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Brain development and ADHD

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Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by excessive inattention, hyperactivity, and impulsivity, either alone or in combination. Neuropsychological findings suggest that these behaviors result from underlying deficits in response inhibition, delay aversion, and executive functioning which, in turn, are presumed to be linked to dysfunction of frontal–striatal–cerebellar circuits. Over the past decade, magnetic resonance imaging (MRI) has been used to examine anatomic differences in these regions between ADHD and control children. In addition to quantifying differences in total cerebral volume, specific areas of interest have been prefrontal regions, basal ganglia, the corpus callosum, and cerebellum. Differences in gray and white matter have also been examined. The ultimate goal of this research is to determine the underlying neurophysiology of ADHD and how specific phenotypes may be related to alterations in brain structure.

Keywords: ADHD; Development; Brain; Magnetic resonance imaging; Phenotypes; Basal ganglia; Cerebellum

According to the DSM-IV-TR, Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by excessive inattention, hyperactivity, and impulsivity, either alone or in combination (American Psychiatric Association, 2000). Neuropsychological findings suggest that these overt behavioral signs result from underlying deficits in response inhibition, delay aversion, and executive functioning. In turn, these hypothesized psychological deficits are presumed to be linked to dysfunction of frontal–striatal–cerebellar circuits. In particular, much attention has been paid to the neural circuits connecting the prefrontal cortex and the basal ganglia, which likely modulate response inhibition. Further, the cerebellum, which has traditionally been viewed as a motor coordination center, has also been shown to be closely linked to non-motor regions of the cerebral cortex and to play a role in executive functions such as cognitive planning. Over the past decade, magnetic resonance imaging (MRI) has been used to examine anatomic differences in these regions between ADHD and control children. In addition to quantifying differences in total cerebral volume, specific areas of interest have been prefrontal regions, basal ganglia, the corpus callosum, and cerebellum. Differences in gray and white matter have also been examined. The ultimate goal of this research is to determine the underlying neurophysiology of ADHD and how specific phenotypes may be related to alterations in brain structure. The findings of these studies will be discussed in the following review.

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ADHD is most often diagnosed during childhood and therefore, we will limit our discussion to recent MRI studies of children and adolescents diagnosed with this common psychiatric condition. Anatomic MRI is the principal technology used to examine the pediatric brain because it provides excellent spatial resolution and does not use ionizing radiation. Although other approaches such as computed axial tomography, positron emission tomography, and single photon emission computed tomography also inevitably contribute to our understanding of the pathophysiology of ADHD, they will not be discussed in detail here. Despite the significant advances made by MRI, there are some limitations which require mention when evaluating the available data. First, the substantial cost of obtaining MRI scans usually results in small sample sizes, which tend to yield insufficient statistical power. As Rossi (1990) pointed out, when most studies in a field have statistical power in the range of 50%, then inconsistent results, largely representing type I error, are to be expected. The cost of MRI studies of ADHD can also be increased by loss of scans due to excessive motion, which is to be expected, given that hyperactivity is one of the defining features of ADHD. Second, ADHD is characterized by symptoms that vary depending upon subtype, age, sex, and clinical setting. This heterogeneity makes comparisons across studies difficult, particularly when sample sizes are small. Further complications arise when one considers the widespread use of stimulant medications to treat ADHD. It is difficult to recruit a sample that is medication-naïve in North America. Therefore, studies often include children who are taking medications, those who have been exposed previously to medications, and those who are unmedicated. Third, the field has not yet adopted standard quantitative analytical methods which would improve comparisons across studies. Current methods include hand-tracing of individual regions of interest, which tends to optimize validity at the expense of reliability; fully automated methods, which maximize test–retest reliability but are best applied to large well-defined brain regions; and semi-automated methods, which combine the strengths and weaknesses of the other two alternatives. Finally, another source of inconsistencies in the anatomical literature has derived from a focus on lateralization and indices of asymmetry (Castellanos et al., 1994). Given the compelling evidence of lateralization of language and increasing evidence of lateralization of some aspects of attention, interest in obtaining asymmetry measures is understandable. Unfortunately, asymmetry measures are intrinsically less reliable than the volumetric measures from which they are constructed, with reliability decreasing inversely with the degree of similarity between the right and left sides (Arndt, Cohen, Alliger, Swayze, & Andreasen, 1991; Bullmore, Brammer, Harvey, & Ron, 1995). Despite these concerns, the field continues to conduct MRI studies with the ultimate goal of delineating the brain anatomy of ADHD.

1. Normal brain development

Over the past 20 years, converging studies have shown that over 90% of a young adult's total brain volume is attained by age 5 (Giedd et al., 1996) and that total cerebral volume (TCV) reaches its maximum volume by early adolescence (Courchesne et al., 2000; Giedd, Blumenthal, Jeffries, Castellanos et al., 1999). A recent study of 45 children who received MRI scans 2 years apart between the ages of 5 and 11, showed expansion of the brain to be approximately 1 mm per year, predominantly in the prefrontal cortex (Sowell et al., 2004). More specifically, cross-sectional analyses have shown significant age-related decreases in the thalamus and lenticular nucleus, and increases in ventricular size after controlling for TCV (Sowell, Trauner, Gamst, & Jernigan, 2002). Sex differences are prominent. Both the cerebrum and the cerebellum are significantly larger (by 7–10%) in boys than girls (Giedd et al., 1996; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Sowell et al., 2002). Consistent with this, the absolute size of cortical gray matter is nearly 10% larger in boys than in girls. Subcortical regions such as the putamen and globus pallidus are also significantly larger in boys, even after controlling for total cerebral volume (Giedd et al., 1996). Conversely, the caudate is larger in girls than boys, after controlling for TCV (Giedd et al., 1996; Sowell et al., 2002). There is also some inconsistent evidence of sex differences in developmental patterns. In a cross-sectional study of 104 children between the ages of 4 and 18, Giedd and colleagues (1996) found age-related decreases in caudate and putamen volumes in boys only.

1.1. White and gray matter development

The lack of total brain volume changes during late childhood and adolescence masks complex changes in gray and white matter. Cross-sectional (Courchesne et al., 2000; Reiss et al., 1996; Sowell et al., 2002) and longitudinal (Giedd,