Encyclopedia on Early Childhood Development

Hyperactivity

Table of content

(Last update: 02-21-2012)

Topic Editor: Russell Schachar, MD, University of Toronto, Canada

Synthesis on hyperactivity ii

Attention deficit hyperactivity disorder and cognition
Nanda Rommelse 1-7

ADHD and genetics
Philip Asherson 1-8

ADHD and neuroscience
Samuele Cortese & Francisco Xavier Castellanos 1-7

Children with attention deficit hyperactivity disorder: Epidemiology, comorbidity and assessment
Alice Charach 1-11

ADHD and treatment
Meghan Miller & Stephen P. Hinshaw 1-6

©2010-2012 CEECD / SKC-ECD

Encyclopedia on Early Childhood Development

Hyperactivity

Synthesis

(Published online September 1st, 2011)
(Last update: February 2012)

Topic
Hyperactivity
Topic Editor: Russell Schachar, MD, University of Toronto, Canada

How important is it?

Attention-Deficit/Hyperactivity disorder (ADHD) is a neuropsychiatric disorder defined by developmentally atypical, persistent and impairing restlessness, impulsiveness and inattentiveness starting from an early age. ADHD can be broken down into three subtypes based on the type of behaviours that are most prominent: 1) the inattentive type; 2) the hyperactive-impulsive type; and 3) the combined type depending on the nature of the symptoms. The disorder is diagnosed when the child's symptoms are present and impairing in more than one context such as in school, at home or outside of the home. ADHD is estimated to affect 3 to 7% of school-age children worldwide, and boys show higher rates of ADHD than girls. ADHD tends to co-occur with other psychiatric or developmental disorders (e.g., anxiety, mood disorder, learning or language disabilities, conduct disorder and sleep difficulties) in 50 to 66% of cases. ADHD persists into adulthood in more than half of affected individuals. ADHD symptoms and its concurrent disorders interfere with academic and behavioural functioning at school and so children have lower rates of high school completion. They are also more likely to experience employment difficulties as they grow older. Other negative consequences relating to ADHD include difficult interpersonal relationships and higher prevalence of accidental injuries, driving accidents and teen pregnancy. In sum, ADHD represents an important public health concern and may engender high personal and societal costs.

What do we know?

ADHD is believed to be caused by an interaction of genetic and environmental factors. Symptoms of ADHD are highly heritable (76%), yet the nature of the genetic influence is still unknown. Results from published studies indicate that ADHD shares genetic influences with other conditions so, for example, one finds shared genetic influences between inattentive symptoms and dyslexia, hyperactive-impulsive symptoms and oppositional problems, and ADHD with symptoms of autism. Furthermore, genes responsible for cell division, cell adhesion, and neuronal migration are thought to be related to the onset of ADHD. Among environmental risk factors, researchers have noted the negative influence of prenatal maternal smoking and drinking, maternal depression, low birth weight, poor parenting practices, and living in a disadvantaged neighbourhood.

Children with ADHD experience more academic problems than their schoolmates due to their neuro-cognitive impairments and behaviour. ADHD is often associated with

©2011-2012 CEECD / SKC-ECD

deficits in executive functioning (e.g., planning, organizing, paying attention to important details, and inhibiting impulses). Accordingly, children identified with this disorder are more likely to exhibit learning and/or language disabilities. Results from studies examining the working of the brain suggest that ADHD is associated with atypical activity in the frontal cortex, the brain area responsible for cognitive processes. That said it is important to note that only a subgroup of school-aged children with ADHD (30%) has executive functioning weaknesses, suggesting it is neither necessary nor sufficient to cause the disorder.

What can be done?

Diagnosis

ADHD is usually first identified and treated among school-age children. However, the presence of hyperactive-impulsive or inattentive symptoms during the preschool years is considered central to establishing the diagnosis. Direct observation of the child can suggest the diagnosis but even the most symptomatic child can be calm and attentive in an unusual setting such as in the doctor's office. Consequently, assessment should focus on obtaining a history of the child's behaviour at home, at play and in school from early childhood to the time of the assessment. A typical clinical interview allows an opportunity to discuss how parents and teachers have responded to the child's difficulties and to identify strategies that have worked and those that have not. Assessment should not be limited to ADHD symptoms but should enquire about associated symptoms that might also be evident such as anxiety, mood or conduct problems. Parents are not always aware of how much stressful circumstances can upset their child; therefore, a direct interview with the child can be an important part of the assessment. Concurrent disorders are an important focus of treatment and their presence can alter the effectiveness of therapy.

Many clinicians find that parent and teacher rating scales are helpful in the diagnostic process as a way of obtaining a description of the child's behaviour that can readily be compared to age norms. Some children with high levels of restlessness, inattentiveness and impulsiveness have medical problems or developmental delays that must be identified as part of the assessment. Children with learning difficulties may be symptomatic at school and during homework sessions because they are struggling with the academic material. Other children may be symptomatic at home only suggesting some parenting, social or environmental problem. It can be very difficult to identify which children have specific learning difficulties in the doctor's office. Consequently, consultation with an educational psychologist can be very helpful in getting a complete picture of the child's strengths and difficulties.

Interventions

Stimulant medication (such as methylphenidate, Ritalin™) in various short and long acting preparations plays an important role in the treatment of ADHD. More recently, non-stimulant medications, such as Atomoxetine, have become available and play an important role in treatment. These medications can help a large number of affected individuals by improving their attentiveness, impulse control and reducing their activity level. Also effective are intensive behavioural interventions that involve a combination of self-control training for the child and education in parenting strategies for the parents. Positive parental attention, rewards for appropriate behaviours, and negative consequences for misbehaviours (e.g., prohibiting children from playing with their favourite toy) are recommended procedures in behavioural treatments. Teachers can also apply similar strategies within their classrooms. Available evidence

©2011-2012 CEECD / SKC-ECD

indicates that the best interventions are a combination of medication, behavioural interventions and school-based programming for behaviour and learning. These treatments have to be intensive and long term to have their optimal impact. Direct training of cognitive functions such as working memory (that ability to hold and manipulate information in short-term memory) has shown promise as a potentially effective intervention. Some children may show improved behaviour upon removal of certain foods from their diet although the generality of this effect is not known and training of the brains electrical activities may improve alertness and behaviour in some children. That said a major issue with these treatments pertains to the generalization of improvements across settings. Future research examining factors that affect treatment outcomes (individual and contextual) should be conducted to improve children's treatment gains over time and in different contexts.

To cite this document:

Schachar R, topic ed. Hyperactivity – Synthesis. In: Tremblay RE, Boivin M, Peters RDeV, eds. *Encyclopedia on Early Childhood Development* [online]. Montreal, Quebec: Centre of Excellence for Early Childhood Development and Strategic Knowledge Cluster on Early Child Development; 2011:i-iii. Available at: http://www.child-encyclopedia.com/pages/PDF/synthesis-hyperactivity.pdf. Accessed [insert date].

This topic is produced by:

©2011-2012 CEECD / SKC-ECD

Encyclopedia on Early Childhood Development

Attention Deficit Hyperactivity Disorder and Cognition

NANDA ROMMELSE, PhD

Radboud University Medical Center, Department of Psychiatry, NETHERLANDS

(Published online February 2010)

Topic
Hyperactivity

Introduction
Attention Deficit Hyperactivity Disorder (ADHD) is characterized by a triad of symptoms of inattention, hyperactivity and impulsivity.[1] The disorder is highly heritable and affects around 3-5% of school-aged children.[2,3] In recent decades, the cognitive problems of ADHD have been widely studied. Cognition can be defined as gaining knowledge and comprehension, including thinking, knowing, remembering, judging and problem solving.

Subject
Several causal pathway models have been proposed, trying to combine the findings of biological and cognitive abnormalities frequently found in ADHD. The cognitive models all have in common that deficits in executive functioning (EF) are one of the most prominent characteristics of ADHD. EF has been defined as "those capacities that enable a person to engage successfully in independent, purposive, self-serving behaviour."[4] EF impairments have been reported in many studies with ADHD patients, with problems in inhibition and working memory being the most frequently replicated.[5] Deficits in EF are strongly linked to abnormalities in the in the *prefrontal lobe* and *frontal-subcortical circuitry* found in patients with ADHD.[6,7]

Problem
Even though most causative models of ADHD incorporate deficits in EF as an important factor, it is actually unknown if and to what extent deficits in EF *cause* ADHD. In other words, given that ADHD is a highly heritable disorder, is EF a heritable trait that increases the risks of developing ADHD and in what percentage of patients may it pose a causal factor?

Key Research Questions
Two issues are central in order to examine whether EF deficits are causally related to ADHD:

a) Given that ADHD is strongly heritably, are EF problems themselves also heritable and linked to the same genes as ADHD?
b) What percentage of children with ADHD actually suffers from EF problems?

©2010 CEECD / SKC-ECD

Recent Research Results

Are EF problems heritable and linked to the same genes as ADHD?

A necessary first step in determining if EF deficits are heritable is to study EF performance in a twin design. A twin design allows for disentangling the influence of heritable and environmental influences on EF. Several twin studies have examined EF performance.[12-16] At ages 5 and 12, about 50% of performance on several EF tasks appeared attributable to genetic factors.[16] Other studies have yielded similar percentages of around 40% to 50%,[12,13,15] suggesting performance on EF tasks is moderately heritable. Furthermore, genetic factors appear an important mediator of *stability* of EF during childhood.[14]

A second step in determining if EF deficits are heritable and linked to the same genes as ADHD is to study the EF performance in relatives of ADHD patients. This sheds light on the familiality of EF deficits in ADHD. Siblings, for instance, share on average 50% of their genes. It is therefore likely that non-affected siblings of a child with ADHD carry risk genes for ADHD without having the phenotypic expression of ADHD. If EF deficits are indeed familially linked to ADHD, non-affected siblings will show the same EF deficits, probably to a somewhat lesser extent, than their ADHD affected siblings.

Several studies have targeted EF within ADHD families and results support the hypothesis that EF deficits are familial and also present (to a lesser extent) in non-affected relatives of ADHD patients.[5,17-21] Studies that have specifically targeted inhibition or interference control as an executive function have also reported promising results, with non-affected relatives displaying subtle deficits in this area and relatives resembling each other in their performance.[22-26] These findings suggest that EF deficits are familial. Although this is not sufficient to suggest that EF problems are heritable; it is at least consistent with it.

A final step in examining whether EF deficits are linked to the same genes as ADHD is to examine EF performance in relation to ADHD candidate genes and/or to use EF performance in linkage analyses using ADHD pedigrees. Both of these strategies have rarely been carried out due to the large sample sizes that are required to generate sufficient power for the analyses. Preliminary results indicate that *polymorphisms* in a gene (*Dopamine Receptor D4* gene) that has been most frequently replicated in relation to ADHD indeed also relates to EF.[15,27-30] One linkage study found a genome-wide significant linkage signal on chromosome 13q12.11 using an EF measure (verbal working memory) in ADHD pedigrees, suggesting genes on this location may influence both ADHD and EF performance.[31] In addition, another linkage study indicated that a region on chromosome 3q13 was related to both a composite measure of EF and to inattention symptoms of ADHD, suggesting these EF deficits may relate to the same genes as ADHD.[32]

What percentage of children with ADHD suffer from EF problems?

The percentage of children suffering from EF problems strongly depends on the definition of an executive function deficit (EFD).[8] There is no consensus on what actually constitutes an EFD, but most definitions entail a performance below the 10th percentile of a matching control group on at least one, two or three EF tasks. On a group level, children with ADHD virtually always perform worse on EF measures than children in the

©2010 CEECD / SKC-ECD

control group. However, on an individual level, a proportion of children with ADHD outperform a proportion of the children in the control group.[9] In other words, not every child with ADHD suffers from an EFD. EF weaknesses are neither necessary nor sufficient to cause all cases of ADHD.[9] Rather, other cognitive functions, motivational problems or, in some cases, response to family distress or peer problems, may constitute pathways to ADHD.[10,11] About a third of the children show a moderately severe EFD, defined as being impaired on three or more EF measures.[11]

Research Gaps

In order to determine whether EF deficits found in a proportion of ADHD patients are indeed causative of ADHD in this group, a more comprehensive approach is required than that has currently been undertaken. That is, only a few studies examined EF in a familial context and most studies have been underpowered for genetic analyses. An even larger problem is that results are difficult to compare because of the use of different tasks and methods to measure the same executive function. This is particularly troublesome for attempts to combine cognitive datasets across sites for increased statistical power in genetic analyses. Thus, in order to determine whether EF deficits found in a proportion of ADHD patients are indeed causative of ADHD, it is necessary to administer EF tasks that have good validity, reliability, heritability and norm data. Using the same "golden standard" tasks would make it possible to combine different samples across research sites. This would greatly enhance comparability of data and would boost power for genetic analyses, leading to more robust results hopefully applicable in clinical practice.

Conclusions

Performance on EF tasks is moderately heritable and genetic factors appear an important mediator of *stability* of EF during childhood. EF deficits are familially linked to ADHD and are possibly related to, amongst others, the Dopamine Receptor D4 gene, which is also related to ADHD. In other words, (partly) genetically-based deficits in EF may *cause* ADHD. However, only a subgroup of ADHD patients (about 30%) suffers from moderately severe EF problems, suggesting EF weaknesses are neither necessary nor sufficient to cause all cases of ADHD.

Implications for Parents, Services and Policy

Cognitive tests are still not sensitive or specific enough to be used in daily practice for diagnosing ADHD. We still have to rely on parents' and teachers' reports (or self report in adolescents and adults with suspected ADHD) for diagnosis. However, recent longitudinal data indicates that childhood EF predicts future academic achievement, social functioning and global functioning in ADHD patients.[33] These results suggest it may benefit clinical practice when EF impairments are assessed and treated, particularly in those at high-risk for negative outcomes, in order to prevent long-term difficulties across a range of important functional domains.[33] Intervention strategies for EF deficits are still in their primary phase of development, but already positive results have been obtained.[34,35] A subgroup of children with ADHD that suffers from moderately severe EF deficits (+/- 30%) may benefit from these interventions.

©2010 CEECD / SKC-ECD

REFERENCES

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV*. 4th ed. Washington, DC.: American Psychiatric Association; 1994.
2. Faraone S, Biederman J, Mick E. The age dependent decline of attention-deficit/hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine* 2006;36(2):159-165.
3. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2005;57(11):1313-1323.
4. Lezak MD, Howieson DB, Loring DW. *Neuropsychological assessment*. 4th ed. New York, NY: Oxford University Press; 2004.
5. Rommelse NN, Altink ME, Oosterlaan J, Buschgens CJ, Buitelaar J, Sergeant JA. Support for an independent familial segregation of executive and intelligence endophenotypes in ADHD families. *Psychological Medicine* 2008;38(11):1595-1606.
6. Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nature Reviews Neuroscience* 2002;3(2):617-628.
7. Durston S. A review of the biological bases of ADHD: what have we learned from imaging studies? *Mental Retardation and Developmental Disabilities Research Reviews* 2003;9(3):184-195.
8. Biederman J, Monuteaux MC, Doyle AE, Seidman LJ, Wilens TE, Ferrero F, Morgan CL, Faraone SV. Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children. *Journal of Consulting and Clinical Psychology* 2004;72(5):757-766.
9. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Journal of Abnormal Child Psychology* 2009;37(11):551-564.
10. Wåhlstedt C, Thorell LB, Bohlin G. Heterogeneity in ADHD: neuropsychological pathways, comorbidity and symptom domains. *Journal of Abnormal Child Psychology* 2009;37(4):551-564.
11. Nigg JT, Willcutt EG, Doyle AE, Sonuga-Barke EJ. Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes? *Biological Psychiatry* 2005;57(11):1224-1230.
12. Anokhin AP, Heath AC, Ralano A. Genetic influences on frontal brain function: WCST performance in twins. *Neuroreport* 2003;14(15):1975-1978.
13. Taylor J. Heritability of Wisconsin Card Sorting Test (WCST) and Stroop Color-Word Test performance in normal individuals: implications for the search for endophenotypes. *Twin Research and Human Genetics* 2007;10(6):829-834.
14. Polderman TJ, Posthuma D, De Sonneville LM, Stins JF, Verhulst FC, Boomsma DI. Genetic analyses of the stability of executive functioning during childhood. *Biological Psychology* 2007;76(1-2):11-20.
15. Doyle AE, Faraone SV, Seidman LJ, Willcutt EG, Nigg JT, Waldman ID, Pennington BF, Peart J, Biederman J. Are endophenotypes based on measures of

©2010 CEECD / SKC-ECD

executive functions useful for molecular genetic studies of ADHD? *Journal of Child Psychology and Psychiatry* 2005;46(7):774-803.

16. Polderman TJ, Gosso MF, Posthuma D, Van Beijsterveldt TC, Heutink P, Verhulst FC, Boomsma DI. A longitudinal twin study on IQ, executive functioning, and attention problems during childhood and early adolescence. *Acta Neurologica Belgica* 2006;106(4):191-207.
17. Seidman L, Biederman J, Monuteaux M, Weber W, Faraone SV. Neuropsychological functioning in nonreferred siblings of children with attention deficit hyperactivity disorder. *Journal of Abnormal Psychology* 2000;109(2):252-265.
18. Nigg JT, Blaskey LG, Stawicki JA, Sachek J. Evaluating the endophenotype model of ADHD neuropsychological deficit: Results for parents and siblings of children with ADHD combined and inattentive subtypes. *Journal of Abnormal Psychology* 2004;113(4):614-625.
19. Waldman ID, Nigg JT, Gizer IR, Park L, Rappley MD, Friderici K. The adrenergic receptor alpha-2A gene (ADRA2A) and neuropsychological executive functions as putative endophenotypes for childhood ADHD. *Cognitive, Affective, & Behavioral Neuroscience* 2006;6(1):18-30.
20. Bidwell LC, Willcutt EG, DeFries JC, Pennington BF. Testing for neuropsychological endophenotypes in siblings discordant for attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2007;62(9):991-998.
21. Uebel H, Albrecht B, Asherson P, Börger NA, Butler L, Chen W, Christiansen H, Heise A, Kuntsi J, Schäfer U, Andreou P, Manor I, Marco R, Miranda A, Mulligan A, Oades RD, van der Meere J, Faraone SV, Rothenberger A, Banaschewski T. Performance variability, impulsivity errors and the impact of incentives as gender-independent endophenotypes for ADHD. *Journal of Child Psychology and Psychiatry* 2010;51(2):210-218.
22. Slaats-Willemse D, Swaab-Barneveld H, De Sonneville L, Buitelaar J. Familial clustering of executive functioning in affected sibling pair families with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 2005;44(4):385-391.
23. Slaats-Willemse D, Swaab-Barneveld H, De Sonneville L, Van der Meulen E, Buitelaar J. Deficient response inhibition as a cognitive endophenotype of ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry* 2003;42(10):1242-1248.
24. Crosbie J, Schachar R. Deficient inhibition as a marker for familial ADHD. *American Journal of Psychiatry* 2001;158(11):1884-1890.
25. Schachar RJ, Crosbie J, Barr CL, Ornstein TJ, Kennedy J, Malone M, Roberts W, Ickowicz A, Tannock R, Chen S, Pathare T. Inhibition of motor responses in siblings concordant and discordant for Attention Deficit Hyperactivity Disorder. *American Journal of Psychiatry* 2005;162(6):1076-1082.
26. Goos LM, Crosbie J, Payne S, Schachar R. Validation and extension of the endophenotype model in ADHD patterns of inheritance in a family study of inhibitory control. *American Journal of Psychiatry* 2009;166(6):711-717.
27. Boonstra AM, Kooij JJS, Buitelaar JK, Oosterlaan J, Sergeant JA, Heister JG, Franke B. An exploratory study of the relationship between four candidate genes

©2010 CEECD / SKC-ECD

28. Altink ME, Rommelse NNJ, Slaats-Willemse DIE, Arias Vasquez A, Franke B, Buschgens CJM, Fliers EA, Faraone SV, Sergeant JA, Oosterlaan J, Buitelaar JK. The dopamine receptor D4 7-repeat allele influences neurocognitive functioning, but this effect is moderated by age and ADHD status. *Journal of Child Psychology and Psychiatry*. In press.
29. Durston S, de Zeeuw P, Staal WG. Imaging genetics in ADHD: a focus on cognitive control. *Neuroscience and Biobehavioral Reviews* 2009;33(5):674-689.
30. Loo SK, Rich EC, Ishii J, McGough J, McCracken J, Nelson S, Smalley SL. Cognitive functioning in affected sibling pairs with ADHD: familial clustering and dopamine genes. *Journal of Child Psychology and Psychiatry* 2008;49(9):950-957.
31. Rommelse NN, Arias-Vásquez A, Altink ME, Buschgens CJ, Fliers E, Asherson P, Faraone SV, Buitelaar JK, Sergeant JA, Oosterlaan J, Franke B. Neuropsychological endophenotype approach to genome-wide linkage analysis identifies susceptibility loci for ADHD on 2q21.1 and 13q12.11. *American Journal of Human Genetics* 2008;83(1):99-105.
32. Doyle AE, Ferreira MA, Sklar PB, Lasky-Su J, Petty C, Fusillo SJ, Seidman LJ, Willcutt EG, Smoller JW, Purcell S, Biederman J, Faraone SV. Multivariate genomewide linkage scan of neurocognitive traits and ADHD symptoms: suggestive linkage to 3q13. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 2008;147B(8):1399-1411.
33. Miller M, Hinshaw SP. Does childhood executive function predict adolescent functional outcomes in girls with ADHD? *Journal of Abnormal Child Psychology*. In press.
34. Papazian O, Alfonso I, Luzondo RJ, Araguez N. Training of executive function in preschool children with combined attention deficit hyperactivity disorder: a prospective, controlled and randomized trial. *Revista de Neurologia* 2009;48(suppl 2):S119-S122.
35. Klingberg T, Fernell E, Olesen PJ, Johnson M, Gustafsson P, Dahlström K, Gillberg CG, Forssberg H, Westerberg H. Computerized training of working memory in children with ADHD--a randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 2005;44(2):177-186.

To cite this document:

Rommelse N. Attention deficit hyperactivity disorder and cognition. Schachar R, topic ed. In: Tremblay RE, Boivin M, Peters RDeV, eds. Encyclopedia on Early Childhood Development [online]. Montreal, Quebec: Centre of Excellence for Early Childhood Development and Strategic Knowledge Cluster on Early Child Development; 2010:1-7. Available at: http://www.child-encyclopedia.com/documents/RommelseANGxp.pdf. Accessed [insert date].

©2010 CEECD / SKC-ECD

This article is produced by:

Encyclopedia on Early Childhood Development

ADHD and Genetics

PHILIP ASHERSON, PhD

Kings College London, UNITED KINGDOM

(Published online November 2010)

Topic
Hyperactivity

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a common childhood onset disorder that frequently persists into adulthood and is associated with the development of cognitive and functional deficits and comorbid disorders. The disorder tends to run in families and numerous twin studies find that ADHD is highly heritable, indicating the predominance of genetic influences in the aetiology of the disorder. While such studies do not exclude the importance of environmental factors they suggest that in most cases these interact with genetic factors; although exceptional environments such as severe early deprivation,[1] or exceptional genetic risk factors such as rare *copy number variants*[2] may exert large effects on disease risk in some cases. The nature of the genetic influences on ADHD is largely unknown although it is thought that this largely results from additive and interactive effects of common genetic variation.

Subject

Genetic studies of ADHD are relevant in two main ways. First, quantitative genetic studies enable the investigation of the extent of genetic effects on ADHD and the extent to which these are shared with associated cognitive impairments, brain function deficits and comorbid disorders and traits. Second, molecular genetic studies enable the identification of the specific risk factors involved, enabling a detailed understanding of the underlying molecular and neurobiological mechanisms involved.

Key Research Questions

What are the genetic influences on ADHD and the mechanisms that mediate genetic effects on behaviour? How do genetic and environmental factors interact in the aetiology of ADHD and associated behavioural and cognitive traits?

Recent Research Results

Family and twin studies delineate a disorder that tends to run in families with a risk to first degree relatives in the order of five- to tenfold the population rate.[3,4] The proportion of phenotypic variance explained by genetic factors (heritability) averages around 76%.[5] The analysis of population twin and ADHD *proband-sibling* samples suggest that genetics influence levels of ADHD throughout the population and that ADHD is best

©2010 CEECD / SKC-ECD

perceived as the extreme of one or more continuously-distributed traits.[3] The two symptom domains of ADHD− inattention and hyperactivity-impulsivity− share most but not all their genetic influences, suggesting that unique as well as common genetic and neurobiological processes are involved.[6] Further studies have investigated the degree to which genetic influences are shared between ADHD and associated disorders and traits. These find that ADHD, particularly inattentive symptoms, share genetic influences with dyslexia;[7] hyperactive-impulsive symptoms with oppositional problems;[8] and ADHD with symptoms of autism spectrum disorder.[9] These are thought to be *pleiotropic* effects of genes that are expressed in more than one clinical disorder.

More recently the overlap of familial effects on ADHD and cognitive performance deficits identified two familial cognitive factors.[10] The larger factor, reflecting 85% of the familial variance of ADHD, captured all familial influences on mean reaction time and reaction time variability on a speeded reaction time task; while a second smaller factor, reflecting 12.5% of the familial variance of ADHD, captured all familial influences on omission errors and 60% on commission errors on a *go/no-go task*. Moreover, the cognitive factors were found to be independent of shared genetic effects between ADHD and IQ.[11] These two cognitive performance factors therefore seem to index most of the familial influences on ADHD and are thought to result primarily from genetic factors. As such, further work is now needed to delineate the genetic factors that underlie these two familial cognitive factors and the neurobiological processes involved, and to clarify whether these mediate the genetic effects on behaviour or whether they represent pleiotropic effects.

Molecular genetic studies on ADHD started with candidate gene association studies in the mid-1990s, with the first two reported associations between genetic variants in the *dopamine D4 receptor* (DRD4) and dopamine transporter (DAT1) genes. Subsequently, association was reported with a microsatellite marker near to the dopamine D5 receptor gene (DRD5). Since then there have been numerous replication studies with only a few independent replications, however meta-analysis of available data reported strong evidence for the association with DRD4 and DRD5 that reached genome-wide levels of significance in the study of Li and colleagues.[12] Evidence for the association with DAT1 has been far less consistent, with generally only weak evidence of association,[12] although there are several potential sources of heterogeneity that might account for this, including: specific association with ADHD that is not comorbid with conduct disorder,[13] association with specific haplotypes (correlated sequences of correlated genetic variation),[14,15] and the interaction with environmental measures such as maternal smoking during pregnancy.[16-18] These candidate gene findings are important because they were the first direct evidence that genes regulating neurotransmission, particularly dopamine regulation, are involved directly in risk for ADHD; and confirmed a priori hypotheses derived from the immediate and marked effects of stimulants on ADHD symptoms that are thought to relate to the effects of stimulants on dopamine availability at neuronal synapses.

There have been numerous other candidate gene studies focusing mainly on the *dopamine*, *serotonin* and *noradrenalin* systems. These were recently reviewed by Gizer

and colleagues[19] who reported significant association following meta-analysis for several genes (DRD4, DAT1, DRD5, DBH, ADRA2A, 5HTT, TPH2, MAOA, and SNAP25). Previous research had estimated the overall impact of the most replicated gene findings and found that around 3.3% of the variance was explained by the additive effects of these genes; accounting for only 4.3% of the estimated heritability of ADHD of 76%.[20] Additional work is clearly needed to explain the rest of the genetic influences on ADHD.

Further studies have taken advantage of *single nucleotide polymorphism (SNP) arrays* that enable genotyping of genetically informative markers across the entire human genome. Depending on the density of the arrays these may account for 80% or more of common genetic variation. In ADHD, genome-wide association studies (GWAS) have yet to establish confirmed novel associations, since no individual SNP has yet to reach genome-wide levels of significance. The problem is that conventional levels of significance in the region of .05 to .001 would be found by chance with SNPs throughout the genome, due the very large number independent haplotypes (correlated sequences of correlated genetic variation) across the genome. As a result, higher levels of significance, in the region of 5×10^{-8}, are recommended to adjust for the low prior odds of association.[21] This has meant that for most common complex disorders, 12,000 or more samples are needed to reliably identify a few associated SNPs, since in nearly all cases only small genetic risks have been identified for specific risk *alleles* with odds ratios in the region of 1.1 – 1.4 or less. The first GWAS study of ADHD investigated 438,784 SNPs in 958 combined type ADHD proband-parent trios. No genes of moderate to large effect were identified[22] and no findings passed genome-wide levels of significance. However, when a set of 51 candidate genes was investigated, there was significant group evidence for association from the selected SNPs, implicating mainly dopamine, noradrenalin and serotonin neurotransmitter genes. Similar findings were subsequently reported in a study that combined genome-wide association data from several studies.

Of particular interest is the Cadherin gene (CDH13), which has been found to be associated with ADHD in more than one GWAS study and lies within the only region that reached genome-wide significance in a meta-analysis of linkage studies of ADHD.[23-25] This finding and other hints from GWAS indicate that genes involved in cell division, cell adhesion, neuronal migration and neuronal plasticity may also confer risk for ADHD.[26]

Overall there is a long way to go to delineate the specific genetic factors that explain the high heritability of the disorder. This is, however, a common phenomenon in common disorders research and several potential explanations for the so called 'dark-matter' of heritability has been put forward. Potential reasons include numerous genes of very small effect, genetic heterogeneity with risk conferred by many different genes and variants within genes, higher order interactions between genes and with environment and aetiological heterogeneity. In addition, we do not yet understand the contribution made to ADHD from rare copy number variants (CNVs) or other types of rare genetic variation; although recent data suggest that in a few cases CNVs may be the main cause of the disorder.[2]

©2010 CEECD / SKC-ECD

Finally, the focus of much of the genetic research has moved to the identification of intermediate phenotypes, measures of neurobiological function that mediate genetic effects on ADHD and may be more proximal to gene function. For example there is evidence from a few *fMRI* studies for greater effect sizes from specific genetic variants.[27,28] Were this also to be the case for cognitive variables sharing genetic effects with ADHD it might be possible to identify genetic variants associated with ADHD following genetic investigations of the intermediate phenotypes. As mentioned genetic influences on ADHD appear to be indexed mainly by two familial cognitive factors measured by poor performance leading to slow and variable reaction times and an increase in commission and omission errors on cognitive performance tasks,[10] so that intermediate phenotype could usefully focus on the processes that underlie these cognitive performance impairments in ADHD.

Interestingly, the most replicated genetic association with cognitive performance measures in ADHD is an inverse association between cognitive function and ADHD risk allele from DRD4. Among children with ADHD the high risk 7-repeat allele for ADHD is associated with less cognitive impairment that those carrying non-risk alleles.[29] This unexpected finding has also been found with the gene ZNF804A and schizophrenia,[30] suggesting that this may be a common finding in neuropsychiatric disorders. These findings suggest that cognitive performance may indicate important sources of heterogeneity with the cognitively less impaired group indicating a discrete molecular pathogenesis.

Research Gaps

Further work is needed to identify both common and rare genetic variants that account for the heritability of ADHD; using very large samples and future whole genome sequencing technologies. Neurobiological research needs to focus on measures that are genetically correlated with ADHD and use genetic association data to determine the nature of the cognitive, neuronal and cellular processes that mediate genetic risks on behaviour. Genetic studies of ADHD in adults are only just beginning, but it is expected that some genetic factors will influence risk for persistence and remission of the disorder during the transitional years from childhood to adulthood. Finally, further work is needed to identify environmental risks that act in an additive or interactive way with genetic risks for ADHD.

Conclusions

ADHD is a highly heritable disorder that starts in childhood and often persists into adulthood. Quantitative genetic studies help us to understand the aetiological links between ADHD and co-occurring disorders and traits; and the cognitive processes that mediate genetic effects on behaviour. Further work is needed to understand the processes that underlie the associated cognitive performance deficits such as reaction time and errors performance deficits. Dopamine system genes have been implicated in the aetiology of ADHD, particularly the DRD4 and DRD5 genes, and there is evidence from GWAS studies that other genes regulating neurotransmission and neurodevelopment, such as SNAP-25 and CDH13, are involved. Recent studies have identified rare copy number variants as a major risk for ADHD, but these only appear to affect a few cases.

©2010 CEECD / SKC-ECD

Further work is needed to explain the 'dark matter' of heritability which is yet to be explained by the genetic variants associated with ADHD to date.

Implications

Family, twin and adoption studies have had a major influence on the way that we perceive ADHD, and this in turn has influenced clinical decision making. We know that the disorder is largely inherited and that the genetic influences account for stability of ADHD over time. Furthermore genetic studies have helped our understanding of the development of comorbid disorders. Future work will use genetic data to identify aetiologically distinct sub-groups with the aim of improving the prediction of clinical outcome and developing novel targeted intervention strategies to treat the disorder and prevent its progression into adulthood. These are critical strategies because of the very high personal and societal costs of ADHD, including education and employment problems, high accident rates and risk for the development of anxiety, depression, drug and alcohol addiction and antisocial behaviour.

REFERENCES

1. Stevens SE, Sonuga-Barke EJ, Kreppner JM, Beckett C, Castle J, Colvert E, Groothues C, Hawkins A, Rutter M. Inattention/overactivity following early severe institutional deprivation: presentation and associations in early adolescence. *Journal of Abnormal Child Psychology* 2008;36(3):385-98.
2. Elia J, Gai X, Xie HM, Perin JC, Geiger E, Glessner JT, D'arcy M, deBerardinis R, Frackelton E, Kim C, Lantieri F, Muganga BM, Wang L, Takeda T, Rappaport EF, Grant SF, Berrettini W, Devoto M, Shaikh TH, Hakonarson H, White PS. Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. *Molecular Psychiatry* 2010;15(6):637-46.
3. Chen W, Zhou K, Sham P, Franke B, Kuntsi J, Campbell D, Fleischman K, Knight J, Andreou P, Arnold R, Altink M, Boer F, Boholst MJ, Buschgens C, Butler L, Christiansen H, Fliers E, Howe-Forbes R, Gabriëls I, Heise A, Korn-Lubetzki I, Marco R, Medad S, Minderaa R, Müller UC, Mulligan A, Psychogiou L, Rommelse N, Sethna V, Uebel H, McGuffin P, Plomin R, Banaschewski T, Buitelaar J, Ebstein R, Eisenberg J, Gill M, Manor I, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Sonuga-Barke E, Steinhausen HC, Taylor E, Thompson M, Faraone SV, Asherson P. DSM-IV combined type ADHD shows familial association with sibling trait scores: a sampling strategy for QTL linkage. *American Journal of Medical Genetic Part B-Neuropsychiatric Genetic* 2008;147B(8): 1450-60.
4. Faraone SV, Biederman J, Monuteaux MC. Toward guidelines for pedigree selection in genetic studies of attention deficit hyperactivity disorder. *Genetic Epidemiology* 2000;18(1):1-16.
5. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2005;57(11):1313-23.

©2010 CEECD / SKC-ECD

6. McLoughlin G, Ronald A, Kuntsi J, Asherson P, Plomin R. Genetic support for the dual nature of attention deficit hyperactivity disorder: substantial genetic overlap between the inattentive and hyperactive-impulsive components. *Journal of Abnormal Child Psychology* 2007;35(6):999-1008.
7. Paloyelis Y, Rijsdijk F, Wood AC, Asherson P, Kuntsi J. The genetic association between ADHD symptoms and reading difficulties: The role of inattentiveness and IQ. *Journal of Abnormal Child Psychology* 2010;38(8):1083-95.
8. Wood AC, Rijsdijk F, Asherson P, Kuntsi J. Hyperactive-impulsive symptom scores and oppositional behaviours reflect alternate manifestations of a single liability. *Behavior Genetics* 2009;39(5):447-60.
9. Ronald A, Simonoff E, Kuntsi J, Asherson P, Plomin R. Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. *Journal of Child Psychology and Psychiatry* 2008;49(5):535-42.
10. Kuntsi J, Wood AC, Rijsdijk F, Johnson KA, Andreou P, Albrecht B, Arias-Vasquez A, Buitelaar JK, McLoughlin G, Rommelse NN, Sergeant JA, Sonuga-Barke EJ, Uebel H, van der Meere JJ, Banaschewski T, Gill M, Manor I, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Steinhausen HC, Faraone SV, Asherson P. Separation of cognitive impairments in attention deficit hyperactivity disorder into two familial factors. *Archives of General Psychiatry* 2010;67(11):1159-67.
11. Wood AC, Rijsdijk F, Johnson KA, Andreou P, Albrecht B, Arias-Vasquez A, Buitelaar JK, McLoughlin G, Rommelse NN, Sergeant JA, Sonuga-Barke EJ, Uebel H, van der Meere JJ, Banaschewski T, Gill M, Manor I, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Steinhausen HC, Faraone SV, Asherson P, Kuntsi J. The relationship between ADHD and key cognitive phenotypes is not mediated by shared familial effects with IQ. *Psychological Medicine* 2010:1-11.
12. Li D, Sham PC, Owen MJ, He L. Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Human Molecular Genetics* 2006;15(14):2276-84.
13. Zhou K, Chen W, Buitelaar J, Banaschewski T, Oades RD, Franke B, Sonuga-Barke E, Ebstein R, Eisenberg J, Gill M, Manor I, Miranda A, Mulas F, Roeyers H, Rothenberger A, Sergeant J, Steinhausen HC, Lasky-Su J, Taylor E, Brookes KJ, Xu X, Neale BM, Rijsdijk F, Thompson M, Asherson P, Faraone SV. Genetic heterogeneity in ADHD: DAT1 gene only affects probands without CD. *American Journal of Medical Genetic Part B-Neuropsychiatry Genetic* 2008;147B(8):1481-7.
14. Asherson P, Brookes K, Franke B, Chen W, Gill M, Ebstein RP, Buitelaar J, Banaschewski T, Sonuga-Barke E, Eisenberg J, Manor I, Miranda A, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Steinhausen HC, Faraone SV. Confirmation that a specific haplotype of the dopamine transporter gene is associated with combined-type ADHD. *American Journal of Psychiatry* 2007;164(4):674-7.
15. Brookes KJ, Xu X, Anney R, Franke B, Zhou K, Chen W, Banaschewski T, Buitelaar J, Ebstein R, Eisenberg J, Gill M, Miranda A, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Sonuga-Barke E, Steinhausen HC, Taylor E, Faraone

©2010 CEECD / SKC-ECD

16. Brookes KJ, Mill J, Guindalini C, Curran S, Xu X, Knight J, Chen CK, Huang YS, Sethna V, Taylor E, Chen W, Breen G, Asherson P. A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. *Archives of General Psychiatry* 2006;63(1):74-81.
17. Becker K, El-Faddagh M, Schmidt MH, Esser G, Laucht M. Interaction of dopamine transporter genotype with prenatal smoke exposure on ADHD symptoms. *Journal of Pediatrics* 2008;152(2):263-9.
18. Kahn RS, Khoury J, Nichols WC, Lanphear BP. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. *Journal of Pediatrics* 2003;143(1):104-10.
19. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. *Human Genetics* 2009;126(1):51-90.
20. Kuntsi J, Neale BM, Chen W, Faraone SV, Asherson P. The IMAGE project: methodological issues for the molecular genetic analysis of ADHD. *Behavioral and Brain Function* 2006;2:27.
21. Dudbridge F, Gusnanto A. Estimation of significance thresholds for genomewide association scans. *Genetic Epidemiology* 2008;32(3):227-34.
22. Neale BM, Lasky-Su J, Anney R, Franke B, Zhou K, Maller JB, Vasquez AA, Asherson P, Chen W, Banaschewski T, Buitelaar J, Ebstein R, Gill M, Miranda A, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Steinhausen HC, Sonuga-Barke E, Mulas F, Taylor E, Laird N, Lange C, Daly M, Faraone SV. Genome-wide association scan of attention deficit hyperactivity disorder. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics* 2008;147B(8):1337-1344.
23. Zhou K, Dempfle A, Arcos-Burgos M, Bakker SC, Banaschewski T, Biederman J, Buitelaar J, Castellanos FX, Doyle A, Ebstein RP, Ekholm J, Forabosco P, Franke B, Freitag C, Friedel S, Gill M, Hebebrand J, Hinney A, Jacob C, Lesch KP, Loo SK, Lopera F, McCracken JT, McGough JJ, Meyer J, Mick E, Miranda A, Muenke M, Mulas F, Nelson SF, Nguyen TT, Oades RD, Ogdie MN, Palacio JD, Pineda D, Reif A, Renner TJ, Roeyers H, Romanos M, Rothenberger A, Schäfer H, Sergeant J, Sinke RJ, Smalley SL, Sonuga-Barke E, Steinhausen HC, van der Meulen E, Walitza S, Warnke A, Lewis CM, Faraone SV, Asherson P. Meta-analysis of genome-wide linkage scans of attention deficit hyperactivity disorder. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics* 2008;147B(8):1392-8.
24. Lasky-Su J, Neale BM, Franke B, Anney RJ, Zhou K, Maller JB, Vasquez AA, Chen W, Asherson P, Buitelaar J, Banaschewski T, Ebstein R, Gill M, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Sonuga-Barke E, Steinhausen HC, Taylor E, Daly M, Laird N, Lange C, Faraone SV.. Genome-wide association scan of quantitative traits for attention deficit hyperactivity

disorder identifies novel associations and confirms candidate gene associations. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics* 2008;147B(8):1345-54.

25. Lesch KP, Timmesfeld N, Renner TJ, Halperin R, Röser C, Nguyen TT, Craig DW, Romanos J, Heine M, Meyer J, Freitag C, Warnke A, Romanos M, Schäfer H, Walitza S, Reif A, Stephan DA, Jacob C. Molecular genetics of adult ADHD: converging evidence from genome-wide association and extended pedigree linkage studies. *Journal of Neural Transmission* 2008;115(11):1573-85.
26. Franke B, Neale BM, Faraone SV. Genome-wide association studies in ADHD. *Human Genetics* 2009;126(1):13-50.
27. Munafo MR, Brown SM, Hariri AR. Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biological Psychiatry* 2008;63(9):852-7.
28. Green AE, Munafò MR, DeYoung CG, Fossella JA, Fan J, Gray JR. Using genetic data in cognitive neuroscience: from growing pains to genuine insights. *Nature Reviews Neuroscience* 2008;9:710-720.
29. Kebir O, Tabbane K, Sengupta S, Joober R. Candidate genes and neuropsychological phenotypes in children with ADHD: review of association studies. *Journal of Psychiatry and Neuroscience* 2009;34(2):88-101.
30. Walters JT, Corvin A, Owen MJ, Williams H, Dragovic M, Quinn EM, Judge R, Smith DJ, Norton N, Giegling I, Hartmann AM, Möller HJ, Muglia P, Moskvina V, Dwyer S, O'Donoghue T, Morar B, Cooper M, Chandler D, Jablensky A, Gill M, Kaladjieva L, Morris DW, O'Donovan MC, Rujescu D, Donohoe G. Psychosis susceptibility gene ZNF804A and cognitive performance in schizophrenia. *Archives of General Psychiatry* 2010;67(7):692-700.

To cite this document:

Asherson P. ADHD and genetics. Schachar R, topic ed. In: Tremblay RE, Boivin M, Peters RDeV, eds. *Encyclopedia on Early Childhood Development* [online]. Montreal, Quebec: Centre of Excellence for Early Childhood Development and Strategic Knowledge Cluster on Early Child Development; 2010:1-8. Available at: http://www.child-encyclopedia.com/documents/AshersonANGxp.pdf. Accessed [insert date].

This article is produced by:

Centre of Excellence for Early Childhood Development

STRATEGIC KNOWLEDGE CLUSTER ON EARLY child development

Encyclopedia on Early Childhood Development

ADHD and Neuroscience

[1]*SAMUELE CORTESE, MD, PhD*
[2]*FRANCISCO XAVIER CASTELLANOS, MD*

NYU Langone Medical Center Child Study Center, USA[1,2]
Nathan Kline Institute for Psychiatric Research, USA[2]

(Published online December 2010)

Topic
Hyperactivity

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent childhood neuropsychiatric condition estimated to affect 3 to 7% of school-age children worldwide.[1] Because of ADHD symptoms and frequently associated psychiatric comorbidities, individuals with ADHD are at risk for family conflict, poor peer relationships and academic/work failure. Therefore, ADHD exacts an enormous burden on society.[2]

Problems

- Currently, ADHD is diagnosed according to a set of behavioural criteria,[1] fostering controversy because of the "subjective" nature of the diagnosis.
- Individuals with ADHD may differ in the clinical presentation, leading to confusion in clinical as well as in research settings.
- Current classification does not account for developmental variations in symptoms.
- No long-term curative treatments are currently available.[3]

Subject

Insights from the emerging field of pediatric neuroscience are required to transition from a classification based on the clinical description of symptoms toward a model based on the causes of the disorder. Such mechanistic models are expected to lead to objective characterization of patients with more precisely defined subtypes of ADHD and to the eventual development of effective physiopathology-based treatments.

Research Context

The most fruitful contributions to understanding ADHD are likely to derive from a multidisciplinary translational research framework including physiology, psychology, neurology, psychiatry, bioinformatics, neurogenetics, cellular and molecular biology, and systems neuroscience.

©2010 CEECD / SKC-ECD

Key Research Questions

Among the issues amenable to investigation by neuroscience methods, the following are pivotal:

- Is the brain of individuals with ADHD morphologically different from non-ADHD controls?
- Does the brain of individuals with ADHD function differently?
- Does brain neurochemistry differ in ADHD?
- What are the causes of the supposed dysfunctions?
- What are the developmental pathways of brain abnormalities?

Recent Research Results

Is the brain of individuals with ADHD morphologically different?

Early structural *MRI* (Magnetic Resonance Imaging) studies have reported several significant morphological differences in ADHD vs. controls, although the findings have not always been consistent.[4] A meta-analysis[5] demonstrated that the brain regions showing the largest area or volumetric reductions in ADHD vs. controls include some specific regions of the brain involved in movement control and organization, as well as the total and right cerebral volume. However, most of these studies were based on a region-of-interest approach with an undue concentration on relatively few and easily measurable cerebral structures. A more recent meta-analysis[6] of *voxel-based morphometric* studies (which are spatially unbiased) found that only right *putamen* volume loss was significant across studies, although this conclusion remains tentative given the limited number (seven) of available studies. Recently, previously overlooked aspects such as thickness, curvature, depth of folds of the brain, and shape of cerebral structures have also been considered. Atypical pattern and decrease in surface area as well as shape anomalies in structures scarcely explored in early studies, such as the *limbic system* and the *thalamus*, have been reported.[7]

Finally, recent studies of *Diffusion Tensor Imaging*, which allow quantitative exploration of white matter, point to altered structural connectivity in tracts connecting the right *prefrontal cortex* to the *basal ganglia* as well as the *cingulate gyrus* to the *entorhinal cortex*.[8]

Does the brain of individuals with ADHD function differently?

The functional imaging literature in ADHD is too extensive to be systematically explored here. We report results of the main available systematic review/meta-analyses.

Pooled evidence[9] from functional MRI studies shows frontal hypoactivity affecting various regions of the cortex (*anterior cingulate*, dorsolateral prefrontal, inferior prefrontal, and orbitofrontal cortex), as well as related regions (such as portions of the basal ganglia, thalamus and *parietal cortex*). Interestingly, these findings mirror, in general, the anatomy implicated by structural imaging studies.

A meta-analysis of quantitative *EEG* studies found *theta power* increase and *beta power* decrease in ADHD vs. controls.[10] The most consistent finding from *event-related potential* studies is *reduced posterior P3* in the auditory *oddball* task.[11] Taken together,

©2010 CEECD / SKC-ECD

the structural and functional findings suggest widespread anomalies encompassing multiple brain structures.

Indeed, currently, researchers in the field are focusing on the study of dysfunction in *distributed networks*. A relatively novel approach assessing functional connectivity during rest and task states seems to be particularly promising for gaining insight into the complex network anomalies presumably underlying ADHD.[12] Preliminary evidence supports the so-called default-mode interference hypothesis of ADHD, according to which ineffective modulation of default network fluctuations interferes with optimal functioning of the neuronal circuits underlying active task performance.[13]

Does brain neurochemistry differ in ADHD?
Converging genetic, *neuroimaging*, neuropsychophamacological and animal model data suggest that several neurotransmitter systems (like dopaminergic, noradrenergic, serotonergic and, possibly, nicotinic cholinergic systems) are involved in the pathophysiology of ADHD.[14]

Altered ratios to *creatine* of several compounds (choline compounds, N-acetyl-aspartate and glutamate/glutamine [a regulator of *dopamine*]) have been reported in preliminary spectroscopic studies.[15]

What are the causes of the supposed dysfunctions?
ADHD is highly heritable (heritability ~0.76).[16] However, the findings from genetic studies have been disappointing so far. A genome-wide scan meta-analysis found genome-wide significant linkage only for a region on chromosome 16, suggesting that many genes of moderately large effect are unlikely to exist.[17] A recent meta-analysis of genome-wide association studies failed to find any significant associations.[18] A small but significant contribution of several single candidate genes involving mainly the dopaminergic system (DRD4, DRD5, DAT1, HTR1B and SNAP25) has been supported by meta-analyses but data are inconsistent for many other candidate genes.[19] Recently, the potential role of a novel gene, latrophilin 3 (LPHN3) has been highlighted by genome-wide significant association and linkage identified by positional cloning and multiple replications.[20;21]

Among several candidate environmental risk factors, a recent systematic review[22] has confirmed a plausible role for premature delivery and maternal smoking during pregnancy.

What are the developmental pathways of brain abnormalities?
A recent longitudinal study reported a delay in brain maturation in ADHD of about three years. Persistent ADHD was characterized by a deviant developmental trajectory, while remission tended to be associated with normalization of anatomic deficits.[7]

©2010 CEECD / SKC-ECD

Research Gaps

- How are structural and functional connectivity abnormalities related?
- At which developmental stages do disruptions in neural networks first emerge and manifest clearly?
- Can genetic factors with small effects be identified if we assemble appropriately large samples? What would be the relevant phenotypes for such large-scale approaches?
- What are the roles of genetic factors beyond *single nucleotide polymorphisms*? A recent study found increased *copy-number variations* (CNV) in ADHD.[23] These structural variations in DNA, such as insertions, deletions and duplications, occur frequently in the population, but their specific clinical significance is uncertain.
- How best can the interactions of genes and environmental (biological as well as psychosocial) variables be understood?
- How do various etiological factors lead to neuronal anomalies?
- What are the potential benefits of pathophysiology-based interventions? For example, neurofeedback[24] and, to a less extent, transcranial magnetic stimulation[25] are promising approaches, although more evidence is needed.

Conclusions

Insights from neuroscience have unequivocally shown that the brains of children with ADHD differ from those of controls. Recently, research on the neurobiological bases of ADHD has shifted from a model based on brain regional differences to a framework characterized by altered connectivity among several areas. Currently, we are still mostly obtaining information on individual elements of these networks. In the near future, we need to gain insight on how these pieces fit together.

We are also discovering, although technical and methodological obstacles remain, the genetic bases of these dysfunctions and the possible environmental factors that interact, in a complex way, with the genetic underpinnings.

Challenging and expensive longitudinal studies have begun to yield insights into the developmental pathways of brain abnormalities and their relationships with ADHD symptoms. As these elements become clearer, the field will be better able to design etiopathophysiologically-based interventions for ADHD with the potential for long-term effectiveness.

Implications for Parents, Services and Policy

Although neuroscience has helped to advance our knowledge of the etiopathophysiology of ADHD, so far we have not found sensitive and specific neurobiological markers. Therefore, parents need to be aware that ADHD diagnosis is still based on behavioural criteria.

However, the veritable explosion of ADHD research grounded in neuroscience, combined with the rapid pace of technologic advances, will make the next years exciting and fruitful for understanding ADHD. Possible future neurobiological tests for ADHD will not replace clinical judgment. However, in the near future, services will need to

©2010 CEECD / SKC-ECD

integrate methods from neuroscience into clinical practice. Large networks of researchers in the fields of imaging and genetics will be necessary to confront future research challenges. Inevitably, substantial funding will be necessary to support this work but the potential results and their implications in terms of public health are expected to justify the economic costs.

REFERENCES

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSMIV-TR)*. 4th ed. Arlington, VA: American Psychiatric Publishing inc; 2000.
2. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet* 2005;366:237-248.
3. Vitiello B. Long-term effects of stimulant medications on the brain: possible relevance to the treatment of attention deficit hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 2001;11:25-34.
4. Castellanos FX. Toward a pathophysiology of attention-deficit/hyperactivity disorder. *Clinical Pediatrics* 1997;36:381-393.
5. Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2007;61:1361-1369.
6. Ellison-Wright I, Ellison-Wright Z, Bullmore E. Structural brain change in attention deficit hyperactivity disorder identified by meta-analysis. *BMC Psychiatry* 2008;8:51.
7. Shaw P, Rabin C. New insights into attention-deficit/hyperactivity disorder using structural neuroimaging. *Current Psychiatry Reports* 2009;11:393-398.
8. Konrad K, Eickhoff SB. Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. *Human Brain Mapping* 2010;31:904-916.
9. Dickstein SG, Bannon K, Castellanos FX, Milham MP. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. *Journal of Child Psychology Psychiatry* 2006;47:1051-1062.
10. Snyder SM, Hall JR. A meta-analysis of quantitative EEG power associated with attention-deficit hyperactivity disorder. *Journal of Clinical Neurophysiology* 2006;23:440-455.
11. Barry RJ, Johnstone SJ, Clarke AR. A review of electrophysiology in attention-deficit/hyperactivity disorder: II. Event-related potentials. *Clinical Neurophysiology* 2003;114:184-198.
12. Castellanos FX, Kelly C, Milham MP. The restless brain: attention-deficit hyperactivity disorder, resting-state functional connectivity, and intrasubject variability. *Canadian Journal of Psychiatry* 2009;54:665-672.
13. Sonuga-Barke EJ, Castellanos FX. Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. *Neuroscience & Biobehavioral Reviews* 2007;31:977-986.

©2010 CEECD / SKC-ECD

14. Russell VA. Reprint of "Neurobiology of animal models of attention-deficit hyperactivity disorder". *Journal of Neuroscience Methods* 2007;166(2):I-XIV.
15. Perlov E, Philipsen A, Matthies S, Drieling T, Maier S, Bubl E, Hesslinger B, Buechert M, Henning J, Ebert D, Tebartz Van Elst L. Spectroscopic findings in attention-deficit/hyperactivity disorder: review and meta-analysis. *World Journal of Biological Psychiatry* 2009;10:355-365.
16. Mick E. Molecular genetics of attention deficit hyperactivity disorder. *Psychiatry Clinics of North America* 2010;33:159-180.
17. Zhou K, Dempfle A, Arcos-Burgos M, Bakker SC, Banaschewski T, Biederman J, Buitelaar J, Castellanos FX, Doyle A, Ebstein RP, Ekholm J, Forabosco P, Franke B, Freitag C, Friedel S, Gill M, Hebebrand J, Hinney A, Jacob C, Lesch KP, Loo SK, Lopera F, McCracken JT, McGough JJ, Meyer J, Mick E, Miranda A, Muenke M, Mulas F, Nelson SF, Nguyen TT, Oades RD, Ogdie MN, Palacio JD, Pineda D, Reif A, Renner TJ, Roeyers H, Romanos M, Rothenberger A, Schäfer H, Sergeant J, Sinke RJ, Smalley SL, Sonuga-Barke E, Steinhausen HC, van der Meulen E, Walitza S, Warnke A, Lewis CM, Faraone SV, Asherson P. Meta-analysis of genome-wide linkage scans of attention deficit hyperactivity disorder. *American Journal of Medicine Genetics part B: Neuropsychiatric Genetics* 2008;147B:1392-1398.
18. Neale BM, Medland SE, Ripke S, Asherson P, Franke B, Lesch KP, Faraone SV, Nguyen TT, Schäfer H, Holmans P, Daly M, Steinhausen HC, Freitag C, Reif A, Renner TJ, Romanos M, Romanos J, Walitza S, Warnke A, Meyer J, Palmason H, Buitelaar J, Vasquez AA, Lambregts-Rommelse N, Gill M, Anney RJ, Langely K, O'Donovan M, Williams N, Owen M, Thapar A, Kent L, Sergeant J, Roeyers H, Mick E, Biederman J, Doyle A, Smalley S, Loo S, Hakonarson H, Elia J, Todorov A, Miranda A, Mulas F, Ebstein RP, Rothenberger A, Banaschewski T, Oades RD, Sonuga-Barke E, McGough J, Nisenbaum L, Middleton F, Hu X, Nelson S; Psychiatric GWAS Consortium: ADHD Subgroup. Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder. *Journal of the American Academy Child and Adolescent Psychiatry* 2010;49:884-897.
19. Banaschewski T, Becker K, Scherag S, Franke B, Coghill D. Molecular genetics of attention-deficit/hyperactivity disorder: an overview. *European Child and Adolescent Psychiatry* 2010;19:237-257.
20. Arcos-Burgos M, Jain M, Acosta MT, Shively S, Stanescu H, Wallis D, Domené S, Vélez JI, Karkera JD, Balog J, Berg K, Kleta R, Gahl WA, Roessler E, Long R, Lie J, Pineda D, Londoño AC, Palacio JD, Arbelaez A, Lopera F, Elia J, Hakonarson H, Johansson S, Knappskog PM, Haavik J, Ribases M, Cormand B, Bayes M, Casas M, Ramos-Quiroga JA, Hervas A, Maher BS, Faraone SV, Seitz C, Freitag CM, Palmason H, Meyer J, Romanos M, Walitza S, Hemminger U, Warnke A, Romanos J, Renner T, Jacob C, Lesch KP, Swanson J, Vortmeyer A, Bailey-Wilson JE, Castellanos FX, Muenke M. A common variant of the latrophilin 3 gene, LPHN3, confers susceptibility to ADHD and predicts effectiveness of stimulant medication. *Molecular Psychiatry* 2010.
21. Ribasés M,Ramos-Quiroga JA, Sánchez-Mora C, Bosch R, Richart C, Palomar G, Gastaminza X, Bielsa A, Arcos-Burgos A, Muenke M, Castellanos FX, Cormand B, Bayés M, Casas M.Contribution of Latrophilin 3 (LPHN3) to the genetic

©2010 CEECD / SKC-ECD

susceptibility to ADHD in adulthood: a replication study. *Genes Brain and Behavior*. In press.

22. Faraone SV. The aetiology of ADHD: Current challenges and future prospects. Paper presented at the 1st International EUNETHYDIS meeting. 26-28 May, 2010. Amsterdam, Netherlands.
23. Williams NM. Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. *Lancet*. In press.
24. Arns M, de RS, Strehl U, Breteler M, Coenen A. Efficacy of neurofeedback treaArns M, de RS, Strehl U, Breteler M, Coenen A. Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis. *Clinical & EEG Neuroscience Journal* 2009;40:180-189.
25. Bloch Y, Harel EV, Aviram S, Govezensky J, Ratzoni G, Levkovitz Y. Positive effects of repetitive transcranial magnetic stimulation on attention in ADHD Subjects: a randomized controlled pilot study. *World Journal of Biological Psychiatry* 2010;11:755-758.

To cite this document:

Cortese S, Castellanos FX. ADHD and neuroscience. Schachar R, topic ed. In: Tremblay RE, Boivin M, Peters RDeV, eds. *Encyclopedia on Early Childhood Development* [online]. Montreal, Quebec: Centre of Excellence for Early Childhood Development and Strategic Knowledge Cluster on Early Child Development; 2010:1-7. Available at: http://www.child-encyclopedia.com/documents/Cortese-CastellanosANGxp1.pdf. Accessed [insert date].

This article is produced by:

Centre of Excellence for Early Childhood Development

STRATEGIC KNOWLEDGE CLUSTER ON EARLY child development

Encyclopedia on Early Childhood Development

Children with Attention Deficit Hyperactivity Disorder: Epidemiology, Comorbidity and Assessment

ALICE CHARACH, Msc, MD

Hospital for Sick Children, CANADA

(Published online March 2010)

Topic
Hyperactivity

Epidemiology of ADHD
Children with Attention Deficit Hyperactivity Disorder (ADHD), characterized by developmentally excessive levels of inattention, over-activity and impulsiveness, are most frequently identified and treated in primary school. Studies worldwide identify a prevalence rate for ADHD equivalent to 5.29% (95% Confidence Interval: 5.01-5.56) of children and adolescents.[1] Rates are higher for boys than for girls, and for children under 12 years of age compared with adolescents.[1,2] Prevalence estimates vary based on method of ascertainment, diagnostic criteria used, and whether functional impairment criteria are included.[1] Overall, estimates are remarkably similar from country to country with the exception of African and Middle Eastern countries where rates are lower compared with North America and Europe.[1]

Symptoms generally interfere with academic and behaviour functioning at school, and often disrupt family and peer relationships.[3,4] Children with ADHD use more health services and sustain more injuries than those without.[5,6] While hyperactivity symptoms lessen in adolescence, the majority of children with ADHD continue to show some cognitive impairment, (eg. poor executive functioning, impaired working memory) relative to same-age peers through their teen years and into adulthood.[7,8] Outcome studies identify lower rates of high school completion, earlier onset of alcohol and illicit substance use, and increased rates of cigarette smoking and driving accidents among teens with ADHD.[9-14] Childhood hyperactivity is also associated with subsequent onset of other psychiatric disorders, including anxiety, conduct problems, mood disorders and suicidal behaviour and antisocial personality disorder.[13,15-18]Adults with childhood history of ADHD have higher than expected rates of injuries and accidents, marital and employment difficulties, teen pregnancy and children born out of wedlock.[15,17,19-21] ADHD is an important public health concern, not only for the long-term impairments facing individuals and families but also for the heavy burden on educational, health and criminal justice systems.[22-24]

Population studies identify that childhood inattention and hyperactivity are more common in single parent families, with low parent education attainment, parent unemployment,

©2010 CEECD / SKC-ECD

and low family income.[17,25,26] Evidence from family studies identify that symptoms of ADHD are highly heritable,[27] however, early environmental factors contribute as well. History of prenatal maternal smoking and drinking, low birth weight, and developmental problems are associated with high levels of inattention and hyperactivity.[26,28] More recently, examination of longitudinal data from the Canadian National Longitudinal Survey of Children and Youth identified that approximately 7% of children show persistent high levels of parent reported hyperactivity from 2 years until early primary school.[29] Prenatal maternal smoking, maternal depression, poor parenting practices and living in a disadvantaged neighborhood in the first year of life are all associated with later childhood behaviour problems, including inattention and hyperactivity four years later.[29-31]

Clinical identification and treatment of ADHD in North America can vary geographically, apparently reflecting differences in community practices or access to services.[32-34] Treatment with stimulant medications for inattentive and hyperactive symptoms increased in the early to mid 1990s, and likely reflects longer periods of use with treatment extended into adolescent years as well as an increased number of girls identified and treated.[35-38]

Concurrent (or Comorbid) Disorders

Half to two thirds of school children identified with ADHD also have concurrent psychiatric and developmental disorders, including oppositional and aggressive behaviours, anxiety, low self esteem, tic disorders, motor problems, and learning or language disabilities.[39-46] Sleep difficulties, including enuresis (bed-wetting), are common, with sleep-disordered breathing, a potentially correctable reason for increased inattention.[47,48] Global impairment in children with ADHD increases with increasing numbers of concurrent disorders.[13,49] The concurrent conditions also increase the likelihood of additional difficulties developing as children become adolescents and young adults.[10,15,16,50-55]

Neurocognitive difficulties are an important source of impairment in children with ADHD. Areas of executive functioning and working memory as well as specific language and learning disorders are common in clinic groups.[56,57-64] Approximately a third of children referred for psychiatric, often behaviour problems, may have previously unrecognized language difficulties.[65] Whenever possible the potential for cognitive problems requires evaluation so that appropriate academic interventions can be implemented.

ADHD in Preschoolers

Attention Deficit Hyperactivity Disorder, usually begins before children enter school. However in the preschool age group ADHD is characterized not only by impairment in attention span, excessive impulsivity and over-activity but also is frequently accompanied by severe temper tantrums, demanding, uncooperative behaviour and aggressiveness that can interfere with attendance at daycare or preschool, avoidance of family gatherings, and high family burden of care and distress.[66,67,68] These disruptive behaviours are often the target of parental concern, and many[66] receive a diagnosis of oppositional defiant

©2010 CEECD / SKC-ECD

disorder. Early identification can be helpful to address the range of developmental issues children with ADHD can have.

Assessment of ADHD in School-Age Children

Among primary school children, concerns about learning style and behaviour difficulties are often brought to the parents' attention by classroom teachers. Educators generally anticipate that by senior kindergarten and grade 1, children should be able to follow classroom routines, follow simple instructions, play cooperatively with peers, and remain focused for 15 to 20 minutes at a time on academic tasks. Concerns raised by teachers, especially experienced ones, provide important details about a child's academic and social functioning.

The formal diagnosis of ADHD reflects pervasive and detrimental levels of inattention, distractibility, overactivity and impulsiveness. The child's symptoms must be developmentally excessive and cause impaired functioning, most often in academic or social skills, peer or family relationships. Difficulties generally have been present since preschool, although is not always recognized. The troublesome behaviours are present in more than one context, at home, at school or in the community, for example on outings to the park or to a grocery store.

There are two sets of formal diagnostic rules used in Canada, DSM IV TR (Diagnostic and Statistical Manual, Fourth Edition, Text Revised) and ICD-10 (International Classification of Disorders, Tenth Edition). The DSM IV Diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD) reflects consensus understanding of the diagnosis largely from the United States. There are three subtypes of ADHD, primarily inattentive type, where the child shows six of nine prescribed inattentive symptoms, primarily hyperactive-impulsive type, where the child shows six out of nine hyperactive-impulsive symptoms, and combined type, where the child shows high levels of both types of symptoms (see Chart 1 for diagnostic symptoms). The ICD-10 diagnosis of Hyperkinetic Disorder is used more often by physicians who do not practice in North America. There is a great deal of overlap in the underlying concept, with the ICD-10 Hyperkinetic Disorder identifying a smaller group of children who must meet criteria for both high levels of activity as well as inattention and distractibility. However, when aspects of overall clinical picture are taken into account, children with ADHD, especially those with combined type, show similar impairments in functioning and need for intervention as those with Hyperkinetic Disorder.[69]

The clinical assessment of a child with ADHD is best done by a health professional familiar with pediatric mental health and psychosocial assessments. Since young children frequently respond to stressful circumstances with increased levels of activity and distractibility as well as difficulties in learning and social relationships, assessments of developmental, family and social contexts are required to identify alternative explanations for the impairing symptoms where appropriate. Physical contributions such as poor sleep, or chronic medical conditions should also be evaluated as explanations for or contributors to the child's difficulties. Ideally, the clinician can obtain information about the child social and academic functioning from more than one informant who

©2010 CEECD / SKC-ECD

knows the child in different situations, for example, the child's parent and a teacher. Self-report surveys for parents and teachers are widely used to elicit information about specific child's behaviours in the home or school settings, respectively.[4] In addition, a detailed clinical interview with the parents of younger children, and, for older children, with the child or youth him/herself, is essential. Reviewing school reports over several years is also helpful to provide a longitudinal perspective from several teachers. An important aspect of the assessment includes identification of concurrent disorders, including learning and language disorders, as reviewed in the section above. Psychosocial or developmental concerns should also be identified as they may complicate treatment of the ADHD and impact the long-term prognosis.

©2010 CEECD / SKC-ECD

Chart 1: DSM IV TR[a] Criteria for Attention Deficit Hyperactivity Disorder

A. *Either (1) or (2):*
Inattention

1. six or more of the following symptoms of *inattention* have persisted for at least 6 months to a degree that is maladaptive and is inconsistent with developmental level:
   a. often fails to give close attention to details or makes careless mistakes
   b. often has difficulty sustaining attention in tasks or play activities
   c. often does not seem to listen when spoken to directly
   d. often does not follow through on instructions and fails to finish schoolwork, chores or duties (not due to oppositional behaviour or failure to understand instructions)
   e. often has difficulty organizing tasks and activities
   f. often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort
   g. often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books or tools)
   h. is often easily distracted by extraneous stimuli
   i. is often forgetful in daily activities

2. six or more of the following symptoms of *hyperactivity-impulsivity* have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:
   Hyperactivity
   a. often fidgets with hands or feet or squirms in seat
   b. often leaves seat in classroom or in other situations where remaining seated is expected
   c. often runs about or climbs excessively in situations in which it is inappropriate
   d. often has difficulty playing or engaging in leisure activities quietly
   e. is often "on the go' or often acts as if "driven by a motor"
   f. often talks excessively

   Impulsivity
   g. often blurts out answers before questions have been completed
   h. often has difficulty awaiting turn
   i. often interrupts or intrudes on others (eg. butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
C. Some impairment from the symptoms is present in two or more settings (eg. at school and home).
D. There must be clear evidence of clinically significant impairment in social, academic or occupational functioning.
E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (eg. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

---

[a] American Psychiatric Association. *Diagnostic and statistical manual of mental disorders Text Revision (DSM-IV-TR)*. 4th Ed. Washington, DC: American Psychiatric Publishing, Inc., 2000.

©2010 CEECD / SKC-ECD

REFERENCES

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *American Journal of Psychiatry* 2007;164(6):942-948.
2. Waddell C, Offord DR, Shepherd CA, Hua JM, McEwan K. Child psychiatric epidemiology and Canadian public policy-making: the state of the science and the art of the possible. *Canadian Journal of Psychiatry* 2002;47(9):825-832.
3. American Academy of Pediatrics. Subcommittee on Attention-Deficit/ Hyperactivity Disorder and Committee on Quality Improvement. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. *Pediatrics* 2001;108(4):1033-1044.
4. Pliszka S, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 2007;46(7):894-921.
5. Bruce B, Kirkland S, Waschbusch D. The relationship between childhood behaviour disorders and unintentional injury events. *Paediatrics & Child Health* 2007;12(9):749-754.
6. Leibson CL, Katusic SK, Barbaresi WJ, Ransom J, O'Brien PC. Use and costs of medical care for children and adolescents with and without attention-deficit/hyperactivity disorder. *JAMA-Journal of the American Medical Association* 2001;285(1):60-66.
7. Brassett-Harknett A, Butler N. Attention-deficit/hyperactivity disorder: an overview of the etiology and a review of the literature relating to the correlates and lifecourse outcomes for men and women. *Clinical Psychology Review* 2007;27(2):188-210.
8. Spencer TJ, Biederman J, Mick E. Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. *Journal of Pediatric Psychology* 2007;32(6):631-642.
9. Barkley RA, Fischer M, Edelbrock C, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria–III. Mother-child interactions, family conflicts and maternal psychopathology. *Journal of Child Psychology and Psychiatry* 1991;32(2):233-255.
10. Barkley RA, Fischer M, Edelbrock CS, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. *Journal of the American Academy of Child & Adolescent Psychiatry* 1990;29(4):546-557.
11. Biederman J, Faraone S, Milberger S, Guite J, Mick E, Chen L, Mennin D, Marrs A, Ouellette C, Moore P, Spencer T, Norman D, Wilens T, Kraus I, Perrin J. A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. *Archives of General Psychiatry* 1996;53(5):437-446.
12. Mannuzza S, Klein RG, Konig PH, Giampino TL. Hyperactive boys almost grown up. IV. Criminality and its relationship to psychiatric status. *Archives of General Psychiatry* 1989;46(12):1073-1079.

©2010 CEECD / SKC-ECD

13. Fergusson DM, Horwood LJ. Early onset cannabis use and psychosocial adjustment in young adults. *Addiction* 1997;92(3):279-296.
14. Barkley RA, Guevremont DC, Anastopoulos AD, DuPaul GJ, Shelton TL. Driving-related risks and outcomes of attention deficit hyperactivity disorder in adolescents and young adults: a 3- to 5-year follow-up survey. *Pediatrics* 1993;92(2):212-218.
15. Fergusson DM, Horwood LJ, Ridder EM. Show me the child at seven: the consequences of conduct problems in childhood for psychosocial functioning in adulthood. *Journal of Child Psychology and Psychiatry* 2005;46(8):837-849.
16. Copeland WE, Miller-Johnson S, Keeler G, Angold A, Costello EJ. Childhood psychiatric disorders and young adult crime: a prospective, population-based study. *American Journal of Psychiatry* 2007;164(11):1668-1675.
17. Fergusson DM, Boden JM, Horwood LJ. Exposure to single parenthood in childhood and later mental health, educational, economic, and criminal behavior outcomes. *Archives of General Psychiatry* 2007;64(9):1089-1095.
18. Woodward LJ, Fergusson DM, Horwood LJ. Driving outcomes of young people with attentional difficulties in adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry* 2000;39(5):627-634.
19. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M. Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. *Archives of General Psychiatry* 1993;50(7):565-576.
20. Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M. Adult psychiatric status of hyperactive boys grown up. *American Journal of Psychiatry* 1998;155(4):493-498.
21. Biederman J, Petty CR, Fried R, Kaiser R, Dolan CR, Schoenfeld S, Doyle AE, Seidman LJ, Faraone SV. Educational and occupational underattainment in adults with attention-deficit/hyperactivity disorder: a controlled study. *Journal of Clinical Psychiatry* 2008;69(8):1217-1222.
22. Birnbaum HG, Kessler RC, Lowe SW, Secnik K, Greenberg PE, Leong SA, Swensen AR. Costs of attention deficit-hyperactivity disorder (ADHD) in the US: excess costs of persons with ADHD and their family members in 2000. *Current Medical Research & Opinion* 2005;21(2):195-206.
23. Leibson CL, Long KH. Economic implications of attention-deficit hyperactivity disorder for healthcare systems. *Pharmacoeconomics* 2003;21(17):1239-1262.
24. Secnik K, Swensen A, Lage MJ. Comorbidities and costs of adult patients diagnosed with attention-deficit hyperactivity disorder. *Pharmacoeconomics* 2005;23(1):93-102.
25. St Sauver JL, Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. Early life risk factors for attention-deficit/hyperactivity disorder: a population-based cohort study. *Mayo Clinic Proceedings* 2004;79(9):1124-1131.
26. Szatmari P, Offord DR, Boyle MH. Correlates, associated impairments and patterns of service utilization of children with attention deficit disorder: findings from the Ontario Child Health Study. *Journal of Child Psychology and Psychiatry* 1989;30(2):205-217.

©2010 CEECD / SKC-ECD

27. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2005;57(11):1313-1323.
28. Fergusson DM, Woodward LJ, Horwood LJ. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. *Archives of General Psychiatry* 1998;55(8):721-727.
29. Romano E, Tremblay RE, Farhat A, Cote S. Development and prediction of hyperactive symptoms from 2 to 7 years in a population-based sample. *Pediatrics* 2006;117(6):2101-2110.
30. Elgar FJ, Curtis LJ, McGrath PJ, Waschbusch DA, Stewart SH. Antecedent-consequence conditions in maternal mood and child adjustment: a four-year cross-lagged study. *Journal of Clinical Child & Adolescent Psychology* 2003;32(3):362-374.
31. Kohen DE, Brooks-Gunn J, Leventhal T, Hertzman C. Neighborhood income and physical and social disorder in Canada: associations with young children's competencies. *Child Development* 2002;73(6):1844-1860.
32. Brownell MD, Yogendran MS. Attention-deficit hyperactivity disorder in Manitoba children: medical diagnosis and psychostimulant treatment rates. *Canadian Journal of Psychiatry* 2001;46(3):264-272.
33. Rappley MD, Gardiner JC, Jetton JR, Houang RT. The use of methylphenidate in Michigan. *Archives of Pediatrics & Adolescent Medicine* 1995;149(6):675-679.
34. Jensen PS, Kettle L, Roper MT, Sloan MT, Dulcan MK, Hoven C, Bird HR, Bauermeister JJ, Payne JD. Are stimulants overprescribed? Treatment of ADHD in four U.S. communities. *Journal of the American Academy of Child & Adolescent Psychiatry* 1999;38(7):797-804.
35. Charach A, Cao H, Schachar R, To T. Correlates of methylphenidate use in Canadian children: a cross-sectional study. *Canadian Journal of Psychiatry* 2006;51(1):17-26.
36. Miller AR, Lalonde CE, McGrail KM, Armstrong RW. Prescription of methylphenidate to children and youth, 1990-1996. *CMAJ − Canadian Medical Association Journal* 2001;165(11):1489-1494.
37. Robison LM, Sclar DA, Skaer TL, Galin RS. National trends in the prevalence of attention-deficit/hyperactivity disorder and the prescribing of methylphenidate among school-age children: 1990-1995. *Clinical Pediatrics* 1999;38(4):209-217.
38. Safer DJ, Zito JM, Fine EM. Increased methylphenidate usage for attention deficit disorder in the 1990s. *Pediatrics* 1996;98(6 Pt 1):1084-1088.
39. Fliers E, Vermeulen S, Rijsdijk F, Altink M, Buschgens C, Rommelse N, Faraone S, Sergeant J, Buitelaar J, Franke B. ADHD and Poor Motor Performance From a Family Genetic Perspective. *Journal of the American Academy of Child & Adolescent Psychiatry* 2009;48(1):25-34.
40. Drabick D, Gadow K, Sprafkin J. Co-occurrence of conduct disorder and depression in a clinic-based sample of boys with ADHD. *Journal of Child Psychology and Psychiatry* 2006;47(8):766-774.
41. Baeyens D, Roeyers H, Van Erdeghem S, Hoebeke P, Vande Walle J. The prevalence of attention deficit-hyperactivity disorder in children with

©2010 CEECD / SKC-ECD

nonmonosymptomatic nocturnal enuresis: a 4-year followup study. *Journal of Urology* 2007;178(6):2616-2620.

42. Angold A, Costello EJ, Erkanli A. Comorbidity. *Journal of Child Psychology and Psychiatry* 1999;40(1):57-87.
43. Corkum P, Moldofsky H, Hogg-Johnson S, Humphries T, Tannock R. Sleep problems in children with attention-deficit/hyperactivity disorder: impact of subtype, comorbidity, and stimulant medication. *Journal of the American Academy of Child & Adolescent Psychiatry* 1999;38(10):1285-1293.
44. Kadesjo B, Gillberg C. The comorbidity of ADHD in the general population of Swedish school-age children. *Journal of Child Psychology and Psychiatry* 2001;42(4):487-492.
45. Shreeram S, He JP, Kalaydjian A, Brothers S, Merikangas KR. Prevalence of enuresis and its association with attention-deficit/hyperactivity disorder among U.S. children: results from a nationally representative study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2009;48(1):35-41.
46. Biederman J, Newcorn J, Sprich S. Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. *American Journal of Psychiatry* 1991;148(5):564-77.
47. Corkum P, Tannock R, Moldofsky H. Sleep disturbances in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 1998;37(6):637-646.
48. Owens JA, Maxim R, Nobile C, McGuinn M, Msall M. Parental and self-report of sleep in children with attention-deficit/hyperactivity disorder. *Archives of Pediatrics & Adolescent Medicine* 2000;154(6):549-555.
49. Biederman J, Milberger S, Faraone SV, Kiely K, Guite J, Mick E, Ablon JS, Warburton R, Reed E, Davis SG. Impact of adversity on functioning and comorbidity in children with attention-deficit hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 1995;34(11):1495-1503.
50. Fischer M, Barkley RA, Edelbrock CS, Smallish L. The adolescent outcome of hyperactive children diagnosed by research criteria: II. Academic, attentional, and neuropsychological status. *Journal of Consulting & Clinical Psychology* 1990;58(5):580-588.
51. Fischer M, Barkley RA, Fletcher KE, Smallish L. The adolescent outcome of hyperactive children: predictors of psychiatric, academic, social, and emotional adjustment. *Journal of the American Academy of Child & Adolescent Psychiatry* 1993;32(2):324-332.
52. Fergusson DM, Horwood LJ. Early conduct problems and later life opportunities. *Journal of Child Psychology and Psychiatry* 1998;39(8):1097-1108.
53. Fergusson DM, Horwood LJ, Lynskey MT. The effects of unemployment on psychiatric illness during young adulthood. *Psychological Medicine* 1997;27(2):371-381.
54. Biederman J, Monuteaux MC, Mick E, Spencer T, Wilens TE, Klein KL, Price JE, Faraone SV. Psychopathology in females with attention-deficit/hyperactivity disorder: a controlled, five-year prospective study. *Biological Psychiatry* 2006;60(10):1098-1105.

©2010 CEECD / SKC-ECD

55. Costello EJ, Erkanli A, Federman E, Angold A. Development of psychiatric comorbidity with substance abuse in adolescents: effects of timing and sex. *Journal of Clinical Child Psychology* 1999;28(3):298-311.
56. Solanto MV, Gilbert SN, Raj A, Zhu J, Pope-Boyd S, Stepak B, Vail L, Newcorn JH. Neurocognitive functioning in AD/HD, predominantly inattentive and combined subtypes. *Journal of Abnormal Child Psychology* 2007;35(5):729-744.
57. Hinshaw SP, Carte ET, Fan C, Jassy JS, Owens EB. Neuropsychological functioning of girls with attention-deficit/hyperactivity disorder followed prospectively into adolescence: evidence for continuing deficits? *Neuropsychology* 2007;21(2):263-273.
58. Thorell LB, Wahlstedt C. Executive functioning deficits in relation to symptoms of ADHD and/or ODD in preschool children. *Infant and Child Development* 2006;15(5):503-518.
59. Loo SK, Humphrey LA, Tapio T, Moilanen IK, McGough JJ, McCracken JT, Yang MH, Dang J, Taanila A, Ebeling H, Jarvelin MR, Smalley SL.. Executive functioning among Finnish adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 2007;46(12):1594-1604.
60. Barkley RA, Edwards G, Laneri M, Fletcher K, Metevia L. Executive functioning, temporal discounting, and sense of time in adolescents with attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD). *Journal of Abnormal Child Psychology* 2001;29(6):541-556.
61. Beitchman JH, Brownlie EB, Inglis A, Wild J, Ferguson B, Schachter D, Lancee W, Wilson B, Mathews R.. Seven-year follow-up of speech/language impaired and control children: psychiatric outcome. *Journal of Child Psychology and Psychiatry* 1996;37(8):961-970.
62. Clark C, Prior M, Kinsella G. The relationship between executive function abilities, adaptive behaviour, and academic achievement in children with externalising behaviour problems. *Journal of Child Psychology and Psychiatry* 2002;43(6):785-796.
63. Calhoun SL, Dickerson Mayes S. Processing speed in children with clinical disorders. *Psychology in the Schools* 2005; 42(4):333-343.
64. Rabiner D, Coie JD, Conduct Problems Prevention Research Group. Early attention problems and children's reading achievement: a longitudinal investigation. *Journal of the American Academy of Child & Adolescent Psychiatry* 2000;39(7):859-867.
65. Cohen NJ, Davine M, Horodezky N, Lipsett L, Isaacson L. Unsuspected language impairment in psychiatrically disturbed children: prevalence and language and behavioral characteristics. *Journal of the American Academy of Child & Adolescent Psychiatry* 1993;32(3):595-603.
66. Cunningham CE, Boyle MH. Preschoolers at risk for attention-deficit hyperactivity disorder and oppositional defiant disorder: family, parenting, and behavioral correlates. *Journal of Abnormal Child Psychology* 2002;30(6):555-569.

©2010 CEECD / SKC-ECD

67. Keown LJ, Woodward LJ. Early parent-child relations and family functioning of preschool boys with pervasive hyperactivity. *Journal of Abnormal Child Psychology* 2002;30(6):541-553.
68. Greenhill LL, Posner K, Vaughan BS, Kratochvil CJ. Attention deficit hyperactivity disorder in preschool children. *Child & Adolescent Psychiatric Clinics of North America* 2008;17(2):347-366.
69. Lee SI, Schachar RJ, Chen SX, Ornstein TJ, Charach A, Barr C, Ickowicz A. Predictive validity of DSM-IV and ICD-10 criteria for ADHD and hyperkinetic disorder. *Journal of Child Psychology and Psychiatry* 2008;49(1):70-78.

To cite this document:

Charach A. Children with attention deficit hyperactivity disorder: Epidemiology, comorbidity and assessment. Schachar R, topic ed. In: Tremblay RE, Boivin M, Peters RDeV, eds. *Encyclopedia on Early Childhood Development* [online]. Montreal, Quebec: Centre of Excellence for Early Childhood Development and Strategic Knowledge Cluster on Early Child Development; 2010:1-11. Available at: http://www.child-encyclopedia.com/documents/CharachANGxp.pdf. Accessed [insert date].

This article is produced by:

Centre of Excellence for Early Childhood Development

STRATEGIC KNOWLEDGE CLUSTER ON EARLY child development

©2010 CEECD / SKC-ECD

Encyclopedia on Early Childhood Development

ADHD and Treatment

MEGHAN MILLER, MA
STEPHEN P. HINSHAW, PhD

University of California, Berkeley, USA

(Published online February 2012)

Topic
Hyperactivity

Introduction
Attention-deficit/hyperactivity disorder (ADHD) is a common and impairing neurodevelopmental disorder that originates in childhood and tends to persist across the lifespan. ADHD is strongly heritable, affects approximately 5-8% of young persons, and occurs more commonly in males than females. As described in the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition,[1] ADHD consists of symptoms that are developmentally extreme, highly impairing and cross-situationally displayed. Such symptoms fall into two categories: (a) inattention/disorganization and (b) hyperactivity/impulsivity. Individuals who display significant symptoms of inattention/disorganization are considered to have the Inattentive subtype; those who display significant symptoms of hyperactivity/ impulsivity are categorized in Hyperactive-Impulsive subtype. The most common clinical presentation of ADHD is the Combined type, in which the individual displays significant symptoms from both classes. Current evidence-based interventions for ADHD consist of psychotropic medications and behaviour therapy.[2,3,4,5]

Subject
Determining the most effective intervention strategies for ADHD is highly relevant. It is critically important to determine which components of evidence-based treatments are most effective (including evaluation strategies for making this determination), to identify how treatment strategies can optimally be combined, to establish the best means of promoting generalization and maintenance of treatment gains, and to determine the factors that contribute to ideal treatment outcomes.

Problems
Years of intervention research have identified and honed evidence-based treatments for ADHD, including behavioural interventions and medication treatment. Yet such treatments, although evidence-based, are not curative and do not result in significant improvements for all who are treated. Additionally, effects of current evidence-based treatments are not generally long-term and tend not to generalize across settings.

©2012 CEECD / SKC-ECD

Research Context

The voluminous research on risk factors, correlates, long-term outcomes and underlying processes related to ADHD has still not been fully translated into mechanism-specific interventions. Still, a number of well-controlled single-case reports and randomized, controlled clinical trials attest to the viability of behaviour therapy and medication interventions for ADHD.

Key Research Questions

A key research question involves evaluating the effectiveness of interventions for ADHD, including behavioural, medication and combined behavioural-medication interventions. Additional critical research issues focus on identifying factors that explain how and how well treatments work, and for whom.[6] Such factors may include sex, ADHD subtype, developmental level, comorbidity, parental factors, medication dosage, cognitive changes, and family discipline styles.[6,7,8,9,10]

Recent Research Results

Current evidence-based treatments for ADHD include medication and behavioural interventions. Medication treatments for ADHD typically consist of psychostimulants, although other types are often concurrently prescribed in order to address comorbid disorders. Psychostimulants used to address ADHD symptoms include methylphenidate, dextroamphetamine, and mixed amphetamine salts, which all enhance the transmission of *dopamine*. Atomoxetine, a *norepinephrine reuptake inhibitor*, has also been found to be effective. Both dopamine and norepinephrine are neurotransmitters (messengers in the brain) that are involved in many mental processes. Whereas such medications have been shown to reduce ADHD-related symptoms and functional impairments across settings,[4] effects tend to last only as long as the medication is active within the body and brain.

As a result, and to promote active skill-building, non-medication treatments are often recommended as well. Behaviour therapy is the only consistently evidence-based intervention for ADHD aside from medication. Behavioural treatments typically involve interventions with parents, teachers and the child.[2,11] Specific components of behavioural interventions for ADHD include direct contingency management and clinical behaviour therapy. Direct contingency management consists of teachers or counselors directly rewarding target skills and employing effective consequences when problems arise. More commonly-used clinical behaviour therapy procedures involve (1) parent training on topics including behaviour management (e.g., positive parental attention, rewards for appropriate behaviour, negative consequences for misbehaviour) and (2) teacher training on topics such as use of prompts and rewards in the classroom. Across most relevant investigations, the greatest likelihood of normalization of symptoms occurs when medication and behavioural treatments are combined, particularly with respect to functional outcomes.[12,13,14]

Although evidence-based interventions for ADHD have been identified, few randomized controlled trials have focused on identifying specific individual factors that influence treatment outcome. Key factors emerging from the Multimodal Treatment of children with ADHD (MTA) Study included the presence of a comorbid anxiety disorder, family

©2012 CEECD / SKC-ECD

public assistance, ethnicity/race, severity of ADHD, parental depressive symptomatology, child IQ, attendance, medication use in the community and negative/ineffective parental discipline.[6]

Finally, cognitive enhancements of contingency-based interventions (e.g., social skills training with parent training) as well as cognitive training to ameliorate neuropsychological deficits commonly associated with ADHD (i.e., executive function deficits, which include difficulties planning, staying organized, inhibiting inappropriate responses, setting and carrying out goals) may be viable but evidence is currently limited. A critical issue with the current evidence-based behavioural interventions for ADHD – including combination treatments of medication and behavioural interventions – is that treatment gains often are not maintained over periods of time, nor are gains generalized across settings.[3]

Research Gaps

A major issue with current evidence-based treatments for ADHD concerns generalization.[16] Specifically, individuals with ADHD tend not to translate gains obtained in one setting to other key life settings. Thus, future treatment development efforts should focus on determining components of interventions that promote long-lasting maintenance of treatment gains across settings. An additional issue involves developing treatments that can address functional impairments that often accompany ADHD (e.g., social difficulties, academic struggles, organizational skills deficits). Successful interventions in these domains may have significant long-term effects, with the potential for contributing to the elusive goal of maintaining gains. Finally, a critical gap in the literature pertains to early, preventive interventions. Such interventions, if successful, could alter the trajectory of ADHD from the start, preventing later problems. Although this approach is being used in other neurodevelopmental disorders (e.g., autism spectrum disorders), such methodology has rarely been used in the study of ADHD.[17] One key problem relates to false-positives: how many preschool-aged children at risk for ADHD will actually proceed to the full disorder?

Conclusions

ADHD is a common and impairing neurodevelopmental disorder that requires intensive intervention. Much research has focused on identifying evidence-based interventions for ADHD. Current evidence-based treatment options include behavioural interventions and medication treatment (mainly psychostimulants); evidence exists that the greatest symptom reduction occurs when medication and behavioural interventions are combined. Although these treatment options are useful for decreasing core symptomatology (i.e., inattention/disorganization, hyperactivity/impulsivity), they do not appear to remediate core deficits related to ADHD, and they tend not to produce long-term, generalized gains. It will be essential to promote translational research linking biological and contextual risk factors to development of improved treatment strategies. Important areas for future research include identifying specific factors that influence treatment outcome, developing of interventions that produce effects that can be generalized and maintained over time, determining ways to address the functional impairments commonly present in individuals with ADHD, and ascertainment of the potential benefits of preventive measures.

©2012 CEECD / SKC-ECD

Implications for Parents, Services and Policy

Professional organizations (e.g., American Association of Child and Adolescent Psychiatry and America Academy of Pediatrics)[18,19] have published assessment and treatment guidelines for ADHD, but there is little or no enforcement of such professional guides, nor is it clear that reimbursement always or even usually covers such standards. Families need to be aware of the need for relevant health professionals to have demonstrated expertise in ADHD and its common comorbidities and impairments; policy-makers need to assure adequate assessment and treatment standards. Furthermore, large regional variation in rates of diagnosis and treatment of ADHD exists within the U.S.[20] and internationally.[21] Policy-related factors such as high-stakes achievement testing, training of professionals, insurance coverage and advertisements for treatment (particularly medication) may all be relevant regarding this wide variation. Overall, knowledge of ADHD, reduction of stigma regarding its identification and treatment, enlightened policies that provide for evidence-based services, and proper means of assessing treatment-related gains are essential goals if youth and their families are to receive optimal services.

REFERENCES

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.* 4th ed., text rev. Washington, DC: Author; 2000.
2. Hinshaw, S. P., Klein, R. G., & Abikoff, H. Childhood attention-deficit hyperactivity disorder: Nonpharmacologic treatments and their combination with medication. In: Nathan, P. E. & Gorman, J. M. eds. *A guide to treatments that work*, 3rd ed. New York: Oxford University Press; 2007:3-27.
3. Miller, M. & Hinshaw, S. P. Treatment for children and adolescents with ADHD. In Kendall, P. C. ed. *Child and Adolescent Therapy*, 4th Edition: Cognitive-Behavioral Procedures. New York: Guilford Press; 2011:61-91.
4. Paykina, N., & Greenhill, L. L. (2007). Pharmacological treatments for attention-deficit/ hyperactivity disorder. In Nathan. P. E. & Gorman, J. M. eds. *A guide to treatments that work*, 3rd ed. New York: Oxford University Press; 2007:29-70.
5. Evans, S. W., & Hoza, B. (Eds.) *Treating attention deficit hyperactivity disorder: Assessment and intervention in developmental context*. Kingston, NJ: Civic Research Institute; 2011.
6. Hinshaw, S. P. Moderators and mediators of treatment outcome for youth with ADHD: Understanding for whom and how interventions work. *Journal of Pediatric Psychology*. 2007;32(6):664-675.
7. Jensen, P. S., Hinshaw, S. P., Kraemer, H. C., Lenora, N., Abikoff, H. B., Conners, C. K. et al. ADHD comorbidity findings from the MTA study: Comparing comorbid subgroups. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2001;40(2):147–158.
8. MTA Cooperative Group. Moderators and mediators of treatment response for children with ADHD: The MTA Study. *Archives of General Psychiatry*. 1999a;56(12):1088-1096.
9. Owens, E. B., Hinshaw, S. P., Kraemer, H. C., Arnold, L. E., Abikoff, H. B.,

©2012 CEECD / SKC-ECD

Cantwell, D. P. et al. Which treatment for whom for ADHD? Moderators of treatment response in the MTA. *Journal of Consulting and Clinical Psychology*. 2003;71(3):540-552.

10. Kazdin, A. E., & Weisz, J. R. Identifying and developing empirically supported child and adolescent treatments. *Journal of Consulting and Clinical Psychology*. 1998;66(1):19–36.
11. Pelham, W. E., & Fabiano, G. A. Evidence-based psychosocial treatments for attention-deficit/ hyperactivity disorder. *Journal of Clinical Child & Adolescent Psychology*. 2008;37(1):184-214.
12. Conners C. K., Epstein J. N., March, J. S., Angold, A., Wells, K. C., Klaric, J. et al. Multimodal treatment of ADHD in the MTA: An alternative outcome analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2001;40(2):159–167.
13. Swanson, J. M., Kraemer, H. C., Hinshaw, S. P., Arnold, L. E., Conners, C. K., Abikoff, H. B. et al. Clinical relevance of the primary findings of the MTA: Success rates based on severity of ADHD and ODD symptoms at the end of treatment. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2001;40(2):168–179.
14. MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*. 1999b;56(12):1073-1086.
15. Hinshaw, S. P., Owens, E. B., Wells, K.C., Kraemer, H.C., Abikoff, H.B., Arnold, L.E., et al. Family processes and treatment outcome in the MTA: Negative/ineffective parenting practices in relation to multimodal treatment. *Journal of Abnormal Child Psychology*. 2000;28:555-568.
16. Abikoff, H. ADHD psychosocial treatments: Generalization reconsidered. *Journal of Attention Disorders*. 2009;13(3):207-210.
17. Sonuga-Barke, E. J. S. & Halperin, J. M. Developmental phenotypes and causal pathways in attention deficit/hyperactivity disorder: Potential targets for early intervention? *Journal of Child Psychology and Psychiatry*. 2010;51(4):368-389.
18. American Association of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2007;46(7):894-921.
19. American Academy of Pediatrics. ADHD: Clinical practice guidelines for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2011;128(5):1007-1022.
20. Fulton, B. D., Scheffler, R. M., Hinshaw, S. P., Levine, P., Stone, S., Brown, T. T., et al. National variation of ADHD diagnostic prevalence and medication use: Health care providers and educational policies. *Psychiatric Services*. 2009;60(8):1075-1083.
21. Hinshaw, S. P., Scheffler, R. M., Fulton, B. D., Aase, H., Banaschewski, T., Cheng, W., et al. International variation in treatment procedures for ADHD: Social contexts and recent trends. *Psychiatric Services*. 2011;62(5):459-464.

©2012 CEECD / SKC-ECD

To cite this document:

Miller M, Hinshaw SP. ADHD and treatment. Schachar R, topic ed. In: Tremblay RE, Boivin M, Peters RDeV, eds. *Encyclopedia on Early Childhood Development* [online]. Montreal, Quebec: Centre of Excellence for Early Childhood Development and Strategic Knowledge Cluster on Early Child Development; 2012:1-6. Available at: http://www.child-encyclopedia.com/documents/Miller-HinshawANGxp1.pdf. Accessed [insert date].

This article is produced by: