Brain Imaging Studies of Schizophrenia

- Recent Advances in the Neurobiology of Schizophrenia

Neuroimaging techniques have revolutionized the study of schizophrenia. Findings dating from the 1970s have demonstrated that there are clear brain structural abnormalities associated with the condition (97). Structural studies performed on the postmortem brains of schizophrenics reveal many areas to be abnormal, the most robust findings being ventricular enlargement and loss of temporal lobe gray matter, although the disordered lives of the patients may admittedly involve extensive medication and dietary abnormalities that may themselves alter brain anatomy [for review, see (98, 99)]. A number of other changes have also been reported, but with less consistency.

Recent MRI research has identified brain characteristics associated with the early stages of psychosis. At first-episode psychosis, patients already show a range of structural brain changes, including deficits in temporal lobe (i.e., gray matter, superior temporal gyrus, and hippocampus), reduced whole brain volume, reduced prefrontal cortical gray matter volume, significant enlargement of lateral and third ventricles, and reduced thalamic volume [sensory – Paranoid Schizophrenia malfunction of the sensory gating] (100–103). Because these abnormalities exist early in the illness, they cannot arise from artifacts due to medication, trauma, or diet. Structural or functional defects of the thalamus, because it is associated with filtering sensory information and gating mechanisms, may be particularly important in the pathogenesis of schizophrenia; indeed, problems of information filtering may underlie disturbed thought processes (102, 104). Although some PET studies suggest low activity levels in the thalamus of schizophrenic subjects [CATATONIC](105–109), other data suggest elevated activity in schizophrenic [PS – PSYCHOSIS] (110). In patients with first-episode schizophrenia, volume reduction of the superior temporal gyrus, including...
bilateral Heschl’s gyrus gray matter and left planum temporale gray matter, may provide an anatomical basis for the pathophysiological mechanisms that give rise to deficits in language and thought processing in schizophrenia (100).

A recent series of MRI studies has generated enthusiasm for a “neurodegenerative hypothesis of schizophrenia” that posits that there may be destruction of neural tissue associated with psychosis (78, 86, 111, 112). Supporting this position, a recent controlled longitudinal MRI study of chronic schizophrenia demonstrated accelerated frontotemporal cortical volume decline (83). Interestingly, greater clinical severity was associated with faster rates of the brain volume changes. It is, however, hard to imagine how the magnitude and duration of changes observed in MRI studies of schizophrenia could be occurring as a neurodegenerative process, whether by cell necrosis or apoptosis, without observable evidence of neuronal loss and other related changes in postmortem tissue (113).

Studies using fMRI have identified neural structures associated with observed cognitive problems, and show cortical responses in relation to psychopathological aspects of schizophrenia. Specifically, fMRI analysis of working memory tasks (e.g., two-back or continuous performance test) reveals reduced activity in frontal areas of the brain such as the dorsolateral prefrontal cortex (114, 115) and the anterior cingulate cortex (116, 117). Some fMRI studies also suggest that auditory hallucinatory states are associated with activation in the inferior and frontal insular, anterior cingulate, bilateral temporal cortex (with greater responses on the right), right thalamus, inferior colliculus, left hippocampus, and parahippocampal cortex (118, 119). Silbersweig and colleagues (120), using PET, reported similar results.

Magnetic resonance spectroscopy (MRS) has been increasingly used to measure in vivo metabolite levels in particular regions of the brain in schizophrenia, although it has less spatial resolution [for review, see (121–123)]. The results of $^{31}$P-MRS suggest decreased synthesis and increased degradation of membrane phospholipids in prefrontal cortical regions and medial temporal lobe structures at certain phases of schizophrenia. Some, but not all, $^1$H-MRS studies also indicate a decrease in neuronal cell mass in the hippocampal region and the frontal lobes, which supports direct volumetric studies. In addition, $^1$H-MRS studies of schizophrenics show increased levels of glutamine and glutamate
in frontal lobe voxels, which are associated with illness duration and reduced by atypical antipsychotic drug treatment (115).

Developing Novel Antipsychotic Drugs

Neurodevelopmental Hypothesis of Schizophrenia