Regional Cerebral Blood Flow Changes in Motor Cortical Areas after Transient Anesthesia of the Forearm

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To study the effect of deafferentation on cortical areas activated by movement of the proximal muscles, we measured regional cerebral blood flow with positron emission tomography and 15O-labeled water. Flexion-extension movements of the right elbow before deafferentation were associated with an increase of regional cerebral blood flow in the primary sensorimotor area bilaterally, posterior supplementary motor area bilaterally, ipsilateral cerebellum, contralateral putamen, premotor area, anterior cingulate area, and posterior parietal region. Transient anesthesia of the right forearm induced by ischemic block caused an increase of regional cerebral blood flow in the primary sensorimotor area bilaterally at rest, but there was no change of regional cerebral blood flow with movement, indicating that the movement-related change in cerebral blood flow was reduced. These findings are consistent with increased excitability of neurons as a result of deafferentation. In the supplementary motor area, anesthesia did not induce any change in regional cerebral blood flow at rest, but there was a decline with movement, again indicating a reduction of the change in cerebral blood flow related to movement. This might be due to a reduction in sensory feedback because of the anesthesia.


Modification of sensory input influences cortical organization. In animal models, motor outputs are reorganized after peripheral nerve lesions [1], amputation of body parts [2], and reversible limb deafferentation by local anesthesia [3]. Cortical output reorganization could be triggered by modification of sensory input to the primary motor area [1]. Transcranial magnetic stimulation (TMS) studies in humans showed that reorganization of corticospinal pathways after spinal cord injury or limb amputation leads to increased excitability of motor pathways targeting muscles proximal to the level of interruption of afferents to the central nervous system [4, 5]. With TMS, recordings of motor evoked potentials (MEPs) in arm muscles before, during, and after anesthetic block of the forearm showed reversible enlargement of the amplitude of MEPs from the biceps [6]. A decrease in inhibitory inputs to the corticomotoneuronal pathways targeting the biceps, secondary to deafferentation of the hand and forearm, may be the mechanism underlying the enlarged MEP amplitudes.

These findings led us to analyze, with positron emission tomography (PET) and 15O-labeled water, the effect of transient anesthesia of the hand and forearm on the cortical areas that show an increase in activity with elbow movement. Findings with PET should be useful in the interpretation of the TMS results. In addition, in contrast with TMS, which evaluates only the motor cortex, PET allows measurement of regional cerebral blood flow (rCBF) in the entire brain.

Subjects and Methods
Subjects were 7 healthy volunteers (3 men, 4 women), aged 18 to 52 years (mean, 26.9 years). All subjects were right-handed, by self-report, and all had normal findings on a neurological examination. The protocol was approved by the Institutional Review Board, and all subjects gave their written informed consent for the study.

PET scanning was performed with a Scanditronix PC 2048-15B (Uppsala, Sweden) 15-slice tomograph with interslice spacing of 6.5 mm. Images were reconstructed to a full width at half maximum (FWHM) of 6.5 mm. Field of view and pixel size of the reconstructed images were 256 mm and

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2 mm, respectively. A transmission scan was obtained with a rotating germanium-68 source, and from the reconstructed transmission images, the subject's head was positioned for coverage of the primary sensorimotor cortex (SM1), sacrificing views of the lower cerebellum. A rigid thermoplastic face mask was used to immobilize the subject's head, and the subject's eyes and ears were covered.

A 30-mCi dose of 15O-labeled water was injected into the left antecubital vein, and images of cerebral blood flow (CBF) were obtained by summing the activity occurring in the 60-second period following the initial increase in cerebral radioactivity. No arterial blood sampling was performed, and thus the images were those of tissue activity. Tissue activity recorded by this method is linearly related to rCBF [7, 8].

Each subject had ten consecutive scans (five resting scans and five movement scans), performed at 10-minute intervals. A steady 2-Hz beat of a metronome began 45 seconds before injection of the isotope and continued for the duration of the scan. For the resting scans, the subject lay quietly and listened to the sound of the metronome. For the movement scans, the subject performed 1-Hz flexion-extension movements of the right elbow, making alternate movements with each beat of the metronome. The tasks were performed in the same order by all subjects, alternating resting and movement. In the first four scans, a pneumatic tourniquet, placed below the subject's right elbow, was not inflated. Just after the fourth scan ended, the tourniquet was inflated to a pressure 25 to 30% higher than the subject's systolic blood pressure and maintained for the rest of the experiment. Testing for forelimb anesthesia (pinprick on the right hand, light touch with a thread on the right hand, and sense of position of the distal interphalangeal joint of the right index finger) was performed just before the start of the fifth scan and after the fifth to tenth scans. At each examination, subjects performed spontaneous sequential opponent finger and wrist movements of the right hand. No attempt was made to control the content of the subject's thought.

Data analysis was performed with SPM software (MRC Cyclotron Unit, United Kingdom) in PROMATLAB (Mathworks, Natick, MA) using ANALYZE image display software (BRU, Mayo Foundation, Rochester, MN). The data from each subject were standardized for brain size and shape and reconstructed parallel to the intercommissural line [9–11]. Each image was smoothed to account for the variation in normal gyral anatomy, using a gaussian filter (FWHM$_{\text{x}}$ x FWHM$_{\text{y}}$ x FWHM$_{\text{z}}$ = 10 x 10 x 6 mm). In the standard space, each voxel was 2 x 2 x 4 mm. The effect of global differences in rCBF between scans was removed by analysis of covariance (ANCOVA) [12].

Planned linear comparisons of the adjusted mean images followed (Table 1). All image analyses were performed on a pixel-by-pixel basis. Maps of mean rCBF were derived for each of four conditions: resting without anesthesia (scans 1 and 3), movements without anesthesia (scans 2 and 4), resting with anesthesia (scans 7 and 9), and movement with anesthesia (scans 8 and 10). Anesthesia was confirmed in all subjects for scans 7 to 10. Scans 5 and 6 were excluded from analysis, because anesthesia was not confirmed. The t test was used to compare the difference in mean rCBF, on a pixel-by-pixel basis, pooling the subjects and conditions and adjusting by ANCOVA. The value of t for each pixel in each comparison was then transformed to a normal standard distribution (z values), independent of the degree of freedom of the error. The resulting set of z values constituted a statistical parametric map, as in the report from Friston and coauthors [11].

To identify the cortical area representing the elbow movement, linear comparisons were performed using scans 1 to 4 and scans 7 to 10 (see Table 1). Significance was defined as $p < 0.05$.

Effect of movement on rCBF without anesthesia (M1 + M2) = (R1 + R2).

Effect of movement on rCBF with anesthesia (AM1 + AM2) = (AR1 + AR2).

Effect of anesthesia on rCBF at rest (AR1 + AR2) = (R1 + R2).

Effect of anesthesia on rCBF with movement (AM1 + AM2) = (M1 + M2).

Effect of movement on rCBF without anesthesia (AM1 + AM2) = (AR1 + AR2).

Effect of movement on rCBF with anesthesia (R1 + M1) = (AR1 + AM1).

Table 1. Layout of Comparisons

<table>
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<tr>
<th>Condition</th>
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| rCBF = regional cerebral blood flow; $\Delta$CBF = change in cerebral blood flow; M = movement without anesthesia; R = rest without anesthesia; AR = rest with anesthesia; AM = movement with anesthesia.

To identify the transient deafferentation effect on rCBF at rest and with movement, and on change in CBF ($\Delta$CBF) due to movement, the significance was assessed within the search volume that showed activation by the elbow movement without anesthesia. An increase in rCBF at rest and with movement, as well as an increase or decrease in $\Delta$CBF due to movement, was assessed with linear comparisons, as defined in Table 1. The local maximal foci within the search volume were then identified. This procedure sought to describe the effect of deafferentation of the forearm on the brain areas that are normally associated with elbow movement. The z value at each local maximal point was reported. In addition, a three-dimensional Bonferroni-type correction was performed within the search volume, using the methodology of Worsley and coworkers [13], but pooling the variance across conditions for each voxel, as reported by Friston and coauthors [11]. The probability of a false-positive at least as large as z in the statistical parametric map was calculated by using the concept of RESELS, or resolution elements (R), where the number of RESELS is given by

$$R = V/(\text{FWHM}_x \times \text{FWHM}_y \times \text{FWHM}_z)$$
which is the search volume \( V \) divided by the product of FWHMs, in the following equation:

\[
p = R(4\log2)^{3/2}(2\pi)^{-1.5}(t^2 - 1)\exp[-0.5t^2]
\]

where \( R > 30, p < 0.1 \). Here, the volume searched \( V \) was the brain region that showed significant activation by the elbow movement before the anesthesia (1,622 voxels = 25,952 mm³) and FWHM, × FWHM, × FWHM, = 600 mm³, making \( R = 43 \). For \( R = 43 \), one-sided \( p < 0.05 \) (after the three-dimensional Bonferroni-type correction) corresponds to \( z > 3.80 \). The adjusted \( p \) values using this formula were reported. Values represented as rCBF refer to values of local maxima under rest or movement conditions. Values represented as ΔCBF refer to changes between rest and movement conditions.

In the same way, within the search volume that showed activation by the elbow movement with anesthesia, ΔCBF was assessed to determine any areas that were newly activated by the anesthesia or areas in which activation was accentuated by the anesthesia. The search volume was not larger than that without anesthesia; hence, \( z > 3.80 \) was used to identify regions.

The experimental order (or replication) effect was also analyzed, using the one degree of freedom contrast of Table 1.

### Results

#### Cortical Areas Representing Elbow Movement Without Deafferentation

Flexion-extension movements of the right elbow caused a significant ΔCBF at several sites in the brain. The main changes were seen in the SM1 bilaterally, supplementary motor area (SMA) bilaterally, ipsilateral cerebellum, contralateral insula, contralateral putamen, contralateral anterior cingulate gyrus, and contralateral posterior parietal area (Table 2, Fig. top). The contralateral SM1 had a local maximal focus of \(-24, -26, 56\) (Talairach’s coordinates) with a significant (23.6%) ΔCBF. The adjacent areas, including the premotor and sensory association areas, were also activated. The activated focus in the ipsilateral SM1 (22, -24, 56), which was less activated (7.5%) than the contralateral one, was symmetrical in location. The SMA was significantly activated mainly on the contralateral side and posterior to the vertical projection of the anterior commissural line. The cerebellar vermis and ipsilateral cerebellar hemisphere were also activated.

### Table 2. Areas of the Brain Activated by Movement of the Right Elbow Without Ischemic Anesthesia of the Right Forearm

| Brain Area                     | Talairach’s Coordinates | z Score of Peak Activation \( \Delta \) | Increase in rCBF (%)
|-------------------------------|--------------------------|-----------------------------------------|------------------------
| SM1/premotor, left            | -24, -26, 56            | 9.31                                    | 23.6                   |
| Cerebellar vermis, right      | 8, -58, -12             | 6.81                                    | 15.5                   |
| SMA, mainly left              | -6, -6, 52              | 6.35                                    | 15.1                   |
| Superior parietal lobule, left| -26, -40, 44            | 6.27                                    | 13.4                   |
| Paracentral lobule, left      | -2, -20, 52             | 5.41                                    | 11.7                   |
| Insula, left                  | -36, -34, 20            | 5.41                                    | 11.9                   |
| Paracentral lobule, left      | -6, -26, 48             | 5.34                                    | 11.9                   |
| Putamen, left                 | -26, -8, 4              | 5.10                                    | 11.1                   |
| Cingulate, left               | -8, -2, 36              | 4.65                                    | 11.8                   |
| SM1, right                    | 22, -24, 56             | 4.36                                    | 7.5                    |
| Cerebellar hemisphere, right  | 24, -58, -20            | 4.31                                    | 8.3                    |

*Significance is defined as \( p < 0.05 \) (ANOVA with two-dimensional Bonferroni-type adjustment).

rCBF = regional cerebral blood flow; SMA = supplementary motor area; SM1 = primary sensorimotor area.
Effects of the Ischemic Block

Within the motor areas correlating with elbow movements before anesthesia, transient deafferentation of the right forearm caused some change in rCBF (Table 3; Fig, bottom). There was an increase of the rCBF level during rest \( (z = 4.68, p < 0.005) \), but not with movement, in the contralateral SM1 \((-36, -26, 52)\), indicating a reduction in ΔCBF. The ipsilateral SM1 \((20, -26, 56)\) showed the same tendency (see Table 3). In the SMA, anesthesia did not induce any change in rCBF at rest, but there was a decline with movement \( (z = -4.27, p < 0.02) \), indicating a tendency for an anesthesia-induced decline of ΔCBF in the contralateral SMA \((-8, -4, 52)\) \( (z = -4.0, p = 0.056) \). The contralateral anterior insula \((-34, -8, 20)\), where no significant activation occurred before the anesthesia, showed a 10.2% increase in rCBF with anesthesia, which did not reach the predetermined threshold \( (z = 3.34) \).

The overall order effect was not significant, except for the ipsilateral SM1, wherein the second trial rCBF was higher than the first by an average of 1.24 ml/min/100 ml.

Discussion

In this study, there was a confounding of the effect of the anesthesia and the order of the experiments. All the measurements without anesthesia were made first to avoid the prolonged effect of posts ischemic paresthesia. A shorter time effect, studied by comparing the same task repeated twice, was not significant, except for the ipsilateral SM1, where a slight increase of rCBF \( (1.24 \text{ ml/min/100 ml}) \) was observed in the second trial. However, this does not affect the conclusions.

The areas of the brain activated with elbow movement are all well-established parts of the motor system. In the cerebral hemisphere contralateral to the elbow movement, activation occurred in a large area centered on the SM1, the coordinates of which are consistent with the somatotopy previously reported \([14-16]\). Because of the limited spatial resolution of PET, a large area of activation centered on the SM1 could be explained by a large increase of rCBF confined to the primary motor area, involvement of a larger area, or both. As primary motor cortex has strong connections with both premotor cortex and somatosensory cortex \([17-20]\), these areas might be coactivated with elbow movement. In normal subjects, activation of ipsilateral SM1 has been observed with sequential finger movements \([21, 22]\), visually guided tracking with the index finger \([23]\), and shoulder movements \([14]\). Shibasaki and colleagues \([21]\) reported that complex sequential finger movements caused larger activation of ipsilateral SM1 than did simple, repetitive opponent finger movements. Colebatch and coworkers \([14]\) observed that the increase of rCBF in the ipsilateral sensorimotor cortex with proximal (shoulder) movement was significantly larger than that with more distal (hand) movements. The descending corticospinal fibers terminating ipsilaterally distribute preferentially to motor neurons of axial and proximal limb muscles \([24]\). These findings suggest that complex or proximal movements are more likely to recruit the ipsilateral SM1. The SMA, putamen, and anterior cingulate gyrus are important members of the parallel segregated circuits linking basal ganglia and cortex \([25]\).

Change of rCBF in the SM1 with ischemic block is of particular interest, because electrophysiological studies suggest that deafferentation might contribute to modulation of primary motor cortex. Using TMS, Brasil-Neto and associates \([6, 26]\) observed the rapid and reversible modulation of human primary motor cortex by temporary deafferentation. The excitability of muscles immediately proximal to ischemic anesthesia of the forearm increased rapidly. This change took place without a change in excitability at the spinal seg-
mental level. The amplitude of MEPs to TMS, but not to transcranial electrical stimulation, was larger during ischemic deafferentation of the limb. These findings imply a change in the excitability of the intracortical network, because TMS stimulates the neurons mostly presynaptically, whereas electrical stimulation acts predominantly on the axons of corticospinal motorneurons [27, 28]. These findings are compatible with the present results, since the increase of CBF at rest can be interpreted as sensory deprivation increasing synaptic activity of the intracortical network of SM1 at rest.

Modulation of the motor cortex may result from either establishment of new connections (sprouting) or unmasking of existing connections (disinhibition) [29]. Several experimental results favor disinhibition of the cortical areas, as caused by sensory deprivation. The excitability of the motor cortex by transient deafferentation increases within several minutes of the deafferentation [6]. The speed of the change strongly supports disinhibition as the underlying mechanism. Cues for primary motor cortical reorganization after motor nerve injury may be withdrawal of a sensory input to primary motor area output cells [1]. In the rat, modulation of the cortical motor map by a peripheral nerve lesion was similar to adjustments produced by regional administration of a gamma-aminobutyric acid (GABA) antagonist, which was interpreted to mean that preexisting lateral excitatory connections were unmasked by decreased intracortical inhibition [30].

In our study, there were no significant increases of the rCBF level with movement, with or without deafferentation, in the SM1 bilaterally. This finding suggests that the amount of neuronal activity necessary to produce a movement is constant regardless of the resting condition, which is consistent with the observation of motor cortical output modulation before and after peripheral deafferentation [31]. They observed that with slight voluntary contraction of target muscles proximal to the deafferented portion, the amplitudes of responses to TMS stimulation of the primary motor area in the affected limbs were similar to control values. In the relaxed state, however, the electromyographic (EMG) response increased in comparison with the pre-deafferentation states, as also found by Brasil-Neto and coworkers [6]. These observations could be explained as deafferentation-induced disinhibition through a reduction in GABAergic activity, making cells in the primary motor cortex more excitable. To make a movement, it is easier to activate cells, and hence, less excitatory synaptic drive is needed. The excitability level of cells needs to be controlled precisely in order to make a specific voluntary movement; hence, with anesthesia, there is no change in the response to TMS with contraction or in rCBF levels with movement.

In this experiment, the effect of the discomfort associated with ischemic block could not be completely eliminated. After the procedure, when the subjects were asked about anesthesia-induced discomfort, 3 of the 7 mentioned a dull sensation in the right forearm during the last PET scan. However, it is unlikely that it affected our results or their interpretation. If increased CBF in the primary somatosensory area (S1) due to painful input were a cause of the increased rCBF in the SM1 during ischemic block of the forearm, the rCBF with movement also would have changed with ischemia. Because of the relatively poor resolution of PET, the rCBF value is the mean of the value for the primary motor area and S1. If the increased CBF in the S1 caused the significant increase of the mean rCBF at rest, it is expected to affect the rCBF with movement to the same extent, assuming that the rCBF increase due to pain is constant at rest and with movement. In addition, the pattern differs. Painful heat caused significant activation of the anterior cingulate, S1, and secondary somatosensory area (S2) confined to the side contralateral to the stimulus [32]. Compared with no painful heat stimuli, painful heat elicited highly significant increases in blood flow in the contralateral cingulate cortex, thalamus, and lenticular nucleus [33]. Anesthesia induced bilateral changes in SM1, and did not cause changes in areas responsive to pain. Another concern is attentional modulation of rCBF due to pain. In human SM1, the CBF response to vibrotactile stimulation of the fingers was 13% higher when the subjects attended to the stimulus than when they were simultaneously engaged in a distraction task [34], but in our patients, such an increase is unlikely because the changes were bilateral.

The increase of the rCBF level at rest, observed in the ipsilateral SM1, suggests that an increase of excitability at rest may be transferred interhemispherically, although its route (whether transcallosal or subcortical) is not known. In the flying fox, homotopic regions of SM1 are linked such that plasticity induced in one hemisphere is immediately mirrored in the other hemisphere [35].

Increased activity in the SMA is associated with the initiation of movement, motor programming [36], motor planning [22, 23, 37], readiness to move [38], motor learning [39–41], complexity of movement [21], and responsiveness to internal cueing of movements [42], or to the selection of movement [43]. Activation of the SMA by the elbow movement without anesthesia in this study is consistent in location with that observed by Colebatch and associates [14]. Reduction of activation after transient nerve block suggests that the activation may be peripherally generated (i.e., a consequence of movement) and might not be related to motor planning or readiness. This view is supported by an electrical source analysis of the movement-related cortical potentials during stereotyped unilateral hand
movements, which implied that the SMA had significant activity immediately after movement [44]. The SMA is known to have dense input from the S1 and S2 [45]. Previous PET studies [34, 46] showed significant activation of the SMA induced by cutaneous vibratory stimulation. A reciprocal relationship between SMA and SM1 has been found [47]. These findings suggest that the SMA may play a role in the processing of feedback information.

The contralateral anterior insula was activated with elbow movement after, but not before, anesthesia. The insular cortex is known to have dense input from primary and somatosensory association areas, as well as the premotor area, and may be involved in somatosensory-skeletonmotor functions [48]. Abnormally high activation of the anterior insula in 7 of 8 patients with capsular infarction was reported [49]. These findings suggest the anterior insula is an accessory motor area that can be called into play in special circumstances.

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