SECTION

Emerging Imaging Technologies and Their Application to Psychiatric Research

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In a series of chapters on advances in neuroimaging techniques, it is ironic that images per se of the brain's structures or of neural activity have actually diminished in importance since publication of the American College of Neuropsychopharmacology's Fourth Generation of Progress. The focus of neuroimaging in cognitive neuroscience and psychiatry is widening beyond initial questions of where normal and pathologic functions are localized in the brain, to begin to include questions of how cognitive operations are carried out and why they sometimes fail. For these more mechanistic questions, images become simply measurements for testing hypotheses and are not an end in themselves.

Structural imaging of the brain with magnetic resonance imaging (MRI) is a good example of a field that is no longer restricted to simple localization of pathology in psychiatric disease. Indeed, there are few psychiatric cases that are characterized by clear pathology that is visible in MRI pictures. By contrast, the new analytic approaches to measuring the size of structures in MRI images described by Evans in this section allow one to track small changes in structures over time, which can potentially reveal abnormal patterns of development in either gray or white matter. Recently, for example, these techniques have been used to track the distribution of gray and white matter during development in childonset schizophrenia, which is characterized by an abnormal time course of gray matter reductions in several different

brain systems. These abnormal trajectories suggest possible concomitant abnormalities in synaptic pruning, which is known to take place throughout development. New diffusion-tensor imaging techniques in MRI, described by Makris et al. in this section, add the ability to track major fiber bundles in the white matter, which can give some insight into cortical connectivity. Makris et al. discuss the current limitations with this technique, including the difficulty in following fiber bundles to their termination.

Another evolutionary change in neuroimaging has been the continued shift from positron emission tomography (PET) to MRI-based techniques for indirect measurement of neural activity. However, as described by Fujita and Innis, PET and single photon emission computed tomography (SPECT) remain the only viable techniques for studying ligand binding in the brain, and the resolution of PET is continuing to increase as new detectors are developed. Fujita and Innis review the status of radiotracer development in PET and SPECT and describe new tracers for measuring postreceptor signal transduction and even gene expression. Another relatively new approach to mapping the distribution and concentration of specific molecules in the brain is magnetic resonance spectroscopy (MRS), described by Rothman et al. in this section. The focus of this chapter is on measurements of metabolites involved in neuroenergetics and amino acid neurotransmission, especially the flux through glutamate/glutamine and y-aminobutyric acid (GABA)/glutamine cycles during neural activity. GABA metabolism, in particular, appears to be sensitive to both psychiatric disorders, such as depression, and to pharmacologic treatment.

Some of the biggest advances in functional MRI (fMRI) methodology for the indirect measurement of neural activity have been in the time domain. Bandettini describes new methods for improving the temporal resolution of fMRI, in particular event-related designs. In more traditional blocked-trial designs, the BOLD signal is averaged for many seconds, typically for several trials of a behavioral task. However, with event-related designs, one can measure BOLD changes for events lasting less than 2 seconds, which allows one to distinguish activity changes in one part of a trial from another, e.g., from the encoding to the retrieval phase of a trial in a memory task.

The specific application of both fMRI and brain-lesion analyses to studies of mood and emotion is the focus of the chapter by Davidson. The brain systems important for the regulation and expression of mood and emotion are highly distributed, and thus it is essential to take a systems approach to imaging and lesion data in this field, rather than a "function per brain structure" approach. Davidson also describes how basic behavioral research lays the necessary groundwork for studying mood and anxiety disorders, and he gives specific examples of basic research into fear and anxiety and its implications for understanding disorders such as social phobia.

Despite improvements in the temporal resolution of fMRI, the technique will never approach the temporal resolution of event-related potential (ERP) methods, which is at the millisecond level. As described by Hillyard and Kutas, new analytic techniques have improved the spatial resolution of ERPs, and there has been considerable progress in combining the spatial resolution of fMRI with the temporal resolution of ERPs. Perhaps even more important than these technologic advances, there have been conceptual advances in understanding the functional components of ERP signals

through the application of cognitive theory to ERP paradigms. For example, there are characteristic signals found in visual tasks for the arrival of visual information in a cortical region, for the modulation of this signal by attention, and for the decoding of the visual information into semantic information. With the appropriate task design and with the large base of information acquired on the timing of these cognitive operations in normal subjects, one can then begin to ask how these operations differ in schizophrenia, for example.

Finally, the techniques described in the chapters in this section allow one to create and test models of the functional interactions between different brain structures, but they provide no direct evidence of functional connectivity. One new, direct approach to functional connectivity is an analytic technique known as effective connectivity mapping, described by Büchel and Friston. Here, one makes use of the moment-to-moment relationships between fMRI signals in different brain regions to create structural equations, which can quantify the contribution of activity in one brain structure to the activity in another. An even more direct approach to measuring connectivity is through the combined use of transcranial magnetic stimulation (TMS) and fMRI, described by George and Bohning. They describe studies in which brain structures are directly stimulated with TMS, and the resulting effects on far-removed brain structures, including in the opposite hemisphere, are measured using

The chapters in this section describe an impressive armamentarium of techniques now available to brain imaging researchers, and they outline some promising new directions in the application of these techniques to mental illness. Together, the chapters show that the key to progess in brain imaging studies of pathophysiology will be to see beyond the images.