Altered Hemodynamic Responses in Patients After Subcortical Stroke Measured by Functional MRI

R. Pineiro, MD; S. Pendlebury, MRCP; H. Johansen-Berg, MSc; P.M. Matthews, FRCP

Background and Purpose—Blood oxygenation level–dependent (BOLD) functional MRI (fMRI) is a promising method for defining brain recovery after stroke quantitatively. Applications thus far have assumed that the BOLD hemodynamic response in patients after stroke is identical to that in healthy controls. However, because of local vascular compromise or more diffuse vascular disease predisposing to infarction, this assumption may not be justified after stroke. We sought to test whether patients who have suffered a lacunar stroke show BOLD fMRI response characteristics identical to those of healthy controls.

Methods—We measured the BOLD fMRI signal time course in the sensorimotor cortex contralateral to the affected hand with finger- or hand-tapping tasks for minimally or mildly impaired right-handed patients (n = 12) after lacunar strokes causing limb weakness and for healthy controls (n = 20).

Results—With a right-handed sequential finger-tapping task, the rate of rise and maximum increase of the BOLD signal in the contralateral sensorimotor cortex were >30% lower (P = 0.01) in the stroke patients. Similar relative decreases were found for the same task performed with the left hand. These changes were found in patients both in the hemisphere affected by stroke and in the unaffected hemisphere, suggesting that the BOLD fMRI time course differences observed arise from a diffuse functional pathology. The difference between patients and controls is not a result of age alone, since differences were not found between the younger (n = 10; aged 22 to 38 years) and the older (n = 10; aged 56 to 83 years) healthy controls. The effect also does not seem to be dependent on the specific hand movement task used.

Conclusions—The magnitude of the BOLD fMRI response can be reduced in stroke patients even if infarcts do not involve the cortex. This may be a consequence of the stroke, but the observation that the BOLD signal time course is similar in the affected and unaffected hemispheres suggests that it also could result from preexisting pathophysiological changes in the cerebral microvasculature. (Stroke. 2002;33:103-109.)

Key Words: hemodynamics ■ ischemia ■ magnetic resonance imaging, functional ■ motor cortex ■ rehabilitation ■ stroke

Lacunar infarcts or diffuse ischemic changes in periventricular white matter are believed to result primarily from small-vessel disease.1 Risk factors for such strokes include smoking, age, hypertension, and diabetes mellitus. The latter in particular are associated with fibrohyaline deposition with concentric thickening of the walls of small penetrating arteries and arterioles.2 These structural changes may alter functional properties of the microvasculature.

Blood oxygenation level–dependent (BOLD) functional MRI (fMRI) is based on the measurement of signal intensity changes arising in response to locally increased demands for tissue perfusion with brain activation. Particularly at higher magnetic field strengths, this response is believed to reflect primarily microvascular responses to neuronal activity.3 The technique offers a promising approach for defining functionally intact tissue and patterns of brain reorganization after stroke.4–6

Thus far, interpretations of activation differences between stroke patients and healthy controls have assumed that the 2 groups have similar hemodynamic responses. However, Doppler studies of brain perfusion in patients after lacunar stroke or with chronic hypertension or diabetes have demonstrated a reduction in perfusion reserve,7,8 suggesting that changes in microvascular reactivity accompany these chronic conditions common in stroke patients. The ratio of cerebral blood flow to blood volume also changes with ischemia,9 and models predict that alteration of the relative tissue blood volume also should alter the BOLD response, which depends on activation-associated changes in blood oxygenation, flow, and volume.10

In this study we tested directly whether the BOLD fMRI response is identical in stroke patients and healthy controls. We chose to study fully recovered or only mildly hemiparetic patients without sensory impairments to allow good matching.
of performance between the 2 groups. Only patients with subcortical ischemic strokes were studied in an effort to avoid the potential confounding effects of cortical perfusion deficits around infarcts. The potential effects of age and task complexity in determining the BOLD response differences between patients and controls were investigated specifically.

Subjects and Methods

Patients

Twelve right-handed patients (median age, 67 years; range, 42 to 76 years) (Table 1) were recruited from outpatient clinics after a first ischemic stroke resulting in a pure motor deficit. Eight of 12 patients had a history of hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg), and 6 of 12 had a history of smoking in addition to age as a risk factor for stroke. None of the patients had significant (≥70% stenosis) carotid atherosclerotic disease defined by duplex Doppler ultrasonography or clinical evidence of cardioembolic disease. Patients with a cortical infarction apparent on clinical imaging, hemorrhagic stroke, primarily sensory or ataxic symptoms or signs, other coexistent neurological disease or cognitive impairment (as assessed by medical history or Mini-Mental State Examination), or contraindications to MRI were excluded. Healthy younger (n = 10; median age, 27 years; range, 22 to 38 years) or older (n = 10; median age, 67 years; range, 56 to 83 years) control volunteers without histories of stroke or other neurological disease, hypertension, diabetes, cardiac disease, or smoking were recruited. Ethical approval was obtained from the Central Oxford Ethics Committee, and informed consent was obtained for all studies.

Functional Assessment

Functional assessments, including a neurological examination using the Motricity Index and determination of maximum finger-tapping rate, were performed on the day of the fMRI scan. The maximum tapping rate was performed with all 4 fingers moving together with flexion at the metacarpal-phalangeal joints. The patient-reported tapping rate was performed with all 4 fingers moving together with limited movement above the base after being positioned in the magnet. The sequential finger-tapping task involved lifting each finger from the surface serially, starting with the second digit and ascending to the fifth digit, when the sequence was reversed until the second digit was reached again, and the process was recommenced. The task was cued visually at a fixed rate of 1 Hz with a schematic representation of the hand viewed on a projection screen that could be seen with prism glasses at the end of the magnet bore. This task was performed once with the right hand for the younger healthy controls and with both hands for the older healthy controls and for the stroke patients.

The second task involved grouped 4-finger tapping: the 4 fingers were raised and lowered together alternately with the arm and palm of the hand resting on the scanner bed. Note that this involved finger movements identical to those of the sequential task and was different only in that the fingers were moved together rather than separately. Subjects wore a commercially available wrist splint to limit movement to the metacarpal-phalangeal joint when performing this task. The task was cued visually at 75% of the maximum rate for each individual. This task was performed with each hand by the older healthy controls and the stroke patients. The mean maximum control rate was 4 Hz. Stroke patients showed a mean 22% reduction in maximum rate (range, 10% to 33%).

The paradigms were organized in an ABAB pattern, where A = rest and B = movement, with each block lasting 30 seconds. There were a total of 6 rest and movement cycles in each task. Before subjects entered the magnet, they were shown the visual cues and trained to perform the task in time with the cue. Hand movements were monitored visually by the experimenter during the task to ensure that only the hand being tested moved. Mirror or other extraneous movements were observed neither in test trials outside of the magnet nor during the imaging examinations.

MRI and fMRI Data Acquisition

Data were acquired with a Siemens/Varian 3-T MRI scanner with a custom-made head radiofrequency transmitter-receiver coil (E. Barberi, University of Western Ontario). Multishot echo-planar images were obtained continuously in a transverse orientation with the use of the following acquisition parameters: repetition time (TR) = 3.0 seconds; echo time (TE) = 30 ms; 6-mm slice thickness; 21 slices; field of view = 256 × 256 mm; 64 × 64 matrix. A T1-weighted (turbo fast low-angle shot [FLASH] inversion recovery sequence; TR = 15 ms; TE = 5 ms; TI = 500 ms; flip angle = 15°; 3-mm slice thickness; field of view = 256 × 256 mm; 256 × 256 matrix) structural scan was

<table>
<thead>
<tr>
<th>Patient</th>
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<th>Sex</th>
<th>Time to Scan, d</th>
<th>Affected Side</th>
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<td>12</td>
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<td>F</td>
<td>300</td>
<td>L</td>
<td>76</td>
<td>Internal capsule</td>
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</table>

Mean 64.4
SD 10.3

*Graded from 0 (no movement) to 100 (normal movement).
†Localization inferred from clinical presentation in the absence of a demonstrable lesion on MRI.
acquired for anatomic registration of the functional image. A T2-weighted (spin-echo; TR=2.5 seconds; TE=70 ms; flip angle=90°; 5-mm slice thickness; field of view=256×200 mm; 256×256 matrix) image was acquired for better definition of the subcortical pathology.

Image Processing and Analysis

Image processing and statistical analysis were performed with the use of MEDx version 3.0 (Sensor Systems, Inc). Correction (Automated Image Registration [AIR], developed by Dr R. Woods, University of California at Los Angeles) of images for small amounts of head movement and smoothing of signal changes for optimum signal-to-noise ratio (Gaussian smoothing with full width at half maximum=5 mm) were performed before statistical analysis. The MEDx software was modified in-house (courtesy of S. Smith, D. Flitney, and M. Jenkinson) for automation of sequential steps and to allow temporal filtering (matched bandpass filter with σ=2.8 seconds and high-pass frequency cutoff set to 4 times the task block length). Maps expressing relative activation were calculated as a Z score of relative signal change in active versus rest blocks of a trial with the use of an unpaired Student’s t test. Cluster detection was performed on all voxels above Z=2.3 to determine those significantly activated (P<0.01). This method relies on information concerning signal intensity changes both in the voxel of interest and in adjacent voxels to determine the significance of changes, with correction for multiple comparisons as well.14 The cluster detection output was used to mask the original Z score image, and the result was registered with the structural image with the use of FLIRT (www.fmrib.ox.ac.uk/fsl), a locally developed linear registration tool (12-parameter fit). To determine cluster localization in a standard brain “space” in which relative distances are normalized to a common brain map (allowing direct comparisons between brains of different sizes and shapes), FLIRT was used to register the functional image with the structural image and the structural image with the Montreal Neurological Institute 305 brain.15 The combined transforms (IMRI—structural, structural→305 brain) were used to register the individual functional images in the standard space. A random effects model was used for analysis of group data.16

Geometric centers of activation for activation clusters are reported as coordinates in the Montreal Neurological Institute 305 brain space (x, y, and z). Clusters were defined neuroanatomically in the group analysis relative to a standard atlas.17 Activation clusters for individual brains then were defined neuroanatomically with respect to the group activation clusters. The sensorimotor cortex activation cluster typically included confluent activation of voxels within the posterior superior frontal (premotor, Brodmann’s area 6), precentral (primary motor, Brodmann’s area 4), and postcentral (primary sensory, Brodmann’s areas 1, 2, and 3) gyri. No attempt was made to neuroanatomically segment this cluster into separate functional subregions because any subsequent measurement of geometric centers for segmented subregions of interest would be determined as much by the assumptions used for the segmentation as by the pattern of activation. Specifically, we did not attempt to distinguish the premotor from the primary sensorimotor cortex because there is overlap between the 2 areas.18

The analysis of the activation time course reported here is only for the contralateral sensorimotor cortex because this region showed the largest activation intensity changes for both patients and healthy controls (see below). The mean time course of the signal intensity change for voxels in the contralateral sensorimotor cortex activation cluster was defined and normalized to a common signal intensity baseline (after a linear correction for signal drift through the experiment). Each trial had 6 cycles of rest alternating with hand movement. An average time course for a single movement/rest task cycle was generated from the second through sixth cycles in each task. The first cycle in each task was discarded to ensure that blocks were comparable, reducing interference from any potential novelty effects introduced by data from the first block. The maximum signal change in the averaged time course was defined as the excursion from the baseline at the time of the movement cue to the maximum value during the movement period. The rate of signal intensity change was taken as the (signal change at the first major point of inflection in the time course after movement starts)/(time from the movement cue).

Comparisons of results (eg, signal intensity change or rate of signal intensity change) between patient and control groups were performed with the use of a Wilcoxon signed rank test in SPSS version 9, with a significance level of P<0.05. Results are reported as mean±1 SD.

Results

BOLD fMRI Activation With Sequential Finger Tapping for Stroke Patients and Healthy Controls

BOLD fMRI was used to map brain activation patterns associated with sequential finger tapping in right-handed healthy control subjects (n=20) and patients (n=12) who had suffered from subcortical, lacunar strokes causing minimal or mild hemiparesis (5 with weakness on the right and 7 on the left) (Table 1). Although the time after stroke was variable, all of the patients had only 1 hand affected and had shown good recovery (patient 6 presented with only mild weakness lasting for 24 hours and had recovered clinically normal limb function by the time of examination). All patients could perform the required hand movements and were able to continue hand movements for the full period of each of the task blocks in the fMRI paradigms without additional movements in other limbs.

Consistent with previous reports,4–6 there were similar patterns of BOLD fMRI brain activation for the healthy controls and the patients (Figure 1). Random effects analysis of patterns of activation common to each group showed that the contralateral sensorimotor cortex and the supplementary motor area were the 2 most significantly activated regions for both groups (Table 2). Cerebellar activation also was observed. In images with identical thresholds, there was a
5.2-fold greater volume of activation in the contralateral sensorimotor cortex for controls relative to patients. This suggested a lower magnitude of BOLD response for the patients relative to controls, despite absence of direct cortical involvement by the infarcts or substantial impairment of performance. To test this hypothesis directly, we characterized the BOLD fMRI signal response in the contralateral sensorimotor cortex for each individual subject from the 2 groups.

**Rate of Rise and Maximum Signal Intensity Changes for BOLD fMRI Response Reduced in Patients Relative to Controls**

The time courses for signal intensity changes between active and rest blocks for significantly activated voxels in the contralateral sensorimotor cortex were measured for patients and controls (Figure 2). The minimum resolution in the time course was 3 seconds, the time required for acquisition of the whole-brain multislice data set. After initiation of movement, there was an increase in the signal intensity over 12 to 15 seconds to maximum level, which then did not change significantly over the period of movement. The signal intensity decreased to baseline within approximately 12 seconds after cessation of movement. There was a trend for a small "undershoot" of the signal intensity soon after movement cessation, as previously described.19

For the healthy control subjects, the BOLD response signal intensity time course was similar regardless of the hand moved. The maximum signal changes with movements of the right and left hands were identical (right, 1.79±0.45%; left, 1.79±0.42%), and there was no significant difference between the rate of rise of the motor signal response with dominant hand movements was a mean of 36% slower in the patients (P=0.01). The maximum increase in signal response also was a mean of 32% lower in the patient group than in the normal controls (P≤0.001).

**Figure 2.** Time course for signal intensity change in healthy controls (◊) and patients (●) for the sequential finger-tapping task. The time course starts with the stimulus for movement. Patients show a significantly slower rate of rise and maximum signal intensity change relative to the controls. Values are mean with 1 SD.

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<tbody>
<tr>
<td>CMC</td>
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<td>−26±6</td>
<td>54±5</td>
<td>−29±7</td>
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<tr>
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<td>−21±7</td>
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<tr>
<td>SMA</td>
<td>−2±4</td>
<td>−11±2</td>
<td>51±4</td>
<td>−1±3</td>
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</table>

CMC indicates primary sensorimotor cortex; IMC, ipsilateral primary sensorimotor cortex; and SMA, supplementary motor area. Each point in the standard brain space is defined by a coordinate (x, y, z). In a comparable set of brains, corresponding anatomic structures therefore share similar coordinates.
Thus were asked to perform a simple hand-tapping task at 75% of their individual maximum rates. The same regions of brain showed significant activation with hand tapping as with sequential finger movements (data not shown). With this task the control group showed similar rates of signal increase and maximum signal change relative to those found with the sequential finger-tapping task (Table 3). The stroke patients again showed a lower maximum signal intensity change than the controls ($P=0.007$ for data from movements of either hand). With right-hand movements, the maximum signal intensity change was 14% lower ($P=0.05$). For left-hand tapping, the maximum signal intensity change was 25% lower ($P=0.05$). Similar relative decreases were observed for the affected and unaffected hands. In this task the absolute rate of hand tapping individually varied between subjects, but there was no correlation found between individual rates of hand tapping and BOLD signal intensity changes (data not shown).

### Discussion

We have characterized the BOLD fMRI response quantitatively in patients with minimal or mild motor impairments from lacunar strokes and found that the rate of signal increase and the maximum signal magnitude were reduced. This was found even with movement of the unimpaired hand, for which

<table>
<thead>
<tr>
<th>TABLE 4. Maximum BOLD fMRI Signal Intensity Increases and Rates of Increase in the Contralateral Primary Sensorimotor Cortex for Healthy Controls in the Older and Younger Subgroups for the Sequential Finger-Tapping Task</th>
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<tr>
<td>Maximum signal intensity change</td>
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<td>Right hand</td>
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<td>Left hand</td>
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<td>Rate of signal intensity change</td>
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<tr>
<td>Right hand</td>
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<td>Left hand</td>
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There were similar findings for the patients when they made nondominant (left) hand movements.

**BOLD Signal Time Course for Activation in Contralateral Sensorimotor Cortex Similar in Affected and Unaffected Hemispheres of Stroke Patients**

The time course for the BOLD signal change in the contralateral sensorimotor cortex on the side of the stroke was contrasted with that from the unaffected hemisphere for the patients. Surprisingly, no differences were found between mean changes in the hemisphere affected by the stroke relative to the contralateral, unaffected hemisphere for either the maximum rate of rise or the maximum signal intensity change (Table 3). Both the rates of signal intensity increases and the maximum signal intensity increases were reduced for both affected and unaffected hand movements relative to healthy controls ($P=0.05$).

### Differences in BOLD fMRI Time Course for Contralateral Sensorimotor Cortex Activation Are Not Age Dependent

To test whether the differences between the patient and control groups could be due solely to differences in age, BOLD responses from the older and younger control subjects were contrasted. The BOLD signal time courses for activation in the contralateral sensorimotor cortex for these 2 groups then were compared. Identical rates of increase and maximum signal change in the contralateral sensorimotor cortex were found (Table 4).

**Differences in BOLD fMRI Time Course for Contralateral Sensorimotor Cortex Activation Between Healthy Controls and Stroke Patients Also Found With Simpler Hand Movement**

We reasoned that if the aforementioned differences arise from fundamental physiological differences in microvascular physiology, then they also should be able to be defined with another movement task. Six patients and the older controls
performance was indistinguishable from that of the control group. There thus is a need for some caution in making quantitative interpretations of fMRI activation changes in terms of the underlying neuronal activity for patients with vascular disease relative to healthy controls.

The hemodynamic response is a consequence of increased synaptic activity.\(^{20,21}\) The BOLD response includes contributions from multiple factors, including increased blood flow and an increase in blood volume in cortical tissue in addition to effects of an increase in the proportion of oxygenated relative to deoxygenated hemoglobin.\(^{10,22}\) However, the effect generally is thought to be dominated by the increase in oxygenated relative to deoxygenated blood. This is determined both by the extent of the local increase in blood flow after brain activation and the magnitude of the increase in the cerebral metabolic rate for oxygen consumption (CMRO\(_2\)).\(^{10}\) In our study the patients and controls showed identical behavioral performance (in the sequential finger-tapping task), and there is no evidence for a hypermetabolic state with increased CMRO\(_2\) in patients after ischemic stroke (in fact, more typically there are decreases).\(^{23,24}\) Differences in cerebral blood volume changes also could lead to differences in BOLD response,\(^{10}\) but such changes are not expected to be generalized in patients with focal infarcts.\(^9\) Our observation of a decreased BOLD signal increase after activation with sequential finger movements (and a similar trend with the easier hand-tapping task) therefore suggests that there is a smaller increase in local tissue perfusion associated with increased synaptic activity in the patients than in healthy controls, both in the hemisphere affected and in the hemisphere unaffected by subcortical stroke.

BOLD fMRI therefore may be sensitive to physiological changes associated with subcortical ischemic disease. If this conclusion is confirmed, then quantitative BOLD fMRI could provide an index of local microvascular coupling that is complementary to that from large-vessel studies by methods such as transcranial Doppler sonography.

A number of specific changes may be responsible for the apparent changes in neurovascular coupling reported here. The patients in the present study all had lacunar strokes and risk factors for pathological narrowing of small vessels of the brain, including age and hypertension.\(^{25}\) With aging and hypertension arterioles also become more tortuous, which generates turbulence and further resistance to changes in flow.\(^{26}\) In addition, chronic hypertension can lead to impairment of release of nitric oxide, a candidate molecule for coupling of neuronal activation to the hemodynamic response.\(^{27-29}\) Some patients were smokers, and smoking can alter cerebral blood flow.\(^{30}\) The patients were on different medications (angiotensin-converting enzyme inhibitors, \(\beta\)-blockers, diuretics) for hypertension, but in separate experiments we have found that the BOLD response (measured with either photic or auditory stimulation) appears unaffected by these standard treatments in elderly hypertensive patients (S. Saini, MSc, et al, unpublished data, 2001).

Previous data are consistent with the notion that there may be diffuse changes in vascular coupling to neuronal activity or cerebrovascular reserve even in cortical regions distant from the subcortical infarcts themselves. Cortical regions overlying internal capsule lesions show decreased perfusion.\(^{31}\) More diffuse changes also have been reported. For example, duplex Doppler studies, which reflect global perfusion changes in both gray and white matter, have shown decreased microvascular reactivity in patients with subcortical, white matter lesions.\(^{32}\) Patients with chronic hypertension or diabetes mellitus (another cause of microvascular pathology in the brain) show similar differences in acetazolamide- or CO\(_2\)-induced reactivity relative to healthy controls.\(^{33,34}\)

Nonetheless, interpretation of these data should be regarded as only preliminary. A primary concern for interpretation is that, because all of the patients already had suffered from ischemic stroke, it is uncertain whether the BOLD response abnormalities arise from factors contributing to the underlying susceptibility to ischemic injury or from a consequence of the injury itself. Although these results are consistent with differences in perfusion coupling to neuronal activation, direct demonstration of differences in activation-induced perfusion changes between controls and patients would be necessary to confirm this.\(^{35}\) There also was clinical heterogeneity in the patient group, particularly with regard to the timing of the ischemic event with respect to the examination. However, by ensuring that the patients were clinically stable and that all had subcortical ischemic pathology, we believe that the population is appropriately homogeneous for the most critical parameters.

One technical issue concerns the problem of matching tasks between patients and healthy controls. For the sequential finger-tapping task, the rates of performance were matched directly between patients and healthy controls, but for the hand-tapping task we chose to match movement rates relative to individual maximum rates. It strengthens our conclusion that a similar phenomenon was found in the comparisons between healthy controls and patients for both tasks. A potential concern is that increased motor task rate or complexity generally is associated with an increased volume of activation.\(^{36,37}\) We did not find a correlation between movement rate and activation response for the hand-tapping task in this investigation, but the range of variation in hand movement rates was rather small, and the differences expected from this effect would not account for the magnitude of the changes observed here.\(^{37}\)

An exciting implication of this work is that quantitative BOLD fMRI signal response measurements may be sensitive to functional microvascular pathology in the brain that is associated with stroke. Although we did not address questions of prognosis, it is possible that an index derived from the BOLD response could predict risk for stroke. On the other hand, the observation that there are only modest hemodynamic differences between patients with lacunar infarcts and healthy controls lends greater confidence to interpretations of differences in fMRI-derived activation maps in this group. It will be important to test whether there are greater changes in the BOLD response near areas of injury in patients with cortical ischemic disease.

Acknowledgments

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References

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