FUNCTIONAL NEUROIMAGING IN SCHIZOPHRENIA

KAREN FAITH BERMAN

THEORETICAL PERSPECTIVE

The search for a biological basis of schizophrenia includes a long chapter in which alterations in the characteristics and localization of neural activity are the focus. It is in this arena that functional neuroimaging has had the broadest application and greatest impact in psychiatry. This now extensive body of work has left no doubt that schizophrenia is associated with measurable, objective signs of altered brain function, and clinical and pathophysiologic correlations have begun to emerge. Certain cerebral concomitants of this illness have been consistently demonstrated, although no single pathognomonic neurofunctional abnormality has been delineated yet. Increasingly, it appears that dysfunction of a system of functionally and/or structurally interconnected cortical and limbic brain regions is present to lesser or greater degrees, producing more or less psychopathology in individual patients, and that certain brain regions, such as frontal cortex, may play a special role in this larger picture. Abnormal neurotransmission within these neural circuits appears to be related to core features of schizophrenia, particularly cognitive impairment. Although it is likely that at least some of the functional abnormalities are generative of these features and not simply a response to them, clarification of this "chicken versus egg" issue must be a crucial component of any research program in this area, and the elucidation of the underlying mechanisms is the most important quest of this research at present. Current functional neuroimaging has much to offer in guiding this quest, particularly when combined with new information now available from other fields such as genetics and cognitive science. In this light, the following sections review existing findings, delineate their relationship to other neurobiological and clinical properties of the illness, discuss conceptual issues and controversies, examine methodologic considerations (including technical constraints), summarize new techniques and the new approaches to research design that they allow, and finally describe the most important areas for future research.

HISTORIC PERSPECTIVE

Functional neuroimaging studies utilize the fact that neuronal activation results in regionally increased blood flow and metabolism. This can be measured either by radiotracer methods (e.g., [positron emission tomography] PET regional cerebral blood flow [rCBF] or cerebral glucose metabolic rate) or by a regional effect on the ratio of deoxyhemoglobin to oxyhemoglobin imaged by magnetic resonance techniques (the blood oxygenation level dependent [BOLD] effect). This work began in earnest some 50 years ago with the pioneering studies of Seymour Kety and colleagues who developed the first reproducible, quantitative technique for measuring cerebral blood flow (CBF) as an indicator of neuronal activity, in humans by using nitrous oxide, an inert but soluble gas. When this method was applied to schizophrenia (1), these investigators found no alteration in the overall average CBF level in patients, a result that has largely been confirmed by more recent studies; however, this finding did not rule out the existence of neurophysiologically meaningful changes in specific brain structures.

The next advance came in the 1970s with the establishment of rigorous methods that could differentiate the functional level of specific cortical regions, albeit with only 2-cm anatomic accuracy at best (2). This method, administration of tracer amounts of radioactive xenon, was rapidly applied to the study of schizophrenia. The resulting findings of functional abnormality in the frontal lobe spurred a shift in focus throughout many research domains in the field that remains a prevailing force today. In the 1980s, the advent of tomographic methods, such as single photon emission computed tomography (SPECT) and PET, which both use radioactive compounds as tracers, brought improved interregional spatial resolution on the order of 5 to 6 mm and allowed measurement of subcortical regional function.

In the last decade, functional magnetic resonance imaging (fMRI) has emerged as the premier technique for neuropsychiatric functional neuroimaging. By taking advantage of the differential paramagnetic properties of oxyhemoglobin versus deoxyhemoglobin and the altered ratio between them that occurs when blood volume and blood flow change in response to neural activation, BOLD fMRI uses intrinsic properties of the blood itself rather than an extrinsic contrast or tracer agent, to generate maps of brain function. It is, thus, entirely noninvasive, and measurements can be repeated over time, conferring significant advantage in experiments designed to address important clinical questions in schizophrenia, such as response to medication, correlation with clinical course, differentiation of state versus trait phenomena, determination of the dynamic range of neurophysiological response, and learning. This new methodologic advance brought further improvements in spatial resolution as well as enhanced temporal resolution, which, although still slow (several seconds) compared to neuronal signaling (on the order of 200 ms), improved to the degree that eventrelated neural activity could be recorded with anatomic precision heretofore unavailable with electrophysiologic methods.

TECHNICAL PERSPECTIVE

As can be seen in the preceding brief history, over the years the sophistication of the questions that could be asked and the hypotheses about schizophrenia that could be tested have paralleled the development of new brain imaging technologies and analytic methods. This parallel development is evident in the evolution of the science from the search for regionally specific pathologic function to that in neural systems, and from measures sensitive only to static pathophysiology to explorations of the dynamic interplay among regions in those neural systems. Therefore, a brief discussion follows of the newest methodologic approaches and latest vistas for research in schizophrenia that they offer.

New Vistas in Data Acquisition

Event-related fMRI is a relatively recent class of experimental design within functional neuroimaging that exploits the superior temporal resolution of fMRI. Unlike previous fMRI and PET approaches that blocked together relatively long (e.g., 20 to 60 sec) periods of similar behavioral trials or conditions and examined average neural response over that time period, event-related fMRI documents the neural response during each individual trial or short behavioral period. This approach has much in common with traditional evoked-potential electrophysiology and offers advantages in experimental design. Because different trial types can be randomly intermixed and then separated for analysis, order effects and habituation can not only be controlled for, but also explicitly investigated. A particular advantage for research in schizophrenia is that neural activity during correct and incorrect trials can be measured separately and compared, allowing more incisive study of the mechanism of cognitive failure and better experimental control of potential confounds based in performance discrepancies that often occur between patient and control groups. Eventrelated fMRI has very recently come into wide use in neuroimaging of cognitive systems in healthy subjects, but as of this writing has had only limited application to the study of schizophrenia.

Multimodal neuroimaging, which seeks to determine the relationship of the neurofunctional abnormalities in patients to other neurobiological features, will have an increasingly important role in delineating the mechanism of schizophrenia. In this approach, blood flow and other measures such as MR spectroscopy, neuroreceptor measurements, and electrophysiology (with MEG or EEG) are determined in the same patients. One example of the richness of the data that can be gleaned is the use of PET or fMRI to measure blood flow in conjunction with EEG or MEG. PET and fMRI allow localization of the brain regions that work together during cognition (spatial resolution 3 to 6 mm), but provide relatively little temporal information (temporal resolution in seconds). On the other hand, EEG and MEG have relatively poorer spatial resolution, but provide fine time resolution (i.e., milliseconds). Combining these methods, together with the application of the advanced computational cross-registration and source localization techniques that now exist, provides exponentially more information than any of these techniques alone. For example, this allows the determination of the sequence in which various finely localized regions are activated during cognition and the testing of the hypothesis that this sequence of events is altered in schizophrenia. Although this specific multimodal approach has not been applied in schizophrenia, other examples are described in the following.

New Vistas in Data Analysis

The analytic approaches for the two data collection modalities discussed, event-related fMRI and fusion of spatial and temporal neurofunctional data (i.e., PET or fMRI with EEG or MEG), are in their infancy and beyond the scope of this chapter. Another recent set of analytic methods addresses the growing appreciation that the transduction between neural and mental events is not anatomically segregated (i.e., one brain region per one mental or cognitive activity), but rather that even the simplest of cognitive activities requires coordinated actions across widely distributed components of neural systems (interregional integration of neural function). Questions about functional integration and coordinated interregional activity are likely to have particular relevance for schizophrenia, as discussed in later sections. Although the segregational view can be

tested with univariate statistics (multiple t-tests or ANO-VAs), hypotheses about interregional integration require multivariate approaches. The influence that one brain region exerts or experiences from another is most simply examined via the correlations between brain activity measures for the two anatomic structures; as an operational definition two brain regions can be considered to be functionally coupled if their activities are correlated (3); however, this approach cannot elucidate how other nodes in the network mediate these relationships. To model this mediation requires analysis of the covariance matrix of regions studied in its entirety. Several new methods have been developed. These include structural equation modeling (SEM) and eigenimage analysis. SEM, used in conjunction with acknowledged anatomical models, can characterize and quantify the "functional connectivity" among the multiple components of neural systems. A model of known or hypothesized anatomic pathways is defined first; then a functional model of interest is tested against this model by iterative fitting of the interregional correlational weights. It should be borne in mind that the regional components examined are preselected based on putative pathways and the results from this approach are only as good as the model. In contrast, eigenimage analysis is a data-driven approach that examines patterns of correlation across the entire brain and how they vary in a time-series, revealing distributed brain systems and their temporal dynamics. Single value decomposition or principal component analysis is used to present the percentage of variance accounted for by different patterns of activity or spatial modes, and canonical variates analysis, conceptually similar to factor analysis, can be used to extract connectivity patterns across the entire brain that are most different between the studied groups. Thus, these recently developed methods permit characterization of normal and altered neural connectivity using neuroimaging.

THE FINDINGS

The explosion of functional neuroimaging studies of schizophrenia has resulted in many "findings" and many discrepancies. Nonetheless, several trends spanning the various experimental and methodologic techniques were apparent several years ago (4). First, when brain activity or metabolism is averaged across the entire brain (i.e., "global" function), patients have relatively normal values, unlike in primary degenerative disorders. Second, when scanned during so-called resting conditions (i.e., with no cognitive or motor activities required and no specific sensory input), abnormalities are inconsistent when seen. Although patients may have relatively normal regional patterns of resting brain activity, there appear to be associations between specific resting regional CBF patterns and symptom profiles (5). Changes in lateralization of brain function also have been described (6, 7). Third, when scanned during cognitive activation, patients tend to be different from normal controls. In particular, they show abnormal prefrontal activity (8) during tests involving working memory (i.e., the system used to hold information in temporary storage to complete a task). They show deficits in cingulate cortex as well as alterations in frontal—temporal and other intracortical functional relationships (12,13) during other cognitive tasks, such as cued verbal recall (9) and the Stroop test (10), and in some studies at rest (11). In general, most of these findings have been reproduced in acute, untreated patients, thus excluding a primary role for medication artifacts.

More recent functional brain imaging studies in schizophrenia have focused on: (a) further characterization of the locales and cognitive and behavioral context of neurophysiologic deficits in schizophrenia; (b) delineation of the relationship of the deficits to clinical symptoms and other neurobiological features of the illness; and, most important; (c) attempts to elucidate the pathophysiologic mechanism(s) of the deficits. The following section reviews these areas of observation and others. The most enlightening of these results have emerged from experimental paradigms designed to actively engage neural systems in cognitive or other activities; the most consistent findings concern the function of the prefrontal cortex.

Frontal Lobe Circuits

The frontal lobes have played a prominent role in formulations of schizophrenia since the conceptualization of the illness. In earlier times this role was inferred by clinical analogy with known frontal lobe disorders and findings in neuropsychology and nonhuman primate studies. Substantial indirect but compelling evidence from these multiple domains conferred the status of best studied and most implicated region in schizophrenic pathophysiology on the frontal lobes. Early functional neuroimaging studies substantiated this role, beginning with Ingvar and Franzen's 1974 seminal finding that patients with schizophrenia had relatively lower blood flow to frontal regions (14). Changes in rCBF in response to cognitive activation were also first observed in these early studies; this approach has been greatly refined and now has largely replaced the inherently ill-defined and variable resting state as the cornerstone of functional brain imaging studies in schizophrenia. These data presaged the body of literature that emerged over the ensuing 15 to 20 years, most of which had similar frontal lobe findings (Table 54.1).

Characterization of Dorsolateral Prefrontal Functional Alterations

The relatively subtle prefrontal functional alterations observed in schizophrenia have been increasingly brought into focus by recent advances in the available neuroimaging armamentarium. Table 54.1 lists activation studies published

TABLE 54.1. FRONTAL LOBE FINDINGS WITH ACTIVATION PARADIGMS IN SCHIZOPHRENIA SINCE 1985

First Author	Publication Year	Reference Number	Imaging Technique	
Studies Reporting Decreased Frontal Lobe Activation in Schizophrenia				Activation Paradigm
Berman KF, et al.	1986	69	Xenon-133 rCBF	WCST/NMT
Weinberger DR, et al.	1986	70	Xenon-133 rCBF	WCST/NMT
Volkow ND, et al.	1987	71	Carbon-11 LCMRglu PET	Eye tracking
Weinberger DR, et al.	1988	45	Xenon-133 rCBF	WCST/NMT
Guich SM, et al.	1989	72	Fluorine-18 LCMRglu PET, E	CPT
Buchsbaum MS, et al.	1990	73	Fluorine-18 LCMRglu PET	CPT
Daniel DG, et al.	1991	44	Xenon-133 SPECT rCBF	WCST
Cantor-Grae E, et al.	1991	15	Xenon-133 rCBF	RPM, VT, WCST
Rubin P, et al.	1991 ^a	22	Tc-SPECT rCBF	WCST
Andreasen NC, et al.	1992ª	24	Xenon-133 rCBF	TOL
Berman KF, et al.	1992	18	Xenon-133 rCBF	WCST/NMT
Buchsbaum MS, et al.	1992ª	26	Fluorine-18 PET	CPT
Lewis SW, et al.	1992	74	Tc-SPECT rCBF	Verbal fluency
Kawasaki Y, et al.	1993	75	Tc-SPECT rCBF	WCST
Nakashima Y, et al.	1994	76	Oxygen-15 Water PET rCBF	Volitional saccade
Guenther W, et al.	1994	77	Fluorine-18 LCMRglu PET	Complex motor task
Catafau AM, et al.	1994 ^a	25	Tc-SPECT rCBF	WCST
Parellada E, et al.	1994ª	78	SPECT rCBF	WCST
Rubin P, et al.	1994 ^a	23	Tc-SPECT rCBF	WCST
Siegel BV, et al.	1995	79	Fluorine-18 LCMRglu PET	CPT
Steinberg JL, et al.	1996 ^a	80	Xenon-133 rCBF	WCST/NMT
Yurgelun-Todd D, et al.	1996	81	fMRI	Verbal fluency
Ganguli R, et al.	1997	82	Oxygen-15 Water PET rCBF	Supraspan memory
Shajahan PM, et al.	1997	83	Tc-SPECT rCBF	Oddball task
Volz HP, et al.	1997	84	fMRI	WCST
Gracia Marco R, et al.	1997	85	Tc-SPECT rCBF	WCST
Callicott JH, et al.	1998	86	fMRI	N-back Working memory
Carter CS, et al.	1998	87	Oxygen-15 water PET rCBF	N-back Working memory
Ragland JD, et al.	1998	88	Oxygen-15 water PET rCBF	WCST PART
Curtis VA, et al.	1998	89	fMRI	Word generation
Fletcher PC, et al.	1998	55	Oxygen-15 water PET rCBF	Graded working memory
Parellada E, et al.	1998 ^a	90	Tc-SPECT rCBF	Rest, WCST
Stevens AA, et al.	1998	91	fMRI	Tone/auditory working memory
Crespo-Facorro B, et al.	1999	92	PET rCBF	Verbal learning
Volz H, et al.	1999	93	fMRI	CPT
Artiges E, et al.	2000	94	Oxygen-15 water PET rCBF	Random number generation
Higashima M, et al.	2000	95	Tc-SPECT rCBF	Auditory discrimination
Heckers S, et al.	2000	96	Oxygen-15 gas inhalation PET	Visual object recognition
Holcomb HH, et al.	2000	97	Oxygen-15 water PET rCBF	Auditory recognition
Russell TA, et al.	2000	98	fMRI	Mental state attribution
Studies Reporting Increas	sed Frontal Lobe Act	ivation in Schizophren	ia	
Heckers S, et al.	1998	48	Oxygen-15 gas inhalation PET	Verbal episodic memory
Manoach DS, et al.	1999	99	fMRI	Sternberg working memory
Manoach DS, et al.	2000	100	fMRI	Sternberg working memory
Callicott JH, et al.	2000	40	fMRI	N-back working memory
Studies Reporting No Ber	tween-Group Differe	ences		
Frith CD, et al.	1995	101	Oxygen-15 gas inhalation PET	Verbal fluency
Buckely PF, et al.	1997	102	fMRI	Motor
Spence SA, et al.	1998	103	Oxygen-15 water PET rCBF	Motor
Curtis VA, et al.	1999	104	fMRI	Semantic decision task
Braus DF, et al.	2000	105	fMRI	Motor

^aNeuroleptic-naive patients.
CPT, continuous performance test; fMRI, functional magnetic resonance imaging; LCMRglu, local cerebral metabolic rate of glucose;
NMT, number matching task; PART, paired associate recognition task; PET, positron emission tomography; RPM, Raven's Progressive Matrices;
SPECT, single photon emission computed tomography; Tc, technetium99m; TOL, Tower of London; WCST, Wisconsin Card Sorting Test.

over the past 15 years that report frontal lobe results. The overwhelming majority of these investigations have detected abnormal prefrontal responses to a variety of cognitive activities designed to access and/or control frontal neural circuitry, particularly working memory. The prefrontal site most commonly affected is the dorsolateral prefrontal cortex (DLPFC), and, until recently, the physiologic abnormality in this brain region was consistently seen as hyporesponsivity. Indeed, from the time of Ingvar and Franzen's first study and throughout most of the last decade researchers were satisfied that the qualitative nature of the frontal lobe abnormalities was known. However, the relative universality with which the schizophrenic prefrontal cortex had been reported to be hypofunctional, in the past several years, has given way to the notion that the aberrant neural responses in prefrontal cortex are more complex, including hyperfunction under some circumstances. It is noteworthy that abnormally increased prefrontal response has been primarily seen in studies carried out with fMRI, rather than PET, and mainly when the cognitive paradigms take advantage of the temporal properties of fMRI in order to employ shorter blocks of task performance, and/or require task switching. This fact suggests that the anatomic and/or chemical perturbations of the schizophrenic prefrontal cortex can be manifest by inappropriate over recruitment of prefrontal neural circuitry during relatively brief cognitive challenge and failure to sustain this recruitment over longer periods; however, more work is required to understand the implications of these recent observations and to fully characterize them. Regardless of the direction of prefrontal physiologic abnormality, the functional neuroimaging literature leaves little doubt that such abnormality exists. A variety of potential epiphenomenological explanations for this pathophysiology have been considered, and a number of neurobiologically plausible mechanisms have been proposed.

Effect of Neuroleptic Treatment

One potential epiphenomonological confound is the possibility of a causative role of antipsychotic medications, an important consideration because the majority of functional neuroimaging studies have been carried out in patients who were either receiving neuroleptics at the time of study or previously treated and then withdrawn for some prior period. However, taken as a whole, the literature provides little evidence that neuroleptics generate the functional neuroimaging abnormalities. First, although additional longitudinal investigations with newer techniques are necessary, an 18year follow up (15) showed that prefrontal hypofunction in chronic patients is remarkably stable over time and unaffected by long-term consistent neuroleptic treatment. Second, prefrontal abnormalities like those observed in schizophrenia are not seen in other illnesses in which neuroleptics are used, such as Huntington's disease (16,17). Third, a study of monozygotic twins concordant for schizophrenia,

but with differing lifetime histories of neuroleptic intake, found that in most pairs the twin with less exposure to neuroleptics was actually the more hypofrontal of the pair during a prefrontally linked task (18), a result opposite to that expected if neuroleptics caused hypofrontality. Fourth, studies examining metabolic or rCBF changes occurring when patients go from the unmedicated to the medicated state are quite inconsistent (4,8). Fifth, frontal lobe functional abnormalities have been found in first-degree relatives of patients with schizophrenia who have not been treated with neuroleptics or hospitalized (19-21). Finally and perhaps most conclusively, frontal lobe abnormalities during cognition have been found in a number of studies of young patients who have never received neuroleptics (22-26). Thus, in summary, there are little convincing data that neuroleptic treatment is a major factor in frontal lobe functional abnormalities.

The Link with Cognitive Performance

Most prominent among potential epiphenomena and confounds examined has been the effect of poor performance. It is undisputed that patients with schizophrenia perform poorly on the very cognitive tasks that best show prefrontal pathophysiology—the Wisconsin Card Sorting test (WCST), the N-back test, the Tower of London, or others. This is not surprising for the reason that the tasks are chosen because they are thought to reflect core deficits of the illness and they access neural systems relevant to it; however, considerable controversy has arisen around the possibility that the poor performance—or differences in attention or effort and motivation—somehow cause the frontal pathophysiology, rather than the more neurobiologically plausible explanation that underlying pathophysiology is responsible for the poor performance. It is clear that if patients are simply not engaged in a cognitive task during scanning they will not activate relevant brain regions; such results are obviously artifactual. It is less clear what should be predicted if patients (or healthy subjects) are manifestly working at a task, but performing it abnormally.

The relationship between performance level and the degree to which the brain neurophysiologically responds is complex, even in the presumptive absence of pathology in healthy control subjects. Several studies have found significant correlations between prefrontal neural activity and cognitive function, suggesting that these two variables are paradigmatically linked, but both positive and negative (27) relationships have been described (8). The research challenge has been to (a) understand this relationship and (b) tease apart abnormal cognitive performance and abnormal brain activity in patients to determine which is primary. This is a difficult issue to investigate experimentally, and no single study alone can answer the question; however, convergent evidence derived from several different research

directions leads to the conclusion that prefrontal pathophysiology cannot be accounted for as an epiphenomenon (8).

First, studies have been carried out on patient populations who, like schizophrenics, perform poorly on frontal lobe tasks but who have disorders other than schizophrenia. In principal, if the prefrontal physiologic deficit found in patients with schizophrenia is an epiphenomenon of poor performance per se, then other subjects who perform as poorly should have similar prefrontal function. Pathophysiology quite distinct from that characterizing schizophrenia has been reported in Huntington's disease (28) and normal aging (29,30) where performance is matched to that in schizophrenia, as well as in Down's syndrome (31) in which performance is worse. These findings indicate that poor performance per se does not necessarily produce the pathophysiologic picture seen in schizophrenia.

A second way to experimentally attack this "chicken and egg" question, and at least on the face of it the most direct way, is to match patients and normal controls for level of performance. However, ensuring good performance in patients (by using different versions of the task for patients and controls or by making the task extremely easy) does not guarantee that the effort involved or the cognitive operations used by the two groups are equated. Moreover, in the absence of neuropsychologic impairment, the neural systems accessed and findings may have very little to do with the illness. Thus, the strategy of employing "easy" tasks that result in some measures of performance being "normal" in patients is not as straightforward an approach to exploring neurophysiologic abnormalities in schizophrenia as it may appear (4,8). An alternative to "matching" for good performance is to study normal controls who perform as *poorly* on a given task as the patients. This strategy at least addresses the question of whether normals and patients fail by the same pathophysiologic mechanisms. In a study designed on this premise, patients performing the WCST were found to activate DLPFC less overall than performance-matched normals, but they activated a more anterior area of prefrontal cortex that is not recruited in normals as a group. Moreover, the more a given normal subject activated this "schizophrenic card sort area," the more he or she perseverated (8).

This overactivation of an aberrant area (or of an appropriate area, for that matter) would be difficult to explain on the basis of disengagement from the task and poor performance per se. In a similar example, affected members of monozygotic co-twins discordant for schizophrenia showed hypofunction of prefrontal cortex accompanied by hippocampal hyperfunction during the WCST (32). Analogous results have been described by Friston and colleagues using paced verbal production (33) and have recently been demonstrated with eigenimage analysis in a study of medication-free patients performing the N-back working memory task (34).

Yet a third approach to inform the performance conundrum is to model the abnormal cognition in normal controls. Both underactivation and overactivation have been

described in the context of performance difficulties. Goldberg and associates (1998) found that healthy subjects performing a dual task, working memory plus auditory and verbal shadowing, had significant decrements in both performance and DLPFC blood flow (35). Callicott and coworkers (1999) demonstrated that normal controls pushed beyond their working memory capacities also demonstrate reduced DLPFC responses (36). Electrophysiologic recordings in working memory-related neurons of nonhuman primates provide a neurobiological framework for these observations, where failed working memory trials are accompanied by decreased firing rates (37,38). Thus, findings of decreased prefrontal response in schizophrenia can be seen as part of an expected curve between working memory load and neural response—a dose-response curve that is shifted in the face of patients' reduced prefrontal capacities. Given the fact that other poorly performing patient populations with pathology that is different than schizophrenia do not show the same prefrontal response one (28,30,31), this particular shift in the dose-response curve with poor performance is neither inevitable nor the only possible one.

The DLPFC overactivition response in schizophrenia also has a precedent in the normal neurocognitive imaging literature. Rypma and D'Esposito (1999) found in healthy subjects that the longer the reaction time (an indicator of difficulty with a task), the greater the DLPFC neural response (27). Although this may simply represent increased "time on task," it again provides a context in which to view recent findings of overactivation in patients. Although some clues about the cellular mechanism underlying patients' aberrant prefrontal function are discussed in the following, it remains for future research to determine whether patients and controls share the same source for abnormal prefrontal responses (both underactivation and overactivation) in the context of performance difficulties.

The data summarized in the preceding leave little doubt that, although the patients' poor performance is certainly an integral, primary component of their illness, it is not the cause of the abnormal neural function, rather it is an effect of that pathophysiology. Given this conclusion and the now extensive literature documenting it, the most efficacious use of functional neuroimaging in future schizophrenia research will occur if the poor performance and prefrontal abnormalities are considered as inextricably linked and studies are designed to elucidate the mechanism of these linked phenomena.

Putative Underlying Mechanisms

A number of clues about potential pathophysiologic mechanisms emerge when the neuroimaging findings are considered in light of other neurobiological hallmarks of schizophrenia and findings from different clinical neuroscience research modalities. First, it is likely that cellular pathology in DLPFC contributes to the cognitively linked dysfunc-

tion. The degree of both hyperfunction and hypofunction of DLPFC in patients are predicted by decreased *n*-acetylaspartate (NAA), an MR spectroscopy measure of cellular integrity (39,40). Second, several compelling lines of evidence suggest a prominent role for dopaminergic dysfunction. It is well documented in nonhuman primates that optimal dopamine function is necessary for maximal working memory and DLPFC physiologic function (41). Similar, albeit less direct, evidence also exists in humans: Pharmacologically altering dopaminergic tone with agents such as amphetamine affects DLPFC activity in both healthy subjects (42,43) and patients (44); and a relationship between DLPFC rCBF during the WCST and CSF levels of the dopamine metabolite homovanillic acid has been found in schizophrenia (45). Third, converging data increasingly point to developmental mechanisms. A considerable body of literature now documents that disruption of corticolimbic connectivity in neonatal animals via hippocampal lesions models many features of schizophrenia, including working memory impairment, reduced prefrontal NAA, and dopamine dysregulation (53). Developmental pathology with a genetic basis also appears likely. A recent study links a genetic attribute that affects prefrontal dopamine to both working memory performance and DLPFC activation in patients, their sibs, and unrelated healthy individuals (21). Moreover, an association of schizophrenia with the allele that confers poor prefrontal function (a functional polymorphism in the catechol-o-methyl transferase [COMT] gene that affects enzyme activity) is indicated by several familybased studies. Investigations of this type, which explore the interaction of genetic and neurophysiologic characteristics, hold the greatest promise for elucidating the etiology of the illness and effecting innovative treatments.

Other Frontal Lobe Subregions

Dysfunction, primarily hypofunction, of portions of the frontal lobes other than the DLPFC has also been described. Just as a cognitive foundation for DLPFC dysfunction has been found in working memory and executive function, the dorsal anterior cingulate is classically considered to play an important role in vigilance, attention, and effort. It may, thus, be especially prone to epiphenomenologic effects. In normal subjects the region is activated by a variety of cognitively demanding tasks requiring stimulus-response selection in the face of competing information, such as the Stroop test, complex motor control tasks, verbal fluency, and working memory. These observations have led cognitive neuroscientists to propose more refined cognitive roles such as on line monitoring, conflict monitoring, and error detection (46). Further research is necessary to clarify which of these putative cognitive roles, or which epiphenomena, may be linked to the finding of anterior cingulate underactivation in schizophrenia (9-11). Orbitofrontal cortex, along with the ventral portion of the anterior cingulate, has been most linked to emotion. Few studies have been carried out that formally investigate the function of these regions in schizophrenia.

Lateral And Medial Temporal Lobe

The temporal lobe is of interest in schizophrenia for several reasons. Diseases of the medial temporal lobe can be associated with psychotic symptoms, and some neuropsychological aspects of schizophrenia implicate both lateral and medial temporal lobe. A number of neuroimaging studies have reported functional abnormalities in both lateral and medial temporal lobe structures (47). The data as a whole, however, are less compelling than for frontal lobe, and confounds and potential mechanisms are less well explored. Findings of both hyperfunction and hypofunction have been reported, but the bulk of the evidence leans toward overactivity. Heckers and colleagues (48) reported reduced hippocampal activation during the effort to retrieve poorly encoded material; however, it is of interest that, hippocampal activity appeared to be increased at baseline, again emphasizing the task-dependence of neurofunctional findings in general (48). Several studies point to a role for lateral temporal cortex in hallucinations and other positive symptoms—abnormal functional interactions between temporolimbic and prefrontal structures are also discussed in the following.

Miscellaneous Regional Changes

Functional abnormalities, primarily hypofunction, of many other regions have been reported. Although most are unreplicated, several are worth mentioning. Both increased and decreased basal ganglia activity have been found, but a role for neuroleptic treatment in such findings must be considered. Several investigators have suggested that schizophrenia is characterized by increased posterior cortical activity. In fact, Ingvar and Franzen's seminal 1974 rCBF study of schizophrenia suggested that the hypofrontal pattern represented a redistribution of flow with relatively lower flow to frontal areas as well as relatively higher flow to posterior cortex (14).

Such changes in activity patterns or distributions have received considerable attention. In particular, the notion that schizophrenia may involve disordered functional lateralization has been explored using a variety of methods. Left temporal overactivation was seen in this light in early studies. More recent work suggests that apparent alterations in functional laterality in schizophrenia may not actually reflect abnormal lateralization per se, but rather a failure to organize a lateralized response (6,49). For example, Mattay and associates (1997) reported less lateralized and localized lateral premotor area activation in patients during a simple finger movement paradigm (50). This may also be viewed

within the more general context of nonfocalized, less efficient, neurophysiologic responses in schizophrenia.

Interregional Relationships and Functional Connectivity

As the foregoing indicates, a number of brain areas have been shown to function abnormally in schizophrenia, often depending on the cognitive or other conditions under which the scanning is performed. It has been proposed that such multiple, seemingly local changes may be indicators of more ubiquitous dysfunction throughout widely distributed and interactive brain networks (12,51), a heuristically appealing pathophysiologic model for schizophrenia given the apparent subtlety of the neurophysiologic abnormalities in the face of the devastating and complex nature of the illness. This conceptualization is consistent with recent trends in viewing higher brain processes as parallel and distributed functions.

Because of the particularly extensive connectivity of the frontal lobe with other cortical and thalamic relay areas and its special role in schizophrenia, it is not surprising that many putative aberrant networks in the illness also involve it. Although the specifics of this network will obviously vary by task, a consistent finding in studies of working memory is a coactivation of prefrontal, anterior cingulate and parietal structures. Consistent with this, Bertolino and colleagues found a tight correlation between DLPFC NAA (indicative of neuronal integrity) and rCBF activation during the WCST, not only in DLPFC, but also with the other nodes in the working memory pathway (39). Because this was not evident in healthy controls, these findings appear to reflect a rate-limiting factor related to the disease process of schizophrenia.

Neurofunctional evidence of abnormal interactions between prefrontal and temporal/limbic areas has accrued for a number of years. Weinberger and associates (52) found in monozygotic twins discordant for schizophrenia an inverse relationship between the volume of the hippocampus (the structural variable that best differentiated well from ill twins) and the degree of dorsolateral prefrontal activation during prefrontal cognition (the physiologic variable that best differentiated the co-twins). This suggests dysfunction of neocortical-limbic connectivity in schizophrenia and is consistent with, if not confirmatory of, a neurodevelopmental mechanism (53). It has been suggested that abnormal development or plasticity of hippocampal connectivity affects the development and function of prefrontal cortex or, alternatively, that both regions are "put at risk" by the same pathologic mechanism (e.g., genetic variation) (54).

The new analytic tools recently developed to search more incisively for evidence of subtle and multidimensional abnormalities across the entire brain (see the foregoing) have provided results that are consistent with and extend the notion of temporohippocampal and prefrontal circuitry fail-

ure (13,33). During working memory, Meyer-Lindenberg and colleagues (34), using an eigenimage method (discussed in the preceding), uncovered differences between patients and controls in task-independent functional connectivity patterns charcterized by hypofrontality coexisting with increased temporal/hippocampal and cerebellar overactivity in the patients; another, task-related, pattern involving the working memory system (including DLPFC and inferior parietal lobule) was found to be more variable (i.e., showed altered modulation) in the patients, specifically during the working memory condition. Friston and Frith (12), using PET data from a verbal fluency experiment and a method that allowed them to assess patterns of activation most different between normals and patients, found that the prefrontal and temporal coactivations in normals were uncoupled (i.e., did not appear in the same pattern) in the patients. Fletcher and colleagues (55) reported similar results, and Jennings and co-workers (56) using structural equation modeling found altered neural interactions among frontal regions as well as between the frontal and temporal cortices in schizophrenics during a semantic processing task. Disruption of frontal-temporal connectivity has also been found using an EEG coherence measure (57).

Other studies have focused on medial prefrontal and cortical-striatal-thalamic circuit abnormalities (49); Biver and colleagues (58) and Mallet and associates (59), calculating correlations between various regions of glucose metabolic rate in PET, found decreased intrafrontal, as well as frontal-posterior connectivity. Andreasen (60) has advanced a hypothesis implicating compromised connectivity among prefrontal regions, several thalamic nuclei, and the cerebellum as the cause of a fundamental cognitive deficit in schizophrenia. She called the disruption in this circuitry "cognitive dysmetria," signifying "poor coordination of mental activities" that manifests itself in difficulty in prioritizing, processing, coordinating, and responding to information. This hypothesis is based on a number of studies from her group (61-63) in which the structures enumerated above were found to differ in activation between schizophrenics and controls during several unrelated tasks and in different cohorts, and on the fact that the circuit described is anatomically connected.

In summary, taken together, the functional brain imaging evidence is consistent with the notion that schizophrenia involves dissolution of neuronal interactions and that many features of schizophrenia may best be viewed as dysfunctional interregional circuitry. The details of this circuitry dysfunction differ, depending on the distributed network called into play during the particular behavior, but prefrontal cortex may play a special role.

The Relationship of the Neurofunctional Abnormalities to Clinical Hallmarks

The importance of linking pathophysiologic findings in schizophrenia to clinical aspects of the illness was recognized

early on. Ingvar and Franzen (14) noted that "hypofrontality" was most prominently seen in the most withdrawn, inactive, socially isolative, and "hypointentional" patients, whereas they related the hyperfunction in posterior areas that they observed to a "hypergnostic" component of the illness. The attempt to delineate the clinical and neurobiological implications of the physiologic abnormalities remains an important focus. Studies have primarily searched for neurophysiologic associations with cognitive deficits, symptom clusters, and individual clinical features such as hallucinations. The small sample sizes of some studies and the necessarily phenomenologic nature of research into the neurophysiologic underpinnings of clinical symptoms makes firm conclusions difficult, but some consistent findings have emerged. Frontal lobe dysfunction is consistently linked to negative symptoms and cognitive deficits, particularly working memory and executive function. For example, Goldberg and colleagues (64) used an intra-twin pair difference method in which unaffected co-twins served as individual controls for each patient in the NIMH monozygotic twin sample. Although left hippocampal size predicted a parameter of verbal memory, prefrontal blood flow and perseveration on the WCST were related. These data are part of a growing literature implicating medial temporal and prefrontal regions in symptom expression and some neurocognitive deficits of the illness.

In general, hallucinations are associated with sensory modality-specific activation in brain regions involved in normal sensory processing (65). For example, auditory hallucinations appear linked to language-related regions such as Broca's area (66) and left superior temporal cortex. Silberswieg and co-workers (67) made similar findings using a technique that quantifies the relationship between brain activity and density of hallucinations during the scanning period.

Specific cerebral blood flow patterns have been associated with distinct syndromes of schizophrenic symptoms (5): psychomotor poverty with decreased activity in DLPFC; disorganization and impaired suppression of inappropriate responses with increased activity in the right anterior cingulate gyrus; and reality distortion, which may arise from disordered internal monitoring, with increased activity medial temporal lobe at a locus activated in normal subjects during internal monitoring of eye movements. Thought disorder has been linked to temporal lobe overactivity. Kaplan and associates (68) found an association of marked psychomotor poverty with superior parietal as well as prefrontal areas, hallucinations and delusions with abnormalities in left temporal cortex, and disorganization with left inferior parietal lobule abnormalities. Further work undoubtedly will refine these interesting clinical and pathophysiologic correlates.

QUESTIONS FOR THE FUTURE

Further characterization of the abnormalities delineated by functional neuroimaging in schizophrenia is a clear goal for

the future. One important advance will come from temporal dissection of the abnormal neurophysiologic signals that have now been localized with great anatomic precision. For example, the particularly high degree of both segregation and interaction of the frontal lobe complex appears to be essential for regulating and monitoring the functions it supports via multisynaptic feedback loops modulating posterior brain areas. It is likely that the functional disconnection in schizophrenia described in the preceding includes abnormalities in these feedback loops, which operate on a time scale less than 200 msec. Progress in understanding the etiology of frontal lobe dysfunction in schizophrenia, therefore, requires a methodology that has optimal resolution both spatially (in order to reliably differentiate functionally segregated areas) and temporally (to tap into the time scale in which the feedback loop organization operates). The simultaneous combination of PET or fMRI studies (which afford relatively high spatial resolution) with methods having excellent temporal resolution such as EEG or MEG (which provide temporal resolution in the order of milliseconds) will allow explicit investigation of specific hypotheses about prolongation of the feedback and feed-forward latencies and about disease-related changes in the order in which components of distributed neural systems come into play in schizophrenia.

A second important way in which characterization of the abnormal neurophysiologic signals must advance is further investigation into their relationship to other neurobiological features of the illness. One question that requires closer scrutiny is the relation of the neurophysiologic abnormalities to dopaminergic and other neurochemical parameters. Hypotheses about neurochemical mechanisms can be tested directly with functional brain imaging, both by examining the effects of pharmacologic interventions and direct in vivo measurements of various components of neurochemical systems. Also, the relationship of the functional abnormalities to the neurostructural and neurochemical findings described in other chapters must be further elucidated. Not only does such a multimodal approach provide critical crossvalidation of the information gleaned from the different technologies and help to rule out epiphenomena, but it is also a means to more closely approach causality and mechanism. For example, links with dopaminergic dysfunction can elucidate putative genetic mechanisms (21). Similarly, the fact that the prefrontal functional abnormalities may relate to structural pathology in other (particularly limbic) areas lends credence to the notion of a neurodevelopmental mechanism, although it does not provide proof; further work, perhaps expanding on insights from animal models (53), will be necessary to test the roles of the temporal lobe and aberrant neural development in the genesis of schizophrenic psychopathology.

Clarifying the mechanism by which the pathophysiology and illness arise is the most important question that can be addressed with functional brain imaging. Considerable work remains to be done, although some clues have emerged, particularly with regard to the frontal lobe. Longitudinal studies are necessary to differentiate trait from state phenomena. Brain imaging undoubtedly will also continue to impact the current effort on many fronts to uncover the genetic foundations of schizophrenia, by offering new targets for linkage and association studies and providing clues to direct hypothesis-driven genetic investigations, as discussed in this chapter. Such studies provide a unique perspective from which to view brain function, one that offers the possibility of uncovering basic fundamental principals important in the genesis of schizophrenia and that has the potential to lead to direct intervention.

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