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METHODOLOGICAL AND CONCEPTUAL ISSUES IN FUNCTIONAL MAGNETIC RESONANCE IMAGING: Applications to Schizophrenia Research*

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■ **Abstract** Functional magnetic resonance imaging (MRI) is a noninvasive, highly repeatable, and increasingly available method to study disordered brain activity among patients with psychological or neurological disorders. In this chapter the biophysical principles underlying functional MRI are presented, and methodological limitations of the method are discussed. Artifacts related to the biophysical basis of the functional MRI signal or associated with image acquisition methods are presented, as are artifacts related to baseline effects—especially those associated with medication, caffeine, and nicotine use. The difficulties associated with the comparison of groups of subjects differing in performance receive special attention. The limitations of cognitive subtraction designs for functional MRI are also discussed. Functional MRI studies of schizophrenia patients are used to illustrate these points.

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INTRODUCTION

Over the past three decades, neuropharmacologic, neuropathological, neuropsychological, and neuroimaging studies have shown schizophrenia to be a biological disorder. Among the various methods used to investigate the neurobiology of schizophrenia, functional neuroimaging plays a special integrative role. This special role can be understood by visualizing how functional imaging techniques relate to the levels of neural organization involved in understanding brain function (Shepherd 1994). Figure 1 is an adaptation of Shepherd's neural hierarchy describing the two important general contributions that functional brain imaging makes to the neurobiological study of neuropsychiatric disorders. First, functional brain imaging couples behavior—whether patient symptoms or neurocognitive function—to brain activity. This coupling is done by associating variations in behavioral state with variation in local or distributed brain activity. Second, functional brain imaging modalities are available to integrate molecular and system information about brain function. As Figure 1 shows, both magnetic resonance imaging (MRI) and positron emission tomography (PET) integrate, within a single modality, neural information at molecular and system levels.

In this chapter, we discuss the potential, pitfalls, and pragmatics of using functional magnetic resonance imaging (fMRI) to study disordered brain function among individuals with schizophrenia. Although we focus on a single psychological disorder, many of the issues we discuss generalize straightforwardly to other neuropsychiatric diseases. Functional MRI has several advantages over other functional brain imaging methods. Like PET, fMRI is more accurate in localizing signal sources than are electrophysiological methods (Cohen & Bookheimer 1994). However, because the functional contrast used in most fMRI studies arises naturally as a by-product of neural activity, fMRI studies are noninvasive and more highly repeatable than PET studies. Moreover, MRI methods are unsurpassed by any other noninvasive imaging modality in the integration of anatomical, neural system, and molecular information. In a single session, investigators using MRI methods can collect anatomical images at a one-millimeter resolution, obtain information about brain activity at a temporal resolution of a few seconds, and survey the metabolic integrity of the brain regions studied. Finally, MRI facilities are more readily

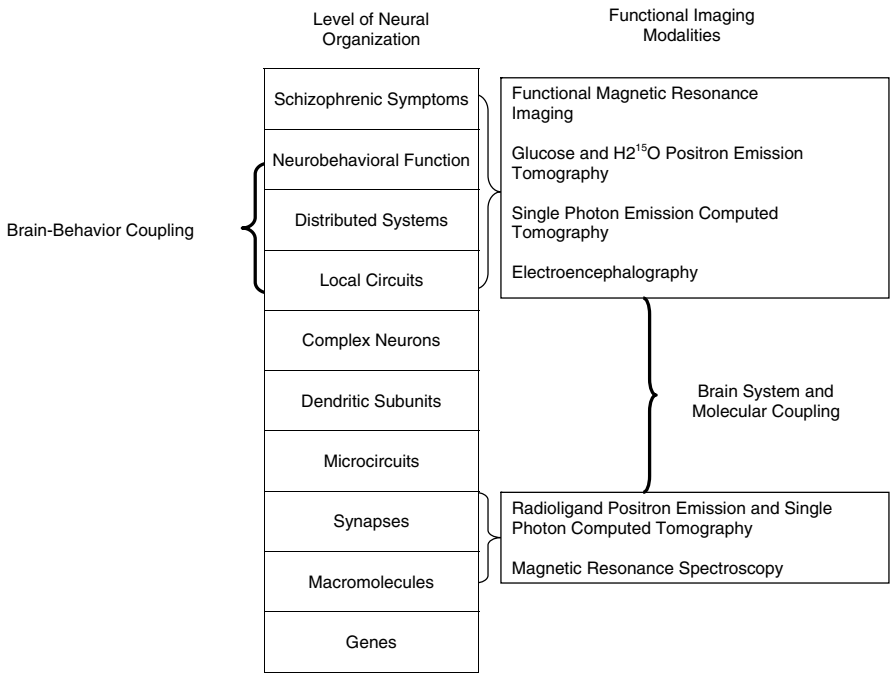

Figure 1 Neural hierarchy showing how functional imaging modalities are related to levels of neural organization. The left bracket shows the coupling of behavioral and system levels of neural organization. The right bracket shows the coupling of brain system and molecular levels. Brain imaging methods involved in the two forms of coupling can bridge the behavioral level of neural organization with the molecular level. Adapted from Shepherd (1994).

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available to clinical researchers than are PET facilities, with 5,000 U.S. MRI sites identified in 2004 versus 1500 U.S. PET sites identified in 2003 (Latest IMV PET 2004, Latest IMV Study 2005). Although not all of these MRI facilities are capable of the high-speed imaging needed for fMRI work, systems currently being shipped from all major magnet manufacturers include the hardware and software necessary to do basic fMRI. Because fMRI scans require careful manipulation of an individual's behavioral state, the widespread availability of fMRI methods could create an important avenue for the migration of psychological methods and theory into medical practice.

The use and interpretation of fMRI in patient populations is complicated by challenging questions regarding the effects of disease on brain structure and function, the impact of variation of baseline vascular status and vascular responsiveness on the blood oxygen level–dependent (BOLD; see Glossary) signal, the effects of performance level on brain activation, and the influence of prescribed and

nonprescribed drugs on fMRI signals. An understanding of the biophysical basis of fMRI is essential to understanding how the field is attempting to respond to these complex questions.

BIOPHYSICAL BASIS OF FUNCTIONAL MAGNETIC RESONANCE IMAGING

Physical Principles of Magnetic Resonance

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The basic components of an MRI study involve establishing a baseline energy state, perturbing the baseline state, and monitoring the return to baseline—a measurement paradigm familiar to all behaviorally trained psychologists. The baseline energy state is achieved by placing the study sample into a static magnetic field, called the B_0 field. The use of strong magnetic fields to create a baseline energy potential is possible because the nuclei of some atoms possess spin, the property of nuclei in a magnetic field to assume one of only a discrete number of orientations, each associated with a discrete energy level (Buxton 2002).

MR would not be very interesting if the static external magnetic field merely induced differences in energy state. However, as the word "spin" implies, individual nuclei possess angular momentum that causes them to precess around the static magnetic field, B_0. The rate at which an MR-observable nucleus precesses is given by the Larmor equation: $\omega = \gamma B_0$, where ω is the precession rate, γ is the gyromagnetic ratio (a resonance frequency that varies from nucleus to nucleus), and B_0 is the strength of the static magnetic field, measured in Tesla (T) units. Because MR-observable nuclei, such as the nuclei of hydrogen, phosphorus, and fluorine, have different gyromagnetic ratios, MR receiver coils (see Glossary) can be used to tune into the baseline state of distinct nuclei. The MR baseline is perturbed by introducing radio frequency (rf) energy into the ensemble of nuclei through a radiofrequency transmitter coil (see Glossary). By using the Larmor equation to determine the frequency of the introduced energy, different nuclei can be selected for study. At a B_0 field strength of 1.5 T, the radio frequency field should oscillate at about 63.87 megahertz to select protons, the nucleus of hydrogen, but oscillate at about 25.875 Mhz to select phosphorus nuclei. The introduction of rf energy increases the number of nuclei in higher energy states.

Once the rf transmitter coil is turned off, rf energy is released and the system relaxes back to baseline. The rf energy is released near the same frequency at which it was introduced, making it easy to record by a receiver coil. The rate of relaxation is governed by two intrinsic relaxation processes involving interactions between the spin of a particular nucleus, say a proton, and its molecular environment and interactions with spins of adjacent nuclei. The rate of relaxation determined by interactions with a nucleus's molecular environment is T_1. The rate of relaxation determined by spin-spin interactions, which cause neighboring spins to precess out of phase, is T_2. Although T_1 is always much larger than T_2, the two relaxation

parameters can become dissociated in real-world physical and biological systems, giving rise to different forms of image contrast. A complexity arises when attempting to measure T_2. Local inhomogeneities in a magnetic field cause protons that would ideally precess in phase to precess at different phases by exposing different protons to slightly different magnetic fields. Magnetic field inhomogeneities combine with spin-spin interactions to determine an observed or effective rate, T_2^*, which is usually different from the intrinsic spin-spin relaxation rate T_2.

Blood Oxygen Level Dependent Contrast

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All of the fMRI studies described below used BOLD contrast (Buxton 2002) to measure brain activity. BOLD contrast reflects variation in the deoxyhemoglobin content (see Glossary) of cerebral vessels induced by changes in the level of neuronal activity. Because neural activation increases cerebral blood flow and blood volume out of proportion to oxygen utilization, blood oxygenation increases and deoxyhemoglobin content decreases with neural activation (Buxton 2002). Deoxyhemoglobin is paramagnetic, so that changes in the local deoxyhemoglobin of blood produce magnetizability gradients around the hemoglobin molecule and around blood vessels containing hemoglobin. The intravascular and extravascular gradients cause a loss of phase of spins that experience slightly different magnetic fields along the gradients and alter the observed spin-spin decay rate for the MR signal, T_2^* (Buxton 2002). On T_2^*-weighted images, the local MR signal increases with decreases of local deoxyhemoglobin content. Variations in the amount of deoxyhemoglobin at different levels of neural activity provide a naturally occurring marker of neural activity that can be noninvasively imaged.

BOLD contrast depends on how well the MR signal tracks changes in cognitive and behavioral state. Thus BOLD images must be interpreted together with knowledge of the cognitive and behavioral conditions under which the individual was imaged. In most applications, the investigator uses cognitive challenge tasks to control an individual's mental state. Such tasks typically involve block designs or single-trial, event-related designs governing the presentation of items (Buxton 2002). In a block design, similar items are presented contiguously within a block of trials. Blocks composed of dissimilar items are presented in an interleaved manner throughout the scanning period. In an event-related design, the timing of item presentation is determined so that dynamic changes in the MR signal can be tracked after individual items are presented. Such single-trial designs allow for greater randomization of item presentation and permit the investigator to classify trials based on an individual's response, such as comparing items responded to correctly versus incorrect items. Additionally, event-related designs permit investigators to decompose the poststimulus MR signal into hypothetical information-processing stages (Zarahn et al. 1997).

In the typical fMRI experiment, the investigator acquires a time series of MR signal intensities within each volume element (i.e., voxel; see Glossary) imaged. The investigator then derives a statistic to measure the degree to which the MR signal in

each voxel changes in tandem with manipulations of the stimulus or with changes in some response variable. The magnitude of these correlated changes—often expressed as a regression weight—is typically color-coded to display local variations in the magnitude of the BOLD response. Choices about the statistic to display and the methods for correcting for false positives when inferential statistics are presented are important sources of variation in BOLD studies (Jernigan et al. 2003).

LIMITATIONS AND ARTIFACTS

The core limitation of MRI is its intrinsically low signal-to-noise ratio (Gadian 1982) (see Glossary). To detect a signal from an MR-observable nucleus requires the nucleus to be present in the sample at millimolar concentrations (Gadian 1982). Moreover, when the molecules containing the target nuclei are tightly bound into macromolecules, the molecules might spin so slowly that the relaxation due to the interaction of a spin with its molecular environment is beyond the range detectable by typical MR protocols (Elster & Burdette 2001). Because MR-observable nuclei cannot be detected in all of the molecular environments in which they participate, their effective concentration is reduced, aggravating the already low sensitivity of MR methods. The insensitivity of MR means that biologically interesting compounds present in low concentrations, such as many neurotransmitters, are not MR detectable using current methods. We discuss further limitations of BOLD contrast fMRI below.

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Limitations Related to Localization

THE BRAIN-VEIN PROBLEM BOLD contrast reflects the differential deoxyhemoglobin content of blood at different levels of neural activity. However, the native deoxyhemoglobin content of blood differs among arteries, veins, and capillaries. In arteries, especially those leaving the lungs, 97% of the hemoglobin is saturated with oxygen, whereas the oxygen saturation of venous hemoglobin is 70% or less (Guyton 1977). Because neural activation reduces the deoxyhemoglobin content of cerebral vessels, veins have a much greater dynamic range than do arteries or capillaries. Thus the most intense areas of BOLD contrast usually come from veins downstream from capillaries supplying the neural pools that generate the increased metabolic demand. Unfortunately, the venous signal can be as far as one centimeter removed from the cortex generating the neural response, causing a mislocalization of the neural event that stimulated the BOLD response (Buxton 2002).

Several solutions to the brain-vein problem have been proposed. The researcher could discard the largest BOLD signals, reasoning that they came from veins. This strategy might be augmented by using MR venograms to screen for areas with large veins. Special pulses can be applied to neutralize the intravenous signal from larger vessels (Buxton 2002). Both of these strategies leave only weak signals to study. A promising alternative for cognitive activation studies is to use arterial spin labeling

(ASL) to measure cerebral perfusion with MR (Buxton 2002). ASL signals tend to be generated by arterioles and capillaries rather than veins. Although ASL signals are usually less consistently associated with changes in behavioral state than are BOLD signals, methods are being developed to improve the contrast to noise (see Glossary) of ASL data (Liu et al. 2002). If the goal of an fMRI experiment is to study the responsiveness of a broad brain region to changes in behavioral state, then signals from veins need not be problematic. However, if the goal of a study is the fine-grain anatomical mapping of a brain region, then methods to attenuate the mislocation caused by venous signals will need to be used.

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SIGNAL DROPOUT The different physiological compartments of the head—brain, cerebrospinal fluid, bone, and air—are characterized by different magnetizabilities, i.e., by different magnetic susceptibilities (Elster & Burdette 2001). Boundaries involving the air and brain compartments, in particular, will be sites of broad magnetic field gradients that will offset the precessing frequency from the target frequency and dephase spins, reducing the MR signal. This dephasing causes signal dropout, especially in the orbital frontal and anterior medial temporal regions, adjacent to nasal sinuses, or lateral temporal regions adjacent to the auditory canal (Figure 2*A*). In all of these regions the air-brain boundaries cause relatively strong magnetic gradients across large portions of the head. These strong magnetic gradients diminish T_2^* in areas of signal dropout and greatly reduce the signal-to-noise ratio (Robinson et al. 2004). Signal dropout is typically more severe at 3T than at lower field strengths, and it depends on the volume of the imaging voxels, the orientation of the slices acquired, and the pulse sequence to acquire images (Buxton 2002, Robinson et al. 2004). Larger voxels in regions with strong field gradients will have lower MR signal values, as a larger array of spin phases will be included in the image volume. Contrary to the typical impact of signal averaging, reductions of the in-plane resolution of an image pixel and decreases in slice thickness increase signal to noise and improve image contrast of T_2^*-weighted images—within regions of signal dropout (Buxton 2002, Robinson et al. 2004). Some MR scientists have found that orienting axial imaging planes obliquely (see Glossary) reduces signal dropout in the anterior medial temporal lobe (Robinson et al. 2004). The gradient echo pulse sequences (see Glossary) typically used in fMRI studies are more susceptible to signal dropout artifacts than spin echo sequences (Buxton 2002) (see Glossary). However, the same characteristic that makes spin echo images more robust to signal dropout makes them less sensitive to BOLD contrast (Buxton 2002). Thus, the current view is for investigators to optimize image acquisition for gradient echo images rather than use a less-susceptible image sequence.

IMAGE DISTORTION In an MR experiment, the user prescribes the number of voxels and slices to be acquired. Implementing the slice prescription involves the system's gradient coils (see Glossary). Nonlinearity of the gradient fields distorts the geometry of the 3D coordinate system in which the imaged object is reconstructed

(See Figure 2*B*). Significant variation in image distortion occurs for images collected on the magnets of different vendors (Wang et al. 2004). Unless corrected, intervendor differences in magnet distortion would either limit magnet sites available for multisite studies or introduce localization errors into group analyses when multivendor data are combined. Even within a single site, geometric distortions create problems combining images from subjects with different brain volumes and shapes and limit the use of automated atlases that require images to be warped to a common anatomical space. Vendors' software to correct gradient distortions typically correct only for in-plane distortions (Wang et al. 2004). Several research groups are developing full 3D corrections. Until 3D corrections become available, combining images across subjects and sites will remain a significant research challenge.

In addition to gradient distortions, off-frequency artifacts can further warp images. Like signal dropout, frequency-offset image distortion becomes worse with increasing field strength (Buxton 2002). Because these image distortions are related to local field inhomogeneities, phase maps of the field offsets can localize the distortions (Wang et al. 2004). These maps can be used to correct some of the distortions produced by resonance offsets. In our experience, it is important to visually inspect the unwarped image to insure that the unwarping algorithm adequately corrected the image (see "warped image" in Glossary).

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Limitations Related to the Blood Oxygen Level Dependent Signal

BASELINE EFFECTS The BOLD signal depends on changes in levels of deoxyhemoglobin, which in turn are determined by local cerebral blood flow, blood volume, and cerebral oxygen metabolism. Factors that alter the baseline levels of any of these three physiological processes can alter the dynamic range of the BOLD response (Davis et al. 1998). Studies using carbon dioxide, breath holding, and the vasodilating drug acetazolamide show that increased baseline levels of blood flow and blood volume can reduce the magnitude of the BOLD response (Brown et al. 2003, Bruhn et al. 1994). Baseline changes in blood flow and volume due to disease and/or due to drugs can mismatch schizophrenia patients and controls on vascular variables that alter the dynamic range of the BOLD response (see below). In such cases, group differences in the BOLD signal would be due to differences in the vascular filter transducing the underlying neural signal rather than to differences in the underlying neural activity. Ongoing research is focusing on methods to correct the BOLD response for differences in baseline blood flow and volume or to measure the dynamic range of the BOLD response to a purely vascular stimulus, such as breath hold, in order to calibrate the BOLD response to a behavioral stimulus.

TEMPORAL CHARACTERISTICS The typical time course of the BOLD response obtained from a block design begins with an initial dip from baseline over the first two seconds. This slight dip is followed by an increase in the MR signal that peaks

approximately five to nine seconds after the first trial in the block. Following offset of the stimulus, the MR signal declines and often falls below the baseline value. This period of signal undershoot might last as long as tens of seconds (Buxton 2002). The delay, dispersion, and complex dynamics of the hemodynamic response complicates the use of fMRI to estimate timing of the neural response. The dispersion of the BOLD response produces temporal correlations between responses produced by consecutive stimuli. The mathematical method of deconvolution (see Glossary) can separate responses to temporally correlated stimuli. However, in fMRI research, mathematical separation of responses to consecutive stimuli is limited by how quickly images can be collected, by imprecise knowledge of the shape of the hemodynamic response to stimuli, and by noise. Nonetheless, because many behavioral events occur more slowly than neural events, fMRI data can be useful to test hypotheses about the timing of slowly evolving behavioral processes in carefully designed experiments (Liu 2004).

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Limitations Related to Schizophrenia

IMPACT OF STRUCTURAL ABNORMALITIES ON FUNCTIONAL SIGNAL In an oft-quoted paper, Shenton and colleagues (2001) reviewed all volumetric MRI studies of schizophrenia patients published from 1988 to August 2000. They found that 80% of these studies reported enlarged lateral ventricles and that 73% of studies found enlarged third ventricles. Regional gray matter changes were also observed, with 68% of studies finding abnormal basal ganglia volumes and 74% of studies reporting reduced medial temporal lobe volumes. In an especially intriguing finding, all 12 studies that measured gray matter in the superior temporal lobe reported reduced volumes. The global and regional reduction of gray matter volumes and the increase in ventricular volumes reported in these studies can produce partial volume effects, where schizophrenia patients and healthy controls differ in the amount of gray matter, white matter, and cerebrospinal fluid combined into an image voxel. Moreover, increases in cerebrospinal fluid spaces can complicate the warping of images into a common image space for intersubject and group comparisons (Senjem et al. 2005).

MOVEMENT ARTIFACT Perhaps the most important practical challenge to obtaining reliable and valid fMRI measures is movement. Movements may be behavioral, generated voluntarily or involuntarily by the subject, or physiological, generated by cardiac or respiratory rhythms (Hu et al. 1995). Brain pulsations tied to cardiac rhythms can cause brain tissue to move as much as 0.5 mm (Poncelet et al. 1992). Movements of only a fraction of a voxel can produce signal changes in the 1% to 5% range at borders of strong tissue contrast, such as cortical edges (see Figure 3). By comparison, BOLD responses less than 1% can be statistically significant and theoretically meaningful. Movement is an especially challenging problem when it is correlated with transitions between stimulus blocks (Hajnal et al. 1996).

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Whether drug-induced or spontaneous, movement disorders are common among schizophrenia patients. Between 50% and 60% of schizophrenia patients taking first-generation antipsychotic medications, which block dopamine 2 receptors, develop extrapyramidal symptoms (EPS). Although the risk of EPS might be reduced among schizophrenia patients taking second-generation antipsychotics, which block both dopamine and serotonin receptors, a large percentage of patients taking these drugs experience EPS (Mauskopf et al. 2002). Moreover, many schizophrenia patients experience movement disorders unrelated to medication use. Spontaneous dyskinesia is present in 25% of drug naïve patients between 30 and 50 years of age (Fenton 2000). Parkinsonian symptoms have been reported to be present in 18% to 28% of first-episode, drug-naïve schizophrenia patients, depending on the motor rating scale used (Cortese et al. 2005). Given the prevalence of motor disorders among schizophrenia patients, movement artifacts are likely to be confounded with diagnosis in fMRI studies of schizophrenia. When patient movements are unrelated to the experimental and control stimuli, they are likely to introduce noise into the statistical analysis, producing false negatives in the patient group. When correlated with transitions among types of stimuli, movement can produce false positives in the patient group.

HETEROGENEITY OF BASELINE FLOW Drugs that alter the physiological activity of the vascular smooth muscle or stimulate the autonomic nervous system that controls vascular dilation can have an impact on baseline blood flow and blood volume, thus altering BOLD response. Some medications, such as calcium channel blockers used to treat cerebral vasospasm and systemic hypertension, are designed to have their impact on vascular smooth muscle (Alborch et al. 1995). Such medicines, which relax blood vessels by altering the influx of calcium into cells, increase cerebral blood flow and alter cerebrovascular reactivity (Alborch et al. 1995). Like calcium channel blockers, cholinergic drugs are vasodilators, although their precise mode of action is still being investigated (Edvinsson et al. 1987). Several animal studies confirm that dopamine, a neurotransmitter, and haloperiodol, which blocks dopamine 2 receptors, can alter both baseline blood flow and the vasodilatory response to a vascular stimulus (Stahl 2000, Turenne et al. 2001, von Essen et al. 1980). The magnitude and direction of these changes depends on dose and chronicity of the drug administration.

Caffeine is an adenosine antagonist that blocks both neural and neurovascular adenosine receptors, altering neurobehavioral function, especially attention, and constricting cerebral vessels (Dunwiddie & Masino 2001). By constricting cerebral vessels, caffeine should reduce baseline blood flow, increase deoxyhemoglobin levels, and increase the dynamic range of the BOLD response (Mulderink et al. 2002). Studies generally find an increased BOLD response to a behavioral challenge in the caffeine condition, although significant individual differences in the regression of BOLD response to resting perfusion are observed (Laurienti et al. 2002, Mulderink et al. 2002). The increased BOLD response can be large, ranging from 22% to 37% more than the caffeine-free condition in one study of visually

cued motor performance (Mulderink et al. 2002). Chronic caffeine use tends to upregulate adenosine receptors, a finding that implies the BOLD response among heavy caffeine users might differ from the response of light users (Johansson et al. 1993). In the one study that explored the impact of history of caffeine use on BOLD response, heavy users experienced larger BOLD responses than light users when all participants were administered caffeine (Laurienti et al. 2002). Caffeine not only increases the magnitude of the BOLD response, but also changes the shape of the hemodynamic response, reducing the time to peak activation and reducing the duration of the early phase of the return to baseline (Liu et al. 2004).

Several surveys have found a high prevalence of caffeine use among schizophrenia patients (Gurpegui et al. 2004). Moreover, an upregulation of adenosine 2A receptors has been implicated in the pathophysiology of schizophrenia (Deckert et al. 2003). Caffeine use is likely to be a significant within-group and between-group variable that should be controlled in fMRI studies of schizophrenia patients. However, the choice of appropriate controls is a complex issue. The majority of schizophrenia patients use caffeine. Discarding caffeine users would reduce the generalizability of the resulting findings. Moreover, because upregulation of adenosine 2A receptors might be involved in the pathophysiology of schizophrenia (Deckert et al. 2003), excluding users of caffeine, an adenosine antagonist, from the sample might bias the study toward less severely involved patients. Asking caffeine users to abstain from their normal dietary intact might influence their performance on behavioral challenge tasks. Additionally, the impact of abstinence on cerebrovascular response among caffeine users is unknown.

The prevalence rate of cigarette smoking among schizophrenia patients is two to four times the rate of smoking in the general population (Kumari & Postma 2005), making any effects of nicotine on baseline blood flow or on vasoreactivity a concern to researchers using BOLD contrast to monitor neural function in schizophrenia. Nicotinic cholinergic receptors appear to play some role in maintaining cerebrovascular tone, as the injection of nicotine in animals increases cerebral blood flow, presumably by dilating vessels (Uchida et al. 1997). Moreover, in animal studies the infusion of nicotine blunts the additional vasodilation of cerebral arterioles by acetylcholine, presumably due to ceiling effects (Fang et al. 2003). This restriction of the vasoreactivity range following nicotine administration should diminish the BOLD response to a fixed neural stimulus compared with a nicotine-free condition (Davis et al. 1998).

Human studies of the impact of nicotine on cerebral blood flow reveal a complex picture, in part because the administration of nicotine has neural as well as vascular effects. In one human study, the extent of flow increase following nicotine administration among tobacco smokers correlated with arterial plasma levels of nicotine in some brain regions (Domino et al. 2004), providing strong evidence that nicotine influences resting cerebral blood flow among smokers. Several laboratories have studied the impact of nicotine on BOLD response to a behavioral challenge. BOLD findings from behavioral challenge studies in which nicotine is administered to abstinent smokers have produced a complex array of findings.

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Two studies found improved performance and increased BOLD response (Kumari et al. 2003, Lawrence et al. 2002). One study found no effect of nicotine on BOLD response (Jacobsen et al. 2002). Another found speeded performance but reduced parietal BOLD response during reorientation of visual attention following nicotine administration (Thiel et al. 2005). The designs of the above studies did not permit the separation of the vascular effects of nicotine on BOLD signal from its neural effects. To distinguish vascular from neural effects, future nicotine studies should combine vascular challenge manipulations with behavioral challenge.

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DESIGNING A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY INVOLVING SCHIZOPHRENIA PATIENTS

Functional MRI studies involving patients with schizophrenia hold great promise for increasing our understanding of the neurophysiology of the disorder, which in turn may lead to better strategies for treatment or prevention. There are many challenges for the scientist wishing to use fMRI as a tool in this population, however. Some of these challenges are reviewed below.

Selecting Participants

All studies of schizophrenia must contend with the thorny issue of how to select an appropriate sample. Functional MRI studies are no exception, and may even be more sensitive to heterogeneity among patients than are other types of investigations. It has been suggested that case-control designs that compare groups based on the presence or absence of a clinical diagnosis of schizophrenia are likely to be misleading or inaccurate, given the enormous variation between individuals with a schizophrenia diagnosis (Bentall & Pilgrim 1993). An alternative design is to group individuals based on absence or presence of symptoms rather than diagnosis. This approach cuts across diagnostic categories but also presents challenges because symptoms are likely to vary greatly over time, which reduces their reliability as a grouping variable (Honey et al. 2002). Other strategies have been to use a dimensional approach based on symptoms (e.g., Type I/Type II; Crow 1985) or to categorize individuals based on presumed genetic loading for schizophrenia (e.g., family history positive or negative). These designs have not been employed as often in fMRI studies, but they merit further use.

The basic case-control design has been by far the most prevalent in fMRI studies. Although researchers are generally careful to present detailed information about the nature of the sample collected, this is not always the case, and even when the information is provided, wide variation among studies in sample characteristics makes it difficult to draw global conclusions. Unfortunately, few investigators have tackled the issue head on by investigating within a single study the patient characteristics, such as age of onset or education, that might correlate with fMRI measures. Although some investigators have matched cases and controls on

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demographic variables, case-control matching may not be adequate if the diagnosis interacts with any of these factors (e.g., education level). Some factors that may influence brain response and may systematically differ between schizophrenia patients and controls typically have not been controlled for, such as caffeine and nicotine intake or anxiety levels. Thus, fMRI researchers are faced with significant challenges when selecting the optimal sample. If a case-control design is used, homogeneity of patient-related variables and careful patient-control matching is desirable, but potential limits to generalizability must also be kept in mind. If the focus of the fMRI study is to identify predictors of brain response, then the patient sample should be maximally variable and well distributed over the characteristics of interest. A control group that also has variation in those measures should be included if possible, but such a group does not always exist (e.g., correlations with age of onset for schizophrenia can only be examined in patients).

Medication Effects

Another factor that potentially influences the interpretation of fMRI studies in schizophrenia is the issue of psychotropic medications. With the exception of studies of drug-free samples, which are rare and difficult to recruit, most case-control fMRI studies compare a patient group that is taking psychotropic medication with healthy volunteers that are not. Therefore, any differences that are observed between the two groups may be due, at least in part, to the medications as opposed to the schizophrenia disease process. The problems are potentially less severe in longitudinal studies of patients or when two patient groups are compared, as long as there is adequate matching of medication status between time points or groups. Still, it is unclear whether matching should be based on type or dose of current or lifetime medication usage, or some combination. Even in the case of studies designed specifically to examine the effects of psychopharmacologic interventions, matching of prewashout medication status may be important.

What is the evidence that antipsychotic medications can alter brain response as measured by fMRI? Davis et al. (2005) reviewed longitudinal studies of brain response to psychopharmacological interventions and found four fMRI studies that addressed this issue. Two of them examined brain changes due to antipsychotics and two due to augmenting agents targeting cognitive symptoms. Normalization of brain function in frontal regions during a working memory task (Honey et al. 1999) was seen following treatment by risperidone, an antipsychotic medication that blocks dopamine and serotonin receptors (Stahl 2000), and normalization of cerebellar connectivity was observed during a motor task (Stephan et al. 2001) in response to olanzapine, which like risperidone is an antipsychotic medication that blocks dopamine and serotonin receptors (Stahl 2000). Donepezil, a drug that inhibits the breakdown of the neurotransmitter acetylcholine (Stahl 2000), increased frontal and insular activity (Nahas et al. 2003), and D-cycloserine, an antibiotic medication that may enhance excitatory glutamate neurotransmission, increased superior temporal lobe response (Yurgelun-Todd et al. 2005) during a

verbal fluency task, presumably in the direction of normalization, although controls were not tested. Thus, at least for the agents that have been examined with fMRI, it appears that medication serves to decrease differences between patients and healthy comparison groups.

What data exist about the possible cerebrovascular confounds of antipsychotic medications? As discussed above, animal studies indicate that dopamine might reduce baseline blood flow, whereas haloperidol might alter cerebrovascular responsiveness. Both altered baseline flow and impaired cerebrovascular responsiveness could complicate the interpretation of BOLD response among medicated schizophrenia patients. Unfortunately, little research has been done with schizophrenia patients using a vascular stimulus to elicit cerebral blood flow changes. Mathew & Wilson (1990) reported a diminished, global, cerebral blood flow response to 5% CO_2 inhalation among schizophrenia patients on first generation antipsychotics compared with healthy controls. Notice that globally constricted reactivity will appear as a diminished focal cerebral blood flow response for tasks that induce focal brain activation. Taylor et al. (1999) reported greater perfusion increase in rostral anterior cingulate cortex among schizophrenia patients than in healthy controls following acetazolamide administration. Acetazolamide inhibits the removal of carbon dioxide from the brain, decreases tissue pH, and causes cerebral blood flow to increase (Vorstrup et al. 1984). As in other studies, patients showed a hypoperfusion in the rostral anterior cingulate in the baseline state in the Taylor et al. (1999) study. These studies suggest that differences between patients and controls in baseline blood flow and reactivity can complicate the use of blood flow–related measures, such as BOLD contrast, when inferring the neural status of schizophrenia patients.

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Abnormal Anatomy

Many studies have observed differences in the shape and volume of brain structures between patients with schizophrenia and comparison groups (Shenton et al. 2001). Anatomical abnormalities must therefore be considered in the interpretation of functional brain-imaging results. There are two potential confounding effects of anatomical abnormalities: inaccurate magnitude estimation and mislocalization. If brain response among schizophrenia patients is found to be less in magnitude or extent compared with healthy individuals, it is difficult to know whether this is due to poor functioning of an adequate amount of brain tissue or normal functioning of an inadequate amount of brain tissue. Cortical thinning has even been associated with increased BOLD response in Alzheimer's disease (Johnson et al. 2000). To study the relationship between cortical thinning and fMRI response, investigators have used automated or manual tissue segmentation methods to separate gray matter from white matter and cerebrospinal fluid (Johnson et al. 2000). The impact of global or regional cortical thinning on fMRI response can then be studied using standard regression techniques.

Tissue loss or ventricular enlargement can also lead to spatial displacement of remaining structures relative to the normal brain. In many fMRI studies, each

participant's brain is spatially normalized by warping into a common coordinate system (Buxton 2002). If this warping involves a rigid body transformation, it would not account for intersubject differences in gyral or ventricular shape or size. Thus, even after warping to a common coordinate space, it is possible that an identified voxel that is squarely in the basal ganglia of all controls could be in the lateral ventricle for a proportion of patients. The development of automated, spatial normalization methods that correct for such mislocalization, even in atrophic brains, is an active area of imaging research (Senjem et al. 2005).

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Cognitive Subtraction and Choosing a Control Condition

A large challenge in most fMRI studies is the design of an appropriate control condition. Because the BOLD signal is a relative measure, at least two conditions must always be compared. In designing comparison conditions, many investigators rely on the assumption of "pure insertion," that is, the assumption that adding a cognitive process to a comparison condition to create an experimental condition does nothing to alter the nature of the comparison condition (Friston et al. 1996, Sternberg 1969). In fMRI studies, the pure insertion assumption is doubled. The insertion of the target cognitive process should have an additive effect on brain activity as well as cognitive function. When the dual pure insertion assumption is met, brain response to the comparison condition can be subtracted from that related to the experimental condition and the result will be the unique brain response to the added process (Friston et al. 1996, Sternberg 1969). There are many reasons to believe that "cognitive subtraction" is unlikely to work well for most fMRI studies (Friston et al. 1996), but these designs are still widely used. In studies with patient groups, there are additional concerns that the nature of any failures of cognitive subtraction may differ between groups. For example, component processes may be additive for healthy individuals, but may interact for patients. Unstructured or resting baseline conditions may be particularly susceptible to differences between patients and comparison groups because of the possibility for hallucinatory experiences or delusional thinking associated with schizophrenia. Even more structured baseline conditions may provoke unexpected responses among patients. For example, a schizophrenia patient in remission, upon hearing about a baseline condition that involved repeated presentation of the same stimulus, commented that while he was psychotic he would have attached a great significance to this repeated object (L.T. Eyler, personal communication). Most healthy individuals, in contrast, would be likely to habituate to a repeated stimulus or become more automatic in their processing. Thus, a traditional block design that alternates between an experimental and control condition, although powerful for detecting brain response, may not always be ideal for fMRI studies of schizophrenia.

One way to address these concerns is to build in more than one baseline condition, for example, one that relies on cognitive subtraction and one that is relatively unstructured. A second approach is to parametrically vary the component cognitive process of interest (Friston et al. 1996). A third approach is to use a factorial

design, which allows for explicit testing of the interaction between experimental factors and, presumably, tests for the additivity of latent neurocognitive processes (Friston et al. 1996, Sternberg 1969).

The Performance-Activation Dilemma

Early studies of brain activation using fMRI found that the magnitude of the BOLD response can be related to performance level (Bandettini et al. 1995, Boynton et al. 1996). Bandettini and colleagues (1995) provided a clear demonstration of this effect when they instructed subjects to extend and flex the fingers of the right hand at various rates to match a metronome and found the rate of flexion to be monotonically related to the magnitude of the BOLD response. Because the magnitude of the BOLD response can depend on performance level, interpretation of group differences of the BOLD response is complicated when there is a large performance difference between two groups on the same task (Weinberger & Berman 1996). For example, lower magnitude of brain response among the more poorly performing group might reflect an underlying abnormality of neuronal functioning that in turn results in poor performance, but both might be due to a third factor, such as underarousal. If schizophrenia patients are not engaged in the challenge task, the disengagement might simply result in a failure to initiate use of an otherwise intact neural system that subserves the cognitive process of interest. Even when greater brain response is observed among patients than among comparison participants, differential performance can cloud the interpretation. Although it is tempting to interpret areas of hyperactivity as a reflection of inefficient processing leading to poor performance, it is also possible that it is an artifact of a longer duty cycle ("time on task") among patients relative to baseline and/or reflective of anxiety or other emotional response to repeated failure.

Investigators studying schizophrenia have broadly interpreted performance BOLD data from studies such as that of Bandettini and colleagues (1995) in two different ways. One interpretation is that BOLD data from patients cannot be unambiguously interpreted unless the patient and control groups are matched on performance (Callicott et al. 1998). The other interpretation is that when groups are mismatched on performance, nonspecific factors that might cause performance decrements, such as poor motivation, lack of cooperativeness or inattentiveness, must be ruled out (Crespo-Facorro et al. 2001). These differing interpretations have engendered different ways to address the issue of differential performance across groups.

One way is to attempt to match performance between groups. This can be done post hoc, by selecting subsamples with equivalent performance, or using statistical covariation (Callicott et al. 1998, Thermenos et al. 2005). However, selecting subsamples of high-performing patients and low-performing healthy individuals can result in biased samples that are not generalizable to either patients or controls (Chapman & Chapman 1973). In particular, patients with the most severe neurobehavioral disorders will be systematically excluded from study. Additionally,

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as Meehl (1970) has shown with behavioral data, matching on one variable can systematically mismatch groups on another variable, covertly biasing the samples. Given the small sample sizes of most fMRI studies involving patients, tests on subgroups of subjects are likely to be greatly underpowered. Finally, the effectiveness of matching on performance is attenuated by statistical regression (Chapman & Chapman 1973). Unless both the behavioral and BOLD measures are highly reliable, the mean BOLD response of the matched schizophrenia patients is likely to regress toward the mean of the schizophrenia population from which the patients were selected, while the BOLD response of controls is likely to regress toward the control mean to produce a mismatch on the BOLD response.

Event-related fMRI designs offer a retrospective approach to match on the type of response. One example of this strategy would involve contrasting BOLD response during correctly performed trials with BOLD response during incorrectly performed trials within each group. Studying schizophrenia patients both when they are performing successfully and when failing can help determine whether the brain responses of schizophrenia patients are qualitatively different from nonpsychotic individuals. Contrasting brain response during successful versus failed performance might help identify the nature and limitations of compensatory brain systems among schizophrenia patients. Assuming that there are adequate trials of each type in both groups, the fact that there are more correct trials in one group than in the other is of less importance then when analyses are based on intermixed trials.

Performance matching could be done prospectively. This is one of the most practical solutions to interpretive challenges caused by the disparate performance of patients and controls. If samples are selected a priori to have matched performance, adequate power can be maintained, but the threats of sampling bias and regression toward the mean would need to be managed. Sampling bias can be minimized by sampling from a subpopulation of healthy participants whose performance on the task of interest is comparable to that of schizophrenia patients (population matching rather than subgroup matching). Sampling healthy participants from a subpopulation expected to perform at levels similar to patients also reduces the likelihood of regression toward the mean (Chapman & Chapman 1973). Notice that prospective matching maintains the representativeness of the schizophrenia sample while restricting the representativeness of healthy control data. This solution requires that appropriate behavioral data be available on various populations of controls, yet control data on the task of interest is often not available prior to a study. When task-specific control data are unavailable, some investigators have used a broad cognitive variable, such as intelligence test scores, to match populations from which patients and healthy controls are sampled. The broad-variable sampling strategy has been used extensively in cognitive deficit studies involving schizophrenia patients, and readers are encouraged to review standard sources about the strengths and weakness of this strategy (Chapman & Chapman 1973). Perhaps the main limitation of matching strategies occurs when studying severe cognitive deficits in schizophrenia. The deficits might be so severe

that the individuals in the general population with similar levels of performance are unlikely to be available unless they have brain disease.

The general aim of functional neuroimaging studies of schizophrenia patients is to identify the brain circuits that underlie disordered behavioral function. The strong form of the matching strategy assumes that the disordered brain function underlying abnormal cognition or behavior in schizophrenia can only be identified during conditions where the performance of patients does not differ from controls. However, matching performance between patients and controls on a behavior that is abnormal at the population level means that some aspect of the design (patients studied, items studied, controls studied) must not be representative of the conditions determining the original abnormality. This particular expression of the performance-activation dilemma is a tension between internal and external validity of study results.

Some investigators have used analysis of covariance to correct BOLD response for group differences in performance (Ramsey et al. 2002). However, conventional linear analysis of covariance should not be used whenever groups differ on the slope of the regression of BOLD response onto performance (Winer et al. 1991). Group differences in the direction of the relationship between performance and BOLD response have been reported in some fMRI studies comparing schizophrenia patients with healthy volunteers (Callicott et al. 1998, Eyler Zorrilla et al. 2002a). Moreover, the regression of performance onto BOLD response is not always linear, making conventional linear model adjustments to BOLD response inappropriate (Gould et al. 2003). A serious limitation to covariance adjustments of BOLD data for performance differences involves the interpretation of results. In this application of ANCOVA, the grouping variable (diagnostic group) is related to both the dependent measure (BOLD response) and to the covariate (performance). Many authors warn against using ANCOVA to "correct" the dependent variable for the effects of the covariate when the covariate is correlated with the grouping variable (e.g., Evans & Anastasio 1968, Miller & Chapman 2001). Among the concerns articulated by these authors, a core criticism is that once the covariate is removed from the dependent measure, the residual might no longer be a valid measure of the construct the original dependent variable was intended to measure (Miller & Chapman 2001). If the covariate is a meaningful component of the dependent variable, removing variance related to the covariate is likely to undermine the construct validity of the dependent variable (Evans & Anastasio 1968). When studying the neurocognitive deficits of schizophrenia, is it meaningful to study the brain substrate of abnormal performance after removing the variation in brain function related to performance? That this strategy is not always meaningful is another manifestation of the underlying performance-activation dilemma.

An alternative approach to understanding how brain function and performance are related is to manipulate important study variables. These designs can help measure directly the relationship of performance to brain response. For example, parametric designs in which difficulty is manipulated within individuals during scanning can be used to investigate some of the potential nonlinearities in brain

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response related to performance increases or decreases. Parametric designs produce variations in the level of performance that can permit investigators to compare schizophrenia patients and controls when performance is matched and when it is not (Jansma et al. 2004).

One escape from the performance-activation dilemma is evident when considering the second of the two interpretations of Bandettini and colleagues' (1995) motor flexion study. In this view, the relevant lesson from this study is that the relationship between performance and brain activation was determined by a third variable, the intended tapping rate governed by the task directions. For schizophrenia researchers, the concern is that group differences of intention or other organismic variables not under control of the experimenter might jointly moderate levels of performance and of brain activity. In such circumstances, the brain-behavior differences between patients and healthy controls might be due to processes other than those that are the focus of the study. Candidate confounding variables include motivational differences between groups, differential attending to environmental sounds, distracting hallucinations in the schizophrenia groups, and differences in arousal related to group differences in prescribed drugs, nicotine, or caffeine (Davison 1974). The role of these potentially confounding organismic variables must be considered when interpreting group differences in BOLD response. As with issues related to matching, interpretive problems caused by group differences in motivational and other organismic variables have been discussed in the schizophrenia literature on cognitive deficit (Chapman & Chapman 1973).

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PATTERNS OF FINDINGS IN FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDIES OF SCHIZOPHRENIA

Diminished Blood Oxygen Level Dependent Response

Early functional brain imaging studies of schizophrenia patients searched for a functional brain lesion (Ingvar & Franzen 1974). The functional lesion model predicts reduced neural activity, blood flow, and metabolism during resting conditions and diminished brain response to behavioral challenges during activation studies. Reviews of the literature on functional brain imaging among schizophrenia patients have found greater evidence of functional brain abnormalities during cognitive challenge tasks than during resting conditions (Berman & Weinberger 1990). Diminished BOLD response to behavioral challenges in groups of schizophrenia patients has been reported in many brain regions, including the right lateral fusiform gyrus during face processing, the superior temporal gyrus during mismatch negativity, basal ganglia and superior parietal cortex during spatial working memory, the medial temporal lobe during novel picture learning, and the dorsolateral prefrontal cortex during a verbal N-back working memory task (Callicott et al. 1998, Eyler Zorrilla et al. 2002b, Kindermann et al. 2004, Quintana et al. 2003a, Wible et al. 2001). Moreover, when performing language tasks such as verbal

fluency and semantic processing, schizophrenia patients experience diminished BOLD response in several prefrontal regions (e.g., left dorsal prefrontal cortex, left rostral supplementary motor area or pre-SMA, left inferior frontal cortex) normally active in healthy controls (Curtis et al. 1999, Kubicki et al. 2003, Yurgelun-Todd et al. 1996). Several studies have found altered BOLD response among schizophrenia patients but not among patients with major depression, supporting the potential specificity of disordered neurobehavioral dysfunction to schizophrenia, at least for some types of cognitive function (Barch et al. 2003, Holmes et al. 2005).

Several studies finding diminished BOLD response in schizophrenia attended to the methodological issues described in the previous section. Several used a positive internal control to establish the regional specificity of the aberrant response (Callicott et al. 1998, Eyler Zorrilla et al. 2002b, Kindermann et al. 2004). Studies testing movement correction parameters have found equivalent degrees of stimulus correlated or random movement between groups of schizophrenia patients and healthy controls (Eyler Zorrilla et al. 2002b, Kindermann et al. 2004). One study carefully matched subgroups of patients and controls for variation in BOLD response across study epochs and still found diminished BOLD response on an N-back working memory task (Callicott et al. 1998). Some studies found diminished BOLD response even when patient and control groups did not differ on task performance (Eyler Zorrilla et al. 2002b, Kindermann et al. 2004). A working memory study found no relationship between performance and failure to activate the dorsolateral prefrontal cortex among schizophrenia patients studied on an N-back task (Callicott et al. 1998). None of the studies reviewed above corrected the BOLD response for potential group differences in hemodynamic responsiveness that might be related to medication. However, impaired BOLD response in the prefrontal cortex has been observed in medication-naïve patients with schizophrenia on the A-X version of the Continuous Paired Associates Test, on the Wisconsin Card Sorting Test, and when viewing a moving checkerboard (Barch et al. 2001, Braus et al. 2002, Riehemann et al. 2001).

The studies reviewed above found diminished regional BOLD response among schizophrenia patients in many brain regions, as predicted by the functional lesion model. These results are compatible with theories of impaired multifocal dysfunction in schizophrenia. Studies reporting normal brain response in control brain regions contradict theories of global brain dysfunction in schizophrenia. Some results are compatible with a single lesion in an executive brain region that has downstream effects on multiple brain areas, as in Goldman-Rakic's model of schizophrenia (Goldman-Rakic 1999). However, several investigators have found impaired brain function in nonfrontal regions even though schizophrenia patients and controls did not differ in dorsal or ventral prefrontal activation (Kindermann et al. 2004, Quintana et al. 2003a, Wible et al. 2001). Such results would challenge the view that deficient neural function in the dorsolateral prefrontal cortex is a necessary determinant of neurobehavioral dysfunction in schizophrenia.

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Enhanced Blood Oxygen Level Dependent Response

Given evidence supporting the functional lesion hypothesis, the observation that schizophrenia patients might experience increased BOLD response to a behavioral challenge has been both surprising and intriguing. Enhanced BOLD response is not an isolated finding. It has been reported in studies of verbal working memory, smooth pursuit eye movements, face processing, and depth of semantic processing (Hong et al. 2005, Kubicki et al. 2003, Manoach et al. 1999, Quintana et al. 2003a, Yoo et al. 2005). Areas of increased BOLD response to behavioral challenges include the dorsolateral prefrontal gyrus, the superior temporal gyrus, the occipitotemporal gyrus, and the left inferior parietal lobe (Hong et al. 2005, Kubicki et al. 2003, Manoach et al. 1999, Quintana et al. 2003a, Yoo et al. 2005). The finding of increased BOLD response among schizophrenia patients performing the Sternberg Memory Scanning task has been replicated in a second sample (Manoach et al. 2000). The finding of increased signal activation to behavioral challenge tasks has been one of the more important contributions of functional MRI to the functional brain imaging literature involving schizophrenia patients.

Why do some fMRI studies show reduced amplitudes of BOLD response, whereas others show enhanced BOLD response? Most investigators interpret the BOLD response in schizophrenia, whether enhanced or diminished, as a reflection of underlying differences in neural response. However, as discussed above, antipsychotic medications, caffeine, and nicotine may influence the magnitude or shape of the hemodynamic response that mediates the neural information in the BOLD signal. Thus, drug-mediated variation in hemodynamic response could explain some of the variable pattern of diminished and enhanced BOLD response seen in this literature. Studies of medication-naïve patients have reported mixed results regarding the impact of medications on the magnitude of BOLD response. A study using logical reasoning as a target challenge task found significantly elevated BOLD response in the right hemisphere (including dorsolateral prefrontal cortex) among medication-naïve schizophrenia patients, after statistically controlling for performance level (Ramsey et al. 2002). However, a study of motor function in schizophrenia reported significant reductions of BOLD response in the supplementary motor area of medicated patients compared with medication-naïve patients and healthy volunteers (Braus et al. 1999). The authors concluded that both first- and second-generation antipsychotic medications themselves influence fMRI activation, although the pattern of effect differs by medication class (Braus et al. 1999). We were unable to locate any published studies investigating the effect of caffeine on BOLD response obtained from schizophrenia patients. We did locate two studies of the effects of nicotine. Both demonstrated enhanced BOLD response in the nicotine condition compared with placebo (Jacobsen et al. 2004, Tregellas et al. 2005). None of the studies reviewed above investigated the impact of a hemodynamic challenge stimulus, such as CO_2, breath hold, or acetazolamide, on the dynamic range of the hemodynamic response. In all studies reviewed, the hemodynamic and neural effects of the drugs studied were confounded.

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In a review of the disparate BOLD findings involving working memory function in schizophrenia, Manoach (2003) discussed the role of statistical, measurement, subject, and task factors that might account for the variable findings. Some of these factors, such as poor motivation, inattention, and task reliability are discussed above. We focus here on the impact of intersubject averaging and on the impact of performance on BOLD response. Several studies have found greater variation in the spatial location of BOLD activation among schizophrenia patients than among healthy volunteers (Manoach 2003). In one study reviewed by Manoach (2003), clusters of activated voxels of individual healthy volunteers were more than three times more likely to overlap with their group-averaged maps than was the case for schizophrenia patients. Greater spatial variation is likely to lead to diminished BOLD response in mean image maps because near-zero values in a given voxel of one patient might be averaged in with nonzero values from other patients. When the number of brain voxels activated among schizophrenia patients in a particular study is the same as controls, or when the magnitude of the BOLD response is as large or larger than that of controls, inconsistent localization of activation between patients and controls can lead to disparate conclusions when comparing the results from individual analyses with the results of group findings. Manoach (2003) hypothesizes that developmental abnormalities may lead to greater spatial heterogeneity in BOLD response among individuals with schizophrenia.

When considering the role of task demands in accounting for disparate working memory findings, Manoach (2003) postulates an inverted U relationship between BOLD response and working memory load. The relationship between load and BOLD response is assumed to be identical among patients and controls except that the curvilinear regression is shifted among patients, so that lower levels of load in patients predicts the same level of BOLD response as some higher load level among controls. The model predicts that for a high level of load, schizophrenia patients would show diminished BOLD response, whereas for intermediate load levels, patients would show elevated BOLD responses compared with controls. Moreover, a similar magnitude of BOLD response would require comparisons across different load levels when comparing patients and controls. Manoach's own data confirmed two of the three predictions. At moderately high levels of load on the Sternberg memory scanning paradigm (set size $= 5$), schizophrenia patients showed a larger BOLD response than healthy volunteers in the dorsolateral prefrontal cortex, whereas the two groups showed similar BOLD levels when controls studied at a set size load of 5 were compared with patients studied at a load of 2. A study parametrically varying working memory load on an N-back task confirmed the prediction that as working memory load increases, a load will be reached beyond which the BOLD response of patients declines more rapidly than that of controls with further increases of load (Jansma et al. 2004). In particular, increasing working memory load from 2-back to 3-back caused a sharper decline of BOLD response among schizophrenia patients than controls in the dorsolateral prefrontal cortex. The Jansma et al. (2004) study also found similar levels of

BOLD response when patients and controls were compared at different loads, where performance for the two groups was similar.

Areas of increased BOLD response in schizophrenia studies can be divided into those that occurred in a study's regions of interest and those that were unanticipated. Different interpretations of increased BOLD response to behavioral challenges have been offered depending on whether or not the increased activation occurred in a region of interest (ROI). The pattern of mildly impaired or normal performance in the presence of increased BOLD response in an ROI has been taken by some investigators to be the signature of inefficient but viable neural functioning (Callicott et al. 2000, Manoach 2003). Inefficient neural function is postulated to occur when greater metabolic activity than normal is required in an ROI to process information at normal or near-normal levels (Rypma & D'Esposito 1999). Between-subject differences of inefficient processing has been used to identify responders in recent studies using the second-generation antipsychotic olanzapine to treat working memory impairment in schizophrenia (Bertolino et al. 2004).

When enhanced BOLD response occurs in schizophrenia patients outside regions activated among healthy volunteers, the enhanced response is often interpreted as a form of compensation. For example, in a study of smooth pursuit eye movements, patients showed reduced BOLD response in frontal and supplementary eye fields and other brain areas normally activated by predictive pursuit (Hong et al. 2005). However, patients showed an increased BOLD response in the occipitotemporal region (Hong et al. 2005). The authors concluded that because schizophrenia patients were impaired in brain regions needed to move the eyes to extraretinal targets, the patients relied on increased processing of retinal information to perform pursuit tasks. In a well-designed study, Quintana and colleagues (2003a) showed that whether schizophrenia patients showed diminished or enhanced BOLD response in the prefrontal cortex during a working memory task depended on whether the task demands elicited increased BOLD response in the posterior parietal cortex. These results emphasize the importance of interpreting the findings of BOLD studies in schizophrenia patients from the perspective of a dynamic, adaptive functional network.

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FUTURE DEVELOPMENTS

Functional MRI studies of the brain substrate underlying the cognitive, motoric, and perceptual abnormalities observed among individuals with schizophrenia suggest a more dynamic account of brain dysfunction than predicted from traditional lesion models. It is likely that dynamic accounts of brain dysfunction will guide much of the future imaging research into the brain basis of schizophrenia. However, future studies testing dynamic models of schizophrenia will need to be more attentive to potential artifacts involving group differences in hemodynamic reactivity, movement, and drug effects than has been the case in previous studies. Data indicating that varying patterns of diminished or enhanced neural activation are

observable in multiple brain regions will also need to be understood within a framework of systems neuroscience. A systems approach will require the greater use of multivariate models to evaluate how functional connections among brain regions covary with the diagnosis of schizophrenia and with symptoms and risk factors. Adopting a systems framework when studying brain dysfunction in schizophrenia will also require the increased use of multiple imaging modalities to acquire data needed to integrate information across levels of neural activity (Figure 1).

Ongoing functional imaging studies—ranging from studies of genetic risk for schizophrenia to studies of brain changes in the peri-symptom onset period to studies of late-life psychosis—are beginning to provide a comprehensive description of the dynamic changes in brain function across the life span of individuals with schizophrenia. The integration of genetic and imaging methods is an especially exciting development in the field of imaging (Hariri & Weinberger 2003). However, future functional imaging studies of genetic risk of schizophrenia will need to separate findings related to the risk of the disorder from findings related to the disease itself. A structural imaging study of monozygotic and dizygotic twins discordant for schizophrenia shows the importance of this distinction (Cannon et al. 2002). When comparing affected and unaffected twins, the authors found cortical density differences primarily in the dorsolateral prefrontal cortex, the superior temporal gyrus, and the superior parietal lobe. These findings were related to the disease itself. Mapping cortical density by the genetic distance to a patient revealed genetic risk effects involving only the orbital and dorsolateral prefrontal cortex. The cortical effects of the genetic risk of schizophrenia and of disease-related changes were partially dissociable, suggesting that somewhat different neurobiological substrates were operating in these states. The dynamic view of brain dysfunction in schizophrenia is a hopeful perspective that might lead to new treatments to mitigate the impact of risk factors and to new treatments to support compensatory processes already occurring in the nervous system of schizophrenia patients.

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GLOSSARY

Axial/oblique: Orientations of slice acquisition for MRI scans. Axial (or transverse) slices cut a plane perpendicular to the main axis of the body and oblique slices cut a plane at some angle of this plane.

BOLD: Blood oxygen level dependent signal is measured in many fMRI experiments and reflects the ratio of oxyhemoglobin to deoxyhemoglobin in the local vessels. The signal is greater in regions where more hemoglobin is in the oxygenated state, as is the case when oxygen delivery has outpaced oxygen utilization in an active area.

Contrast-to-noise ratio: A ratio of the strength of the contrast in signal between two measurement conditions (e.g., experimental versus control stimulus presentation) to the noise of the signal (as defined by variability in the signal across either time or space).

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Deconvolution: A process used to recover the shape of an impulse response function given the presented stimuli. In the case of fMRI data, the impulse response function of interest is the hemodynamic response function and the presented stimulus is often a trial of a cognitive paradigm.

Deoxyhemoglobin: The hemoglobin protein transports oxygen in the blood. When the protein is not carrying an oxygen, it is referred to as deoxyhemoglobin, and the shape of the protein is such that the iron (or heme) group within the structure is exposed, thus giving it paramagnetic properties that decrease the T_2^* signal.

Gradient coil: A hardware element of the MR scanner that consists of coiled wire and serves to create local magnetic field gradients within the scanner machine. The field gradients allow for signal localization by creating a gradient of different nuclear precession rates where the frequency and phase of the local spins code location.

Gradient echo pulse sequences: A type of image acquisition protocol used to create the images that typically form the basis of fMRI. Gradient echo protocols combine a single radio frequency pulse with the reversal of the polarity of a localization gradient to regenerate a degraded magnetic resonance signal. The regenerated signal is called an echo, and the extent of regeneration is limited by fluctuating magnetic fields, such as those associated with temporal changes in the deoxyhemoglobin content of a region.

Radiofrequency transmitter: A hardware element of the MR scanner that transmits energy in the radiofrequency part of the spectrum into the participant in order to alter the spins of biological molecules.

Receiver coil: A hardware element of the MR scanner that is often placed near the body part of interest (e.g., the head) and consists of coiled wire that allows sensitive detection of signals resulting from magnetic alterations induced by spin relaxation.

Signal-to-noise ratio: A ratio of the strength of the fMRI signal (often measured in raw MR scanner units) to the noise of the signal (as defined by variability in the signal across either time or space).

Spin echo pulse sequences: A type of image acquisition protocol that uses two radio frequency pulses to generate image contrast. The first pulse sets up the initial magnetic resonance signal. The second pulse regenerates a signal echo after a period of decay. Like gradient echo protocols, spin echo protocols are sensitive to fluctuating variations in local magnetic fields, although usually less so than gradient echo protocols.

Voxel: A "volume element" in a three-dimensional image, with the shape of a rectangular prism. Voxel size is expressed either as a cubic measurement (e.g., 4 mm^3) or by the length of all three sides (e.g., 3.5mm $\times$ 3.5mm $\times$ 7mm) with in-plane resolution generally listed first and the slice thickness generally listed last.

Warped image: An image that has been converted from one coordinate system to another, often involving the process of interpolation.

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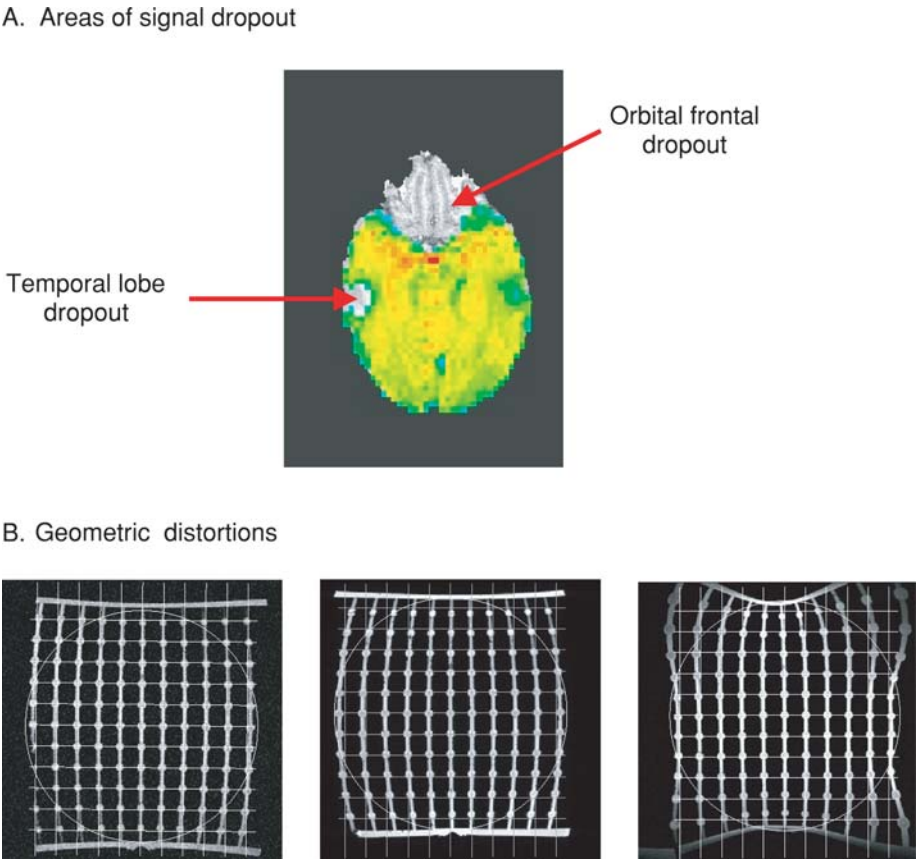

Figure 2 (*A*) Two areas of signal dropout are identified in an axial echoplanar image that cuts through the temporal and orbital frontal lobes. Threshold was set to exclude very low signal values to highlight the areas of diminished signal. (*B*) Magnetic resonance images of a water-filled geometrical phantom grid taken in three different magnets. Note the variations in the distortion patterns caused by differential nonlinearities in the gradient fields between magnets. (With permission from A. Dale, L. Wald, F. Schmitt, unpublished work.)

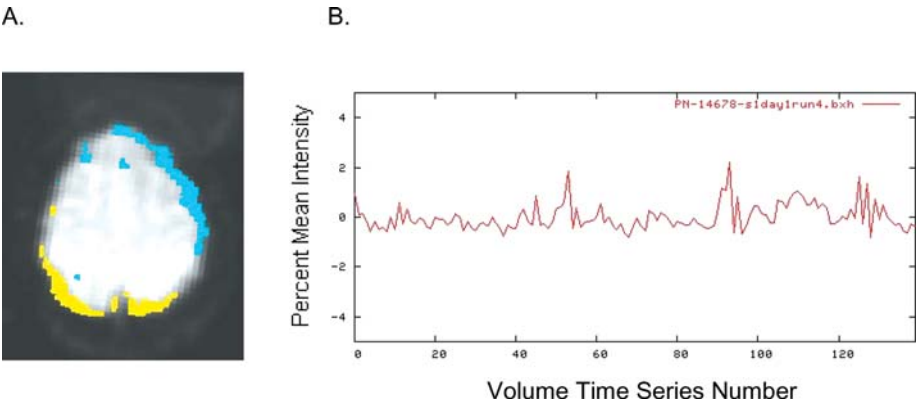

Figure 3 (*A*) Echoplanar image overlaid with colors indicating change in MR signal intensity with task demands (*yellow*, positive correlation; *blue*, negative correlation) in a pattern highly suggestive of movement artifact ("activation" at the interface of brain and air and opposite in direction in spatially opposite locations). (*B*) Percent signal intensity within a voxel, showing several spikes of movement (near time points 55, 95, and 130), which if correlated with changes in task conditions, could be falsely interpreted as activation.

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