Chapter Thirteen

NONINVASIVE BRAIN IMAGING AND THE STUDY OF HIGHER BRAIN FUNCTION IN HUMANS

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INTRODUCTION

Many clues to human brain function have accumulated from focal lesions, electrical stimulation, and recordings during neurosurgical procedures in man. Unfortunately, these approaches are restricted to patients with neurological dysfunction. The ideal tool for objective study of normal human brain neurophysiology is one that can be applied, atraumatically, to the neurologically normal subject. A variety of such "noninvasive" techniques exist; they can be classified into nonimaging and imaging procedures. The nonimaging category includes measures of endogenous electrical potentials (electroencephalography or EEG, and evoked potentials) and measures of magnetic fields (magnetoencephalography, see Williamson and

Kaufman, 1981). Imaging techniques may be subdivided into tomographic (three-dimensional) and topographic (two-dimensional) methods. Three tomographic techniques exist: positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI). Currently, two topographic methods exist: single-photon emission topography (SPET) and brain electrical activity mapping (BEAM). This chapter will review studies using a subset of the imaging techniques. Of these, MRI is the most resolute and least invasive. Due to technological limitations MRI is currently limited to anatomical studies in humans, but in conjunction with appropriate labels, MRI promises to allow detailed studies of tissue metabolism in the future. BEAM, a recently developed clinical tool for EEG and evoked potential analysis, is the only imaging technique that provides real-time (instantaneous) information. The application of BEAM to neurophysiological studies is just beginning; the reader is referred to Duffy (1986) for a summary of current research in this area. Similarly, the SPECT method is new and few neurophysiological studies have appeared using this technique. This review will address the use of PET measurements of brain metabolism and SPET measurements of blood flow for the study of human brain function.

In 1890, Roy and Sherrington first proposed that a compensatory vascular dilation occurs in response to increased metabolism within the brain. Fulton provided clinical evidence in support of this proposition in 1928; auscultating blood flow through an arteriovenous malformation in the occipital lobe of a patient, he noted an increase in bruit intensity when the patient read. In 1948, Kety and Schmitt reported a method for measuring total brain blood flow in human subjects. Using this technique, Sokoloff et al. (1955) found a nonsignificant increase in whole brain blood flow when subjects began to perform mental arithmetic. This negative finding prevailed until a decade later when techniques using radiotracers were developed to measure *regional* blood flow in humans noninvasively. This technique demonstrated that focal changes in blood flow can occur in discrete cortical foci, as the human subject performs certain tasks. This suggested that the study of blood flow could provide insight into which cortical areas are "activated" during specific experimentally imposed conditions.

In recent years PET and the 2-deoxyglucose method of Sokoloff have provided measures of regional brain metabolism. The noninvasive techniques can provide additional information about regional brain "activation" in humans. This chapter reviews the use of these techniques for the study of humans during rest, sensory stimulation, motor performance, and cognitive tasks.

METHODOLOGIES

Metabolism of the central nervous system is not constant. Energy is continuously consumed in pumping ions against electrochemical gradients, synthesizing proteins, release and reuptake of neurotransmitters, and maintaining an optimal ionic milieu, among other things. Alterations in discharge frequency and synaptic input to a neuronal population cause an obligatory change in local metabolism. Thus, changes in metabolic rates within a circumscribed region of brain under experimentally imposed conditions can provide insight into which regions of the brain are involved in performing certain tasks. Since the central nervous system, under normal conditions, derives energy exclusively from the oxidation of glucose, the uptake of oxygen and glucose parallels cellular metabolism.

In order to supply fuel to areas of metabolic demand, flow through the neural microvasculature is modulated with local energy consumption. Local flow responds to changes in neural activity within 2–4 s (Moskalenko, 1975). Raichle et al. (1976) found a close correlation between regional cerebral blood flow (rCBF) and oxygen uptake during a state of rest. More recently however, Fox and Raichle (1986) have demonstrated that within focally activated cortical areas blood flow and oxygen utilization may become uncoupled. A 29% increase in rCBF within somatosensory cortex, produced by vibration of the subject's fingers, was accompanied by a nonsignificant 5% increase in oxygen consumption. This suggests that blood flow measurements may be more sensitive to changes in neural activity than metabolic measures. The reader is referred to this paper for a current discussion of the relation between metabolism and blood flow. What follows is a review of techniques used to measure metabolism and regional cerebral blood flow within human subjects in a noninvasive manner.

Measures of Metabolism

The rate of glucose uptake by a cell is proportional to glucose need. Immediately upon uptake, glucose is phosphorylated by hexokinase to glucose-6-phosphate and is rapidly oxidized in the glycolytic pathway. 2-deoxyglucose (2-DG) is taken up by glucose-transporting enzymes, but once phosphorylated by hexokinase it is a poor substrate for the glycolytic or hexose-monophosphate pathways. Since glucose-6-phosphatase activity is low in neural tissue (Sokoloff and Smith, 1985; see also Fox, 1984; Cunningham and Cremer, 1985), this glucose analogue becomes trapped. Consequently, the intracellular concentration of 2-deoxyglucose-6-phosphate

provides a stable and sensitive measure of cellular metabolism. Sokoloff pioneered the study of local cerebral glucose consumption by developing a kinetic model for ^{14}C-2-deoxyglucose uptake and sequestration (Sokoloff et al., 1977). An excellent illustration of the precision that this technique allows can be found in Kennedy et al. (1976). In this study, ^{14}C-2-deoxyglucose was injected into monkeys during monocular visual stimulation. Applying quantitative autoradiography to histologically prepared brain slices, they were able to document the local cerebral metabolic rate for glucose (in mg/100 g brain/min) within single, labeled ocular dominance columns. Using the same technique, Hand et al. (1979) demonstrated laminar-specific labeling of a single rat cortical barrel after selective stimulation of a single vibrissa. Greenberg et al. (1979), using ^{14}C-iodoantipyrine (an agent which extravasates in proportion to local blood flow) showed that stimulating single vibrissae produced local blood flow increases in the somatosensory cortex of the rat that were as specific as the ^{14}C-2-deoxyglucose labeling seen by Hand et al. Reviews of the deoxyglucose and other radiotracer techniques have appeared recently (Sokoloff, 1985; Sokoloff and Smith, 1985).

In man, 2-DG labeled with a positron-emitting isotope can be used to measure local cerebral metabolic rate for glucose using an appropriate kinetic model and a positron emission tomographic (PET) scanner. A brief summary of the technique will be given here; for further information the reader is referred to the reviews of Phelps et al. (1975, 1982, 1985) and Raichle (1983). Positrons emitted from such isotopes travel a few millimeters before colliding with an electron (Fig. 1). Annihilation of these antiparticles produces two 511-keV photons that travel in diametrically opposite directions. Both gamma rays can often be detected externally, since attenuation of such high-energy photons is low within the brain and skull. A circular array of scintillation detectors collimated in a plane transverse to the head can be used to detect the coincident arrival of photons. The source of a photon pair that falls within this plane can be localized to the line between detectors. Single–photon counts are excluded, as are lower energy photons from Compton scatter. When sufficient numbers of coincident pairs are recorded in the detector array, a series of two-dimensional slices of count density can be constructed by various computer algorithms. Corrections are made for brain attenuation and false coincidence. The densities on the slices are converted to the physiologically relevant parameter, depending upon the labeled compound used and its appropriate model of distribution. Three-dimensional tomograms are constructed using stacked arrays of ring detectors, performing the same analysis in parallel, or by translating the subject relative to a stationary detector

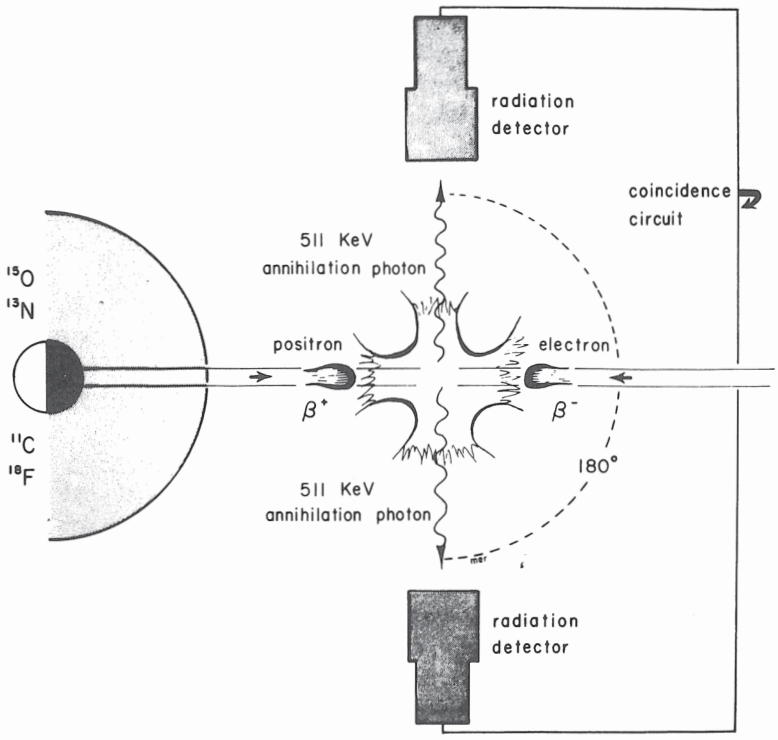


FIGURE 1. Schematic diagram of radionuclide decay and event detection employed in positron emission tomography (PET). Decay of these short half-life radionuclides produces a positron (β+) which collides with an electron (β−) within 1–6 mm of its source. Annihilation of these antiparticles produces two 511-keV photons traveling in opposite directions. Scintillation detectors arranged in a ring array are connected to a coincidence circuit which detects simultaneous arrival of photons. Computer analysis of events reconstructs the density of sources in the plane of the ring. Newer technologies can provide better spatial resolution within the section plane by measuring minute differences in the times of arrival of the photon pair. (From Raichle, 1983.)

array. Tomographic slices are often displayed in pseudocolor to enhance contrast, and the image can be related to anatomy by using a proportional stereotaxic atlas or by superimposing X-ray computed tomography slices, which outline skull, and magnetic resonance tomograms to localize cortical gyri and subcortical structures.

To minimize the radiation exposure to human subjects, 2-DG can be labeled with a short half-life (110 minutes) positron isotope, ^{18}Flourine (Reivich et al., 1979). In a typical paradigm, a subject is engaged in a certain behavior designed to test the function of the observed brain regions; then 5–10 mCi of flourodeoxyglucose (FDG) is injected intravenously. The sub-

ject maintains the behavior in a steady-state fashion for approximately 40 min to allow equilibration of the tracer with cerebral tissues and sufficient decay of plasma tracer concentration. Arterial or venous blood is continuously sampled to record the specific activity of plasma. The subject is then scanned until sufficient coincident pairs are recorded (45 min to 2 h). Thus, the tomogram represents average cerebral metabolic rate over the uptake period, skewed toward the time of injection. Also, repeat scans must be separated by at least 11 h to allow for sufficient decay of ^{18} Fluorine. Recent advances in PET technology, utilizing positron emitter ^{15}O, reduce both the scan time and the "maintained behavior" time. Labeled oxygen can be used to image both cerebral metabolic rate for oxygen (inhaling $O^{15}O$) and rCBF (injecting $H_2{}^{15}O$) (Raichle et al., 1983, 1985). Scan time is typically less than a minute. ^{15}O has a short half-life (2 min) and may be used in serial measurements in the same subject, with minimal radiation exposure. Limited spatial resolution is the main disadvantage of PET for the study of human neurophysiology. Current resolution of scanners is around 12–14 mm axially and 10–12 mm in the plane of section. Newer technologies that utilize minute temporal differences in the coincidence of photon pairs, so called time-of-flight systems, offer increased resolution. An economic disadvantage of PET is the necessity for an on-site cyclotron to produce isotopes with a short half-life.

Blood Flow Measurements

The study of rCBF first proposed by Conn in 1955 antedates PET technology. Kety (1951), in an extensive review of principles of inert gas distribution within tissues, laid the ground work for rCBF studies. He showed that after exposure to an inert gas, its concentration [$C(t)$] within a perfused tissue is an exponential function of time:

$$C(t) = C_o\, e^{-ft/\lambda} \tag{1}$$

where f is local blood flow in ml/100g tissue/min, λ is the blood-to-tissue partition coefficient for the gas (ml/100 g tissue), and C_o is the initial concentration of gas. When a radioactive inert gas, such as ^{133}Xenon or ^{85}Kr, is injected intra-arterially into the subject, scintillation detectors placed over the scalp record a "washout curve" that can be modeled by two first-order compartments with significantly different time constants. The faster decaying compartment represents gray matter flow while the slower compartment reflects flow in white matter (see the International Symposium of Regional Cerebral Blood Flow, 1965 and Olesen et al., 1971). Blood flow in

each compartment may be quantified by measuring the slope of the clearance curve at different times. White matter flow remains constant between resting and behavioral states, and therefore is usually not reported in noninvasive studies, while gray matter flow may vary significantly. Briefly, solving for f in Equation 1,

$$f_g = \lambda_g \alpha \text{ ml/100g/min} \tag{2}$$

where α is the slope of the initial 15–60 s of the logarithmically transformed clearance curve (counts/min) and λ_g is the blood-to-gray matter partition coefficient for the administered gas. During this time period the clearance curve is dominated by gray matter flow (f_g). This measure, called the "initial slope index," underestimates true gray matter flow by 20–30% (Olesen et al., 1971), but can be measured rapidly. Since both gray and white matter flows are affected by arterial [CO_2] this gas must also be monitored and the flows corrected accordingly. The reader will find further information elsewhere on systematic errors (Kanno and Uemura, 1975), on the two-compartment model and analysis of washout curves (Hoedt-Rasmussen et al., 1966; Olesen et al., 1971). A brief review of this technique has appeared (Kety, 1985).

Conn suggested that ^{133}Xe could be delivered by inhalation and rCBF measured with bilateral scintillation detectors. Bolmsjo (1984), using calibrated sources in water medium, quantified the amount of cross-talk between hemispheres and the contribution of tracer distributed in extracerebral tissue to gray matter flow. He concluded that hemispheric differences can be smoothed as much as 50% with ^{133}Xe inhalation and that flow measurements are sensitive to collimation geometry and photon energy discrimination. This smoothing effect is important to keep in mind when interpreting topographic (i.e., two-dimensional) flow experiments employing inhalation tracers. Lassen and Ingvar (1961) overcame these difficulties by injecting ^{85}Kr, dissolved in saline, directly into the internal carotid artery (ICA), labeling only one hemisphere. This procedure is ethically restricted to patients requiring cannulation of the internal carotid artery for clinical purposes. Early application of the blood flow technique used a single detector placed over the labeled hemisphere. However, several detectors may be used to obtain information about multiple cortical areas simultaneously. In Denmark, a system incorporating 254 scintillation detectors arrayed in 19 columns and 14 rows was developed to provide high-resolution, topographic records of hemispheric flows (Sveinsdottir et al., 1977; Fig. 2). In any system using a collimated scintillation detector, the tissue sampled is a truncated cone with the vertex toward the cortical

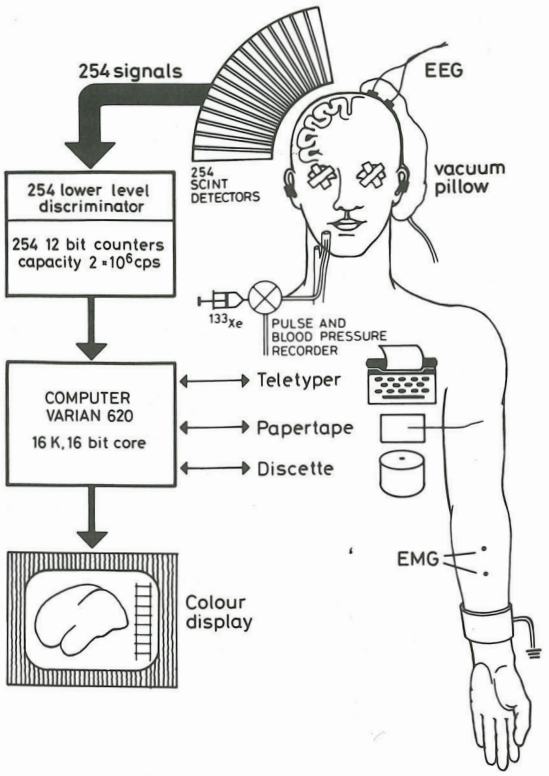


FIGURE 2. Schematic diagram of the Danish high-resolution system for measuring regional cerebral blood flow (rCBF). The patient's head rests against an array of collimators. A saline bolus containing ^{133}Xe is injected into the patient's internal carotid artery. Decay events are counted by an array of 254 detectors and uploaded to a microcomputer. The recorded clearance curves are used to calculate rCBF at detector sites. The rCBF map is then displayed in pseudocolor to enhance contrast. (From Roland et al., 1980a.)

surface and base approximately 25 mm below, the lower limit imposed by attenuation of the ^{133}Xe 91 keV photon. Gray matter deep in sulci is recorded less efficienty than superficial cortex; for example, the 254-detector system cannot detect a 30% increase in basal ganglia blood flow (Roland, 1985b). Although scattered photons can be partially excluded from detection by accepting only photons above a certain energy level, some decay events originating outside the detector collimation do contribute. The Denmark system has a reported resolution of 0.9 cm and can detect a 4 mm displacement of a radioactive line source placed behind the skull of a cadaver (Bolmsjo, 1984). Orientation of the rCBF map to cortical structures is aided by proportional stereotaxic atlas in conjunction with a skull radi-

ograph. The lateral fissure can be localized by observing the initial distribution of label as it emerges in tributaries of the middle cerebral artery. Using these techniques, the central sulcus can be localized within 5 mm. Regional cerebral blood flow maps are typically displayed in pseudocolor with adjacent pixels interpolated between detector sites to smooth the image. However, color-coding may provide misleading impressions; in plate 4, for example, five shades of blue cover the range from 80 to 100% of resting blood flow, while the dramatic contrast change from blue to green represents only a 5% difference.

Measuring blood flow by injection of ^{133}Xe into the internal carotid artery offers several advantages: measurements are rapid (60 s), radiation exposure is low (inert gases are exhaled, accumulating little in body fluids), measurements can be repeated in 20–30 min for intrasubject comparison, and a cyclotron is not necessary. The disadvantages are that subcortical areas cannot be monitored, and only areas of cortex supplied by the ICA may be studied. A recently developed single-photon tomographic scanner allows ^{133}Xe administration by inhalation, circumventing problems of hemispheric cross-talk (Stokely et al., 1980), but few neurophysiological studies have appeared using this device.

All imaging techniques measure some index of metabolism within a circumscribed neural volume. We will adopt the term "activation" to refer to changes in the metabolic index, acknowledging the uncertainty of what is really being measured. Few studies have addressed the underlying mechanisms. Mata et al. (1980) quantified uptake of 2-DG in rat posterior pituitary slices in vitro during electrical stimulation. A 29% increase in 2-DG accumulation produced by stimulation was completely blocked with 10 μm ouabain, a specific blocker of the Na^+-K^+ ATPase. Blocking neurosecretion by lowering Ca^{2+} did not reduce 2-DG accumulation, suggesting that metabolism is most sensitive to sodium pump activity, irrespective of neurosecretion. It is difficult to extrapolate these findings to CNS presynaptic terminals, given the specialized nature of the tissue studied. It remains unclear whether cortical metabolism is correlated more strongly with post-synaptic ion fluxes or spike discharge. An ICA injection of a γ-aminobuteric acid (GABA) agonist decreases cortical rCBF in a dose-dependent manner (Roland and Friberg, 1983), yet, since both average synaptic activity and neuronal activity have decreased with this treatment, no definitive conclusions can be made. Telencephalic regions that maintain a high resting discharge, such as the globus pallidus, do not necessarily maintain high resting blood flows (Roland et al., 1982).

Since noninvasive flow measurements involve averages over extended periods, transiently activated brain regions may fail to manifest significant

"activation." For the same reason, the temporal sequence of activation of different regions cannot be resolved.

ACTIVATION IN THE RESTING STATE

Changes in brain activation are referenced to a state of rest. Resting subjects have typically been defined as subjects who are relaxed, deprived of sensory input, and attempting to "think of nothing." With their eyes closed and occluded with cotton patches, ears plugged, and their somatosensory stimulation minimal and constant, neurologically normal subjects demonstrate 10–30% higher blood flow and metabolic rate in frontal cortex compared to parietal, occipital, and temporal regions. High-resolution techniques reveal that higher flow is localized to the anterior superior prefrontal regions (plate 4A, "rest"). The relatively higher blood flow and metabolism in the frontal regions during rest has been termed "hyperfrontal" by Ingvar (1979); he suggested that this may represent ongoing prefrontal involvement in programming potential future behavior. Prohovnik et al. (1980) suggested that this pattern may represent, among other things, a prefrontal role in inhibition of autonomic and somatomotor activity, which the resting subject is instructed to maintain. Hyperfrontality is not seen in resting schizophrenics, but is restored when they are treated with effective medications (Buchsbaum, 1982; Weinberger et al., 1986). A 10% decrement in frontal metabolism has been reported after section of white matter underlying the frontal lobe (Roland, 1984), suggesting that subcortical drive is in part responsible for this resting activation. Repeated measurements during rest show little variation in relative values of rCBF (Roland and Larsen, 1976). However, a net decrease in mean hemispheric flow of 2–5% is seen consistently between successive measurements at rest. Prohovnik et al. (1980) noted that both rCBF and its variance decreased from the first to the third flow measurements. In a group of 18 subjects, Reivich et al. (1983) found a significant relationship between anxiety (using Spielberg's state-trait anxiety inventory) and cerebral metabolism in posterior fronto-orbital and middle frontal areas. It is not surprising that the procedures required for these studies could provoke anxiety and that during subsequent measurements subjects become more accustomed to the testing conditions.

Using PET, Mazziotta et al. (1982a) provided evidence of interhemispheric differences in metabolism during the "rest" state. When subjects closed their eyes but had their ears open an anterior/posterior metabolic asymmetry appeared bilaterally. With both auditory and visual deprivation the anterior/posterior gradient increased, mostly due to a reduction in

parietal, occipital and temporal metabolism. In addition, left–right asymmetries appeared: in the right hemisphere, posterior superior temporal, inferior prefrontal and lateral occipital cortical metabolic rates decreased relative to their homologous regions in the left hemisphere. This was repeatable within and across normal subjects. As discussed below, cortical metabolism in areas other than prefrontal cortex may increase during specific sensory stimulation. This suggests that the anterior/posterior gradient may be produced by loss of afferent drive during sensory deprivation.

It is interesting to contrast brain activation during "rest" and during sleep. Heiss et al. (1985) reported a net 13% reduction in fluorodeoxyglucose uptake over the whole brain in three subjects during dreamless sleep (compared to rest while awake). Cortical metabolism was reduced from 9 to 21% in a regionally dependent fashion. Prefrontal metabolism declined more than other cortical regions (from Table 1 Heiss et al.), reducing hyperfrontality. In contrast, brain metabolism increased during dreaming; for a subject who reported having a nightmare during sleep, overall cortical metabolism increased from 4.3 to 30%, depending on region (16% for the whole brain). Focal increases occurred in superior frontal, insular, inferior parietal, visual and visual association cortex, and in the hippocampus. Studies of blood flow during sleep have demonstrated a sleep-stage dependent reduction in blood flow (−10% for stage I, −14% for stage II, and −28% for stages III and IV), but a 41% increase in mean cortical flow during rapid eye movement sleep (Sakai et al., 1980). This higher metabolism and blood flow during REM sleep may reflect cortical involvement in dreaming. In narcoleptic patients, Meyer et al. (1980) found greater blood flow increases in right than left parietal, occipital, and posterior temporal cortex in narcoleptic patients who were having vivid, visual dreams. No studies have appeared which correlate dream content and regional cortical activation in normal subjects.

During sensory stimulation, motor activity or during specified cognitive activity, subjects invariably show a generalized, nonspecific increase in cortical blood flow or metabolism. Changes in metabolism above this nonspecific, or "extrafocal" increase are interpreted as evidence for regional cortical involvement during the specified test condition. Focal reductions in these parameters may occur in individual subjects but are not consistent across subjects regardless of the imposed task.

BRAIN ACTIVATION DURING SENSORY STIMULATION

Although much is known about the organization of primary sensory pathways in animals, no animal studies can elucidate the uniquely human

aspects of sensory perception, such as listening to speech. What follows is a review of noninvasive measurements of brain activation in humans during auditory, visual, vestibular, and somatosensory stimulation, stressing differences in regional activation produced by qualitatively different stimuli.

Auditory Stimulation

To document cortical metabolic responses to monaural stimulation, Greenberg et al. (1981) studied fluorodeoxyglucose uptake in subjects listening to a factual story. They observed a 7% ($p < .001$) greater cerebral metabolism in the transverse superior temporal gyrus contralateral to the stimulated ear compared to the homologous ipsilateral region. Other studies have reported different results. Mazziotta et al. (1982b) studied four normal patients listening to a Sherlock Holmes story presented monaurally (two right ear, two left ear). Independent of the ear stimulated, this produced significant bilateral activation of transverse and posterior temporal cortex plus activation of the left frontal cortex (Plate 1, "verbal"). Using a higher resolution scanner, they noted that a larger cortical area was activated on the left side (Fig. 3). This pattern is consistent with left hemisphere dominance for language, and known anatomical asymmetries of the planum temporale and Heschl's gyrus. Left–right asymmetries in activation were found to be a function of stimulus content rather than the side of stimulation. Four subjects (two right ear, two left ear) who were asked to discriminate differences in chord pairs demonstrated increased metabolism bilaterally in the temporoparietal region. Hemispheric asymmetries, with right metabolism greater than left, occurred in posterior temporal, temporal-occipital, and diffusely in the frontal cortex (Plate 1, "timbre"). However, stimulus content alone may not completely explain left–right differences. Eight subjects were asked to report whether two presentations of a tone sequence differed in a single note ("tonal memory" task). Five subjects had regional metabolism patterns similar to subjects discriminating chord patterns (Plate 1, "nonanalytical"). The other three had significantly more activation on left than right posterior superior temporal cortex, with no greater metabolism in any right area compared to its left homologue (Plate 1, "analytical"). In a poststudy interview the five-subject group reported employing no specific strategy in the task. The group of three, on the other hand, reported use of visual imagery (e.g., "visualizing a frequency histogram"), or "analytic strategy." Although the sample size was small, the metabolic profiles seen were consistent between subjects.

Using ICA injection of ^{133}Xe and the Danish high-resolution system, Nishizawa et al. (1982) studied rCBF in 14 right-handed patients who lis-

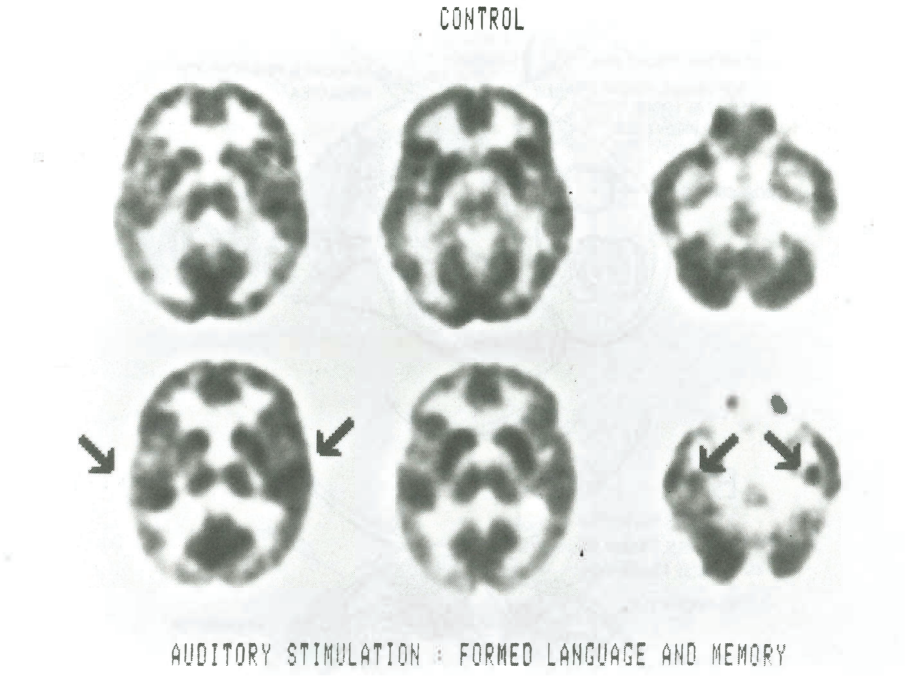


FIGURE 3. PET images of a resting subject with ears plugged (top) and of another subject listening to a Sherlock Holmes story (bottom). Each row contains three transverse tomographic slices, the most rostral slice on the left. Darker regions indicate greater uptake of fluorodeoxyglucose, indicating greater metabolic activity. In the stimulated patient, the label is denser in the left transverse temporal cortex than on the right (arrows on left) in two planes of section. This may correspond to anatomical asymmetry of the planum temporale and Heschl's gyrus. The symmetric label indicated by arrows on the right may represent hippocampal activation, which was not present in the control subject. (From Mazziotta et al., 1982b.)

tened monaurally to onomatopoietic words (''bang,'' ''crack,'' ''whisper,'' etc.). Their results agree with Mazziotta et al.: primary and secondary auditory cortex on the left demonstrated a larger area of activation and exhibited larger flows (29%) compared to the right homologue (18%). In addition, they observed significant activation of anterior superior temporal (left = 24% > right = 13%, $p < .01$), posterior superior temporal (left = 29% > right = 18%, $p < .001$), anterior prefrontal (left = 12% < right = 18%, $p < .05$), bilateral orbitofrontal regions, and bilateral frontal eye fields. These results agreed with a less resolute study by Maximillian (1982). In comparison, Roland et al. (1981b) tested patients in a two-alternative forced-choice discrimination of differences in tone rhythm. Those regions

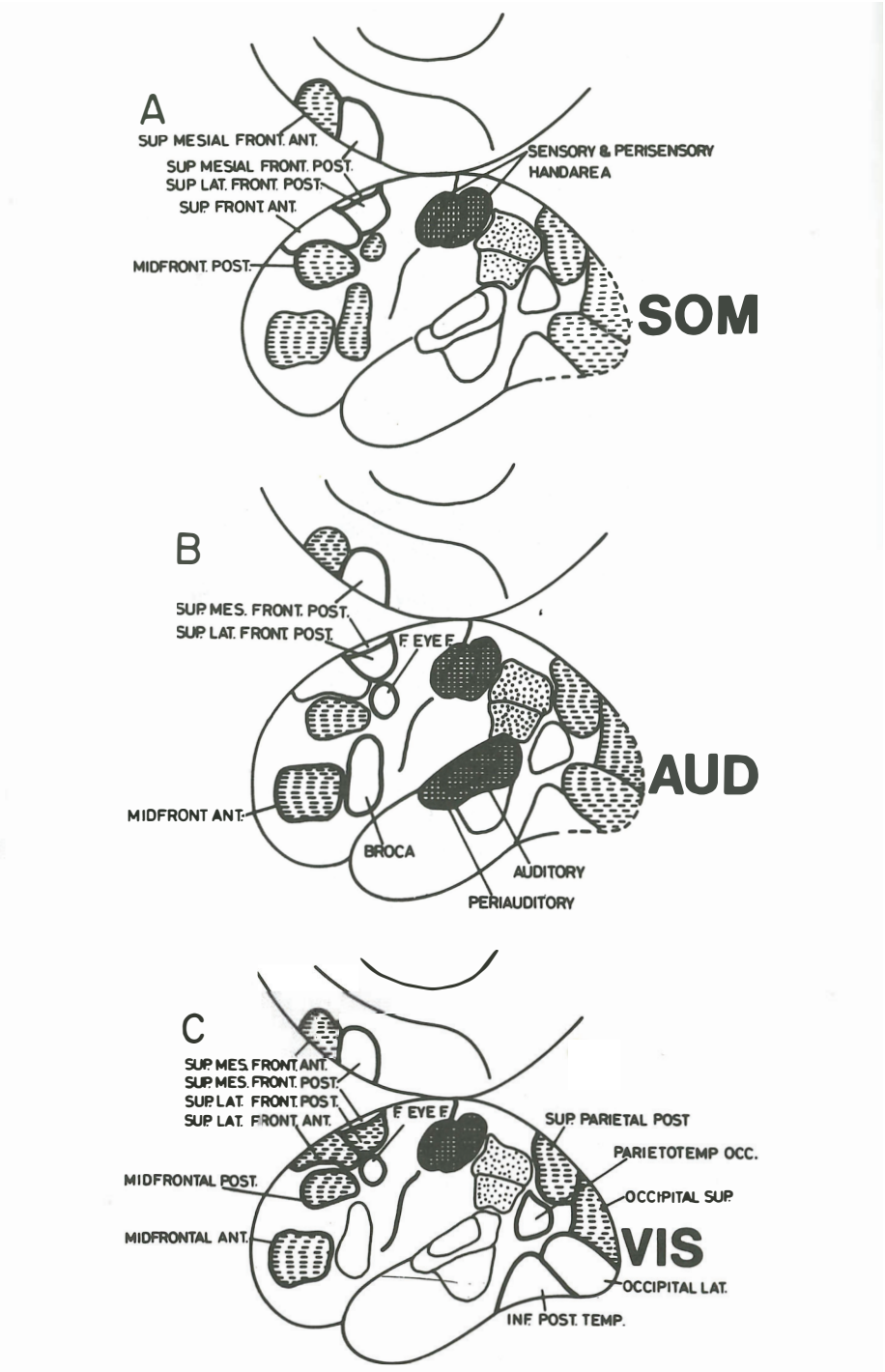
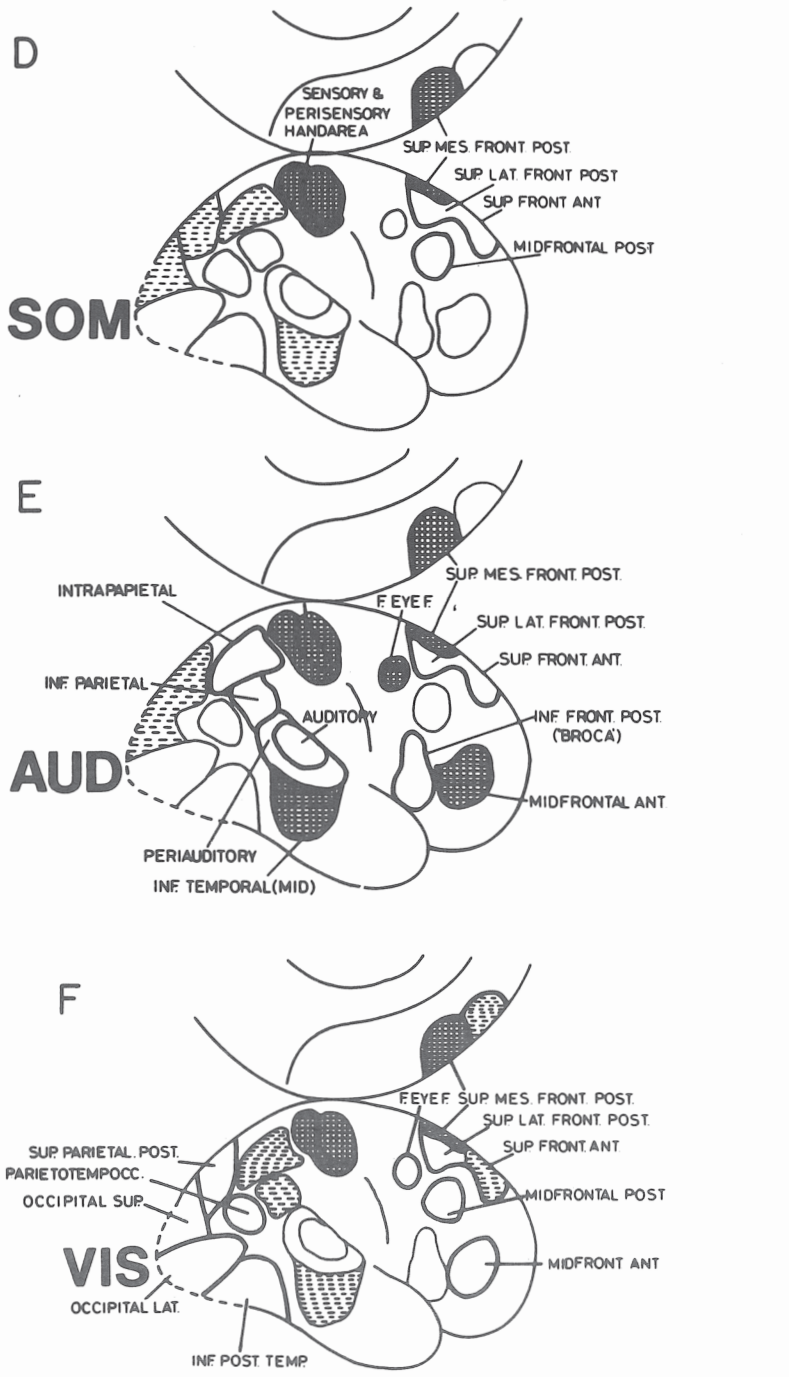


FIGURE 4. Comparison of rCBF increases obtained during stimulation of a single modality (SMS) and during simultaneous stimulation of three modalities, with attention to one (TMS). SOM, AUD, and VIS refer to somatosensory, auditory, and visual stimulation, respectively.



Heavy outlines delimit regions that showed activation during stimulation of that modality alone (SMS). Cross-hatched areas indicate regions that showed greater rCBF for TMS than for SMS. Dashed-line areas indicate regions with rCBF greater for SMS than for TMS. Stippled areas indicate regions that were activated with TMS but not during SMS. (From Roland, 1982.)

significantly activated compared to rest are shown in heavy outlines in Figures 4*b* and *e*. The right temporoparietal regions and right inferior posterior frontal regions had greater increases in rCBF than the left side homologue. Thus, results from two different techniques are in reasonable agreement that left primary auditory and auditory association cortex are more activated with "verbal" processing while the right homologue may specialize in nonverbal information. Furthermore, which side is more activated may depend on the particular strategy used by the subject.

Visual Stimulation

Response to visual stimulation is best studied with PET, since the calcarine cortex and occipital poles are supplied by the basilar artery, and are not usually accessible by ICA injection. To demonstrate the crossed visual pathways in humans, Greenberg et al. (1981) compared fluorodeoxyglucose uptake in the left and right primary visual cortex during visual hemifield stimulation. The primary visual cortex contralateral to the stimulated hemifield exhibited an 8% higher metabolism compared to that region ipsilaterally. During total-field stimulation both the degree and extent of occipital cortex activation depend upon stimulus complexity, as shown by Phelps et al. (1981). For bright white light stimuli they observed a 12% increase in fluorodeoxyglucose uptake in primary visual cortex (PVC) and a 6% increase in associative visual cortex (AVC) (Fig. 5, "white light"). A more complex, alternating checkerboard pattern produced a 29% PVC and 27% AVC increase in metabolism. Finally, when subjects looked through the laboratory window at a complex scene, PVC rose 45% and AVC 59% (Fig. 5, "complex scene"). Thus, as stimulus complexity increases (higher spatial frequency components and movement) both PVC and AVC become more activated. Consistent with this, area 18 and 19 cells have been found to respond to more complex visual shapes than area 17 cells. Although PVC and some of AVC is inaccessible to ^{133}Xe delivered by ICA injection, Roland and Skinhoj (1981a) were able to see lateral and superior occipital rCBF increases during two-alternative forced choice visual discrimination of elliptic shapes. Shown in heavy outlines in Figures 4*c* and *f*, increased rCBF was observed not only in occipital but also in posterior inferior temporal, posterior superior parietal, parietotemporo-occipital, frontal eye field, midfrontal and superiolateral frontal areas. The significance of flow enhancement in extra-occipital regions will be discussed at the end of this section.

Vestibular Stimulation

Recently, a rCBF study by Friberg et al. (1985) has revealed a human cortical area which may be involved with vestibular sensation. During

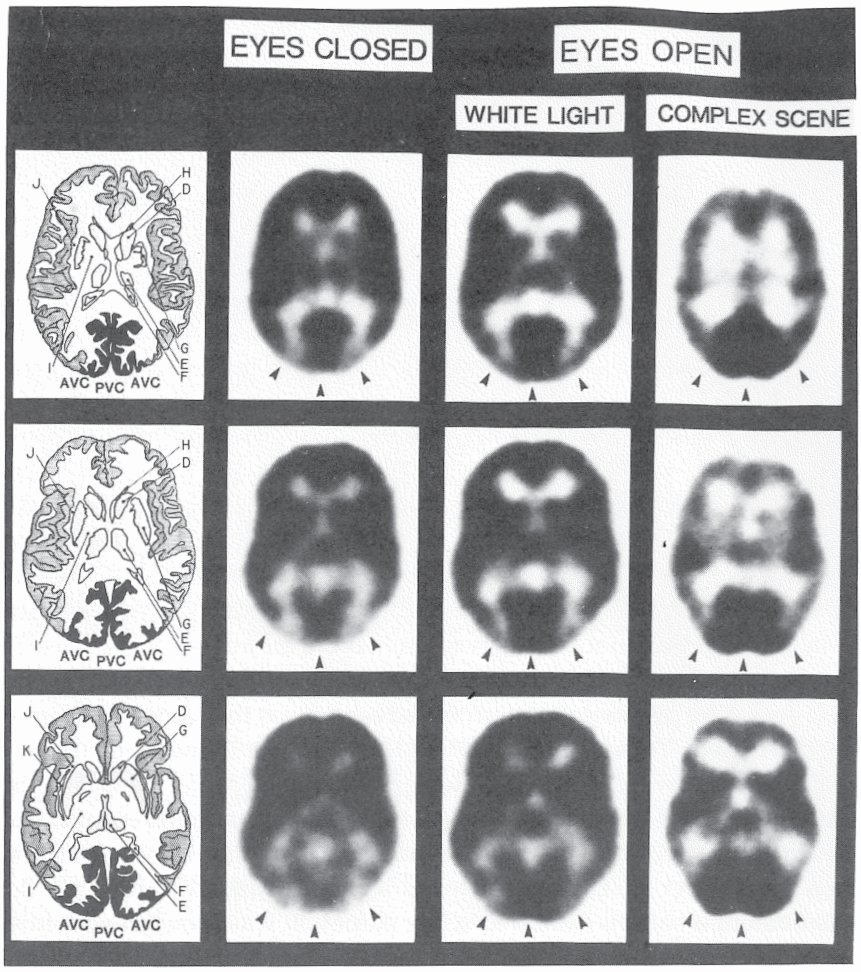


FIGURE 5. PET images of subjects presented with visual stimuli of differing complexity. Three transverse slices are shown for each condition: eyes closed (left), diffuse white light (center), and viewing a complex scene (right). During simple white light stimulation the metabolic response is localized to primary visual cortex (PVC). During more complex stimuli (looking out of the laboratory window) associative visual cortex (AVC) was activated in addition to PVC. (From Phelps et al., 1981.)

caloric-induced vestibular nystagmus, all 10 patients demonstrated rCBF increases in an area corresponding to the lateral projection of the posterior part of the superior temporal gyrus. This region was posterior to areas activated by auditory stimulation. Consistent with this are case reports of epileptic patients with vertiginous auras who have seizure foci in this area (see discussion in this study). However, without a control for eye movements or emotional state of the subjects, it is not possible to conclude that activation of this region is due to vestibular stimulation alone.

Somatosensory Stimulation

Roland and Larsen (1976) studied cortical flow responses during stereognostic testing in human patients. Their patients were asked to discriminate, in a two-alternative forced-choice paradigm, the more oblong of two parallelepipeda palpated by hand. Increases in rCBF were seen in the sensory-motor hand area, and in the superiolateral prefrontal and midfrontal posterior area contralateral to the side of palpation (heavy outlines, Figs. 4*a* and *b*). No focal changes were seen in cortex ipsilateral to the hand studied. The detectors viewed the brain laterally, so increases in mesial frontal regions could not be observed. When the mouth or foot was used in the same paradigm, focal increases were seen in the respective sensory-motor area. The prefrontal pattern of activation was the same regardless of body part used. To separate motor and sensory components of the task, passive patients were studied while parallelepipeda were rolled over one palmar surface. Flow increases failed to appear over the precental hand area but appeared postcentrally, contralateral to the stimulated hand. When the subject alternately squeezed a rubber balloon during the flow measurement a pattern similar to active palpation was seen but with lower flow in the postcentral hand area. After the exercising arm was anesthetized with lidocaine the postcentral flow returned to a level of nonspecific activation.

Directed Attention to Stimulus Modality

To document cortical correlates of the mental process of attending to different sensory modalities, Roland (1982) studied patients during presentation of three discrimination tasks. The tasks were presented individually, to measure activation associated with "single modality stimulation" (SMS); then all three stimuli were presented simultaneously, but the patient was asked to attend to only one and ignore the other two. During the latter "trimodality stimulation" (TMS) differences in flow among the three tasks would be due purely to shifts in attention. The tasks required somatosen-

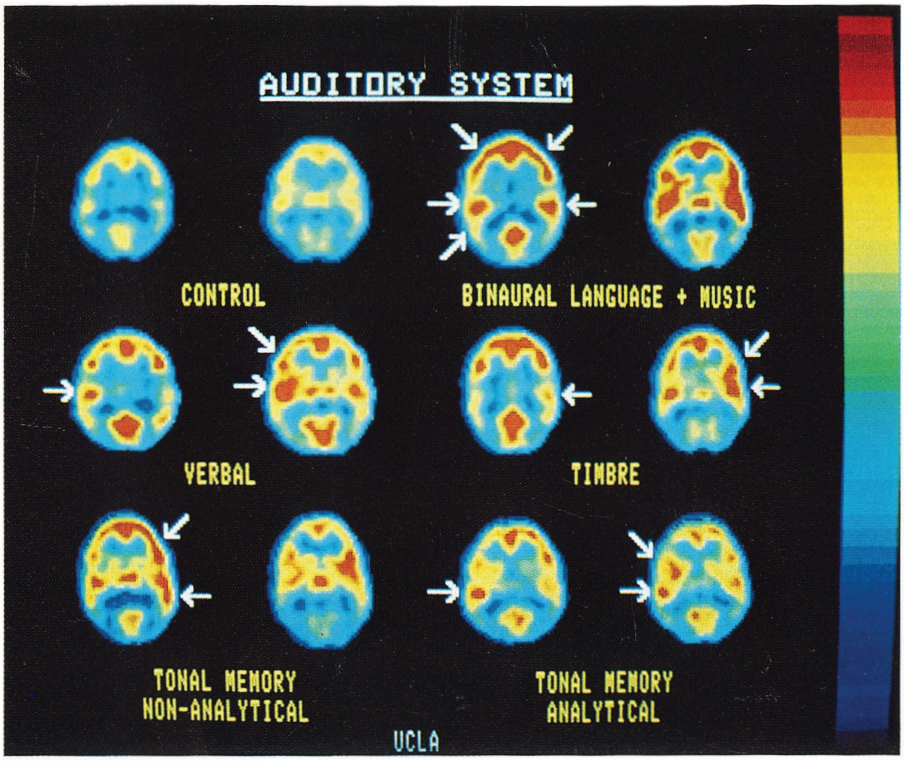


PLATE 1. PET images of subjects presented with various auditory stimuli. Each pair of slices is from a different patient. The more rostral slice is on the left, and the patient's left is on the left side of all images. The "control" shows relative hypometabolism of primary auditory areas in a subject with ears plugged (but free to open eyes). "Verbal" stimulation involved monaural listening to a story. "Binaural language and music" was presented together and produced a more symmetrical activation. "Timbre" involved discrimination of differences in tone pairs. "Tonal Memory" shows two representative results, from subjects who used "analytical" and "non-analytical" strategies. Calibration bar: colors from bottom to top represent increasing glucose consumption. (From Mazziotta et al., 1982b.)

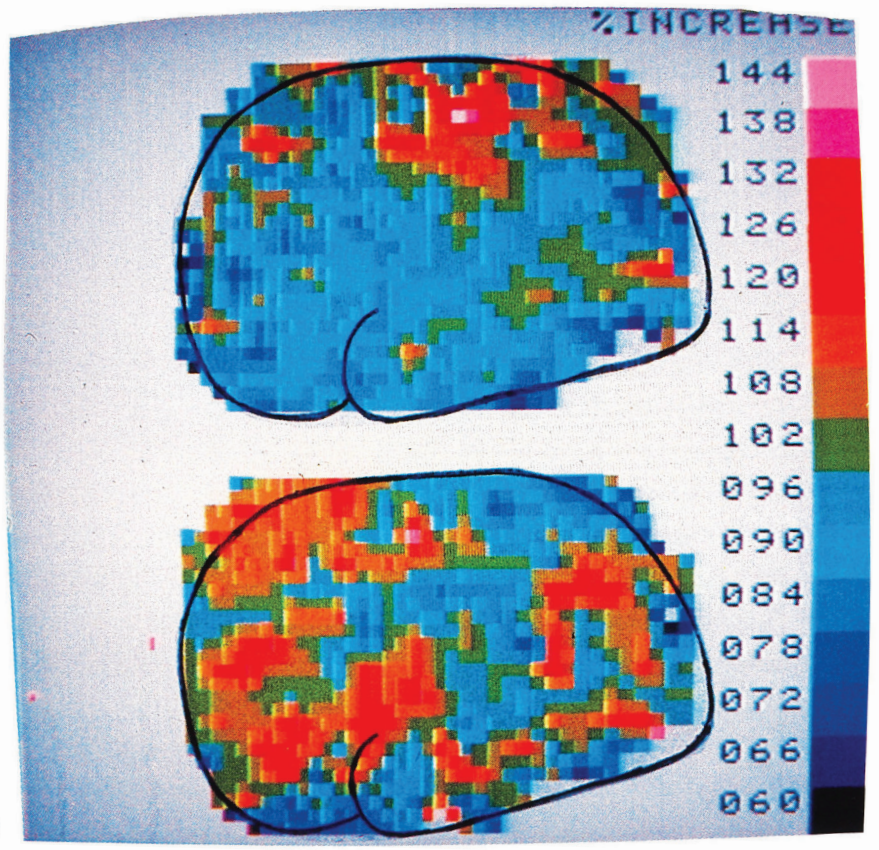
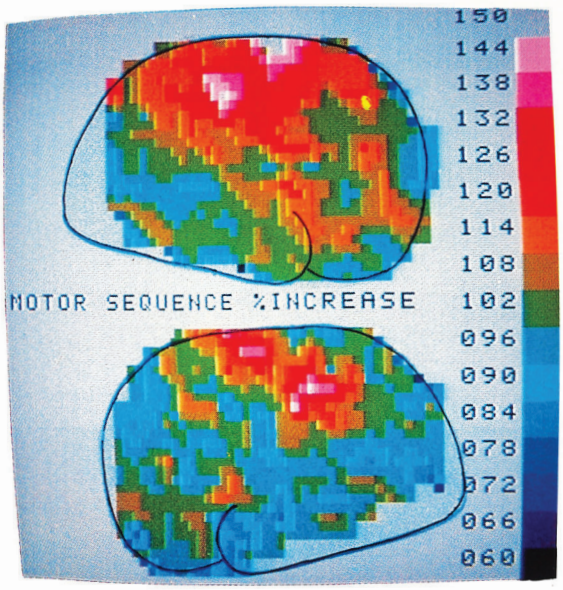
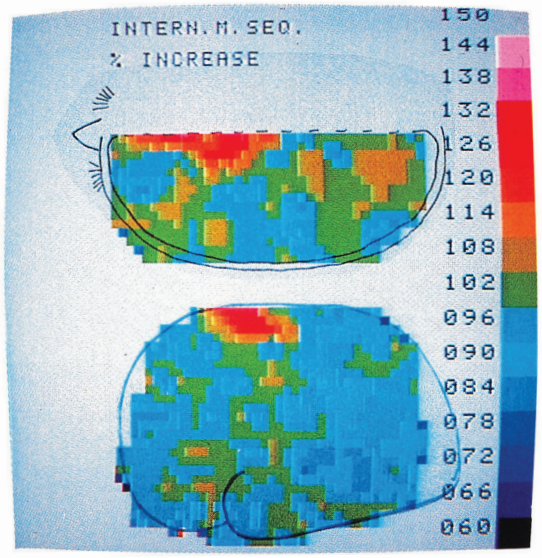


PLATE 2. rCBF response of patients directing attention to different body parts. In the upper panel, *(a)* the patient was expecting the touch of a von Frey hair to his contralateral index finger, but was not touched during the flow measurement. Flow increases are seen over the postcentral hand area. In the lower panel, *(b)* the patient directed attention to his right, upper lip. Note the flow increase over the mouth area. The two subjects differed in the degree of prefrontal activation. (From Roland, 1981.)



(a)



(b)

PLATE 3. rCBF changes during a motor task and during mental rehearsal of the same task. *(a)* rCBF changes during performance of the motor sequence (MS) task involving sequential finger movements (see text). The task was performed with the contralateral hand (top: right hemisphere, bottom: left hemisphere, different subject). *(b)* rCBF changes in a patient mentally rehearsing the movements. Flow increases are no longer present in pre- and postcentral areas but remain in the supplementary motor area. The scale in *a* and *b* is percentage of mean hemispheric flow. (From Roland et al., 1980a.)

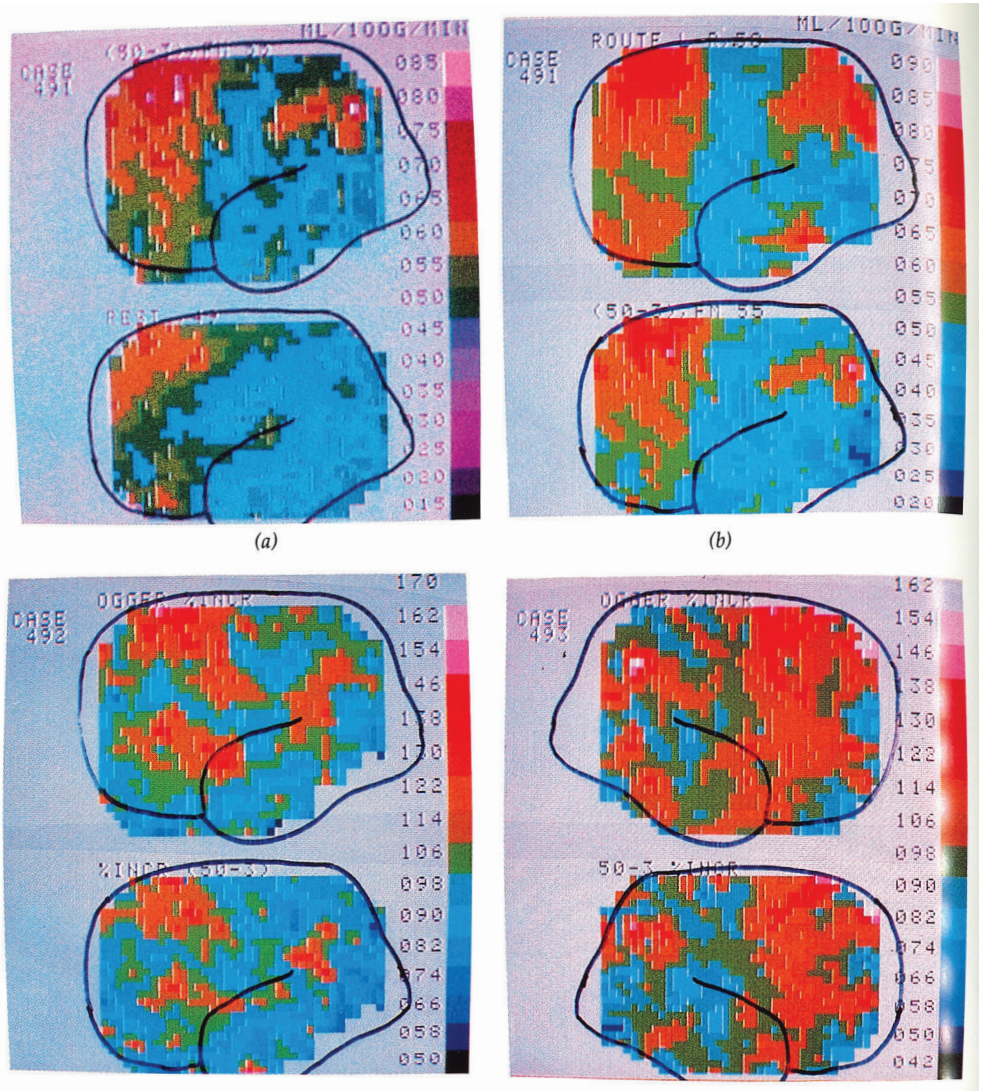


PLATE 4. rCBF profiles in sensory-deprived patients during thinking. *(a)* normal resting pattern (lower). During "50-3" thinking (top) there was an increase in flow in angular cortex and prefrontal cortex. *(b)* repeat measurement in the same subject during "50-3" thinking (bottom), and during "route finding" thinking, imagining that he walked from home, taking turns first right then left (top). *(c)* rCBF during "jingle" thinking, which preferentially activated supramarginal cortex (top) and during "50-3" thinking which activated angular cortex (lower). *(d)* same task as in *c*, but right hemisphere. In *a,b* the scale is ml blood/100g/min; in *c,d* the scale is percentage of mean hemispheric flow. (From Roland and Friberg, 1985.)

sory discrimination of parallelepipeda passively presented to the contralateral hand (SOM), auditory discrimination of tone sequences (AUD), or visual discrimination of differences in elliptic shapes (VIS). Figure 4 illustrates the areas which were significantly activated in both hemispheres under these conditions. The areas outlined with broad borders were activated during individual discrimination of the modality indicated. During trimodality stimulation (with attention to the indicated modality), blood flow increased in these same areas, and also changed in the additional areas delimited by light lines. The relative amount of activation for SMS compared to TMS is indicated by shading: cross-hatched areas exhibited flows significantly greater under TMS than SMS; dashed regions showed greater activation with SMS than TMS, and in unmarked areas the flows were not significantly different.

Figure 6 shows those areas exhibiting flow changes with the modality being discriminated. Significant flow increases occurred in the association area relevant to the modality being discriminated. When attention was directed toward another modality, rCBF in association areas of unattended modalities returned to more basal levels. In addition there was a repeatable, attention-specific flow change in the prefrontal region. No modulation was seen with somatosensory attention, but the second somatosensory and paracentral lobule (somatosensory association areas) were not

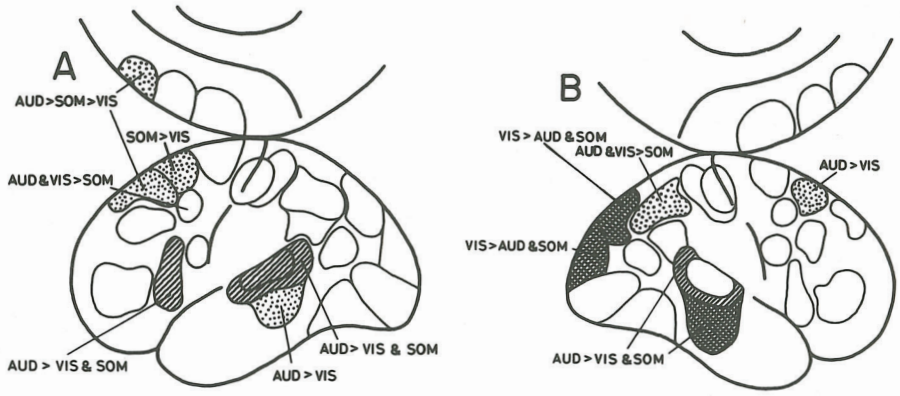


FIGURE 6. Summary of regional activation modulated with shifts in attention, in left hemisphere (*a*) and right hemisphere (*b*). All outlined regions exhibited activations above resting during TMS (see Fig. 4 for abbreviations). Shaded regions indicate significant differences in flow between states of attention (stippled, $p < .05$; hatched, $p < .01$; cross-hatched, $p < .001$). When attention was directed toward auditory or visual stimuli, rCBF was higher in the relevant association areas. (The second somatosensory area and paracental lobule cannot be monitored with this system.) The posterior part of the superior prefrontal cortex also showed modulation when either modality was discriminated. (From Roland, 1982.)

monitored. When significant right–left homologous flow asymmetry existed, flow in the right region exceeded flow in its left homologue. This intriguing study suggests that sensory vigilance may be "gated" at secondary sensory and sensory association areas.

Cortical activation of primary sensory cortex does not require application of a stimulus, as shown by Roland (1981). He studied rCBF in patients told to expect the light touch of a von Frey hair to an index finger. Although subjects were not actually touched during the flow measurement, those that reported being touched showed a 25% flow increase in the contralateral sensory hand area (Plate 2A). When attention was directed toward the contralateral lip, increases were seen in the sensory face area (Plate 2B). Less pronounced increases were seen in the superior prefrontal and midfrontal regions, regardless of direction of attention. Roland used the phrase "differential tuning" to describe this somatosensory activation, possibly caused by the superior and midfrontal areas involved in preparing for an incoming stimulus. Extensive studies of patients with cortical and subcortical lesions indicate that lesions in any of these areas activated during focused attention raise the threshold for somatosensory detection (Roland, 1985a). This includes lesions of the frontal centrum semiovale, which contains connection between activated frontal areas and postcentral hand area.

BRAIN ACTIVATION DURING VOLUNTARY MOTOR PERFORMANCE

In the first study demonstrating cortical blood flow changes during a voluntary motor task, Olesen (1971) used a 35-detector system and ICA injection of ^{133}Xe. He demonstrated repeatable rCBF increases in the upper (medial) parts of the pre- and postcentral region in patients who repetitively clenched their contralateral hand. Although the size of the activated region varied considerably among subjects, all subjects demonstrated flow increases over the sensory-motor hand area. In the study of tactile shape discrimination cited previously (Roland and Larsen, 1976), somatotopy of the pre- and postcentral area was confirmed. When patients palpated the objects with toes, hand, and lateral mouth, contralateral flow increases were seen in upper, middle, and inferior sensory-motor areas, respectively. Pre- and postcentral involvement is consistent with the mixed sensory and motor nature of the task. Ipsilateral pre- and postcentral areas demonstrated no significant focal increases.

Since only lateral views of the head were used in the above study, mesial cortical rCBF changes would be attenuated and merged with changes in

superiolateral cortical areas, resulting in an artificially enhanced flow in upper premotor areas. By placing the detector array over the vertex of the skull, mesial structures can be monitored down to the cingulate sulcus. The supplementary motor area (SMA) is located bilaterally immediately anterior to the motor leg region on the mesial walls of the hemispheres. Electrical stimulation of SMA can cause a variety of motor effects in humans, including an arrest of voluntary movements and speech, postural changes, elaboration of complex, sequential movements (e.g., piano-playing movements of fingers), syllabic speech, or production of simple words. This suggests that the SMAs play a role in the execution of complex, sequential movements. Using the Danish high-resolution system in the vertex position, Orgogozo and Larsen (1979c) studied rCBF profiles in patients during a variety of motor tasks. In addition to expected flow increases in primary sensory-motor areas, rCBF increased bilaterally in SMA for repetitive complex motor tasks. These tasks included sequential toe movements (moving toes once downward, twice upward, three times right and four times left), motor sequence (MS) of fingers (touching thumb to index finger twice, then to middle finger three times, ring finger once and little finger twice, then reverse), and counting aloud. In contrast, sustained, isometric contraction of the foot and counting internally (without speaking) produced no flow changes in SMA. Somatotopy in SMA could not be resolved; the same local area sustained increased rCBF irrespective of the body part moved. Figure 7 demonstrates the wide variability in blood flow between subjects during these measurements (Orgogozo et al., 1979a). The magnitude of SMA flow increase was felt to be a function of subject motivation (Orgogozo et al., 1979b). The range of responses underscores the need for studying a population of subjects in order to demonstrate consistent brain activation.

Roland et al. (1980a) confirmed that SMA was activated in the finger motor sequence task described above (Plate 3A), and that simple repetitive flexion movements of thumb and index finger against a spring load or maintenance of constant load produced no detectable flow changes in this area. In addition, he studied 28 patients who were asked to rehearse the motor sequence *mentally* during the flow measurements without actually moving. To ensure attention to the task the subjects were instructed to begin moving their fingers at the point they had reached in their internal performance upon verbal command by the experimenter. During this task the subjects exhibited no movements during the 45 s of measurement. Surprisingly, a bilateral flow increase was seen in SMA (60% of that seen during performance of the MS task) with no other focal activation (Plate 3B). Roland suggested that the SMAs are "programming areas for motor subroutines and that these areas form a queue of time-ordered motor com-

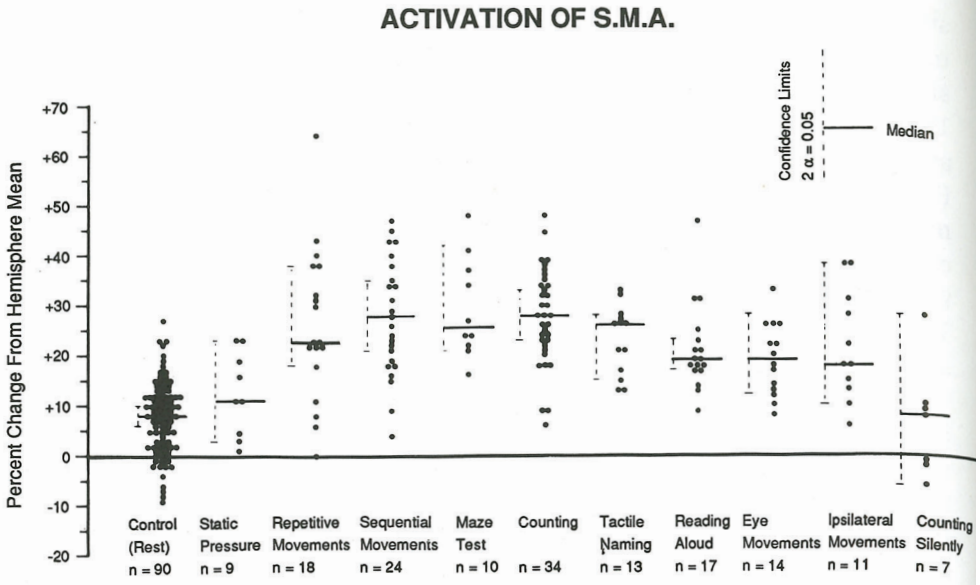


FIGURE 7. rCBF increases in SMA of 90 patients during various motor tasks. *Control:* patient sensory deprived; *static pressure:* maintaining constant force with foot; *repetitive movements:* complex movements of toes; *sequential movements:* complex movements of fingers (MS task); *maze test:* moving hand in a specified direction; *counting:* counting aloud; *tactile naming:* stereognostic testing of hand; *eye movements:* repetitive horizontal saccades. N = number of subjects tested. Note the wide variability in percent increase above hemispheric mean flow among subjects. (From Orgogozo et al., 1979a.)

mands before voluntary movements are executed by way of the primary motor area."

Somewhat different results were obtained by Fox et al. (1985), who studied rCBF during a variety of movements using $H_2{}^{15}O$ and positron emission tomography. During repetitive, bilateral opening and closing of the hands timed with a metronome, they noted bilateral, significant increases in rCBF in SMA. More anterior regions of SMA were activated during saccadic eye movements, suggesting a somatotopic organization. Given this somatotopy, they argued, single-digit movements should activate a smaller cortical region than would whole hand movements. A limitation of radiotracer studies is their inability to measure tracer concentration changes that are distributed over an area that is small compared to the spatial resolution of the detector system (the "point-spread" phenomenon of Mazziotta et al., 1981). Thus, it is difficult to exclude activation of a particular region below the spatial resolution of the measuring system. Since rCBF measurements report the time average of activity during the

40–45 s period after injection of tracer, greater movement should cause more metabolic activity in a population of cells which contain phasically activated neurons. Roland's repetitive finger flexion and MS task were not identical in the number of movements performed (3.5 MS movements per repetitive flexion per unit time) during the rCBF measurements, which could have affected their results. Fox et al. point out that focal activation of SMA during "internal programming" in the MS task could be due to having subject prepare to perform the motor task on command, if the SMAs play a role in "establishing motor set." Other differences limit the direct comparison of these two studies. Roland's MS task was unilateral and self-paced; Fox's task was bilateral and paced to an auditory cue. A follow-up study with sensory-deprived subjects instructed to prepare for movement would help resolve the differences.

Subcortical involvement in voluntary movements has also been investigated with PET techniques. ^{77}Kr is an inert positron emitter which can be used, like $H_2{}^{15}O$, to study rCBF. Using this technique, Roland et al. (1982) studied 10 subjects while they performed the MS task. Bilateral activations in SMA, paracentral lobule, premotor areas, and parietal opercula were seen in order of decreasing intensity. The contralateral sensory-motor hand area was activated as expected. Subcortically, bilateral increases were seen in head of caudate, putamen, and thalamic-subthalamic regions. The contralateral globus pallidus exhibited a flow increase greater than the ipsilateral side. Although variations in absolute flow appeared across subjects, the relative degree of activation in involved areas (SMA, premotor, head of caudate, putamen, pallidum, lower thalamus and contralateral hand area) remained consistent. This constancy of relative flow change was interpreted as evidence for consistent synaptic interaction between these regions. Fox et al. (1985) failed to observe any changes in rCBF of subcortical structures during their motor paradigm. They attributed this to differences in the motor task used in each study.

There is abundant neurophysiological evidence that parietal regions are preferentially involved in performing *limb movements to points in extrapersonal space*. The flow studies above have involved movements in intrapersonal space, that is, movement relative to the body axis or body part (e.g., the MS task). A movement toward an object not connected with the body, and referenced to the environment, was studied by Roland et al. (1980b). In a "spiral task" patients repetitively drew a spiral in the air with their arm and hand during the flow measurement. In a "maze task" patients moved their index finger a specified number of squares left or right, and up or down within a grid they held in their lap; new directions were continually given verbally by the experimenter during the measurement. The subjects

used no visual guidance during either task. In addition to those areas activated during the MS task, both superior and inferior parietal regions were activated bilaterally for both maze and spiral tasks. No differences in rCBF were seen between tasks in parietal areas. Unlike the spiral task, the maze task bilaterally activated the inferior frontal areas, frontal eye fields, and auditory areas. This difference was attributed to the verbal stimulation present in the maze task.

During voluntary *saccadic eye movements* the frontal eye fields (FEFs) demonstrate a significant increase in blood flow. Melamed and Larsen (1979) had patients make repetitive saccades to a rapidly moving object during the rCBF measurement. Irrespective of the hemisphere studied or direction of saccade, both frontal eye fields were activated symmetrically. The same areas were activated during vertical saccades and during reading. In subjects performing repetitive hand and mouth movements, the area activated during saccadic eye movements could be localized between and anterior to hand and mouth precentral cortex. This localization is consistent with cortical stimulation studies of Penfield. During foveation of an object, both frontal eye fields were activated significantly, but less intensely. Listening to words caused a mild increase in this area for one subject. During saccades a significant flow increase was observed in the temporal-occipital areas, consistent with concomitant visual stimulation. Since vertex views were not taken no conclusion about flow changes in SMA can be made. Fox et al. (1985) repeated this study using a paradigm to differentiate between different types of saccades: targeted and untargeted, rhythmic and stochastic, and cued by auditory and visual stimuli. They noted bilateral flow increased in SMA and frontal eye fields independent of the saccade paradigm. In addition, the temporal-occipital area was not activated when subjects were deprived of visual stimulation, suggesting that this region is not significantly involved in saccade generation. Activation of the FEFs can occur in visually deprived subjects. For example, Nishizawa et al. (1982) observed bilateral activation during verbal stimulation, and Roland et al. (1980b) reported FEF activation during movements in extrapersonal space. The role of the frontal eye fields in behavior is probably complex and may include anticipation or directed attention (see Fox et al. 1985; Roland, 1984).

Cortical areas activated during *speech* have also been investigated. Ingvar and Schwartz (1974) were the first to study rCBF in patients during voluntary production of speech. They asked 10 subjects to continually recite names of the months or days of the week, while 32 sites were monitored over the left (dominant) hemisphere. Significant flow increases relative to hemispheric means were seen in upper premotor, middle and inferior sensory-motor areas, and over the middle and anterior lateral fissure.

When subjects read aloud from a magazine held in front of them the same areas, plus the lateral occipital area, were activated. Surprisingly, no consistent flow increase was observed in the left, posterior inferior frontal area (area 44 of Brodmann) corresponding to Broca's area. Using the Danish system, Larsen et al. (1978) studied patients who counted to 20 or recited the days of the week. Vertex and lateral views of both hemispheres showed bilateral flow increases in SMA, lower precentral (face area) and posterior superior temporal cortex; the right SMA was less active than the left. Like Ingvar and Schwartz, Larsen et al. saw no significant activation of Broca's area. This seems inconsistent with clinical evidence that Broca's area is involved in the motor production of speech. This anterior speech area is connected through the arcuate fasciculus to the supramarginal gyrus of the parietal lobe and Wernicke's area, situated lateral to primary auditory cortex. Mohr et al. (1978) have questioned whether Broca's area is, in fact, an obligatory link in speech production. Patients with lesions confined to Broca's area in the dominant hemisphere suffered only a temporary mutism which usually resolved completely with time, in contrast to "Broca's aphasia" where recovery is less complete and patients are left with some degree of mutism. The latter patients exhibit more extensive lesions, including the insula and frontal parietal operculum. Broca's description of the brain of his first aphasic patient confirmed involvement of these more posterior regions in addition to the Broca area proper. Broca ignored the total extent of the lesion and implicated only the most anterior region as causing the language disorder. The failure to detect significant flow increases in this area may reflect methodological limitations or may indicate that Broca's area undergoes no significant net change in neural activity during simple, automatic speech. In contrast to the above studies, Lassen et al. (1978) did find significant flow increases in Broca's area when patients read silently or aloud. A possible explanation, consistent with clinical observations, is that Broca's area may be more involved in processing the grammatical components of speech. It is interesting that auditory discrimination of tones activates Broca's area bilaterally (Figs. 4(*b*) and (*e*)). The observed activation of the right-side homologue of Broca's area during auditory stimulation may be related to perception of speech prosody (Ross et al., 1979). The reader will find a more detailed discussion of regional cortical activation during speech in Ingvar (1983).

BRAIN ACTIVATION DURING COGNITION

While noninvasive measurements in man confirm previous evidence on the cortical areas involved with sensory and motor tasks, they provide new

insights into cortical areas involved with specific higher functions. Ingvar and Risberg (1967) were the first to measure focal blood flow changes during a cognitive task. Subjects were asked to repeat in reverse order a series of digits presented aurally. Using four detectors they were able to demonstrate a significant rise in flows in suprasylvian areas; unfortunately, since their subjects received auditory stimulation this change cannot be attributed purely to cognitive processes. In 1973, Risberg et al. reported flow changes with a 32-detector system in patients performing this "digit-span backward test," and during a reasoning task requiring patients to specify which one of five visually presented objects differed in some way. During the digit-span test flow increases were seen in superior and middle frontal, and precentral regions. During the reasoning tests the midfrontal increases failed to appear and flow in lateral and superior occipital and posterior temporal areas increased. Flow increases in these areas can be accounted for simply by sensory stimulation. Thus, in studies of human cognition it is necessary to control for specific sensory stimulation.

As mentioned above, focal attention to a finger tip, directed attention to specific sensory modalities, and, perhaps, preparation to move can alter regional cortical blood flow. In the first paradigm the difference between rest and test could only be due to processes performed by the brain according to prior instruction, not secondary to sensory drive. To determine whether "thinking" causes measurable flow changes in the human brain, Roland and Friberg (1985), using the Danish system, studied rCBF in patients performing three different mental tasks. They defined thinking as "brain work in the form of operations on internal information done by an awake subject." The three tasks are as follows: arithmetic, or "50 minus 3" thinking, requiring patients to start at 50 and continually subtract 3, "jingle thinking," requiring patients to skip every second word in a well-known, nine-word Danish jingle, and "route finding," requiring patients to imagine their path as they left their home and alternately turned to the left or right at each opportunity. Plate 4 shows results from three patients and Figure 8 represents values averaged across subjects. All flow increases were bilateral. No flow increases were seen in primary sensory or their immediate association areas, consistent with the patients' sensory deprivation. Some cortical regions were activated exclusively for a certain paradigm. The right midtemporal region was activated only for jingle thinking, the same area that was activated in auditory discrimination. Route thinking exclusively activated the superior occipital, posterior superior parietal and posterior inferior temporal regions, all intermediate or remote visual association areas. These areas also showed increased flow in the visual discrimination task. In addition the left anterior inferior frontal region also in-

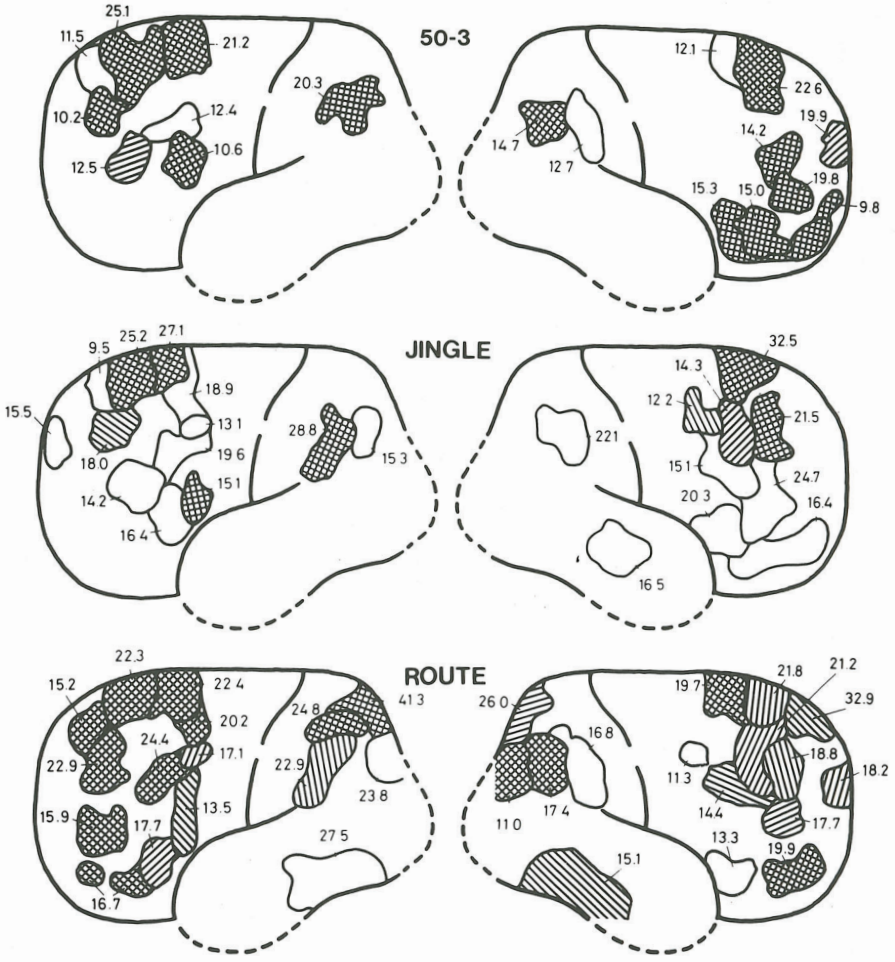


FIGURE 8. Summary of rCBF percent increase and average distribution in patients performing various thinking tasks. Note the absence of motor and sensory cortex activation. Right hemisphere, five subjects; Left hemisphere, six subjects. Shading indicates significance of rCBF increase (unshaded, $p < .05$; hatched, $p < .01$; cross-hatched, $p < .005$). (From Roland and Friberg, 1985.)

creased only for route finding. No area was specifically activated by "50 minus 3 thinking" although the angular cortex was activated bilaterally. That lesions in this region in man may cause acalculia is consistent with this finding. This intriguing study suggests that different types of thinking involve cortical association area of the relevant modalities.

In the frontal lobes, increases in flow above resting were seen in the left anterior prefrontal region in each task. This area is also active at rest and in

every study requiring a subject to perform according to prior instruction. Middle superior prefrontal and left posterior superior prefrontal areas, activated in all cognitive tasks, are also activated in many other paradigms. Roland (1984) suggests that the common factor in these studies is involvement of two or more cortical areas, especially when processing in one cortical area is contingent on processing in the other. The reader is referred to Roland (1984) for a discussion of prefrontal cortex activation during various behavioral tasks.

Weinberger et al. (1986) found correlations between performance on a routine, clinical psychological test and rCBF in dorsolateral prefrontal cortex. The Wisconsin card-sorting (WCS) task has been used to screen for prefrontal cortex pathology. Schizophrenics perform poorly on the WCS task but not on a number-matching test. This study showed that prefrontal flows were depressed in resting schizophrenics compared to controls; moreover, the degree of depression correlated with their performance on the WCS test. No correlation was found with number matching test performance, which was included as an intrasubject control. Orbital and medial prefrontal cortex were not monitored, but this study provides further evidence for prefrontal cortical involvement in complex cognitive tasks.

As demonstrated with auditory stimulation, hemispherical activation may depend on the quality of the stimulation. Various lines of evidence suggest that the nondominant hemisphere specializes in the processing of spatial information while the dominant hemisphere specializes in language processing. In a fluorodeoxyglucose-PET study, Gur et al. (1983) studied eight subjects during a verbal task (solving verbal analogies taken from Miller's analogies test) and a spatial line orientation task (Benton's line-orientation test). All material was presented visually and the subjects remained mute. During the verbal task, the left Wernike's area, inferior parietal areas, and frontal eye fields demonstrated greater metabolism on the left than right, while Broca's area and its right homologue were symmetrically activated. In the spatial task all four areas were more activated on the right. Trevarthen (1972) proposed that lateralized cognitive activity may produce a contralateral orientation response, effectively mimicking an orientation response to peripheral stimulation. When asked a question, subjects usually break eye contact while considering their answer. Gaze direction has been shown to correlate with the content of the imposed question (see Gur et al., 1983); for example, verbal questions tend to evoke right-ward gaze. Gur et al. argue that lateralization of FEF activiation on the same side of hemispheric activation supports Trevarthen's hypothesis. They propose a "cognitive-motor" network in which lateralized cognitive activity will influence ipsilateral motor areas.

CONCLUSION

This review has focused on results obtained with two radioisotope imaging methods: PET, which can measure local metabolic rates in tomographic slices and SPET, which provides a topographic measure of local cerebral blood flow; we have further focused on studies dealing with patterns of cortical "activation" in normal human subjects performing specific sensory or motor tasks, and tasks designed to involve "higher functions." We have neglected a considerable literature on the important clinical applications of these techniques to diagnosis of neurological dysfunction. Such studies also provide revealing correlates between the behavior impaired by a lesion and evidence of its location.

It should be clear that the imaging results obtained with normal behaving subjects often depend for their interpretation on information derived from previous anatomic and clinical observations. In turn, the activation patterns largely confirm deductions from these prior observations. Nevertheless, the images of multiple cortical areas activated during specific tasks have provided some new insights. In most paradigms at least one area in prefrontal cortex was activated above its resting value; the significance of these prefrontal activations may become more evident with further studies employing appropriately designed tasks. Studies of human language areas using blood flow measures have provided new evidence on regions involved in language perception and production. For example, the unexpected absence of activation of Broca's area during naming tasks suggests that this region is not significantly involved in simple speech production. Another region whose language function deserves further study is the right hemisphere homologue of Broca's area, which appears to be activated during tonal auditory discrimination, and has been implicated in prosodic speech. The discovery that sensory association areas are selectively activated during attention to the relevant modality suggests that sensory information may be preferentially transmitted to and elaborated in these areas during perceptual tasks. The role of association areas in different types of "thinking" tasks is just beginning to be revealed.

These studies have also raised further questions. In order to better interpret the significance of these observations we need to understand better the underlying mechanisms of brain "activation," and their correlation with information processing. Technological improvements in the spatial resolution of PET and SPET are needed to study brain structures more discretely. Another major limitation of these techniques is the time period required to gather measurements, which severely limits their temporal resolution. This precludes obtaining information about latencies of activa-

tion relative to stimuli or movements, and the relative timing of sequential cortical activation. Such information may be provided by improved topographic anaysis of electrical activity; using computers to process multiple EEG records investigators can generate topographic images which follow instantaneous changes in regional electric activity (Duffy, 1986). Magnetoencephalography (Williamson and Kaufman, 1981), using multiple detectors in parallel, may also provide real-time, three-dimensional representations of endogenously generated fields. Certainly these noninvasive imaging techniques will continue to be instrumental in revealing the function of different brain regions during normal behavior, and in explaining dysfunctions produced by lesions.

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