From Bench to Bedside: The Future of Neuroimaging Tools in Diagnosis and Treatment

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Schizophrenia poses a challenge for diagnosis and treatment at least in part because it remains a syndromal diagnosis without clearly understood neuropathological bases or treatments with clearly understood mechanisms of action. Neuroimaging research promises to advance understanding of the unique pathological processes that contribute to this syndrome, and to foster both better appreciation of how current treatments work, and how future treatments should be developed.

Neuroimaging has revolutionized the diagnosis and treatment of brain disorders. It is difficult to imagine treating patients with brain tumors, cerebrovascular disorders or epilepsy without our current arsenal of imaging tools. The confirmation of structural abnormalities in the brains of people with schizophrenia in the 1980s led to excitement that neuroimaging would also lead to novel rational treatments for this syndrome.

Two subsequent decades of neuroimaging research have contributed enormously to our understanding of structural and functional differences between the brains of people with schizophrenia and healthy people. Imaging now offers insights into the mechanisms of action of drugs used to treat schizophrenia, and the genetic mechanisms that may be at the root of these disorders. Still, there is no "smoking gun" that marks pathophysiology, and imaging protocols to optimize treatment are not ready for clinical practice.

On the one hand, it is critical to recognize the current limitations of these methods for clinical practice. On the other hand, it is important for optimism to be sustained and solid research completed to advance these dramatic methods from the "bench" to the "bedside." We attempt to summarize both key challenges and promising leads from current research.

Phantom Syndrome
Schizophrenia's listing in the DSM-IV conveys a sense of authenticity that belies the lack of hard evidence for a unitary disease entity underlying this complex syndrome. It has long been acknowledged that the likely pathophysiological and etiological heterogeneity of schizophrenia pose major challenges to research and treatment. While it is clear that schizophrenia has a 10-fold increased risk among first-degree relatives of affected patients, concordance is only 50% in monozygotic twins. Furthermore, repeated replication failures in genetic linkage and association studies highlight the virtually certain polygenic substrates of the syndrome. Thus, it is illogical that neuroimaging should serve a diagnostic role or guide specific treatment regimens for the phenotype of schizophrenia per se. Instead, imaging tools will hopefully help dissect the contributions of multiple pathophysiological processes that increase vulnerability, and identify patterns of impaired and preserved neural system function.

This brief overview focuses only on selected structural and functional imaging modalities (the latter narrowly defined to encompass activation imaging and molecular imaging). Activation imaging examines brain metabolism, blood flow or blood oxygenation, either at rest or in response to specific cognitive or pharmacological challenges. Molecular imaging examines the uptake and clearance of specific tracers, generally by their binding to key molecules of interest--usually receptors, transporters or other cellular proteins.

We have not considered a diversity of other methods that may hold great promise. There is a unique and still largely untapped potential of magnetic resonance imaging (MRI) and spectroscopy (MRS). So far, MRI has focused largely on proton imaging. Even proton imaging has generally focused on a subset of possible contrast phenomena, leaving unexamined other biophysical properties of brain. Diffusion effects are now being examined, but magnetization transfer studies are rare. There are very few studies of other nuclear species (including sodium and carbon), and great opportunities to expand the use of MRS to study metabolic processes and drug effects (most studies have focused on a limited set of metabolites, often with low resolution, in the proton or phosphorus spectra). We also
do not cover electrophysiological imaging approaches, including electroencephalography (EEG), event-related potentials (ERP) and magnetoencephalography (MEG). Event-related protocol studies have a very strong track record in schizophrenia research. Indeed one of the most consistent findings in people with schizophrenia is an abnormality in a specific ERP (the P300) that is normally generated in response to deviations in repetitive sensory stimulation (Ford, 1999).

**Structural Imaging**

Structural neuroimaging in schizophrenia gained major ground with the advent of non-invasive computerized tomography (CT) scanning in the 1980s. Widespread availability of structural magnetic resonance imaging (sMRI) in the 1990s revolutionized our ability to obtain detailed images of anatomic structure without risks of ionizing radiation. These methods have now revealed a surfet of findings that statistically differentiate people with schizophrenia from unaffected individuals, but no single abnormality has emerged as the necessary and sufficient substrate of the syndrome. Most individual anomalies show substantial overlap between the patient and healthy distributions of values (Davidson and Heinrichs, 2003).  

Well-replicated findings show enlargements of the ventricular system and subarachnoid cerebrospinal fluid spaces and decreases in the volumes of most cortical gray matter regions. The most attention has been given to regions in the frontal lobe, temporal lobe, hippocampal formation, cingulate gyrus, thalamus and cerebellum (Davidson and Heinrichs, 2003). Some have suggested critical deficits in localized regions of interest, such as the superior temporal gyrus (McCarley et al., 1999; Shenton et al., 2001). However, most current hypotheses focus on likely disturbances of broader systems of interconnected regions (e.g., frontolimbic and frontostriatal systems) (Lencz et al., 2001; Meyer-Lindenberg et al., 2002), or deficits affecting cortical gray matter either in a widespread fashion (Pfefferbaum and Marsh, 1995; Pfefferbaum et al., 1990) or within somewhat more circumscribed cyto-architectonic territories (such as the heteromodal association cortices) (Pearlson, 1997).

Some suggest that the normal asymmetries of the brain may be absent in schizophrenia (Bilder et al., 1994). Initial studies of structural anomalies in the brain tended to focus on measuring the volumes of specific regions. Innovations in image analysis (including voxel-based morphometry and continuum mechanical tensor mapping) now permit mapping of structural variation across the entire brain or over the entire surface of structures such as the hippocampal formation. These studies show the pattern of cortical gray matter thickness deficit across the entire brain and that maximal hippocampal volume reductions are observed in the lateral mid-to-anterior regions of this structure, which implicates specific neural systems linking hippocampal and cortical regions (Narr et al., 2005, 2004). One study used automated image analysis methods to identify a combination of abnormalities that enabled a high level of discrimination between schizophrenia and healthy groups (overall classification accuracy was 81%) (Davatzikos et al., 2005). While such methods are not yet useful diagnostically, future diagnosis and treatment may benefit from rapid characterization of similar subtle features.

Given hypotheses that schizophrenia may be characterized by a failure of communication among important brain regions, one relatively new technique--diffusion tensor imaging (DTI)--has received considerable attention. It examines the patterns of water diffusion in tissue. If water is unconstrained, it diffuses randomly in all directions (i.e., isotropic). When diffusion is constrained by cellular structure (as occurs in white matter tracts), the water flow is more directional (anisotropic). While some studies have shown decreased anisotropy consistent with white matter abnormalities, a review highlights inconsistency of results and suggests that this emerging field will benefit from improved reproducibility as the methodology becomes better standardized (Kanaan et al., 2005). It was once thought unlikely that drugs used to treat schizophrenia would affect neuroanatomy on a level that could be seen in vivo, but it is now accepted that treatment can influence the overall volume of brain structures visible with neuroimaging. Chakos and colleagues (1994) showed increased caudate volume with conventional neuroleptic treatment, which was reversed by subsequent clozapine (Clozaril) treatment, findings attributed to the relative potency of these drugs' actions at D₂ dopamine receptors.

More recent work further suggests that other antipsychotic agents may be associated with volume changes in neocortical regions, although the mechanisms underlying this relationship remain unclear (Hopman et al., 2005; Lieberman et al., 2005). Since early CT scan studies, it was hypothesized that patterns of structural brain abnormality might be used to predict treatment response or outcome, and some research supports the general idea that patients with more severe structural pathology are less likely to respond well to treatments. However, application of structural imaging tools to enable more definitive treatment or prognostication remains elusive. Current practice uses imaging
Activation Imaging

Activation imaging is among the hottest growth areas in neuroscience, promoted largely by the increasing availability of MRI equipment capable of measuring blood-oxygen level-dependent contrast, which generally parallels metabolism and blood flow. This is the foundation of functional MRI (fMRI). Initial reports using positron emission tomography (PET) to study cerebral glucose metabolism or blood flow showed hypofrontality (reduced activity in the frontal lobes) either at rest or while patients attempted cognitive tasks. Other fMRI studies support this concept (Winterer and Weinberger, 2004).

A meta-analysis suggested this is the most robust neuroimaging finding distinguishing schizophrenia (Davidson and Heinrichs, 2003). Another meta-analysis of fMRI studies that used a specific working memory paradigm concluded that the pattern of activation abnormalities (including both decreases and increases) across complex networks including frontal lobe and other linked regions, is more informative (Glahn et al., 2005). Complicating these interpretations, some studies show underactivation, while others show overactivation in response to cognitive challenges. The latter findings are often interpreted as revealing inefficiency of the neural systems involved (Winterer and Weinberger, 2004). Future studies will likely employ more sophisticated designs to characterize the dynamic response of frontal lobe and related regions to challenges of varying complexity. This will effectively offer a graded stress test to see how these systems respond to changing demands. Exciting new research combines activation imaging with pharmacological manipulations and/or genetic information. For example, Honey and colleagues (1999) showed normalization of frontoparietal fMRI activation in response to a working memory challenge. Patients with schizophrenia were switched from conventional antipsychotics to risperidone (Risperdal).

Several studies have now shown effects of genetic polymorphisms on the patterns of activation elicited by cognitive challenges, and even complex four-way interactions between diagnosis, cognitive challenge condition, genotype and pharmacological manipulation. For example, a polymorphism in the gene coding for the enzyme catechol-O-methyltransferase (COMT) has a significant effect on the breakdown of dopamine. Patients with schizophrenia who have the form of this gene linked to lower prefrontal dopamine showed greater inefficiency of prefrontal activation response to cognitive challenge, and also altered change in this response when given amphetamine (Mattay et al., 2003).

Another report examined the gene DISC1 (disrupted in schizophrenia 1), which was previously associated with a higher incidence of psychopathology in a family study (Callicott et al., 2005). Overtransmission of a certain polymorphism (Ser704Cys) was associated with reduced gray matter volume, as well as deficits in performance and activation in fMRI experiments. Future imaging studies will characterize patients by their responses to specific cognitive and pharmacological challenges, considering the genetic variations that impact these responses.

Molecular Imaging

While many current hypotheses about the mechanisms of antipsychotic agents are linked to receptor-binding profiles observed in vitro, neuroimaging has been instrumental in advancing knowledge of receptor modulation in vivo. Early versions of the dopamine hypothesis (i.e., that there is excessive transmission of dopamine) were based on the observation that effective antipsychotic agents blocked dopamine D$_2$ receptors. Molecular imaging studies using specific ligands to map dopamine receptor binding and other indices of dopamine metabolism show that the situation is not so simple.

In an excellent review of this literature, Abi-Dargham and Laruelle (2005) concluded that evidence supports a complex pattern of excessive D$_2$ stimulation subcortically and decreased transmission (at D$_1$ receptors) cortically, and suggested that this may be consistent with a primary abnormality in N-Methyl-D-aspartate transmission. Comparisons of first- and second-generation antipsychotics show that reduced extrapyramidal side effects (EPS) can be explained by lower D$_2$ occupancy. However, it is possible that the 5-HT$_2A$ binding of some novel antipsychotic agents, together with D$_2$ blockade, indirectly increase D$_1$ transmission cortically and thereby have beneficial effects. Some PET studies also have examined the therapeutic window for D$_2$ occupancy. There is some consensus that a D$_2$ occupancy of approximately 50% may be necessary to achieve therapeutic efficacy for positive symptoms, while an occupancy greater than 80% may produce EPS (Kapur and Mamo, 2003). While the current expense of PET may rule out its widespread clinical use, this knowledge already has affected research and prescribing practices, so that lower doses of D$_2$-blocking agents are often used. As new ligands are developed and our understanding of the neuropsychopharmacology of
complex frontolimbic and striatal systems matures, there is hope that future prescriptions and dose titration will be decided based on receptor occupancy and pharmacodynamic responses.

**Future Directions**

Structural imaging has provided important clues about a multiplicity of pathophysiological processes that may underlie schizophrenia, and helped the field appreciate the likely neurodevelopmental roots of this complex syndrome. Future work can be expected to clarify the onset and developmental trajectory of these abnormalities by studying individuals at risk for psychosis by virtue of heredity or behavior, and perhaps foster clearer subtyping and better prognostication (Cannon, 2005). The functional and molecular imaging tools are rapidly changing our concepts of treatment, both at the level of receptor binding and more complex neural systems engagement during cognitive stress tests. We remain optimistic that realizing this vision is not a matter of if but when.

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