Primary Somatosensory Cortex Activation Is Not Altered in Patients With Ventroposterior Thalamic Lesions

A PET Study

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Background and Purpose—We know remarkably little about the mechanisms underlying cortical activation. Such mechanisms might be better understood by studying the effect of well-localized lesions on the cortical activations in simple paradigms.

Methods—We used H$_2^{15}$O and positron emission tomography to measure regional cerebral blood flow (rCBF) at rest and during hand vibration in 7 patients with unilateral thalamic lesion involving the ventroposterior (VP) somatosensory thalamic relay nuclei. We compared the results with those obtained in 6 patients with thalamic lesions sparing the VP nuclei and 6 healthy controls.

Results—The patients with VP lesions had a selective hypoperfusion at rest in the ipsilesional primary sensorimotor cortex (SM1). This hypoperfusion was significantly correlated with the degree of contralateral somatosensory deficit. This abnormality may reflect the deafferentation of SM1 from its somatosensory thalamic input. Despite this deafferentation, the ipsilesional SM1 was normally activated by the vibration of the hypesthetic hand.

Conclusions—The fact that a lesion of the somatosensory thalamic relay nuclei alters the rCBF at rest in SM1 but not its activation by hand vibration indicates that the mechanism of cortical activation is complex, even in the case of simple sensory stimulation. In addition, a dissociation may occur between obvious neurological deficits and apparently normal activation patterns, which suggests that activation studies should be interpreted cautiously in patients with focal brain lesions. (Stroke. 1999;30:2651-2658.)

Key Words: cerebral blood flow • somatosensory cortex • thalamus • tomography, emission computed • vibration
Subjects and Methods

Subjects
These studies were approved by the local Ethical Committee for Human Studies, and all subjects gave their informed consent. Handedness was assessed with the Edinburgh inventory.23

Patients
We studied 13 right-handed patients aged 25 to 83 years, with a unilateral thalamic lesion (stroke in 12 subjects and abscess in 1) demonstrated by CT scan or MRI. They were divided into 2 groups according to the presence (n=7; 62±14 years old) or absence (n=6; 46±12 years old) of a lesion of the VP nuclei of the thalamus. The existence of a lesion of the VP thalamus was supported by the following criteria: (1) a somatosensory deficit contralateral to the thalamic lesion, and (2) the reconstruction of the lesion obtained from individual MRI performed on the day of the PET examination (see below). As shown in Figure 1, the VP was involved in the lesion in all patients with a contralateral somatosensory deficit (patients 1 through 7). The 6 patients who had no somatosensory deficit but, rather, cognitive symptoms had lesions of more anteromedial parts of the thalamus that always spare the VP (Figure 2). In Tables 1 and 2, the main clinical details of all patients are indicated, including a score of somatosensory deficit that is described below.

Control Subjects
Six healthy right-handed male volunteers aged 20 to 40 years (mean±SD, 29±8 years) were studied. All had a normal clinical examination and a normal brain MRI.

Clinical Examination
On the day of the PET study, all patients had a bedside examination carried out by a single examiner (P.R.) who used a fixed protocol.17

The Canadian Neurological Scale24 score was used to measure the degree of motor deficit. In addition, we used a standardized scale to determine the degree of permanent somatosensory deficit.17 The total score ranges from 0 to 70, with increasing values indicating increasing deficit. The following somatosensory modalities were tested. (1) Discriminative touch (0–21): This included (a) measuring stereognosia (0–3), by placing 3 common objects successively in each hand of the subjects with each incorrect recognition scored as 1 point; (b) graphesthesia (0–6), for which 3 numbers were drawn on the forearm and 3 others on the thigh and each error in recognizing the number was scored as 1 point; and (c) 2-point discrimination (0–12), assessed using Weber’s compasses. Two different areas were tested for the upper limb (fingertip of the third finger and forearm) and lower limb (dorsal foot and anterior part of the thigh). The first distance at which 2 points were discriminated on at least 3 different trials was measured. This distance was then compared for each
cutaneous area tested with the measures obtained in the intact side, and a percent difference was determined as follows: \[100 \times \left(\frac{\text{impaired side}}{\text{normal side}} - 1\right)\] for each of these trials, the patients scored 1 point if the sensation was reported to be diminished compared with the contralateral (intact) side and 2 points if they did not detect the vibration. In addition, 1 point was scored if the vibrator used for the PET stimulation was felt with less intensity in the hypesthetic hand than in the normal hand and 2 points if the vibration was not perceived. The perception of passive movements was assessed by asking the patients to identify the directions of 5 up-down movements applied to the second finger and first toe. Each error was scored as 1 point. (3) Temperature (0 – 6): The thermal sense was assessed with 2 different test tubes filled with cold water (\(< 5^\circ C\)) or warm water (\(> 40^\circ C\)). The subject had to recognize the temperature (“cold” or “warm”). Three trials were performed for each limb. The score corresponds to the number of errors. (4) Pin-prick (0 –10): For each limb 5 stimulations were performed. The subject had to identify the stimulus (pin or prick). The score corresponds to the number of errors. (5) Pain (0 –4): 1 point was scored if the patient had transient pain in the hemibody contralateral to the brain lesion; 2 points if the pain was permanent; 3 if the pain increased during hand vibration; and 4 in the case of severe central pain, such as complete Déjerine-Roussy syndrome. (6) Paresthesia (0 –5): Paresthesia was scored as 1 if transient and 2 if continuous, for each limb. One point was added if paresthesia occurred to the face.

The subjects were blindfolded during all testing. Each hemibody was similarly tested, and the score is given for 1 side.

Brain Imaging Studies
These studies were performed 1 to 37 months (mean ±SD, 11 ±10 months; n = 13) after the occurrence of the lesion. This delay did not significantly differ between the groups (with somatosensory deficit, 10 ±9 months; without somatosensory deficit, 13 ±12 months).

Brain imaging studies consisted of MRI and PET images acquired on the same day for each subject. The detailed information obtained from the MRI allowed us to perform an individualized anatomic localization of brain regions for the functional PET image analysis for each subject.\textsuperscript{17,25}

Anatomic Images
MR images were obtained with a 0.5-T MR imager (MRMAX, General Electric). Each subject was positioned so that MRI axial slices were parallel to the bicommissural line (AC-PC),\textsuperscript{26} which was verified on a midsagittal image. Skin marks were applied where indicated by the MR imager positioning laser. Contiguous T1-weighted 3-mm-thick axial slices and 5-mm-thick coronal T2-weighted slices were then obtained throughout the entire brain.

Functional Images
Scanning was performed with a LETI-TTV03 tomograph (CEA), the characteristics of which have been described elsewhere.\textsuperscript{27} Briefly, this scanner collects 7 parallel transaxial planes, 9 mm thick and 12 mm apart, with a reconstructed 7-mm in-plane resolution (full width at half maximum).\textsuperscript{27} We used the skin marks drawn on the subjects’ face in the MR imager to ensure an exact repositioning of the head in the PET session. In addition, the crossed laser beams permanently attached on the PET tomograph allowed us to monitor the subjects’ head position throughout the examination. During each PET scan, the room was darkened and the only ambient noise was the cooling system. The effects of radiation attenuation by the head were corrected using a transmission scan collected during exposure to a \(^{68}\text{Ge}\)germanium source. In each condition, an rCBF study was performed with a method derived from the H\textsubscript{2}\(^{15}\text{O}\) autoradiographic method, except no arterial catheters were used.\textsuperscript{28} We injected an intravenous bolus of 3 mL of saline containing 2960 to 3700 MBq \(^{15}\text{O}\)-labeled water, and an 80-second scan was initiated when the tracer bolus entered the brain. The first frame showing the arrival of...
radioactivity in the brain was identified. From this time point the radioactive counts for the ensuing 80 seconds were summed to generate rCBF images.\textsuperscript{17,25} There was a 15-minute interval between each rCBF measurement.

\textbf{Tasks}

Three different conditions were studied: (1) rest (subjects were asked to remain in a resting awake state), (2) vibration of the right hand, and (3) vibration of the left hand. The order of conditions (2) and (3) was counterbalanced across subjects. One of the 6 controls received stimulation only on the left hand. The stimulations were performed by a single examiner using a vibrator that produces 2-mm-amplitude movements with a frequency of 130 Hz (Daito),\textsuperscript{13} and involved all the fingers. The subjects were asked not to grasp the vibrator, but instead to let the examiner maintain their fingerpads in contact with the vibrator.\textsuperscript{29} To avoid any surprised reaction to the task, subjects

\begin{table}
\centering
\caption{Patients With VP Thalamic Lesions}
\begin{tabular}{llllllllll}
\hline
\textbf{Patient} & 1 & 2 & 3 & 4 & 5 & 6 & 7 & \textbf{Mean} & (SD) \\
\hline
\textbf{Age/Sex} & 45/F & 59/M & 62/M & 78/F & 55/M & 55/M & 83/F & 62.4 & (13.5) \\
\textbf{Lesion} &  &  &  &  &  &  &  &  &  \\
\textbf{Side} & R & R & L & L & L & L & R &  &  \\
\textbf{Type} & Abcess & Hem & Hem & Hem & Hem & Lac & Lac &  &  \\
\textbf{Canadian Neurological Scale score (0–15)} & 9 & 9 & 15 & 8 & 10.5 & 15 & 10 & 10.9 & (2.9) \\
\textbf{Somatosensory Score} &  &  &  &  &  &  &  &  &  \\
\textbf{Discriminative touch (0–21)} & 10 & 18 & 6 & 13 & 5 & 5 & 19 & 10.9 & (6.0) \\
\textbf{Sensory discrimination (0–6)} & 3 & 4 & 1 & 3 & 3 & 2 & 5 & 3.0 & (1.3) \\
\textbf{Stereognosis (0–3)} & 2 & 2 & 0 & 2 & 0 & 0 & 2 & 1.1 & (1.1) \\
\textbf{2-point discrimination (0–12)} & 5 & 12 & 5 & 8 & 2 & 3 & 12 & 6.7 & (4.1) \\
\textbf{Vibration/position sense (0–24)} & 12 & 13 & 3.5 & 8 & 7 & 10 & 21 & 9.4 & (6.7) \\
\textbf{Tuning fork (0–12)} & 6 & 7 & 2 & 5 & 5 & 5 & 11 & 5.9 & (2.7) \\
\textbf{Vibrator (0–2)} & 1 & 1 & 0.5 & 1 & 1 & 1 & 1 & 0.9 & (0.2) \\
\textbf{Position sense (0–10)} & 5 & 5 & 1 & 2 & 1 & 4 & 9 & 3.9 & (2.9) \\
\textbf{Lemniscal score (0–45)} & 22 & 31 & 9.5 & 21 & 12 & 15 & 40 & 21.5 & (10.9) \\
\textbf{Temperature (0–6)} & 4 & 5 & 3 & 3 & 3 & 2 & 5 & 3.6 & (1.1) \\
\textbf{Pain (0–4)} & 6 & 7 & 5 & 4 & 7 & 3 & 8 & 5.7 & (1.8) \\
\textbf{Extralemniscal score (0–20)} & 3 & 2 & 1 & 0 & 0 & 0 & 0 & 0.9 & (1.2) \\
\textbf{Paresthesia (0–5)} & 13 & 14 & 9 & 7 & 10 & 5 & 13 & 10.1 & (3.4) \\
\textbf{Total Somatosensory Score (0–70)} & 22 & 29 & 19.5 & 22 & 21 & 54 & 32.9 & 32.9 & (13.8) \\
\hline
\end{tabular}
\end{table}

Hem indicates hemorrhage; Isch, ischemic stroke; and Lac, lacunar stroke. The Canadian Neurological Scale score\textsuperscript{24} measures the motor deficit. The somatosensory score\textsuperscript{17} is described in Subjects and Methods; increasing values indicate increasing deficit.

\begin{table}
\centering
\caption{Patients With Anteromedial Thalamic Lesions}
\begin{tabular}{llllllllll}
\hline
\textbf{Patient} & 8 & 9* & 10 & 11 & 12 & 13 & \textbf{Mean} & (SD) \\
\hline
\textbf{Age/sex} & 43/M & 25/F & 48/M & 46/M & 54/M & 59/M & 45.8 & (11.7) \\
\textbf{Lesion} &  &  &  &  &  &  &  &  \\
\textbf{Side} & L & L & L & L & R & L &  &  \\
\textbf{Type} & Hem & Lac & Isch & Lac & Hem & Isch &  &  \\
\textbf{Canadian Neurological Scale score (0–15)} & 13 & 15 & 14.5 & 15 & 13 & 15 & 14.1 & (1.0) \\
\textbf{Aphasia} & + & – & + & – & – & + &  &  \\
\textbf{Confusion} & – & – & + & + & + & – &  &  \\
\textbf{Total somatosensory score (0–70)} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & (–) \\
\hline
\end{tabular}
\end{table}

*In patient 9, the stroke was discovered on CT scan performed for hypertension and headache.
were acclimated to the vibrator before the PET session, and stimulation began 30 seconds before tracer injection.\textsuperscript{17}

**Data Analysis**

**Regions of Interests**

We focused our interest on the primary sensorimotor cortex and used an individual anatomic analysis to take into account the anatomic variability between brains of different subjects.\textsuperscript{30} PET and MRI data were transferred to a VAX computer (Digital Equipment Corporation) and the MRI-PET images put in register as described previously.\textsuperscript{17,25} Briefly, 3 digitized 3-mm-thick axial slices of the MRI were combined to obtain images with the same thickness as the PET slices (9 mm). MRI and PET were coregistered with isodensity contours and custom software allowing in-plane translation and rotation. Using this software, MRI isocountours were then superimposed on PET images in all slices. The accuracy of this registration was assessed by checking that a successful superimposition was simultaneously obtained at all brain levels. Such a simultaneous superimposition cannot be achieved if registration error exceeds 5 millimeters in any of the x, y, and z axes. This procedure was repeated for each set of rCBF images to rule out head movements between rCBF measurements.

The primary sensorimotor cortex (SM1) was a priori defined in each hemisphere for analysis. In addition, a global cortical area was defined in each hemisphere, including all cortical areas that were not analyzed for their involvement in sensorimotor function (we excluded the parietal cortex). This global cortical area (mainly temporal, frontal, and occipital cortex) was defined as a cortical ribbon having a 14-mm thickness. All regions of interest (ROIs) were drawn on individual MR images and copied onto corresponding PET images. Their boundaries were determined according to the identification of the main sulci.\textsuperscript{17,25,29,31,32}

**Data Analysis**

Since the change in local tissue radioactivity is linearly related to blood flow, relative changes in tissue activity are taken to indicate relative changes in blood flow.\textsuperscript{28} One should note, however, that the relationship between rCBF increase and neuronal activation is not necessarily linear.\textsuperscript{33} To correct for intercondition changes in the global activity of the brain, all PET images were normalized so that for each emission scan, each pixel of each slice was divided by the mean pixel value of all slices.\textsuperscript{28,34} The analysis based on individual ROIs and comparison of normalized activity values in each subject avoids any bias induced by different levels of atrophy in the 3 groups.

Our main analysis aimed at detecting abnormal somatosensory cortical activations induced by the vibration of the hand contralateral to a thalamic lesion.\textsuperscript{19} The asymmetry of the rCBF induced by hand vibration were determined for each subject by calculating the difference in the normalized activity between each somatosensory task and rest using the formula $\Delta t\%=100 \times (\text{activation} - \text{rest}) / \text{rest}$. For the 6 controls the data obtained during right and left hand vibration were considered, but 1 of the controls had a stimulation of the left hand only. The statistical significance of the activations was analyzed with a 1-sample Student's $t$ test. We then compared the activations obtained in the 3 groups of subjects (controls, patients with, and patients without VP lesions) using a 2-way ANOVA with the group as intersubject variable and the brain side (lesioned and nonlesioned for the patients and right and left for the controls) as intrasubject variable. Post hoc analysis was performed with the Fisher protected least significant difference test.

Finally, the rCBF asymmetry in the resting state determined whether some of the selected ROIs were hypoperfused in the lesioned hemisphere independent of any stimulation. This was measured by calculating for each region an asymmetry index: $A_{\text{rest}}=100 \times (\text{normal hemisphere} - \text{lesioned hemisphere}) / \text{normal hemisphere}$. In controls, the $A_{\text{rest}}$ was determined as follows: $200 \times (\text{right side} - \text{left side}) / (\text{right side} + \text{left side})$. The statistical significance of this asymmetry was analyzed with a Student $t$ test. The rest asymmetries ($A_{\text{rest}}$) in the 2 groups of patients were compared by an ANOVA with the Scheffé $S$ post hoc test. Finally, we made a correlation analysis between clinical scores and the rCBF parameters.

**Results**

**Activations Induced by Hand Vibration**

**Control Subjects**

In control subjects, hand vibration strongly and significantly ($P<0.001$, Student $t$ test) activated the contralateral SM1 when compared with rest: left SM1, +12.8 ± 4.6%; right SM1, +12.7 ± 4.0%. The asymmetry between activation obtained in left and right SM1 was 0.0 ± 4.5% (range −6.8% to +5.5%, n=5; Figure 3).

**Patients**

**Patients With VP Lesion**

The vibration of the hypesthetic hand significantly activated the contralateral SM1 (+9.2 ± 6.2%, $P<0.01$). SM1 activation in the lesioned hemisphere did not significantly correlate with any of the somatosensory scores. More specifically, the vibratory score was not significantly correlated with the asymmetry of response in SM1 ($A_{\text{vib}}$, $r=0.48$, $P=0.29$) or with the amplitude of activation in SM1 in the lesioned hemisphere ($r=-0.15$, $P=0.76$). In addition, there was no correlation between the level of activation in SM1 and the degree of rCBF asymmetry measured at rest ($r=0.27$, $P=0.57$).

The vibration of the normal hand of these patients induced comparable activations in the contralateral SM1 (+9.3 ± 3.9%, $P<0.001$). The activations were thus symmetrical in the normal and lesioned hemisphere, because the amplitude of asymmetry in SM1 ($A_{\text{vib}}$) was 0.1 ± 4.8% (range −7.4% to +6.5%). This asymmetry was comparable with that observed in controls (0.0 ± 4.5%, range −6.8% to +5.5%; Figure 3 and 4).
Patients Without VP Lesion
In patients without somatosensory deficit, the SM1 activation induced by contralateral hand vibration was significant in the lesioned (+13.5±4.4%, P<0.001) and in the normal (+12.1±5.6%, P<0.01) hemispheres.

Between-Group Comparisons
No significant difference or interaction was found when comparing the activations observed in SM1 of the different groups, using an ANOVA with the group as intersubject variable and the hemisphere as intrasubject variable (F<sub>2,15</sub>=1.3, P=0.3). In addition, since the SD value of the activation of SM1 in the lesioned hemisphere is higher than in the other groups, we compared these SD values with an F test. This test demonstrated no significant difference in the SD values of SM1 activation between patients with VP lesion and patients without VP lesion (F<sub>5</sub>=1.82) or controls (F<sub>5</sub>=1.99).

Asymmetry at Rest
We found no significant asymmetry at rest in the control subjects. The patients with VP lesion had a slight rCBF asymmetry in the cortical ribbon (AI<sub>rest</sub>=2.7±1.5%, P<0.01, Student t test), and a marked asymmetry in SM1 (7.3±5.2%, P<0.01). The patients without VP lesion had a marked rCBF asymmetry in the cortical ribbon (AI<sub>rest</sub>=6.6±2.1%, P<0.001). The comparison of asymmetries between the 2 groups of patients showed a significant interaction between patients and regions (F<sub>1,11</sub>=15.2, P<0.005), because the AI<sub>rest</sub> was higher in the SM1 region of patients with VP lesion than in the patients without VP lesion, whereas the reverse was found for the cortical ribbon (7.3±5.2% and 1.4±3.4%, respectively).

The rest asymmetry in SM1 of patients with VP lesion was significantly correlated with the vibration-proprioception subscore of the somatosensory scale (df=5, r=0.96, P<0.0005; Figure 5), the lemniscal score (r=0.85, P=0.01), and the total score of somatosensory deficit (r=0.80, P=0.03).

Discussion
The main result of this study is that patients with thalamic lesions involving the VP thalamic somatosensory relays have a normal activation of somatosensory cortical areas during the vibration of the contrallesional, hypesthetic hand. The activation of SM1 is symmetrical to the activation during the vibration of the normal hand in the same subjects and lies in the range of activations observed in controls or in patients with thalamic lesions outside the VP somatosensory relays.

In this study, the thalamic lesions appear to have little effect on the rCBF SM1 activation provoked by hand vibration but induce different patterns of rCBF abnormalities at rest in the 2 groups of patients. The patients without VP lesion had a widespread cortical hypoperfusion ipsilateral to the thalamic lesion, as evidenced by a significant rCBF asymmetry in the cortical ribbon. This widespread effect is a
lesion. Accordingly, we found a significant correlation between the SM1 rCBF asymmetry at rest and the somatosensory deficit in these patients.

Despite the clear-cut effect on rCBF at rest, the thalamic lesions appear to have little effect on the rCBF cortical activations induced by hand vibration. The SM1 activation was normal in the 2 groups of patients, even in the patients with VP lesion during the vibration of the hypesthetic hand, which was much less perceived than the vibration of the normal hand. Despite this clear asymmetry of perception, the level of activation was symmetric in both hemispheres of patients with VP lesion (Figures 3 and 4). Thus, the interruption of the somatosensory input at the VP level alters the perception of vibration and the synaptic activity at rest in SM1 but does not impede the activation of this region by hand vibration. These results might be limited by the lack of absolute rCBF quantitation, since this normal activation is associated with a lower absolute rCBF in this region both during rest and hand vibration. However, the subjects with VP lesion still have a preserved ability to activate their ipsilesional SM1 despite the lesion of the somatosensory relays at the thalamic level. One possible explanation is that the SM1 region is only partially deafferented. Although somatosensory evoked potentials could not be performed in our patients to assess the amount of residual connectivity between VP thalamus and SM1, it is evident that none of the patients had a complete anesthesia. However, this hardly explains the normal SM1 activation, because the level of this activation did not correlate with the score of somatosensory deficit. For example, patient 7, who had the most severe deficit of vibration/position sense (score 21/24), still had a 7.7% increase of blood flow in SM1 during vibration of the hypesthetic hand. In addition, the SM1 rCBF increase induced by hand vibration is symmetrical in both hemispheres of patients with VP lesion despite the clear asymmetry of perception. These results are finally in line with those of a previous report which show that the complete section of the thalamic lemniscal pathways at the spinal cord level does not abolish the SM1 activation induced by vibration. Taken together, these data indicate that the cortical activation caused by contralateral vibration does not require the integrity of the well-identified VP thalamocortical circuitry. They suggest that other ascending systems may play a role in specific cortical activation. In line with this hypothesis, we recently reported that SM1 activation induced by hand vibration is abolished in patients with tactile extinction who present considerably fewer somatosensory deficits than patients with VP lesion. Thus, even in this simple paradigm, cortical activation emerges as a complex phenomenon that might be viewed as a cortical "gating" mechanism: the light-up of specialized cortical areas will allow them to process the flow of information conveyed by modality-specific thalamic relay nuclei. Although hypothetical, this view is consistent with the effects of selective attention on the level of cortical activation, which are now established in different sensory activation paradigms, including hand vibration. Little is known about the underlying neuroanatomic bases of these activation mechanisms. Here, some parallel lemniscal ascending pathways might have been spared by the VP lesion. Alternatively, the extralemniscal system might be involved, since, unlike the lemniscal system, it sends divergent fibers (ie, spinoreticulothalamic and spinothalamic) to extrathalamic targets, which were not damaged in our patients. But how some of these collaterals are able to activate specific somatosensory cortical maps—through either dedicated pathways or interactions with different cortical activating systems—remains to be investigated. This will become an important field of clinical research, since understanding the mechanisms of cortical activation may be a major step to link localization and function in the human brain. Here for example, the preserved activation of SM1 contrasting with its hypofunctional activation at rest might be an important cue to understand the dissociation between preserved awareness and decreased perception of somatosensory stimuli, which is a typical clinical feature of patients with VP lesion.

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References


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