

CHAPTER FOUR

POSITRON EMISSION TOMOGRAPHY AND FUNCTIONAL MAGNETIC RESONANCE IMAGING

ERIC M. REIMAN, RICHARD D. LANE, CYMA VAN PETTEN, & PETER A. BANDETTINI

Psychophysiology traditionally involves manipulations of psychological state in intact human beings coupled with examination of central and peripheral physiological changes using sensors on the *surface* of the body, face, or skull. Although the details of the associated brain functions have been of great interest, until relatively recently the methodology for examining brain function in intact human beings in an anatomically precise way was not available. In the past 30 years, however, there has been a revolution in the ability to visualize the three-dimensional structure and function of the brain, based in part on the advent of computer algorithms used to generate these images.

Computerized tomography (CT) and magnetic resonance imaging (MRI) scanning greatly advanced our ability to study brain structure noninvasively. Positron emission tomography (PET) was the first high-resolution technique to examine functional activity in the living human brain, beginning in the 1970s (Phelps et al. 1975). The advent of short half-life radiotracers, such as ^{15}O , transformed PET and brought it into the field of psychophysiology, enabling the examination of the neural substrates of brief mental events in intact people with far greater spatial resolution than was previously possible. Functional magnetic resonance imaging (fMRI), an extension and refinement of structural MRI, has – in the short time since its inception in 1991 (Belliveau et al. 1991) – become the leading functional neuroimaging technique and is likely to remain so in the future. However, many methodological challenges remain to be resolved with fMRI, and PET is a proven technique that is the method of choice in a number of applications.

In this chapter, we begin by presenting a review of PET methodology. Next we compare PET and fMRI along multiple dimensions of interest to psychophysicologists. (The reader is referred to Chapter 36 by Bandettini et al. for a detailed review of fMRI.) The goal of these methodological reviews is to enable researchers to understand and

distinguish between these techniques in a thoughtful manner as they review published work or design research to address specific research questions. In the third and final section we illustrate these principles by presenting the application of PET and fMRI to the study of cognition. Because the ultimate goal of this chapter is to promote the use of PET and fMRI in the generation of new knowledge, we place particular emphasis in this final section on the advantages and disadvantages of PET and fMRI as they pertain to issues of experimental design.

Positron Emission Tomography

PET is an imaging technique that provides information about biochemical and physiological processes in the brain and other organs of the body (Raichle 1983). Neuroscientifically, PET is used to investigate the brain regions, pathways, and chemical processes that participate in normal human behaviors, those that are involved in normal development, aging, and the response to injury, and those that are involved in the pathophysiology and treatment of behavioral disorders. In order to understand the capabilities and limitations of this technique, it is helpful to understand the components of PET studies (see Table 1).

TABLE 1. Components of a PET Study

1. Positron emitting radiotracer
2. PET imaging system
3. Image processing
4. Tracer kinetic model
5. Experimental design
6. Image analysis
7. Data interpretation

POSITRON EMITTING RADIOTRACER

PET studies require the synthesis and administration of a positron emitting radiotracer, a physiological or pharmacological compound that is labeled with a positron emitting radioisotope. Commonly used positron emitting radioisotopes include ^{15}O (half-life 2 min), ^{13}N (half-life 10 min), ^{11}C (half-life 20 min), and ^{18}F (half-life 110 min). Since oxygen, nitrogen, and carbon are normal constituents of the body and pharmaceutical compounds, these elements can be incorporated into physiological compounds, pharmacological compounds, and their analogs without affecting their behavior in the body. Since fluorine can serve as an analog of hydrogen, it can also be incorporated into some of these compounds without affecting their behavior in the body. For this reason, PET has the potential to study a wide variety of substrates, substrate analogs, and pharmacological compounds. For instance, ^{15}O -water is commonly used to measure cerebral blood flow (CBF) (Fox & Mintun 1989; Herscovitch, Markham, & Raichle 1983; Raichle et al. 1983); ^{18}F -fluorodeoxyglucose is commonly used to measure the cerebral metabolic rate for glucose (CMRgl) (Huang et al. 1980; Phelps et al. 1979; Reivich et al. 1979), and ^{11}C -raclopride can be used to estimate the density of available dopamine D2 receptors in the brain (Farde et al. 1985, 1986).

The commonly used positron emitting radiotracers have a radioactive half-life of 2–110 min, so these compounds must be produced in relatively close proximity to the imaging system. The synthesis of a positron emitting radiotracer typically involves a particle accelerator, most commonly a cyclotron, and sometimes complicated radiochemistry techniques (Nozaki & Hazue 1995; Saha, MacIntyre, & Go 1992). The cyclotron produces positron emitting radioisotopes by bombarding a target with rapidly accelerated protons or deuterons. Automated or manual techniques use these radioisotopes (generated in the form of a radiolabeled precursor) and other compounds to synthesize radiotracers. Quality adherence procedures are used to confirm that each batch of radiotracer material (e.g., ^{18}F -fluorodeoxyglucose dissolved in normal saline) is radiochemically pure, chemically pure, and free of pyrogens. In order to reduce the cost and simplify the process involved in radiotracer synthesis, an ultracompact cyclotron is available for the production of ^{15}O -water (the cerebral blood flow tracer most commonly used in brain mapping studies) and other ^{15}O -labeled tracers (Cherry & Phelps 1996; Nozaki & Hazue 1995), and small linear accelerators are becoming available for the production of a variety of positron emitting radioisotopes. For clinical studies, replaceable generators are also available for the production of the myocardial perfusion tracers, such as $^{82}\text{rubidium}$ (^{82}Ru) and certain other radioisotopes (Knapp, Brihaye, & Callahan 1995). Most PET centers have a cyclotron and radiochemistry facility on-site, but some imaging centers

receive the longer-lived radiotracers from a regional radiotracer distribution center that is less than a few minutes away (for both ^{11}C and ^{18}F) or a few hours away (for ^{18}F) by ground or air transportation. Although the short half-lives of positron emitting radioisotopes contribute to the high cost of PET studies, they make it possible to study subjects with relatively low radiation exposures, since radioactivity in the body is almost gone about five half-lives after radiotracer administration.

Once the tracer is synthesized, it is rapidly transported to the PET laboratory and administered to the subject intravenously or by inhalation. The administered radiotracer decays by the emission of a positron from the unstable nucleus of the radioisotope. A positron is a subatomic particle with the mass of an electron and a positive charge. Each positron travels a short distance (root mean square range 0.4–1.4 mm; Cherry & Phelps 1996) before it comes to rest and interacts with an electron in the surrounding tissue. This distance, which contributes to PET's theoretical limitation in spatial resolution, is directly related to the energy of the emitted positron; it is longest for ^{15}O and shortest for ^{18}F among the most commonly used radioisotopes (Cherry & Phelps 1996). The positron–electron pair undergoes annihilation, converting its combined mass into two high-energy (511-keV) photons, known as gamma rays, which travel in virtually opposite directions. These photons are detected by the PET imaging system. The principles of positron emission and annihilation are illustrated in Figure 1.

Brain Mapping Tracers

Since CBF and CMRgl are markers of local neuronal activity, CBF and CMRgl tracers are often used. The most commonly used CBF tracer is ^{15}O -water; other CBF tracers include ^{15}O -butanol and ^{15}O -carbon dioxide. The most commonly used CMRgl tracer is ^{18}F -fluorodeoxyglucose (FDG). Radiotracer techniques are also available for the measurement of cerebral blood volume (CBV) and the cerebral metabolic rate for oxygen (CMRO₂). Whereas increases in local neuronal activity are associated with increases in regional CBF, CBV, and CMRgl (Raichle 1987), they do not appear to be associated with increases in CMRO₂ (Fox & Raichle 1986). As discussed by Bandettini (Chapter 36 of this volume), the observation that local neuronal activity is associated with an increase in CBF in excess of oxygen demand appears to account for the ability of functional magnetic resonance imaging to detect regional increases in brain oxygenation in conjunction with increases in local neuronal activity using a technique known as "blood oxygenation level dependent" (BOLD) contrast.

Advantages of ^{15}O -water include the ability to acquire an image relatively quickly (typically, about 60 sec, but as quickly as 15–20 sec – Cherry et al. 1995; Volkow et al. 1991) and the ability to make multiple images in the same

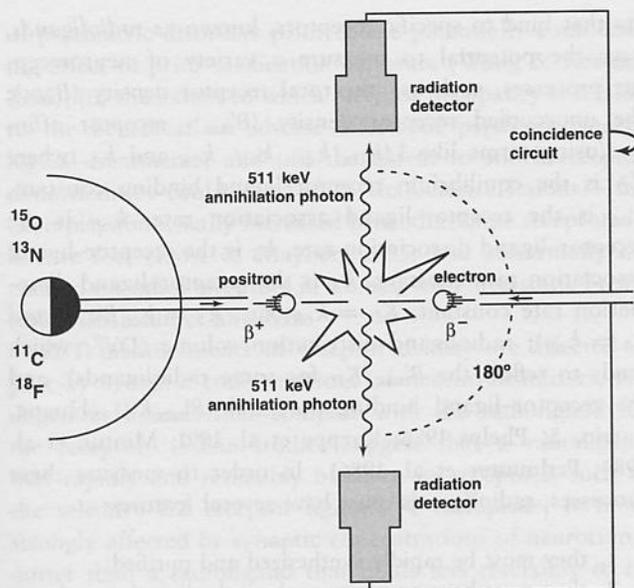


Figure 1. Physics of positron emission and coincidence detection. Radioisotopes employed in PET studies decay by the emission of positrons (+), particles that have the mass of an electron but a positive charge, from a nucleus that is unstable owing to a deficiency of neutrons. Positrons lose their kinetic energy after travelling about 0.4–1.4 mm, come to rest, and interact with local electrons (-). The two particles undergo annihilation, and their mass is converted into two high-energy (511-keV) photons that travel in opposite directions (approximately 180°). The two photons are detected by opposing detectors in the imaging system, which are connected by an electronic coincidence circuit that records an event only when the two photons reach the detectors at the same time. Redrawn with permission from Raichle, "Positron emission tomography," *Annual Review of Neuroscience*, vol. 6, pp. 249–67. Copyright 1983 Annual Reviews, Inc.

subject with an interval of only 10 min between scans. The ability to acquire images relatively quickly is attributable to the rapid transport of ^{15}O -water to the brain and its almost complete diffusibility across the blood–brain barrier during a single pass. During a single pass through the brain, the initial ^{15}O -water "uptake phase" is especially sensitive to the detection of increases in local neuronal activity (Cherry et al. 1995; Volkow et al. 1991); still, scans commonly continue through the radiotracer "washout phase" and beyond in order to accumulate more PET counts and thus reduce noise in the image. Since scans can be acquired relatively quickly, ^{15}O -water studies make it possible to study individuals during a relatively brief behavioral state (e.g., an experimentally induced emotion or a particular stage of sleep) and during a relatively uncomfortable behavioral state (e.g., experimentally induced anxiety or pain). The ability to acquire multiple sequential images is attributable to the 2-min half-life of ^{15}O and the resulting rapid decay of radioactivity from the preceding image.

^{15}O -water studies permit subjects to serve as their own control during a single scanning session. For this reason, this tracer is especially well suited for studies that benefit from the acquisition of multiple images during a

single scanning session: investigating brain regions that participate in aspects of normal human behaviors, such as perception, motor control, attention, memory, language, emotion, the sleep–wake cycle, and consciousness (Fraczkowiak et al. 1997; Raichle 1987), as well as for investigating regions of the brain that are selectively affected by rapidly induced behavioral syndromes, such as biochemically induced panic attacks and behaviorally induced anxiety syndromes (Reiman 1997). Due to the brevity of scans, the main disadvantage of this brain mapping tracer is that the acquired images contain relatively few PET counts (on the order of 7–8 million counts per brain image). Because such images are relatively noisy, they are usually smoothed to a lower spatial resolution: about 10–20 mm full width at half-maximum (FWHM) in order to improve the signal-to-noise or S/N ratio (i.e., image quality). Furthermore, ^{15}O -water studies typically involve averaging conditions across subjects to further improve S/N. Nonetheless, the ability to compare images within subjects during experimental and baseline images – the ability to subtract the baseline image from the experimental image in order to generate a voxel-by-voxel "subtraction image" of state-dependent changes in regional CBF – usually outweighs concerns about poor spatial resolution.

Although ^{15}O -water is the radiotracer most commonly used in brain mapping studies, it does not completely diffuse across the blood–brain barrier in a single pass; this leads to a slight underestimation in CBF measurements, particularly at higher rates (Herscovitch, Markham, & Raichle 1987). In contrast, the radiotracer ^{15}O -butanol is completely diffusible; it thus provides a more accurate measure of blood flow and, at least theoretically, avoids underestimates of state-dependent increases in regional blood flow (Herscovitch et al. 1987). Since the underestimation of CBF with ^{15}O -water is small and the synthesis of this tracer is fully automated, most laboratories favor it over butanol in brain mapping studies.

Whereas CBF images are commonly acquired in the 1 min following the intravenous bolus injection of ^{15}O -water and its arrival to the brain, FDG images are commonly acquired over a 30–60-min period following the intravenous administration of FDG, its transport into brain cells, and its phosphorylation. As an analog of glucose, deoxyglucose undergoes phosphorylation (the initial step of glycolysis), leading to the accumulation of ^{18}F -fluorodeoxyglucose-6-phosphate (Huang et al. 1980; Phelps et al. 1979; Reivich et al. 1979; Sokoloff et al. 1977). Unlike glucose-6-phosphate, this metabolite cannot be further metabolized and is "trapped" in brain cells. The first 15–30-min interval following the intravenous administration of FDG is known as the *radiotracer uptake* period, during which the tracer is delivered to the brain and phosphorylated; radiotracer uptake during this period is reflected by changes in regional brain activity. The next 30–60-min

interval is known as the *scanning* period (though scans can begin even earlier). During the scanning period, the image of brain activity is like a slowly degrading photograph and is relatively unaffected by the subjects' behavioral state. Advantages of FDG in brain mapping studies include the generation of relatively high-quality images (due to the relatively long scans and, when necessary, to completing the radiotracer uptake period outside the imaging system). The relatively long FDG scan leads to the acquisition of images with relatively high PET counts (on the order of 50–150 million counts per brain image), resulting in higher-quality images than those acquired using ^{15}O -water. It is thus easier to distinguish biological signals from noise in these images and so there is less need to smooth the images to a lower spatial resolution in order to improve the contrast between signal and noise. The ability to acquire images outside the imaging system is sometimes helpful in patients with unusually severe claustrophobia (a much less significant problem with PET than with MRI), in unusual circumstances that are not easy to replicate in the PET laboratory (e.g., an experimental provocation of an acrophobia), and in environments in which the clinical demand leads to restrictions in scanning time. Disadvantages of this radiotracer technique include the inability to repeat scans in the same subject during a single scanning session (it takes several hours for the residual brain activity to dissipate); the inability to study relatively brief or uncomfortable behavioral states (e.g., rapid-eye-movement or REM sleep; experimentally induced anxiety syndromes) or behavioral states that might be confounded by psychophysiological habituation during the radiotracer uptake period (although state-dependent changes in brain activity most strongly reflect the first few minutes of uptake); head movement during the scan; and the relatively small number of scans that one can acquire in a research subject due to the relatively longer half-life of ^{18}F , its accumulation in the bladder (the dose-limiting organ), and concerns about the safety of low-level radiation exposure. Nonetheless, the quality of FDG images makes them particularly well suited for comparing regional brain activity across scanning sessions in between-group comparisons (investigating alterations in regional brain activity in patients versus healthy control subjects, males versus females, older versus younger subjects, etc.) as well as between-session comparisons (studying the same subject on different days to investigate regions of the brain that are selectively affected by age, different stages of the menstrual cycle, the response to brain injury, medication and nonmedication treatments, the natural history of behavioral disorders, etc.).

Neurochemical Tracers

Researchers continue to develop, test, and apply positron emitting radiotracers with the potential for characterizing neurotransmitter and neuroreceptor processes. Radiotrac-

ers that bind to specific receptors, known as *radioligands*, have the potential to measure a variety of neuroreceptor processes, such as: the total receptor density (B_{\max}); the unoccupied receptor density (B'_{\max}), receptor affinity (using terms like $1/K_D$, k_{on} , k_{off} , k_3 , and k_4 , where K_D is the equilibrium receptor–ligand binding constant, k_{on} is the receptor–ligand association rate, k_{off} is the receptor–ligand dissociation rate, k_3 is the receptor–ligand association rate constant, k_4 is the receptor–ligand dissociation rate constant; $K_D = k_{\text{off}}/k_{\text{on}}$, $k_3 = k_{\text{on}}B'_{\max}$, and $k_4 = k_{\text{off}}$); radioligand distribution volume (DV'' , which tends to reflect the B'_{\max}/K_D for some radioligands); and the receptor–ligand binding potential ($B'_{\max}K_D$) (Huang, Barrio, & Phelps 1986; Koeppe et al. 1991; Mintun et al. 1984; Perlmutter et al. 1986). In order to measure these processes, radioligands must have several features:

1. they must be rapidly synthesized and purified;
2. they must have no pharmacological, clinical, or adverse effects in the radiotracer doses employed;
3. they must easily penetrate the blood–brain barrier;
4. they must bind to the receptor subtype of interest (e.g., dopamine D2 receptors) without binding to other receptors of the same type (e.g., other subtypes of dopamine receptors), a feature known as “receptor subtype selectivity”;
5. they must bind the receptor of interest in much higher affinity than they bind to nonspecific, nonsaturable receptors (just about anything to which a radioligand might stick), a feature known as “receptor specificity”;
6. they must not produce labeled or potentially confounding active metabolites during the scanning period; and
7. their kinetics must be compatible with the tracer kinetic model used to transform images of activity into neuroreceptor measurements (Huang et al. 1986; Sedvall et al. 1986).

When studies find an increased density of unoccupied receptors using many of the better-established radiotracer techniques, it could reflect an increase in total receptor density itself (e.g., an increase in dopamine D2 receptor density) or a decrease in the synaptic concentration of endogenous ligand (a decrease in the synaptic concentration of dopamine).

At this time, promising positron emitting radioligands have been developed for the characterization of dopamine D1, D2, D3, D4, and transporter receptors (although the concentrations of imaged D3 and D4 receptors are not very high), the serotonin 1A, 2A, and transporter receptors, acetylcholine muscarinic and nicotinic receptors, opiate mu and mu/delta receptors, the glutamate NMDA receptor, benzodiazepine 1 and 2 receptors, and estradiol receptors (Langstrom & Dannals 1995; Sedvall et al. 1996; Stocklin 1995). To the extent that these radiotracer techniques are validated, they can be used to investigate (i) the role of receptor subtype abnormalities in the pathophysiology

of psychiatric disorders prior to the potentially confounding effect of prior medication exposure (Wong & Resnick 1995), (ii) the extent to which receptor occupancy is related to the beneficial or adverse effects of psychopharmacological treatments, and (iii) the extent to which receptor abnormalities could be used to characterize lesions – for example, abnormally increased benzodiazepine receptors in seizure foci (Frost & Mayberg 1995) and abnormally increased estradiol receptors in women with metastatic breast cancer (Mintun et al. 1991).

PET measurements of receptor density are affected in part by synaptic concentrations of neurotransmitters, endogenous ligands that compete with the radioligand for the receptor. Some studies suggest that a radioligand that rapidly and reversibly binds to its receptors, such as the selective D2 receptor ligand ^{11}C -raclopride, is more strongly affected by synaptic concentrations of neurotransmitter than a radioligand that binds less reversibly to its receptors, such as the D2/5HT2 receptor ligand ^{11}C -N-methyl-spiperone. Researchers have actually capitalized on this potential confound in order to estimate how synaptic concentrations of neurotransmitters (including synaptic concentrations of dopamine, serotonin, acetylcholine, and endorphins) are locally affected in response to pharmacological challenges (Dewey et al. 1990, 1992; Smith et al. 1997, 1998) and during behavioral tasks (Koepp et al. 1998). This technique can be used to investigate how synaptic neurotransmitter concentrations are regionally involved in the pathophysiology, medication treatment, and nonmedication treatment of psychiatric disorders, how they are regionally affected during different behavioral tasks or states (thus helping to characterize the chemical neuroanatomy of normal behaviors and experimentally induced behavioral syndromes), and potentially important neurotransmitter actions. Thus, PET can now be used to map the chemical processes that are involved in normal and abnormal human behaviors.

Finally, radiochemists have developed radiotracers for the characterization of other neurotransmitter processes, including estimates of DOPA decarboxylase activity (an enzyme involved in dopamine synthesis that provides a marker of intact dopaminergic neuronal terminals and is reduced in patients with Parkinson's disease), serotonin synthesis, and concentrations of monoamine oxidase A and B (enzymes involved in the degradation of norepinephrine, serotonin, and dopamine) (Langstrom & Dannals 1995; Stocklin 1995).

Other Tracers

In addition to the tracers just described, radiotracer techniques have been developed for other physiological processes. These include: amino acid uptake, which provides clinically useful information about the spatial extent of low-grade and high-grade tumors; CMRO_2 , which has been used in conjunction with measures of CBF and

CBV in the assessment of cerebrovascular disorders; the permeability–surface area product for water (PSw), a measure of blood–brain barrier permeability to water that is regulated by the central adrenergic system and increased by most antidepressants; and brain tissue pH, a reduction in which has been postulated to trigger anxiety attacks in patients with panic disorder (Conti 1995; Heiss & Podreka 1995; Herscovitch 1995; Reiman 1990). Radiochemists continue to develop and test positron emitting radiotracers with the potential for measuring biochemical and physiological processes of interest to researchers and clinicians. For this reason, the versatility of PET is limited only by the ingenuity and persistence of radiochemists and the interest (and patience) of researchers who wish to use the radiotracers to address interesting and important problems.

THE PET IMAGING SYSTEM

After the radiotracer is administered, an imaging system is employed to make regional measurements of PET counts in the brain. Available PET systems consist of concentric rings of detectors into which the head or body is placed (Cherry & Phelps 1996). Each detector consists of a scintillator crystal that transforms an incoming 511-keV photon (i.e., a gamma ray) into a flash of light and a photomultiplier tube that transforms the light into an electric current. Most commercial systems use the crystal bismuth germanate (BGO). Older commercial systems use the crystal cesium fluoride, which has the capacity to acquire counts with less dead time at higher rates and thus to acquire ^{15}O -water images with sufficient counts in a shorter period of time. Some commercial systems use the crystal sodium iodide, which is less expensive, less powerful, and less suitable for ^{15}O -water studies. Manufacturers have recently investigated the use of lutetium oxyorthosilicate (LSO), an expensive crystal with the potential to increase the detection of gamma rays by a factor of five (Cherry & Phelps 1996). Manufacturers have also considered the use of solid-state devices in place of, or in addition to, photomultiplier tubes to provide more accurate and less expensive imaging systems.

Each detector is connected to multiple opposing detectors by coincidence circuits. Coincidence circuits record those events in which the opposing detectors sense two annihilation photons simultaneously. Coincidence circuits thus record the number of annihilation events that have occurred somewhere along a straight line joining the two detectors. (These circuits also record a relatively small number of “random coincidence events” in which unrelated photons strike opposing detectors simultaneously and a small number of “scattered coincidence events” in which gamma rays have been deflected somewhere in the body to another detector, leading to inaccurate localization of the annihilation event.) Typically, PET systems record at least one million coincidence events per PET

slice during a single scan. Measurements of regional PET counts in the head are reconstructed from the record of coincidence events by means of a computer-applied mathematical reconstruction algorithm (Cherry, Dahlbom, & Hoffman 1992; Cherry & Phelps 1996). The principle of coincidence detection was illustrated in Figure 1.

Until recently, most PET systems restricted the acquisition of coincidence events to those that struck opposing detectors in the same or adjacent horizontal planes by placing septa between adjacent rings that projected beyond the detectors into the field of view. While this two-dimensional (2D) mode of image acquisition greatly reduces the number of random and scattered events, it also decreases sensitivity to detect true coincident events to about 0.5%, because it misses the coincidence events that occur across sections (Cherry & Phelps 1996; Townsend 1991). The latest commercial systems enable the septa between adjacent rings to be retracted automatically, thus permitting the three-dimensional (3D) mode of image acquisition. By acquiring coincidence events using opposing detectors from any of the rings, the sensitivity to detect true coincidence is increased to about 3.0% (Townsend 1991). Three-dimensional imaging characteristically leads to higher-quality images (i.e., an increase in S/N), particularly at low counting rates (Cherry, Dahlbom, & Hoffman 1991). The 3D mode of image acquisition provides a particular benefit for neurotransmitter and neuroreceptor studies, increasing S/N by a factor of about five, since these processes occur in minute concentrations (Cherry & Phelps 1996; Townsend 1991). Although the 3D mode of image acquisition may be less useful for higher counting rates, it is now used in many ^{15}O -water studies (Cherry, Woods, & Hoffman 1993), since it is possible to acquire images at a lower radiotracer dose and so reduce the subject's radiation exposure. Because 3D imaging increases the number of scattered and random coincident events, involves a computationally intensive 3D-image reconstruction algorithm (Cherry et al. 1992), and involves unusually large data sets, some situations may be more appropriate for 2D imaging. In the future, different detector configurations (e.g., nearly spherical systems), shorter septa lengths, and more precise coincidence timing could provide images with unprecedented image quality (Townsend 1991).

Like other imaging techniques, PET systems can be described in terms of their spatial resolution (ability to image small objects), temporal resolution (ability to acquire data quickly), contrast resolution (ability to distinguish true signals from false signals and noise), and sensitivity (ability to acquire data from small amounts of radioactivity) (Daube-Witherspoon 1995). PET systems differ in other specifications, including: the size of the aperture into which the head or body is placed; the number of horizontal PET slices for which data are simultaneously acquired (an almost anachronistic concept with 3D imaging, but as many as 47 slices in commercially available systems); the distance

between contiguous slices (about 3.5 mm in the latest systems); the thickness of each slice (about 5 mm); the axial field of view (about 15 cm in the latest systems, permitting researchers to acquire data in the entire brain); the ability to acquire images in only 2D versus either 2D or 3D mode; the external radiation source used to acquire transmission images before (or, possibly, at the same time as) the emission scan; and the electronics, computers, and software used in image processing (Daube-Witherspoon 1995).

The spatial resolution of an imaging system reflects the smallest distance between two point sources that permits a distinction between their respective images. When a point or line source is imaged, a count profile assumes the approximate shape of a Gaussian curve; the spatial resolution is most commonly defined as the width of the curve at half of its maximum value (i.e., the full width at half-maximum or FWHM). The latest generation of PET systems has a spatial resolution of about 3–5 mm FWHM in the plane of each slice, although the reconstructed images are typically smoothed further in order to improve contrast resolution (S/N). The theoretical limit of PET's spatial resolution is about 2–3 mm FWHM, owing to (i) the distance the positron must travel from the radionuclide before it interacts with an electron and (ii) the small extent to which the resulting gamma rays that arise from an annihilation event deviate from a 180° angle (Cherry & Phelps 1996). For this reason, PET is ultimately limited in its ability to detect and represent accurately data from very small structures (such as brainstem nuclei) and in the extent to which it can be used to study small animals. The extent of this limitation depends on: the resolution of the system; the radioisotope (best for ^{18}F owing to the lower energy and smaller distance travelled by the emitted positron; worst for ^{15}O); the size, shape, and orientation of the structure of interest; and the contrast in radioactivity between the structure of interest and its neighbors (Daube-Witherspoon 1995; Mazziotta et al. 1981).

Despite the PET system's limited spatial resolution, experimental studies can be designed to localize and discriminate regional changes in PET measurements that are as close as 1–2 mm apart (Fox et al. 1986; Mintun, Fox, & Raichle 1989). Thus, it has been possible to map the retinotopic organization of visual cortex and the somatotopic organization of supplementary motor cortex with remarkable precision (Fox et al. 1986; Fox, Burton, & Raichle 1987; Frackowiak et al. 1997).

PET's temporal resolution – the time it takes to acquire an image with adequate S/N – depends on the radiotracer technique (the time it takes for FDG uptake and phosphorylation, the time it takes to reach a state of equilibrium in most neuroreceptor studies, etc.); the time it takes to acquire sufficient PET counts (a factor that is influenced by the radiotracer dose and the sensitivity of the PET system for neurotransmitter, neuroreceptor, and other studies involving low count rates); and the ability to tolerate high

count rates without significant dead time (the cumulative time interval during which the detectors are saturated and incoming photons are not detected, a factor in ^{15}O -water studies). The administered PET dose should be limited to that which produces dead time amounting to less than 20%–30% of the imaging period (Cherry & Phelps 1996).

PET is more sensitive than other imaging techniques, such as single photon emission tomography (SPECT), MRI, and magnetic resonance spectroscopy (MRS). For this reason (and the versatility of potential radiotracer techniques), PET continues to offer special promise in the study of neurotransmitters, neuroreceptors, and other processes that exist in minute concentrations.

PET's contrast resolution is directly related to the number of acquired counts. Thus, there is a trade-off between contrast resolution and the radiotracer dose employed (since higher doses are associated with more counts), temporal resolution (since more counts are acquired during longer scanning periods), spatial resolution (since counts from neighboring voxels contribute to data in each voxel), and the number of images acquired during the same state in one or more individuals that are averaged together. These factors can affect the radiotracer dose employed, the filters used to smooth the images, the number of scans acquired in a single subject, and the number of subjects that participate in a study.

IMAGE PROCESSING

PET images can be significantly affected by radiation attenuation (the extent to which gamma rays are absorbed by the tissue through which they pass, preventing them from reaching the detector), random coincidence events, scattered coincidence events, differences in detector efficiency, and the effects of dead time (especially at higher counting rates). Procedures are commonly used to correct for random events and dead time, normalize the detectors, correct for scatter and attenuation, and calibrate the images using a known radiation source. Images of PET counts can thus be converted into images of radioactivity in units of mCi/ml (Cherry & Phelps 1996; Daube-Witherspoon 1995).

Because of differences in tissue density and the distance a gamma ray must pass through the head or body to reach detectors, only a minority of gamma rays emitted ever reach opposing detectors. Two alternative methods are used to correct an emission image (an image that measures gamma rays that arise inside the head or body) for radiation attenuation. The *measured* attenuation correction method uses a transmission image (an image that measures radiation transmitted through the head from an external radiation source, in this case $^{68}\text{Ge}/^{68}\text{Ga}$) to correct the emission images for attenuation on a voxel-by-voxel basis. The transmission image is typically acquired just prior to the emission images and assumes that there is minimal head movement between scans; efforts are now underway

to acquire transmission and emission images simultaneously, addressing the potential problem of misalignment (Daube-Witherspoon 1995). Alternatively, the *calculated* attenuation correction method uses the contours of the head and knowledge about the extent to which brain tissue and skull attenuate gamma radiation to correct emission images for attenuation. Although less precise, this procedure is commonly used in FDG studies if the subject is not in the scanner during the radiotracer uptake period (since radioactivity inside the head would confound the transmission image) and avoids the potentially confounding effect of movement between transmission and emission scans.

An image reconstruction algorithm is used to convert information about PET counts (originally represented as a sinogram) into horizontal images. The conventional algorithm used in the reconstruction of PET images is known as the filtered back-projection method (Cherry & Phelps 1996). A modification of this method, known as the back-projection-re-projection method, is used to reconstruct data collected in the 3D mode (Cherry et al. 1993; Cherry & Phelps 1996). The filter, which is applied to the data prior to image reconstruction, reduces noise in a manner that results in a reconstructed image with higher S/N but a lower spatial resolution. The filter one chooses to reduce noise and smooth the image depends on the number of acquired counts and a subjective assessment of image quality (Daube-Witherspoon 1995). Iterative algorithms, such as the maximum likelihood algorithm, repeatedly refine the image to achieve an optimal correspondence with the raw data. Although these techniques are quite labor-intensive, they have the potential not only to reduce noise and improve spatial resolution in the reconstructed image, particularly for images involving relatively few counts (e.g., neurotransmitter, neuroreceptor, and ^{15}O -water studies), but also to incorporate additional information (e.g., information from co-registered MRIs about the distribution of gray matter, white matter, and cerebrospinal fluid; Leahy & Yan 1991).

TRACER KINETIC MODELS

The imaging system provides an image of regional PET counts, corresponding to the local concentration of radionuclides (mCi/ml) in the brain. To convert this information into biochemical and physiological processes, a tracer kinetic model must be employed (see e.g. Chen et al. 1998, Huang et al. 1980, or Patlak, Blasberg, & Fenstermacher 1983 for CMRgl measurements; Herscovitch et al. 1983 for CBF; Farde et al. 1986, Huang et al. 1986, Mintun et al. 1984, Perlmutter et al. 1986, or Wong, Gjedde, & Wagner 1986 for dopamine D2 receptor measurements; and Koeppe et al. 1991 for benzodiazepine receptor measurements). A tracer kinetic model consists of mathematical equations that account for the behaviors of the radiotracer in the body, including its radioactive half-life, its

rate of transport to the brain, its distribution into various tissue compartments (e.g., plasma, extracellular brain tissue, intracellular brain tissue, etc.), its active and labeled metabolites, and – in the case of neurotransmitter and neuroreceptor measurements – its specific and nonspecific binding. Models are commonly used to reduce these processes into different compartments (e.g., plasma FDG, brain FDG, brain FDG-6-phosphate, and four transport rate constants in a three-compartment model representing the kinetics of FDG) (Gjedde 1995). Some tracer kinetic models rely on data acquired after the radiotracer reaches a state of equilibrium; others rely on dynamically acquired data, capturing images in sequential frames each lasting a few seconds to a few minutes.

Tracer kinetic models often require the acquisition of peripheral measurements during the performance of PET scans. For instance, the tracer kinetic models used to measure CBF and CMRgl typically rely on multiple, sequential measurements of radioactivity through a radial artery catheter to estimate the rate of radiotracer delivery to the brain. By obtaining a series of samples, one can generate a time-activity curve; this permits the calculation of absolute radioactivity in the sample at any previous moment. Since the radiotracer is injected into a vein, passed through the heart, and distributed evenly into the arterial system, values in the radial artery (which is comparable in distance from the heart to the major cerebral arteries) provide an excellent estimate of the values in the cerebral arteries. The radioactivity detected in the PET scan is corrected for attenuation due to bone, muscle, and other tissue that the signal must pass through. When this information and that from the blood samples are combined, one can determine the absolute amount of radioactivity and thus blood flow (based on the tracer kinetic model) at any location in the brain.

A technique is now available to estimate the rate of FDG delivery to the brain using dynamically acquired images of the internal carotid arteries and a single measurement of venous activity after the scan is complete (Chen et al. 1998). This technique, which eliminates the discomfort (and, in seriously ill patients, the small risk) associated with arterial catheterization, has the potential to be applied to other radiotracer techniques, especially those involving radionuclides other than ^{15}O .

In most cases, the accuracy of biochemical and physiological measurements with PET ultimately depends on the validity of the tracer kinetic model and its underlying assumptions. However, it is possible to conduct brain mapping studies without converting images of brain activity (in units of PET counts of mCi/ml) into quantitative measurements of CBF (in units of ml/min/100 g) or CMRgl (in units of mg/min/100 g) (Fox & Mintun 1989). With ^{15}O -water or FDG and conventional radiotracer techniques, there is a relatively linear relationship between the distribution of activity and CBF or CMRgl in the brain, respectively. In

brain mapping studies, the regional data are typically normalized for the variation in absolute measurements using a linear scaling factor (e.g., a regional/whole-brain ratio) or the general linear model (e.g., analysis of covariance) (Fox & Mintun 1989; Frackowiak et al. 1997), resulting in a unitless term regardless of whether one uses nonquantitative information (PET counts) or quantitative information (in biochemical or physiological units). Thus, if one assumes that whole-brain CBF or CMRgl is not significantly different during experimental and baseline conditions, then it is not necessary to acquire quantitative measurements of CBF or CMRgl, perform an uncomfortable arterial catheterization, or make multiple measurements of arterial activity in order to investigate state-dependent changes in local neuronal activity. Still, it is important to recognize conditions associated with changes in whole-brain CBF (including decreases with sedation, non-REM sleep, and decreased PCO_2 levels) and to consider the use of quantitative measurements in these conditions.

EXPERIMENTAL DESIGN

In general, PET studies are designed to maximize the detection of potentially subtle alterations in CBF, CMRgl, and other PET measurements, to relate these alterations to specific traits and states, and to minimize the effects of possible confounds. In brain mapping studies, researchers commonly investigate regions of the brain that are preferentially involved in potentially dissectable behaviors. In within-group comparisons (i.e., studies involving multiple CBF studies acquired during experimental and control conditions in multiple subjects), researchers commonly study 6–12 subjects and acquire 6–12 images per scanning session. In considering sample size and the number of images in each condition, one considers the problem of statistical power; in considering maximal number of scans per imaging session, one considers subject tolerance (e.g., remaining in the same position during a 2-hr scanning session) and radiation dosimetry. Depending on the question being investigated, it is usually helpful to maximize the intensity of the task during the experimental condition (e.g., maximize the frequency of a visual stimulus, the number of previously seen items in a memory recognition task, or the intensity of an emotion), to choose a baseline condition that controls for aspects of the experimental condition (e.g., the visual stimulus, eye movements, motor response) that are thought to be unrelated to the behavior of interest, to measure other variables that could be related to alterations in local neuronal activity (e.g., reaction time, “hits” and “misses” in a memory recognition task, or psychophysiological expressions of emotion), and to consider the inclusion of an additional no-task baseline condition (e.g., eyes closed and directed forward) to provide an additional perspective about the CBF differences observed between experimental and baseline conditions.

Some experiments call for qualitative differences between experimental and baseline conditions (e.g., emotion versus emotionally neutral conditions), some call for quantitative differences between these conditions (e.g., high or low memory demand), and some call for an investigation of interactions (e.g., greater differences in film-generated than recall-generated emotion).

Because 20–60 seconds are typically required to acquire a ^{15}O -water PET image, behavioral conditions must be studied in blocks. Thus, if one were to conduct a PET study in subjects during an explicit memory task that has been previously studied (outside of a neuroimaging context) using randomly presented familiar and unfamiliar stimuli, it would be helpful to revise the experiment to address the needs of PET. For example, it would be useful to: (1) present as many familiar stimuli as possible during a recall condition without inducing a ceiling effect in the subject's recognition response and present as many unfamiliar stimuli as possible during a control condition; (2) conduct a "dress-rehearsal" study in representative subjects outside the PET laboratory to verify that the expected behavioral responses are observed in these blocked conditions; and then (3) repeat the procedure in a different group of subjects in the PET laboratory. To the extent that it is possible, scans should be randomized or counter-balanced to address the potentially confounding effects of scan order.

In the comparison of known groups, which is one type of between-group comparison (e.g., patients with a psychiatric disorder versus controls), it is helpful to:

1. identify homogeneous patient samples (e.g., only those who satisfy extremely rigorous criteria for a psychiatric disorder) who do not have comorbid psychiatric, neurologic, or serious medical disorders, centrally acting medications, or other possible confounds;
2. identify control subjects who have neither psychiatric, neurologic, or serious medical disorders nor centrally acting medications and who have no other confounds (e.g., age, gender, sociodemographic variables, intelligence, phase of the menstrual cycle);
3. consider the subjects' cognitive-emotional-behavioral state at the time of the scan (i.e., the extent to which a finding is related to the pathophysiology of the disorder or to differences in the subject's current state with regard to eye movement, task compliance, level of arousal, or anxiety);
4. consider the role, if any, of provocation and treatment studies (e.g., to investigate regions of the brain that participate in the predisposition to, elicitation of, and medication or nonmedication treatment of panic disorder); and
5. consider the possible role of specific cognitive activation conditions during the imaging study to help relate specific regions of the brain to dysfunctional mental operations.

At this time, some researchers prefer to acquire PET images in patients and controls during a resting baseline state (e.g., eyes closed and directed forward with no movement and minimal sensory stimulation) in order to avoid the potentially confounding effects of differential performance on a standardized task; some researchers prefer to acquire these images during a well-characterized task that is thought to be unaffected by the disorder (e.g., a relatively simple sensory stimulation or attentional task) in order to reduce possible variations in the subject's cognitive-emotional-behavioral state at the time of the scan; and some researchers prefer to acquire these images during a task that is differentially performed in patients and controls (e.g., a frontal lobe task or a masked facial emotion recognition task) in order to enhance postulated differences in specific brain regions. A potential problem with this last approach is the chicken-or-egg question of whether patients fail to perform the task as well because the investigated region is dysfunctional or, conversely, whether patients fail to activate the investigated region because (for other reasons) they are not complying with the task as well. Various approaches have been taken to deal with this issue, such as varying the difficulty of the task across groups so that performance is comparable in each group or examining whether performance and neural activity are correlated or otherwise systematically related.

Although the subtraction approach has yielded important new findings, its limitations are increasingly being recognized (Friston et al. 1996b; Price & Friston 1997; Sarter, Berntson, & Cacioppo 1996). The subtraction approach is based on the assumption of "pure insertion" – that the only difference between the experimental and control condition is the phenomenon of interest. This approach does not take into account any interaction between the cognitive context and the cognitive function in question. Thus, factorial designs have become increasingly popular since they are tailored to address exactly such interaction effects (Frackowiak et al. 1997). For example, in PET protocols involving 12 scans, 2×3 (with one repetition of each condition) or 2×6 factorial designs are common. Experimental designs that permit more detailed examination of differences also permit greater latitude in the examination of commonalities. Thus, statistical techniques for so-called conjunction analyses (Price et al. 1997) have been developed that permit the identification of regions of statistically significant overlap across conditions or methods.

Finally, experimental studies should attempt to address important questions; they should be designed to test specific hypotheses and generate additional hypotheses that can be tested in the future; they should capitalize on the capabilities of this technology and interpret findings in the context of its limitations; and they should complement other kinds of behavioral neuroscientific studies in human and nonhuman species.

IMAGE ANALYSIS

This section considers techniques used to analyze data from ^{15}O -water studies. Many of the principles (e.g., those involved in anatomical localization, image deformation and averaging, and statistical analysis) are applicable to other radiotracer techniques.

Although it is sometimes helpful to analyze data in pre-selected regions of interest (ROIs), automated algorithms are commonly used to detect state-dependent changes in regional brain activity. Currently used software packages have several components:

1. a smoothing procedure to increase S/N;
2. an interpolation procedure to provide data between slices and generate a three-dimensional image;
3. a method to normalize each PET image for the variation in whole-brain measurements;
4. an iterative procedure to align multiple, sequential PET images acquired in the same subject in case of subtle head movement;
5. an optional co-registration method to align each subject's PET image with a T1-weighted volumetric MRI;
6. an image deformation algorithm to transform each subject's PET images or co-registered PET and MRI images into the spatial dimensions of a standard brain atlas;
7. statistical procedures to compare spatially standardized images acquired during the same experimental and baseline states in different subjects (or, less commonly, multiple images acquired during the same experimental and baseline state in a single subject); and
8. statistical or experimental efforts to address the statistical problem of multiple comparisons (type-I error) (Fox et al. 1988; Frackowiak et al. 1997).

Let us consider some of these issues in more detail.

Smoothing

As previously noted (and illustrated in Figure 2), image smoothing reduces noise in an image, effectively increasing the number of counts that contribute to the measurement in each voxel (Daube-Witherspoon 1995). The extent to which an image is smoothed depends on the quality of the image and the size of certain regions of interest. Images consisting of fewer PET counts (e.g., CBF images that are acquired in a short period of time) require more smoothing than images of higher PET counts (e.g., FDG images). Note that if one analyzes data from a preselected ROI, then image smoothing is less important. By averaging the data from all voxels within the region, one decreases noise and thus increases the signal-to-noise ratio without increasing the contributions of measurements in neighboring voxels via partial volume averaging.

Interpolation

Although PET images are typically displayed in the form of two-dimensional horizontal slices, linear interpolation

methods can be used to fill in data in the gaps between the slices, even when the image is acquired and reconstructed in two dimensions (Fox et al. 1988; Mintun et al. 1989). Once the data are represented in three dimensions, PET images can be reformatted in any plane, deformed into a standard size and shape, and compared in different subjects.

Normalization for the Variation in Absolute Brain Measurements

In order to characterize state-dependent alterations in local neuronal activity, one must normalize regional measurements of CBF, CMRgl, ^{15}O -water uptake, and FDG uptake for the variability in absolute brain measurements on a voxel-by-voxel or regional basis. For instance, unit recordings find a predictable relationship between increases in the frequency of a visual stimulus (an annular reversing checkerboard pattern) and increased neuronal activity in primary visual cortex; PET studies find the same relationship between the frequency of this stimulus and measurements of CBF and ^{15}O -water uptake in the same brain region after the PET data are normalized for the variation in whole-brain measurements (Fox & Raichle 1984). The *proportional scaling* method uses a simple ratio to normalize every PET image in a study to the same whole-brain value (Fox et al. 1988; Fox & Mintun 1989; Frackowiak et al. 1997). In many CBF studies, every voxel in the image is multiplied by 50 ml/min/g (a standard value for whole-brain blood flow) and divided by whole-brain measurements of CBF or ^{15}O -water activity in the particular image. The *general linear model* method normalizes regional PET measurements for the variation in absolute measurements using analysis of covariance (Frackowiak et al. 1997; Friston et al. 1990). The proportional scaling method may be preferable in experiments that involve a relatively small number of scans (since it is not adversely affected by fewer degrees of freedom) and those that involve substantial variations in whole-brain measurements (more likely in qualitative studies of whole-brain PET counts than in quantitative studies of whole-brain CBF or CMRgl; Frackowiak et al. 1997). The general linear model method is a more rigorous statistical method for normalizing the data in experiments that involve a relatively large number of scans and only minor variations in whole brain measurements (Frackowiak et al. 1997).

Whenever a normalization procedure is used, it is assumed that there are no significant differences in whole-brain activity during the experimental and control scans. For conditions in which such differences are apparent (e.g., a reduction in whole-brain CBF associated with hypocapnia, reductions in whole-brain CBF and CMRgl associated with sedative/hypnotic medication or sleep), it may be difficult to know whether an observed change in normalized measurements represents altered neuronal activity in this

region, unchanged neuronal activity in this region in comparison to the rest of the brain, or some combination of these factors.

In some instances, there are significant reductions in regional CBF or CMRgl in many regions of the brain. In such cases (e.g., comparing measurements in patients with Alzheimer's dementia to normal control subjects, since this disorder is associated with reductions in whole-brain CMRgl during the latter stages of the illness), it may be preferable to normalize the data using a region of interest known to be relatively unaffected in the condition of interest (e.g., the pons in studies of Alzheimer's disease; Minoshima et al. 1995a) rather than the data from the whole brain.

Alignment of Sequential PET Images

In order to compare multiple PET images from the same subject, it is important to minimize the misalignment between scans. During the PET procedure, several procedures (e.g., thermoplastic facial masks and head molds) are commonly used to help minimize this problem, but they do not fully address it; although stereotactic devices that drill holes directly into the skull have a role in a small number of neurosurgery patients and experimental animals, they are too invasive for most research applications. Iterative algorithms are now available to characterize and correct for head movement (i.e., up to three translations and three rotations) between scans (Minoshima et al. 1992; Woods, Cherry, & Mazziotta 1992). The Woods algorithm is commonly used in brain mapping studies. Still, these techniques do not correct for misalignment between transmission and emission scans or head movements during a single-frame scan.

Localization, Co-registration, and Deformation

Since PET images consist of low-resolution physiological or biochemical images that lack precise anatomical landmarks, it is usually difficult to identify neuroanatomical ROIs in the PET image. Several strategies have been used to identify regions of interest, compare data from different subjects in these regions, and compare findings from different laboratories. These strategies include (1) visual inspection of the PET image, (2) visual comparison with a brain atlas, (3) definition of an ROI identification in a co-registered structural brain image, and (4) automated methods for the transformation of brain images into the coordinates of a standard brain atlas.

Although visual inspection is a simple method, it is a relatively inaccurate and unreliable way to identify ROIs in the PET image. Furthermore, the choice of a brain region relies on the inspection of the functional data (the dependent variable of interest), increasing the chance of observer bias. Some laboratories acquire PET images in horizontal planes that are parallel to identifiable craniofa-

cial landmarks, such as the orbitomeatal or canthomeatal line, and then attempt to compare these images visually to a tomographic atlas of the brain that uses the same landmarks. Unfortunately, this approach fails to account for the variable relationship between these craniofacial landmarks and the brain, including its angle and vertical extent (Fox, Perlmutter, & Raichle 1985). This strategy, too, relies on the inspection of the functional data and so increases the chance of observer bias.

A more sophisticated approach uses an automated algorithm to co-register each subject's PET image(s) with his or her own structural brain image (i.e., a computed tomography image or an MRI) (Collins et al. 1994a; Evans 1995; Evans et al. 1991; Pellizzari et al. 1989; Woods, Cherry, & Mazziotta 1993). Algorithms have sought to match homologous points (using anatomical or fiducial landmarks), brain surfaces, or voxel-by-voxel features in the PET and MRI brain images. PET-MRI co-registration can be used to identify precisely the structural correlates of PET images and PET subtraction images (when state-dependent CBF changes are distinguishable from noise) in an individual subject. For instance, this approach can be used in brain mapping studies designed to identify and avoid "eloquent" brain areas – regions that are critically involved in a clinically important behavior, such as articulation – in candidates for neurosurgery (Duncan et al. 1997; Fried et al. 1995; Leblanc & Meyer 1990; Leblanc et al. 1992; Pardo & Fox 1993); it can also be used to identify precisely preselected ROIs that have well-defined anatomical landmarks (e.g., a study that wishes to test the hypothesis that the amygdala is activated during a facial recognition task). Co-registration can be used in conjunction with other procedures to help "correct" PET images for the potentially confounding effects of atrophy and partial volume averaging (e.g., to determine the extent to which reductions in regional or whole-brain PET measurements are related to an increased contribution of cerebrospinal fluid; Evans 1995), and it can be incorporated into the procedure used to transform each person's PET images into the dimensions of a standard brain atlas. Limitations of this procedure include minor errors in co-registration accuracy (about 1–2 mm) and the problem of identifying ROIs where there are no precise anatomical landmarks (e.g., divisions of prefrontal cortex). In addition, there are problems associated with any procedure that relies exclusively on preselected ROIs: an inability to determine if the maximal alteration in brain function resides in the ROI or in a neighboring region (due to partial volume averaging), failure to detect differences in subregions (if the ROI is too large), an inability to determine the spatial extent of the alteration in brain function, and an inability to characterize alterations in explored regions. To the extent that this procedure localizes well-defined anatomical ROIs with greater accuracy than available image deformation algorithms, the analysis of preselected ROIs could complement voxel-by-voxel brain maps.

At this time, the most powerful brain mapping algorithms rely on procedures that automatically deform each person's PET images or coregistered PET and MRI images into the coordinates of a standard brain atlas (Collins, Peters, & Evans 1994b; Evans 1995; Fox et al. 1988; Frackowiak et al. 1997; Friston et al. 1991, 1995; Greitz et al. 1991; Kosugi et al. 1993; Miller et al. 1993; Minoshima et al. 1992, 1994; Seitz et al. 1990). By transforming every person's images into the same spatial coordinates, one can compare data from different subjects, use intersubject image averaging procedures that reduce noise and thus increase S/N in statistical brain maps, and compare findings generated in different laboratories. The standard coordinate system is that provided by the atlas of Talairach and Tournoux (1988); coordinates are reported as the distance in millimeters to the left or right of midline (the *x*-axis), the distance anterior or posterior to a coronal plane through the anterior commissure (the *y*-axis), and the distance superior or inferior to a horizontal plane through the anterior and posterior commissures (the *z*-axis). (Earlier studies used coordinates from Talairach et al. 1967, the previous version of this atlas; since the *y*-axis was computed as the distance anterior or posterior to a coronal plane midway between the anterior and posterior commissures, one needs to add 12 mm to a formerly published *y*-axis coordinate to translate it into the currently used coordinate system.) Some image deformation methods are trilinear – adjusting each person's brain image for its orientation and its size in the *x*, *y*, and *z* dimensions but making no adjustments for variations in shape or the position of individual structures. These methods work surprisingly well in brain mapping studies, for they provide a precision of about 5–8 mm depending on the structure's location in the brain (i.e., more accurate for voxels closer to the reference landmarks, less accurate for voxels at the periphery of the image) and permit substantial improvements in S/N when brain maps are superimposed from different subjects (because the imprecision in anatomical standardization is compensated in part by partial volume averaging in the relatively low-resolution PET images) (Fox et al. 1988). Other methods rely on relatively crude nonlinear image deformation algorithms to make additional adjustments for brain shape – an issue that is particularly important to studies that attempt to characterize between-group differences in regional PET measurements. Researchers continue to develop and test nonlinear image deformation algorithms with even greater accuracy (Bookstein 1989; Collins et al. 1994b; Friston et al. 1995; Miller et al. 1993; Minoshima et al. 1994, 1995b; Yun 1996).

Statistical Comparisons

As illustrated in Figure 2, statistical procedures can improve the ability to detect and localize regions of the brain that participate in normal and abnormal behaviors. This section considers image subtraction, intersubject and

within-subject image averaging, statistical tests, and the problem of multiple comparisons.

Perhaps the simplest comparison involves the subtraction of an image acquired during a baseline control state (e.g., the resting state without movement) from an image acquired in the same subject during a behavioral state of interest (e.g., a fist-clenching and -unclenching task) on a voxel-by-voxel basis (after the data are normalized for the variation in whole-brain measurements). The resulting subtraction image (Figure 2) consists of a large number of changes in regional blood flow, some of which may be state-dependent but most of which are random (i.e. noise). An individual subtraction image makes it possible to localize a large state-dependent change in regional blood flow within 1–2 mm despite the limited resolution of PET (Fox et al. 1986; Mintun et al. 1989); it also improves the ability to detect these changes. In comparison to the original images, one can see that the subtraction image improves our ability to detect state-dependent increases in regional CBF (e.g., a large increase in left sensorimotor cortex and smaller increases in the supplementary motor area and right cerebellar vermis). However, it is still difficult to distinguish subtle state-dependent changes from noise in a single subtraction image. Additional steps are needed to reduce the noise.

Subtraction images derived from data repeatedly acquired during the same experimental and control states in one or more subjects can be averaged together on a voxel-by-voxel basis to produce an image of mean changes in regional CBF (see Figure 2). This procedure leads to predictable reductions in noise (since random changes cancel each other out in a predictable relationship to the total number of PET counts), preservation in state-dependent changes (assuming that regions are consistently activated during the behavioral state and that the voxels are in the same spatial coordinate system), and thus an increase in S/N (Fox et al. 1988). In brain mapping studies, *intersubject* image averaging is commonly performed by transforming subtraction images from 6–12 subjects into the coordinates of Talairach's brain atlas and computing an image of mean changes in regional CBF (Fox et al. 1988; Frackowiak et al. 1997). In some cases, *intrasubject* image averaging can utilize two or more subtraction images from the same subject to generate an image of mean changes in regional CBF. Although this procedure assumes that there is little psychophysiological habituation during repeated performance of the experimental or baseline conditions in the same subject, the image of mean increases in regional CBF (or a statistical map representing the same data) can be superimposed onto the subject's co-registered MRI with or without any transformation into standard spatial coordinates.

One can generate images of the mean change in regional CBF, yet statistical tests can further characterize these changes. In order to contrast mean differences in

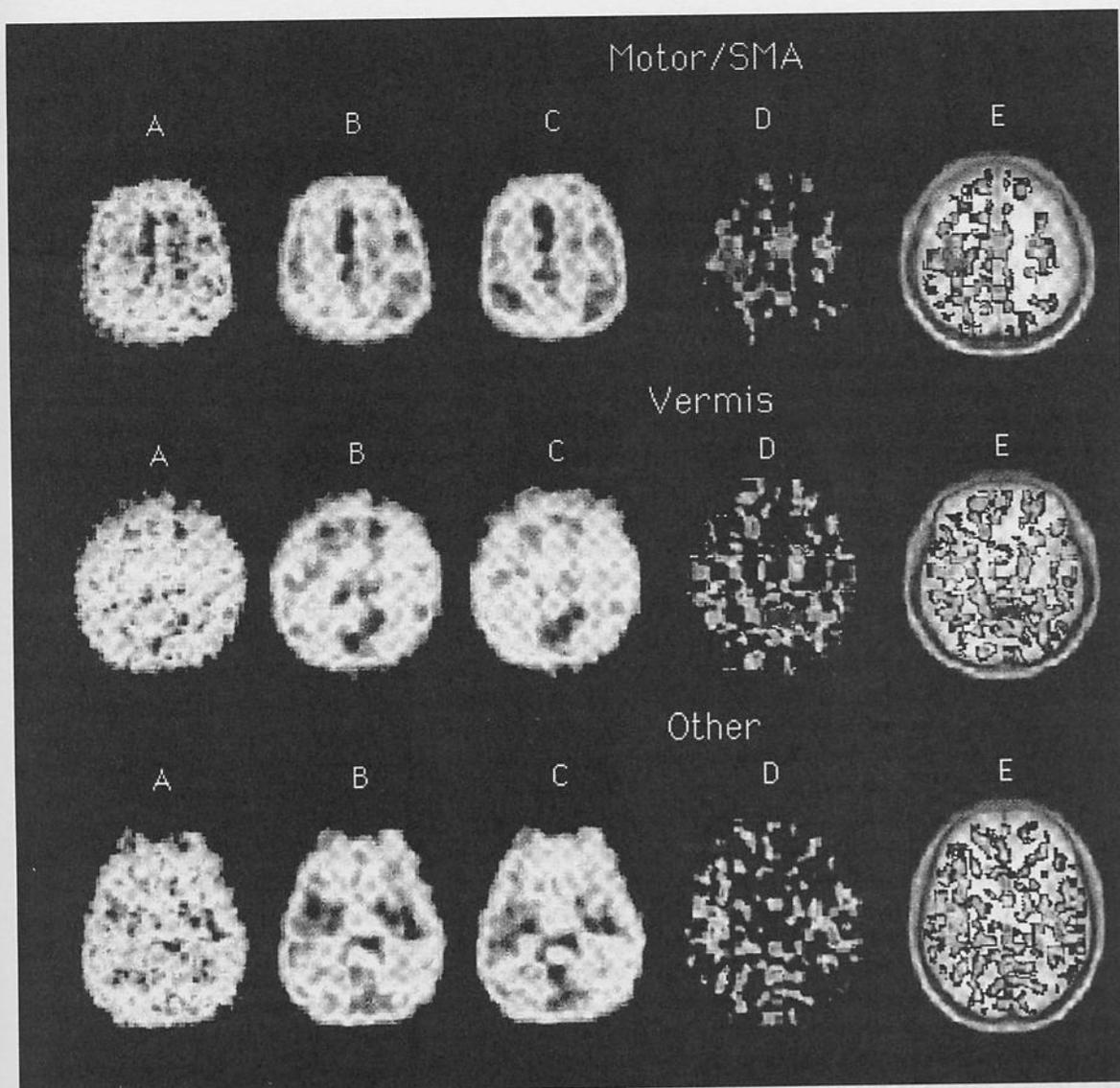


Figure 2. Image analysis techniques used to identify state-dependent changes in regional CBF. This figure illustrates how PET CBF images, image smoothing, image subtraction, PET-MRI co-registration, and intersubject image averaging improve the ability to detect and localize state-dependent changes in local neuronal activity. CBF images were normalized for the variation in whole brain measurements and warped into the same spatial coordinates. Each column shows three sections from a multislice, spatially standardized brain image. Top row: A section (Motor/SMA) containing (i) primary sensorimotor cortex (Motor), which participates in the execution of fist clenching, and (ii) the supplementary motor area (SMA), which participates in the planning and initiation of fist clenching. Middle row: A section containing the cerebellar vermis (Vermis), which participates in the coordination of fist clenching. Bottom row: A section containing none of the regions (Other) that actively participate in fist clenching. Column A: Sections from a high-resolution PET CBF image acquired in one subject during a baseline control state without fist clenching. The image is noisy and thus needs to be smoothed to improve image quality. Column B: Sections from the same baseline control CBF image smoothed to a lower spatial resolution. Noise in the image is greatly reduced. Column C: Sections from a smoothed CBF image acquired in the same subject as she repeatedly opened and closed her right hand. Note how difficult it is to detect and localize state-dependent changes in regional CBF in these blurry physiological images. Column D: A subtraction image, computed by subtracting the baseline image (column B) from the experimental image (column C) on a voxel-by-voxel basis. It is relatively easy to distinguish state-dependent CBF increases in the left sensorimotor cortex from noise. Indeed, it is possible to localize these large, discrete CBF changes within 1–2 mm. However, it is difficult to distinguish relatively subtle state-dependent CBF increases from noise, such as those in SMA and vermis. Column E: Subtraction image co-registered onto the subject's T1-weighted volumetric MRI. (The gray color scales were manually adjusted to help visualize the CBF increase in left motor cortex.) Co-registration makes it possible to localize anatomical regions of interest in the PET image and state-dependent changes in regional CBF (such as the cerebellar vermis) that are large enough to detect in a single subject. Column F: Statistical map of significant, state-dependent increases in regional CBF generated from CBF and co-registered MRI images in six subjects; $z > 2.58$, $P < 0.005$, uncorrected for multiple comparisons. Intersubject image averaging reduces noise (no longer visible in any of the sections) and improves the power to distinguish state-dependent changes in local neuronal activity (e.g., in SMA and vermis) from noise.

regional CBF on a voxel-by-voxel basis, researchers have commonly used *t*-score or *z*-score maps. Change distribution analysis, the original intersubject image averaging procedure, computes *z*-scores by characterizing the population of maximal mean changes in the image (i.e., the peaks and valleys) and comparing each mean change to the standard deviation of the population of mean changes (Fox et al. 1988). Another extensively used procedure computes *z*-scores using voxel-by-voxel information about the mean value in each set of images and a mean (or "pooled") variance computed from all of the voxels (Evans et al. 1992). Statistical parametric mapping (SPM), which is used in the largest number of laboratories, in its simplest application computes normalized *t*-score (i.e., *z*-score) maps using voxel-by-voxel information about the mean value and variance in each set of images (Frackowiak et al. 1997). It is important to recognize that not all *z*-score maps are alike: articles should specify the procedures used to normalize data for absolute measurements, the procedures used to deform data into standard spatial coordinates, and the procedures used to compute statistical maps.

The creators of SPM continue to update their methods; at the time of this writing, their latest version is SPM99. Statistical parametric mapping now permits a full application of the general linear model to the determinants of activity in each individual voxel. Thus, it readily permits the generation of maps of main effects and interactions (to examine the extent to which a CBF change in one comparison is significantly different from a CBF change in another comparison; Friston et al. 1996a) (Frackowiak et al. 1997), as well as the ability to examine or exclude the effects of covariates (e.g., age, a rating scale score, or a psychophysiological measurement). One can also use this approach to identify statistically significant asymmetries in activation (i.e., the extent to which a CBF change in one voxel is significantly different from a change in the homologous voxel in the opposite hemisphere).

In addition to parametric or nonparametric contrasts, it is possible to generate maps that relate PET measurements in one region to those in other regions. *Functional* connectivity refers to the simultaneous activation of two or more regions without specifying the cause or direction of this association, whereas *effective* connectivity examines the effect that a given region has on another given region using structural equation modeling and path analysis (Frackowiak et al. 1997; Friston et al. 1993a,b; McIntosh & Gonzalez-Lima 1994; McIntosh et al. 1994, 1996). This represents a considerable advance in the power of functional neuroimaging, as it begins to address the components and functional interactions within neural circuits that mediate specific functions.

Researchers like to test specific hypotheses, but they also like to explore findings throughout the brain. Since potentially significant findings could be identified in over 50,000 voxels, researchers must consider the statistical problem of multiple comparisons: as the number of comparisons in-

creases, it becomes increasingly likely that one or more voxels will have statistical value greater than the critical value by chance alone (i.e., a type-I error). Before considering this issue, it is important to recognize that the multiple comparison problem is related to the number of independent comparisons. Owing to the smoothness (i.e., limited spatial resolution) of images, the analysis of a statistical map involves no more than several hundred independent resolution units or "resels" (Worsley et al. 1992), a concept now incorporated in some of the most sophisticated statistical methods used to address the problem of multiple comparisons (Frackowiak et al. 1997). But even this number overestimates the number of independent measurements owing to the extent to which data in different brain regions are functionally connected. For this reason, the optimal statistical approach for correcting multiple comparisons is not known – but it should maximize the trade-off between sensitivity to the detection of relatively subtle changes (a crucial issue, since brain mapping studies have limited statistical power) and the number of type-I errors (Frackowiak et al. 1997).

Procedures commonly used to correct for multiple comparisons include: those that depend on the magnitude (or intensity) of the maximal statistical value relative to the number of resels (or, less commonly, the number of identified "maxima") in the image (Evans et al. 1992; Fox et al. 1988; Worsley et al. 1992); those that depend on the spatial extent of voxels exceeding a particular statistical value (Friston et al. 1994); and those that depend on the combination of magnitude and spatial extent. See Frackowiak et al. (1997) for a detailed discussion of these issues and other image analysis strategies.

Another commonly used strategy is to use an empirically derived critical value (e.g., a *z*-score of 2.58 or 3.09; $p < 0.005$ or 0.001, uncorrected for multiple comparisons) to at least partially address the problem of type-I errors (Frackowiak et al. 1997; Reiman et al. 1997). In a study of relatively smooth PET images acquired in multiple subjects during well-characterized behavioral and control tasks, we found that a critical *z*-score of 2.58 yielded 0–1 type-I errors in the entire data set (much lower than expected if one does not consider the contribution of connectivity) and the best trade-off between type-I and type-II errors (Reiman et al. 1997). The extent to which this finding can be applied to higher-resolution PET or MRI data (in which one would expect more type-I errors), different sample sizes, and differences in the number of accumulated PET counts remains to be determined. Procedures less commonly used to address the problem of multiple comparisons include the gamma-2 statistic, an omnibus procedure empirically established to identify images that contain one or more significant changes in regional CBF in the population of local maxima (Fox et al. 1988) as well as a nonparametric procedure that uses permutation test theory to derive empirically a critical value in each data set (Holmes et al.

1996). The latter method might be especially well suited for studies involving a relatively small number of scans (e.g., those involving intrasubject image averaging) (Frackowiak et al. 1997). Perhaps the optimal way to address the multiple comparison problem is an independent replication of findings. Thus, an initial exploratory study could test hypotheses about alterations in specific brain regions and explore alterations in the rest of the brain. These additional alterations (i.e., the newly generated hypotheses) could be tested in a replication study.

When presenting data in a research article, one commonly includes a table listing the anatomical region, estimated Brodmann's areas, atlas coordinates, and statistical values for regions above a certain critical value. Figures commonly include entire brain maps together with: (a) multiple sections superimposed onto a single spatially standardized MRI, an average of spatially standardized MRIs acquired in all subjects, an average of spatially standardized MRIs from 305 subjects studied at the Montreal Neurological Institute (Evans et al. 1993), or a digitized brain atlas; (b) three-dimensional surface projection maps that project regional changes onto the medial and lateral surface of a spatially standardized brain MRI (Frackowiak et al. 1997; Minoshima et al. 1995b; Reiman et al. 1996); or (c) two-dimensional projection maps that project regional changes onto sagittal, coronal, and transverse sections (Frackowiak et al. 1997). Although brief reports commonly illustrate their findings using selected brain sections – and sometimes do so using their most convincing cases – these figures should not distract the reader from a careful inspection of the data. Since a failure to reject the null hypothesis does not prove that the alternative hypothesis is untrue, a “negative finding” does not rule out the possibility that the investigated region is not affected. For that reason, it is useful to report possibly significant findings even if one cannot rule out the possibility of type-I errors; the provisional nature of these exploratory findings should be emphasized in the discussion section.

DATA INTERPRETATION

When interpreting PET findings, it is important to consider the limitations of this imaging technique. Limitations in the spatial resolution of PET images, the contrast resolution of individual PET images, and the accuracy of the image deformation algorithm used to compute statistical maps all make it difficult to specify regions (e.g., specific thalamic nuclei) that are responsible for observed changes in regional brain measurements. Since increases in regional brain activity appear to reflect the activity of terminal neuronal fields (Schwartz et al. 1979) – including those from local interneuron and afferent projections arising in other sites – it is difficult to specify the neuronal projections that account for observed changes in regional activity. Although PET and other imaging techniques provide infor-

mation about the neuroanatomical correlates of emotion, lesion studies (including experimental lesions in laboratory animals, neurological patients with selective brain injuries, and perhaps the induction of temporary functional lesions in human subjects using transcranial magnetic stimulation) are required in order to determine whether the implicated regions are necessary or sufficient to produce the behavior of interest (e.g., an emotion) or its potentially dissectable components (e.g. experiential, expressive, and evaluative aspects of emotion). See Sarter et al. (1996) for a more extended discussion of this issue.

As previously noted, PET studies raise the possibility of type-I errors that merit confirmation in an independent data set. Even more problematic, failure to detect significant alterations in PET measurements (type-II errors) could reflect limitations in spatial resolution, statistical power, heterogeneity in the strategies used to perform a task, or a change in the pattern rather than the level of neuronal activity. It is also important not to overinterpret unilateral changes as being significantly lateralized, since a change in one hemisphere relative to that in the opposite hemisphere may not reach statistical significance; in order to identify lateralized changes, one needs to directly compare activity changes in one hemisphere to those in the other hemisphere on a regional or voxel-by-voxel basis. Similarly, one needs to directly compare voxel-by-voxel maps of state-dependent changes in regional brain activity to conclude that changes in one comparison are significantly greater than those in another comparison.

In studies that compare data from patients and controls, it is important to consider the possibility that observed differences are related to the pathophysiology of the disorder – for example, a genetic or learned predisposition to panic attacks in patients with panic disorder – or to differences in the subjects' behavioral state at the time of the study (e.g., anxiety, the attempt to refrain from compulsive rituals in patients with obsessive-compulsive disorder, eye movements, or differences in the performance of a behavioral task). One should also consider the possibility that observed differences in regional CBF or CMRgl are related to alterations in local neuronal activity, the density of glial cells or terminal neuronal fields that innervate a region, or the combined effects of atrophy and partial volume averaging. In some studies, additional procedures are required to address the combined and potentially confounding effects of partial volume averaging, carotid artery activity, and temporalis muscle activity on measurements in the anterior temporal lobe (Chen et al. 1996; Reiman 1997). Finally, it is important to consider other experimental confounds that could account for the observed findings.

RISKS TO HUMAN SUBJECTS

An important consideration in the performance of PET studies is the risk to human subjects. The usual risks to

subjects who participate in PET studies can be attributed to radiation exposure and vascular catheterization.

Positron emitting radiotracers produce low-level, low-linear energy transfer (LET) radiation that consists of positrons and gamma rays. For appropriate diagnostic indications, the clinical benefit of PET studies typically exceeds the small risks of radiation exposure. For research studies, laboratories have relatively strict guidelines about the maximal radiation dose that a research volunteer can receive in a single scanning session or year. The dose depends on the radiation exposure of different radiotracers to individual organs and the whole body. The maximal radiation dose to a research subject must be lower than the limits established by the Food and Drug Administration (United States Code of Federal Regulations) and lower than an "effective dose equivalent" (computed from estimates of the radiation exposure to different organs and the susceptibility of each organ to radiation-induced cancer) of 50 millisieverts (5 rem). The limit for volunteers under 18 years of age is one tenth of this amount, severely restricting scientific PET studies of children unless the procedure has a clinical benefit. (Even if one could study children with a psychiatric disorder for strictly scientific purposes, it would be difficult to justify the study of control subjects.)

Exposure to very low-level, low-LET radiation exposure in PET studies and other radiological procedures may be associated with a small risk of leukemia and cancer of solid organs later in life. However, the risk is too small to measure directly, extrapolations from the study of Japanese atomic bomb survivors continue to be debated, and it remains unknown whether there is a threshold below which radiation is associated with no adverse effects (ICRP 1991; NRCC 1990). In our laboratory, we give research volunteers information about the risk of radiation-induced cancer and attempt to relate crude estimates of this risk to other everyday risks, such as smoking a carton of cigarettes in one's lifetime and exposure to the air pollution in a large city for one year (Brill et al. 1982). For a comparable number of scans, the risk of radiation exposure can be reduced by a factor of three using 3D imaging (Cherry et al. 1993).

Experts have studied additional risks of low-level LET radiation. The risk to the developing embryo (ICRP 1991; NRCC 1990) makes it necessary to exclude pregnant women from participating in PET studies. The risk of genetic abnormalities in subsequent generations due to irradiation of germ cells appears to be extremely small (ICRP 1991). Finally, the risks of infertility, aging, cataract formation, skin or blood changes, and radiation sickness require much higher levels of radiation exposure than is received in PET studies (NRCC 1990).

Most PET studies require venous catheterization for the purpose of radiotracer administration. This procedure is associated with only transient discomfort. Many quantitative PET studies also require arterial catheterization and

blood sampling, typically through the radial artery, in an effort to estimate the rate of radiotracer transport to the brain. Arterial catheterization typically causes transient discomfort and sometimes causes an uncomfortable bruise. If an Allen's test is performed to assure collateral circulation to the hand through the ulnar artery, the risk of developing inadequate circulation to the hand almost never occurs in healthy subjects. Unless there is an interest in characterizing alterations in whole-brain CBF, arterial catheterization is usually not performed in ^{15}O -water studies.

EXPENSE AND AVAILABILITY

Another consideration in the performance of PET studies is their considerable expense. Installing a cyclotron, radiochemistry facility, and imaging system can cost from \$3–\$6 million (though the cost can be reduced using less expensive accelerators or centrally located radiotracer distribution facilities). In addition, the major PET centers rely on numerous personnel (e.g., radiochemists or radiopharmacists, physicists or engineers, nuclear medicine technologists, computer scientists, physiologists and biomathematicians, physicians, and researchers from related fields); the operating budget is commonly \$1–\$2 million per year. The break-even cost of each PET procedure is estimated to be between \$615 and \$2,780, depending on procedure volume (Evens et al. 1983); the typical procedural cost of a PET session is about \$1,500 to \$2,000.

A Comparison of Functional MRI and PET

In this section we compare fMRI and PET across a variety of domains. This comparison is based on the foregoing discussion of PET and a detailed review of fMRI methods in Chapter 36 of this volume. There are three types of fMRI imaging, which use blood flow, blood volume and blood oxygenation level-dependent (BOLD) signals. The BOLD signal has the highest functional contrast and is the most commonly used method for fMRI imaging. Therefore, the comparison of PET and fMRI will focus on BOLD imaging unless otherwise noted. This comparison addresses physical and technical issues, experimental design, artifact, ancillary measures during scanning, scanning environment, and accessibility issues; see Table 2 for a summary. Wherever possible, basic principles will be illustrated with examples drawn from the literature on functional neuroimaging of emotional states.

PHYSICAL AND TECHNICAL CONSIDERATIONS

Functional MRI has the distinct advantage of no radiation. There is no known limit to the number of times someone can be studied safely. By contrast, PET involves a significant amount of radiation that is a function of the

TABLE 2. Comparison of PET and BOLD fMRI

	BOLD fMRI	PET
Physical/Technical		
Radiation	None	++
Spatial resolution	3 mm	3 mm and 8–15 mm
Temporal resolution	From 4–8 sec to 200 msec	30 sec
Technical complexity	+	+
Whole-brain coverage	Some areas difficult to image	+
Origin of signal	Partially understood	Well understood
Quantifiability of signal	Percent change in signal	Relative and absolute CBF
Neurotransmitter release	Not possible	+
Experimental Design		
State-related	+	+
Event-related	+	Not possible
Repeat studies	++ (in theory)	Possible (dose limited)
Single-subject studies	+(common)	Possible but rarely done
Artifact		
Motion sensitivity	Extreme	Readily controlled
Spatially dependent hemodynamic response fx	A problem with high spatial resolution	Not a problem
ECG	Can be removed	None
Respiration	Can be removed	None
Large vessel	Can be removed	Can be removed
Temporalis muscle	Not a problem	Can be removed
Other Measures during Scans		
EEG/ERP	Interleave between scans	+
EOG	Interleave between scans	+
EMG	Interleave between scans	+
ECG	+	+
Skin conductance	+	+
Startle	Any movement an issue	More feasible
Scan Environment		
Noise	Constant across conditions	No problem
Claustrophobia	5%–10% of subjects	No problem
Visual presentation	Some restrictions (size, resolution)	Fewer limitations
Accessibility of subject	Limited during scanning run	Readily accessible between scans
Verbal ratings	Any movement an issue	No problem between scans
Miscellaneous		
Number of centers (worldwide)	100–200 (1000s)	20–30 (300 cameras total)
Cost per subject	\$500	\$2,000
Amount of data to process	Major issue	Minor issue

Key: + denotes that this factor is present or feasible; ++ denotes that this factor is highly relevant or significant.

total dose of radiotracer and its nature. The risks associated with radiation exposure during PET imaging have just been described. Typically, subjects can participate in only one PET study per year.

Spatial resolution is superior with fMRI. Although spatial resolution of fMRI is a complex topic and varies as a function of imaging parameters, a useful estimate is that spatial resolution with conventional 1.5-Tesla systems is approximately 3 mm. Higher-strength magnets may increase spatial resolution down to 1 mm. As discussed previously,

there is an inherent theoretical limit in the spatial resolution of PET, on the order of about 3 mm. In recent studies, the effective resolution of PET is on the order of 8–15 mm when standard image processing procedures (such as spatial normalization and a smoothing filter) are utilized.

Temporal resolution is also superior with fMRI. As indicated in Table 3, temporal resolution varies depending on how the functional neuroimaging data are being used. With any brain imaging technique, there is an inherent limit of temporal resolution that is a function of

TABLE 3. Time Resolution of fMRI

Maximum on-off switching rate	16 sec optional 4-8 sec possible
Minimum detectable stimulus duration	~30 msec
Minimum detectable difference in activation duration	100 msec
Minimum detectable stimulus interval in a single region	1 sec
Minimum detectable stimulus interval across separate brain regions	200 msec
Minimum time to create a functional (whole-brain) image	5 sec
Maximum image acquisition rate	20-40 frames/sec

hemodynamic response. Whereas the peak blood flow response occurs 6-9 sec after stimulus onset, the complete response and recovery lasts about 16 sec. It is possible to detect a "new" response 4-8 sec after the first stimulus. However, within that context there are several other time intervals of interest to researchers.

For example, a stimulus duration as brief as 30 msec can be detected with fMRI, and the minimum detectable difference in duration of regional brain activation is 100 msec. A stimulus interval as brief as 1 sec can be detected in a single region, but across two regions the minimum detectable stimulus interval is 200 msec. The minimum time to create a whole brain image is 5 sec, and the maximum image acquisition rate is 20-40 frames (or images) per second. By contrast, the temporal resolution of PET images in routine applications is about 30 sec (corresponding to the period of maximum signal acquisition). In theory, one could systematically vary stimulus duration across PET imaging conditions, thereby generating subtraction images corresponding to a stimulus duration difference. However, it is probably preferable to pursue research questions related to these temporal characteristics with fMRI because of its greater availability, lesser expense, and absence of radiation exposure.

PET and fMRI are comparable in technical complexity. Both require a physicist to design the image acquisition, an expert technologist to run the scanning system, and a statistical consultant to assist in the data analysis. Depending on the experimental design, technical assistance may be required for stimulus presentation or psychophysiological data collection in an fMRI context. PET may also require a radiochemist for radiotracer synthesis, although automated systems for generating radiotracers such as ^{15}O are now available.

There are no limits to the areas of the brain that can be imaged with PET. However, some of the older PET systems have an axial field of view of about 10 cm, which means that either the very top or very bottom of the brain is not included in the image. This typically does not

influence the outcome of the study. By contrast, specific regions are more difficult to image using fMRI owing to the differences in magnetic susceptibility across tissues or between tissue and air. Magnetic field inhomogeneities are created at these interfaces, causing signal dropout and/or image distortion. For example, orbitofrontal cortex can be difficult to image because of its proximity to the nasal sinuses. Specific solutions to these problems come with some expense in S/N, sensitivity, imaging time, or whole-volume imaging capability.

The signal measured with PET is a function of blood flow and is therefore very well understood. The area of blood flow increase is greater than the area of neural activation (the analogy of "watering the entire garden for the sake of one thirsty flower" is useful as a first approximation), but the lower spatial resolution of PET makes this irrelevant for all practical purposes.

By contrast, the BOLD signal results from a combination of blood flow changes, blood volume changes, and oxygen consumption (Boxerman et al. 1995; Buxton, Wong, & Frank 1997; Davis 1998; Frahm et al. 1996; Kim & Ugurbil 1997). The inherent physiological meaning of what is detected with BOLD fMRI is not fully understood (i.e., additional details regarding coupling between flow, volume, and metabolic rate during activation are still needed; see Mandeville 1998). Furthermore, it is not known whether the BOLD signal arises from venules or capillaries (Bandettini & Wong 1997), a distinction that can influence the interpretation of findings. Thus, the greater spatial resolution of fMRI raises questions not encountered in PET. These questions must be answered if the technical advantages of fMRI are to be fully exploited.

With PET one can obtain a resting image and compare resting images between subjects; the value obtained in the resting state is relative to a preset normalized mean for all subjects to which all blood flow values are statistically adjusted. In BOLD fMRI what is measured is a percentage change in signal in one condition relative to another. Such relative changes are very useful in a PET context as well, but with PET (as well as with arterial spin labeling-based or blood volume-based fMRI - Detre et al. 1992; Edelman, Siewert, & Darby 1994; Kim 1995; Kwong et al. 1995; Wong, Buxton, & Frank 1996, 1997) there is the option of comparing one condition across subjects. The reason for this difference between PET and BOLD fMRI is that the BOLD fMRI signal contains structural as well as functional information (more of the former than the latter), leading to greater variability between subjects. In contrast, PET provides purely functional information; when that information is placed in a standardized spatial template, the contribution of structural information is minimized and essentially eliminated when the smoothing filter is applied.

Another advantage of PET is that the signal can be absolutely quantified, as described previously. Absolute

quantification is not possible with BOLD fMRI (but is possible with arterial spin labeling fMRI and with blood volume fMRI). It should be noted that several groups are now attempting to quantify BOLD contrast using the physiological stressor of hypercapnia.

This capacity for absolute quantification is particularly useful when using PET for neurochemical measurements. One can examine the binding of a radiotracer to a receptor in competition with an endogenous ligand. This provides an indirect measure of the binding of endogenous ligand. These methods can be used to quantify the number of receptors as well as the amount of released endogenous neurotransmitter. Such direct neurochemical measurements cannot be performed with fMRI. However, one can combine neurochemical manipulations – for example, fenfluramine injection versus placebo (Meyer et al. 1996) or apomorphine versus placebo (Dolan et al. 1995) – with indices of activation using ^{15}O or BOLD measurements to determine where changes in regional activation occur in association with such neurochemical changes.

EXPERIMENTAL DESIGN

It is customary in PET and fMRI studies to present stimuli in blocks (e.g., a series of pictures evoking emotional responses of a particular type), which can be compared with a baseline condition (Chertkow & Bub 1994). By contrast, a great advantage of fMRI for psychophysiological studies is the recently developed capacity to study event-related phenomena. The first studies of event-related fMRI have begun to appear in the literature (e.g. Büchel et al. 1998; see also Chapter 36 for a comprehensive list). For example, one could present a mixture of pleasant, unpleasant, and neutral pictures in a scanning block. With event-related analysis techniques it is possible to pick out the neural activation patterns associated with each individual stimulus and then average across events of a particular type. One could also examine whether the neural activation pattern differs as a function of whether it follows one particular valence condition as compared with another. This method also makes it possible to detect neural events whose time course may be too brief to be detected in the 30-sec scanning window associated with PET. For example, the activation pattern associated with a pinprick has been reported with fMRI but could not be detected with PET because of its lower temporal resolution (Tanaka et al. 1998).

In theory, another major advantage of fMRI is the capacity to perform repeat studies (Karni et al. 1993; Zarahn, Aguirre, & D'Esposito 1997). This option is not available in PET studies owing to annual limits in permissible radiation exposure – unless one modifies the number of scans and radiation dose so that the total exposure across repeat studies does not exceed that of a single study. In practice, it has been difficult to replicate results across or even

within fMRI sessions by comparing identical conditions at the beginning and the end. The reasons for such “session effects” are not fully understood. Most likely explanations involve motion artifact, problems in co-registration of images, changes in physiological state of the subject (e.g. fatigue), or habituation effects. Once this problem is solved it will significantly extend the range of questions that can be addressed with fMRI.

Single-subject studies are rarely performed with ^{15}O PET because the signal-to-noise ratio is relatively low, which is why intersubject image averaging is used to enhance it. One advantage of the latter is that it involves statistically analyzing the data from all of the subjects in the study, thus avoiding bias through the selective presentation of data. Single-case studies with FDG PET are common and are used clinically.

Single-case studies with fMRI are common and often yield results that are highly statistically significant. In fact, the reader of the fMRI literature should be aware that – when results are combined across subjects – spatial resolution is decreased because data are fit into normalized space and a smoothing filter is applied. Therefore, data will often be presented in the form of single cases with the statement that “similar results were obtained in other subjects.” The reader should pay particular attention to whether the coordinates of the activations in other subjects are reported and, if so, whether they are consistent with the conclusion that the same region is activated in each subject. One way of ensuring that activity in the same location is being reported is to use a region-of-interest approach. In that case, the question becomes the degree to which the entire pattern of activity is similar across subjects.

ARTIFACTS

The PET signal (gamma rays) emanating from a point in the brain does not change when the head moves, but the scanner will falsely attribute that signal to another location in the image because the template used to create the image does not move. It is therefore important to place the head in exactly the same position prior to each scan as well as to control head movement during each scan. Just prior to each scan, the head can be positioned in the scanner in exactly the same location by precisely positioning landmarks on the subject's face with laser beams (located in the gantry of the scanner for this specific purpose). Various types of headholders are available to restrict movement during and between scans. After PET data are acquired, algorithms are applied to align the scans within each subject to one another. This typically leads to adjustments of only a few millimeters in any direction, particularly if care has been taken by the researcher to restrict motion during image acquisition. Application of attenuation correction algorithms is dependent upon adequate restriction

of motion. In sum, motion can be adequately controlled with PET if properly attended to.

By contrast, motion artifact is a major issue in fMRI research. With the significantly greater spatial resolution of fMRI, moving the head less than 1 mm during the course of image acquisition heightens the need for precise co-registration of images. More importantly, the fMRI signal results from an interaction between exogenously applied magnetic gradients and the magnetic properties of the tissues in the head. In fMRI, head movement changes the signal emanating from any given locus in the brain and also (as with PET) creates a mismatch between the true locus of the altered signal and the location of that signal in the image. Therefore, considerable attention is given to minimizing head movement during fMRI image acquisition, including limiting the duration of scanning sessions. If one were content to adjust fMRI data through smoothing (or by other means, such as adjustment of voxel size to a spatial resolution comparable to that of PET) then motion artifact would be less of an issue.

Another source of movement artifact is physiological motion. Assuming the skull is stationary, the brain moves several millimeters with each cardiac and respiratory cycle, a source of motion artifact that can be measured. Just as event-related changes can be quantified and positively identified, motion of the brain associated with the cardiac and respiratory cycles can be modeled in this context and removed during the data processing step.

It is typically assumed that neural activation in all areas of the brain leads to the same absolute blood flow response (i.e., that the hemodynamic response is spatially independent). This may or may not be the case; the area is currently under investigation. This is an issue with high-spatial resolution fMRI, as a given percentage change in signal could mean different things in different regions.

The aforementioned artifacts are issues for fMRI because of its high spatial resolution. There are sources of artifact that are relevant for PET because of its relative spatial imprecision – for example, large vessel artifact and temporalis muscle artifact. Both are correctable if properly attended to. The latter is not a problem with fMRI because of its high spatial resolution, but large vessel artifacts do exist with fMRI.

The internal carotid artery passes near to the midbrain and just medial to the medial temporal lobe. Under certain conditions (such as emotional arousal), cardiac output may increase in a state-dependent manner. This can lead to a greater concentration of radiotracer in the internal carotid arteries shortly after injection of the radiotracer (during the first 30 sec, when signal acquisition is at its maximum) relative to the control conditions. Because of partial volume averaging (adjacent voxels contribute to the blood flow value measured at any given voxel), greater blood flow may appear to be present in specific brain areas (e.g. hippocampus or amygdala) owing to greater activity in the internal

carotid arteries. Although each PET image is typically corrected for global blood flow, this correction applies to the accumulated activity in the entire brain for the entire scan and may not eliminate this regionally specific increase. A procedure for eliminating large vessel artifact from PET images, developed by Chen and colleagues (1996), consists of identifying the pattern associated with activity in the internal carotid arteries in a separate study and subtracting this activity from the blood flow pattern of interest. Although conservative, if the medial temporal activation persists after this subtraction then it cannot be due to this artifact. In fMRI, special procedures are currently being evaluated and tested for restricting signal changes to capillary effects and for identifying and eliminating the contributions to signal change of large collecting veins or arteries.

During certain types of emotional arousal (e.g., anticipatory anxiety), subjects may clench their teeth, which leads to increased activity in the temporalis muscle. The latter lies only a few millimeters from the temporal pole, a structure that has been activated in several emotion studies. Since ^{15}O -water travels through the entire bloodstream, any structure that requires increased blood flow to meet its metabolic demands will receive an incremental increase in radiotracer delivery in proportion to the blood flow increase. Because of partial volume averaging, an increase in temporalis muscle activity could be misattributed to activity in the temporal pole. A procedure similar to that just described for internal carotid artery activity has been used to eliminate blood flow due to temporalis muscle activity (Reiman et al. 1997). Other procedures to correct this artifact include co-registration of PET and structural MRI data as well as measurement of temporalis EMG (electromyographic) activity and statistical elimination of this activity from the PET image in a covariance analysis.

OTHER MEASURES DURING SCANS

The psychophysiological measurements acquired during functional neuroimaging can add extremely useful information that can aid considerably in the interpretation of brain imaging data and add another dimension of physiological information. In the context of emotion research, for example, skin conductance and facial EMG data can be used to validate the success of the valence and arousal conditions being studied. When combined with quantitative EEG (electroencephalogram) data, PET or fMRI data can aid considerably in dipole localization.

An advantage of PET is that psychophysiological measures can be obtained without difficulty. In contrast, fMRI and psychophysiological data acquisition can interfere with one another. Special techniques are under development to deal with these issues, but it is important to emphasize that psychophysiological data collection in the context of fMRI is much more technically challenging.

Metal of any kind is dangerous in the MRI environment, since the strong magnetic fields can turn any metal object into a flying missile. Metal (e.g. electrodes) on the body surface can heat up and burn the subject. Furthermore, the presence of metal anywhere in the vicinity of the object being scanned can severely distort the MRI signal. This is particularly true for EEG or facial EMG electrodes. Thus, nonferromagnetic electrodes made of tin or graphite are being developed for psychophysiological data collection during fMRI scanning.

A magnetic field change will induce current in a wire. The rapidly changing magnetic gradients associated with fMRI induce currents in traditional copper wires that will appear as noise in the psychophysiological tracing. This source of noise can be filtered out of low-frequency signals such as ECG (electrocardiogram) or respiration. However, with EEG the frequency range of the signal overlaps with that of the changing magnetic gradients. Therefore, low- or high-pass filters will not eliminate the electrical artifacts. One solution is to record artifact-free EEG during the interval between each scan (typically about 1 sec, but this interval between scans can be extended if needed). Another option is to use a nonmetallic conducting medium for the electrical signals.

Recording skin conductance from the plantar surface of the foot has been explored to maximize the distance of the electrodes from the head coil. These skin conductance recordings were found to be inadequate because of the paucity of sweat glands in the foot. It has subsequently been observed in preliminary studies that electrodes on the palmar surface of the hand do not distort the functional neuroimaging signals and are the optimal location for skin conductance recordings (Margaret Bradley, personal communication).

The startle probe causes movement and is therefore to be avoided in the fMRI environment. However, the startle probe could be administered in the context of PET, which is relatively insensitive to tiny movements. To our knowledge, this has not yet been done.

SCAN ENVIRONMENT

The changing magnetic gradients create a loud noise, which requires that the subject use earplugs. The consistency of this auditory stimulus across all scanning conditions minimizes its effect on experimental results. New strategies are being developed that are based on image acquisition grouping and temporal spacing to minimize the interaction of the hemodynamics induced by scanner noise and the hemodynamics induced by the task. By contrast, auditory noise is not a significant consideration in PET experiments.

It is common in PET studies to converse with and obtain verbal ratings from the subject between scans, but manual rather than verbal responses *during* scans are pre-

ferred in order to avoid the head movement associated with speaking. During fMRI scanning, auditory noise interferes with (but does not prevent) verbal communication between subject and experimenter. Verbal communication by the subject during fMRI scanning is undesirable because the flow of air through the nose and mouth alters magnetic susceptibility of the nasopharynx and therefore the ability to image neighboring brain structures. Although a brief motion associated with speaking causes an immediate motion artifact, the induced hemodynamic change takes 5 sec or so. Therefore, one advantage of fMRI is its potential to decouple the motion artifact from the induced hemodynamic effect.

Approximately 5%–10% of subjects cannot undergo MRI scanning because of claustrophobia associated with being surrounded by the head coil and scanner. Although this could create a bias in the sample, it is typically not considered a significant issue.

Other aspects of the scanning environment are worth noting. With the head surrounded by the head coil, routine viewing of a computer or television monitor (as in PET) is not possible. Alternatives in fMRI include back-projection of images (onto a screen located at the foot of the scanning bed) that can be viewed with mirrors by the subject in the supine position. An alternative approach involves goggles through which the visual stimuli are presented. These systems are expensive but have resolution characteristics comparable to a computer monitor.

ACCESSIBILITY

A distinct advantage of fMRI is its greater accessibility relative to PET. At present there are only about 300 PET cameras in the world, and it is estimated that there are only about 20–30 PET centers publishing functional neuroimaging research. The number of PET centers could increase owing to the clinical utility of PET in detecting metastases (Silverman et al. 1998) and myocardial ischemia (Schwaiger 1995) and in differentiating brain tumors from radiation necrosis (Conti 1995), but the multimillion-dollar investment required means that this technology is likely to be available only in major medical or research centers. In addition to the capital investment required to establish a PET center, the cost per subject is approximately four times higher with PET than with fMRI (\$2,000 vs. \$500).

By contrast, there are probably thousands of MRI machines in medical centers around the world, and the cost of upgrading structural MRI systems for functional neuroimaging is “only” in the hundreds of thousands of dollars. At present there are about 100–200 U.S. centers conducting fMRI research. There are many more fMRI than PET investigators, which is likely to facilitate the development of solutions to the numerous technical challenges described here.

One factor that makes fMRI slightly less accessible is the computer resources needed to support it. The amount of data generated in scanning one fMRI subject is about one order of magnitude greater than with PET (gigabytes vs. hundreds of megabytes). The requirements for fMRI data transfer, data analysis, and data storage are considerable, whereas the quantity of data constitutes a relatively minor issue in PET research.

Functional Imaging Studies of Cognition

In this section we apply the principles discussed previously to research on cognition. The methodological issues that have been raised are carried a step further by illustrating how the advantages and disadvantages of PET and fMRI influence experimental design and thus the generation of new knowledge.

BETWEEN-SUBJECT VERSUS WITHIN-SUBJECT DESIGNS

Within-subject experimental designs compare among conditions, all of which are administered to a homogeneous group of participants. Between-subject designs include groups of participants that differ in the experimental conditions they partake of (e.g., different stimulus conditions, different pharmacological treatments) or in some stable pre-existing characteristic (e.g., age, gender). In functional imaging research, between-subject designs are most often used to investigate the brain regions and/or processes impaired in a clinically defined group relative to some control group. PET scans of regional cerebral glucose metabolism with the FDG tracer can reveal hypometabolism extending beyond the locus of a lesion visible in structural images or postmortem observations (Baron 1989; Szeliés et al. 1991). Hypometabolism may arise because a lesion has deprived an area of some of its normal input or damaged one of its efferent targets, or because the disease process itself produces cellular damage or dysfunction short of cell death. Reduced function in these brain areas may contribute as much to an observed cognitive deficit as frank damage observable in structural images, so that correlations between regions of hypometabolism and cognitive performance are part of the neuropsychological strategy of understanding brain function by characterizing its dysfunctions.

Paller and colleagues (1997) exploited this capability to explore the similarity of the neural circuitry underlying two amnesic syndromes: (i) those following localized damage to the medial temporal lobe; and (ii) Korsakoff's syndrome, in which the primary structural damage appears to be localized to the diencephalon. Compared with alcoholic subjects without a memory impairment, the Korsakoff's subjects displayed reduced glucose metabolism in widespread areas of the frontal and parietal lobes. Surprisingly,

however, the Korsakoff's patients did not differ from controls in medial temporal glucose metabolism. These results thus failed to support the idea that the memory impairments of Korsakoff's and medial temporal lobe amnesia share a common anatomical locus; instead they suggest that disrupted thalamocortical interactions can also impair learning.

The Korsakoff's study of Paller and colleagues is fairly typical of PET studies in patient populations in its use of FDG as the radiotracer. Because FDG scans readily allow the quantification of single-subject data, they are well suited for detecting regional differences in resting metabolism between individuals. However, such differences may be accentuated by administering a "behavioral challenge" prior to the scan, during the uptake period for the radioisotope. For instance, most studies comparing Alzheimer's patients to normal controls have yielded good discrimination between groups when participants rested quietly prior to the scan yet perhaps even clearer separation when a cognitive task has been administered during the uptake period (Kessler et al. 1991; Miller et al. 1987; see also Duara et al. 1992).

The disadvantages of glucose metabolism measurements with FDG are that the maximum safe dosage of this isotope allows only one or two scans per subject and that its long half-life makes it most sensitive to brain activity that persists for some 45 min. These qualities make FDG scans a bad match for experimental designs that either require more than two conditions or involve cognitive activities that are difficult to sustain for long periods of time. Most studies of normal cognition have thus utilized the ^{15}O radioisotope, a measure of blood flow rather than glucose metabolism. Use of a ^{15}O tracer allows a larger number of shorter-duration scans within the same subject, up to twelve 40–60-sec scans. Even if an experimental design includes fewer than twelve distinct conditions, this larger number of scans allows each condition to reoccur at different times during the session so that one can avoid confounding experimental effects with practice or fatigue effects. The primary drawback of ^{15}O scans is a lower S/N, which precludes easy analysis of single-subject data. Instead, the most typical method of analysis collapses across subjects to discover regional differences between conditions. Anatomical variability between subjects will thus decrease the spatial precision of measurements and make it difficult to distinguish between adjacent brain structures. Another important difference between the two radioisotopes is in the timing of any experimental task that the subjects perform. For blood flow measures, the task and data collection are coincident; this constrains possible tasks to those that can be performed lying supine and without head movement. Measures of glucose metabolism impose fewer constraints on the selection of a behavioral challenge because the critical time frame occurs before the scanning.

The PET literature to date has been marked by a strong correlation between the choices of (1) radioisotope, (2) between- versus within-subject designs, and (3) normal versus disordered populations. For example, most comparisons between normal and clinically defined groups use long-duration FDG scans, whereas most studies of the normal population use within-subject designs and shorter-duration ^{15}O scans. But these are only the most typical cases; the procedures for any given experiment should be selected according to the goals of the study. Within-subject measures of glucose metabolism have been applied to questions about skill acquisition in normal subjects by comparing a scan conducted after initial performance to one conducted after well-practiced performance (Haier et al. 1992). Conversely, cerebral blood flow measurements have been used to compare normal and dyslexic readers (Rumsey et al. 1997); the multifaceted nature of reading calls for designs with more than two conditions and is thus more amenable to ^{15}O than FDG scans.

In contrast to ^{15}O PET, the signal-to-noise ratio in functional magnetic resonance imaging using the BOLD method is high enough that single-subject data can be examined and statistically analyzed. It is a strength of this methodology that the contribution of intersubject anatomical variability will not reduce the spatial resolution of data from individual subjects. Of course, the observation of a significant relationship between an experimental condition and a brain region in one subject does not guarantee that the relationship will generalize to the population. It may be useful to consider an analogy between fMRI and event-related potential (ERP) data, given that the impact of an experimental manipulation can also be easily visualized in ERP data from a single subject (see Chapter 3 of this volume). In theory, the voltage at each of the time points in two ERP waveforms obtained from the same subject could be compared with each other to indicate which time points are significantly influenced by the experimental manipulation, where the sample size is equal to the number of time points ($N = [\text{epoch length in seconds}] \times [\text{sampling rate in Hertz}]$). In practice, however, ERP researchers typically measure voltage at the same time points in each subject and condition and use analyses in which sample size is equal to the number of subjects.¹ A statistically significant experimental effect is thus one that occurs in most of the subjects tested. In most cognitive ERP studies, variability in the timing of an experimental effect across subjects has not been a major stumbling block to a multisubject analysis or to comparisons between groups of subjects (see e.g. Iragui, Kutas, & Salmon 1996; Neville et al. 1993; Van Petten et al. 1997). Given that experimental effects in cognitive paradigms usually persist for at least 100 msec, voltage is typically measured not at a single time point but as an average across contiguous time points in a latency window based on prior results, or by inspection of a grand average of all the subjects. Although the latency window selected

for analysis may not correspond to the exact onset and offset of an experimental effect for any given subject, this measurement strategy evaluates the commonality across subjects by quantifying the same time frame in each individual. For fMRI data sets, it is less trivial to decide what counts as measuring the same thing across individual subjects. A cortical region can be defined by its (1) location relative to standard brain landmarks (e.g., the location of the anterior and posterior commissures in the coordinate system of Talairach & Tournoux 1988), (2) location relative to the gyral/sulcal patterns of an individual's cortex, (3) response to a standard stimulus that is not part of the experimental paradigm, or (4) response to the experimental stimuli.

The fMRI methods used for analyzing data from multiple subjects are still in a state of development, so that variants of each of these strategies can be found in the literature. Büchel, Turner, and Friston (1997) performed a spatial normalization on the structural MR images of each subject's brain to align them with the brain in Talairach's atlas, formed a grand average of the aligned functional images, and contrasted the activity of each voxel during visual stimulation versus rest. The spatial normalization procedure was successful in that activity of the lateral geniculate nucleus apparent in each individual subject was also apparent, and statistically significant, in the average across subjects. It will be of some interest to see if this procedure is equally successful in cognitive paradigms where the regions of greatest interest are in cortical association areas, which may show greater individual variability (Clark & Plante 1998). In a comparison of sentences to meaningless consonant strings, Bavelier and colleagues (1997, p. 668) report that "while the foci of activation fell within the same broad anatomical areas for all subjects, there was a large variability in the exact distribution of the activation within a given anatomical area across subjects." These investigators assessed the similarity of results across subjects by first dividing each brain into 62 regions (based on each individual's sulcal anatomy, apparent in structural MR images) and then measuring the percentage of voxels differentially active between conditions and the percentage of oxygenation change in those active voxels for each subject and region. This strategy for dealing with intersubject anatomical variability seems a reasonable one, but its effectiveness depends both on the extent to which cortical function follows sulcal boundaries and on the size of functionally specialized cortical areas, two parameters that are largely unknown for most of the human cortex.

For some parts of the human brain – most notably, visual cortex – functional neuroimaging data and prior knowledge of monkey neuroanatomy have converged to yield good descriptions of the location and function of single cortical areas (Tootell et al. 1996). Demb and colleagues applied this knowledge to the long-standing but controversial issue of whether or not developmental dyslexia involves

a visual deficit. Given that the general location and stimulus preferences of primary visual cortex and area MT+ were known, these investigators used standard stimulus sequences to define the borders of both areas in each individual subject before proceeding to the main experimental paradigm (Demb, Boynton, & Heeger 1997). The central comparisons between the normal and dyslexic groups could thus be made with some degree of confidence that the same functionally defined cortical area had been measured in each subject. Because they had a strong a priori hypothesis about dyslexia and visual motion processing, Demb and colleagues were able to capitalize on existing anatomical data to produce a priori definitions of the regions of interest.

As the functional imaging database expands, more experiments should approach the ideal case of using prior results to make specific anatomical predictions about a new task or population. At present, a more typical situation is one in which the regions of interest are only weakly constrained by prior neuropsychological data or are essentially unknown. For example, neurologists and neuropsychologists over the last century have inconsistently defined "Wernicke's area" to include various parts of the left middle and superior temporal gyri, superior temporal sulcus, and even the angular and supramarginal gyri (Bogen & Bogen 1976), so that current investigators have some justification for making similar broad cuts when evaluating whether or not individual subjects show activations in the "same" region. We can hope, though, that the improvement in spatial localization offered by imaging over natural lesions will similarly sharpen our characterization of structure-function relationships.

TASK VERSUS ITEM MANIPULATIONS

Cognitive experimental designs can be broadly divided into (a) those that vary the task a subject performs on relatively similar subsets of stimuli versus (b) those that vary stimulus parameters within a single assigned task. Both experimental strategies have played important roles in the oldest method of cognitive neuroscience – neuropsychology. In studies of brain-damaged patients, dissociations between tasks have often played a pivotal role in the interpretation of structure-function relationships. For instance, the finding that anterior aphasics with "agrammatic" production and comprehension could nonetheless distinguish grammatical from ungrammatical sentences in a simple good-bad task forced a revision of the idea that these regions of frontal cortex *stored* grammatical knowledge and instead focused attention on their role in *deploying* grammatical knowledge (Bates & Goodman 1997; Linebarger, Schwartz, & Saffran 1983). Observations of intact versus impaired performance contingent on item type have been equally important for cognitive theories derived from neuropsychological data. For instance, the dual-route model

of reading aloud draws critical support from the existence of patients who can read words with irregular pronunciations but not nonwords (presumably because a lexical route from spelling to sound is intact but a rule-based route is impaired) and also from the existence of other patients with the opposite pattern of performance (Coltheart et al. 1993; Marshall & Newcombe 1980; Patterson & Morton 1985).

In studies of the normal population, the *item design* has been more prevalent than the *task design* for experiments using behavioral, ERP, or MEG (magnetoencephalographic) measures. In language processing experiments, subjects are typically asked to perform one task (e.g., pronounce words as rapidly as possible, make lexical decisions, read silently) while the experimenter compares reaction times, accuracies, or electrophysiological responses to semantically plausible versus implausible words, correctly versus incorrectly inflected verbs, rhyming versus nonrhyming words, regular versus irregular past tenses, high- versus low-frequency words, phonologically regular versus irregular words, words from dense versus sparse orthographic neighborhoods, and so forth. In memory experiments, the experimenter is likely to examine recall or recognition of previously studied versus unstudied items, items studied during "deep" versus "shallow" processing tasks, new items that are similar versus dissimilar to those previously studied, and so on.

Task manipulations have also played an important role in behavioral and ERP studies of cognition, but typically via their interactions with item type. In psycholinguistics, for example, it is generally assumed that lexical characteristics that are fundamentally important in word recognition will be evident across distinct tasks. Task-by-item interactions are often interpreted as an indication that a given factor may be relevant for a particular, arbitrary, artificial laboratory task but not for natural reading or listening. In memory research, interactions between stimulus type and test type (recall vs. recognition vs. various implicit tests, item vs. source recognition, etc.) have been a major tool for fractionating memory into subsystems and component processes (Paller 1990; Schacter & Tulving 1994; Senkfor & Van Petten 1999).

In contrast to the strong focus on item designs in behavioral and electrophysiological research, the first decade of functional imaging has relied heavily on pure task designs to activate the brain regions involved in a given cognitive process. A memory experiment may thus compare regional cerebral blood flow when subjects perform a yes-no recognition task to when they merely read previously studied and unstudied words (Cabeza et al. 1997). A language experiment may compare blood flow as subjects generate words related to the stimulus items with their blood flow while reading the stimulus items aloud (Petersen et al. 1989). Both examples are drawn from the PET literature, but the smaller cognitive fMRI literature to date has similarly

focused on differences in blood oxygenation level between different tasks performed on similar subsets of stimuli.

The task design for functional imaging has at least two clear strengths. First, it is easy to ensure that the stimuli themselves do not trigger sensory or cognitive processes that differ between conditions, because very similar or identical stimuli can be used in each condition. Equating stimuli for characteristics that are not of interest in a particular experiment is a critical issue for all psychophysiological paradigms, more so than in behavioral experiments. Assessing performance in a particular task narrows the range of potentially influential variables in a way that brain activity measures do not. For accuracy and reaction time (RT) measures, the dependent measure is directly produced by the task – no task, no data. In behavioral studies, the choice of task can eliminate the influence of extraneous stimulus characteristics: lexical decision times will reflect lexical variables but not the fundamental frequency of the speaker's voice; judgments about the speaker's gender will be influenced by fundamental frequency but are unlikely to be influenced by lexical variables. For brain activity measures, the direct link between task and data is broken. Whether or not a subject is asked to do anything, some brain regions will respond to sound, light, or mechanical energy impinging on the sensory surfaces. Using the same stimuli across experimental conditions protects against confounds introduced by stimulus sets that differ in ways that are unknown to the experimenter.

The second strength of the task design for functional imaging is that explicitly instructing participants to engage different cognitive processes may maximize the likelihood that different brain regions will be active across tasks. Task manipulations are a straightforward means of encouraging qualitatively different processing across conditions. In contrast, pure task effects in behavioral measures are often difficult to interpret because accuracy and RT are simple scalars that do not reveal whether experimental effects are quantitative or qualitative in nature. Increased difficulty of a single cognitive process and addition of a second distinct process may yield similar behavioral effects. Similarly, electrophysiological experiments are typically designed to avoid direct comparisons between ERPs elicited in different tasks, because a qualitative change in the component structure of a voltage waveform across tasks may obscure quantitative differences in the amplitude or latency of components present in both tasks, and vice versa (Kutas & Van Petten 1994). Given that brain images are neither a unidimensional measure (like accuracy) nor subject to the problem of cancellation between temporally overlapping components (like ERPs), qualitative differences among conditions can be a desirable outcome of an experimental manipulation rather than an interpretative hazard.

One challenge in using a pure task design strategy is evaluation and control of task difficulty. In the most typical case, an experimenter will design two tasks that require

different processes for successful performance. An additional difference in overall difficulty level will not alter the qualitative distinctions between tasks but may introduce additional brain activity that is not strictly necessary for task performance. A more difficult task may engender higher levels of internal accuracy monitoring, error detection, error correction, and – at the extreme – some level of frustration or irritation at one's poor performance. Conversely, an easier task may allow additional uncommitted time between stimuli to engage in anticipation of the next item or preparation of the next response; some of these metaprocesses are likely to have a common anatomical locus across tasks. It has been suggested that (among other functions) the anterior cingulate participates in error detection (Jueptner et al. 1997; Miltner, Braun, & Coles 1997), whereas the motor, premotor, and supplementary motor cortices are undoubtedly involved in response preparation (Miller, Riehle, & Requin 1992; Richter et al. 1997; Roland et al. 1980). But it is possible that other, as yet poorly characterized, brain areas are involved in domain-specific aspects of monitoring and preparation. Some advance knowledge about the relative difficulty of experimental tasks gathered via accuracy and RT measures will be beneficial in distinguishing specific from generic consequences of task difficulty. Finally, comparisons between regional activations in imaging experiments and the performance of patients with damage to those regions serve as the strongest test of whether a given region is merely active during a task or rather is actually critical for the successful performance of that task (Sarter et al. 1996; Swick & Knight 1996; Thompson-Schill et al. 1998).

There are also clear drawbacks to the pure task design for functional imaging. Perhaps the worst-case scenario is that differing instructional sets simply fail to influence the cognitive activity of interest, yielding no observable difference in brain regions that are indeed substrates for that cognitive process. This outcome is likely to arise not because the active task fails to engage the targeted process but rather because the baseline task does so as well. Presentation of similar stimuli across conditions may trigger similar cognitive operations, regardless of whether these are explicitly requested or required for performance of the assigned task. For example, the very first PET investigation of language processing yielded a surprising null effect in that a comparison designed to isolate semantic processes – production of a related verb versus reading aloud – failed to activate any portion of the cortical territory traditionally regarded as Wernicke's area (Petersen et al. 1989). In retrospect, this outcome was far from surprising given the robust behavioral evidence for semantic processing in reading aloud: faster RTs in the presence of semantic context make the pronunciation task a routine tool in psycholinguistic investigations of semantic processing. Mental operations above and beyond those strictly required during a baseline task are no less likely in the

domain of memory research. Mere presentation of previously studied items is almost certain to trigger some level of spontaneous retrieval, as evidenced by the similarity of old–new differences in explicit recognition tasks and nonmemory tasks including incidentally repeated stimuli (Rugg & Doyle 1994; Van Petten & Senkfor 1996; but see Swick & Knight 1997). It can be argued that such incidental, uninstructed processing is ubiquitous across cognitive domains. After finding that electrical field potentials in large and widespread cortical and subcortical regions differentiated standard and rare tones in a simple auditory discrimination task, Halgren and colleagues (1995, p. 246) concluded that:

the brain seems to adopt the strategy of engaging all potentially useful areas, even though the probability that they will contribute to immediate task performance is very low. The potential benefit of engaging multiple structures is that incidental learning can occur, behavioral accuracy and consequences can be monitored and, more generally, stimulus information achieves a widespread integration with context and memory. While such “conscious” processing is intentionally rendered superfluous in many psychological tasks, it could be essential for survival and reproduction in the natural environment. In comparison to these benefits, the cost of such a strategy would seem to be minimal, given that in homeotherms all brain areas must be metabolically supported in any case, regardless of whether they are engaged by the task or not.... If areas tend to be engaged even if they have only a very slight probability of being needed, then it is likely that many of the essential areas in the “active” task will also be engaged in the “baseline” task, even though they are not essential. The subtraction may not reveal such areas and thus greatly underestimate the extent of the brain involved in a given cognitive process.

Although such underestimation may be the norm for experimental strategies that rely on contrasts between active and baseline tasks, steps can be taken to alleviate this problem. One is the inclusion of a “resting” baseline without stimulus presentation; although comparisons between rest and any task will not isolate any aspect of perception or cognition, comparisons between each experimental task and a common baseline will allow visualization of regional activations shared by all the tasks. A second strategy is to design baseline and active tasks that are fairly demanding, so that cognitive resources are diverted in the desired direction and a subject’s ability to engage in extraneous cognitive activities is reduced. One simple way of increasing the demands of both tasks is by rapid stimulus presentation; correlational analyses have demonstrated that activity in at least some brain areas increases monotonically with stimulus presentation rate (Price et al. 1994; Wise et al. 1991).

The second major drawback to a pure task design strategy is that – even as tasks are designed to identify and

isolate brain regions involved in particular cognitive processes – we have an imperfect understanding of which cognitive processes are required or engaged by any particular task. In the short history of functional imaging research, investigators have largely relied on their intuitions when designing tasks; hence rhyme judgments on word pairs, generating a rhyming word, phoneme monitoring, and syllable counting have all been used as “phonological” tasks, and an even larger number of “semantic” tasks have been employed. The exact nature of the task requirements has been a focal point in a recent controversy surrounding a robust positive result in both PET and fMRI studies. Although activation of the left inferior frontal gyrus (IFG) has been observed in numerous comparisons between semantic and nonsemantic tasks (Gabrieli, Poldrack, & Desmond 1998), others have argued that it is difficult to separate the contribution of semantic analyses from spontaneous phonological processes in the word generation tasks that have been a mainstay of this research (Price et al. 1997) or from a more general cognitive process of selecting among competing sources of information (Thompson-Schill et al. 1997).

Controversies of this sort seem inevitable when one considers that neuropsychologists have been arguing about the proper description of the left IFG (Broca’s area) in language processing for several decades. Rather than a sign of trouble, such arguments can be taken as reflecting a healthy research program that extends beyond the simple goal of mapping known functions onto locations. After all, characterizing the fundamental components of cognition is as much a part of functional imaging research as the other subdisciplines of cognitive science. We can hope that such arguments will both arise and be settled at a more rapid pace in functional imaging research than in neuropsychology, given that normal subjects are easier to find than patients with specific lesions. Explicit comparisons between nominally similar tasks (e.g., a set of phonological tasks each compared to a resting baseline) are likely to be more common as the capability of fMRI for repeated testing of the same subjects is more fully exploited, and such comparisons may be especially useful in identifying core cognitive processes.

Another powerful method for circumventing questions about the exact nature of a task contrast will be greater use of the item design in functional imaging research. Item manipulations within a single task can be used to create a gradient of difficulty; convergent results from easy-versus-difficult and active-versus-baseline comparisons will provide stronger support for structure–function conclusions than either experimental strategy alone. Moreover, it will be easier to forge links between functional imaging results and behavioral or electrophysiological studies using similar item-based designs. It is possible that conditions explicitly designed to vary along a unitary dimension will yield weaker hemodynamic contrasts than those designed

to vary qualitatively, but several recent studies demonstrate the feasibility of the former approach. In a sentence comprehension task, Just and colleagues (1996) observed a graded influence of syntactic complexity in both Broca's and Wernicke's areas when three sentence types were each compared to a resting baseline. In a verb generation task, Thompson-Schill and colleagues (1997) compared nouns possessing a strongly associated verb (e.g. *scissors - cut*) to those with many possible answers (e.g. *rope - hang/tie/cut/stretch*). Greater activity in Broca's area for the "high selection" condition was paralleled in two other tasks using stimuli that varied in their demand for selecting among different sources of information (Thompson-Schill et al. 1997). In a task of detecting occasional animal names, we observed differential blood flow in the left superior temporal and angular gyri for lists of semantically related versus unrelated words (Van Petten, Reiman, & Senkfor 1995).

Item-based experimental designs need not start with the assumption that stimulus classes vary along some unitary dimension; they can also be used to explore the possibility that qualitatively different mechanisms are invoked by different stimulus types. For example, Fiez and Petersen (1998) reviewed PET studies comparing orthographically consistent and exception words (i.e., those like *lint* whose pronunciations follow regular grapheme-to-phoneme conversion rules versus those like *pint* with irregular pronunciations). Domains of partial regularity combined with exceptions abound in language (as in the past-tense system for English verbs), so that such contrasts between regular and irregular words have been at the heart of arguments pitting single-mechanism models against those that postulate a rule-based system for regular items and direct memory look-up for irregular items (Plaut et al. 1996; Plunkett & Marchman 1993). As Fiez and Petersen (1998) noted, the PET results to date can be accommodated by either single-mechanism or dual-route models, but these results suggest new critical comparisons that can be tested in neuropsychological studies. The relationship between orthography and phonology is only one circumscribed issue in cognition, but it has been an exemplary case where the use of similar paradigms has allowed psycholinguistic, computational, neuropsychological, and functional imaging methods to tackle the same problem.

Although item designs are now being used to good effect in language processing experiments, the picture has not been as bright in memory research. In recognition tasks, differential responses to studied versus unstudied items are mandatory for deriving a behavioral accuracy measure, and different brain responses for remembered old items (hits) versus new items have been a basic tool in electrophysiological studies of memory (Van Petten & Senkfor 1996). PET contrasts between studied and unstudied items have revealed less consistent results. The majority of experiments have found that blocks of old items elicit greater

blood flow in prefrontal cortex than new items, yet greater, lesser, and null changes in blood flow have been observed in the medial temporal lobe (Dolan & Fletcher 1997; Henke et al. 1997; Nyberg et al. 1995; Schacter et al. 1997; Tulving et al. 1996). A different strategy for localizing brain areas sensitive to successful retrieval of episodic memories has been to compare conditions with high recall or recognition rates (engendered by additional or deeper study prior to scanning) to those with lower accuracy rates. These contrasts have similarly revealed both positive and negative relationships between medial temporal blood flow and accuracy (Pettersson, Elfgren, & Ingvar 1997; Rugg et al. 1997). One possible account of these discrepant findings is that the medial temporal lobe is involved in both the encoding of new (or poorly learned) stimuli and the retrieval of well-learned items. In an fMRI study comparing studied to unstudied items, Gabrieli and colleagues (1997) reported increased activity in one region of the medial temporal lobe but decreased activity in a neighboring region. It is possible that opposing activity changes in small adjacent brain structures are vulnerable to blurring and cancellation by PET methods of intrasubject averaging, so it will be of some interest to pursue old-new differences in fMRI experiments that allow examination of individual brains.

Item designs have been the minority of functional imaging studies because ^{15}O PET and the first generation of fMRI methods require averaging activity over 30–60 sec. Many of the item manipulations used to good effect in behavioral and electrophysiological studies are not amenable to blocked presentation of a given condition. Predictability as to what will come next undermines a good deal of the specific effort required to resolve a perceptual, linguistic, or memory challenge. The literature to date has included some methods for circumventing this problem of blocked presentation; for instance, contrasts between old and new items during recognition memory tests have been conducted by comparing blocks with *mostly* (~90%) old items to those containing mostly new items. Comparing stimulus blocks with different probabilities of stimulus types offers a compromise between the technical requirement of using long epochs and the cognitive requirement of avoiding complete predictability.

Some of the limitations on experimental design in functional imaging are eliminated by newer event-related analyses of fMRI data that selectively average responses from epochs corresponding to randomly intermixed stimuli (Rosen, Buckner, & Dale 1998). The most conservative use of this method is with slow presentation rates that allow the prolonged hemodynamic response to each item to begin and end before onset of the next item. Even in tasks for which a behavioral or electrophysiological response can be elicited within a second of stimulus onset, the BOLD signal may persist for close to 10 sec (Buckner et al. 1996; McCarthy et al. 1997). Using long stimulus-onset asynchronies (SOAs) affords a temporal separation between

trial types but may also result in few trials and a low S/N. Very slow presentation rates may also alter cognitive processes in undesirable ways: most selective attention paradigms would be ruled out, and sentence comprehension at six words per minute would be a very different process than natural reading or listening. However, some recent studies have suggested that responses to sequential stimuli add in a nearly linear fashion, so that the contribution of one stimulus type can be distinguished from temporally adjacent stimuli with SOAs as short as 2 sec (Dale & Buckner 1997; Josepfs, Turner, & Friston 1997; Kim, Richter, & Ugurbil 1997). As presentation rates approach or exceed two items per second, the BOLD signal is likely to saturate and the activity elicited by individual items will be unrecoverable (Friston et al. 1998; Rees et al. 1997). However, for many cognitive paradigms, this lower limit will not be problematic. More critical will be the analytic procedure used for isolating responses to one stimulus type from temporally overlapping responses. Preliminary studies have dealt with this problem by ensuring that each trial type is preceded and followed by each other trial type equally often, so that simple subtraction can be used to estimate and eliminate response overlap (Dale & Buckner 1997). Such perfect randomization of trial order is not possible for all cognitive questions. One may wish to compare trials accompanied by correct and incorrect behavioral responses (for instance, hits to false alarms in recognition memory), but these cannot be foreseen in advance of the subject's behavior. In sentence processing studies, grammar does not allow words of a particular class to be placed in any random order (in English, for example, articles are followed by nouns and never by verbs). Such cases of differential response overlap in different conditions pose the same analytical problem as that encountered in ERP research (Woldorff 1993), so that similar correction methods are under development (Buckner et al. 1998).

Full development of event-related fMRI methods will ease comparisons among hemodynamic, electrical, and magnetic measures of brain activity (George et al. 1995). These may or may not prove equally sensitive to the variety of mechanisms the brain uses to process information (see e.g. Riehle et al. 1997), but all will offer some view of the "enchanted loom where millions of flashing shuttles weave a dissolving pattern, always a meaningful pattern, though not ever an abiding one" (Sherrington 1940).

NOTE

1. This analytic strategy is the same as that used in most cognitive studies with reaction time measures. A single-subject analysis is possible with reaction times because each trial can be considered as a single data point and multiple trials from two conditions within one individual can be statistically compared. In practice, however, most researchers

compute average reaction times from each subject in each condition and then compare these averages across a sample of subjects.

REFERENCES

- Bandettini, P. A., & Wong, E. C. (1997). Magnetic resonance imaging of human brain function: Principles, practicalities, and possibilities. *Neurosurgery Clinics of North America*, 8, 345-71.
- Baron, J. C. (1989). Depression of energy metabolism in distant brain structures: Studies with positron emission tomography in stroke patients. *Seminars in Neurology*, 9, 281-5.
- Bates, E., & Goodman, J. C. (1997). On the inseparability of grammar and the lexicon: Evidence from acquisition, aphasia, and real-time processing. *Language and Cognitive Processes*, 12, 507-84.
- Bavelier, D., Corina, D., Jezard, P., Padmanabhan, S., Clark, V. P., Kami, A., Prinster, A., Braun, A., Lalwani, A., Rauschecker, J. P., Turner, R., & Neville, H. (1997). Sentence reading: A functional MRI study at 4 Tesla. *Journal of Cognitive Neuroscience*, 9, 664-86.
- Belliveau, J. W., Kennedy, D. N., McKinstry, R. C., Buchbinder, B. R., Weisskoff, R. M., Cohen, M. S., Vevea, J. M., Brady, T. J., & Rosen, B. R. (1991). Functional mapping of the human visual cortex by magnetic resonance imaging. *Science*, 254, 716-19.
- Bogen, J. E., & Bogen, G. M. (1976). Wernicke's region - Where is it? *Annals of the New York Academy of Sciences*, 280, 834-43.
- Bookstein, F. L. (1989). Principal warps: Thin-plate splines and the decomposition of deformations. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 11, 567-85.
- Boxerman, J. L., et al. (1995). MR contrast due to intravascular magnetic susceptibility perturbations. *Magnetic Resonance in Medicine*, 34, 555-66.
- Brill, A. B., Adelstein, S. J., et al. (1982). *Low Level of Radiation Effects: A Fact Book*. New York: Society of Nuclear Medicine.
- Büchel, C., Morris, J., Dolan, R. J., & Friston, K. J. (1998). Brain systems mediating aversive conditioning: An event-related fMRI study. *Neuron*, 20, 947-57.
- Büchel, C., Turner, R., & Friston, K. (1997). Lateral geniculate activations can be detected using intersubject averaging and fMRI. *Magnetic Resonance in Medicine*, 38, 691-4.
- Buckner, R. L., Bandettini, P. A., O'Craven, K. M., Savoy, R. L., Petersen, S. E., Raichle, M. E., & Rosen, B. R. (1996). Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences U.S.A.*, 95, 891-8.
- Buckner, R. L., Goodman, J., Burock, M., Rotte, M., Koutstaal, W., Schacter, D., Rosen, B., & Dale, A. M. (1998). Functional-anatomic correlates of object priming in humans revealed by rapid presentation event-related fMRI. *Neuron*, 20, 285-96.
- Buxton, R. B., Wong, E. C., & Frank, L. R. (1997). A biomechanical interpretation of the BOLD signal time course: The balloon model. *Proceedings of the ISMRM 5th Annual Meeting*. Vancouver.
- Cabeza, R., Kapur, S., Craik, F. I. M., McIntosh, A. R., Houle, S., & Tulving, E. (1997). Functional neuroanatomy of recall

- and recognition: A PET study of episodic memory. *Journal of Cognitive Neuroscience*, 9, 254–65.
- Chen, K., Bandy, D., Reiman, E. M., et al. (1998). Noninvasive quantification of the cerebral metabolic rate for glucose using positron emission tomography, 18F-fluorodeoxyglucose, the Patlak method, and an image-derived input function. *Journal of Cerebral Blood Flow and Metabolism*, 18, 716–23.
- Chen, K., Reiman, E. M., Lawson, M., Yun, L.-S., Bandy, D., & Palant, A. (1996). Methods for the correction of vascular artifacts in PET O-15 water brain mapping studies. *IEEE Transactions on Nuclear Science*, 43, 3308–14.
- Cherry, S. R., Dahlbom, M., & Hoffman, E.J. (1991). Three dimensional positron emission tomography using a conventional multislice tomograph without septa. *Journal of Computer Assisted Tomography*, 15, 655–68.
- Cherry, S. R., Dahlbom, M., & Hoffman, E.J. (1992). Evaluation of a 3D reconstruction algorithm for multi-slice PET scanners. *Physics in Medicine and Biology*, 37, 779–90.
- Cherry, S. R., & Phelps, M. E. (1996). Imaging brain function with positron emission tomography. In A. W. Toga & J. C. Mazziotta (Eds.), *Brain Mapping Methods*, pp. 191–221. San Diego: Academic Press.
- Cherry, S. R., Woods, R. P., Doshi, N. K., et al. (1995). Improved signal-to-noise in PET activation studies using switched paradigms. *Journal of Nuclear Medicine*, 36, 307–14.
- Cherry, S. R., Woods, R. P., & Hoffman, E. J. (1993). Improved detection of focal cerebral blood flow changes using three-dimensional positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism*, 13, 630–8.
- Chertkow, H., & Bub, D. (1994). Functional activation and cognition: The ¹⁵O-water PET subtraction method. In A. Kertesz (Ed.), *Localization and Neuroimaging in Neuropsychology*, pp. 151–84. San Diego: Academic Press.
- Clark, M. M., & Plante, E. (1998). Morphology of the inferior frontal gyrus in developmentally language-disordered adults. *Brain and Language*, 61, 288–303.
- Collins, D. L., Neelin, P., Peters, T. M., & Evans, A. C. (1994a). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *Journal of Computer Assisted Tomography*, 18, 192–205.
- Collins, D. L., Peters, T. M., & Evans, A. C. (1994b). An automatic 3D non-linear image deformation algorithm procedure for determination of gross morphometric variability in human brain. In *Proceedings of the 4th Conference on Biomedical Computing*, pp. 180–94. SPIE.
- Coltheart, M., Curtis, B., Atkins, P., & Haller, M. (1993). Models of reading aloud: Dual route and parallel-distributed processing approaches. *Psychological Review*, 100, 589–608.
- Conti, P. (1995). Oncology: Brain and spinal cord. In Wagner, Szabo, & Buchanan, pp. 1041–54.
- Dale, A. M., & Buckner, R.L. (1997). Selective averaging of rapidly presented individual trials using fMRI. *Human Brain Mapping*, 5, 1–12.
- Daube-Witherspoon, M. E. (1995). Positron emission tomography: Operational guidelines. In Wagner, Szabo, & Buchanan, pp. 346–62.
- Davis, T. L. (1998). Calibrated functional MRI: Mapping the dynamics of oxidative metabolism. *Proceedings of the National Academy of Sciences U.S.A.*, 95, 1834–9.
- Demb, J. B., Boynton, G. M., & Heeger, D. J. (1997). Brain activity in visual cortex predicts individual differences in reading performance. *Proceedings of the National Academy of Sciences U.S.A.*, 94, 13363–6.
- Detre, J. A., et al. (1992). Perfusion imaging. *Magnetic Resonance in Medicine*, 23, 37–45.
- Dewey, S. L., Brodie, J. D., Fowler, J. S., et al. (1990). Positron emission tomography (PET) studies of dopaminergic/cholinergic interactions in the baboon brain. *Synapse*, 6, 321–7.
- Dewey, S. L., Smith, G. S., Logan, J., et al. (1992). GABAergic inhibition of endogenous dopamine release measured in vivo with 11C-raclopride and positron emission tomography. *Journal of Neuroscience*, 12, 3773–80.
- Dolan, R. J., & Fletcher, P. C. (1997). Dissociating prefrontal and hippocampal function in episodic memory encoding. *Nature*, 388, 582–5.
- Dolan, R. J., Fletcher, P., Frith, C. D., Friston, K. J., Frackowiak, R. S., & Grasby, P. M. (1995). Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. *Nature*, 378, 180–2.
- Duara, R., Barker, W. W., Chang, J., Yoshii, F., Loewenstein, D. A., & Pascal, S. (1992). Viability of neocortical function shown in behavioral activation state PET studies in Alzheimer disease. *Journal of Cerebral Blood Flow and Metabolism*, 12, 927–34.
- Duncan, J. D., Moss, S. D., Bandy, D. J., Manwaring, K., Kaplan, A. M., Reiman, E. M., Chen, K., Lawson, M. A., & Wodrich, D. L. (1997). Use of positron emission tomography for presurgical localization of eloquent brain areas in children with seizures. *Pediatric Neurosurgery*, 26, 144–56.
- Edelman, R., Siewert, B., & Darby, D. (1994). Qualitative mapping of cerebral blood flow and functional localization with echo planar MR imaging and signal targeting with alternating radiofrequency (EPISTAR). *Radiology*, 192, 1–8.
- Evans, A. C. (1995). Correlative imaging. In Wagner, Szabo, & Buchanan, pp. 405–21.
- Evans, A. C., Collins, D. L., Mills, S. R., et al. (1993). 3D statistical neuroanatomical models from 305 MRI volumes. *Proceedings of the IEEE Nuclear Science Symposium and Medical Imaging Conference*. Piscataway, NJ: IEEE.
- Evans, A. C., Collins, L., Worsley, K., Dai, W., Milot, S., Meyer, E., & Bub, D. (1992). Anatomical mapping of functional activation in stereotactic coordinate space. *Neuroimage*, 1, 43–53.
- Evans, A. C., Marrett, S., Torrescorzo, J., et al. (1991). MRI-PET correlative analysis using a volume of interest (VOI) atlas. *Journal of Cerebral Blood Flow and Metabolism*, 11, A69–A78.
- Evens, R. G., Siegel, B. A., Welch, M. J., et al. (1983). Cost analyses of positron emission tomography for clinical use. *American Journal of Roentgenology*, 141, 1073–6.
- Farde, L., Ehrin, E., Eriksson, L., et al. (1985). Substituted benzamides as ligands for visualization of dopamine receptor binding in the human brain by positron emission tomography. *Proceedings of the National Academy of Sciences U.S.A.*, 82, 3863–7.
- Farde, L., Hakan, H., Ehrin, E., et al. (1986). Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. *Science*, 231, 258–61.
- Fiez, J. A., & Petersen, S. E. (1998). Neuroimaging studies of word reading. *Proceedings of the National Academy of Sciences U.S.A.*, 95, 914–21.

- Fox, P. T., Burton, H., & Raichle, M. E. (1987). Mapping human somatosensory cortex with positron emission tomography. *Journal of Neurosurgery*, 65, 34-63.
- Fox, P. T., & Mintun, M. A. (1989). Noninvasive functional brain mapping by change-distribution analysis of averaged PET images of $H_2^{15}O$ tissue activity. *Journal of Nuclear Medicine*, 30, 141-9.
- Fox, P. T., Mintun, M. A., Raichle, M. E., et al. (1986). Mapping human visual cortex with positron emission tomography. *Nature*, 323, 806-9.
- Fox, P. T., Mintun, M. A., Reiman, E. M., & Raichle, M. E. (1988). Enhanced detection of focal brain responses using intersubject averaging and distribution analysis of subtracted PET images. *Journal of Cerebral Blood Flow and Metabolism*, 8, 642-53.
- Fox, P. T., Perlmutter, J. S., & Raichle, M. E. (1985). A stereotactic method of anatomical localization for positron emission tomography. *Journal of Computer Assisted Tomography*, 9, 141-53.
- Fox, P. T., & Raichle, M. E. (1984). Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated with positron emission tomography. *Journal of Neurophysiology*, 51, 1109-21.
- Fox, P. T., & Raichle, M. E. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in man. *Proceedings of the National Academy of Sciences U.S.A.*, 83, 1140-4.
- Frackowiak, R. S. J., Friston, K. J., Frith, C. D., Dolan, R. J., & Mazziotta, J. C. (1997). *Human Brain Function*. San Diego: Academic Press.
- Frahm, J., et al. (1996). Dynamic uncoupling and recoupling of perfusion and oxidative metabolism during focal activation in man. *Magnetic Resonance in Medicine*, 35, 143-8.
- Fried, I., Nenov, V. I., Ojemann, S. G., & Woods, R. P. (1995). Functional MR and PET imaging of rolandic and visual cortices for neurosurgical planning. *Journal of Neurosurgery*, 83, 854-61.
- Friston, K. J., Ashburner, J., Frith, C. D., et al. (1995). Spatial registration and normalization of images. *Human Brain Mapping*, 2, 165-89.
- Friston, K. J., Frith, C. D., & Frackowiak, R. S. J. (1993a). Time-dependent changes in effective connectivity measured with PET. *Human Brain Mapping*, 1, 69-80.
- Friston, K., Frith, C., Liddle, P., Dolan, R., Lammertsma, A., & Frackowiak, R. (1990). The relationship between global and local changes in PET scans. *Journal of Cerebral Blood Flow and Metabolism*, 10, 458-66.
- Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. J. (1991). Plastic transformation of PET images. *Journal of Computer Assisted Tomography*, 15, 634-9.
- Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. J. (1993b). Functional connectivity: The principal component analysis of large (PET) data sets. *Journal of Cerebral Blood Flow and Metabolism*, 13, 5-14.
- Friston, K. J., Josephs, O., Rees, G., & Turner, R. (1998). Non-linear event-related responses in fMRI. *Magnetic Resonance in Medicine*, 39, 41-52.
- Friston, K. J., Poline, J.-B., Holmes, A. P., Frith, C. D., & Frackowiak, R. S. J. (1996a). A multivariate analysis of PET activation studies. *Human Brain Mapping*, 4, 140-51.
- Friston, K. J., Price, C. J., Fletcher, P., Moore, C., Frackowiak, R. S., & Dolan, R. J. (1996b). The trouble with cognitive subtraction. *Neuroimage*, 4, 97-104.
- Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., et al. (1994). Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping*, 1, 214-20.
- Frost, J. J., & Mayberg, H. S. (1995). Epilepsy. In Wagner, Szabo, & Buchanan, pp. 564-75.
- Gabrieli, J. D. E., Brewer, J. B., Desmond, J. E., & Glover, G. (1997). Separate neural bases of two fundamental memory processes in the human medial temporal lobe. *Science*, 276, 264-6.
- Gabrieli, J. D. E., Poldrack, R. A., & Desmond, J. E. (1998). The role of left prefrontal cortex in language and memory. *Proceedings of the National Academy of Sciences U.S.A.*, 95, 906-13.
- George, J. S., Aine, C. J., Mosher, J. C., Schmidt, D. M., Ranken, D. M., Schlitt, H. A., Wood, C. C., Lewine, J. D., Sanders, J. A., & Belliveau, J. W. (1995). Mapping function in the human brain with magnetoencephalography, anatomical magnetic resonance imaging, and functional magnetic resonance imaging. *Journal of Clinical Neurophysiology*, 12, 406-31.
- Gjedde, A. (1995). Tracer kinetics: Compartment models. In Wagner, Szabo, & Buchanan, pp. 451-62.
- Greitz, T., Bohm, C., Holte, S., & Eriksson, L. (1991). A computerized brain atlas: Construction, anatomical content and some applications. *Journal of Computer Assisted Tomography*, 15, 26-38.
- Haier, R. J., Siegel, B. V., Jr., MacLachlan, A., Soderling, E., Lottenberg, S., & Buchsbaum, M. S. (1992). Regional glucose metabolic changes after learning a complex visuospatial/motor task: A positron emission tomographic study. *Brain Research*, 570, 134-43.
- Halgren, E., Baudena, P., Clarke, J. M., Heit, G., Marinkovic, J., Devaux, B., Vignal, J.-P., & Biraben, A. (1995). Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. *Electroencephalography and Clinical Neurophysiology*, 94, 229-50.
- Heiss, W.-D., & Podreka, I. (1995). Cerebrovascular disease. In Wagner, Szabo, & Buchanan, pp. 531-48.
- Henke, K., Buck, A., Weber, B., & Wieser, H.G. (1997). Human hippocampus establishes associations in memory. *Hippocampus*, 7, 249-56.
- Herscovitch, P. (1995). Cerebral blood flow, volume, and oxygen metabolism. In Wagner, Szabo, & Buchanan, pp. 505-14.
- Herscovitch, P., Markham, J., & Raichle, M. E. (1983). Brain blood flow measured with intravenous $H_2^{15}O$. I: Theory and error analysis. *Journal of Nuclear Medicine*, 24, 782-9.
- Herscovitch, P., Markham, J., & Raichle, M. E. (1987). Positron emission tomographic measurement of cerebral blood flow and water permeability with $O-15$ water and $C-11$ butanol. *Journal of Cerebral Blood Flow and Metabolism*, 7, 527-42.
- Holmes, A. P., Blair, R. C., Watson, J. D. G., & Ford, I. (1996). Non-parametric analysis of statistic images from functional mapping experiments. *Journal of Cerebral Blood Flow and Metabolism*, 16, 7-22.
- Huang, S., Barrio, J. R., & Phelps, M. E. (1986). Neuroreceptor assay with positron emission tomography: Equilibrium versus dynamic approaches. *Journal of Cerebral Blood Flow and Metabolism*, 6, 515-21.

- Huang, S., Phelps, M. E., Hoffman, E. J., et al. (1980). Noninvasive determination of local cerebral metabolic rate of glucose in man. *American Journal of Physiology*, 238, E69–E82.
- ICRP [International Commission on Radiological Protection] (1991). *1990 Recommendations of the ICRP*. Oxford, U.K.: Pergamon.
- Iragui, V., Kutas, M., & Salmon, D. P. (1996). Event-related brain potentials during semantic categorization in normal aging and senile dementia of the Alzheimer's type. *Electrophysiology and Clinical Neurophysiology: Evoked Potentials*, 100, 392–406.
- Josephs, O., Turner, R., & Friston, K. (1997). Event-related fMRI. *Human Brain Mapping*, 5, 243–8.
- Jueptner, M., Stephan, K. M., Frith, C. D., Brooks, D. J., Frackowiak, R. S. J., & Passingham, R. E. (1997). Anatomy of motor learning: Frontal cortex and attention to action. *Journal of Neurophysiology*, 77, 1313–24.
- Just, M. A., Carpenter, P. A., Keller, T. A., Eddy, W. F., & Thulborn, K. R. (1996). Brain activation modulated by sentence comprehension. *Science*, 274, 114–16.
- Karni, A., et al. (1993). Stimulus dependent MRI signals evoked by oriented line-element textures in human visual cortex. *Book of Abstracts, Society for Neuroscience 23rd Annual Meeting*. Washington, DC.
- Kessler, J., Herholz, K., Grond, M., & Heiss, W. D. (1991). Impaired metabolic activation in Alzheimer's disease: A PET study during continuous visual recognition. *Neuropsychologia*, 29, 229–43.
- Kim, S.-G. (1995). Quantification of relative cerebral blood flow change by flow-sensitive alternating inversion recovery (FAIR) technique: Application to functional mapping. *Magnetic Resonance in Medicine*, 34, 293–301.
- Kim, S.-G., Richter, W., & Ugurbil, K. (1997). Limitations of temporal resolution in functional MRI. *Magnetic Resonance in Medicine*, 37, 631–6.
- Kim, S.-G., & Ugurbil, K. (1997). Comparison of blood oxygenation and cerebral blood flow effects in fMRI: Estimation of relative oxygen consumption change. *Magnetic Resonance in Medicine*, 38, 59–65.
- Knapp, F. F., Jr., Brihaye, C., & Callahan, A. P. (1995). Generators. In Wagner, Szabo, & Buchanan, pp. 150–65.
- Koepp, M. J., Gunn, R. N., Lawrence, A. D., Cunningham, V. J., Dagher, A., Jones, T., Brooks, D. J., Bench, C. J., & Grasby, P. M. (1998). Evidence for striatal dopamine release during a video game. *Nature*, 393, 266–8.
- Koepp, R. A., Holthoff, V. A., Frey, K. A., et al. (1991). Compartmental analysis of [¹¹C] flumazenil kinetics for the estimation of ligand transport rate and receptor distribution using positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism*, 11, 735–44.
- Kosugi, Y., Sase, M., Kuwatani, H., et al. (1993). Neural network mapping for nonlinear stereotactic normalization of brain MRI images. *Journal of Computer Assisted Tomography*, 17, 455–60.
- Kutas, M., & Van Petten, C. (1994). Psycholinguistics electrified: Event-related brain potential investigations. In M. Gernsbacher (Ed.), *Handbook of Psycholinguistics*, pp. 83–143. New York: Academic Press.
- Kwong, K. K., et al. (1995). MR perfusion studies with T1-weighted echo planar imaging. *Magnetic Resonance in Medicine*, 34, 878–87.
- Langstrom, B., & Dannals, R. F. (1995). Carbon-11 compounds. In Wagner, Szabo, & Buchanan, pp. 166–78.
- Leahy, R., & Yan, X. (1991). Incorporation of anatomical MR data for improved functional imaging with PET. In A. Colchester & D. Hawkes (Eds.), *Information Processing in Medical Imaging*, pp. 105–19. Wye, U.K.: Springer-Verlag.
- Leblanc, R., & Meyer, E. (1990). Functional PET scanning in the assessment of cerebral arteriovenous malformations. *Journal of Neurosurgery*, 73, 615–19.
- Leblanc, R., Meyer, E., Bub, D., et al. (1992). Language mapping with activation PET scanning. *Neurosurgery*, 31, 369–73.
- Linebarger, M. C., Schwartz, M. F., & Saffran, E. M. (1983). Sensitivity to grammatical structure in so-called agrammatic aphasics. *Cognition*, 13, 361–92.
- Mandeville, J. B. (1998). Dynamic functional imaging of relative cerebral blood volume during rat forepaw stimulation. *Magnetic Resonance in Medicine*, 39, 615–24.
- Marshall, J. C., & Newcombe, F. (1980). The conceptual status of deep dyslexia: An historical perspective. In M. Coltheart, K. Patterson, & J. C. Marshall (Eds.), *Deep Dyslexia*, pp. 1–21. London: Routledge & Kegan Paul.
- Mazziotta, J. C., Phelps, M. E., Plummer, D., & Kuhl, D. E. (1981). Quantitation in positron emission computed tomography: 5. Physical-anatomical effects. *Journal of Computer Assisted Tomography*, 5, 734–43.
- McCarthy, G., Luby, M., Gore, J., & Goldman-Rakic, P. (1997). Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. *Journal of Neurophysiology*, 77, 1630–4.
- McIntosh, A. R., Bookstein, F. L., Haxby, J. V., & Grady, C. L. (1996). Spatial pattern analysis of functional brain images using partial least squares. *Neuroimage*, 3, 143–57.
- McIntosh, A. R., & Gonzalez-Lima, F. (1994). Structural equation modelling and its application to network analysis in functional brain imaging. *Human Brain Mapping*, 2, 2–22.
- McIntosh, A. R., Grady, C. L., Ungerleider, J. V., et al. (1994). Network analysis of cortical visual pathways mapped with PET. *Journal of Neuroscience*, 14, 655–66.
- Meyer, J. H., Kapur, S., Wilson, A. A., DaSilva, J. N., Houle, S., & Brown, G. M. (1996). Neuromodulation of frontal and temporal cortex by intravenous *d*-fenfluramine: An [¹⁵O]H₂O PET study in humans. *Neuroscience Letters*, 207, 25–8.
- Miller, J. D., de Leon, M. J., Ferris, S. H., Kluger, A., George, A. E., Reisberg, B., Sachs, H. J., & Wolf, A. P. (1987). Abnormal temporal lobe response in Alzheimer's disease during cognitive processing as measured by ¹¹C-2-deoxy-D-glucose and PET. *Journal of Cerebral Blood Flow and Metabolism*, 7, 248–51.
- Miller, J., Riehle, A., & Requin, J. (1992). Effects of preliminary perceptual output on neuronal activity of the primary motor cortex. *Journal of Experimental Psychology: Human Perception and Performance*, 18, 1121–38.
- Miller, M., Christensen, G., Amit, Y., & Grenander, U. (1993). Mathematical textbook of deformable neuroanatomies. *Proceedings of the National Academy of Sciences U.S.A.*, 90, 433–4.
- Miltner, W. H. R., Braun, C. H., & Coles, M. G. H. (1997). Event-related brain potentials following incorrect feedback in a time-estimation task: Evidence for a generic neural system for error detection. *Journal of Cognitive Neuroscience*, 9, 788–98.

- Minoshima, S., Berger, K. L., Lee, K. S., & Mintun, M. A. (1992). An automated method for rotational correction and centering of three-dimensional functional brain images. *Journal of Nuclear Medicine*, 33, 1479-1585.
- Minoshima, S., Frey, K. A., Foster, N. L., & Kuhl, D. E. (1995a). Preserved pontine glucose metabolism in Alzheimer's disease: A reference region for functional brain image (PET) analysis. *Journal of Computer Assisted Tomography*, 19, 541-7.
- Minoshima, S., Frey, K. A., Koeppe, R. A., et al. (1995b). A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. *Journal of Nuclear Medicine*, 36, 1238-48.
- Minoshima, S., Koeppe, R. A., Frey, K. A., & Kuhl, D. E. (1994). Anatomic standardization: Linear scaling and nonlinear warping of functional brain images. *Journal of Nuclear Medicine*, 35, 1528-37.
- Mintun, M. A., Fox, P. T., & Raichle, M. E. (1989). A highly accurate method of localizing regions of neuronal activation in the human brain using positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism*, 9, 96-103.
- Mintun, M. A., McGuire, A. H., Welch, M. J., Siegel, B. A., & Katzenellenbogen, J. A. (1991). PET imaging of estrogen receptors in breast cancer. In D. E. Kuhl (Ed.), *In Vivo Imaging of Neurotransmitter Functions in Brain, Heart, and Tumors*, pp. 277-92. Washington, DC: American College of Nuclear Physicians.
- Mintun, M. A., Raichle, M. E., Kilbourn, M. R., et al. (1984). A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. *Annals of Neurology*, 15, 217-27.
- Neville, H. J., Coffey, S. A., Holcomb, P. J., & Tallal, P. (1993). The neurobiology of sensory and language processing in language-impaired children. *Journal of Cognitive Neuroscience*, 5, 235-53.
- Nozaki, T., & Hazue, M. (1995). Accelerators. In Wagner, Szabo, & Buchanan, pp. 144-50.
- NRCC [National Research Council Committee on the Biological Effects of Ionizing Radiation] (1990). *BEIR V. Health Effects of Exposure to Low Levels of Ionizing Radiation*. Washington, DC: National Academy Press.
- Nyberg, L., Tulving, E., Habib, R., Nilsson, L.-G., Kapur, S., Houle, S., Cabeza, R., & McIntosh, A.R. (1995). Functional brain maps of retrieval mode and recovery of episodic information. *Neuroreport*, 7, 249-52.
- Paller, K. A. (1990). Recall and stem-completion priming have different electrophysiological correlates and are modified differentially by directed forgetting. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 16, 1021-32.
- Paller, K. A., Acharya, A., Richardson, B. C., Plaisant, O., Shimamura, A. P., Reed, B. R., & Jagust, W. J. (1997). Functional neuroimaging of cortical dysfunction in alcoholic Korsakoff's syndrome. *Journal of Cognitive Neuroscience*, 9, 277-93.
- Pardo, J. V., & Fox, P. T. (1993). Preoperative assessment of the cerebral hemispheric dominance for language with CBF PET. *Human Brain Mapping*, 1, 57-68.
- Patlak, C., Blasberg, R. G., & Fenstermacher, J. D. (1983). Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *Journal of Cerebral Blood Flow and Metabolism*, 3, 1-7.
- Patterson, K. E., & Morton, J. (1985). From orthography to phonology: An attempt at an old interpretation. In K. E. Patterson, J. C. Marshall, & M. Coltheart (Eds.), *Surface Dyslexia*, pp. 335-59. Hillsdale, NJ: Erlbaum.
- Pellizzari, C. A., Chen, G. T. Y., Spelbring, D. R., et al. (1989). Accurate three-dimensional registration of CT, PET and/or MRI images of the brain. *Journal of Computer Assisted Tomography*, 13, 20-6.
- Perlmutter, J. S., Larson, K. B., Raichle, M. E., Markham, K. J., Mintun, M. A., Kilbourn, M. R., & Welch, M. J. (1986). Strategies for in vivo measurement of receptor binding using positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism*, 6, 154-69.
- Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., & Raichle, M. E. (1989). Positron emission tomographic studies of the processing of single words. *Journal of Cognitive Neuroscience*, 1, 153-70.
- Petersson, J. M., Elfgren, C., & Ingvar, M. (1997). A dynamic role of the medial temporal lobe during retrieval of declarative memory in man. *Neuroimage*, 6, 1-11.
- Phelps, M. E., Hoffman, E. J., Mullani, N. A., & Ter-Pogossian, M. M. (1975). Application of annihilation coincidence detection to transaxial reconstruction tomography. *Journal of Nuclear Medicine*, 16, 210-24.
- Phelps, M. E., Huang, S. C., Hoffman, E. J., et al. (1979). Tomographic measurement of local cerebral metabolic rate in humans with [F-18] 2-fluoro-2-deoxy-D-glucose: Validation of method. *Annals of Neurology*, 6, 371-88.
- Plaut, D. C., McClelland, J. L., Seidenberg, M. S., & Patterson, K. (1996). Understanding normal and impaired word reading: Computational principles in quasi-regular domains. *Psychological Review*, 103, 56-115.
- Plunkett, K., & Marchman, V. A. (1993). From rote learning to system building: Acquiring verb morphology in children and connectionist nets. *Cognition*, 48, 21-69.
- Price, C. J., & Friston, K. J. (1997). Cognitive conjunction: A new approach to brain activation experiments. *Neuroreport*, 5, 261-70.
- Price, C. J., Moore, C. J., Humphreys, G. W., & Wise, R. J. S. (1997). Segregating semantic from phonological processes during reading. *Journal of Cognitive Neuroscience*, 9, 727-33.
- Price, C. J., Wise, R. J. S., Watson, J. D. G., Patterson, K., Howard, D., & Frackowiak, R. S. J. (1994). Brain activity during reading. The effects of exposure duration and task. *Brain*, 117, 1255-69.
- Raichle, M. E. (1983). Positron emission tomography. *Annual Review of Neuroscience*, 6, 249-67.
- Raichle, M. E. (1987). Circulatory and metabolic correlates of brain function in normal humans. In B. V. Mountcastle, F. Plum, & S. R. Geiger (Eds.), *Handbook of Physiology, The Nervous System, V. Higher Functions of the Brain*, pp. 643-74. Bethesda, MD: American Physiological Society.
- Raichle, M. E., Martin, M. R. W., Herscovitch, P., et al. (1983). Brain blood flow measured with intravenous H₂¹⁵O, II: Implementation and validation. *Journal of Nuclear Medicine*, 24, 790-8.
- Rees, G., Howseman, A., Josephs, O., Frith, C. D., Friston, K. J., Frackowiak, R. S. J., & Turner, R. (1997). Characterizing

- the relationship between BOLD contrast and regional cerebral blood flow measurements by varying the stimulus presentation rate. *Neuroimage*, 6, 270–8.
- Reiman, E. M. (1990). PET, panic disorder, and the study of anxiety. In J. C. Ballenger (Ed.), *Neurobiology of Panic Disorder*, pp. 245–70. New York: Wiley-Liss.
- Reiman, E. M. (1997). The application of positron emission tomography to the study of normal and pathological emotions. *Journal of Clinical Psychiatry*, 58, 4–12.
- Reiman, E. M., Caselli, R. J., Lang, S. Y., Chen, K., Bandy, D., Minoshima, S., Thibodeau, S. N., & Osborne, D. (1996). Preclinical evidence of Alzheimer's disease in persons homozygous for the $\epsilon 4$ allele for apolipoprotein E. *New England Journal of Medicine*, 334, 752–8.
- Reiman, E. M., Lane, R. D., Ahern, G. L., Schwartz, G. E., Davidson, R. J., Friston, K. J., Yun, L.-S., & Chen, K. (1997). Neuroanatomical correlates of externally and internally generated human emotion. *American Journal of Psychiatry*, 154, 918–25.
- Reivich, M., Kuhl, D., Wolf, A., et al. (1979). The [18F] fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circulation Research*, 44, 127–37.
- Richter, W., Andersen, P. M., Georgopoulos, A. P., & Kim, S. G. (1997). Sequential activity in human motor areas during a delayed cued finger movement task studied by time-resolved fMRI. *Neuroreport*, 8, 1257–61.
- Riehle, A., Grun, S., Diesmann, M., & Aertsen, A. (1997). Spike synchronization and rate modulation differentially involved in motor cortical function. *Science*, 278, 1950–3.
- Roland, R. E., Larsen, B., Lassen, N. A., & Skinhoj, E. (1980). Supplementary motor area and other cortical areas in organization of voluntary movements in man. *Journal of Neurophysiology*, 43, 118–36.
- Rosen, B. R., Buckner, R. L., & Dale, A. M. (1998). Event-related MRI: Past, present, and future. *Proceedings of the National Academy of Sciences U.S.A.*, 95, 773–80.
- Rugg, M. D., & Doyle, M. C. (1994). Event-related potentials and stimulus repetition in direct and indirect tests of memory. In H.-J. Heinze, T. F. Munte, & G. R. Mangun (Eds.), *Cognitive Electrophysiology*, pp. 124–48. Boston: Birkhäuser.
- Rugg, M. D., Fletcher, P. C., Frith, C. D., Frackowiak, R. S. J., & Dolan, R. J. (1997). Brain regions supporting intentional and incidental memory – A PET study. *Neuroreport*, 8, 1283–7.
- Rumsey, J. M., Nace, K., Donohue, B., Wise, D., Maisog, J. M., & Andreason, P. (1997). A positron tomographic study of impaired word recognition and phonological processing in dyslexic men. *Archives of Neurology*, 54, 562–73.
- Saha, G. B., MacIntyre, W. J., & Go, R. T. (1992). Cyclotron and positron emission tomography radiopharmaceuticals for clinical imaging. *Seminars in Nuclear Medicine*, 22, 150–61.
- Sarter, M., Berntson, G. G., & Cacioppo, J. T. (1996). Brain imaging and cognitive neuroscience: Toward strong inference in attributing function to structure. *American Psychologist*, 51, 13–21.
- Schacter, D. L., & Tulving, E. (1994). *Memory Systems 1994*. Cambridge, MA: MIT Press.
- Schacter, D. L., Uecker, A., Reiman, E., Yun, L.-S., Bandy, D., Chen, K., Cooper, L. A., & Curran, T. (1997). Effects of size and orientation change on hippocampal activation during episodic recognition: A PET study. *Neuroreport*, 8, 3993–8.
- Schwaiger, M. (1995). Left ventricular failure. In Wagner, Szabo, & Buchanan, pp. 826–37.
- Schwartz, W. J., Smith, C. B., Davidsen, L., et al. (1979). Metabolic mapping of functional activity in the hypothalamo-neurohypophysial system of the rat. *Science*, 205, 723–5.
- Sedvall, G., Farde, L., Persson, A., et al. (1986). Imaging of neurotransmitter receptors in the living human brain. *Archives of General Psychiatry*, 43, 995–1005.
- Seitz, R. J., Bohm, C., Greitz, T., et al. (1990). Accuracy and precision of the computerized brain atlas programme for localization and quantification in positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism*, 10, 188–99.
- Senkfor, A. J., & Van Petten, C. (1999). Who said what? Electrophysiological dissociations of source and item memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 21, 1005–25.
- Sherrington, C. S. (1940). *On Man and His Nature*. Cambridge University Press.
- Silverman, D. H., Hoh, C. K., Seltzer, M. A., Schiepers, C., Cuan, G. S., Gambhir, S. S., Zheng, L., Czernin, J., & Phelps, M. E. (1998). Evaluating tumor biology and oncological disease with positron-emission tomography. *Seminars in Radiation Oncology*, 8, 183–96.
- Smith, G. S., Dewey, S. L., Brodie, J. D., et al. (1997). Serotonergic modulation of dopamine measured with [11C]raclopride and PET in normal human subjects. *American Journal of Psychiatry*, 154, 490–6.
- Smith, G. S., Schloesser, R., Brodie, J. D., et al. (1998). Glutamate modulation of dopamine measured in vivo with positron emission tomography (PET) and 11C-raclopride in normal human subjects. *Neuropsychopharmacology*, 18, 18–25.
- Sokoloff, L., Reivich, M., Kennedy, C., et al. (1977). The [14C]deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure and normal values in the conscious and anesthetized albino rat. *Journal of Neurochemistry*, 28, 897–916.
- Stocklin, G. (1995). Fluorine-18 compounds. In Wagner, Szabo, & Buchanan, pp. 178–94.
- Swick, D., & Knight, R. T. (1996). Is prefrontal cortex involved in cued recall? A neurophysiological test of PET findings. *Neuropsychologia*, 34, 1019–28.
- Swick, D., & Knight, R. T. (1997). Event-related potentials differentiate the effects of aging on word and nonword repetition in explicit and implicit memory tasks. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 23, 123–42.
- Szelies, B., Herholz, K., Pawlik, G., Karbe, H., Hebold, I., & Heiss, W.-D. (1991). Widespread functional effects of discrete thalamic infarction. *Archives of Neurology*, 48, 178–82.
- Talairach, J., Szikla, G., Tournoux, P., et al. (1967). *Atlas d'Anatomie Stereotaxique du Telencephale*. Paris: Masson.
- Talairach, J., & Tournoux, P. (1988). *Co-Planar Stereotaxic Atlas of the Human Brain*. New York: Thieme Medical Publishers.
- Tanaka, N., Josephs, O., Friston, K., & Frackowiak, R. S. J. (1998). Cortical responses to single episodes of mechanical pain: an event-related fMRI and PET study. *Neuroimage*, 7, S421.
- Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., & Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proceedings of the National Academy of Sciences U.S.A.*, 94, 14792–7.

- Thompson-Schill, S. L., Swick, D., Farah, M. J., D'Esposito, M., Kan, I. P., & Knight, R. T. (1998). Verb generation in patients with focal frontal lesions: A neuropsychological test of neuroimaging findings. *Proceedings of the National Academy of Sciences U.S.A.*, *95*, 15855-60.
- Tootel, R. B. H., Dale, A. M., Sereno, M. I., & Malach, R. (1996). New images from human visual cortex. *Trends in Neurosciences*, *19*, 481-9.
- Townsend, D. W. (1991). Optimization of signal in positron emission tomography scans: Present and future developments. In D. J. Chadwick & J. Whelan (Eds.), *Exploring Brain Functional Anatomy with Positron Emission Tomography* (Ciba Foundation Symposium no. 163), pp. 57-75. West Sussex, U.K.: Wiley.
- Tulving, E., Markowitsch, H. J., Craik, F. I. M., Habib, R., & Houle, S. (1996). Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cerebral Cortex*, *6*, 71-9.
- Van Petten, C., Reiman, E., & Senkfor, A. J. (1995). PET and ERP measures of semantic and repetition priming [Abstract]. *Psychophysiology*, *32*, S81.
- Van Petten, C., & Senkfor, A. J. (1996). Memory for words and novel visual patterns: Repetition, recognition, and encoding effects in the event-related brain potential. *Psychophysiology*, *33*, 491-506.
- Van Petten, C., Weckerly, J., McIsaac, H., & Kutas, M. (1997). Working memory capacity dissociates lexical and sentential context effects. *Psychological Science*, *8*, 238-42.
- Volkow, N. D., Mullani, N. A., Gould, L. K., et al. (1991). Sensitivity of measurements of regional brain activation with oxygen-15 water and PET to time of stimulation and period of image reconstruction. *Journal of Nuclear Medicine*, *32*, 58-61.
- Wagner, H. N., Szabo, Z., & Buchanan, J. W. (Eds.) (1995). *Principles of Nuclear Medicine*. Philadelphia: Saunders.
- Wise, R., Chollet, F., Hadar, U., Friston, K., Hoffner, E., & Frackowiak, R. (1991). Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain*, *114*, 1803-17.
- Woldorff, M. G. (1993). Distortion of ERP averages due to overlap from temporally adjacent ERPs: Analysis and correction. *Psychophysiology*, *30*, 98-119.
- Wong, D. F., Gjedde, A., & Wagner, H. N., Jr. (1986). Quantification of neuroreceptors in the living human brain. I. Irreversible binding of ligands. *Journal of Cerebral Blood Flow and Metabolism*, *6*, 137-46.
- Wong, D. F., & Resnick, S. M. (1995). Mental illness: Neurotransmission. In Wagner, Szabo, & Buchanan, pp. 590-4.
- Wong, E. C., Buxton, R. B., & Frank, L. R. (1996). Quantitative perfusion imaging using EPSTAR and FAIR. *Proceedings of the ISMRM 4th Annual Meeting*. New York.
- Wong, E. C., Buxton, R. B., & Frank, L.R. (1997). Implementation of quantitative perfusion imaging techniques for functional brain mapping using pulsed arterial spin labeling. *NMR in Biomedicine*, *10*, 237-49.
- Woods, R. P., Cherry, S. R., & Mazziotta, J. C. (1992). Rapid automated algorithm for aligning and reslicing PET images. *Journal of Computer Assisted Tomography*, *16*, 620-33.
- Woods, R. P., Cherry, S. R., & Mazziotta, J. C. (1993). MRI-PET registration with automated algorithm. *Journal of Computer Assisted Tomography*, *17*, 536-46.
- Worsley, K. J., Evans, A. C., Marrett, S., & Neelin, P. (1992). A three-dimensional statistical analysis for CBF activation studies in the human brain. *Journal of Cerebral Blood Flow and Metabolism*, *12*, 900-18.
- Yun, L.-S. (1996). Scattered data modeling and deformation with transfinite constraints. Dissertation, Arizona State University, Tempe.
- Zarahn, E., Aguirre, G., & D'Esposito, M. (1997). A trial-based experimental design for fMRI. *Neuroimage*, *6*, 122-38.