

Anatomical MRI of the Developing Human Brain: What Have We Learned?

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ABSTRACT

Objective: To critically review and integrate the existing literature on magnetic resonance imaging (MRI) studies of the normally developing brain in childhood and adolescence and discuss the implications for clinical MRI studies. **Method:** Changes in regional brain volume with age and differences between the sexes are summarized from reports in refereed journal articles pertaining to MRI of the developing human brain. **Results:** White matter volume increases with age. Gray matter volumes increase during childhood and then decrease before adulthood. On average, boys have larger brains than girls; after correction for overall brain volume the caudate is relatively larger in girls, and the amygdala is relatively larger in boys. Differences are of clinical interest given gender-related differences in the age of onset, symptomatology, and prevalence noted for nearly all childhood-onset psychiatric disorders. Attention-deficit/hyperactivity disorder is frequently used as an example to demonstrate these points. **Conclusions:** Understanding the developmental trajectories of normal brain development and differences between the sexes is important for the interpretation of clinical imaging studies. *J. Am. Acad. Child Adolesc. Psychiatry*, 2001, 40(9):1012–1020. **Key Words:** brain, development, magnetic resonance imaging, review.

Advances in neuroimaging techniques have opened unprecedented access to the developing human brain. Magnetic resonance imaging (MRI) is particularly well suited to the study of children as it provides exquisitely accurate anatomical images without the use of ionizing radiation. This permits not only scanning of children, but also repeated scanning of the same individual over time. This allows us to explore the relationship between the significant leaps in motor, cognitive, and social learning that take place during childhood and adolescence (Dawson and Fischer, 1994) and the functional maturation of the neural networks that subserve these functions. Although the field of pediatric neuroimaging is in its infancy, a number of studies have been con-

ducted to map the anatomical course of normal pediatric brain development. To our knowledge this is the first review of these normative studies.

This article complements several recent reviews of clinical neuroimaging studies, including those by Eliez and Reiss (2000) and Hendren et al. (2000). Those reviews provide an overview of imaging methods and studies of attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, Tourette's syndrome, childhood-onset schizophrenia, childhood depression, autism, and anorexia nervosa, reporting abnormalities in size or symmetry of brain regions relative to matched controls. The clinical relevance of differences in volume between groups is most obvious when the normal developmental trajectories have been charted (Giedd et al., 1996a). For example, Castellanos et al. (1996) demonstrated a loss of normal age-related decrease in volume and normal asymmetry of the caudate nucleus in ADHD, as well as volume loss in right striatal and anterior frontal areas, indicating a deviation from normal development of right frontostriatal systems in ADHD. Thus the characterization of normal brain development during a period when a number of developmental disorders emerge is important for our understanding of the underlying mechanisms and possible etiology of these disorders.

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The current review discusses MRI studies of the normally developing brain in the context of interpreting clinical studies. We underscore the importance of relating changes in brain morphometry to specific behaviors and symptomatology in neuropsychiatric disorders. Changes in regional brain volume with age and differences between the sexes are discussed. These differences are important to consider in relation to the differences in age of onset, symptomatology, and prevalence observed between the sexes for nearly all neuropsychiatric disorders. Thus gender- and timing-specific aspects of development may prove important in understanding the neural basis of

these disorders. This review covers the most reliable findings reported to date and raises questions regarding the reliability and validity of measures, sample selection biases, lack of longitudinal data, and lack of behavioral correlates, all issues that should be considered in relation to the interpretation of clinical imaging studies.

METHOD

The articles summarized were retrieved through *Medline* and included healthy subjects younger than 18 years of age (Table 1). *Healthy* is defined as either normal volunteers or, in some cases, non-psychiatric patients. Twenty-two articles were included. Fifteen nor-

TABLE 1
Studies of Normal Development

Study	Structures	Age ^a	No. ^b	Screening ^c
Courchesne et al., 2000	Total brain, gray matter, white matter	1-12, 12-80	50, 66	Screened
Gilbert et al., 2000	Intracranial volume, thalamus	8-17	21	Screened
Thompson et al., 2000	Total brain, corpus callosum, ventricles, caudate	3-15	6	Screened
Giedd et al., 1999 ^a	Total brain, white matter, gray matter	4-20	145	Screened
Giedd et al., 1999 ^b	Total brain, corpus callosum	4-18	139	Screened
Paus et al., 1999	White matter tracts	4-17	111	Screened
Pfuger et al. (total brain), 1999 ^d	Total brain, hippocampus	0-15	50	Selected scans
Sowell et al., 1999	Total brain, gray matter, white matter, CSF	7-10, 12-16	9, 9	Screened
Szabo et al., 1999 ^d	Hippocampus	1-7	11	Selected scans
Utsunomiya et al., 1999 ^d	Hippocampus, temporal lobe	0-14	42	Selected scans
Filipek et al., 1997	Total brain, white matter, lateral ventricles, caudate, hippocampus, amygdala	8-19	15	Screened
Giedd, 1997	Total brain, lateral ventricles, corpus callosum, caudate, putamen, globus pallidus, amygdala, hippocampus, temporal lobe	4-18	129	Screened
Giedd et al., 1997	Total brain, lateral ventricles, corpus callosum, caudate, putamen, globus pallidus, amygdala, hippocampus, temporal lobe	4-18	121	Screened
Caviness et al., 1996	Total brain, cerebellum, ventricular system, white matter, caudate, putamen, pallidum, hippocampus, amygdala	7-11, 17-33	30, 20	Screened
Giedd et al., 1996 ^a	Total brain, corpus callosum	4-18	114	Screened
Giedd et al., 1996 ^b	Total brain, cerebellum, lateral ventricles, caudate, putamen, globus pallidus	4-18	104	Screened
Giedd et al., 1996 ^c	Total brain, amygdala, hippocampus, temporal lobe	4-18	99	Screened
Reiss et al., 1996 ^d	Total brain, gray matter, white matter, caudate, CSF	5-17	85	Screened
Pfefferbaum et al., 1994 ^d	Gray matter, white matter, CSF	0-30	88	Selected scans
Rauch and Jinkins, 1994 ^d	Corpus callosum	0-19, 20-87	45, 117	Selected scans
Pujol et al., 1993 ^d	Corpus callosum	11-61	90	Selected scans
Allen et al., 1991 ^d	Corpus callosum	2-15, 16-80	24, 122	Selected scans
Jernigan et al., 1991 ^d	Gray matter, white matter, caudate, CSF	8-20, 21-35	23, 16	Screened
Jernigan and Tallal, 1990 ^d	Gray matter, white matter, caudate, CSF	8-10, 25-39	15, 9	Screened
Schaefer et al., 1990 ^d	Corpus callosum	0-20	95	Selected scans

Note: CSF = cerebrospinal fluid.

^a Ages of subjects included in the study (in years).

^b Number of subjects included. If the subjects were split into groups by age, the numbers in this column refer to each age group in the previous column.

^c Subjects were either screened before inclusion (screened), or magnetic resonance imaging scans that had been read as normal were included in the study (selected scans).

^d Slice thickness >3.0 mm.

mative articles were excluded as they reported qualitative or area measures rather than quantitative or volumetric measures. The only exception was studies of the corpus callosum, as all relied on area measures. Thirty-five articles about childhood disorders were also reviewed. Three of these were included, as they reported their results for control subjects but had not published them separately. Measurements were based on T₁-weighted scans with slice thickness of between 1.5 mm and 7.5 mm. Several papers report data for an overlapping group of subjects (e.g., Giedd, 1997; Giedd et al., 1999a,b, 1997, 1996a-c; Paus et al., 1999; Thompson et al., 2000).

Findings are summarized in Tables 2 and 3. Differences are discussed in terms of change in regional brain volume with age and differences between the sexes. Where possible, estimates of percent difference in volume are given. Percentages are based on data provided or were estimated from graphs and regression lines given in the original reports. Differences associated with age are always between the youngest and oldest in the sample. Cerebrum, excluding the cerebellum, is often used instead of total brain volume. Some reports included cerebrospinal fluid in these measures.

RESULTS

Developmental Changes

Consistent with postmortem studies (Kretschmann et al., 1986), total brain size does not increase significantly after age 5. This relative stability of total brain volume belies a dynamic interplay of simultaneously occurring progressive and regressive events, with different regions following different time courses.

White matter volume increases significantly during childhood and into adulthood. This is probably related to ongoing myelination of axons by oligodendrocytes, following a pattern throughout the brain of inferior to superior and posterior to anterior (Yakovlev and Lecours, 1967). Reiss et al. (1996) showed the largest increase in the prefrontal region in their sample of 5–17 year olds. Much myelination occurs before birth (Grodd, 1993; Hansen et al., 1993; Wang et al., 1998) and during the first 2 years (Barkovich et al., 1988; Grodd, 1993; Holland et al., 1986; Lan et al., 2000; Martin et al., 1988; Nakagawa et al., 1998; Van der Knaap et al., 1991), but it continues throughout life (Yakovlev and Lecours, 1967). The largest white matter tract, the corpus callosum, continues to increase in size, probably because of ongoing myelination. Contrary to the typical pattern of caudal to rostral development, anterior regions, which have been related to primary sensory and motor functions, mature earlier, whereas the posterior corpus callosum areas do not mature until adolescence (Giedd et al., 1999b; Thompson et al., 2000). One explanation may be that these measurements are based on area measurement in a single midsagittal slice rather than volumetric measurements and are therefore more prone to error.

In contrast to white matter, cortical gray matter generally exhibits a net decrease in volume across this age span. Longitudinal studies suggest a childhood increase in gray matter volumes followed by a decrease before adulthood (Giedd et al., 1999a). This decrease may be due to the ongoing process of pruning and cell death among both neurons and glial cells. Most of the neuronal proliferation and selective cell death takes place in utero (Rabinowicz, 1986), although it continues during childhood and puberty (Jacobson, 1991). Neuronal cell death is thought to influence that of glial cells (Jacobson, 1991), and this may contribute to the decrease in tissue volume. As this effect is widespread, it could, in part, explain the nonspecific increase in the volume of the lateral ventricles.

Subcortical gray matter shows a similar pattern to cortical gray matter. The basal ganglia typically decrease in volume with age. Thompson et al. (2000) recently suggested that, for the caudate, most of the tissue loss takes place in the head of this structure. They used an elastic deformation algorithm to calculate the difference in surface of structures from two longitudinal scans from the same subject, and then calculated a tensor map, representing the direction and rate of growth from the volumetric deformation. In contrast to the basal ganglia, the temporal lobe structures (amygdala and hippocampus) appear to increase in volume with age. This difference is interesting from a clinical perspective, as neuropsychiatric disorders that are thought to involve the basal ganglia have an earlier age of onset (e.g., ADHD and Tourette's syndrome) than disorders involving temporal lobe structures (e.g., schizophrenia and depression) (Eliez and Reiss, 2000; Hendren et al., 2000).

Sex Differences

On average, the male brain is 10% larger than the female brain (Table 3). Most structures in the brain display this 10% difference; however, the caudate, and possibly globus pallidus and hippocampus, are disproportionately larger in female brains, whereas the amygdala is disproportionately smaller. It is tempting to hypothesize that these differences may be mediated by sex hormones. This notion is supported by primate studies that show that the amygdala contains predominantly androgen receptors, whereas the hippocampus contains predominantly estrogen receptors (Clark et al., 1988; Morse et al., 1986; Sholl and Kim, 1989). However, other factors, such as X- or Y-chromosome effects and environmental influence, could all play a role in sex-related differences in the brain.

TABLE 2
Developmental Changes

	Change With Age	Difference ^a	Age ^b	No. ^c	References
Total brain	—	25%	7–11	30	Caviness et al., 1996
	↑		1–15	50	Courchesne et al., 2000
	—		4–18	129	Giedd, 1997
					114, 104, 99, 121
White matter			8–39	24	Jernigan and Tallal, 1990
			8–35	39	Jernigan et al., 1991
	↑	117%	0–15	27	For males (Pfluger et al., 1999)
		71%	0–15	23	For females (Pfluger et al., 1999)
	—		5–17	85	Reiss et al., 1996
	↑	16%	7–33	30	Caviness et al., 1996
		74%	1–15	50	Courchesne et al., 2000
		12%	4–22	145	Giedd et al., 1999a
			8–39	24	Jernigan and Tallal, 1990
			8–35	39	Jernigan et al., 1991
Cortical gray matter		71%	0–30	88	Pfefferbaum et al., 1994
	↑ ^d	16%	5–17	85	Reiss et al., 1996
	↑	13%	1–9	116	Courchesne et al., 2000
	↓	28%	9–80		
	↑preadolescent ↓postadolescent		4–20	145	Giedd et al., 1999a (except occipital)
	↓ ^d		8–39	24	Jernigan and Tallal, 1990
			8–35	39	In superior areas (Jernigan et al., 1991)
	↑	13%	0–4	88	Pfefferbaum et al., 1994
	↓	32%	4–30		
	↓ ^d	23%	5–17	85	Reiss et al., 1996
Total CSF			7–10	9	In parietal & frontal areas (Sowell et al., 1999)
			3–15	6	Thompson et al., 2000
	↑	160%	1–55	116	Courchesne et al., 2000
	↑	152%	4–18	79	For males (Giedd, 1997)
Lateral ventricles		74%	4–18	79	For females (Giedd, 1997)
		144%	4–18	55	For males only (Giedd et al., 1996b)
		63%	4–18	71	For males only (Giedd et al., 1997)
			8–35	39	Jernigan et al., 1991
Ventricular CSF	↑		8–39	24	Jernigan and Tallal, 1990
				39	Jernigan et al., 1991
Nonventricular CSF	—		0–30	88	Pfefferbaum et al., 1994
	—		0–30	88	Pfefferbaum et al., 1994
Corpus callosum	↑	7%	5–17	85	Reiss et al., 1996
	↑	51%	2–15	24	Allen et al., 1991
			4–18	129	Giedd, 1997
		31%	4–18	114	Giedd et al., 1996a
			4–18	121	Giedd et al., 1997
		20%	4–18	145	Giedd et al., 1999a
		11%	11–19	14	Pujol et al., 1993
		247%	0–9	29	Rauch and Jinkins, 1994
		18%	10–19	16	
		33%	0–20	95	Schaefer et al., 1990
Caudate	↑ ^e		0–20	95	Schaefer et al., 1990
	↓	15%	4–18	55	For males only (Giedd et al., 1996b)
	↓ ^d		8–35	39	Jernigan et al., 1991
Putamen	↓		3–15	6	Thompson et al., 2000
	↓	9%	4–18	55	For males only (Giedd et al., 1996b)
	↓		4–18	71	For males, on left only (Giedd et al., 1997)
Globus pallidus	↓		4–18	104	Giedd et al., 1996b
	↓		4–18	79	For males only (Giedd, 1997)
Amygdala	—	53%	4–18	53	For males, on left only (Giedd et al., 1996c)
	↑	45%	4–18	53	For males only (Giedd et al., 1997)
			4–18	71	For males only (Giedd et al., 1997)

— Continued

TABLE 2
(Continued)

	Change With Age	Difference ^a	Age ^b	No. ^c	References
Hippocampus	↑	12%	4–18	50	For females only (Giedd, 1997)
		20%	4–18	46	For females, on right only (Giedd et al., 1996c)
			4–18	121	Giedd et al., 1997
		100%	0–15	50	Pfluger et al., 1999
			1–7	11	Szabo et al., 1999
Temporal lobe	—		0–14	42	Utsunomiya et al., 1999
			4–18	99	Giedd et al., 1996c
			0–14	42	Utsunomiya et al., 1999
Cerebellum	—		4–18	104	Giedd et al., 1996b
			8–39	24	Jernigan and Tallal, 1990

Note: CSF = cerebrospinal fluid; ↑ = increase; ↓ = decrease; — = no change.

^a Estimated difference is based on the youngest age compared with the oldest in the sample.

^b Ages of subjects included in the study (in years).

^c Number of subjects included.

^d Corrected for total brain volume.

^e Corrected for intracranial area.

(Jacobson, 1991). Clinically, it is interesting that the caudate nucleus is relatively larger in female brains, as this nucleus is implicated in ADHD and Tourette's syndrome, which are more common in males (Castellanos et al., 1996). Conversely, the amygdala is relatively smaller and has been implicated in affective disorders, such as depression and anxiety disorders, which are more common in females (Drevets, 2000).

DISCUSSION

While the reviewed reports describe an increase in brain volume over the first few years, significant decreases in regional volumes and overall stability in brain size are shown to occur during later childhood and adolescence, contrary to general misconceptions of brain growth over this period. Regional changes in brain volume throughout childhood and adolescence are relevant in relation to landmarks in behavioral development and the emergence of clinical disorders over this age period.

Relevance to Behavior

By linking emerging knowledge of anatomical development to behavioral changes in the child, we may learn more about the functional organization of the brain, its development and disruption in developmental disorders. For example, the basal ganglia have a number of projections to and from the frontal cortex and both brain regions mature relatively late (Sowell et al., 2000), presumably reflecting the development of cognitively driven actions throughout adolescence. However, few studies

have linked these changes in brain development to behavior. An exception is a study by Casey et al. (1997a) that showed correlations between performance on measures of response inhibition and volumetric measures of the prefrontal cortex and basal ganglia in healthy children, that was not present or reversed, in children with ADHD. In another study of healthy children between 6 and 18 years (Casey et al., 1997b), a correlation was found between the size of the anterior cingulate gyrus—a structure that is thought to be critical in executing control—and the speed with which subjects switched attentional set. This correlation remained significant, even after controlling for age, IQ, and cerebral volume, making this study one of the first to demonstrate MRI-based anatomical correlates of normal behavior. Although such correlational analyses provide an indirect link between brain and behavior, advances in current imaging methods allow more direct linking of the two.

New Directions and Evolving Technology

Developments in noninvasive neuroimaging present an exciting new stage in developmental science. New imaging techniques allow for novel approaches to the study of human brain function. For example, functional MRI (fMRI) utilizes a change in MR signal, caused by differences in blood oxygenation level to image activation in the brain during cognitive activity. Activity in a brain region causes inflow of fresh, oxygenated blood. This inflow results in an increase in MR signal relative to deoxygenated regions, which is known as the BOLD (or blood oxygen level dependent) signal. A difference image of the

TABLE 3
Sex Differences

	Direction	Difference	Age ^a	No. ^b	References	
Total Brain	M>F	7%	7–11	30	Caviness et al., 1996	
		9%	4–18	129	Giedd, 1997	
			4–18	114, 104, 99, 121	Giedd et al., 1996a–c, 1997	
		11%	4–18	139	Giedd et al., 1999b	
White matter	M>F	10%	5–17	85	Reiss et al., 1996	
			4–22	145	Reiss et al., 1996	
Cortical gray matter	M>F	10%	0–30	88	Giedd et al., 1999a	
			M=F ^c			Pfefferbaum et al., 1994
			M>F ^d	11%	5–17	85
Total CSF	M=F		0–30	88	Pfefferbaum et al., 1994	
Lateral ventricles	M=F		4–18	121	Giedd et al., 1997	
			0–30	88	Pfefferbaum et al., 1994	
Nonventricular CSF	M<F ^d		5–17	85	Reiss et al., 1996	
Corpus callosum	M=F		2–15	24	Allen et al., 1991	
			M=F ^d		4–18	129
Caudate	M=F			114, 121, 145	Giedd et al., 1996a, 1997, 1999a	
				11–61	90	Pujol et al., 1993
				0–87	162	Rauch and Jinkins, 1994
				7–11	30	Caviness et al., 1996
Putamen	M<F ^d		4–18	104, 121, 129	Giedd et al., 1996b, 1997; Giedd, 1997	
				7–11	30	Caviness et al., 1996
Globus pallidus	M=F ^d		4–18	129, 121	Giedd, 1997; Giedd et al., 1997	
				4–18	104, 121	Giedd et al., 1996b, 1997
				7–11	30	Caviness et al., 1996
Amygdala	M>F ^d	19%	4–18	129, 104, 121	Giedd, 1997; Giedd et al., 1996b, 1997	
				7–11	30	Caviness et al., 1996
Hippocampus	M=F ^d		4–18	129	Giedd, 1997	
				4–18	99, 121	Giedd et al., 1996c, 1997
				7–11	30	Caviness et al., 1996
Temporal lobe	M>F ^d		4–18	99	Giedd et al., 1996c	
				4–18	99, 121	Giedd et al., 1996c, 1997
Thalamus	M=F		8–17	21	Gilbert et al., 2000	
Cerebellum	M>F	6%	7–11	30	Caviness et al., 1996	
		8%	4–18	104	Giedd et al., 1996b	
			8–39	24	Jernigan and Tallal, 1990	

Note: CSF = cerebrospinal fluid; M = male; F = female.

^a Ages of subjects included in the study (in years).

^b Number of subject included.

^c Corrected for intracranial area.

^d Corrected for total brain volume.

task condition compared with a baseline condition is overlaid on an anatomical MRI. This technique can help visualize which brain areas are involved in various forms of behavior. By correlating the MR signal in a given region with performance, we can assess which areas are driving a behavior or symptom. As yet, few normative developmental fMRI studies have been published (see Casey et al., 2000, for review), but the results are promising. Children show different patterns of activation than adults, recruiting either larger areas or different brain regions to perform the same task (Casey et al., 1997c).

This may represent differences in functional organization, or alternatively in ability or strategy. Differences in performance can be addressed by parametrically manipulating task difficulty by varying either the speed or memory load across a task. Parametric designs like these, together with event-related fMRI, which allows individual behavioral trials to be linked to MR signal changes, are promising new approaches.

Diffusion tensor imaging (DTI) is another evolving technique that allows the tracking of white matter fiber tract development. It assesses the regularity and myelina-

tion of fibers more directly than conventional MRI by quantifying the diffusion of water molecules in the brain (Klingberg et al., 1999). As these molecules move along fibers more easily than across fibers, this technique allows for the directional mapping of white matter fiber tracts. It provides a more direct measure of myelination and has already been used successfully with developmental populations (Klingberg et al., 1999).

Genetic influences on brain development can be investigated by performing sibling and twin studies, in which brain anatomy is compared between individuals with varying levels of genetic similarity. Another approach is to correlate well-known and frequently occurring genetic polymorphisms with brain morphometry and behavior (Casey et al., 2001; Castellanos et al., 1998)

General Limitations

A number of limitations of imaging studies need to be acknowledged in the context of both clinical and normative studies. Issues include the validity and reliability of measures (e.g., using measurements that rely on a representative slice versus whole volume or do not correct for total brain volume). Also, bias in subject selection is important (e.g., exclusion of lower socioeconomic groups through extensive screening or the inclusion of patients in the sample who have had their scans read as normal). Sample size is a major issue, as imaging techniques require considerable statistical power. For example, studies of ADHD using small sample sizes have suggested a pattern of right-greater-than-left asymmetry for the caudate nucleus, and the opposite in normal development (Hynd et al., 1993; Semrud-Clikeman et al., 2000). However, other studies of larger samples showed the reverse pattern of a loss of normal, right-greater-than-left caudate asymmetry in this disorder (Castellanos et al., 1996). The issue of small samples is especially important to keep in mind with the increasing number of imaging studies in rare disorders (e.g., Williams syndrome and autism). Finally, the key question in neuroanatomical MRI studies is what a change in the volume of a brain region in a given disorder means. Although gross differences in size or symmetry of brain structures can be quantified, individual cells and cell layers cannot yet be visualized. This means that, although the volume and shape of brain structures may be determined, the underlying cause of any differences cannot.

Clinical Implications

Childhood psychiatric disorders are increasingly being conceptualized as neurodevelopmental in origin, although the mechanisms behind such altered development are not understood. This review illustrates how regional volumetric changes with age and sexual dimorphism of brain structures are relevant to both the age of onset and gender ratios of specific developmental disorders. Whereas the pattern of brain growth as indexed by MRI over the first 2 years is an overall increase in volume, organized development, involving both volumetric increases and decreases, takes place during later childhood and adolescence. For example, portions of the basal ganglia, such as the caudate nucleus, show gradual decreases in volume, particularly in males, between the ages of 6 and 12 years. This is clinically interesting as the basal ganglia have been implicated in a number of childhood disorders that affect males preferentially and are diagnosed during this period of development (e.g., ADHD [Castellanos et al., 1996], Tourette's syndrome [Peterson et al., 1993], obsessive-compulsive disorder [Rosenberg et al., 1997], and childhood-onset schizophrenia [Frazier et al., 1996]). Castellanos et al. (1996) report that boys with ADHD do not show the gradual decrease in caudate volume reported in normal development, but rather that the caudate begins and remains smaller across this period of development. This observation suggests that children may be predisposed to clinical disorders involving the basal ganglia during earlier developmental periods. Casey et al. (2001) report a fourfold increase in ADHD as well as the presence of tics and anxiety in school-age children with histories of perinatal insults involving the basal ganglia. Moreover, males were four times more likely than females to have a disorder. Thus this exemplifies how imaging studies can identify a sensitive period of development that may predispose a child to clinical disorders.

The sexual dimorphism reported across a number of the reviewed studies has significant clinical relevance. For example, the caudate nucleus is relatively larger in maturing females than males. As stated, this is interesting in view of the higher prevalence in males for disorders involving this nucleus. Conversely, the amygdala is relatively smaller in maturing girls and has been implicated in depression and anxiety disorders, which are more common in females (Drevets, 2000). Findings such as these suggest a vulnerability in the development of certain brain regions that differs for the sexes and may predispose them to different clinical syndromes.

Another important clinical issue is to what extent differences in the volume of brain regions relate to clinical symptomatology or its severity. As discussed previously, a few studies have started to relate MRI-based morphometry to symptomatology. This approach, combined with new technologies such as fMRI and DTI, will advance the understanding of the disruption of neural systems and their development in clinical disorders.

In sum, the study of normal brain development using MRI can aid the understanding of deviant development in childhood neuropsychiatric disorders. With the evolution of new technologies, rapid developments are being made that will allow new perspectives on the study of the developing human brain.

Conclusions

1. Magnetic resonance imaging studies of the developing human brain reveal distinct developmental patterns, involving both regional increases and decreases in volume.
2. Clinical imaging studies may be most informative on etiology when they show how brain development in a given disorder deviates from normal patterns of development as a function of age.
3. Sexual dimorphism observed in normally developing children can suggest differential vulnerability of brain regions between the sexes that may predispose them to different clinical disorders.
4. In the interpretation of clinical imaging studies, methodological issues need to be given adequate consideration. Sample size is critical, given the large number of rare disorders currently under investigation.

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