Serious and chronic childhood psychiatric disorders have long been assumed to reflect relatively subtle abnormalities of brain development. Although diagnostic brain imaging is well established in pediatric neurology, it has not yet permitted quantitative assessment of brain abnormalities in children with psychiatric illnesses. Recent advances in brain magnetic resonance imaging (MRI) allow reliable, automated, quantitative measurement of multiple brain regions. The noninvasive nature of MRI also allows periodic rescanning for research purposes, making prospective longitudinal study of brain development feasible in large numbers of healthy children and those with psychiatric illness. Longitudinal MRI of the brain also makes possible the mapping of region-specific changes in brain volume over time.

Large, prospective MRI studies of the brains of hyperactive, psychotic, and, perhaps most important, healthy children and adolescents aged 4 to 18 years have been undertaken at the National Institute of Mental Health, Bethesda, Md, since 1990. These studies have allowed unprecedented understanding of healthy and abnormal brain development during childhood and adolescence, with several novel and important findings. For example, we now understand that during the first 2 decades of life, a remarkable regional heterogeneity in normal brain cortical development occurs. Unexpectedly, the corpus callosum matures in a back-to-front manner during this same period. Results of ongoing studies of healthy identical and fraternal twin pairs showed, for the first time, interesting patterns of heritability. Using automated volume measurements from monozygotic and dizygotic twins, it is possible to calculate heritability indices for individual brain regions. As expected, volume measurements of most brain regions are more highly correlated for monozygotic than for dizygotic twins. However, unlike most of the other volumetric measures, the volumes of cerebellar hemispheres are not more correlated for monozygotic than for dizygotic twins. This finding indicates a low level of heritability for this structure (J.G., unpublished data, May 2002).

Small sample size ($N<20$) and lack of standardized methods have limited anatomical and brain MRI studies of attention-deficit/hyperactivity disorder (ADHD). In the 2 largest studies that included 57 boys and 50 girls with ADHD and 105 matched control subjects, the boys and girls with ADHD were found to have smaller overall brain size, abnormalities of the caudate nucleus (eg, lack of normal asymmetry, decreased right-sided caudate volume), and decreased volume of the posterior inferior cerebellar vermis. This subtle and global (equal for gray and white matter) nonprogressive reduction in brain volume seen in ADHD is in marked contrast to the region-specific progressive cortical gray matter loss seen in parietal, frontal, and temporal regions in childhood-onset schizophrenia (COS) (Figure 1).

Imaging studies of subjects with COS show continuity with adult subjects with respect to the abnormalities of smaller brain and enlarged lateral ventricles. Most longitudinal imaging studies in adult subjects with schizophrenia find slight or no loss of gray matter. In contrast, longitudinal volumetric MRI measurements obtained during adolescence in subjects with COS ($n=46$) and...
in matched healthy controls show striking progressive loss of cortical gray matter spanning the parietal, frontal, and temporal regions. The loss of gray matter slows as the children reach adult age. Furthermore, a recent study of 12 adolescent patients with COS who underwent MRI 3 times in 5 years shows a unique "wave" of back-to-front tissue loss. The early parietal gray matter loss was followed by frontal and temporal gray matter loss later in adolescence. Use of a medication-matched nonpsychotic control group ruled out drug treatment as a cause of loss of brain volume.

**METHODS**

Magnetic resonance images consist of volume elements, or voxels, each of which is assigned a certain number based on the magnetic characteristics of the tissue within the voxel. A typical MRI will contain approximately 8 million 1-mm³ voxels. The goal of image analysis is to classify each voxel as gray or white matter or cerebrospinal fluid and to determine to which brain structure or region the voxel belongs. Tissue types are then classified based on voxel intensity, using artificial neural networks. This classification is then combined with a probabilistic brain atlas to determine the structure or region to which the classified voxel belongs. The most advanced automated image analysis methods use this technique to measure regional gray and white matter volumes. Longitudinal rescans then make it possible to assess brain volumetric changes over time. Although such automated measures carry a distinct advantage of unbiased measurements of brain volume, the "gold standard" for the quantification of many small structures such as the globus pallidus, hippocampus, amygdala, and thalamus remains hand tracing by experts. A new technique has been designed recently to map regional cortical volume while retaining anatomical landmarks. In this technique, 3-dimensional distribution of gray matter in the brain is computed and then compared from one scan to the next. The method uses a computational cortical pattern–matching strategy that aligns corresponding landmarks on the cortical surface across time and subjects. This permits mapping of region-specific brain cortical development across time and between subject groups with far greater spatial reso-

![Figure 1. Longitudinal studies of normal and abnormal brain development reveal disease-specific patterns. ADHD indicates attention-deficit/hyperactivity disorder; COS, childhood-onset schizophrenia.](image)
RATIONALE AND DIAGNOSTIC SENSITIVITY THAN PREVIOUSLY POSSIBLE (FIGURE 2).

RELEVANCE TO THE PRACTICE OF NEUROLOGY

Despite statistically significant group differences in the size of various brain structures in healthy and affected children, MRI is not yet of diagnostic value in any of the major childhood-onset psychiatric disorders. However, with the acquisition of larger sample populations, it may become possible to establish standard curves of healthy and disease-specific regional brain maturation and volumetric changes. These developments could hold significant potential for clinical application. For instance, region-specific patterns of loss of brain tissue in COS may identify groups at high risk for schizophrenia and may provide useful diagnostic information for difficult clinical manifestations. Furthermore, these findings could ultimately be used as new targets for determining development and effectiveness of drug therapy. Similarly, global reduction in brain volume in ADHD may predict treatment course or follow-up outcome. Thus, more subtle profiles of brain development may be incorporated as part of a clinical examination. At present, the abnormalities presented herein have only potential relevance to the practice of neurology, and there is no indication for routine brain MRI in childhood neuropsychiatric disorders. With the likelihood of increased homogeneity of methods across centers, there may be a place for clinical use of anatomical brain MRI measurements within the next decade.

RELEVANCE TO THE STUDY OF NEUROSCIENCE

Although there are no immediate clinical implications of these findings, their usefulness for the understanding of normal brain development and disease pathophysiology is great. Longitudinally acquired scans during the critical period of brain development provide clues to the underlying disease mechanism. For instance, we now know that regional structural modulations probably reflective of synaptic and dendritic remodeling are ongoing in the brain throughout adolescence. The shape of the developmental curves seen in children with ADHD almost parallels normal brain development (Figure 1), indicating a fixed and probably early developmental abnormality. The anatomical MRI studies and symptom and neuropsychological test profiles support the postulated dysfunction of cerebellar-striatal-prefrontal circuitry in ADHD. On the other hand, the progressive and region-specific nature of gray matter loss in COS shows this to be, in part, a late neurodevelopmental disorder. We speculate that the earlier tissue loss seen might trigger the onset of psychosis. Thus, these 2 illnesses of childhood appear to involve different developmental trajectories. With the advent of sophisticated brain-mapping techniques, it is now possible to map the progressive tissue loss in a region-specific...
This development could allow correlation of the clinical symptoms, and pathophysiology of the illness with localized structural alterations. Thus, early parietotemporal gray matter loss in COS could partially explain the premorbid speech and language deficits seen in these children. Similarly, regional tissue loss in COS can be examined in relation to heritability patterns. For example, young unaffected siblings of COS probands appear to share the parietal gray matter volume reduction. This finding strongly suggests a genetic vulnerability to this complex illness (N.G., unpublished data, May 2002). Postmortem studies show regional heterochronicity in synaptic pruning during childhood and adolescence, and schizophrenia is postulated to be a disorder of “overpruning,” in which loss of neuropil is seen without any neuronal loss. This hypothesis is supported by the imaging findings of regional and progressive loss of gray matter seen in schizophrenia without any white matter changes. The finding is compatible with the results of molecular studies of schizophrenia in adults. For example, a recent study using postmortem tissue and gene microarrays found reduced expression of transcripts associated with the regulation of presynaptic function in the prefrontal cortex in schizophrenia. Alterations in 2 of the most consistently abnormal transcripts in this gene group, N-ethylmaleimide-sensitive factor and synapsin II, could lead to altered synapse formation, pruning, or both and may ultimately lead to loss of neuropil and gray matter volume. Thus, the MRI abnormalities may provide clues to candidate mechanisms of this illness.

Advances in brain MRI thus have the potential to supplement preclinical and postmortem data on healthy and abnormal brain development. Detailed understanding of healthy brain development for the first time can permit meaningful MRI measurement, which can ultimately help early diagnosis in childhood neuropsychiatric disorders.

Accepted for publication January 8, 2002.

Author contributions: Study concept and design (Drs Gogtay, Giedd, and Rapoport); acquisition of data (Dr Rapoport); analysis and interpretation of data (Drs Gogtay, Giedd, and Rapoport); drafting of the manuscript (Drs Gogtay, Giedd, and Rapoport); critical revision of the manuscript for important intellectual content (Drs Gogtay, Giedd, and Rapoport); obtained funding (Dr Rapoport); administrative, technical, and material support (Dr Rapoport); and study supervision (Dr Rapoport).

Further information about automated imaging methods can be obtained from Alan Evans, PhD, at the Montreal Neurobiological Institute (email: alan@pet.mni.mcgill.ca) and from Collins et al and Thompson et al.

Figure 3. INSECT (Intensity-Normalized Stereotaxic Environment for Classification of Tissue) is an automated program for classifying each voxel of brain magnetic resonance imaging (MRI) into gray or white matter or cerebrospinal fluid based on the intensity of the voxel. ANIMAL (Automatic Nonlinear Image Matching and Anatomical Labeling) is also an automated approach that labels a voxel’s location in space based on prior anatomical knowledge. The Montreal Neurobiological Institute program is unique in that it combines the 2 techniques. This allows for an automated voxel intensity and anatomically informed classification of the brain tissue.
Corresponding author and reprints: Judith L. Rapoport, MD, Child Psychiatry Branch, National Institute of Mental Health, National Institutes of Health, Bldg 10, Room 3N202, 10 Center Dr, MSC 1600, Bethesda, MD 20892-1600 (e-mail: rapoport@helix.nih.gov).

REFERENCES


Call for Papers

ARCHIVES Express

The ARCHIVES launched a new ARCHIVES Express section in the September 2000 issue. This section will enable the editors to publish highly selected papers within approximately 2 months of acceptance. We will consider only the most significant research, the top 1% of accepted papers, on new important insights into the pathogenesis of disease, brain function, and therapy. We encourage authors to send their most exceptional clinical or basic research, designating in the cover letter a request for expedited ARCHIVES Express review. We look forward to publishing your important new research in this accelerated manner.

Roger N. Rosenberg, MD
Editor