

## Overview of attention deficit hyperactivity disorder in young children

Ajay Singh,<sup>1</sup> Chia Jung Yeh,<sup>2</sup>  
Nidhi Verma,<sup>3</sup> Ajay Kumar Das<sup>4</sup>

<sup>1</sup>Department of Early Childhood and Elementary Education, College of Education and Human Services, Murray State University, Murray, KY, USA;

<sup>2</sup>Human Development and Family Science, College of Health and Human Performance, East Carolina University, Greenville, NC, USA; <sup>3</sup>Department of Psychology, Kurukshetra University, Kurukshetra, India; <sup>4</sup>Department of Adolescent, Career and Special Education, Murray State University, Murray, KY, USA

### Abstract

Attention deficit hyperactivity disorder (ADHD) is a complex disorder, which can be seen as a disorder of life time, developing in preschool years and manifesting symptoms (full and/or partial) throughout the adulthood; therefore, it is not surprising that there are no simple solutions. The aim of this paper is to provide a short and concise review which can be used to inform affected children and adults; family members of affected children and adults, and other medical, paramedical, non-medical, and educational professionals about the disorder. This paper has also tried to look into the process of how ADHD develops; what are the associated problems; and how many other children and adults are affected by such problems all over the world basically to understand ADHD more precisely in order to develop a better medical and or non-medical multimodal intervention plan. If preschool teachers and clinicians are aware of what the research tells us about ADHD, the varying theories of its cause, and which areas need further research, the knowledge will assist them in supporting the families of children with ADHD. By including information in this review about the connection between biological behavior, it is hoped that preschool teachers and clinicians at all levels will feel more confident about explaining to parents of ADHD children, and older ADHD children themselves about the probable causes of ADHD.

### Overview of attention deficit hyperactivity disorder in young children

Literally thousands of studies have been

conducted on attention deficit hyperactivity disorder (ADHD) and its various predecessors in diagnostic nomenclatures prior to DSM-V (The Diagnostic and Statistical Manual of Mental Disorders-V). Despite this long research history, ADHD is not necessarily well understood among the lay public, given the many controversies and public misconceptions concerning the disorder.<sup>1,2</sup> Longitudinal evidence suggests that childhood ADHD persists into young adulthood in 60-70% of the cases when defined relative to same-age peers and in 58% of the cases when DSM-V criteria and parental reports are used.<sup>3-6</sup> These early studies of childhood hyperactivity excluded many children that would currently meet the DSM criteria for ADHD, particularly the inactive sub-type.<sup>7</sup> The scientific status of ADHD is one of the most controversial issues in child health.<sup>8-10</sup> This paper examines the overview of ADHD in children in relation to its genetics, taxonomy, neurobiology, comorbidity, diet, treatment, and concludes with a discussion.

### Précis of attention deficit hyperactivity disorder

ADHD is recognized as a common childhood psychiatric disorder and has a strong genetic, neuro-biologic, and neurochemical basis.<sup>11,12</sup> It is characterized by symptoms of inattention and/or impulsivity and hyperactivity which can significantly impact many aspects of behavior as well as performance, both at school and at home.<sup>13</sup> ADHD is characterized by pervasive and impairing symptoms of inattention, hyperactivity, and impulsivity according to DSM-V.<sup>14-16</sup> The World Health Organization (WHO) uses a different name hyperkinetic disorder (HD)-but lists similar operational criteria for the disorder.<sup>17</sup> Regardless of name used, ADHD is one of the most thoroughly researched disorders in medicine.<sup>18</sup> The DSM diagnostic criteria for ADHD were based on reviews of existing research and a field trial in which alternative diagnostic criteria were evaluated.<sup>19</sup>

Classification of what constitutes ADHD has changed dramatically over the last 32 years, with each successive revision of the Diagnostic and Statistical Manual, the diagnostic criteria used to describe the disorder. Current classification for combined type ADHD requires a minimum of six out of nine symptoms of inattention of hyperactivity/impulsivity.<sup>16,17,20</sup> In addition there must be some impairment from symptoms in two or more settings (*e.g.* home and school) and clear evidence of significant impairment in social, school or work functioning. The DSM also allows the classification of two sub-type disorders: i) predominantly inattentive where the child only meets criteria for inattention; and

Correspondence: Ajay Singh, Department of Early Childhood and Elementary Education, College of Education and Human Services, Murray State University 3103, Alexander Hall, Murray, KY 42071, USA  
Tel.: +1.270.809.3098.  
E-mail: ajaysingh363@gmail.com

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ii) predominantly hyperactive-impulsive where only the hyperactive-impulsive criteria are met.

### Prevalence of attention deficit hyperactivity disorder

The relatively prevalence of the disorder is high, affecting approximately 4% of all children, although estimates vary widely from 3% to 11% or more.<sup>21,22</sup> The disorder usually begins in early childhood and is characterized by excessive activity, even when developmental level and limited behavioral control are taken into consideration.<sup>23,24</sup> reviewed the findings of six large epidemiological studies that identified cases of ADHD within these samples. The prevalences found in these studies ranged from a low of 2% to a high of 6.3%, with most falling within the range of 4.2% to 6.3%. Other studies have found similar prevalence rates in elementary school-age children (4-5.5%; in Breton *et al.*,<sup>25</sup> 7.9% in Briggs-Gowan *et al.*,<sup>26</sup> 5-6% in DuPaul,<sup>27</sup> and 2.5-4% in Pelham *et al.*<sup>28</sup> Lower rates result from using complete DSM criteria and parent reports (2-6% in Breton *et al.*,<sup>25</sup> and higher ones if just a cutoff on teacher ratings is used (up to 23% in DuPaul,<sup>27</sup> 15.8% in Nolan *et al.*,<sup>29</sup> 14.3% in Trites *et al.*<sup>30</sup> Sex and age differences in prevalence are routinely found in research. For

instance, prevalence rates may be 4% in girls and 8% in boys in the preschool age group,<sup>29</sup> yet fall to 2-4% in girls and 6-9% in boys during the 6- to 12-year-old age period based on parent reports.<sup>25</sup> The prevalence decreases again to 0.9-2% in girls and 1-5.6% in boys by adolescence.<sup>25,31-33</sup> Overall ADHD affects 2% to 9% in school age children.

## Etiological elucidation of attention deficit hyperactivity disorder

Underlying etiological explanations of ADHD can be simply divided into biological and environmental. In simple terms biological explanations include genetics, brain structure and their influence on neuropsychology, while predominant environmental explanations include problems during and after birth, exposure to environmental toxins, parenting and diet.

### Heredity of attention deficit hyperactivity disorder

Heredity of ADHD has been an important issue.<sup>34</sup> For years, researchers have noted the higher prevalence of psychopathology in the parents and other relatives of children with ADHD. Between 10% and 35% of the immediate family members of children with ADHD are also likely to have the disorder, with the risk to siblings being approximately 32%.<sup>35-37</sup>

Even more striking is the finding that if a parent has ADHD, the risk to the offspring is 57%.<sup>12</sup> Thus, ADHD clusters significantly among the biological relatives of children with the disorder, strongly implying a hereditary basis to this condition.<sup>38</sup> Subsequently, these elevated rates of disorders have been noted in African American samples with ADHD,<sup>39</sup> as well as in girls with ADHD compared to boys.<sup>40</sup>

### Genetic factor

The heredity basis for psychiatric disorders was already recognized at the turn of the nineteenth century by Enail Kraepelin.<sup>41</sup> There is now little doubt that ADHD is a condition in which genetic factors (genetic differences between children) make a substantial contribution to the risk of the disorder.<sup>42</sup> Genetic factors are accounted for 80% of the etiology of ADHD, while more recent studies have begun to examine which particular genes might be implicated in ADHD.<sup>43,44</sup> reported an association between ADHD and a null allele of the C4B complement locus in the *MHC*-gene region of chromosome 6, a locus also associated with reading disability.<sup>45</sup> Interest in a potential genetic mechanism underlying ADHD increased with reports of an association with a single dopamine transporter gene,<sup>46</sup> and with

reports of variations within the D4 receptor gene.<sup>47</sup> Genetic studies have focused mainly on candidate genes involved in dopaminergic transmission. Several reasons exist for this particular focus, dopaminergic drugs (methylphenidate) are clinically efficacious in addressing the core problems associated with ADHD. A gene related to dopamine, the *DRD4* (repeater gene), has been the most reliably found in samples of children with ADHD.<sup>48</sup> It is the seven-repeat form of this gene that has been found to be overrepresented in children with ADHD.<sup>47</sup> Such a finding is quite interesting, because this gene has previously been associated with the personality trait of high novelty-seeking behavior; because this variant of the gene affects pharmacological responsiveness; and because the gene's impact on postsynaptic sensitivity is primarily found in frontal and prefrontal cortical regions believed to be associated with executive functions and attention.<sup>49</sup> The finding of an overrepresentation of the seven-repeat *DRD4* gene has now been replicated in a number of other studies, not only of children with ADHD, but also of adolescents and adults with the disorder.<sup>42,48</sup>

Monitoring the correspondence between the intended and actually executed action, a fundamental mechanism of behavioral regulation, is reflected by error-related negativity (ERN), an ERP component generated by the anterior cingulate cortex. Based on this process assumption, a study by LaHoste *et al.*<sup>50</sup> examined genetic influences on the ERN and other components related to action monitoring (correct negativity, CRN, and error positivity,  $P_e$ ). A flanker task was administered to adolescent twins (age 12) including 99 monozygotic (MZ) and 175 dizygotic (DZ) pairs. Genetic analysis showed substantial heritability of all three ERP components (40-60%) and significant genetic correlations between them. This study provides the first evidence for heritable individual differences in the neural substrates of action monitoring and suggests that ERN, CRN, and  $P_e$  can potentially serve as endophenotypes for genetic studies of personality traits and psychopathology associated with abnormal regulation of behavior.<sup>50</sup>

### Cognitive genetics

The sequencing of the human genome and the identification of a vast array of DNA polymorphisms has afforded cognitive scientists with the opportunity to interrogate the genetic basis of cognition with renewed vigor. Advances in the understanding of the neural substrates of sustained and spatial attention arising from the cognitive neurosciences can help guide putative linkages in cognitive genetics.<sup>51</sup> In line with catecholamine models of sustained attention, associations have been reported between sustained attention and allelic variation in the dopamine beta hydroxy-

lase gene (*DBH*), the dopamine D2 and D4 receptor genes (*DRD2*, *DRD4*) and the dopamine transporter gene (*DAT1*).<sup>51</sup> Much evidence implicates the cholinergic system in spatial attention. Accordingly, individual differences in spatial attention have been associated with variation in an alpha-4 cholinergic receptor gene (*CHRNA4*). APOE-4 allele dosage has been shown to influence the speed of attentional reorienting in independent samples of unaffected individuals. Preliminary evidence in both healthy children and children with ADHD suggests association with variants of the *DAT1* gene and the control of spatial attention across the hemifields.<sup>51</sup>

### Fronto-striatal circuitry in attention deficit hyperactivity disorder

Imaging studies using positron emission tomography (PET), and magnetic resonance imaging (MRI) techniques have implicated the fronto-striatal circuitry in ADHD, an area rich in dopaminergic activity. However certain meta-analytic studies have questioned the robust association between dopaminergic genes and ADHD.<sup>52</sup> Other candidate genes have also been investigated including serotonin transporter genes.<sup>53</sup> Genetic investigations aim to examine whether different genes contribute to specific aspects of ADHD. For example, a meta-analysis by Bellgrove and Mattingley has shown that the dopamine transporter gene *DAT1* is more closely associated with the ADHD combined sub-type than with the inattentive +sub-type.<sup>54</sup> Future molecular genetic studies aim to examine gene-environment interactions, the extent to which environmental factors moderate genetic risks for ADHD. As well as gene-gene interactions, the extent to which having a cocktail of different genetic influences might elevate risk for ADHD.

### Brain structure

A wealth of literature has examined the anatomical structure of the brain in children with ADHD. Using brain scanning technology such as MRI these studies suggest that the brain circuits linking the prefrontal cortex, striatum and cerebellum are not functioning normally in children with ADHD.<sup>55</sup> Further evidence has examined the relationship between brain structure and behavioral measures of inhibition and attention. These results suggest that compromised brain morphology of selected regions is related to behavioral measures of inhibition and attention.<sup>56</sup> Another study suggests that abnormalities in circuits important for motor response selection contribute to deficits in response inhibition in children with ADHD.<sup>57</sup> This lends support to the growing awareness of ADHD-associated anomalies in medial frontal regions which are important for the control of voluntary actions. Studies using

PET to assess cerebral glucose metabolism have found diminished metabolism in adults with ADHD, particularly in the frontal region.<sup>58,59</sup> Using a radioactive tracer that indicates dopamine activity,<sup>60</sup> found abnormal dopamine activity in the right midbrain region of children with ADHD, and discovered that severity of symptoms was correlated with the degree of this abnormality. Another study pointed that children with ADHD were found to have a smaller corpus callosum, particularly in the area of the genu and splenium and that region just anterior to the splenium.<sup>61</sup> Interestingly, the study by Zametkin *et al.*<sup>62</sup> also found smaller cerebellar volume in those with ADHD. This would be consistent with views that the cerebellum plays a major role in executive functioning and the motor pre-setting aspects of sensory perception that derive from planning and other executive actions.<sup>63</sup> MRI showed no differences between groups in the regions of the corpus callosum in either of the other studies.<sup>62,64</sup> Further investigations of anatomical structure may allow the development of pharmacological interventions for ADHD,<sup>65</sup> which are better targeted to specific sites of action in the brain.

## Neurobiology of attention deficit hyperactivity disorder

Neurobiology of ADHD has been another valued topic of investigation.<sup>66</sup> Researchers describe at least 11 different neuroanatomical theories of ADHD.<sup>67</sup> These theories can be categorized into two domains. The *bottom-up* theories propose disturbances in subcortical regions, such as the thalamus, and hypothalamus and reticular activating systems are responsible for ADHD symptomology. The *top-down* theories attribute the dysfunction to frontal and prefrontal and sagittal cortices. Smaller frontal lobe or right prefrontal cortex was found for the ADHD groups in all studies that examined this measure. Five of six studies found a smaller anterior or posterior corpus callosum. Four of six found loss of the normal caudate asymmetry, and these four also found a smaller left or right globus pallidus.<sup>68</sup> Neuroimaging studies of children with ADHD have investigated and found evidence of abnormalities in the frontal cortex, basal ganglia, corpus callosum, and cerebellum.<sup>69-72</sup> The cerebellum is functionally linked with the prefrontal cortex, and three anatomical measures, namely the right globus pallidus volume, caudate asymmetry, and left cerebellum volume, correlate highly with ADHD in children.<sup>68</sup> Preliminary evidence has not found differences in the thalamus in children with ADHD.<sup>62,73</sup>

## Role of the basal ganglia

The role of the basal ganglia in ADHD has been given serious importance in neuropsychological research. The basal ganglia are a collection of large subcortical structures that can be divided into two sets of core structures: i) the striatum consisting of the caudate, putamen, and ventral striatum and ii) the pallidum or globus pallidus consisting of the external segment, internal segment, and ventral pallidum. The striatum receives input from the entire cerebral cortex, thalamus, substantia nigra, and amygdala and sends projections to the pallidum and substantia nigra. The pallidum sends input to the thalamic nuclei and additional subcortical nuclei, where information will be sent back to the frontal or prefrontal cortex.<sup>74</sup> The organization of the striatum is important in the execution of motor planning, sequencing, and coordination, as well as feedback and learning after motor execution,<sup>75</sup> suggest that the striatum serves as a *crossroads*, combining sensory-motor information with emotional processing from the amygdala and dopamine mediated reinforcement. The primary neurotransmitter involved in modulation of the basal ganglia is dopamine, and disruption of this system has been found in ADHD. Initial studies found higher levels of the dopamine metabolite, and homovanillic acid in cerebral spinal fluid were positively correlated with the amount of hyperactivity in boys.<sup>62</sup> A recent genetic study found that alleles of the gene encoding dopamine beta hydroxylase, an enzyme that breaks down dopamine, may be related to the expression of ADHD.<sup>76</sup> Further support for dopamine dysfunction in ADHD comes from a functional MRI study that found children with ADHD had reduced activity in the frontal-striatal regions and impaired performance on response inhibition tasks.<sup>77</sup> Additionally, methylphenidate, which acts on the dopamine transporter (DAT), increased both frontal-striatal activity and performance on response inhibition tasks. A study using single PET-CT found that adults with ADHD had increased levels of striatal DAT compared to normal controls, which may lead to decreased availability of striatal dopamine in ADHD.<sup>78</sup>

Research on the role of the basal ganglia in ADHD has primarily focused on the caudate.<sup>79</sup> The caudate has been implicated in a *complex loop*, receiving information from the association cortices and indirectly sending it via the thalamus to the prefrontal cortex.<sup>80</sup> Studies have found neuroanatomical differences in the caudate of children with ADHD with mixed results.<sup>56,62,69,81-83</sup> Found that boys with ADHD had a smaller right caudate; recently, this finding was not replicated in ADHD girls.<sup>69</sup> In boys with ADHD, smaller right caudate volumes were found to significantly correlate with poor accuracy on sensory selection tasks, and left

and right caudate volumes were negatively correlated with mean reaction times.<sup>81</sup> Conflicting results found ADHD adolescents had larger right caudate than normal adolescents, and the right caudate volume was associated with poorer performance on attention tasks and higher ratings of hyperactivity and impulsivity.<sup>83</sup> Another study found that children with ADHD had smaller left caudate volumes.<sup>73,82</sup> More recently, Manor *et al.*<sup>56</sup> reported that boys with ADHD were found to have a decreased volume of the left head of the caudate. These children were also more likely to show a reversed caudate asymmetry when compared to healthy controls, with the left being smaller than right. Moreover, a significant relationship between the reduction in left caudate volume and performance on behavioral inhibition tasks was found. In addition, children displaying reversed caudate asymmetry (L<R) were more likely to perform poorly on tasks of behavioral inhibition and attention regardless of group membership.<sup>56,81</sup> It has been also previously found that reversed caudate asymmetry was related to deficits in response execution tasks in ADHD. This evidence suggests that asymmetry of the caudate regardless of volume has important implications in attention and behavioral control. Finally, functional imaging studies have found decreases in blood flow to the caudate in ADHD.<sup>62,84</sup>

## Role of the putamen

The role of the putamen has also been studied as an etiological factor for the ADHD.<sup>85</sup> The putamen is hypothesized to be part of the *motor loop* because it receives information from the sensory-motor cortex and then sends it indirectly back to the premotor regions of the frontal cortex. Based on the putamen's anatomical connections and function, a role for the putamen in ADHD is possible although currently unclear because of equivocal evidence.<sup>80</sup> There are relatively few studies investigating the neuroanatomical role of the putamen in ADHD.<sup>69</sup> Another study have not found volumetric differences in the putamen between children with ADHD and healthy controls.<sup>62</sup> In addition, they found that the volume of the putamen did not correlate with performance on response inhibition tasks. However, two studies suggest that the putamen may actually be important in the expression of ADHD symptomology. Researchers found that the ADHD diagnosis was significantly associated with the titer of two ant streptococcal antibodies.<sup>86</sup>

In addition, they found that higher antibodies titers were associated with larger volumes in the left putamen and right globus pallidus in children with ADHD.<sup>86</sup> Although this study found structural evidence for the role of the putamen in ADHD, the second study demon-

strates functional differences in the putamen of children with ADHD. Recent advances in functional MRI technology have provided new methods to investigate blood flow to various regions of the brain. Functional MRI relaxometry allows researchers to investigate the resting or steady state conditions and medication-related changes and were able to indirectly assess blood volume to the striatum (caudate and putamen).<sup>75</sup> They found that blood flow to both sides of the putamen was decreased in ADHD children compared to normal children. In addition, they found that blood flow to the left was more decreased than blood flow to the right side. They found no differences in blood flow to the thalamus and caudate, although there was a non-significant trend in the right caudate. Methylphenidate administration significantly altered the blood flow to the right and left putamen, and changes were correlated to the child's unmedicated state.

There were no significant differences in blood flow to the caudate off or on medication. Filipek *et al.*<sup>75</sup> found strong associations between measures of activity and inattention with T2-RT measures in the putamen. They propose that ADHD symptoms are closely related to functional abnormalities in the putamen, which is closely involved in the control of motor behavior. These hypotheses lay the foundation for our study of the neuroanatomy of the putamen in children with ADHD. Investigators in their study using magnetic resonance imaging scans of boys in residential treatment with symptoms of ADHD and psychopathic traits found no differences in the total, left and right putamen volumes across the ADHD or control group. A significant reversal of asymmetry across groups was found; children with ADHD more frequently had a smaller left putamen than right. In contrast, the control group more frequently has a smaller right than left putamen.

Several studies have examined cerebral blood flow using single-photon emission computed tomography (SPECT) in children with ADHD and normal children.<sup>68,72</sup> They have consistently shown decreased blood flow to the prefrontal regions (most recently in the right frontal area), and to pathways connecting these regions with the limbic system via the striatum and specifically its anterior region known as the caudate, and with the cerebellum.<sup>87,88</sup>

## Neuropsychology of attention deficit hyperactivity disorder

Studies examining the neuropsychology of ADHD provide an opportunity to understand the relationship between underlying biological processes and symptoms of ADHD. For many

years it was accepted that symptoms of ADHD were the result of cognitive dysregulation.<sup>89</sup> The behavior of a child with ADHD resulted from insufficient forethought, planning and control.<sup>90</sup> Evidence to support this view point came from many studies using neuropsychological tests which demonstrated that children with ADHD performed less well on these tests than did matched controls to match familiar figures, children with ADHD demonstrated more impulsive responding and higher error rates than did matched controls.<sup>91,92</sup>

### Cognitive dysregulation

A summary of ADHD as a disorder of *cognitive dysregulation* suggested that the relationship between biology and behavior in children with ADHD was mediated by inhibitory dysfunction.<sup>93</sup> In contrast to the dominant view, researchers offered an alternative view of ADHD, not as a disorder of cognitive dysregulation, but as a motivational style. This viewed ADHD as a functional response by the child, aimed at avoiding delay. This alternative viewpoint of ADHD was based on other studies,<sup>92</sup> which showed that most of the neuropsychological evidence to support ADHD as a result of cognitive dysregulation was confounded by delay. To demonstrate this, researchers got children with ADHD and match control children to participate in the matching familiar figures test, and found the same results as previous studies.<sup>92</sup> Children with ADHD made more impulsive responses and more errors. However, researchers pointed out that all these studies involved trial constraints where as soon as one trial ended the next began and were confounded with delay.<sup>92</sup> In other words, children with ADHD made more impulsive responses because it allowed them to complete the task quicker and therefore escape delay. When researchers re-ran their study under time constraint (for a fixed period of time where early or impulsive responses had no influence on delay), children with ADHD performed no differently from controls.<sup>92</sup> Results of these studies lead to the development of the delay aversion hypothesis,<sup>94</sup> which characterized the influence of delay on behavior dependent upon whether the child has control over their environment or not. When the child is in control of their environment they can choose to minimize delay by acting impulsively, *e.g.* by skipping the queue at the end of the slide! When the child is not in control of their environment, or at least where they are expected to behave in certain ways or face sanctions, the child would choose to distract themselves from the passing of time. For example, in a classroom context during literacy lessons the child could achieve this either by daydreaming (inattention) or by fidgeting (hyperactivity). A summary of ADHD as a motivational style suggests that the relationship

between biology and behavior in ADHD is mediated by delay aversion.

Traditionally these two different accounts of ADHD have both sought to independently explain the disorder. However, a study by Sonuga-Barke *et al.*<sup>95</sup> compared the measurement of both of these hypotheses in a head-to-head study. Results of this study showed that measures used to test each hypothesis were uncorrelated, demonstrating that they measured different constructs. Both sets of measures were correlated with ADHD, and when combined were highly diagnostic, correctly distinguishing 87.5 of cases from non-cases. These results suggested that both accounts appeared to help to explain ADHD, but that neither explanation was the *single theory of ADHD* which both theoretical camps had been searching for. Based on these findings, researchers proposed his dual pathway model of ADHD.<sup>93</sup> This model proposed two possible routes between biology and ADHD behavior. The first one is through cognitive dysregulation and another via motivational style. Clinically the dual pathway model suggests that there may be merit in targeting different sub-types with specific treatments, as well as allowing the development of novel interventions, perhaps aimed at desensitizing delay. Some have suggested ways in which the greater understanding about the influence of delay aversion on the development of ADHD could be used to develop alternative interventions.<sup>93,96</sup> These suggestions include the use of delay fading, a technique to systematically reorganize the child's delay experience, as a means of increasing tolerance for delay, and reducing ADHD symptoms.

### Prenatal

Some studies have not found a greater incidence of prenatal (pregnancy or birth complications) in children with ADHD compared to normal children whereas others have found a slightly higher prevalence of unusually short or long labor, fetal distress, low forceps delivery, and toxemia or eclampsia in children with ADHD.<sup>97</sup> Nevertheless, though children with ADHD may not experience greater pregnancy complications, prematurity, or lower birth-weight as a group, children born prematurely or who have markedly lower birth-weights are at high risk for later hyperactivity or ADHD.

Researchers found that smoking and maternal stress during the pregnancy is associated with onset of ADHD during early childhood. Similarly observed that parental smoking during pregnancy predicts non-responsiveness to intervention targeting ADHD symptoms in elementary school children. Hartsough *et al.* observed that behavioral symptoms of ADHD were predicted by a lower ponderal index ( $\text{kg}/\text{m}^3$ ),<sup>98</sup> a smaller head circumference, and a smaller head-circumference-to-length ratio.

Length of gestation, mother's age, tobacco and alcohol during pregnancy and pre-pregnancy, body mass index or parity, the monthly gross income of family, child's BMI at the age of five or six years or gender didn't have any significant effect on the behavioral symptoms of ADHD at the age of five or six.

### Exposure to environmental toxins

Exposure to environmental toxins specifically lead has also been reviewed as a causal factor for ADHD. An amazing variety of toxins extent in the modern environment have deleterious effects on the central nervous system that range from severe organic destruction to subtle brain dysfunction.<sup>99,100</sup> Toxic metals are ubiquitous in the modern environment, as are organohalide pesticides, herbicides, and fumigants, and a wide range of aromatic and aliphatic solvents.<sup>101</sup> All these categories of environmental pollutants have been linked to abnormalities in behavior, perception, cognition, and motor ability that can be subtle during early childhood but disabling over the long term.<sup>102</sup> Children exposed acutely or chronically to lead, arsenic, aluminum, mercury, or cadmium are often left with permanent neurological sequelae that include attentional deficits, emotional lability, and behavioral reactivity.<sup>101</sup> Elevated body lead burden has been shown to have a small but consistent and statistically significant relationship to the symptoms of ADHD.<sup>103,104</sup> However, even at relatively high levels of lead, fewer than 38% of children in one study were rated as having the behavior of hyperactivity on a teacher rating scale,<sup>104</sup> implying that most lead-poisoned children do not develop symptoms of ADHD. And most children with ADHD likewise, do not have significantly elevated lead burdens.<sup>105</sup>

### Environmental influences

Environmental influences on ADHD have also been reviewed extensively. Attention deficit hyperactivity disorder is best viewed as a gene  $\times$  environment interaction.<sup>106</sup> Children who have a genetic predisposition will express the disorder when put in the correct environment, typically one characterized by chaotic parenting.<sup>107</sup> The best evidence for environmental influences on ADHD come from intervention studies which have demonstrated improvements in ADHD symptoms, when parents have been taught alternative parenting skills.<sup>108,109</sup> Results of these studies do not necessarily imply that parents of children with ADHD are bad parents. In fact, influence of parenting on ADHD is best viewed from an interactionist viewpoint. The relationship between ADHD and parenting may result from both negative aspects of the child influencing the parents' behavior, and negative aspects of the parents influencing the child's behavior. Studies examining mother-child interaction have found that children with ADHD are less

often on task, less compliant, less responsive and more active than controls; researchers investigated both mother-son and father-son interactions and found that parents of boys with ADHD were more demanding, aversive and power assertive;<sup>110-112</sup> while the findings of Buhrmester *et al.*<sup>113</sup> have demonstrated that mothers of children with ADHD have been found to be more negative, controlling, intrusive and disapproving, and less rewarding and responsive than mothers of children without ADHD.

Research finds that ADHD affects the interactions of children with their parents, and hence the manner in which parents may respond to these children.<sup>114</sup> Those with ADHD are more talkative, negative and defiant; less compliant and cooperative; more demanding of assistance from others; and less able to play and work independently of their mothers.<sup>115-118</sup> Their mothers are less responsive to the questions of their children, more negative and directive, and less rewarding of their children's behavior.<sup>107,116</sup> Mothers of children with ADHD have been shown to give both more commands and more rewards to sons with ADHD than to daughters with the disorder,<sup>119,120</sup> but also to be more emotional and acrimonious in their interactions with sons.<sup>112</sup> Children and teens with ADHD seem to be nearly as problematic for their fathers as their mothers.<sup>112,118,121</sup> Contrary to what may be seen in normal mother-child interactions, the conflicts between children and teens with ADHD (especially boys) and their mothers may actually increase when fathers join the interactions.<sup>112,121</sup> So while parents of children with ADHD may engage in less than optimal parenting, it is easy to see how such responses might have evolved.

In addition, genetic studies highlight the familial basis of ADHD.<sup>122,123</sup> Children with ADHD are more likely to have a parent with ADHD. ADHD symptoms in parents usually interfere with consistent and appropriate parenting. Researchers found that ADHD in parents prevented effective parental monitoring and consistent use of constructive parenting techniques.<sup>124</sup> Other researchers found that parental ADHD symptoms were associated with lax discipline,<sup>125</sup> while Harvey *et al.*<sup>126</sup> found that high ADHD symptoms in mothers were a barrier to successful psychosocial intervention for pre-school children with ADHD.

### Medication

Most widely researched and commonly prescribed treatments for ADHD are the psychostimulants, including methylphenidate, amphetamine, and pemoline.<sup>2,127</sup> Several studies have demonstrated the short-term efficacy

of stimulant compared to placebo conditions in improving both core ADHD symptoms and important ancillary features of the disorder.<sup>128</sup> Controlled studies of stimulants have shown their effect on reducing interrupting in class, reducing task-irrelevant activity in school, improving performance on spelling and arithmetic tasks, improving sustained attention during play, and improving parent-child interaction.

Meaningful effects have been documented across a wide array of outcome domains, cognitive attentional performance, school behavior, and learning, parent-child interactions, interaction with peers, and with a wide variety of assessment approaches, direct observations of behavior in natural and laboratory settings, and objective laboratory performance.<sup>129</sup>

### Diet

Diet is another environmental influence, often cited by parents as having an adverse influence on the ADHD symptoms of their child.<sup>130</sup> Specifically, food additives, refined sugars and fatty acid deficiencies have all been associated with ADHD symptoms.<sup>131</sup>

However, the majority of this literature comes from older studies, with a variety of methodological problems, and small sample sizes.<sup>131</sup> In fact, a large recent randomized control trial examined the influence of food colorings and benzoate preservatives on pre-school hyperactivity. Results demonstrated a general adverse effect of food coloring and benzoate preservatives on hyperactive behavior of pre-school children, based on parental reports, but not on simple clinic assessment. Children with high levels of hyperactivity were no more vulnerable to this effect than children with low levels of hyperactivity.<sup>132</sup> While improving children's diet might impact on their general health and improve their overall behavior, the clinical importance of dietary change as a means of remediating ADHD remains doubtful.<sup>133</sup>

### Co-morbidity

ADHD appears to be associated with a wide variety of other psychiatry problems, which are often co-morbid with it. ADHD co-occurs with other childhood disorders far more often than it appears alone.<sup>134</sup> Notable associations exist with Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), tic disorder, mood disorder, autism spectrum disorder, specific learning disorder such as dyslexia,<sup>135,136</sup> depression and anxiety. About 50-60% of children with ADHD meet criteria for ODD, even

in the pre-school period.<sup>137</sup> Busch and colleagues (2002) reported that ADHD children in primary care settings were significantly more likely than non-ADHD clinic controls to demonstrate mood disorders (57%) such as depression, multiple anxiety disorders (31%), and substance use disorders (11.5%). However, in the recent British Child Mental Health Survey,<sup>138</sup> anxiety was not associated with ADHD when adjustment was made for the presence of a third disorder. It is widely accepted that ADHD is a co-morbid disorder. Copeland *et al.*<sup>135</sup> point out that co-morbidity can mean a common underlying etiology which leads to two or more different disorders, or that one disorder leads to another, or even that two unrelated disorders co-occur. The term co-morbid also implies that their entities are morbid conditions, *i.e.* diseases. High rates of comorbidity with either other neurodevelopmental disorders (*e.g.*, mental retardation, and learning disabilities) or psychiatric disorders (*e.g.*, anxiety) make delineation of the phenotype difficult.<sup>139</sup>

Some studies found that 47% children with ADHD have co-morbid ODD,<sup>140-142</sup> 27% have anxiety disorder and 7% have mood disorder. 38% of children with ADHD were found to have CD and 13% have depression. In fact, the vast majority of co-morbidities with ADHD represent functional impairments and symptoms, which are not rooted in specific diseases.<sup>135</sup> Studies of clinic-referred children with ADHD find that between 54% and 67% will meet criteria for a diagnosis of ODD by 7 years of age or later. ODD is a frequent precursor to CD, a more severe and often (though not always) later occurring stage of ODD.<sup>143</sup> The co-occurrence of CD with ADHD may be 20-50% in children and 44-50% in adolescence with ADHD.<sup>144</sup> By adulthood, up to 26% may continue to have CD, while 12–21% will qualify for a diagnosis of antisocial personality disorder (ASPD).

In addition to associations with other psychiatric disorders children with ADHD are also more likely than their non-ADHD counterparts to experience a substantial array of developmental, social and health risks. It therefore seems important to discuss associated problems along with co-morbidity.

### Motor coordination

Children with ADHD often demonstrate poor motor co-ordination or motor performance and balance.<sup>145-147</sup> Substantial evidences have been observed for problems in motor development and motor execution children with ADHD.<sup>148</sup> Clinical and epidemiological studies report that 30% to 50% of children with ADHD suffer from motor coordination problems.<sup>146</sup> These percentages are dependent of the type of motor assessment, referral sources and the cut-off points used.<sup>149-151</sup> As noted by Needleman *et al.*,<sup>105</sup> children with ADHD display greater dif-

ficulties with the development of motor coordination, planning and execution of complex, lengthy tasks, and novel chains of goal directed responses.

### Academic functioning

Children with ADHD have an impaired academic functioning and are usually at an educational disadvantage upon school entry.<sup>152,153</sup> ADHD children are more likely than their non-ADHD peers to demonstrate difficulties with basic mathematics and pre-reading skills during their first year at school.<sup>147,154,155</sup> Executive academic functions were found to be core deficits specific to ADHD. Girls with ADHD were found to be less impaired than boys with ADHD.<sup>156</sup> Even pre-school children with ADHD demonstrate educational disadvantage, DuPaul *et al.*<sup>157</sup> demonstrated that their sample of pre-school ADHD children demonstrated deficits in pre-academic skills even prior to formal school entry. The pre-school ADHD children in their sample scored on average one standard deviation lower on the Battelle Developmental Index,<sup>158</sup> than did their non-ADHD control group. Researchers emphasized the importance of look away behavior (inattention) as a major reason for poor academic achievement.<sup>159</sup>

Clinic-referred children with ADHD often present with lower scores on intelligence tests than control groups, specifically verbal intelligence with differences ranging from 7 to 10 standard score points.<sup>160</sup> Studies with community samples of ADHD children have also demonstrated negative associations between ADHD and intelligence.<sup>161,162</sup>

Children with ADHD demonstrate serious difficulties with psychosocial functioning. Social adjustment is often given little attention on assessment protocols, given its designation as an associated feature of ADHD.<sup>15</sup> However, the high levels of disruptive behavior demonstrated by ADHD children increases the likelihood of negative reactions from parent, teachers and also peers.<sup>163</sup> In addition, negative social interactions with peers ultimately lead to peer's rejection,<sup>164</sup> because these social difficulties are often resistant to psychosocial and pharmacological treatment,<sup>165</sup> they are expected to continue into adolescence, and even adulthood when criteria for the disorder may no longer be met.<sup>166</sup> The patterns of disruptive, intrusive, excessive, negative, and emotional social interactions that have been found between children with ADHD and their parents, have also been found to occur in the children's interactions with teachers and peers.<sup>157,167,168</sup> It should come as no surprise, then, that those with ADHD receive more correction, punishment, censure, and criticism than other children from their teachers, as well as more school suspensions and expulsions, particularly if they have ODD/CD.<sup>168,169</sup>

In their social relationships, children with ADHD are less liked by other children, have fewer friends, and are overwhelmingly rejected as a consequence,<sup>170</sup> particularly if they have comorbid conduct problems.<sup>107,125,171,172</sup> Another research study demonstrated that the co-occurrence of conduct disorder and anxiety disorder with ADHD in childhood predicted a more severe course for ADHD in adolescence.<sup>173</sup>

### Unintentional physical injury

Children with ADHD appear to be at a greater risk for unintentional physical injury and accidental poisoning.<sup>157,174</sup> In one of the first studies of the issue, Stewart and colleagues found that four times as many hyperactive children as control children (43% *vs.* 11%) were described by parents as accident-prone. Later studies have also identified such risks; up to 57% of children with hyperactivity or ADHD are said to be accident-prone by parents, relative to 11% or fewer of control children.<sup>175,176</sup> Most studies find that children with ADHD experience more injuries of various sorts than control children. In one study, 16% of the hyperactive sample had at least four or more serious accidental injuries (broken bones, lacerations, head injuries, severe bruises, lost teeth, etc.), compared to just 5% of control children.<sup>2,177</sup> found that 68% of children with DSM-IV-TR ADD, compared to 39% of control children, had experienced physical trauma sufficient to warrant sutures, hospitalization, or extensive/painful procedures. Several other studies likewise found a greater frequency of accidental injuries than among control children. Researchers found that children with ADHD were at a greater risk for suffering fractures,<sup>178</sup> most likely as a result of hyperactive and impulsive behavior. Children with AD/HD are also more likely than their non-ADHD counterparts to be injured as pedestrians, to inflict injuries to themselves, to sustain injuries to multiple body regions and to experience head injury.<sup>179</sup> Knowledge about safety does not appear to be lower in these children; implying interventions aimed at increasing knowledge about safety may have little impact.<sup>180</sup>

### Sleep disturbances

Studies report an association between ADHD and sleep disturbances found that sleep problems occurred twice as often in ADHD as in control children.<sup>181-184</sup> The problems are mainly more behavioral and include settling difficulties, a longer time to fall asleep, and instability of sleep duration, tiredness at awakening or frequent night waking. The direction of effect, between ADHD and sleep problems is unclear. It is possible that sleep difficulties increase ADHD symptoms during the daytime, as the research on normal children implies.<sup>105</sup> Yet some research finds that the sleep prob-

lems of children with ADHD are not associated with the severity of their symptoms; this suggests that the disorder, not the impaired sleeping, is what contributes to impaired daytime alertness, inattention, and behavioral problems.<sup>184,185</sup>

While knowledge about the associations between ADHD and other related variables is useful in terms of diagnostic profiles, less is known about the impact of related variables on the long-term outcome for the disorder. Even less is known about the specificity of these associated problems to ADHD. In the pre-school years a wealth of evidence now exists comparing the symptoms of pre-school ADHD symptoms to its school-aged counterpart. Children with a pre-school variant of ADHD present with the same symptom structure,<sup>186,187</sup> similar associated impairment and developmental risk,<sup>187</sup> and similar patterns of neuropsychology.<sup>188</sup> Despite the similarities between pre-school ADHD and school-aged ADHD, little is known about what constitutes impairment during the pre-school years although school readiness should be what clinicians focus on. And even less is known about the relationship between early hyperactivity and later expression of the ADHD disorder.<sup>189</sup>

While originally conceived of as a disorder of childhood and adolescence, evidence suggests scientific merit and clinical value in examining ADHD in adulthood,<sup>40,189</sup> as well as the pre-school period.<sup>189</sup> ADHD symptoms have been shown to persist into later life with up to 40% of childhood cases continuing to meet full criteria in the adult years.<sup>190,191</sup> Adult ADHD appears to share many characteristics of the childhood disorder. Similar to their childhood counterparts, adults with ADHD display impairment in the interpersonal, vocational and cognitive domains.<sup>192-194</sup> The adult and childhood disorders also appear to share a common neuropathology,<sup>195,196</sup> and demonstrate a similar response to treatment.<sup>197</sup>

## Conclusions

We have discussed two different possible causes of ADHD in neurological research. The top down theory says that ADHD begins with frontal and pre-frontal lobe dysfunction. The other theory says that the sub-cortical regions, the thalamus and the hypothalamus are responsible for ADHD. Neuro-imaging doesn't show abnormality in the thalamus, but does show changes in the frontal and prefrontal area. Researchers agree that genetic factors are a strong contribution to the occurrence of ADHD.

DSM-IV has an aura of scientific legitimacy, many authors have written about its shortcomings in terms of reliability and validity.<sup>198,199</sup>

The primary function and goal of the DSM,<sup>200</sup> is to lend credibility to the claim that certain (mis) behaviors are mental disorders and that such disorders are medical diseases. Although the DSM-IV is often used when discussing mental illnesses, be it in a research setting or a clinical practice setting. Researchers apply points out that such extensive use does not in itself guarantee either its validity or reliability.<sup>201</sup> The DSM-IV is purely descriptive and presents no new scientific insights about the causes of the many mental disorders it lists. Despite a wide level of acceptance, ADHD is not an uncontested condition.<sup>202</sup> For example, another researcher has argued that ...*the working dogma that ADHD is a disease or neurobehavioral condition does not at this time hold up.*<sup>203,204</sup> A more recent perspective presented by Lollar has also stated that there are no valid neurological markers for the diagnosis of ADHD.<sup>205</sup> Additionally, Shaw *et al.*<sup>206</sup> observe that there is currently no verifiable objective evidence to support the claims of ADHD advocates. Given the lack of validity as a medical condition, it is important to ask why the label of ADHD is applied, and under what conditions?

Another researcher found no association between DAT1 and ADHD.<sup>207</sup> Another gene for which there have been many studies is the dopamine receptor D4, DRD4, on chromosome 11. Another researchers found no evidence of an association between ADHD and DRD4.<sup>208</sup> Environmental effects could also include child-specific experiences of salient environmental influences such as maternal lifestyle or parenting.<sup>209</sup> Childhood ADHD symptoms do remit across time for some,<sup>4,210</sup> but not all children.<sup>209</sup>

Some of the controversial treatments have involved dietary management, herbs and antioxidants. The removal of artificial food colorings and preservatives from the diet is an indispensable and practicable clinical intervention in ADHD, but rarely is sufficient to eliminate symptomatology.<sup>102</sup> Up to 88 percent of ADHD children react to these substances in sublingual challenge testing, but in blinded studies no child reacted to these alone. Allergies to the foods themselves must also be identified and eliminated.<sup>211</sup> Sugar intake makes a marked contribution to hyperactive, aggressive, and destructive behavior.<sup>212,213-222</sup> Overall body of evidence currently does not support dietary use as sole therapy for ADHD. There is a group of children with ADHD who do not respond well to treatment. More resources should be made available to help them, through clinical research and clinical-based treatment.<sup>214</sup>

The actual degree to which genetic heritability may predispose to childhood onset of ADHD is still an open question.<sup>102</sup> Population studies indicate attentional problems, conduct

problems, and emotional problems tend to cluster within families.<sup>215,223,224</sup> Genetics and environment are notoriously difficult to separate within the family unit, and researchers suggested the genetic predisposition to ADHD might fuel a negative family atmosphere that exacerbates latent ADHD in the child,<sup>102,225,226</sup>

It is unknown whether the association of motor coordination problems with ADHD is comparable across ages. The limitation in daily life caused by poor motor performance varies with age.<sup>146</sup> Four to six years old children mainly have problems with dressing, use of scissors, drawing, trying shoelaces, and riding a bike. Children seven to ten years old encounter difficulties in writing, dressing, swimming, constructional play, ball skills and outdoor play, while eleven to nineteen year olds have problems of clumsiness in writing, drawing, ball skills, poor table manners and tool use.<sup>218</sup>

Research on long term effects and safety of ADHD medications has been especially lacking.<sup>36,219</sup> According to researchers of a study of psychotropic drugs used with preschoolers, earlier ages of initiation and longer duration of treatment means that *the possibility of adverse effects on the developing brain cannot be ruled out.* Another research study of longer term ADHD treatments suggested the side effects such as depression, worrying, and irritability from ADHD medications.<sup>227,228</sup> In some of these children, drug therapy is insufficient because of persistent symptoms of coexisting conditions.<sup>228,229</sup> Future studies will be needed to define the subgroups clearly. There is much to learn about it.

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