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20. We thank J. Prescott at the New England Aquarium and S. Ridgeway at the Naval Ocean Systems Center in San Diego for allowing us to use their animals and facilities and W. Watkins at the Woods Hole Oceanographic Institution for assistance with the frequency analysis. The diving studies were conducted at the West Indies Laboratory at St. Croix. Supported by NASA grant NGR22-004-024 and Boston University Graduate School.

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Metabolic Mapping of Functional Activity in Human Subjects with the [^{18}F]Fluorodeoxyglucose Technique

Abstract. *The 2-[^{18}F]fluoro-2-deoxy-D-glucose technique was used to measure regional cerebral glucose utilization by human subjects during functional activation. Normal male volunteers subjected to one or more sensory stimuli (tactile, visual, or auditory) exhibited focal increases in glucose metabolism in response to the stimulus. Unilateral visual hemifield stimulation caused the contralateral striate cortex to become more metabolically active than the striate cortex ipsilateral to the stimulated hemifield. Similarly, stroking the fingers and hand of one arm with a brush produced an increase in metabolism in the contralateral postcentral gyrus, compared with the homologous ipsilateral region. The auditory stimulus, which consisted of a monaurally presented factual story caused an increase in glucose metabolism in the auditory cortex in the hemisphere contralateral to the stimulated ear. These results demonstrate that the technique is capable of providing functional maps in vivo related to both body region and submodality of sensory information in the human brain.*

Using the recently developed 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) technique (*1*) for measuring local cerebral glucose metabolism we have determined which areas of the brain are activated by a specific sensory stimulus, thus enabling brain function to be mapped in vivo. The classical techniques for measuring human cerebral metabolism (*2*) do not provide regional data. We have now measured local cerebral metabolic rates for glucose in a series of volunteers subjected to a variety of specific sensory stimuli (*3*).

We measured the regional brain activity of both FDG and 2-[^{18}F]fluoro-2-deoxy-D-glucose-6-phosphate (FDG6P) with position emission transaxial tomographs [PETT III and PETT V (*4–7*)] and determined the arterial time course of ^{18}F and glucose from arterial blood samples drawn after the FDG injection. With these data and knowledge of certain constants of the FDG model, we calculated the metabolic rate of glucose in various regions of the brain (*1, 1a*).

Twenty-seven healthy men (20 to 28 years old) were subjects in the experiment. After radial artery catheterization under local anesthesia, each was made comfortable in the tomograph, and the head was secured with a foam head restraint. The head was extended to make the scan plane parallel to the orbit-al-meatal (OM) line defined as the plane through the lateral canthus and the external auditory meatus. Each volunteer was subjected to a tactile, a visual, or an auditory stimulus (*8*).

The tactile stimulus consisted of rapid but light stroking (2 to 3 Hz) of the volar and dorsal surface of the fingers and hand of one arm (left, $N = 2$; right, $N = 3$) with a hand-held brush, which was just stiff enough to cause an appreciable stimulus without causing any discomfort. Subjects were blindfolded to eliminate visual input and wore earplugs to minimize auditory input.

In the visual study, either the left ($N = 4$) or right ($N = 6$) visual hemifield was stimulated so as to ensure only hemifield stimulation (*9*). The stimulus consisted of a well-illuminated, slowly moving, high-contrast black-and-white pattern of small lines at various orientations as well as abstract color images presented into one visual hemifield. The subjects wore earplugs.

The auditory system was studied in six subjects with normal hearing (*10*) who listened to a tape-recorded factual story presented through earphones to only one ear (left ear, $N = 3$; right ear, $N = 3$) (*11*). Attentiveness to the story was assessed by testing the subject's recall. These subjects were also blindfolded.

Six subjects that were blindfolded and wore earplugs acted as controls for all the studies.

Section scans were started 30 minutes after the FDG injection (*12*). Each scan took 10 to 14 minutes, depending on the count rate, and six to eight scans were obtained at 1-cm levels through the region of interest of the brain. Quantification of metabolic rates (*13*) was performed as discussed by Reivech *et al.* (*1*).

The somatosensory input caused the postcentral gyrus contralateral to the stimulus to become metabolically more active (mean ± standard deviation, 9 ± 10.2 percent) than the homologous area in the ipsilateral cortex (Fig. 1). This was not significantly different from the controls [1 ± 6.8 percent, $t(9) = 1.5$, $P > .1$]. The nonsignificance is due to the large variance in the control subjects at the level of the postcentral gyrus.

The visual stimulus caused the visual cortex contralateral to the stimulated hemifield to become 8 ± 3.0 percent more active that the ipsilateral visual cortex (Fig. 2). The asymmetry is significant in comparison with the controls [$t(14) = 4.06$, $P < .01$], who showed a left-right asymmetry of only 0.5 ± 3.0 percent.

The monaurally presented auditory stimulation elevated the metabolic rate in the temporal cortex contralateral to the stimulated ear (Fig. 3). This cortex had a metabolic rate of 7 ± 2.5 percent higher than the ipsilateral temporal cortex. This asymmetry is significant in comparison with the controls [$t(8)$

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= 6.02, $P < .001$], who showed a left-right asymmetry of only 1 ± 2 percent.

There are various sources of error in attempting to quantitate regional cerebral glucose metabolism by emission tomography (*14*). To minimize the effects of these errors, we analyzed our data with reference to a group of unstimulated control subjects as well as with regard to the hemispheric differencs within a particular scan of each subject. In six unsti-

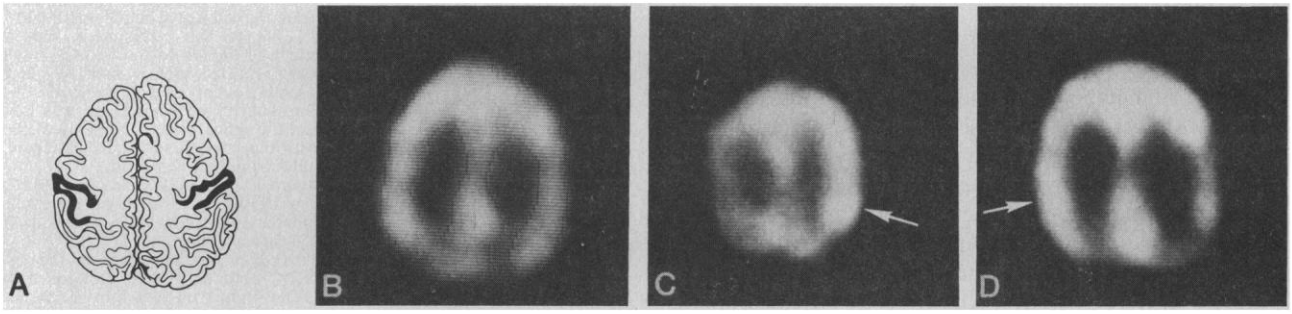

Fig. 1. Quantitative emission tomographic images of the brains of normal volunteer subjects obtained during somatosensory stimulation. Bright areas correspond to regions with a high uptake of FDG and hence a high cerebral metabolic rate for glucose, while darker areas represent lower metabolic rates. The sections are parallel to the OM plane and are indicated in centimeters above it. (A) Schematic of a horizontal section through the brain at OM + 9 with the hand representation indicated in black. (B) Horizontal section (OM + 9) through the brain of an unstimulated subject. The symmetry of labeling indicates approximately equal glucose metabolism for both hemispheres. (C) Scan from a subject in which the fingers and hand of the left arm are stroked with a brush. Activity in the right cortex including the postcentral gyrus (arrow) was increased compared with that in the left cortex. Glucose metabolism in the right postcentral gyrus in this subject is 15 percent greater than in the homologous area in the right hemisphere. In a subject in which the right fingers and hand were stimulated (D), a section scan at OM + 9 shows that glucose metabolism in the left hemisphere including the postcentral gyrus (arrow) was 12 percent higher than in a homologous area on the right side. An extensive area of the cortex, of which the postcentral gyrus is only a part, was activated by the stimulus.

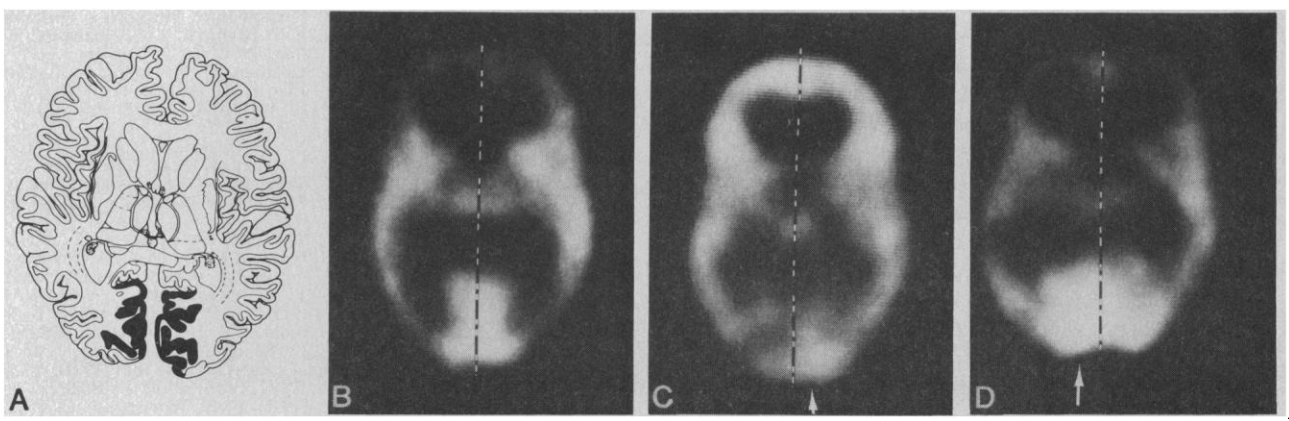

Fig. 2. Images of the brains of subjects stimulated visually. A dotted line defines the midline of each image. (A) Schematic of the horizontal section through the brain at OM + 4 with the striate cortex indicated in black. In a blindfolded, visually unstimulated subject, the visual cortex of the occipital pole is symmetrical (B), whereas the left visual hemifield stimulation causes asymmetrical glucose metabolism, with the right striate cortex 25 to 30 percent more active than the left (C). Stimulation of the right visual hemifield causes this pattern to reverse, with the left striate cortex having a metabolic rate 18 percent greater than a homologous area in the right hemisphere (D).

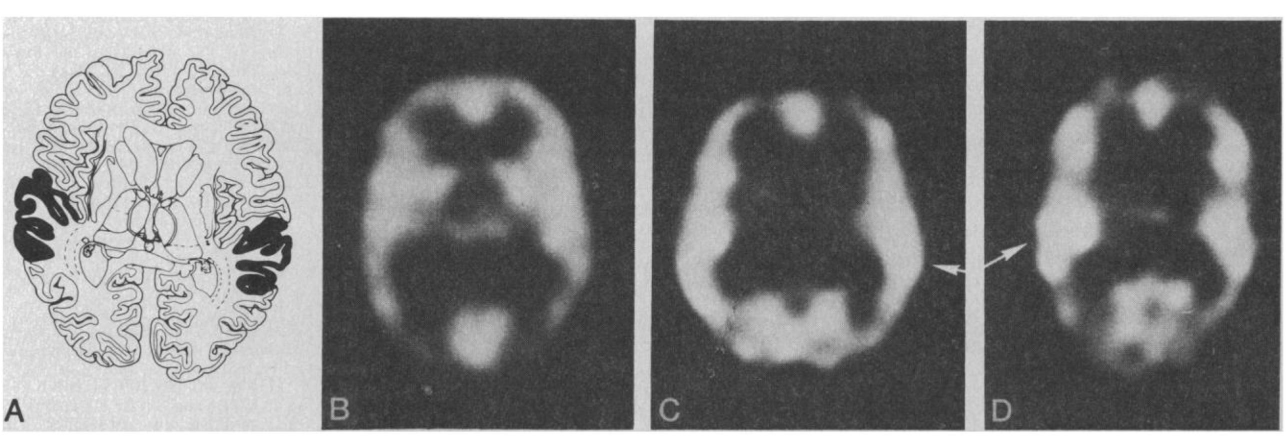

Fig. 3. Emission tomographs of the brains of subjects listening to a factual story with only one ear. (A) Primary auditory cortex schematically indicated in black at OM + 4. (B) Unstimulated control subject with symmetrical temporal cortices. Monaural auditory stimulation resulted in metabolic rate increases in the temporal cortex contralateral to the stimulated ear. (C) Left ear stimulated. (D) Right ear stimulated. The region of activation was also more extensive than merely the primary auditory cortex (arrow in C).

mulated control subjects, the mean side-to-side difference in cerebral metabolic rate for glucose in any region examined did not exceed 4 percent except in the postcentral gyrus, which in two control subjects exhibited an asymmetry of 10 to 12 percent.

These studies demonstrate the regional effects of functional activity on cerebral glucose metabolism in humans. Until now, almost all data describing the regional response of the brain to sensory stimulation has been obtained by measuring regional cerebral blood flow (*15*). The technique for the measurement of blood flow, however, provides only an estimate in a core of tissue and not in localized cerebral structures throughout the brain.

Little information is available concerning the function and anatomical organization of the somatic sensory cerebral cortices of humans (*16*). Unlike our studies of normal human subjects, earlier investigations were undertaken on patients undergoing neurosurgical procedures. Localization of asymmetrical FDG labeling at 8 and 9 cm above the OM plane (OM + 8 and OM + 9), including the postcentral gyrus, after vigorous unilateral brush stroking of the hand and fingers, is in agreement with topographical maps of this gyrus (*16*) as well as with other functional studies (*17*). Although more extensive areas than the postcentral gyrus are activted in our studies, more ventral portions of the postcentral gyrus (presumptive face and lip area) were not asymmetrically labeled (*18*).

The left visual hemifield is represented in the calcarine cortex of the right hemisphere and the right hemifield in the left hemisphere (*19*). We have shown increased glucose utilization in the calcarine cortex contralateral to the visual field stimulated by a patterned light stimulus.

The results of the auditory portion of this study, in which the temporal cortex contralateral to the stimulated ear become more metabolically active than the ipsilateral cortex, are consistent with data suggesting the predominance of the crossed pathways in the human auditory system (*20*). Furthermore, our metabolic data are in agreement with neurophysiologic studies in animals (*21*). Normative data that can be provided by the FDG method are essential in interpreting studies of the diseased central nervous system and subsequent neural plasticity.

Note added in proof: The local metabolic activity of the human brain during visual stimulation has recently been investigated through the use of the ECAT tomograph (*22*). The investigators show that the increase in metabolic rate in the visual cortex depends heavily on the complexity of the visual stimulation, with a complex scene producing a 60 percent increase in glucose metabolism in the primary visual cortex.

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4. The FDG (specific activity at time of injection, 12 to 35 mCi/ml) was prepared immediately before each study at the Brookhaven National Laboratory 60-inch cyclotron (*5*). Each subject received 70 to 140 μCi of FDG per kilogram of body weight as a single bolus into the antecubital vein (typically 5 to 10 mCi). The radiochemical purity determined by thin-layer chromatography was greater than 95 percent; the injectate was sterile and free of pyrogen.
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7. The intrinsic spatial resolutions of the PETT III and PETT V are 1.7 and 1.2 cm full width half-maximum, respectively, as used in these experiments (*6*). Data collection is reproducible over time periods well in excess of the duration of any experiment described. Field uniformity and precision are checked with each use.
8. Informed consent was obtained from each subject after a detailed explanation of the procedure.
9. After positioning the subject in the tomograph, a plexiglass hemisphere (diameter, 18 inches) was positioned 70 cm from him. He was instructed to fixate on a small light located at the center of the hemisphere, which was dimmed at random. The luminance of the fixation stimulus was adjusted so as to be detectable only by foveal vision. Thus the subject's hemifields could be defined relative to the hemisphere, and stimulation could be limited to the desired hemifield. Subjects reported greater than 95 percent of the dimming events, indicating good visual fixation. One half of the hemisphere was painted black and the space around the painted side darkened with black cloth to totally eliminate all visual input from that hemifield.
10. Normal hearing was established as at least 15 dB hearing threshold level (re American National Standards Institute 1969 norm) at frequencies 250 through 8000 Hz.
11. To reduce ambient noise in the test environment, both ears were covered by earphones (TDH 39) housed in auditory enclosures (Maico) providing 30- to 35-dB attenuation; the auditory stimulus was presented to only one ear at 75 dB sound pressure level (20 $\mu N/m^2$).
12. The stimulus was started 2 minutes before FDG administration to allow the system to attain a steady state before glucose metabolism measurement began; it was continued for 60 minutes.
13. The quantification of the ^{18}F activity was performed by comparing section scans from the subjects with identical scans obtained on a phantom containing accurately known amounts of ^{18}F. The functional anatomical areas were located on the scan images by comparing the set of images with an atlas of the brain with the same reference plane [S. J. DeArmond, M. M. Fusco, M. M. Dewey, *Structure of the Human Brain* (Oxford Univ. Press, New York, 1976)].
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