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The Neurobiological Profile of Girls with ADHD

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Abstract

Since boys are more commonly diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) than girls, the majority of theories and published research studies of ADHD have been based on samples comprised primarily (or exclusively) of boys. While psychosocial impairment in girls with ADHD is well established, the neuropsychological and neurobiological basis of these deficits is less consistently observed. There is growing evidence that boys' and girls' brains develop and mature at different rates, suggesting that the trajectory of early anomalous brain development in ADHD may also be sex-specific. It remains unclear, however, whether earlier brain maturation observed in girls with ADHD is protective. In this review, we outline the current theory and research findings that seek to establish a unique neurobiological profile of girls with ADHD, highlighting sex differences in typical brain development and among children with ADHD. The review highlights findings from neurological, neurocognitive, and behavioral studies. Future research directions are suggested, including the need for longitudinal neuroimaging and neurobehavioral investigation beginning as early as the preschool years, and continuing through adolescence and adulthood, with consideration of identified sex differences in the development of ADHD.

Keywords

childhood; development; executive functions; neuroimaging; ADHD; gender

INTRODUCTION

Research on the neurobiological and functional anomalies associated with Attention Deficit Hyperactivity Disorder (ADHD) has evolved over the past two decades [Bush, 2008; Kieling et al., 2008]. Following a shift away from recognizing the disorder as one of "attention" problem to one of executive dysfunction [Barkley, 1997; Nigg et al., 2004; Willcutt et al., 2005], ADHD is now known to present with a wide range of cognitive deficits, including motivational dysfunction [Carlson and Tamm, 2000], delay aversion [Sonuga-Barke, 2005], inefficient motor speed and coordination [Waternberg et al., 2007], slowed processing speed [Clarke et al., 2003; Willcutt et al., 2008], and variability of responding [Castellanos et al., 2005; Johnson et al., 2007]. Contributing to this change in focus is the rapid increase in neuroimaging research citing evidence of volumetric, functional, and white matter differences in children with ADHD when compared to controls [Bush, 2008; Kieling et al., 2008]. Yet, most of the published research on children with

ADHD is based on samples comprised primarily (or exclusively) of boys. Although boys are much more commonly diagnosed with ADHD than girls, and are more often treated [Derks et al., 2007], the functional and psychosocial impairment in girls with ADHD is well established [Greene et al., 2001; Staller and Faraone, 2006; Hinshaw et al., 2007; Ohan and Johnston, 2007]. While sex-specific behavioral differences in ADHD have been identified [Carlson et al., 1997], the available research is yet to specify a clear behavioral or neurobiological profile distinct to girls with ADHD [Biederman et al., 1999, 2002, 2005; Sharp et al., 1999; Seidman et al., 2006]. The purpose of this review is to outline current theoretical and research findings that seek to establish a unique neurobiological profile of girls with ADHD, highlighting sex differences in typical development (brain and behavior) and among children with ADHD, and to set forth hypotheses to explain the limited progress in this area. First, the literature on sex differences in typical brain development and among children with ADHD is reviewed. Second, a review of recent neurological, neurocognitive, and behavioral findings in girls with ADHD is presented. Finally, we outline suggestions for future directions that may lead to better identification and specification of the neurobiological profile unique to girls with ADHD.

REGIONAL BRAIN DEVELOPMENT

While development of the human nervous system begins before birth and continues at least into early adulthood, the trajectory of development is nonlinear and progresses in a region-specific manner that coincides with functional maturation [Giedd et al., 1999; Gogtay et al., 2004; Halperin and Schulz, 2006]. Brain development begins in utero and has a rapid period of growth in the first 2 years of life. By age 2 years, the brain is ~80% of its adult size [Giedd et al., 1999]. Synapse formation [Huttenlocher and Dabholkar, 1997] and myelination [Kinney et al., 1988] proceed rapidly up to age 2 years, followed by a relative plateau phase, during which neurons begin to form complex dendritic trees [Mrzljak et al., 1990]. Maximum synaptic density (i.e., synaptic overproduction) is observed at age 3 months in the primary auditory cortex and at age 15 months in the prefrontal cortex [Huttenlocher and Dabholkar, 1997]. After age 5 years, brain development is marked by continued neuronal growth, pruning, and cortical organization. Onset of puberty accelerates the experience-dependent pruning of inefficient synapses [Giedd et al., 1996; Gogtay et al., 2004] and eventually reduces synaptic density to 60% of maximum [Huttenlocher and Dabholkar, 1997].

The general pattern of brain maturation is for regions subserving primary sensorimotor functions to mature earliest and for higher order association areas to mature later [Giedd et al., 1999; Gogtay et al., 2004]. Phylogenetically older regions (e.g., basal ganglia) mature earlier than newer regions (e.g., neocortex); thus, the pattern of “normal” gray matter loss that characterizes maturation begins in the brainstem, progresses to the cerebellum, and then involves the basal ganglia, where neuronal loss begins before puberty and continues through adolescence [Castellanos et al., 2002]. Cortical maturation progresses from primary sensorimotor areas and spreads rostrally over the frontal cortex and caudally and laterally over the parietal, occipital, and finally to the temporal cortex [Giedd et al., 1999; Gogtay et al., 2004; Halperin and Schulz, 2006].

Regionally specific age-related changes in white matter have also been described. Using diffusion tensor imaging (DTI) to examine cross-sectional age-related changes among healthy children and adolescents ages 6–19 years, Barnea-Goraly et al. [2005] noted significant age-related increases in fractional anisotropy (a measure representing directional organization of white matter) in prefrontal regions, internal capsule, basal ganglia, ventral visual pathways, and corpus callosum, suggesting that, during childhood, rapid anisotropy changes occur in brain regions considered to be critical for attention, motor skills, executive

functions, and memory [Barnea-Goraly et al., 2005]. Other investigators used longitudinal tensor mapping to demonstrate a rostro-caudal wave of growth in the corpus callosum. Between ages 3 and 6 years, peak growth rates were detected in the anterior regions of the corpus callosum, considered to be important in the executive and motor control [Thompson et al., 2000].

SEXUAL DIMORPHISM IN HUMAN BRAIN DEVELOPMENT

There is growing evidence that boys' and girls' brains develop and mature at different rates. Giedd and coworkers compiled normative growth curves for each of the lobes of the brain, demonstrating the heterochronous nature of brain development, in which the different lobes develop at different rates [Giedd et al., 1999; Thompson et al., 2005; Lenroot et al., 2007]. From age 4 to 20 years, linear increases in white matter volume with age were observed, whereas age-related changes in gray matter were nonlinear, regionally specific, and differed for boys and girls. In particular, frontal lobe gray matter volume increased during preadolescence, peaked around 10.5 years for boys (9.5 years for girls), and declined during postadolescence resulting in an overall net decrease across the age span. Results were similar for parietal lobe volumes and differed only in that the slope of the curve was steeper and volumes peaked 1.5 years earlier for each gender (9.0 years for boys, 7.5 years for girls). Similarly, temporal lobe volumes peaked at the age of 11 years for boys and 10 years for girls. Total cerebral gray matter volume was 10% larger in boys, but peaked much earlier in girls than boys (10.5 years vs. 14 years). The trajectory was identical for the caudate nucleus, which also showed peak at the age of 10.5 years for girls and 14 years for boys.

Using a longitudinal design, Shaw et al. [2006a] demonstrated a negative correlation between IQ and cortical thickness in young children, suggesting that *timing* and *trajectory* of changes in gray matter volume are associated with efficiency of cognitive functioning. Specifically, in young children, higher IQ was associated with thinner cortex, particularly in the frontal/temporal lobe regions; however, this relationship reversed in late childhood, with positive correlations observed between cortical thickness and IQ. Interestingly, children with superior IQ had thinner superior prefrontal cortex at an early age, with a rapid increase in cortical thickness peaking at age 13 years and attenuating into late adolescence. These results suggest that outcomes are better explained by *trajectory* of brain development, rather than by examining brain volume alone at a given cross-sectional age [Shaw et al., 2006].

There is growing evidence to suggest that subcortical white matter, cerebellum, and cerebral cortex share a pattern of reciprocal influence in early development. White matter injury in premature infants is followed by marked reduction in cortical gray matter at term [Inder et al., 1999]. In infants, unilateral cerebral injury is associated with significantly decreased volume of the contralateral cerebellar hemisphere; similarly, early unilateral cerebellar injury is associated with decrease in contralateral supratentorial brain volume [Limperopoulos et al., 2005]. Taken together, these findings suggest a pattern of reciprocal influence (i.e., "crossed trophic effect") between cerebral and subcortical structures, such that early injury to supratentorial periventricular white matter impairs not only the cerebral cortical development, but also the development of remote developing cerebellum, and vice versa. These results have particular importance in understanding the mechanisms of abnormal brain development observed in children with developmental disorders such as ADHD, in which anomalous brain development has been identified in cortex, basal ganglia, and cerebellum [Bush, 2008]. In particular, it remains unclear whether ADHD develops initially due to anomalous development of the basal ganglia and/or cerebellum, with subsequent reduction in growth of the cerebral cortex (or vice versa), and whether these anomalous developmental processes are different in boys and girls.

In summary, the findings from developmental neuroimaging research suggest that when studying brain development, boys and girls should be analyzed separately. Further, drawing inferences about developmental processes from cross-sectional data is also fraught with methodological problems [Shaw et al., 2006]. To better understand age- and sex-specific developmental processes in children and how these processes manifest in developmental disorders, future investigations may need to target the trajectories of development (rather than static cross-sectional comparisons).

ANOMALOUS BRAIN DEVELOPMENT IN ADHD

Multiple anatomic MRI (aMRI) studies of ADHD have revealed abnormalities in frontal areas [Castellanos et al., 1996, 2000, 2002; Filipek et al., 1997; Hesslinger et al., 2002; Kates et al., 2002; Mostofsky et al., 2002] and interconnected subcortical structures including the caudate [Hynd et al., 1993; Castellanos et al., 1996; Filipek et al., 1997; Mataro et al., 1997], putamen [Wellington et al., 2006], globus pallidus [Basser and Pierpaoli, 1996], and cerebellum [Castellanos et al., 1996; Berquin et al., 1998; Mostofsky et al., 1998]. At the cerebral cortical level, observation of decreased volume of several frontal [Castellanos et al., 1996; Filipek et al., 1997; Hesslinger et al., 2002; Mostofsky et al., 2002] and nonfrontal [Kelly et al., 2007] regions suggests that abnormalities are not localized to a specific area. Unfortunately, most of these studies reported findings on ADHD samples that were predominantly (or exclusively) male or for which conclusions could not be drawn about female-specific anomalies due to small sample size.

At the level of the basal ganglia, volumetric abnormalities have been associated with ADHD, especially in boys. To specify localization of these abnormalities, Qui et al. [in press] used large deformation diffeomorphic metric mapping (LDDMM), to examine effects of ADHD, gender, and their interaction on basal ganglia shapes in 47 children (27 boys, 20 girls) with ADHD and 66 controls (35 boys, 31 girls), ages 8–12 years. Boys with ADHD showed significantly smaller basal ganglia volumes compared to control boys. LDDMM identified markedly different basal ganglia shapes in boys with ADHD (compared to control boys), with volume compression seen bilaterally in the caudate head and body, anterior putamen, left anterior globus pallidus, and right ventral putamen, and volume expansion in posterior putamen. In contrast, no volume or shape differences were revealed in girls with ADHD, compared to control girls.

There have been few longitudinal studies of brain development in ADHD. Of those published, most have emphasized boys, and have studied school aged children and adolescents, with little discussion of the early developmental trajectories associated with ADHD. Castellanos et al. [2002] reported growth curves highlighting the different developmental trajectories of regional brain volumes. For most regions of interest (including total cranial volume and cerebellum, but not caudate), the growth curves of children with ADHD (relative to controls) were parallel, but on a lower track. There was no interaction between diagnosis and sex—implying that both boys and girls with ADHD show stable reductions in brain volume, relative to controls [Castellanos et al., 2002]. While this study included children as young as 4 years, the vast majority of the participants (and data collection points) were obtained at school age; therefore, conclusions about the early trajectory of anomalies associated with ADHD were difficult to make. In fact, the authors specifically remarked, “future studies should focus on younger patients being enrolled into treatment studies while in preschool and on the development of improved quantitative measures of brain anatomy and of component endophenotypes of ADHD” [Castellanos et al., 2002, p. 1747].

More recently, Shaw et al. [2006b] reported findings from a series of longitudinal studies of children with ADHD using measures of cortical thickness (mean age of entry = 8.9 years). They found that children with ADHD showed global thinning of the cortex, most prominently in medial and superior prefrontal regions. Children with ADHD were also delayed in cortical maturation (i.e., attaining peak thickness) throughout the cerebrum, with the most prominent area of delay in the lateral prefrontal cortex. In contrast, primary motor cortex was the only cortical area in the ADHD group that showed earlier maturation [Shaw et al., 2007]. It is possible to speculate that early, excessive motor activity among young children with ADHD (particularly boys) activates (and thus facilitates) the spared maturation of motor cortex, thus paradoxically outpacing the other more delayed frontal regions that typically restrict motor hyperactivity. Indeed, the authors found that, within the ADHD group, those with poor behavioral outcome had different trajectories of development (i.e., thinner left medial prefrontal cortex at baseline, but not at follow-up) than those with better behavioral outcome, again highlighting the power of longitudinal analyses. Like many other imaging studies in ADHD, these reports did not identify sex-specific differences in these ADHD-related delays in cortical maturation. It is possible that when studied separately, girls may have a different trajectory.

In a longitudinal study of cerebellar development and clinical outcome, Mackie et al. [2007] examined scans from 36 children (21 boys) with ADHD and found a progressive loss of volume in the superior cerebellar vermis, regardless of outcome; however, those with worse clinical outcome also had progressive loss (compared to controls and ADHD with better outcome) of inferior cerebellar lobes bilaterally. Of note, the children with ADHD in this sample had multiple comorbidities, including learning, mood, and anxiety disorders, all of which appeared to contribute to poorer outcome.

The study of white matter integrity using DTI appears to hold promise in elucidating the neurobiological anomalies associated with ADHD. In one of few published DTI studies of ADHD, Ashtari et al. [2005] found that, compared to controls, children with ADHD (12 boys, 6 girls) had decreased fractional anisotropy (FA) values in right supplementary motor area (SMA), right striatal, right and left cerebellar peduncle and left cerebellum [Ashtari et al., 2005]. These findings are consistent with previous research implicating the role of the SMA in motor response preparation [Amador and Fried, 2004; Suskauer et al., in press], and highlight the role of the frontostriatal regions in response inhibition [Casey et al., 1997; Durston et al., 2003]. Their small sample size precluded examination of the effects of age and sex; thus, the pattern of atypical white matter development in girls with ADHD remains unclear. More recently, Casey et al. [2007] combined DTI and functional MRI in 20 parent/child dyads with ADHD (children: 16 male/4 female; parents: 5 male/15 female). Fractional anisotropy values in right prefrontal fiber tracts correlated with both functional activity in inferior frontal gyrus and caudate nucleus, and with performance (d-prime) on a computerized go/no-go task. Their findings lend support to the heritability of ADHD, with notable disruption to frontostriatal white matter as one possible pathway. Here again, the small number of girls with ADHD in the sample makes interpretation of this finding for girls more difficult.

Although the preponderance of early empirical evidence pointed to anomalies in prefrontal regions (and thus deficits in executive control) as potential causal mechanisms in ADHD [Castellanos et al., 1996; Mostofsky et al., 2002; Durston et al., 2003, 2004], more recent research has argued that other (largely subcortical) brain regions may provide answers to the early etiological differences in children with ADHD. Halperin and Schultz [2006] pointed out that among those with early prefrontal lesions, functional impairment usually does not manifest until later childhood [Anderson et al., 1999; Goldman, 1971], and then tends to get worse upon entry into adolescence [Denckla and Cutting, 2004]. In contrast, hyperactive and

impulsive symptoms of ADHD are almost always evident during the preschool years [Campbell, 1995; Barkley, 2006], and the severity of symptoms (most notably symptoms of impulsiveness and hyperactivity) tends to diminish with age [Biederman et al., 2000; Hinshaw et al., 2006]. As such, Halperin and Schultz [2006] hypothesized that “the prefrontal cortex and its interconnections may be primarily involved in the recovery from ADHD, rather than in the cause of the disorder” (p. 568), and proposed that early damage to other regions is potentially involved in etiology of ADHD, notably the basal ganglia and cerebellum. For example, the basal ganglia serves as the nexus through which prefrontal, premotor, and motor signals inhibit competing motor programs and facilitate intended behaviors [Mink, 1996; Halperin and Schulz, 2006]. Since normalization of reduced caudate volume occurs by late adolescence [Castellanos et al., 1996, 2002], the developmental trajectory of the caudate anomalies in ADHD appears to parallel the reduction of hyperactivity symptoms by adolescence [Biederman et al., 2000]. Alternatively, animal and human infant studies indicate that the cerebellum is among the most vulnerable regions to early insult [Volpe, 1995], and like the basal ganglia, the cerebellum may influence the cognitive operations normally thought to be subserved by the frontal lobes [Middleton and Strick, 2000]. Cerebellar impairment may also be implicated by the prevalence of children with ADHD who have motor control problems [Diamond, 2000; Pitcher et al., 2003].

ADHD IN GIRLS

Diagnosis of ADHD in girls is more complicated than in boys, in part because of the later age of onset, more subtle clinical manifestation, and limitations associated with the DSM diagnostic schema and nomenclature [Keltner and Taylor, 2002]. Even so, it is clear that ADHD is associated with considerable functional and psychosocial impairment in girls, including an increased risk of internalizing disorders (eating disorders, depression, suicide), especially in adolescence and young adulthood [Gaub and Carlson, 1997; Gershon, 2002; Makris et al., 2008; Mikami et al., 2008]. Longitudinal follow-up of a large cohort of girls with ADHD aged 6–18 years at baseline showed that girls with ADHD were at significantly higher risk for elevated prevalence of antisocial, addictive, mood, and anxiety disorders, including Major Depression, Bipolar Disorder, Tourette syndrome, and Nicotine Dependence [Biederman et al., 2006]. Indeed, the gender paradox [Eme, 1992] posits that the sex in which a given disorder is less prevalent (e.g., ADHD in girls) should show greater levels of impairment than the sex in which the disorder is more prevalent (e.g., ADHD in boys). Hinshaw et al. [2006] reported longitudinal data on adolescent girls with ADHD, noting continued impairment 5 years after initial childhood ascertainment. In that time frame, however, symptoms of hyperactivity/impulsivity had a steeper decline than inattentive symptoms. In addition, these girls continued to demonstrate poorer performance on neuropsychological measures of working memory, planning, set maintenance, and set shifting into adolescence than matched controls.

Studies of school-aged children with ADHD routinely find that girls present more commonly with the inattentive subtype than do boys [Weiler et al., 1999; Hinshaw et al., 2006]. Given the earlier maturation of most cortical brain regions in girls, it may be necessary to study girls with ADHD at a younger age, to clarify the brain mechanisms associated with these behavioral problems. On the other hand, while girls may be somewhat protected from the symptoms of ADHD as a function of their earlier maturation, pubertal increases in estrogen and subsequent increases in dopamine receptors lead to an increase in symptoms in adolescence [Keltner and Taylor, 2002]. Therefore, it is equally important to continue to study brain and behavioral development of girls with ADHD into early adulthood.

Behaviorally, symptoms of ADHD tend to decrease in severity with age in parallel with cortical maturation [Gaub and Carlson, 1997; Hinshaw et al., 2007], such that by late elementary school age, the symptoms are more pronounced in boys (compared to girls) with ADHD. However, recent large-scale studies of preschool children with ADHD reveal that the opposite pattern may be true in the preschool years. In preschool children with moderate to severe ADHD studied as part of the multisite Preschool ADHD Treatment Study (PATS), the behavior of girls with ADHD was more deviant, relative to age- and sex-matched peers, than boys with ADHD on the Conners' Parent and Teacher Rating Scales [Posner et al., 2007]. However, the study of girls with ADHD in preschool presents a challenge, as the inattentive symptoms (more commonly observed in girls) are not as evident in the preschool years. In fact, Bryne et al. [2000] reported that only 4% of children diagnosed with ADHD in preschool (boys and girls) met criteria for the inattentive subtype, with the large majority meeting criteria for the hyperactive-impulsive subtype (68%).

There is also emerging evidence that the trajectory of early anomalous brain development within ADHD is sex-specific. By examining EEG activation patterns longitudinally in young boys and girls with ADHD, Baving et al. [1999] demonstrated different patterns and trajectories of cerebral organization (i.e., opposite directions of asymmetry). Boys with ADHD exhibited a less right-lateralized frontal alpha asymmetry than control boys, whereas girls with ADHD displayed a more right-lateralized asymmetry pattern than control girls. This dissociation was present in both preschool (age 4.5 years) and school age (age 8 years) children. Of note, in the girls with ADHD, at age 4 years, the degree of right-lateralization, and difference from age-matched controls and from boys with ADHD, was markedly higher than at age 8 years, suggesting greater atypicality at age 4 years, but a more rapid trajectory of normalization of frontal function by age 8 years in girls with ADHD [Baving et al., 1999]. A similar pattern of sex-specific findings in adolescents with ADHD was observed by Hermens et al. [2005], using simultaneously recorded EEG and electrodermal activity (EDA). Boys with ADHD showed widespread increased theta activity, while girls with ADHD showed localized frontal enhancement of theta, with reduced rate of EDA decrement. The findings were unrelated to ADHD subtype, and interpreted to support a model of anomalous arousal in girls with ADHD, emphasizing both central and autonomic function [Hermens et al., 2005]

Few studies have directly compared regional brain volumes in girls with ADHD to those of healthy female controls. Castellanos et al. [2001] reported a cross-sectional analysis of brain volumes in 50 girls with ADHD (compared to 50 healthy control girls), ages 5–15 years. The girls with ADHD showed significant reductions in left caudate and posterior–inferior cerebellar vermis (lobules VIII–X), but equivocal findings were reported regarding reductions in frontal lobe volumes [Castellanos et al., 2001]. Because this study was completed separately from earlier studies of boys with ADHD, the authors remarked, “conclusions about sex differences in ADHD must remain tentative until verified in contemporaneously collected and analyzed longitudinal scans” [Castellanos et al., 2001, p. 293].

In a recently published paper from our lab, ADHD-related abnormalities in cerebral cortex structure and volume were analyzed. Using an automated surface-based analysis technique to examine ADHD-associated differences in additional morphologic features of cerebral cortical gray matter structure, including surface area, thickness, and cortical folding, children with ADHD had a decrease in total cerebral volume and total cortical volume of over 7 and 8%, respectively, with volume reduction observed throughout the cortex, and with significant reduction in all four lobes bilaterally. The ADHD group also showed a decrease in surface area of over 7% bilaterally, and a significant decrease in cortical folding bilaterally [Wolosin et al., 2007]. In supplemental analyses of these data examining only

girls (19 ADHD, 34 controls), the ADHD group had reduced right hemisphere ($P < 0.05$) and bilateral frontal ($P = 0.01$) cortical surface, but not reduced cortical volume.

Taken together, the available neuroimaging and neurobiological literature yields little consensus on the brain anomalies specific to girls with ADHD; however, these recent findings are consistent with the hypothesis that ADHD-specific anomalies occur *early* in neural development, but that by school age, the differences are more pronounced and widespread in boys with ADHD. Thus, in view of the available evidence from neuroimaging studies [Bush, 2008], when considering neurobiological development in ADHD, it is crucial to consider (simultaneously) all three levels of the CNS (cortex, basal ganglia, cerebellum), and study these regions longitudinally with regard to sex. Given the sex difference in maturation, it may be necessary to study girls with ADHD at younger ages, to fully appreciate the early patterns of anomalous brain development, and their effect on behavior and cognitive development.

SEX DIFFERENCES IN MOTOR AND EXECUTIVE CONTROL AMONG CHILDREN WITH ADHD

Neurological models of frontal lobe structure and function highlight parallel frontal-subcortical circuits [Burruss et al., 2000; Lichter and Cummings, 2001], of which two are related to *motor function*, and three are crucial in *executive control*. These circuits link specific regions of the frontal lobes to subcortical structures, and supply modality-specific mechanisms for interaction with the environment [Castellanos et al., 2006]. Motor and executive control systems develop in a parallel manner, such that both display a protracted developmental trajectory, with periods of rapid growth in elementary years and continued maturation into young adulthood [Diamond, 2000]. Thus, the careful examination of motor and executive control can provide a window into the neurological development of children with and without ADHD.

Motor Assessment in Children with Typical Development

Few studies have contrasted the performance of typically developing boys and girls on standardized motor assessment. Gidley Larson et al. [2007] examined developmental status of the motor system in 144 typically developing children (72 boys) with ages of 7–14 years, using the Revised Physical and Neurological Examination for Subtle Signs (PANESS) [Denckla, 1985]. There were significant sex differences for subtle signs (involuntary movements), gaits and stations, and timed movements; in all cases, girls showed fewer subtle signs and were faster and more proficient than boys, suggesting that motor development follows a different (i.e., earlier-maturing) developmental course in girls than in boys [Gidley Larson et al., 2007].

Age-related change in right- versus left-sided time difference on motor examination may also be an important indicator of cerebral lateralization and maturation, as rapid myelination of the corpus callosum is considered to be related to increased bilateral skill and speed on timed motor tasks. Roeder et al. [2008] compared right versus left differences in finger, hand, and foot speed using the PANESS in 130 typically developing right-handed children (65 boys) of ages 7–14 years. Right versus left time difference values decreased significantly with age on four of six timed tasks, with sex differences noted for heel-toe sequences (boys showing a greater right-left difference than girls), and a significant interaction between age and gender for hand pronation-supination, such that the magnitude of the right-left difference was similar for younger, compared to older girls, while the difference was significantly larger for younger, compared to older boys. Thus, timed motor

tasks reflecting interhemispheric connections equalize in improvement during childhood; for some tasks, the equalization occurs earlier in girls than in boys [Roeder et al., 2008].

Motor Development in Children with ADHD

A similar pattern favoring girls emerges when comparing motor development in ADHD. Cole et al. [2008] examined age-related reduction in subtle signs (overflow, dysrhythmia), emphasizing gender differences in 268 children of ages 7–14 years (99 boys, 33 girls with ADHD; 85 control boys, 51 control girls). Within-sex comparisons revealed that boys with ADHD had more overflow and more dysrhythmia than control boys ($P < 0.05$), while girls with ADHD in this age range did not differ from control girls. Examination of age-related change in girls versus boys with ADHD revealed that, from age 7 to 14 years, girls with ADHD demonstrate a significant reduction in overflow; while boys manifest little age-related change during this period, suggesting that the frontal–striatal and cerebellar brain systems implicated in overflow and dysrhythmia mature earlier in girls versus boys with ADHD [Cole et al., 2008].

Oculomotor Control in Children with ADHD

Oculomotor paradigms provide a mechanism for examining and localizing dysfunction at the interface between movement and cognition, and may be particularly important in girls, given the documented frontostriatal and cerebellar anomalies [Castellanos et al., 2001]. Similar to findings of executive control deficits on oculomotor tasks in boys [Mostofsky et al., 2001], Castellanos et al. [2000] reported that girls with ADHD manifest reduced accuracy of memory-guided saccades (working memory), and increased commission errors (inhibitory control), compared to control girls [Castellanos et al., 2000]. In a more recent study in which boys and girls with ADHD were studied contemporaneously, Mahone et al. [2006] examined sex and group differences on oculomotor tasks reflecting response preparation (prosaccade latency/variability), inhibitory control (antisaccade directional errors, memory-guided saccade anticipatory errors, go/ no-go commissions), and working memory (memory-guided saccade spatial accuracy). Children with ADHD were impaired on all tasks. Importantly, girls with ADHD were impaired (relative to female controls) on all tasks, while boys with ADHD were impaired (relative to age-matched male controls) only on working memory tasks and inhibition, but not on response preparation tasks [Mahone et al., 2006]. This finding represents one of the few instances in which girls with ADHD manifest *greater* relative deficits than age-matched boys with ADHD, highlighting the importance of careful motor and oculomotor examination in understanding the neurobiology of ADHD in girls.

Cognitive and Executive Control in ADHD

The evidence that girls with ADHD have measurable executive dysfunction on neuropsychological tests is inconsistent [Seidman et al., 1997; Bauermeister et al., 2007] and there is growing indication that their relative pattern of deficits may change with age [Seidman et al., 2005]. For example, a longitudinal examination of a large group of girls with ADHD showed that 55% of girls with the combined subtype (and 43% of those with the inattentive subtype) demonstrated performance-based executive dysfunction at baseline (including measures of working memory, planning, set maintenance, and set shifting), with 75 and 55% of girls with the combined and inattentive subtypes, respectively, showing executive dysfunction 5 years later [Hinshaw et al., 2007]. Further, some behavioral measures of executive control may have greater discriminative power in identifying those with ADHD than others, especially when sex differences in performance are taken into consideration. Wodka et al. [2008a] examined 123 children (54 with ADHD, 69 controls) using subtests from the Delis–Kaplan Executive Function System (D-KEFS; Trail Making, Verbal Fluency, Color–Word Interference, Tower) to examine sex-specific patterns of

executive dysfunction associated with ADHD. Children with ADHD performed significantly worse than controls on summary variables for all four tests; the strongest group differences were on Color–Word Interference, while weakest effects were on the Tower test. Sex-specific discriminant function analyses indicated that *different* D-KEFS tests discriminated boys with ADHD (from male controls) and girls with ADHD (from female controls); Tower (Total Achievement) was the strongest predictor for girls, while speed of color and word naming (from Color–Word Interference) best classified boys. Thus, the tests that best classified boys with ADHD involve speed/efficiency of responding, while the tests that best classified girls with ADHD involve visuospatial planning [Wodka et al., 2008a].

As a follow-up to the study above, the authors examined group (ADHD versus control), sex, and ADHD subtype differences on “process” measures of executive function in children, again using the D-KEFS. Girls performed significantly better than boys ($P < 0.05$) on Verbal Fluency (First Interval Total). On Verbal Fluency (Total, % Repetition Errors), boys with ADHD Combined subtype (ADHD-C) performed better than girls with ADHD-C, whereas girls with ADHD-Inattentive subtype (ADHD-I) performed better than boys with ADHD-I. Thus, when sex and subtype were considered, children with the ADHD subtype less common for their sex (i.e., girls with ADHD-C and boys with ADHD-I) were at greater risk [Wodka et al., 2008b].

SUMMARY AND CONCLUSIONS

The research literature is yet to identify a signature pattern of brain anomalies and behavioral deficits associated with ADHD in girls, possibly because girls mature and potentially “age-out” of some of the symptoms earlier than boys, but possibly because the neuroimaging research is yet to follow girls with ADHD longitudinally into adulthood, when new dysfunctional symptom patterns often emerge. With few exceptions, the neuroimaging and behavioral literature in ADHD has emphasized study of school-aged children, boys, and cross-sectional analyses. Thus, there remains a dearth of knowledge about the effects of early brain development and associated behavior in girls with ADHD, and about the later onset brain behavior associations that may be linked more directly to hormonal changes unique to women.

It is well established that girls and boys have different trajectories of brain development—especially with regard to gray matter [Lenroot et al., 2007]; thus, cross-sectional research comparing age-matched boys and girls is suspect because girls are at a different point in their development to maturity than boys at the same age. To that end, it may be that the relative lack of significant findings among girls with ADHD (compared to those published for boys) with regard to brain volume and behavior is due at least in part to the reliance on cross-sectional studies. It may also be due to different underlying neuropathophysiologic processes in boys and girls with ADHD. Alternatively, the relative paucity of findings among girls with ADHD in cortical and subcortical structures [Castellanos et al., 2001] may indicate that the core neuroanatomic abnormalities lie elsewhere in girls with ADHD, or that the methods of assessment lack sensitivity or statistical power to detect the differences. There is increasing evidence that reciprocal frontal–posterior cortical projections are critical to control of intentional movement [Rizzolatti et al., 2001] and higher-order executive processes [Gazzaley et al., 2005; Schumacher et al., 2007]. Thus, to fully understand the development of ADHD symptoms in girls, research must simultaneously consider the trajectories of gray and white matter development alongside behavioral development, taking into consideration the potential for reciprocal influence of each on one another. In this regard, future investigations that include longitudinal design, early assessment, and imaging technology emphasizing volumetric size and shape, as well as white matter organization and

integrity, are likely to be most fruitful in identifying the unique neurobiological profile of girls with ADHD.

Although a pattern of neurological abnormalities has not been identified in girls with ADHD, it is clear that these children manifest greater behavioral and social difficulties than their peers [Gaub and Carlson, 1997; Gershon, 2000]. Given that girls' brains mature as much as 1–2 years earlier in regions identified as anomalous in boys with ADHD [Thompson et al., 2005], it is necessary to examine brain development longitudinally in younger children to fully appreciate the course of ADHD in girls. Further, longitudinal study of ADHD beginning in the pre-school years and continuing through adolescence and young adulthood is critical to elucidate the developmental sequence of brain and behavioral aspects of the disorder, which are expected to differ in boys and girls. Understanding the “girl and boy” sequences in the unfolding of ADHD can ultimately enhance prevention (or at least mitigation) of symptoms/signs in school age children.

The current review highlights a number of skills in which the pattern of dysfunction among girls with ADHD differs from that of boys with ADHD. For example, boys with ADHD manifest atypical motor development earlier and longer than do girls with ADHD, which may be related (at least in part) to differences in basal ganglia development. Not surprisingly, cognitive tasks that emphasize speed represent a particular area of weakness for boys, but not necessarily for girls with ADHD. In the typical elementary school setting, multiple demands for graphomotor control and speed are introduced to children as early as first grade. Here, boys with ADHD may be at a particular disadvantage, and may need to expend tremendous mental effort to function “normally” on tasks involving speed, thus taking focus away from learning activities introduced simultaneously. In contrast, young girls with ADHD may not be as vulnerable under academic demands such as handwriting, or when support for maintaining their optimal level of alertness and arousal is provided externally (e.g., by teachers). However, they may have more difficulty when faced with tasks involving independent planning—particularly when the planning must be done mentally, i.e., without the immediate feedback provided by teachers or other adults. These tasks are much more prominent in the daily lives of middle and high school students. Finally, the reduced oculomotor speed and control in basic eye movements among girls (but not boys) with ADHD is intriguing and requires further exploration, especially as these deficits may contribute to secondary academic difficulties involving reading or other functions dependent on these controlled motor skills.

The present review also suggests a framework for considering the unique neurobehavioral profile of girls with ADHD. First, it is strongly recommended that girls and boys with ADHD be contrasted with sex-specific comparison groups, both in imaging and in behavioral studies. Such research, however, is impeded by the current diagnostic criteria of DSM-IV diagnostic schema in which onset of symptoms is required by age 7 years [Kordon et al., 2006; Waschbusch and King, 2006]. Second, during the core school-age years, girls with ADHD may have a more subtle neuropsychological profile than boys with ADHD; however, this pattern may not hold true for younger (e.g., preschool) children, and for adolescents and young adults. It is in these age groups that the trajectory of development unique to girls can highlight both protective factors and areas of specific vulnerability, again highlighting the need for longitudinal research.

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