J Neurosurg 90:478–483, 1999

Localization of somatosensory function by using positron emission tomography scanning: a comparison with intraoperative cortical stimulation

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Object. To investigate the utility of $[^{15}O]H_2O$ positron emission tomography (PET) activation studies in the presurgical mapping of primary somatosensory cortex, the authors compared the magnitude and location of activation foci obtained using PET scanning with the results of intraoperative cortical stimulation (ICS).

Methods. The authors used PET scanning and vibrotactile stimulation (of the face, hand, or foot) to localize the primary somatosensory cortex before surgical resection of mass lesions or epileptogenic foci affecting the central area in 20 patients. With the aid of image-guided surgical systems, the locations of significant activation foci on PET scanning were compared with those of positive ICS performed at craniotomy after the patient had received a local anesthetic agent. In addition, the relationship between the magnitude and statistical significance of blood flow changes and the presence of positive ICS was examined.

In 22 (95.6%) of 23 statistically significant ($p < 0.05$) PET activation foci, spatially concordant sites on ICS were also observed. Intraoperative cortical stimulation was positive in 40% of the PET activation studies that did not result in statistically significant activation. In the patients showing these results, there was a clearly identifiable t-statistic peak that was spatially concordant with the site of positive ICS in the sensorimotor area. All PET activation foci with a t statistic greater than 4.75 were associated with spatially concordant sites of positive ICS. All PET activation foci with a t statistic less than 3.2 were associated with negative ICS.

Conclusions. Positron emission tomography is an accurate method for mapping the primary somatosensory cortex before surgery. The need for ICS, which requires local anesthesia, may be eliminated when PET foci with high (> 4.75) or low (< 3.20) t-statistic peaks are elicited by vibrotactile stimulation.

Key Words • brain mapping • somatosensory cortex • epilepsy • tumor • positron emission tomography • magnetic resonance imaging

The ability to localize eloquent regions in the cerebral cortex is an important tool in the practice of neurosurgery. When lesions such as tumors, epileptogenic foci, or vascular malformations lie close to, or within, the somatosensory or motor cortex, the goal of surgical treatment is maximum resection of the lesion without causing neurological deficit. Hence precise functional mapping, combined with accurate delineation of the extent of the pathological lesion, is important for defining the safe limit of resection and the optimum operative approach. Until recently, functional localization for surgical purposes has relied on invasive electrical stimulation,[20,38] or intraoperative recording of somatosensory evoked potentials.[36] Electrical stimulation is performed either intraoperatively or via chronically implanted subdural electrode grids. Invasive mapping suffers from several disadvantages that make the development and validation of alternative methods important. Information from direct cortical stimulation cannot be used for presurgical planning. Furthermore, to yield information for presurgical planning, placement of subdural grids requires an additional craniotomy with its attendant risks. Intraoperative stimulation of the primary sensory cortex requires the patient to be awake during stimulation, prolongs operating time considerably, is dependent on a high degree of patient cooperation, and is limited by the extent of cortical surface exposed.

In the absence of a pathological entity, there is a close relationship between the localization of sensory and motor function and the location of primary motor and somatosensory cortices. However, the use of anatomical landmarks, such as the central sulcus or the recently described knob on the precentral gyrus,[40] to identify cortex subserving motor and somatosensory function may be inadequate for surgical planning. Mechanical displacement or distortion of the cortical anatomy may make recognition of the sulcal and gyral patterns difficult. In addition, the plasticity of somatosensory and motor function in the presence of a wide variety of lesions[13,14,26,32,33] including brain tumors[22] and arteriovenous malformations[14] may disturb normal anatomicofunctional relationships. Finally, functional tissue may reside within the abnormal region itself.[28]

Mapping of primary motor and somatosensory areas is increasingly being performed with functional neuroimaging techniques, particularly PET and functional magnetic resonance (MR) imaging. Comparisons of these imaging modalities with direct cortical stimulation in small numbers of patients have indicated the feasibility of using functional neuroimaging for presurgical planning.[3,6,9,16] Positron emission tomography scanning of primary motor and visual cortices, as part of the preoperative evaluation of two patients, was shown to correlate closely with the results of ICS (motor cortex) and functional MR imaging (visual cortex).[6] Nyberg and colleagues[16] found that PET scanning in which vibrotactile stimulation was used to activate the somatosensory cortex in patients with tumors or vascular lesions in the central region permitted the relationship between the lesion and the sensorimotor cortex to be determined in six of 10 patients. Investigators in a recent study, in which PET scanning was compared with electrical stimulation via implanted subdural electrodes for the localization of language areas in seven patients with epilepsy, also found a close spatial correlation between the two techniques.[3]

Using ICS as a yardstick, we examined the utility of PET scanning in the localization of the primary somatosensory cortex in patients undergoing surgery in the central region. By comparing PET sensory activation with ICS in 20 patients undergoing surgery in the central area, it was possible to define t-statistic ranges in which PET scanning accurately predicted the results of the ICS.

Clinical Material and Methods

The study group was composed of 20 patients (14 male and six female) admitted to the Montreal Neurological Hospital for preoperative evaluation before surgery performed in the central cortex. The natures of the patients' lesions are summarized in Table 1. On the basis of the location of the lesion, ICS was considered necessary in all patients by the neurosurgeons (A.O. and A.F.S.). All patients underwent preoperative PET somatosensory activation.

Anatomical MR Imaging and Coregistration of PET and MR Imaging

In all patients a T_1-weighted anatomical MR image (TR 18 msec; TE 10 msec; flip angle 30°) was acquired, yielding approximately 160 sagittal 256 × 256–matrix images composed of 1-mm^3 voxels. Magnetic resonance and PET images were mapped into a common standard (stereotactic) space, using an automated algorithm that maximized the cross-correlation between the images and the average of more than 300 normal MR images manually registered into the coordinate space of Talairach and Tournoux.[30,36,37] Coregistration of PET and MR images was performed using the cross-correlation algorithm, allowing anatomical localization of the PET activation focus.

TABLE 1

Nature of lesions in 20 patients

Pathological Diagnosis	No. of Patients
tumor	
astrocytoma	4
oligodendroglioma	4
glioblastoma multiforme	2
ganglioglioma	3
metastasis	1
meningioma	1
other	
cortical dysplasia	3
gliosis	1
tuberculoma	1

Positron Emission Tomography Scanning

Positron emission tomography scanning was performed using a scanner (CTI/Siemens HR+ PET scanner; CTI, Knoxville, TN) that produces 63 slices at an intrinsic resolution of 4.2 × 4.2 × 4 mm. A foam head mold was fitted to minimize head movement and all studies were performed in a quiet darkened room with the patients' eyes closed. A ^{68}Ge orbiting rod transmission source was used for attenuation correction.

Bolus 10-mCi injections of the cerebral blood flow tracer $[^{15}O]H_2O$ were administered during activation and baseline states. For each patient, two baseline scans (with the patient relaxed) and two scans for each activation condition were obtained. In activation scanning, vibrotactile stimulation commenced 30 seconds before injection of the tracer. Stimulation was provided by a mechanical vibrator (model 91; Daito, Osaka, Japan) at a frequency of 110 Hz and an amplitude of 2 mm. A set of standard stimulation sites was used over the fingers, the angle of the mouth, and the plantar surface of the foot. The choice of sites stimulated in each patient was dependent on the location of the lesion and the operative approach being considered. Stimulation of the face was performed in 13 patients, of the hand in 14, and of the foot in six. The total number of scans was limited to a maximum of 12 according to patient tolerance and to the dose of radiation allowed by institutional and national guidelines. Informed consent was obtained from each patient before the study began, and the study protocol was approved by the Research Ethics Committee of the Montreal Neurological Institute.

Statistical Parametric Mapping

For each activation condition, t-statistic volumes were generated from images of the mean change in regional cerebral blood flow by dividing each voxel by the average standard deviation pooled across voxels.[5] The statistical significance of t-statistic peaks with a t-statistic value exceeding 2.5 was determined by a method based on three-dimensional gaussian random field theory.[39] Here, the critical value at which to set the threshold for the t-statistic images was determined assuming that nonactivated gaussian statistic images were a good lattice representation of a homogeneous stationary gaussian random field. On the basis of the expected Euler characteristic of such fields, the probability that the maximum t-statistic value exceed-

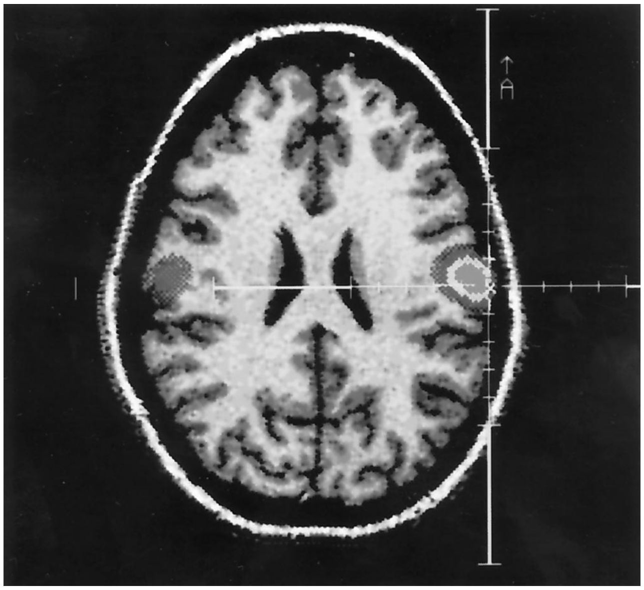

FIG. 1. Coregistration of sites of cortical stimulation *(cross-hairs)* and superimposed PET and MR images by using the Viewing Wand.

ed a given threshold was derived in terms of the volume under consideration and the smoothness of the field by using the method described by Worsley, et al.[39]

Utilization of PET Data With the Image-Guided Surgical System

The t-statistic images generated using PET scanning were transformed into the dimensions of the original MR image by using the inverse of the matrix used for stereotactic transformation. In the operating room, in addition to the standard Viewing Wand apparatus (ISG Technologies Inc., Mississauga, ON), an image-guided surgical system (VIPER)[10] produced in house was used to display combined MR and PET images, along with a representation of an intraoperative probe, the position of which could be tracked during the procedure. The MR images in both systems were registered to the patient by using a landmark matching algorithm.[21]

TABLE 2

*Correlation between the statistical significance of PET activation and ICS**

PET Activation Significance	Positive ICS	Negative ICS
significant ($p < 0.05$)		
hand	10	0
face	9	1
foot	3	0
total	22	1
not significant ($p > 0.05$)		
hand	2	2
face	2	1
foot	0	3
total	4	6

* All positive ICS responses were located within 1 cm of the voxel displaying peak activation on PET scanning.

Intraoperative Cortical Stimulation

Intraoperative cortical stimulation was started at an intensity of 1 V with 1-msec biphasic square-wave pulses set at 60 Hz, delivered to exposed cortex through a monopolar electrode. The patient was instructed to report any sensations and, in addition, was questioned about sensory symptoms after stimulation. A negative stimulation study was defined as a failure to elicit a response at a stimulus intensity of 6 V. The sites of stimulation were marked with tags and, after stimulation, the positions of the tags were recorded using the Viewing Wand probe.[25] The responses elicited by stimulation at each electrode position were recorded and later correlated with the PET findings coregistered with the same MR image (Fig. 1).

Statistical Analysis

The position of the voxel with the maximum t statistic in the PET activation foci and the corresponding site of positive ICS were defined as being spatially concordant if they were located in the same gyrus, within 1 cm of each other. The sensitivity and specificity of PET scanning were determined by comparing statistically significant ($p < 0.05$) and insignificant ($p > 0.05$) foci of increased cerebral blood flow with the findings of ICS, which for the purposes of this analysis was taken to be the gold standard. The positive (proportion of true positive results that test positive) and negative (proportion of true negative results that test negative) predictive values for PET scanning were also derived. The κ statistic was used to account for agreement between PET scanning and ICS that was due to chance alone. A κ value of 1 indicates perfect agreement, whereas a κ value of zero represents only chance agreement.[1] The criteria of Landis and Koch[12] were used to determine if the agreement was slight ($\kappa = < 0.2$), fair ($\kappa = 0.21–0.4$), moderate (κ 0.41–0.6), substantial ($\kappa = 0.61–0.8$), or almost perfect ($\kappa = > 0.81$).

Results

Statistically Significant PET Activation and ICS

The proportions of PET studies in which statistically significant foci of activation ($p < 0.05$) were observed were: 10 (77%) of 13 in the face; 10 (71%) of 14 in the hand; and three (50%) of six in the foot (Table 2). Thirty percent of all PET studies failed to produce statistically significant activation in the contralateral central region. Spatially concordant sites of positive ICS were observed in 22 (95.6%) of the 23 regions with statistically significant PET activation foci. The false positive rate was, therefore, 4.3%. Six (60%) of 10 statistically insignificant PET results were associated with a negative ICS. Using statistical significance as the criterion for PET activation, the sensitivity of PET scanning was 0.85, the specificity 0.86, the positive predictive value 0.96, and the negative predictive value 0.6. The κ value was 0.62, representing substantial agreement between PET and ICS.[12] Although statistically significant PET foci were almost always associated with spatially concordant sites of positive ICS, four (40%) of 10 PET activation foci that failed to reach statistical significance were also associated with spatially concordant sites of positive ICS. In these patients, although the t-statistic peak was not statistically significant, it was clearly identifiable and spatially concordant with the site of positive ICS in the sensorimotor area. This observation led us to evaluate the results in terms of the magnitude of t-statistic peaks.

Positron Emission Tomography t-Statistic Peaks and ICS

There was a close correlation between the value of the t-statistic peaks on PET and spatially concordant sites of positive ICS. When the value of the t statistic was greater than 4.75, 100% (19 of 19) of PET activation foci were associated with sites of positive ICS. When the value of the t statistic was less than 3.2, all PET activation foci were associated with negative ICS. In the intervening t-statistic range (3.2–4.75), discordance between PET activation and ICS was present in two (22%) of nine instances (Fig. 2).

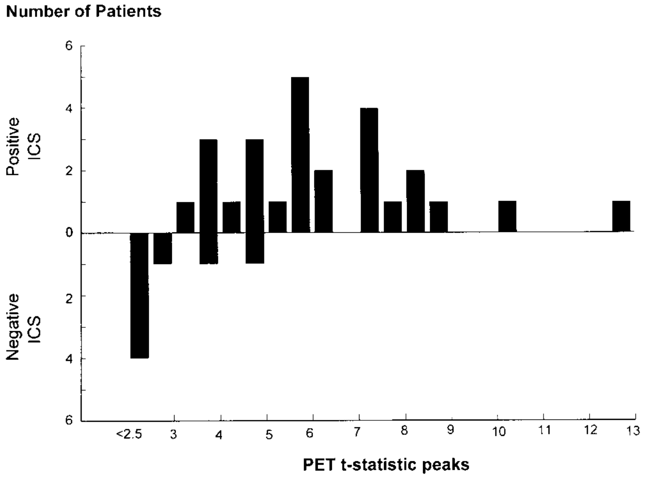

FIG. 2. Bar graph depicting the relationship between peak t statistics obtained with PET activation and ICS. All PET t-statistic peaks with a value exceeding 4.75 were within 1 cm of the site of positive ICS; t-statistic peaks with a value less than 3.2 were associated with negative ICS. Discordance between PET activation and ICS was present in the intervening t-statistic range (3.20–4.75; 2/9).

Discussion

In this comparison of functional localization of primary somatosensory cortex by using PET scanning and ICS, we observed spatially concordant sites of positive ICS in 22 (96%) of 23 statistically significant ($p < 0.05$) PET activation foci. However, positive responses were elicited with ICS in 40% of PET studies that did not have statistically significant activation. Further examination of the relationship between the magnitude of the t-statistic peaks and the results of ICS revealed that t-statistic peaks exceeding 4.75 were associated with positive ICS and all peaks lower than 3.2 were associated with negative ICS. This graded t-statistic scale appeared to be of greater value in the clinical interpretation of t-statistic maps than the simple absence or presence of statistically significant activation.

Functional Mapping

Traditionally, identification of the central sulcus has been used to localize the precentral and postcentral gyri, the regions assumed to subserve motor and somatosensory function, respectively. It is not optimal to rely entirely on anatomical landmarks as a guide to functional anatomy. Although the central sulcus is often easily identified on computerized tomography or MR imaging,[4,8,11,29] complete interobserver agreement is found in only 76 to 79% of normal healthy volunteers.[29,41] Landmarks may be difficult to identify, both on MR imaging and on direct inspection, especially if displaced or distorted by a lesion or by perilesional edema. Alternative methods of localization would be of value when the central sulcus cannot be identified, and to confirm the accurate identification of what is thought to be the central sulcus.

The correlation between functional representation and anatomy may vary between individuals. Using electrocortical stimulation via implanted subdural electrodes, Uematsu and colleagues[31] found that only two thirds of the primary motor responses were located within the precentral gyrus and that less than 30% of primary motor responses in patients with brain lesions were located in this area. The location of primary sensory responses in this study was also variable, with 60% anterior to the rolandic line, a marker for the central sulcus based on skull landmarks. Variability in the correlation between functional representation and anatomy may be greater in the presence of lesions such as brain tumors, situations in which cortical plasticity and remapping may occur.[13,14,26,32,33]

The presence of neural tissue subserving sensorimotor function or language within grossly abnormal cortex[28] cannot be established without functional mapping and may be of clinical importance. Skirboll, et al.,[28] elicited responses (sensory, motor, and language) to intraoperative stimulation of cortical tissue infiltrated by tumor in 7% of patients with supratentorial tumors.

Comparison of PET Scanning With Conventional Methods of Functional Localization

The physiological basis for functional mapping using PET scanning is different from that of ICS. The [^{15}O]H_2O PET activation studies map changes in blood flow that occur with increased neural activity. Local disruption or stimulation of cortical circuits are responsible for the phenomena observed when ICS is used for functional mapping. To some extent discordance between the two modalities may arise from differences in their mechanisms of action. The results of electrical stimulation at the cortical surface depend on the pattern of current that is spread from the surface electrode and on the neuronal structures that are stimulated.[24] Although in general the extent of current spread increases with higher intensities of stimulation, it may be difficult to depolarize neurons located within the depths of sulci. In contrast, if these neurons subserve the activation condition examined with PET scanning, increased focal blood flow would be expected. This may be the case for the primary motor cortex (Brodmann's Area 4) and a substantial portion of the primary somatosensory cortex (Brodmann's Area 3), which lie on the walls of the central sulcus.[34]

The need for noninvasive functional mapping stems from the disadvantages of current techniques of invasive mapping. Intraoperative cortical stimulation cannot really be considered a form of presurgical planning. It lengthens the operation and may provoke intraoperative seizures. Patient cooperation is critical and "awake anesthesia" may be required, rendering the method unsuitable for use in young children.[18] In addition, stimulation of mesial structures such as the foot area risks damage to the superior sagittal sinus or its tributaries.[20]

Positron emission tomography scanning confers several advantages compared with ICS. Positron emission tomography scanning is noninvasive and its risks are confined to mild radiation exposure (approximately three times the average normal annual exposure in North America). Unlike ICS, the whole brain can be examined in a single PET study, an additional advantage if activation occurs in unexpected cortical regions or cortical anatomy is distorted by a lesion. The PET examination can be used for presurgical planning and yields important information in three dimensions on the relationship between functional activation and the brain lesion.

Direct cortical stimulation using subdural electrode grids allows more prolonged testing outside the operating room, but requires a separate craniotomy with its attendant risks. Using subdural electrode grids, discrete somatosensory and motor responses may be elicited by stimulation over a wider area (several centimeters) than with ICS.[18,31] Intraoperative recording of somatosensory evoked potentials may also be used to localize the central sulcus with accuracy and does not require awake craniotomy.[35] Like ICS, this technique is invasive and is not useful for presurgical planning.

Newer, noninvasive techniques for presurgical functional localization include magnetoencephalographic mapping or magnetic source imaging[7] and functional MR imaging.[9,22] These techniques have been shown to be useful in the localization of the central sulcus in patients harboring lesions in the central region, particularly when superimposed on anatomical MR images obtained in the patient.[7,23] Functional MR imaging may prove to be a more practical method than PET scanning in the future, because of its noninvasiveness and relative availability. It has been validated by comparison with PET scanning,[2] as well as by direct correlation with the results of intraoperative electrical cortical stimulation.[22,23]

Methodological Issues

Two issues affect the value of PET scanning as a technique for preoperative functional localization: the accuracy of both the PET–MR imaging coregistration and the surgical guidance system; and interpretation of studies with poor or absent PET activation.

The mean three-dimensional registration error for the automated cross-correlation algorithm used to align PET and MR images is less than 2 mm.[37] In addition to image registration errors, there are errors in the registration of the MR image to the patient in the operating room when a surgical guidance system is used. For the Viewing Wand, errors resulting from positional drift of the patient's head with respect to the stereotactic probe are usually less than 2 mm and can be corrected by reregistration of the reference points.[19,27] Additional errors measuring up to 3 mm, due to brain shift (following resection or cerebrospinal fluid drainage) or edema, may be minimized by the early correlation of the PET activation focus with visible landmarks.[19] The spatial accuracy requirements for functional brain mapping relate to the margin of resection around regions critical for function. A margin of up to 2 cm (or one gyrus) is routinely left for resections of seizure foci near motor or language areas.[17]

Positive ICS occurred in four (40%) of 10 patients without statistically significant PET activation. Although not statistically significant, t-statistic peaks were observed in the contralateral central region in eight of the 10 patients. This suggested that failure to attain statistical significance was due to the limited number of task repetitions and variability in tracer uptake and not to abolition of the blood flow response because of destruction or compression of the cortex by the mass lesion.[15] Hence we examined the correlation between the value of the t statistic peak and the results of ICS and determined t-statistic ranges that predicted the results of ICS more accurately than the simple presence or absence of statistically significant activation. We found that when there is absent or weak PET activation ($t < 3.2$), ICS is invariably negative and unnecessary. Conversely, strong activation ($t > 4.75$) is invariably associated with positive ICS. For t-statistic values in the intermediate range ($3.2 < t < 4.75$), ICS remains necessary. Such a relationship between the magnitude of the t statistic and the results of ICS is not surprising because the t-statistic peak reflects the magnitudes of blood flow increases, which, in turn, are proportional to the number of neurons activated.

Conclusions

We have demonstrated that sensory PET activation can be used for accurate preoperative localization of the primary somatosensory cortex. More than 75% of the PET studies demonstrated statistically significant activation that was spatially concordant with positive ICS. However, the statistical significance of a focus of activation on PET scanning did not always correlate with its biological significance, as evidenced by the results of ICS. We defined t-statistic ranges in which PET activation may reliably replace ICS. Positron emission tomography activation studies are less invasive than ICS and may reduce the requirement for direct cortical stimulation.

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Manuscript received February 5, 1998.

Accepted in final form October 9, 1998.

Dr. Bittar was supported by a University of Sydney Faculty of Medicine Postgraduate Research Scholarship and a Thomas and Ethel Mary Ewing Travelling Fellowship.

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