

Structural and Functional Magnetic Resonance Imaging in Psychiatric Disorders

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Objective: To report on recent advances in both structural and functional brain imaging studies in psychiatry and to highlight their importance for the field.

Method: We reviewed recently published articles dealing with such advances and abstracted them into a selective review of the field.

Results: Some of the more important trends include integration of genetic information into research studies, use of novel quantitative image measurement techniques, studies of new subject populations, the use of pharmacologic probes in functional magnetic resonance imaging (fMRI) studies, the incorporation of elements of virtual reality into fMRI task stimuli, and the methodological innovation of hyperscanning.

Conclusions: A whole series of new approaches and techniques are resulting in rapid advances in neuroimaging in psychiatry. Several of these show the potential for clinical translation.

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Clinical Implications

- Quantitative measurements obtained from brain imaging are beginning to illuminate our understanding of disease mechanisms in schizophrenia and to cross traditional diagnostic boundaries.
- Future definitions of schizophrenia (and many other psychiatric illnesses) will likely come to rely more on such measures.

Limitations

- The more recent, most informative quantitative brain-imaging measurements are currently not widely available outside specialized centres.
- Such measures are also generally more informative at a group, rather than an individual, level.

Key Words: *functional magnetic resonance imaging, diffusion tensor imaging, independent component analysis*

The field of neuroimaging in psychiatric disorders has made enormous advances since the first computed tomography studies of patients with chronic schizophrenia some 30 years ago. Some of the more important recent trends include the integration of genetic information into both structural and functional studies, leading to “neuroimaging genomics.”

Other major influences on psychiatric neuroimaging in the last few years involve the use of a series of novel quantitative image measurement techniques developed for both structural and functional imaging studies, including VBM and algorithms for fusion of images from different imaging modalities (for example, sMRI and fMRI). Although the widespread availability of whole-brain voxel-based measurement

techniques such as VBM has expanded the number of brain structures that can be easily and rapidly assessed, the debate over the comparability of this new technique to the use of traditional hand-drawn ROIs is not fully resolved. Also new is the examination of patients with a far wider spectrum of clinical disorders and the inclusion of unaffected first-degree relatives, as well as research including large numbers of subjects, often necessitating multisite research collaborations. Also discussed are newer strategies in functional neuroimaging, including use of pharmacologic probes in fMRI studies, fMRI task stimuli incorporating elements of virtual reality, and the methodologic innovation of hyperscanning.

Several comprehensive recent reviews describe the brain regions and circuits implicated in various major mental illnesses and enumerate the affected areas.^{1–4} Rather than our resummaring a catalogue of brain regions involved in these disorders, it is of greater intrinsic interest that we review the contemporary themes serving to motivate sMRI and fMRI brain-imaging research in psychiatry. Some of these efforts are not without their controversial aspects, so we also review the debates concerning their application. Let us start with an overview.

Abbreviations used in this article

AD	Alzheimer's disease
BD	bipolar disorder
BDNF	brain-derived neurotrophic factor
BOLD	blood oxygenation level–dependent
COMT	catechol-o-methyl–transferase
cys	cysteine
DISC1 gene	disrupted in schizophrenia 1 gene
DLPFC	dorsolateral prefrontal cortex
DTI	diffusion tensor imaging
EEG	electroencephalogram
fMRI	functional magnetic resonance imaging
ICA	independent component analysis
jICA	joint independent component analysis
met	methionine
MRI	magnetic resonance imaging
PCC	posterior cingulate cortex
PFC	prefrontal cortex
ROI	region of interest
ser	serine
sMRI	structural MRI
SNP	single nucleotide polymorphism
vACC	ventral anterior cingulate cortex
val	valine
VBM	voxel-based morphometry

We will discuss new disciplines such as neuroimaging genomics.⁵ One innovation that we comment on, but do not explore further, is the move away from neuroimaging studies examining single, isolated brain regions and the move toward examining neural circuits. In part, this trend follows from system-based hypotheses of mental illnesses that propose disrupted relations between nodes of distributed networks of “effectively connected” structures that are normally reciprocally interconnected and interdependent and interact to produce manifest behaviour. Other thematic advances include the increasing use of novel analytic methods. These include whole-brain structural methods such as VBM^{6–11} and new approaches based on statistical analyses, such as independent component analysis, for interpretation of fMRI and for cross-modality data fusion.¹² We comment on fresh populations being included in neuroimaging studies, such as unaffected siblings and persons at high risk for developing disorders, and we also comment on cross-disorder comparisons.^{13,14} As well, we comment on innovative functional neuroimaging approaches such as use of pharmacologic probes, in some cases in conjunction with fMRI tasks designed to incorporate virtual reality or simulation,^{15–18} and on the new discipline of hyperscanning.¹⁹

New Imaging Disciplines

Neuroimaging Genomics: Genes, Brain Structure, and Function

Following rapidly on the heels of the scientific efforts to unravel the human genome, advances in genetic knowledge have begun to increasingly influence neuroimaging research. The functional mechanism of many of the disease-risk genes identified and the “big picture” of how these genes combine in a common etiology or physiological final common path remain mostly obscure. However, it is becoming clearer that disease risk for many major mental disorders is mediated by multiple, interacting genes of individually small effect, acting in concert, likely through convergent molecular bottlenecks. With the faster-paced, replicable identification of risk genes for schizophrenia and affective disorders that serves to motivate the field of psychiatric research, we have seen the recent emergence of more comprehensive, testable, etiopathologic models of major mental illnesses. Such models, advanced primarily by Weinberger and Murray,^{5,14,20} span genes, molecular and cellular biology, brain systems, and behaviour. These hypotheses have led to a series of interesting papers in which 2 or more of the above elements have been explored and related to one another.

The morphologic and neuropathological changes seen in schizophrenia are subtle but suggest a hypothesis of schizophrenia as a disorder of connectivity. New life has been provided to this premise by the recent identification of several

putative schizophrenia susceptibility genes. How might these genes relate to abnormal functional activation patterns in schizophrenia? Data from genetics, cognitive function, and fMRI are beginning to converge. Recent studies are enlightening: Given notable working memory deficits in schizophrenia, Egan²¹ and Goldberg et al²² examined a well-known functional Val/Met COMT polymorphism in conjunction with an n-back working memory task in a healthy subject cohort.²² There was a significant COMT genotype effect: Val/Val individuals had the lowest n-back performance and slowest reaction time, and Met/Met individuals had the highest performance. Similar effects were also seen in patients with schizophrenia and in their unaffected first-degree relatives. COMT genotype did not influence attention or IQ measures, suggesting specificity.

Callicott and Egan²³ also examined the effects of COMT genotype on PFC fMRI activation in cohorts of healthy control subjects, in schizophrenia patients, and in their healthy siblings during the n-back task in performance-matched groups. Methionine allele load predicted a more efficient physiological response (less BOLD activation) in the PFC in the 2-back condition. In other words, “the group with relatively more cortical dopamine available at the synapse (i.e. mm) had relatively greater behavioral ‘bang’ for its physiological ‘buck,’”^{12, p 331} irrespective of diagnosis. In both cohorts, siblings and schizophrenia patients showed increased DLPFC activation (inefficiency) relative to control subjects, despite comparable performance, similar to earlier schizophrenia fMRI studies, suggesting heritability of inefficient PFC activation. Schizophrenia patients with the Val/Val genotype performed especially poorly on working memory tasks,²⁴ suggesting abnormal cortical connectivity,²⁵ thus illustrating COMT SNP’s influence on working memory performance and associated fMRI BOLD in normal subjects, schizophrenia patients, and first-degree relatives.

Once a potential schizophrenia risk gene has been identified, a sensible strategy is to explore whether normal SNP variants of the gene have any influence on normal brain structure or function. Discovery of how the gene affects the brain in this manner, particularly in disease-relevant regions, is important to document and helps provide a context for how dysfunction at a genetic level plays out at a brain system level. The DISC1 gene is another promising schizophrenia candidate gene that is expressed predominantly within the hippocampus. Callicott²⁶ hypothesized that allelic variation at a Ser⁷⁰⁴Cys SNP of DISC1 affects hippocampal structure and function in healthy subjects. In fact, the Ser allele was associated with both reduced hippocampal gray matter volume and altered activation of the hippocampus during several cognitive fMRI tasks.^{26,27} Together with other evidence suggesting that allelic variation within the DISC1 gene increases the risk for

schizophrenia, one possible mechanism of this effect involves structural and functional alterations in the hippocampus.

Pezawas²⁷ also examined the themes of genetic risk and hippocampal abnormality in schizophrenia at the level of the hippocampus. In the case of the hippocampus, SNP variants in the DISC1 gene appear to influence both the grey matter volume and hippocampal function during performance of several fMRI cognitive paradigms.

As in the review by Callicott et al,²⁶ Pezawas²⁷ examined the role of one schizophrenia risk gene on the hippocampal grey matter volume, using structural neuroimaging. Because declarative memory (in addition to working memory, discussed above) is often compromised in schizophrenia, gene influences on the structure and function of memory-related brain regions are important to understand. Hippocampal-based learning depends on neural plasticity, where a gene controlling BDNF, a neurotrophin, is an important participant. The BDNF gene is also a schizophrenia-risk gene. BDNF gene expression plays a role in spatial memory in the rodent hippocampus, and suppression of BDNF gene synthesis impairs (hippocampally based) spatial learning. One BDNF SNP variant is implicated in abnormal intracellular trafficking and regulated secretion of the BDNF gene in hippocampal neurons. In prior work, Egan²⁸ linked this genetic variation in healthy control subjects to variation in both memory ability and hippocampal function by showing that one BDNF SNP group performed more poorly on a logical memory task, compared with the other SNP variants. A more recent paper from Pezawas et al²⁷ shows a striking effect of these same SNP variations in the BDNF gene on normal hippocampal volume. These data implicate a specific genetic mechanism in significant normal variation in human declarative memory and link the basic effects of BDNF signalling on hippocampal function in laboratory rodents to humans.

Novel Image Analysis Methods

Voxel-Based Morphometry

VBM is a method for detecting group differences in the relative density or volume of brain matter²⁹; it is used to localize gray matter alterations and differs from the measurement of manually delineated, anatomically defined ROIs within the brain. The current gold standard for morphometry, the ROI method, has many strengths, including substantial anatomical validity. However, it also has limitations that include its being time-consuming; it thus does not easily allow for comparison of multiple brain regions or large subject groups.⁷ Manually delineated ROIs are also subject to inaccuracies because local individual neuroanatomy can be very variable, especially in diseased populations; when such regions are consequently difficult to define, they are thus more subject to error. The

hypothesis-based nature of the ROI method restricts assessments to prespecified regions.³⁰

Until recently, most sMRI brain studies were confined to relatively straightforward (if laborious) ROI-based measurement of brain regions. ROI methodology typically involves a lengthy process of developing reliable and valid anatomic landmarks, of rater training, and of establishing interrater reliability. If only 1 or 2 research groups were able to measure reliably an anatomically complex, but critical, region, then metaanalyses would often conclude that these latter regions were unaffected, owing to the small number of total studies.

More recently, investigators have begun to employ VBM,⁸ a fully automated measurement technique, to examine structural MR images of the whole brain by voxel-wise comparison of the relative local concentrations or volumes of gray matter between 2 groups of subjects. By giving equal weight to every voxel included in the 3D sampling array, VBM provides a nonbiased measure of highly localized regions that might not be examined in hypothesis-based ROI studies and thus provides multiple regional comparisons. Conceptually, VBM tests for residual tissue concentration differences remaining after MRI scans are spatially normalized into standardized stereotaxic space.⁸ Owing to the nature of this normalization procedure, VBM analyses are less sensitive to shape differences and thus may exhibit high reliability at the expense of validity. VBM results can be modulated to account for the variable shape changes in nonlinear normalization⁹ and thus preserve the volume of the particular tissue within a voxel.⁸

Numerous studies have now used VBM to identify brain regions showing variable amounts of gray matter in schizophrenia patients relative to healthy control subjects. These studies generally confirm and extend ROI studies^{31,32} by increasing the anatomical range of volumetric comparisons, showing that schizophrenia patients exhibit less gray matter concentration in multiple cortical and subcortical regions. The primary differences in reports between ROI and VBM studies of similar patient populations likely stem from methodologic differences between voxel-averaged, landmark-based ROI analyses and single, voxel-by-voxel whole brain VBM measurements. For example, the normalization procedures employed in VBM, although highly reliable, make the process less sensitive to group differences in shape or gray–white matter differentiation and are prone to errors caused by misregistration of anatomical structures.^{11,33} The method has, however, been updated and optimized¹⁰ to reduce errors arising from systematic differences in head shape, variations in segmentation, and inconsistent brain stripping as well as errors introduced by spatial normalization. However, because the validity of VBM has been questioned but not yet documented,⁷ different hypotheses may require different VBM parameters and results must be viewed with caution. Giuliani

et al²⁹ directly compared data from a series of MRI scans of schizophrenia patients and control subjects assessed by VBM and previously by ROI methods and concluded that, although VBM is rapid and fully automated, it is not a replacement for traditional ROI-based analyses.⁷ Each method provides different types of information, and they should therefore be used in tandem,⁷ with VBM being used to quickly generate hypotheses by identifying areas that can subsequently be more thoroughly investigated with ROI-based approaches.²⁹

Similarly, Honea et al⁶ reviewed the 15 published studies constituting the literature on the use of VBM in schizophrenia-imaging research. These reported gray and white matter deficits in schizophrenia patients, compared with healthy subjects, in a total of 50 brain regions. However, more than 50% of the studies reported deficits in 2 of these 50 regions; only a single study reported deficits in 9 of the 50 regions. The most consistent findings were of relative deficits in the left superior temporal gyrus and the left medial temporal lobe. Use of a smaller smoothing kernel (4 to 8 mm) led to detection of a greater number of regions implicated in schizophrenia. The authors noted that the diversity of regions reported in VBM studies was in part related to the variables chosen in the automated process, such as smoothing kernel size and linear or affine transformation, as well as to differences in patient groups. They concluded that VBM “can be used as an exploratory whole-brain approach to identify abnormal brain regions in schizophrenia, which should then be validated by using region-of-interest analyses.”^{5, p 2233}

Brain Connectivity: Data Fusion Methods

We next discuss brain connectivity and the use of data fusion methods. The brain is a complex organ with interrelated structural and functional connectivity, and the importance of integrating anatomic information in functional studies is increasingly being recognized. Passingham et al³⁴ propose the concept of a “connectional fingerprint,” that is, that the functions of a cortical area are determined by its extrinsic connections and intrinsic properties. This suggests that functional connectivity has an anatomical basis and that anatomical information is a critical component of brain functional connectivity and can be useful in distinguishing connection patterns. Because there are many types of imaging methods, approaches, and models, it is important to define what is meant when discussing “brain connectivity.” Relevant differences include spatial and temporal resolution and whether the data represent neuron activities, neural ensemble activities, or (electrical or hemodynamic) activities of macroscopic brain regions. As Horwitz³⁵ points out, “using different definitions as to what constitutes functional connectivity may result in different conclusions about whether the associated functional connectivities for a particular neural system are strong or weak.”^{35, p 468} For example, 2 widely used definitions in the

fMRI community specify whether one is interested in either what regions are temporally similar (for example, correlated), so-called functional connectivity, or whether one region is influencing another region(s), called effective connectivity. Although Horwitz³⁵ argues for large-scale neural modelling to investigate relations between various modalities and brain connectivity, he also points out that such analyses have many limitations. Connectivity thus comprises a class of concepts needing operational definition. A useful perspective is as follows: the study of spatial and (or) temporal correspondence in the brain. Achieving this requires, first, a correspondence metric (for example, correlation and modulation) and, second, an imaging modality or modalities. The above definition subsumes both the concepts of functional and effective connectivity and the concepts of individualized or population-based connectivity.

Data fusion as a technique is being newly utilized in brain imaging studies of various types. For example, it has been used to integrate temporal information in EEG data with spatial information in fMRI data.¹² More traditional approaches to this type of problem involve constraining the EEG data with fMRI activation maps³⁶ or constraining DTI fiber tracking by using fMRI activation maps.³⁷ Although these are powerful techniques, a limitation is that they may impose potentially unrealistic assumptions on the DTI data, which fundamentally differ in nature from the fMRI data. Additionally, such methods would not be able to detect a functional change associated with a distant white matter connection. Thus, to examine such relations, some research groups are developing exploratory methods to examine joint associations between data types—examining brain connectivity, for example, by using direct data fusion via a statistical framework (statistical data fusion) and source separation techniques.

The hypothesis that psychiatric disorders could arise from disruption, dysfunctional integration, or disconnection, either between regions within a distributed network of brain regions or between such neural circuits, has gained traction, particularly in regard to schizophrenia.³⁸ As a means of quantifying such disconnections, “functional connectivity,” defined as correlation between 2 or more functional regions³⁹ or among brain regions,^{38,40–43} has considerable utility. For example, analyzing fMRI correlations between brain regions in schizophrenia patients, Liang et al³⁹ reported disrupted functional integration of widespread brain areas. A recent analytic approach, ICA, provides a powerful technique for decomposing and understanding complex data sets. ICA is a method for recovering underlying signals from linear mixtures of these signals and draws upon higher-order signal statistics to determine a set of components that are maximally independent of each other.¹² Spatial ICA is especially useful for revealing brain activity not anticipated by the investigator and for

separating brain activity into networks of brain regions with synchronous BOLD fMRI signals.

The primary assumption guiding spatial ICA, that “different parts of the brain do different things”^{44 p 824} is consistent with the principle of modularity of brain function and is used increasingly for fMRI data analysis. Several recent studies have used ICA in 3 major circumstances. The first is to examine dominant activation differences in patients,^{45,46} particularly during “resting state” scans, which are relatively easy to obtain and do not confound performance (for example, the inability of patients to perform a task) with brain activity.^{47–50} During the resting state, patients in the fMRI scanner are told to relax and not to focus their thoughts on any one particular topic. Such functional imaging studies, for example, those by Greicius et al,^{49,50} reveal that specific brain regions, including the PCC and vACC, consistently show greater activity during resting states than during cognitive tasks.^{47,49,50,52} The PCC is strongly coupled with the vACC and several other brain regions at rest, and activity in these regions diminishes with the degree of engagement in cognitive tasks of increasing complexity, supporting the notion that these regions constitute a cohesive network supporting a default mode of brain function. A simple view is that the resting state represents the brain in an “idling” mode. Thus functional connectivity maps of the PCC and vACC during a simple visual processing task are virtually identical to those obtained during rest.⁵⁰ However, lateral prefrontal regions showing increased activity during a more complex cognitive task show significant inverse correlations among themselves and the PCC, suggesting a mechanism for attenuation of default mode network activity during cognitive processing.⁵⁰

The resting state network has now been examined in several neuropsychiatric diseases. Greicius et al⁴⁹ examined an AD group in the resting state and reported that they displayed decreased resting-state activity in the posterior cingulate and hippocampus, compared with healthy control subjects. Greicius et al suggested that disrupted connectivity between these 2 regions accounts for the posterior cingulate hypometabolism commonly detected in positron emission tomography studies of early AD. A statistical analysis at the individual subject level suggested that activity in the default-mode network may ultimately prove a sensitive and specific biomarker for incipient AD.⁴⁹ Resting-state fMRI scans are also abnormal in schizophrenia and autism.^{39,48}

The second major use of ICA is the use of spatial ICA to analyze complex behaviours studied with fMRI, where experimental time course is less straightforward and not necessarily amenable to traditional block designs. One example is the use of fMRI to study simulated vehicle driving in alcohol-intoxicated subjects.^{15,16,18} The third use of ICA is the use of

jICA in various types of data fusion, for example, joining data from structural and functional MRI.¹²

The acquisition of both sMRI and fMRI data for a given study is common. However, these data are typically examined in separate analyses, rather than in a combined model. A novel method for performing ICA across image modalities—for example, gray matter images and fMRI activation images, together with a joint histogram visualization technique—was published by Calhoun et al.¹¹ jICA was used to decompose a matrix with a given row consisting of an fMRI activation image resulting from auditory oddball target stimuli and an sMRI gray matter segmentation image collected from the same individual. Data collected on a group of schizophrenia patients and healthy control subjects by using the jICA approach were compared. The main finding was that group differences in gray matter in bilateral parietal and frontal regions, as well as in posterior temporal regions, were associated with bilateral temporal regions activated by the auditory oddball target stimuli. A finding of less patient gray matter and less hemodynamic activity for target detection in these bilateral anterior temporal lobe regions was consistent with previous work. An unexpected corollary to this finding was that, in the regions showing the largest group differences, gray matter concentrations were larger in patients, compared with control subjects, suggesting that more gray matter may be related to less functional connectivity in the auditory oddball fMRI task.

Previous studies in functional connectivity have developed from voxel-based or ROI-based correlation analysis, in which one or a small cluster of voxels is chosen whose time course (single or averaged) serves as a reference model for cross-correlation analysis with the remaining brain voxels. Some studies have also analyzed functional connectivity in the entire brain by dividing the brain into multiple regions.³⁹ Van de Ven et al used spatial differences across ICA-generated components' intensity to determine functional connectivity levels.⁵¹ Rakapakse et al performed analyses using structural equation modelling to find connectivity between regions identified with spatial ICA in healthy individuals while performing a task.⁵² Overall, these techniques seem effective for analysis of dysfunctional integration, for example, in the brain in schizophrenia.

Innovative fMRI Approaches

As reviewed by Astur et al,^{17,54} the use of virtual reality in the form of simulated tasks can provide a realistic environment in which to study complex naturalistic behaviours. Ecologic validity is the extent to which laboratory results or conditions generalize to real-life conditions. Most standard neuropsychological measures sacrifice ecologic validity for strong experimental control, but virtual reality can

reintroduce strong ecologic validity by conscious design. Virtual reality has also been used to create and administer tasks for humans that are more similar to those used in nonhumans (for example, in rodent or primate studies), such as the Morris Water Maze Task. Virtual reality can accomplish this because it can command photorealistic graphics and excellent experimental control. Moreover, virtual reality allows a means of evaluating performance in real-life scenarios that may be too complex or involved to examine via alternative methods. Paired with fMRI, virtual reality used as above can help to reveal the brain circuits involved in various tasks relevant to psychiatry. For example, tasks found to be abnormal in animal models of a psychiatric disorder can be more directly tested in humans by using their virtual reality analogs.

Also, virtual reality has been used to study complex paradigms, which are usually not amenable to direct measurement, in conjunction with fMRI. For example, virtual driving and complex cue-induced, drug-craving driving paradigms introduce participants to a simulated environment rather than a series of tasks, allowing for a more realistic experience.^{17,54} However, incorporating them into the fMRI environment creates specific challenges related to the hardware (for example, the simulator must be nonmagnetic and must not generate radio frequency signals that interfere with the fMRI scan), the environment (for example, typical MRI scanners require participants to lie on their backs while driving and also constrain head movement), and the analysis (for example, the brain activation during simulated driving is highly complex owing to the multiple cognitive domains being stimulated). Here, advanced analysis approaches such as ICA are useful.

Moreover, effects of drug administration can be assessed while subjects are navigating through virtual worlds or engaged in complex virtual tasks.^{15,16} It is hoped that the increasing use of these approaches will lead to more effective and real-world diagnostic assessments and neuroscientific investigations, especially in a neuropsychopharmacological context.

Fresh Populations Studied

The distinction between schizophrenia and BD has been fundamental to psychiatry since Kraepelin's time. Because delusions, hallucinations, and thought disorder often occur in mood disorders as well as in schizophrenia, the specificity of associated brain changes needs to be determined. Do patients with bipolar illness with psychotic features share key brain changes with patients diagnosed with schizophrenia, or do they more closely resemble BD patients without psychotic features? Previous reports of the ventricular and hippocampal volumes in patients with BD have been inconsistent in their findings. One possibility is that volumetric abnormalities are determined by disease subtype.

Prior evidence suggests that psychotic and nonpsychotic forms of BD are 2 subtypes that may differ in their pathophysiology. Two recent articles investigated this, using different approaches and reaching different conclusions. McDonald et al¹⁴ used ROI morphometry to volumetrically assess MRI scans in almost 250 subjects, including patients with schizophrenia or schizoaffective disorder and their unaffected first-degree relatives, patients with psychotic BD and their unaffected first-degree relatives, and healthy comparison subjects. Most of the families affected with schizophrenia and all the families affected with BD were multiply affected with the illness. Patients with schizophrenia had increased volume of the lateral and third ventricles and reduced hippocampal volume, but none of these volumetric abnormalities were present in subjects with psychotic BD. Unaffected relatives of schizophrenia patients from multiply affected families had enlarged lateral ventricles but no other volumetric deviations; unaffected relatives of patients with BD had unchanged ventricular and hippocampal volume. McDonald concluded that schizophrenia and psychotic BD differ in ventricular and hippocampal regions and that lateral ventricular enlargement represents a potential morphometric endophenotype for schizophrenia.

A related article by Strasser et al¹³ continues this theme, comparing brain alterations in subjects with psychotic or nonpsychotic BD with the differences from normal seen in subjects with schizophrenia, and reaches a different conclusion. These authors investigated the ventricular and hippocampal volumes in 38 adults with either clearly defined psychotic BD ($n = 23$) or nonpsychotic BD subtypes ($n = 15$), compared with 33 individuals with schizophrenia and 44 healthy community control subjects. The subjects' ventricular and hippocampal volumes were reliably measured on high-resolution anatomic MRI scans. The authors used a multivariate analysis of covariance for comparing the volumes across groups, covarying for the total brain volume. Potential effects of bipolar illness features were explored, and psychotic BD was contrasted with nonpsychotic BD. Compared with the control subjects, significant volume differences were reported in psychotic BD but not in nonpsychotic BD, for the ventricular regions but not for hippocampi. The subjects with schizophrenia had significantly larger ventricular and smaller left hippocampal volumes than the control subjects. These results suggested that psychotic BD, but not nonpsychotic BD, is associated with increased ventricle volumes and a trend toward smaller left hippocampal volumes, as observed in schizophrenia.

Techniques initially developed for functional neuroimaging in social neuroscience, such as hyperscanning,⁵³ where data derived from 2 or more individuals in MRI scanners at different locations are coordinated and compared via the Internet,

will likely play a role in studying not only normal personality variation but also disorders of impaired social communication. These conditions include schizophrenia, autism and its spectrum disorders, and various personality disorders. A new methodology for the measurement of the neural substrates of human social interaction is described. This technology, termed "hyperscan," embodies both the hardware and the software necessary to link magnetic resonance scanners through the Internet. Hyperscanning allows human behavioural experiments in which participants can interact with each other while fMRI is acquired in synchrony with the behavioural interactions. Data are presented from a simple game of deception between pairs of subjects. Because people may interact both asymmetrically and asynchronously, both the design and the analysis must accommodate this added complexity.

Future Trends and Conclusion

Psychiatric research as a whole has been refreshed by the coalescence of ideas and findings from clinical and molecular genetics, cellular biology, brain structural and functional studies, and clinical phenomenology. The papers described above are a small but representative selection from research at this nexus published recently. Scientists from what might have been categorized as silo specialities only a few years ago are now talking to each other increasingly and even having joint meetings, such as the recent Third International Imaging Genetics Conference on genetics and neuroimaging, which took place in January 2007.

At the clinical level, current diagnoses from the DSM-IV are based on cross-sectional phenomenology and course, without reference to genes or neuroimaging. Undoubtedly this will change, with future editions of the DSM perhaps defining psychiatric conditions by integrating accumulating knowledge from these other fields. As a consequence, the question of the clinical specificity of reported brain-imaging research findings will be examined more than at present. Structural or functional alterations in specific brain regions or circuits may be associated with syndromes, such as psychosis, that cross traditional diagnostic boundaries. Clinically, psychiatrists agree that schizophrenia is a collection of diverse entities, but traditional clinical subtypes are mutable over time, and exactly how to subdivide the illness has until now been the subject of much debate and little agreement. The approach reflected in one way or another in these articles does offer a way forward. For example, if unaffected first-degree relatives of schizophrenia patients carry a proportion of the risk genes, then they should share aspects of both the pathology and the structural brain changes associated with the disorder. Over the next few years, we predict that we will see an increasing

number of papers examining unaffected siblings that will result in a shift in our ideas about the boundaries of the illness.

As noted by Abou-Saleh,² the findings that clinical comorbidity is common and that comorbid disorders share biological substrates offer a new perspective in addition to the fact that even psychiatric disorders such as schizophrenia and BD—traditionally thought of as distinct categories—may well share structural and functional neuroimaging abnormalities. These facts have important consequences; studies comparing individuals with clinically overlapping or comorbid syndromes will undoubtedly lead to changes in ideas about how to define and subtype psychiatric disorders. Hopefully, these findings from neuroimaging will ultimately translate into a reclassification of psychiatric disorders, based on their biological underpinnings rather than on traditional phenomenology, in forthcoming editions of the DSM.

In turn, we will focus on the characteristic pathological and morphological changes correlated with schizophrenia risk genes, both alone and in combination, as well as on the corresponding footprints of normal variation in these genes in the healthy brain. These broad themes are beginning to become more dominant in the scientific literature pertaining to schizophrenia. This is true, not only in the areas reviewed here but also in functional neuroimaging and image fusion, where, for example, structural and functional imaging information can be statistically combined to yield a more complete picture than that obtainable by either method alone.

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Résumé : L'imagerie par résonance magnétique structurelle et fonctionnelle des troubles psychiatriques

Objectif : Rendre compte des récents progrès des études par imagerie cérébrale tant structurelle que fonctionnelle en psychiatrie, et souligner leur importance dans le domaine.

Méthode : Nous avons examiné les articles récemment publiés qui traitent de ces progrès et les avons résumés en une synthèse sélective du domaine.

Résultats : Les tendances les plus importantes comprennent l'intégration de l'information génétique aux études de recherche, l'utilisation de nouvelles techniques de mesure quantitative des images, des études de nouvelles populations de sujets, l'utilisation de sondes pharmacologiques dans les études d'imagerie par résonance magnétique fonctionnelle (IMRF), l'incorporation d'éléments de réalité virtuelle dans les stimuli de tâche de l'IMRF, et l'innovation méthodologique du « hyperscanning ».

Conclusions : Une série complète de nouvelles approches et techniques est issue des progrès rapides de la neuroimagerie en psychiatrie. Plusieurs d'entre elles démontrent un potentiel d'application clinique.