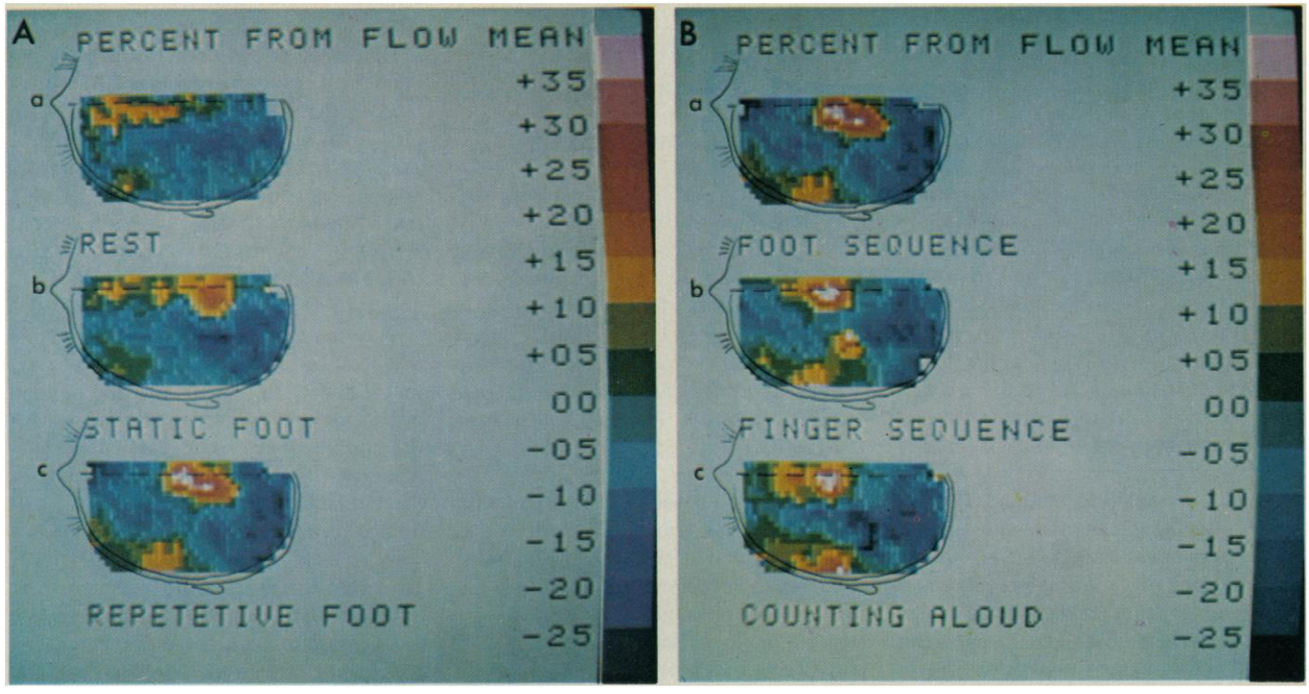


Fig. 1. Serial regional CBF determinations in vertex projection of left hemisphere in the same patient. (Aa) Cerebral blood flow in the patient at rest shows a homogeneous pattern except for a 10 to 15 percent increase in the medial prefrontal region; (Ab) sustained foot contraction elicits a 27 percent increase in blood flow in the sensorimotor foot area; (Ac) during a complex repetitive foot movement, CBF increases 27 percent in the foot sensorimotor area and a second focus of high blood flow appears, just anterior to the foot sensorimotor area, that corresponds to the supplementary motor area. (B) Complex sequential movements of the foot (a), fingers (b), and mouth (c) result in activation of the three corresponding sensorimotor areas along the Rolandic fissure, but the accompanying blood flow increase in the SMA is almost exactly the same in all three situations.

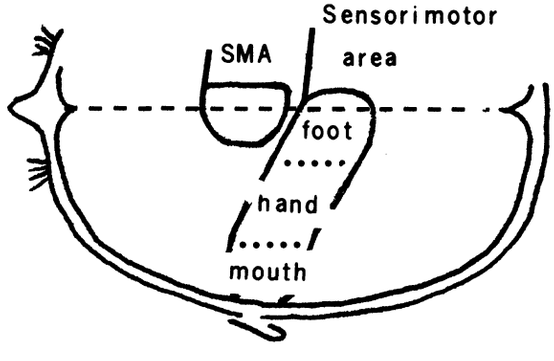
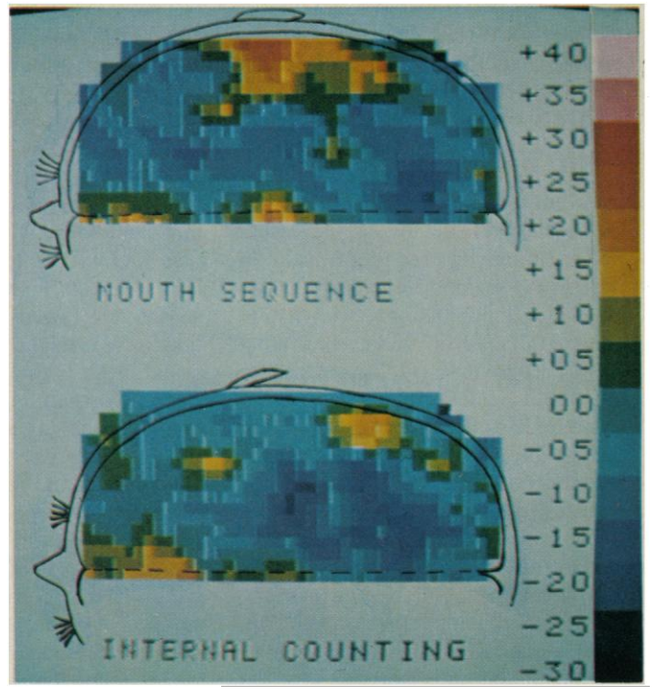


Fig. 2 (left) Diagrammatic representation of the cortical areas shown in (A) and (B). Fig. 3 (right). Comparison between the patterns of activation obtained during sequential mouth movements (a) and silent counting (b) in the right hemisphere of the same patient. Mouth movements are associated with a pronounced activation in the mouth sensorimotor area and the SMA; regional CBF values differ significantly from those in the resting state. Silent counting activates none of these areas. Comparison with Fig. 1B suggests that SMA activation is less during sequential mouth movements than during counting aloud (see Table 1).



tion (Fig. 3 and Table 1). In contrast, simple repetitive mouth movements by two patients resulted in almost the same pattern of activation as counting aloud but with a less pronounced CBF increase in the SMA.

Although the motor sequence tests did not always elicit a CBF increase of the same magnitude in the SMA (range, 8.5 to 23 percent; see Table 1), the increase always occurred under the same detectors in any one patient. When a patient counted aloud, however, the activation seemed to extend more anteriorly, especially in the left hemisphere (Fig. 1B).

These results supplement the finding (*6*) that complex sequential movements of the contralateral hand activate the mesial premotor region whereas tonic contraction or more simple repetitive movements do not. The same applies for movements of the foot and the mouth and, in all likelihood, of the eyes (although only tracing eye movements have been tested). Furthermore, this activation cannot be explained by the involvement of internal language. Our study also shows that premotor activation is restricted to the SMA itself, according to its description in man from electrode stimulation studies (*1*): both approaches delineate a small functional area, located almost entirely in the inner aspect of the hemisphere on the most posterior part of the frontal lobe, immediately anterior to the sensorimotor area for the foot. During lateral stereotactic studies of CBF, we had found (*9*) that the projection of this area is to the same mesial region where electrode stimulations give typical SMA responses (*10*). Activation of the SMA that was associated with movements of the foot, hand, mouth, or eyes was always maximal under the same detectors, there being no obvious somatotopic organization in the SMA. However, during mouth movements and counting aloud, regional CBF increase seemed to extend more anteriorly, in concordance with a previous study on speech (*4*) and some electrophysiological data (*10*). There seems to be a somatotopic organization of the SMA in animals (*11*), and somatotopic anatomical connections of the SMA to areas 4 and 6 and from sensory areas SI, SII, and 5 have been demonstrated in monkeys (*12*). In man, however, somatotopy of the SMA has not yet been confirmed. It has been suggested by some electrophysiological studies (*1*) but not by others (*10*).

Although the role of the SMA in voluntary movements in man remains unclear, the problem seems to be better approached by the regional CBF activation method than by the standard stimulation and ablation techniques. Our method is more truly based on natural function. Electrophysiological studies in which stimulation was used (*1, 10, 11*) promoted the idea that the SMA is mainly involved in the control of posture, whereas microelectrode recording experiments showed a considerable convergence of its afferent input organization for sensory, visual, and acoustic modalities (*13*). This and other studies (*6*) do not support the posture hypothesis, since sustained contractions of any part of the body do not activate the SMA. In an unpublished investigation, a patient who held his arm in an upright position exhibited no CBF increase in the SMA.

Since approximately 1 minute is needed to reliably record changes in regional CBF with our method, it is possible that even if the SMA is involved in

Table 1. Regional CBF changes above mean hemispheric values in the five patients given sequential tests and measured using the vertex projection. The same sequence of tests was not given to all patients. Some tests were omitted in individual cases because of the need to run the whole procedure in a reasonably short time so that other functional tests could be made in an attempt to elicit epileptic foci. Mean values and the probability (method of paired samples) that the measured changes were significantly different from the resting values are displayed in the right-hand column [for details, see (*5*)]. In patients 4 and 5, the values for resting have been taken from the values for the silent counting tests since the averaged values for this test do not differ from the mean values for resting; in patient 3 they are identical in both conditions. Movement of any part of the body is associated with a CBF increase in the appropriate sensorimotor area in all cases. In addition, complex sequential movements and saccadic eye movements induce an increase in activation in the SMA. Sustained contraction or silent speech do not activate the SMA. Percentage of change was determined by dividing the regional CBF at rest by overall CBF at rest, substracting this value from test-condition regional CBF divided by test-condition CBF, and multiplying by 100. Control (resting and silent counting) values: regional CBF divided by overall CBF and multiplied by 100.

Condition	Patient (hemisphere)					Mean
	1 (left)	2 (right)	3 (right)	4 (right)	5 (left)	
Sustained foot contraction						
Foot sensorimotor area	+27	+17	+25	N.D.*	+28	+24.25†
SMA	0	+ 1	− 1		− 2	− 0.5‡
Foot motor sequence						
Foot sensorimotor area	+26.5	+22	+29	+38	+32	+29.5†
SMA	+24	+24	+10	+25	+23	+21.2†
Finger motor sequence						
Hand sensorimotor area	+23	+19	+33	N.D.	+23	+24.5†
SMA	+21	+17	+11		+12	+15.25§
Eye movements						
Frontal eye field	N.D.	N.D.	+12	N.D.	N.D.	+12‖
SMA			+11			+11‖
Counting aloud						
Mouth sensorimotor area	+28	+20	N.D.	N.D.	+19	+22.3†
SMA	+28.4	+16			+24	+22.8†
Mouth motor sequence						
Mouth sensorimotor area	N.D.	N.D.	+26	N.D.	+16.5	+21.25†
SMA			+ 9		+ 8	+ 8.5¶
Counting silently						
Mouth sensorimotor area	N.D.	N.D.	101	101	102	101.5
SMA			103	109	95	102.3
						99.2
Resting						104.2
All sensorimotor areas	100	192	99	N.D.	N.D.	97
SMA	110	103	105			106

*N.D., not done. †$P < .001$. ‡$P > .5$. §$P < .01$. ‖$P < .01$, paired comparison between detectors. ¶$P \simeq .01$.

initiating voluntary movements (*2*), its activation during a tonic contraction could be too short to be detected. This explanation is insufficient, however, since simple repetitive movements do not elicit activation either—in contrast to planned sequential movements and automatic but highly complex movements, which do (*9*).

The lack of SMA activation during silent counting makes it unlikely that internal speech may be responsible for the SMA activations measured in other test conditions. This result is of great importance since "internal programming" of a finger motor sequence in which the fingers are actually not moved activates the SMA and not the other motor or language areas (*6*). Considered together, these data imply a more specific involvement of the SMA in the programming of motor sequences rather than a mere relation of this area to internal language.

Our conclusion is that the SMA plays an important role in the initiation as well as in the regulation of some kinds of voluntary movements. The SMA may contribute to the establishment of new motor programs (*6*) and probably controls the execution of established subroutines according to external and internal inputs. Its anatomical connections and the available physiological data suggest that the SMA could be the place where external inputs and commands are matched with internal needs and drives to enable formulation of a strategy of voluntary movements. This concept, foreseen by Campbell (*14*) in 1905 from histological studies and by Sanides (*15*) in 1964 from embryological studies, is supported by recent studies (*16*) in which ablations of the SMA produced deficits in visually guided reaching behavior and by electrophysiological experiments (*17*) in which a role is suggested for the SMA in "readiness" to move, in the regulation of learned movements after sensory inputs, and as part of the neuronal circuit that elaborates some general features of movement performance. Thus, rather than restricting its role to tonic postural adjustments prior to movement, it seems compelling to consider the SMA as a supramotor area—a functional area of higher hierarchical order than the primary motor Rolandic areas.

J. M. ORGOGOZO
Clinique Neurologique, Hôpital Pellegrin, Université de Bordeaux II, 33000 Bordeaux, France

B. LARSEN
Department of Clinical Physiology, Bispebjerg Hospital, 2400 NV Copenhagen, Denmark

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Calcitonin: Inhibitory Effect on Eating in Rats

Abstract. *Subcutaneous and intracerebral injections of calcitonin inhibited feeding in rats. The anorectic activity of calcitonin was destroyed by exposing the hormone to heat, trypsin, or hydrogen peroxide. Calcitonin did not produce a conditioned taste aversion to saccharin, and maximum inhibition of feeding occurred 4.5 to 8.3 hours after subcutaneous administration. It is concluded that calcitonin inhibits feeding by acting directly on the central nervous system.*

Cells within the mammalian thyroid, known as C cells, secrete the peptide hormone calcitonin (*1*). Since the discovery of calcitonin in 1961, the substance has been found to promote absorption of calcium and phosphate into bone as well as to act in the conservation of skeletal calcium (*2*). Because of these actions, it has been suggested that calcitonin has a physiological role in the prevention of hypercalcemia. In particular, calcitonin may prevent the postprandial hypercalcemia that otherwise would result from absorption of calcium from foods (*3*). Calcitonin may also promote mineralization of the skeleton by way of calcium absorbed from milk in preweanling animals (*4*). In support of these hypotheses, it has been demonstrated that plasma calcitonin concentrations increase after feeding in adult rats (*3*) and after suckling in infant rats (*4*). The fact that calcitonin is secreted postprandially suggested to us that calcitonin might participate in the regulation of subsequent feeding behavior. We studied this possibility by administering calcitonin to animals and found that calcitonin reduces feeding, apparently by a direct action on the central nervous system (CNS).

We previously reported (*5*) that calcitonin strongly inhibited 24-hour food intake of rats and rhesus monkeys when injected subcutaneously in relatively large doses (25 to 50 U/kg, or 5.3 to 10.6 μg/kg). In humans, a significant reduction in body weight was observed during the 24 to 36 hours following a single subcutaneous injection of 2 U/kg. In rats, the inhibition of feeding was dose-related (Fig. 1) and was accompanied by a pronounced diuresis.

To test the hypothesis that inhibition of feeding was due to a direct action on the CNS, we administered calcitonin to rats by intracerebroventricular injection (*6*) in dosages approximately 25 to 50-fold smaller than those that inhibited feeding when administered peripherally. Intake of food and water, excretion of feces and urine, and body weight were recorded during the 2 days before and after the injections.

The intracerebral injections produced large decreases in food intake for 24 hours (Fig. 1); the smaller dosage used (0.2 U or 43 ng) produced a 40 percent decrease in feeding ($P < .02$, Dunnett's multiple comparison). Fecal excretion and body weight decreased in parallel to the reductions in food intake (*7*). Drinking and urine excretion were unchanged, except that the largest dose (1 U) decreased drinking by 38 percent ($P < .01$).

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