

# ADHD: Volumetry, Motor, and Oculomotor Functions

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**Abstract** The use of quantitative neuroimaging (volumetry), motor, and oculomotor assessments for studying children with attention-deficit/hyperactivity disorder (ADHD) has grown dramatically in the past 20 years. Most evidence to date suggests

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that anomalous basal ganglia development plays an important role in early manifestation of ADHD; however, widespread cerebellar and cortical delays are also observed and are associated with the behavioral (cognitive, motor, oculomotor) phenotype in children with ADHD. These motor and “executive” control systems appear to develop in parallel, such that both systems display a similar protracted developmental trajectory, with periods of rapid growth in elementary years and continued maturation into young adulthood. Development of each system is dependent on the functional integrity and maturation of related brain regions, suggesting a shared neural circuitry that includes frontostriatal systems and the cerebellum (i.e., those identified as anomalous in studies of volumetry in ADHD). Motor and oculomotor paradigms provide unique opportunities to examine executive control processes that exist at the interface between movement and cognition in children with ADHD, also linking cognition and neurological development. The observed pattern of volumetric differences, together with the known parallel development of motor and executive control systems, appears to predict motor and oculomotor anomalies in ADHD, which are highly relevant, yet commonly overlooked in clinical settings.

**Keywords** Attention · Childhood · Executive function · MRI · Saccade · Sensorimotor · Volume

## Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
aMRI	Anatomic (MRI)
DAMP	Deficits in attention motor control, and perception
DAT	Dopamine transporter
DCD	Developmental coordination disorder
DRD1/DRD4	Dopamine receptor (D1 or D4 subtype)
LDDMM	Large deformation diffeomorphic metric mapping
MABC	Motor Assessment Battery for Children
MFNA	Motor Function Neurological Assessment (MFNU)
MGS	Memory-guided saccades
MRI	Magnetic resonance imaging
ODD	Oppositional defiant disorder
SMC	Supplementary motor complex
TMS	Transcranial magnetic stimulation

## 1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder involving motor intentional systems that are mediated in part by frontostriatal and fronto-cerebellar circuitry (Durstun et al. 2010). These neuroanatomic anomalies

(delays), observed in children with ADHD, set the stage for deficits in motor and oculomotor coordination and speed, which, when carefully assessed, are ubiquitous to the disorder and contribute to persistent cognitive and academic dysfunction. Children with ADHD commonly exhibit deficits in controlled behavior including difficulties with inhibition, delay aversion, and temporal processing (Sonuga-Barke and Halperin 2010) that are supported by a distributed neural network with cortical and subcortical components, including the frontal cortex and its striatal–thalamic–cerebellar connections (Durstun et al. 2003, 2010) – those identified as most anomalous in ADHD. Indeed, current neurological models of frontal lobe structure and function have their basis in a well-described series of at least five parallel frontal–subcortical circuits (Lichter and Cummings 2001), of which two are related to motor function, originating in skeletomotor and oculomotor regions of the cortex. The other three, originating in dorsolateral prefrontal, orbitofrontal, and anterior cingulate regions, are thought to be crucial in cognitive (“executive”) and socioemotional control. Frontal projections to the basal ganglia and cerebellum form a series of frontal–striatal–thalamo–frontal and frontal cerebello (dentato)–frontal circuits (Krause et al. 2000). These circuits link specific regions of the frontal lobes to subcortical structures, supply modality-specific mechanisms for interaction with the environment, and provide the framework for understanding the neurobiological substrate of ADHD.

## 2 Volumetry in ADHD

The use of quantitative neuroimaging (volumetry) for studying whole brain, as well as regional development in children with ADHD, is now over 20 years old. Compared with the earliest volumetric investigations, researchers now benefit from the availability of MRI scanners with higher field strength (up to 7.0 Tesla) and increased computational power that has enabled the development of more sophisticated analytic methods (Castellanos and Proal 2009). These newer methodologies now allow for the examination of morphology, as well as volume, including thickness of various regions of the cortical mantle, shape analysis of surface changes, and higher resolution of imagery – thereby allowing better demarcation of gray matter, white matter, and cerebrospinal fluid in measurement.

### 2.1 *Frontostriatal Anomalies in ADHD*

Among children with ADHD, the early structural MRI evidence showed consistent reductions in total cerebral volume (3–8%) compared to typically developing children without ADHD (Hill et al. 2003). It soon became clear that the convergence of findings revealed robust abnormalities in frontostriatal systems, including reduced size of the left caudate (Hynd et al. 1993), right caudate (Castellanos et al. 1994), right globus pallidus (Castellanos et al. 1996), and smaller left globus

pallidus (Aylward et al. 1996). Decreased size of frontal regions was also a consistent early finding in ADHD, including bilateral frontal volumes (Hynd et al. 1990), right anterior frontal volumes (Castellanos et al. 1996), right anterior superior white matter (Filipek et al. 1997), and right dorsolateral prefrontal cortex (Hill et al. 2003). Children with ADHD were also found to have decreased area of the rostral body corpus callosum relative to controls (Baumgardner et al. 1996).

Early anatomic MRI (aMRI) studies of the cerebral cortex in ADHD relied on a volumetric approach, in which gray and white matter volumes were measured within parcellated subregions, initially defined by callosal landmarks (Castellanos et al. 1996; Filipek et al. 1997). Multiple aMRI studies of ADHD have continued to reveal abnormalities in frontal areas (Castellanos et al. 2000, 2002; Hesslinger et al. 2002; Kates et al. 2002; Mostofsky et al. 2002). More recently, investigators have used cortical landmarks to define functionally relevant lobar (frontal, parietal, temporal, occipital) and sublobar (e.g., prefrontal, premotor, anterior cingulate) regions. These studies have revealed decreased volumes in both prefrontal and premotor regions (Kates et al. 2002; Mostofsky et al. 2002). Subcortical anomalies in children with ADHD also continue to be identified, and include: the caudate nucleus (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). There is an emerging convergence of findings suggesting ADHD-related reductions in medial prefrontal and anterior and posterior cingulate and precuneus (Castellanos and Proal 2009).

At the cerebral cortical level, the decreased volume of several frontal (Castellanos et al. 1996; Filipek et al. 1997; Hesslinger et al. 2002; Mostofsky et al. 2002) regions suggests that abnormalities are not localized to a specific area: rather, they appear widespread throughout the brain, including superior prefrontal cortex, reduced midsagittal area of the cerebellar vermis, and smaller splenium of the corpus callosum (Hill et al. 2003). Among school-aged children with ADHD (but not controls), prefrontal volume (especially right superior prefrontal) predicted performance on measures of sustained attention (Hill et al. 2003).

One of the challenges to MRI studies of ADHD is the presence of comorbidities that complicate the interpretation of anatomic findings, particularly among diagnostic groups for whom pathological *increases* in regional brain volume may mask the ADHD-related reductions. Further, there have been few studies that carefully contrast the neuroanatomic anomalies associated with ADHD with those of other childhood disorders that present with anomalous brain development while controlling for comorbidities. For example, while children with ADHD and autism spectrum disorders (ASD) both show regional reductions in cortical development, those with ASD show atypical *increases* (compared to controls) in gray matter volume in the right supramarginal gyrus (Brieber et al. 2007) and in frontal white matter (Mostofsky et al. 2007). Further, in studies in which oppositional defiant disorder (ODD) and conduct disorder (CD) comorbidities are taken into account, there are more widespread regions of reduced cerebral volume in children with ADHD, suggesting that these comorbidities may serve to mask some of the volumetric reductions, compared with samples of children with “pure” ADHD

(Sasayama et al. 2010). The same pattern is observed in children with “pure” Tourette syndrome (TS), for whom disproportionate *increases* in frontal white matter and rostral corpus callosum volume were observed (compared to controls) – a pattern that contrasted with that observed in children with “pure” ADHD, in whom reductions in these regions were observed, and in children with comorbid TS and ADHD, in whom no differences with controls were observed in these regions (Fredericksen et al. 2002).

The few meta-analyses of volumetry in ADHD have highlighted frontal anomalies as well as other cortical and subcortical anomalies, including differences in total right and left cerebral volume, cerebellar regions, splenium of the corpus callosum (Valera et al. 2006), and gray matter reduction in right putamen/globus pallidus (Ellison-Wright et al. 2008). However, these meta-analyses highlighted the fact that females have been underrepresented in the ADHD neuroimaging literature (Valera et al. 2006). Many of these early studies reported findings on ADHD samples that were predominantly (or exclusively) male, and so conclusions could not be drawn about female-specific anomalies in ADHD. In what may be the only volumetric study specific to girls with ADHD, Castellanos (Castellanos et al. 2001) reported ADHD-related reductions in left caudate and posterior–inferior cerebellar vermis, with equivocal frontal lobe findings. 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” (p 293).

More recently, Mahone et al. (2009b) examined functionally defined (and manually delineated) frontal lobe subdivisions in contemporaneously recruited samples of boys and girls with and without ADHD. Compared to age-matched controls, children with ADHD showed reduced tissue volumes involving prefrontal and premotor regions, with largest volume reductions (in both boys and girls) observed in the supplementary motor complex (SMC). Further, girls (but not boys) with ADHD showed reduced lateral premotor cortex and increased primary motor cortex volumes. Across groups, however, reduced SMC volume was associated with ADHD symptom severity, suggesting dysfunction in circuits important for motor response selection and inhibition (Mahone et al. 2009b).

## 2.2 Caudate Anomalies in ADHD

Although early empirical evidence highlighted anomalous frontal brain development in ADHD (Castellanos et al. 1996; Mostofsky et al. 2002; Casey et al. 1997; Durston et al. 2004), more recent research has argued that other brain regions (particularly subcortical) may provide answers to the early neurobiological unfolding of ADHD (Valera et al. 2006; Halperin and Schulz 2006). For example, among children with early prefrontal lesions, functional impairment often does not manifest until later childhood (Anderson et al. 1999) and then tends to get worse upon entry into adolescence (Denckla and Cutting 2004). In contrast, symptoms of

ADHD are almost always evident during the preschool years (Barkley 2006), and the severity of symptoms (most notably hyperactive/impulsive symptoms) tends to diminish with age (Hinshaw et al. 2006). This pattern has led some researchers to hypothesize that the prefrontal cortex may be more involved in recovery from ADHD, rather than the cause of the disorder, and that early disruption to other regions, notably the basal ganglia, may be involved in the early development of ADHD (Halperin and Schulz 2006; Soliva et al. 2010), perhaps through underuse of these brain regions, or via poor neural connectivity, giving rise to later delays in the development of cortical volumes (Shaw et al. 2006).

The preceding hypothesis has considerable appeal in explaining the parallel development of regional brain volumes and unfolding of patterns of executive and motor dysfunction in ADHD. The basal ganglia serve as the nexus through which prefrontal, premotor, and motor signals inhibit competing motor programs and disinhibit intended behaviors (Mink 1996; Nachev et al. 2008). In particular, the number of cells that project from the basal ganglia to the supplementary motor cortex (a region critical for response control, which is reduced in ADHD (Mahone et al. 2009b; Ranta et al. 2009) is three to four times the number that project from the cerebellum, suggesting a critical early link between basal ganglia development and response control (Akkal et al. 2007).

Consistent with the hypothesis of early basal ganglia dysfunction is a recent meta-analysis in which the right caudate was among the most frequently assessed and showed the largest ADHD-related reductions, compared to controls (Valera et al. 2006). Further, longitudinal studies of animal models of ADHD (using spontaneously hypertensive rats) highlight the importance of early striatal reductions that stabilize by 6 weeks of age (human equivalent = 7–9 years) (Hsu et al. 2010). Similarly, a longitudinal study of children with ADHD suggests that normalization of reduced caudate volume occurs by puberty (Castellanos et al. 2002). Thus, the developmental trajectory of caudate anomalies in ADHD appears to parallel the pattern of development of hyperactive–impulsive symptoms (Biederman et al. 2000), such that early caudate reduction is associated with increased symptoms that tend to resolve with accelerated growth (normalization in volume) by adolescence. For example, Carmona and colleagues reported bilateral reductions in the volume of the ventral striatum that correlated with maternal ratings of hyperactivity (Carmona et al. 2009).

Indeed, investigations in humans continue to highlight the importance of early caudate anomalies in children with ADHD. In a study of nine monozygotic twin pairs, discordant for ADHD, Castellanos et al. reported that the affected children had smaller total caudate volumes (Castellanos et al. 2003). There is also accumulating evidence that atypical caudate *asymmetry* in ADHD may be an important biomarker in the development of the disorder. For example, among boys with ADHD, there is evidence of reversed asymmetry of the head of the caudate, such that the ADHD group had a smaller volume of left caudate head, while controls had a smaller volume of right caudate head (Semrud-Clikeman et al. 2000). Similarly, among boys with ADHD in residential treatment, reversed caudate asymmetry (right > left) was observed, compared to the more typical

(left > right) asymmetry that was present in controls and no group differences observed for putamen volumes (Wellington et al. 2006). Other investigators have observed that atypical caudate asymmetry is a strong predictor of ADHD symptoms, such that a greater degree of right > left asymmetry predicted inattention symptoms, but not hyperactive/impulsive symptoms (Schrimsher et al. 2002). This pattern of asymmetry may hold promise as a biomarker specific to ADHD, especially among boys. Soliva and colleagues examined patterns of asymmetry of caudate volumes in ADHD in 39 children with ADHD (35 boys). They found that a ratio of right caudate volume to total bilateral caudate volume of 0.48 or lower had 95% specificity in predicting ADHD diagnosis (versus typically developing controls) (Soliva et al. 2010).

To identify early patterns of brain anomalies in ADHD, Mahone and colleagues used volumetric imaging to study 26 preschoolers, aged 4–5 years, who presented with and without symptoms of ADHD. After controlling for total cerebral volume, total caudate (but not frontal lobe) volumes were reduced in the ADHD group. Further, across groups, reduced caudate (but not frontal lobe) volume was associated with increased parent ratings of hyperactive/impulsive symptoms. These preliminary findings suggest that early anomalous caudate (perhaps more than frontal lobe) development is associated with early onset of ADHD symptoms (Mahone et al. 2011).

### **2.3 Cerebellar Anomalies in ADHD**

The cerebellum is among the most vulnerable regions to early insult (Volpe 1995) and, like the basal ganglia, may influence the cognitive operations normally thought to be subserved by the frontal lobes (Middleton and Strick 2001), especially given the prevalence of children with ADHD who have motor control problems (Diamond 2000; Pitcher et al. 2003). While phylogenetically older regions (e.g., basal ganglia) mature earlier than newer regions (e.g., cortex), the cerebellum may also continue to develop into the 20s, a finding that has implications for how cerebellar maturation may relate to the symptom onset and developmental change in ADHD, especially because the cerebellum appears less influenced by genetics and more sensitive to environmental variables (Durstun et al. 2010; Fassbender and Schweitzer 2006; Lantieri et al. 2010; Tiemeier et al. 2010).

Indeed, one of the most consistent findings in ADHD brain imaging studies is a decrease in posterior inferior cerebellar vermis (lobes VIII–X) volume (Hill et al. 2003; Castellanos et al. 1996, 2002; Berquin et al. 1998; Mostofsky et al. 1998; Valera et al. 2006; Castellanos et al. 2001; Durstun et al. 2004; Bussing et al. 2002). However, unlike the pattern observed in basal ganglia reductions in ADHD, longitudinal studies suggest that volumetric reductions in posterior inferior cerebellar vermis tend to persist over time; they also remain associated with ADHD symptom severity over time (Castellanos et al. 2002). Furthermore, in a study that included unaffected siblings, total cerebral and prefrontal volumes were reduced

(compared to controls) in boys with ADHD *and* their unaffected siblings. Right cerebellar volume was the only measure reduced in the ADHD group but not in the unaffected siblings (Durstun et al. 2004), suggesting that the cerebellum may play an important role in the pathophysiology of ADHD that is more associated with environmental (rather than genetic) influences. Anomalies in fronto-cerebellar circuitry are thus also considered key to the development of ADHD, given the efferent outputs from the cerebellum to both the frontal cortex and the basal ganglia (Durstun et al. 2010), and the links between anomalous cerebellar development and deficits in motor response control (Suskauer et al. 2008), motor timing (Van Meel et al. 2005), classical conditioning (Chess and Green 2008), and oculomotor control (Voogd et al. 2010).

## **2.4 Nonfrontal Cortical Anomalies in ADHD**

Although the evidence from individual studies and meta-analyses has pointed to frontostriatal regions as being anomalous (reduced) in ADHD, there is also substantial evidence of structural anomalies outside frontostriatal circuitry (Cherkasova and Hechtman 2009) including reductions in cortical temporal lobes (Castellanos et al. 2002; Sowell et al. 2003; Carmona et al. 2005), parietal lobes (Filipek et al. 1997; Castellanos et al. 2002; Carmona et al. 2005), and occipital lobes (Filipek et al. 1997; Castellanos et al. 2002; Durstun et al. 2004). Reductions in medial temporal volumes, as well as striatal and anterior cingulate volumes, are correlated with performance on measures of response inhibition (i.e., stop-signal reaction time) in boys with ADHD (McAlonan et al. 2009). Using voxel-based morphometry, regions that are reduced in ADHD include bilateral temporal poles, occipital cortex, and left amygdala. These regions were even greater when analyses controlled for the presence of oppositional defiant disorder (ODD) (Sasayama et al. 2010). Among boys with ADHD ( $n = 19$ ), decreased callosal thickness was identified in anterior and posterior corpus callosum regions, with the largest reduction observed in isthmus region (which projects to parietal cortex and may be critical for sustaining attentional control) (Luders et al. 2009).

## **2.5 Cortical Morphology in ADHD**

While development of the human nervous system begins 2–3 weeks after conception (Black et al. 1990) 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 (Halperin and Schulz 2006; Gogtay et al. 2004). By age 2 years, the brain is approximately 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 (Gogtay et al. 2004) and eventually reduces synaptic density to 60% of maximum (Huttenlocher and Dabholkar 1997). Longitudinal studies suggest that cortical gray matter 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 (Halperin and Schulz 2006; Gogtay et al. 2004; Giedd et al. 1999). Prominent volumetric reduction of frontal and parietal cortices occurs during adolescence and is considered to be attributable to synaptic pruning or, more likely, the combination of synaptic pruning and increasing myelination (Sowell et al. 2004). Regionally specific, protracted, age-related changes in white matter have been also been described. For example, myelination of optic radiations and occipital white matter begins 1–2 months before birth and extends to frontal lobes by 9 months postnatal age (Marsh et al. 2008; Paus et al. 2001); cortical myelination also follows a posterior-to-anterior direction, with sensory pathways myelinating first, followed by motor pathways, and finally by association areas (Huttenlocher and Dabholkar 1997). In normal development, this dynamic pattern of myelination and associated cortical volume reduction is associated with improvement in cognitive performance; timing of peak cortical volume is considered to be a marker for maturation (Shaw et al. 2007a). Conversely, patterns of pathological pruning may contribute to the genesis of psychiatric disorders (Marsh et al. 2008; Kotrla and Weinberger 2000) and can contribute to onset and progression of ADHD symptoms, delayed cortical maturation and worse clinical outcome (Sowell et al. 2003; Marsh et al. 2008; Shaw et al. 2007a, b).

While school-aged children with ADHD show widespread decreases in cortical volume, the precise morphologic contributions to these reductions are less clear. For example, decreased cortical volume in ADHD can potentially represent a “thinning” of the cortex or a decrease in the total surface area of the cortex, or a combination of both. As such, the study of volumetry in ADHD has begun to emphasize cortical morphology (including thickness and surface area), as well as patterns of cortical folding and shape (Wolosin et al. 2009). In this context, cortical *thickness* refers to linear *distance* from the gray/white boundary to the pial surface (Fischl and Dale 2000), and *thinning* refers to a reduction in this distance compared to controls (or a reduction over time, compared to one’s own cortical thickness).

Sowell and colleagues were among the first to examine cortical morphology in children with ADHD. They identified reduced surface area in inferior portions of dorsal prefrontal cortices bilaterally (Brodmann areas 44, 45, 46), with reductions correlated with symptoms of hyperactivity (Sowell et al. 2003). Similarly, among medication-naïve children and adults with ADHD, reduced cortical thickness in the right superior frontal gyrus was predictive of ADHD symptom severity (Almeida et al. 2010). In a series of large-scale studies, Shaw et al. found that children with

ADHD had a mean thinning of cortex of 0.09 mm globally. The greatest reduction was in medial/superior prefrontal and precentral regions, and the reduction in medial prefrontal cortex was associated with worse clinical outcomes (Shaw et al. 2007a, b). Narr and colleagues also reported ADHD-related cortical thinning over large areas of frontal, temporal, parietal, and occipital association cortices and aspects of motor cortex (although not within the primary sensory regions) (Narr et al. 2009). Conversely, Wolosin (Wolosin et al. 2009) found reduced volume and surface area (but not thickness) in all four lobes bilaterally in children with ADHD.

## 2.6 Longitudinal Volumetric Studies of ADHD

Critical insights into the development of ADHD have emerged from longitudinal studies investigating trajectories of development in children. Castellanos et al. (2002) reported growth curves highlighting the different developmental trajectories of regional brain volumes. For most regions of interest, the growth curves of children with ADHD (relative to controls) were parallel, but on a lower track. More recently, Shaw et al. (Shaw et al. 2007a; Shaw 2010) reported a series of longitudinal studies of children with ADHD using measures of cortical thickness (i.e., distance between the pial surface and white/gray boundary in the cortex). They found that children with ADHD showed *delay* in cortical maturation (i.e., age of attaining peak thickness) throughout the cerebrum. The most prominent area of delay was the lateral prefrontal cortex, with “delay” approaching 5 years in middle prefrontal cortex in children with ADHD. In a follow-up longitudinal study, the same authors demonstrated that this delay in cortical thinning, especially in prefrontal and premotor cortex, was associated with both the severity of ADHD symptoms and the categorical presence of the disorder itself (Shaw 2010).

In a separate longitudinal study of cerebellar development and clinical outcome, Mackie et al. (2007) examined MRI scans from 36 children with ADHD and found a progressive loss of volume (compared to controls) in the superior cerebellar vermis. Moreover, those in the ADHD group who had *worse* clinical outcome had more rapid loss of inferior cerebellar lobes bilaterally, compared with controls or children with ADHD with better outcome. Different longitudinal patterns of change with regard to cortical asymmetry have also been identified in ADHD (Shaw et al. 2009a). For example, in children with ADHD, the (earlier developing) posterior components of cortical asymmetry were observed to be intact, whereas the (later developing) prefrontal components were lost, suggesting a developmental disruption in the prefrontal function in ADHD (Shaw and Rabin 2009).

While most longitudinal studies of ADHD have shown delayed patterns of development throughout the cortex, Shaw et al. (Shaw 2010) also reported that the primary motor cortex showed earlier maturation (i.e., age of attaining peak thickness) in children with ADHD. One hypothesis for this pattern may be that early, excessive motor activity among young children with ADHD activates (and thus facilitates) connections within the primary motor cortex. In other words, the

development of connections in primary motor cortex outpaces the development of connections in other frontal regions that function to restrict motor hyperactivity. The result of this pattern of uneven functional maturation of the frontal cortex gives rise to hyperactivity and deficits in response control in children with ADHD.

## 2.7 *Shape Analysis Applied to ADHD*

Shape analysis represents an emerging, powerful computational method that enables more detailed definition of local surface changes, based on the degree to which a structure has to be warped to meet a template (Shaw 2010). Several studies have begun to specify more precisely the localization of ADHD-related abnormalities using shape analysis that allows for detection of anomalies beyond regional volume. For example, Plessen et al. investigated the morphology of regional hippocampal volumes in 51 children and adolescents (aged 6–18) with combined subtype ADHD. They found that the head of the hippocampus was *enlarged* in children with ADHD, with enlargement related to ADHD symptom severity (albeit weakly) (Plessen et al. 2006).

More recently, Qiu et al. used large deformation diffeomorphic metric mapping (LDDMM) to examine ADHD-related differences in basal ganglia shapes in 47 children with ADHD and 66 controls, aged 8–12 years. While boys with ADHD showed smaller overall basal ganglia volumes compared with control boys, LDDMM analysis identified markedly different basal ganglia shapes in boys with ADHD (compared with control boys), including bilateral volume *compression* in the caudate head and body, anterior putamen, left anterior globus pallidus, and right ventral putamen, but volume *expansion* in posterior putamen. In contrast, no basal ganglia volume or shape differences were revealed in girls with ADHD, compared with control girls in this age range (Qiu et al. 2009).

## 2.8 *Treatment with Stimulant Medication and Volumetry*

While the majority of volumetry research in ADHD has emphasized group differences without characterization of medication use, interest has risen in the effects of stimulant medication treatment on brain volumes. Current research findings suggest that the reductions or delays in brain development among children with ADHD do not appear to be a result of chronic stimulant medication treatment (Schnoebelen et al. 2010). In fact, the preponderance of evidence suggests a protective or even “normalizing” effect of stimulants on brain development in ADHD (Shaw et al. 2009b). Castellanos et al. demonstrated that, among children with ADHD, those treated with stimulants did not differ from controls in white matter volumes, whereas in medication-naïve children with ADHD, white matter volume was reduced compared to controls (Castellanos et al. 2002). More recently, stimulant-related

“normalization” has been reported for children with ADHD in right anterior cingulate and bilateral caudate volumes (i.e., volumes closer to controls compared to those untreated children with ADHD) (Pliszka et al. 2006), and for cross-sectional area of posterior interior cerebellar vermis (Bledsoe et al. 2009). In a similar investigation, Sobel et al. examined basal ganglia surface morphology and the effects of stimulant medication treatment in children with ADHD. Among medication-naïve participants, there were volume reductions in putamen that were primarily driven by *inward* deformations of structures, including those nuclei within the putamen that are components of limbic, sensorimotor, and associative pathways. In contrast, those treated with stimulants had *outward* deviations of putamen nuclei, suggesting that stimulants may affect, and perhaps facilitate, development of basal ganglia morphology in ADHD (Sobel et al. 2010) in a manner that serves to ameliorate ADHD-related deficits in executive and motor control. Admittedly, comparison of treated versus nontreated children with ADHD is complicated, in part because it is possible that groups may have differed in some systematic way before onset of treatment. For instance, those with more severe and pervasive symptomatology or with comorbidity may opt for stimulant treatment. Nevertheless, in this context, it is even more impressive that those treated with stimulants show greater “normalization” than those not treated.

## 2.9 Genes, ADHD, and Volumetry

ADHD is one of the most heritable childhood neuropsychiatric disorders. Polymorphisms within the dopamine transporter genotype (DAT) and dopamine D4 receptor (DRD4) gene have been frequently implicated in its pathogenesis (Shaw et al. 2007b). As such, investigators have begun to link anatomic MRI with investigation of genetic differences hypothesized to be associated with ADHD. For example, Shook et al. (2010) examined the association between ADHD symptoms and the volume of the head of caudate. This striatal structure has a high dopamine transporter (DAT) expression that is important for inhibitory function and differs in children with ADHD. Overall caudate volumes were smaller in children who were carriers of two copies of the 10-repeat DAT allele than those with one copy, suggesting that altered caudate development, associated with 10-repeat homozygosity of DAT1, may contribute susceptibility to ADHD (Shook et al.). In a related study, Shaw et al. (2007b) examined the effects of the 7-repeat microsatellite in the DRD4 gene on clinical outcome and cortical development in ADHD. Possession of the DRD4 7-repeat allele was associated with a thinner right orbitofrontal/inferior prefrontal and posterior parietal cortex, with overlap in regions found to be thinner in children with ADHD (compared with controls). Participants with ADHD carrying the DRD4 7-repeat allele had a better clinical outcome and a distinct trajectory of cortical development, with this group showing normalization of the right parietal cortical region, which is important for the development of attentional control. By contrast, there were no effects of the

DRD1 or DAT1 polymorphisms on clinical outcome or cortical development, suggesting that the DRD4 7-repeat allele confers a protective effect on volumetric changes and ADHD symptoms. While not a volumetric MRI study, Lantieri et al. (2010) examined the top single-nucleotide polymorphisms (SNPs) that had been identified in a genome-wide association study of ADHD (Neale et al. 2008) using an independent cohort. The two SNPs identified as significant (XKR4 in 8q12.1, and FAM190A in 4q22.1) were both located in genes coding for uncharacterized proteins expressed most prominently in the cerebellum, a region that has shown robust decreases in children with ADHD (Valera et al. 2006).

## ***2.10 Summary: Volumetry in ADHD***

The preponderance of evidence to date highlights widespread “delays” in gray and white matter development that are associated with onset and progression of ADHD symptomatology and do not appear to be associated with chronic stimulant medication use. To the contrary, treatment with stimulants appears to have a protective, or even “normalizing,” effect on brain development in children with ADHD. From a developmental perspective, anomalous basal ganglia development (especially involving the caudate) may play an important role in the early onset of ADHD, while atypical cerebellar development (potentially associated with environmental influences) may be linked with the persistence of symptoms over time. These anatomic anomalies provide the underlying neural substrate for ADHD-related behavioral deficits in motor and executive control, particularly during the elementary school years. In particular, the parallel development of motor and executive control systems suggests a shared neural circuitry that includes frontostriatal systems and the cerebellum (i.e., those identified as anomalous in ADHD), and thus the study of neuroanatomic development in ADHD is inextricably linked with the study of motor and response control skills.

Nevertheless, despite the proliferation of studies, conclusions from existing literature have been complicated by reliance on cross-sectional designs, samples including largely (or exclusively) males, differences related to medication treatment history, and inconsistencies in samples due to comorbidities and ADHD subtypes. The future of volumetric-imaging ADHD is likely to involve more emphasis on shape analysis, genes, and greater attempts to link volumetric imaging developmentally with emergence of (and recovery from) symptoms. Emerging methodologies may also enable investigators to differentiate ADHD subtypes according to empirically supported neuropsychological differences, such as the triple pathway model (inhibitory control, delay aversion, temporal processing) proposed by Sonuga-Barke (Sonuga-Barke and Halperin 2010), or linking these functions more directly to neural circuitry, such as defining a “dorsal fronto-striatal” (cognitive control), “orbitofronto-striatal” (reward processing), or “fronto-cerebellar” (timing) subtypes (Durstun et al. 2010 ).

### 3 Motor Functions in ADHD

When carefully assessed, motor skill deficits are ubiquitous in children with ADHD, likely as a function of the known anomalous development of frontostriatal-cerebellar circuitry associated with the disorder. Unfortunately, the presence of poor motor skills in ADHD is associated with slow and effortful completion of routine tasks, and can increase attentional demands on other processes, such as working memory, thereby creating a bottleneck. Those with ADHD are often left to trade accuracy for speed (Klimkeit et al. 2004), or use more controlled attentional resources to maintain what should be otherwise automatic postural control (Roebbers and Kauer 2009), thereby creating an even greater state of “inattention,” or otherwise exacerbating other skill deficits.

Historically, motor assessment in children has been used to delineate behavioral development patterns that distinguish clinical groups, and to examine the effects of treatment – especially medication. Cognitive and emotional control, however, can be considered “mental” neighbors of motor control, as their respective circuitries are organized in proximity to circuits supporting motor systems. In fact, motor and executive control systems appear to develop in parallel. Both systems display a similar protracted developmental trajectory, with periods of rapid growth in elementary years and continued maturation into young adulthood (Diamond 2000). Furthermore, development of each system is dependent on the functional integrity and maturation of related brain regions, suggesting a shared neural circuitry that includes frontostriatal systems and the cerebellum (i.e., those identified as anomalous *via* volumetry) (Diamond 2000; Pennington and Ozonoff 1996; Rubia et al. 2001). Age and sex are also important mediating factors that need to be considered in motor examination with children (Denckla 1974).

Because the systems that support motor and higher order “cognitive” control both have protracted periods of development, they are vulnerable to disruption via a variety of etiologies – which is likely why so many children with neurodevelopmental disorders (such as ADHD) present with both motor and executive dysfunction. For example, among 5–6-year-old children, motor behavior was associated with executive control (i.e., performance on a Stroop task) as well as with severity of externalizing behaviors (Livesey et al. 2006). A strong association between attention and motor coordination in 7-year-old children has also been identified (Piek et al. 2004). Moreover, deficits in either executive or motor control systems frequently present with coexisting deficits in the other: for example, approximately half of the children with ADHD demonstrate problems with motor coordination (Pitcher et al. 2003; Carte et al. 1996; Denckla and Rudel 1978; Kadesjo and Gillberg 1998; Steger et al. 2001), while approximately half of the children with developmental coordination disorder (DCD) manifest problems with attention (Kaplan et al. 1998), although the presence of both ADHD and DCD is associated with greater risk for poor psychosocial outcome than ADHD alone (Rasmussen and Gillberg 2000). In Sweden, the overlap between attention and motor control has long been recognized and is characterized as part of the

syndrome of deficits in attention, motor control, and perception (DAMP) (Gillberg et al. 1992). Additionally, prominent theories of ADHD, such as the cognitive-energetic model of information processing, link motor behavior to executive control (Sergeant 2000). Thus, assessment of motor function can be critical to understanding both the biological substrates and cognitive phenotypes associated with ADHD (Denckla 2005).

### 3.1 *Subtle Signs and ADHD*

A variety of standardized tests of motor function (speed, coordination, strength) with published normative data are available for school-aged children. Beyond these commercially available tests, careful clinical assessment of basic motor function in children can reveal subtle motor dysfunction. Such neurological subtle signs include *overflow* (also called “associated” or “extraneous”) movements, *involuntary movements* (i.e., limb tremor, odd posturing, choreiform), and *dysrhythmia*. These subtle signs can be reliably assessed (Gustafsson et al. 2010; Stray et al. 2009a) and can serve as markers for inefficiency in neighboring parallel brain systems that are important for control of cognition and behavior. It is common to observe subtle signs in typically developing younger children (Largo et al. 2001). However, there is evidence that persistence of subtle signs into later childhood can be a marker for atypical neurological function – often associated with disorders such as ADHD (Morris et al. 2001; Mostofsky et al. 2003; Cole et al. 2008). In fact (before the institution of the ADHD diagnosis in DSM-III), motor exam results (including speed, overflow, dysrhythmia) correctly classified 89% of boys who scored highly for the “hyperactivity” syndrome (Denckla and Rudel 1978). Similarly, early research in dyslexia typically did not screen for, or measure, ADHD symptoms in their dyslexic samples. When directly screened, children with dyslexia *without* attention problems performed better than children with dyslexia *with* attention problems on five of six rapid movements. The screened dyslexic group also had fewer signs of dysrhythmia or overflow than the unscreened group (Denckla et al. 1985). Although subtle signs can be important biomarkers, they can be variable and their presence alone should be neither considered diagnostic nor the sole basis for explaining complex behavioral and neurological disorders (Touwen and Sporrel 1979; Touwen 1987) such as ADHD.

### 3.2 *Overflow*

Overflow is defined as comovement of body parts not specifically needed to efficiently complete a task. As typically developing children mature, they manifest fewer overflow movements (Largo et al. 2003). The presence of age-inappropriate

overflow may reflect immaturity of cortical systems involved with automatic inhibition (Mostofsky et al. 2003). In particular, observed overflow after 10 years of age may be a strong indicator of developmental dysfunction (Denckla and Rudel 1978). Motor-skill development, particularly the developmental pattern of asymmetries in left-, versus right-, sided performance, may be a marker for maturation of the corpus callosum or for the different rates of development of the cerebral hemispheres – known to be anomalous in ADHD (Roeder et al. 2008).

Among overflow movements, the most studied are mirror movements (i.e., synkinesis), which refers to involuntary movements that accompany voluntary movements on the contralateral side of the body. The presence of mirror overflow movements in adolescents and adults in disorders of both the motor cortex and the corpus callosum suggests that the ability to perform unilateral fine motor movements is dependent upon intact interhemispheric and corticospinal connections (Nass 1985; Knyazeva et al. 1997; Meyer et al. 1998). The supplementary motor complex (SMC) (and in particular the pre-SMC) has dense callosal and interhemispheric connectivity, arguing for a role in voluntary and involuntary movements. In particular, the SMC may have a role in suppressing default movements (Addamo et al. 2007). Mirror overflow may also be due to abnormally active ipsilateral corticospinal tract (reflecting more severe early neurodevelopmental abnormalities), as well as bilaterally active corticospinal tracts, which may occur in normal individuals under conditions of fatigue (Hoy et al. 2007). Mirror overflow movements appear to develop in a U-shaped relationship with age, decreasing rapidly during childhood (suggesting increased inhibition), then increasing with age in late adulthood (suggesting age-related loss of inhibition with aging) (Koerte et al. 2010). Thus, when cortical inhibitory and excitatory systems are immature, overflow movements in children are at their peak. As these cortical systems mature, overflow movements are more difficult to elicit and their presence into adolescence is thought to be associated with delayed cortical maturation (Cole et al. 2008).

As a disorder involving delay in development of brain systems supporting motor inhibition (Shaw 2010), overflow movements may represent important neurobehavioral markers in ADHD, especially as they appear to have linear associations with ADHD symptoms in early years. For example, in 5–6-year-old children, qualitative aspects of motor problems (subtle signs/overflow) as well as dynamic balance and manual dexterity were predictive of ADHD symptoms 18 months later, but not predictive of symptoms of oppositional defiant disorder or conduct disorder (Kroes et al. 2002). In a separate cohort, subtle signs at age 4–6 years were significant predictors of ADHD symptoms, in both low birth weight and normal birth weight children (Sato et al. 2004).

Among school-aged children, there also appears to be an association between motor overflow and performance on tasks of attentional control (Waber et al. 1985), as well as effortful motor response inhibition (Mostofsky et al. 2003; Cole et al. 2008). Children aged 5–11 years, with more evidence of minor neuromotor dysfunction, perform more poorly in school and have more signs of attention deficit (Batstra et al. 2003). Conversely, reduction in overflow movements appears to parallel reduction in ADHD symptomatology. In a large sample of children aged

7–14, controls and girls with ADHD showed steady age-related reduction of overflow and dysrhythmia, whereas boys with ADHD had little improvement in these signs through age 14 years (Cole et al. 2008).

### ***3.3 Approaches to Motor Assessment in ADHD***

Motor deficits may represent an important endophenotype in ADHD. For example, on a computerized tracking task, both children with ADHD and their unaffected siblings expressed deficits, relative to controls (Rommelse et al. 2007). Motor-control difficulties also have specificity for ADHD, compared with other disorders. Among children with Tourette syndrome, for example, those with ADHD have motor slowing, whereas those with Tourette syndrome alone (without ADHD) do not (Schuerholz et al. 1997). Poor motor coordination has been associated with oppositional defiant disorder, but not with conduct disorder (Martin et al. 2010). Iranian boys with ADHD showed deficits (relative to controls) on eight of nine fine motor tasks (cutting, threading buttons, grooved pegboard), despite showing no differences in IQ (Lavasani and Stagnitti 2010). Motor problems in ADHD are readily observed when performing nonautomated (Carte et al. 1996) or skilled movements (e.g., Grooved Pegboard) more than when performing simple repetitive movements (finger tapping) (Meyer and Sagvolden 2006).

Caregiver ratings of motor skills are also important diagnostically. Parents and teachers rate motor skill problems in as many as one-third of children with ADHD (Fliers et al. 2008), although children with ADHD, who show deficits on performance-based tests of motor control, do not tend to rate themselves as having motor problems (Fliers et al. 2010). In a large study of 7–19-year-old children, those with parent ratings of ADHD and motor coordination problems were also rated as having elevated levels of autistic symptoms (Reiersen et al. 2008).

Given their effects on dopamine transmission throughout the brain, stimulant medications can improve not only attentional control but also motor control. For example, unmedicated boys with ADHD showed deficits in postural control (measured via motion analysis of head stability), characterized by increased low levels of baseline head movement, punctuated by higher-amplitude spikes. Following administration of methylphenidate, however, both the baseline and spike amplitudes of the ADHD group were suppressed to levels at or below that of controls (Ohashi et al. 2010). Similarly, treatment with stimulant medication improved handwriting (Flapper et al. 2006) and overall motor performance in children with ADHD and/or DCD on the Motor Assessment Battery for Children (MABC) (Flapper et al. 2006; Bart et al. 2010) and the Motor Function Neurological Assessment (MFNU) (Stray et al. 2009b), although balance was not improved by stimulants (Bart et al. 2006). Other studies similarly found that larger motor skills (as measured by the Test of Gross Motor Development-2) were less affected by stimulant medication treatment (Harvey et al. 2007).

### **3.4 Summary: Motor Skills in ADHD**

The preponderance of evidence from structural imaging studies of ADHD suggests anomalous and/or delayed development of brain systems that are critical to the development of motor skills, including prefrontal and premotor cortex, corpus callosum, basal ganglia, and cerebellar vermis. When carefully assessed, children with ADHD manifest a variety of deficits in motor skills, with co-occurrence of developmental coordination disorder in nearly 50%. These motor skill weaknesses contribute to slowed processing speed, poor automatization of skills, and inefficiency of task completion. Improvements in motor speed and coordination, and reductions in “abnormal-for-age” subtle signs among children with ADHD appear to occur in parallel with the (delayed) development of cortical brain systems supporting motor control. This process of “normalization” of motor functioning occurs earlier in girls with ADHD than in boys with ADHD. While stimulant medication may help with both attention and motor control, treatment plans for children with ADHD (especially boys) should carefully consider the (likely) coexisting motor deficits and plan for intervention and accommodations accordingly.

## **4 Oculomotor Functions and ADHD**

Motor skill deficits are ubiquitous in children with ADHD, likely as a function of the anomalous development of frontostriatal-cerebellar circuitry associated with the disorder. Like the motor system, the oculomotor system is highly relevant in children with ADHD and includes a widely distributed network, incorporating regions of the cerebral cortex as well as the basal ganglia, thalamus, cerebellum, superior colliculus, and brainstem reticular formation. Oculomotor paradigms can provide unique opportunities to examine executive control processes that exist at the interface between movement and cognition (Leigh and Zee 2006). These paradigms can complement other diagnostic and exploratory studies, because they afford a degree of quantification about information processing and timing not found in methods such as MRI or neuropsychological testing. This is because it is virtually impossible to operationalize visual attention without documenting “looking,” which means “where the eyes are fixed” (Lasker et al. 2007). As such, oculomotor paradigms may offer a more precise means of assessing components of visual attention that link cognition and neurological development.

The oculomotor system includes a widely distributed network with regions in the cerebral cortex (frontal eye fields, posterior parietal cortex, supplementary eye fields, presupplementary motor area, dorsolateral prefrontal cortex), as well as the basal ganglia, thalamus, cerebellum, superior colliculus, and brainstem reticular formation (Munoz and Everling 2004). Frontal regions project to the superior colliculus, where cortical and subcortical signals converge and are integrated

(Munoz and Everling 2004). Within the frontal cortex, the frontal eye fields have a critical role in voluntary saccades (Schall 1997). The supplementary eye fields are important for sequencing of saccades and error monitoring (Stuphorn et al. 2000). The DLPFC is involved in spatial working memory and in suppressing reflexive saccades (Pierrot-Deseilligny et al. 1991). These frontal cortical oculomotor regions also project directly and indirectly to the caudate nucleus (Hikosaka et al. 2000), and directly to the paramedian pontine reticular formation, which provides input to the saccadic premotor circuit. Both projections support the initiation and suppression of visual saccades (Munoz and Everling 2004). Of importance is the observation that the same regions involved in oculomotor control are also those in which anomalous or delayed development is observed in children with ADHD. Not surprisingly, children with ADHD are found to have deficits (inefficiency) in both the initiation and suppression of controlled eye movements. These oculomotor deficits in ADHD are associated with slowed processing speed, poor automaticity of skills, and more effortful processing on routine tasks.

#### **4.1 Experimental Assessment of Eye Movements and Oculomotor Control**

Two types of oculomotor skills are examined under experimental conditions: those involving *fixation* of the eyes and those involving *movement* of the eyes. Fixation paradigms require the individual to maintain fixation on a stimulus – often in the face of varying types of distracters. Visual fixation paradigms are associated with activation of premotor, prefrontal, and striatal structures (Paus 1991; Brown et al. 2007; Curtis and Connolly 2008) and, as a result, can be useful in examining oculomotor persistence in ADHD, particularly as poor postural stability of head (Ohashi et al. 2010) is likely to have deleterious effect on eye fixation and oculomotor control.

Experimental examination of eye movements also involves assessment of *saccades*, which are fast eye movements made by the oculomotor system. Their purpose is to bring some part of the visual field onto the fovea where it can be seen and acted upon. Saccades are usually classified into various categories depending on what initiates them. *Reflexive* saccades are usually involuntary and can be triggered by a novel stimulus in the immediate environment. The saccade is usually accompanied by a quick head move in order to bring the eyes quickly on target. In laboratory assessments, reflexive saccade can be approximated by asking individuals to immediately move their eyes to a target light as soon as it comes on (usually with the head movement constrained). In contrast, *volitional* saccades are those eye movements that are made with intent, thus invoking greater executive control demand (so that the eyes go where the individual wishes).

Included within the category of volitional saccades are: delayed saccades, memory-guided saccades, antisaccades, anticipatory saccades, and predictive saccades. *Delayed* saccades are those saccades that are initiated some time after

a target is perceived. The individual knows the target, but is required to inhibit responding until an external signal is given to respond. *Memory-guided* saccades are made some time after the stimulus has disappeared and the individual looks toward his/her last seen position. The *antisaccade* is a saccade that is made in the opposite direction of a presenting target, requiring inhibition of a prepotent or reflexive response. *Anticipatory* saccades are those eye movements made with the idea that a stimulus will occur sometime in the future, but without the knowledge of where or when it will occur. *Predictive* saccades are made to a regularly occurring target and have the distinction of being elicited before the stimulus has occurred. Unlike anticipatory saccades, which can occur any time before the stimulus is presented, predictive saccades occur as a specific response to the repetitiveness of the stimulus.

The types of variables obtained in oculomotor paradigms tend to capture three important components of executive control: *response preparation* (saccade latency and variability), *response inhibition* (antisaccade directional errors; anticipatory errors, go/no-go commission errors), and *working memory* (memory-guided saccade accuracy). Interpretation of saccades in children should take into account age-related change (Munoz et al. 1998; Fukushima et al. 2000), whereby saccadic performance improves rapidly during early childhood and then stabilizes after adolescence, with inhibition and response latency stabilizing at age 14 and 15, respectively, and spatial working memory stabilizing latest (age 19) (Luna et al. 2004). Frontal and parietal cortex and anterior cingulate appear to be involved in a “state of preparedness” for oculomotor tasks. Increased intraindividual variability (observable on oculomotor tasks) has been linked with frontal circuits important for motor response selection and inhibition, particularly those involving the rostral supplementary motor complex (pre-SMC) (Mostofsky and Simmonds 2008).

## 4.2 Assessment of Oculomotor Skills in ADHD

Studies examining oculomotor skills have contributed to the understanding of the neurobiological basis of ADHD. In general, they have supported the “motor intentional deficit” hypotheses, with ADHD groups demonstrating robust abnormalities related to response inhibition (i.e., increased commission errors on antisaccade and go/no-go tasks; greater anticipatory errors) and response preparation (i.e., increased response latency and intraindividual variability). Oculomotor deficits in smooth pursuit eye movements (Castellanos et al. 2000) and working memory have been found less consistently in studies of ADHD (Mahone et al. 2009a).

### 4.2.1 Response Preparation

Children with ADHD have longer and more variable response latency on even the most basic “reflexive” prosaccade tasks (Mostofsky et al. 2001) although, in a later study with a larger sample, the impairment was observed in girls (but not boys) with

ADHD (Mahone et al. 2009a). Goto (Goto et al. 2010) also found increased response latency on prosaccade and antisaccade tasks in children with ADHD, but only among younger age groups (6–8 years); similar deficits were not observed among older children with ADHD. There is also emerging evidence that (like motor skills) oculomotor skills may represent an important endophenotype for ADHD. Van der Stigchel (Van der Stigchel et al. 2007) found that boys with ADHD and their unaffected brothers had slower oculomotor responses across tasks than controls. Across groups, oculomotor response latency correlated with a dimensional rating of ADHD inattentive symptoms, such that greater symptoms were associated with increased response latency.

#### 4.2.2 Response Inhibition

Increased response inhibition errors on oculomotor tasks have been a robust and consistent finding across different studies and paradigms, including children (Mostofsky et al. 2001; Goto et al. 2010; Mahone et al. 2009a) and adults with ADHD (Armstrong and Munoz 2003; Nigg et al. 2002). Compared to typically developing controls, children with ADHD show increased commission errors, more intrusion errors on go/no-go tasks (Ross et al. 1994), and a higher proportion of anticipatory and directional errors than controls (Goto et al. 2010; Hanisch et al. 2006). Similar results are obtained among samples comprising primarily boys (Mostofsky et al. 2001) and those with exclusively girls (Castellanos et al. 2000). In the study of only girls, those with ADHD made twice as many commission errors and three times as many intrusion errors on a go/no-go task than controls (Castellanos et al. 2000), while smooth pursuit performance was equivalent across groups.

Increased inhibition and anticipatory errors have also been observed on antisaccade and delays tasks (Van der Stigchel et al. 2007), with the proportion of intrusive saccades correlating with ADHD symptom severity. Mahone et al. (2009a) found that both boys and girls with ADHD (aged 8–12 years) had increased inhibitory errors (i.e., commissions on antisaccade and go/no-go tasks; anticipatory errors on memory-guided saccades). Among older children (aged 11–14), those with ADHD combined (but not inattentive) subtype had increased antisaccade errors (relative to male controls) but showed significant improvement in these errors following treatment with methylphenidate (O'Driscoll et al. 2005).

#### 4.2.3 Working Memory

ADHD groups (especially those with predominantly or exclusively male samples) have shown inconsistent deficits in the accuracy of memory-guided saccades (MGS), which are thought to assess spatial working memory (Mostofsky et al. 2001; Ross et al. 1994). In one study that included only girls, there was a strong trend ( $p = 0.07$ ) for reduced MGS accuracy (Castellanos et al. 2000) and, in a mixed sample, children with ADHD (aged 8–13) had poorer resistance to peripheral distracters (fixation), inhibition on antisaccades, and poorer spatial working

memory (memory-guided saccades), compared to controls (Loe et al. 2009). However, in a more recent study including a sample of boys and girls with ADHD, matched on subtype, neither boys nor girls with ADHD (as a group) were deficient on the MGS task relative to controls although, across sexes, those with inattentive subtype were deficient on the MGS task (Mahone et al. 2009a).

### **4.3 Summary: Oculomotor Functions in ADHD**

Models of frontal lobe structure and function describe at least five parallel frontal-subcortical circuits (Alexander et al. 1986). The most posterior are related to motor and oculomotor function (originating in skeletomotor and oculomotor regions of the cortex); the more anterior are thought to be crucial in control of higher-order behavior (e.g., cognitive “executive” and socioemotional control). These regions have been identified as anomalous in volumetry. Studies examining oculomotor skills have contributed to the understanding of the neurobiological basis of ADHD, particularly given the utility of oculomotor paradigms to examine the “interface” between motor skills and cognition in ADHD and other neurodevelopmental disorders.

## **5 Conclusions**

ADHD is a disorder involving delayed, anomalous development of the cerebral cortex and subcortical regions, including the basal ganglia (particularly the caudate nucleus), corpus callosum, and cerebellum. From a developmental perspective, brain systems affected in ADHD, including the cortex, subcortical white matter, basal ganglia, and cerebellum, share a pattern of reciprocal influence (“crossed trophic effect”), such that early injury to subcortical structures impairs not only the cerebral cortical development but also the development of the more remote-developing cerebellum, and vice versa. It remains unclear, however, whether behaviors associated with emergence of ADHD are associated with anomalous development of the basal ganglia and/or cerebellum, with subsequent reduction in growth of the cerebral cortex, or vice versa. Volumetric MRI studies of younger children suggest that structures of the basal ganglia, which mature earlier than the cerebellum and cortex, may play a crucial role in the early development of the disorder. Nevertheless, it is clear that when the “normal” timing and trajectory of brain development is altered and that behavioral and cognitive symptoms can persist, even after the brain has “caught up” with regard to size and shape.

While the preponderance of volumetric imaging studies of childhood ADHD highlight anomalous development of frontostriatal regions (especially prefrontal and premotor cortex and caudate) and cerebellar vermis, there have been inconsistencies in the findings as a result of reliance on cross-sectional studies, samples with disproportionate numbers of boys, inconsistent screening for comorbidities,

and different parcellation protocols. More recent research is taking advantage of advanced computational methods to assess more closely the shape and morphology of regions of interest, providing insights beyond those obtained through examination of volumes alone.

The developmental brain anomalies observed in ADHD occur in parallel with developmental anomalies (delays) in motor and oculomotor development. This is not surprising, given the overlap between the brain systems associated with the behavioral symptoms of ADHD and those systems involved in the development of motor and oculomotor control. While motor skill deficits are not presently considered part of the DSM-IV ADHD diagnostic criteria, motor skill deficits commonly co-occur and are often overlooked in assessment and treatment of children with ADHD. Many teachers, however, report that children with ADHD, particularly boys, can be clumsy or have poor handwriting. While these could be by-products of hyperactivity, closer examination shows that children with ADHD often have trouble coordinating motor skills of all types. Thus, as children with ADHD progress through school, increasing demands that include more and more writing can contribute to fatigue, difficulty with sustained performance, less than optimal alertness, and frustration. All these issues can contribute to impressions of increased “distractibility” and to marked difficulties under the demands for simultaneous writing and listening. Similarly, just as children with ADHD have difficulty with arm, finger, and leg movements, they are also slower and less precise when making eye movements. These findings add to the evidence that children with ADHD need more time to complete tasks. Perhaps more importantly, the results suggest that children with ADHD are likely working much harder than their peers whenever they manage to keep pace with others. Thus, they are far more likely to experience fatigue (cognitive, physical) that could adversely affect their availability for learning. Thus, the research findings from volumetric imaging, motor, and oculomotor assessment, suggest that those working with children with ADHD should consider the impact of these neurobiological factors that contribute to increased cognitive load, including demands for multitasking, speeded performance, and simultaneous writing and listening – all of which can adversely affect a variety of life functions.

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