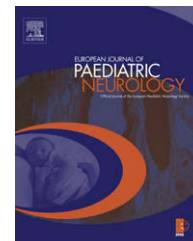




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Review article

The neurobiology of attention deficit/hyperactivity disorder

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ABSTRACT

ADHD is a brain based disorder with structural and functional abnormalities in widespread but specific areas of the brain. The most significant and consistent structural imaging findings include smaller total brain volumes, and reduced volumes in the right frontal lobe, right parietal cortex, caudate nucleus, cerebellar hemispheres, and posterior-inferior lobules of the cerebellar vermis. ADHD involves hypofunction of catecholaminergic circuits, particularly those that project to the prefrontal cortex. A minimum of 18 genes have been reported to be associated with the disorder; among them the DRD4 7-repeat allele has been found associated with a thinner prefrontal and posterior parietal cortex. Epigenetic factors acting during critical periods of prenatal and postnatal development may interact with genetic determinants. Methylphenidate, as well as the catecholaminergic nonstimulant atomoxetine, are effective in improving ADHD symptoms.

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1. Introduction

Attention deficit/hyperactivity disorder (ADHD), one of the most common neurobehavioural disorders with onset in early childhood, is a highly heritable condition with documented brain abnormalities, with prominent associated symptoms and impairments that affect several aspects of the daily life

function.¹ The areas of impairment associated with childhood ADHD include academic and social dysfunctions and skill deficits. Adolescents with ADHD are at high risk for low self-esteem, poor peer relationships, smoking and substance abuse.^{2–8}

ADHD is a multifactorial neurobiological disorder caused by the confluence of many genetic and environmental risk

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factors, each having a small effect on increasing vulnerability to the disorder. Individuals with ADHD present difficulties in several domains of attentional and cognitive functions: problem solving, planning, orienting, alerting, cognitive flexibility, sustained attention, response inhibition, and working memory.^{9,10} Other domains involving affective components, such as motivation and delay aversion, are also affected.^{11–13} Psychiatric comorbidities with childhood ADHD include oppositional defiant disorder, mood and anxiety disorders, learning disorders, tics, and mental retardation. Recently, neuroimaging has caused several important advances in the understanding of the neurobiology underlying the clinical picture of ADHD, showing that there is a clear brain basis to the disorder in regions involved in attention and executive control.^{14,15} Knowledge about neurobiology offers child neurologists a valuable framework to interpret clinical findings of children meeting the criteria for diagnosis of ADHD.¹ In this article we provide a brief overview of the salient neurological aspects of ADHD.

2. Historical background and neurological perspective

ADHD was first described 100 years ago as a childhood disorder found mainly in boys, initially called “hyperactivity” or “hyperkinetic disorder of childhood”; this abnormal behavior was the result of a biological condition rather than a result of poor parenting.¹⁶ After the encephalitis lethargica epidemic that swept the World War I, many children showed hyperkinetic behavioral symptoms and were labeled as brain damaged.¹⁷ Amphetamines were discovered helpful in reducing hyperactive and impulsive behavior.¹⁸ In the 1960s and 1970s much of the focusing of what is now ADHD was on hyperactivity. The presence of excessive movements for that age group has been proposed to result from bilateral cortical activity secondary to a lack of transcallosal-fiber-tract mediated interhemispheric inhibition.¹⁹ Attention deficit disorder with or without hyperactivity entered in DSM-III,²⁰ and later in DSM-IV updated ADHD criteria.²¹ The renaming of the disorder, the subsequent focus on attention, and the clarification of three subtypes²¹ led to a range of neurocognitive and neurobiological hypothesis regarding the etiology and pathophysiology of ADHD within a more specific brain localization perspective. Furthermore, neurocognitive models of ADHD have become more refined, and one particular executive process, inhibition, was considered to be a core deficit.²² Current theories emphasize the central role of attentional and executive dysfunctions in children,^{9,11,23} as well as affective components involving emotional control, and motivational processes.¹³ In the last few years functional neuroimaging has provided new ways to examine the pathophysiology of ADHD showing widespread dysfunction in neural systems involving the prefrontal, striatal and parietal brain regions,^{24,25} and a brain model of deficits in multiple developmental pathways.¹² Recent molecular genetic studies support dysregulation of neurotransmitter systems as the basis of genetic susceptibility to the disorder, and it is becoming clear that the genotype may influence the response to medications.¹² Transcranial magnetic stimulation

provided evidence that intracortical inhibition, as indexed by the immature ipsilateral motor cortex, normalizes with psychostimulant treatment.^{27,28} Progress in understanding the neurological perspective of ADHD is summarized in Table 1.

3. Genetics

Family studies and adoption studies of ADHD have consistently supported the strong familiar nature of this disorder.²⁹ Based on numerous studies of monozygotic twins, the mean heritability for ADHD was shown to be 77%.³⁰ Many different, probably interacting genes, each with a very small effect size, contribute to the neurological phenotype. A minimum of 18 ADHD susceptibility genes,³¹ including dopamine receptors D4 and D5, dopamine transporter, serotonin receptor 1B and SNAP-25 have been reported to be associated with the

Table 1 – Historical background of ADHD.

Year	Authors	Findings
1902	Still ¹⁶	Hyperactivity in males
1935	Bond and Smith ¹⁷	Post-encephalitic behaviour disorder
1937	Bradley ¹⁸	Amphetamine therapy is effective
1959	Pasamanick and Knobloch ⁷²	Minimal cerebral damage
1966	Clements and Peter ⁷³	Attention as a deficit
1978	Denckla ¹⁹	Abnormalities of motor development
1997	Barkley ²²	Constructing a unifying theory
1998	Vaidya ⁵⁷	fMRI evidence of selective effects of MPH
1999	Bush ²⁴	ACC dysfunction revealed by MRI
1999	Rubia ²⁵	fMRI evidence of hypofrontality
2000	Moll ²⁷	Deficient intracortical inhibition
2001	Swanson ⁶⁸	Efficacy of interventions (MTA study)
2002	Castellanos ⁵³	Developmental trajectories of brain volume abnormalities
2003	Durstun ⁷⁴	Differential pattern of striatal activation
2005	Sonuga-Barke ¹²	Brain model of multiple cognitive deficits
2005	Allen ⁷⁵	ATX shows efficacy
2006	Gilbert ²⁶	DAT genotype influences the response to medication
2007	Shaw ⁵⁴	Neuroanatomic evidence of delay in regional cortical maturation
2007	Buchmann ²⁸	Disturbed intracortical motor inhibition is restored by MPH
2008	Becker ⁵⁰	Interaction of DAT genotype with Prenatal Smoke Exposure

MPH: methylphenidate; ACC: anterior cingulate cortex; MTA: multimodal treatment study of children with ADHD; ATX: atomoxetine; DAT: dopamine transporter.

disorder, and a number of these have been replicated in multiple studies.³² Genome scan studies on potential alleles for ADHD have demonstrated linkage on chromosomes 2q24, 5p13, 6q14, 16p13, and 17p11.³³ By far, the gene most strongly implicated in ADHD is the 7-repeat allele of the human dopamine receptor D4 gene (DRD4), suggesting a strong dopamine role in the pathogenesis of ADHD.²⁹

Sometimes ADHD is symptomatic, and it can be related to some established neurogenetic disorders, like Tuberous Sclerosis Complex, Neurofibromatosis I, Turner Syndrome, Williams Syndrome, Velocardiofacial Syndrome (VCF), Prader–Willy Syndrome, and Fragile X Syndrome. Children with Williams Syndrome seem to be more hyperactive, whereas children with VCF tend to be more inattentive. The very high prevalence of ADHD in VCF male children (41%) suggests that the 22q11 deleted region harbors gene or genes that contribute to the etiology of ADHD in this population; recently, an association between the low level of catechol-O-methyl-transferase (COMT) 158 met allele located in this region and ADHD in VCF males has been reported.³⁴ Children with NF1 may be more likely to fulfill diagnostic criteria for attention deficit disorder without hyperactivity.³⁵ High rates of hyperactivity with attention impairment with oppositional behavior have been reported in tuberous sclerosis.³⁶ The most common DSM-IV diagnosis among the fragile X boys is ADHD (73%), followed by oppositional defiant disorder, anxiety disorders.³⁷

4. Environmental risk factors

Several biological and environmental factors have been proposed as risk factors for ADHD, including fetal alcohol exposure, maternal smoking during pregnancy, low birth weight, food additives, lead contamination.^{38–41} Prenatal alcohol exposure is known to induce brain structural anomalies especially in the cerebellum.⁴² Children exposed prenatally to alcohol can become hyperactive, disruptive, impulsive, and are at an increased risk for a range of psychiatric disorders.^{43,44} Maternal smoking produces a 2.7-fold increased risk for ADHD⁴⁵ and a dose-response relationship between maternal smoking during pregnancy and hyperactivity has been reported.⁴⁶ Nicotinic receptors modulate dopaminergic activity, and dopaminergic disruption is believed to be involved in the pathophysiology of ADHD.^{47,48} Nicotine exerts its effects on various neurotransmitter systems and may induce regionally specific abnormalities in cell proliferation and differentiation.⁴⁷

5. Gene–environment interactions

Recent studies focused on the joint effects of gene variants (in DRD4 and DAT1) and prenatal substance exposures on subtypes of ADHD children, demonstrating that smoking during pregnancy is associated with the combined ADHD type in genetically susceptible children.⁴⁹

A significant interaction between DAT1 genotype and prenatal smoke exposure was found in males with prenatal smoke exposure. The patients homozygous for the DAT1

10-repeat allele had higher hyperactivity-impulsivity than males from all other groups.⁵⁰

Despite the heterogeneity of the etiology and pathophysiology of ADHD, abnormal DAT density seems to be common among subjects with ADHD.⁵¹

6. Neuroimaging

The most significant and consistent structural imaging findings in children with ADHD include smaller total brain volumes and reduced volumes, in the right frontal lobe, caudate nucleus, the cerebellar hemisphere and posterior-inferior lobules of the cerebellar vermis.⁵² These early abnormalities of regional brain volumes have also been shown to change over time in children and adolescents with ADHD.^{53,54} Developmental trajectories study showed that volumetric abnormalities in the cerebrum and cerebellum persisted with increasing age, whereas caudate differences versus normal subjects disappeared.^{53,55} Cortical development in children with ADHD shows a marked delay in brain maturation; the gray matter peaks were about 3 years later than in healthy controls. The delay is most prominent in prefrontal regions important for control of cognitive processes including attention and motor planning.^{54,56} Functional neuroimaging studies offered new data to map the brain systems involved in the ADHD, to integrate this findings with clinical symptoms, and to understand mechanism of treatment response.^{54,57} The recruitment of alternative networks by ADHD children to cope with functions that are particularly difficult for them may reflect the neural correlates of differences in specific neuropsychological mechanisms.⁵⁸ Recent fMRI finding of right parietal dysfunction suggests a widespread maturational deficit that may be independent from the developmental stage.⁵⁹

fMRI studies also show promise for understanding mechanisms of treatment response.^{57,60–63} Positron emission tomography studies have shown that methylphenidate hydrochloride blocks DAT and that extracellular dopamine increases in proportion to the level of blockade and to the rate of dopamine release. This process is associated with an enhanced perception of the external stimulus as a salient in subjects with ADHD.⁶²

7. Treatment

The fronto-subcortical circuits (lateral prefrontal cortex, dorsal anterior cingulate cortex, caudate, and putamen) associated with ADHD are rich in catecholamines, which are involved in the mechanism of action of medications used to treat this disorder. Neuropharmacological studies provide evidence that ADHD involves dysregulation of both noradrenaline and dopamine neurotransmitter systems.⁶⁴ Dysregulation of a noradrenaline system is suggested to lead to inefficient function of the posterior cortical attentional system, while dopamine dysregulation leads to impaired function of the anterior executive system⁶⁵ (see Fig. 1).

Strong evidence exists indicating that the stimulant medications, such as methylphenidate (MPH) and dextroamphetamine,

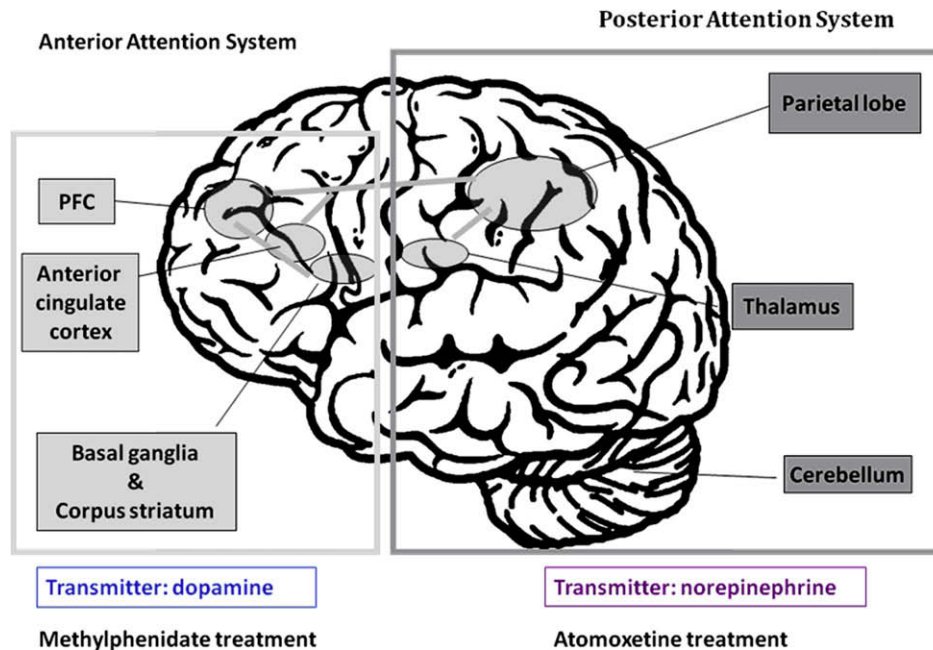


Fig. 1 – Brain model of the multiple cognitive deficit in ADHD.

as well as the catecholaminergic nonstimulant atomoxetine (ATX), are effective in improving ADHD symptoms.^{64,66} Treatment with MPH and ATX both significantly increase activation in key cortical and subcortical regions subserving attention and executive functions. Therefore, alterations in dopaminergic and noradrenergic function are apparently necessary for the clinical efficacy of pharmacological treatment of ADHD.⁶⁷ However, MPH and ATX have both common and distinct neural effects, consistent with the observation that many children respond well to both treatments, and some respond preferentially to one or the other.

Even though pharmacogenetic studies of ADHD are in the early stages, there could be a correlation between the response to MPH and polymorphism of the DRD4 gene, together with an interaction between polymorphism at DRD4 and 5-HTT genes in the response to MPH. Psychopharmacological options improve not only abnormal behaviors of ADHD but also self-esteem, cognition, and social and family functioning. Psychotherapy combined with medication may play role in treating behavioural problems, organizational issues and psychiatry comorbidities.⁶⁸

Although pharmacotherapy for ADHD appears to prepare and facilitate the brain for learning, experiential programs need to elicit compensatory development in the brain. The clinical amelioration of some children after environmental experiential inputs, and early cognitive/behavioral treatment could indicate outcome-associated plastic brain response.⁶⁹ One year treatment with MPH may be beneficial to show enduring normalization of neural correlates of attention. Little is known about the long-term effects of stimulants on the functional organization of the developing brain.⁷⁰ Recent findings have shown that chronic methylphenidate on drug-naïve boys with ADHD enhanced neuropsychological functioning on “recognition memory” component tasks with modest executive demands.⁷¹

8. Future directions

The exciting findings that link the genomic, structural and functional changes in the brain constitute a convincing emerging brain model of dysfunctions in ADHD. Functional imaging studies have made great progress in helping to uncover the neural substrate of ADHD. The virtual explosion of new knowledge provided by the field of cognitive neuroscience regarding the brain's attention system combined with the rapid pace of technological advances promises to make the next few years exciting times for unraveling the mysteries of the neurobiology of ADHD. It is hoped that advances in understanding the underlying neurobiology of ADHD will contribute to identifying more specific and targeted pharmacotherapies, and will help child neurologist to better manage their patients.

REFERENCES

1. Bridge Denckla M. ADHD: topic update. *Brain Dev* 2003;25(6): 383–9.
2. Whalen CK, Jamner LD, Henker B, Delfino RJ, Lozano JM. The ADHD spectrum and everyday life: experience sampling of adolescent moods, activities, smoking, and drinking. *Child Dev* 2002;73(1):209–27.
3. Harpin VA. The effect of ADHD on the life of an individual, their family, and community from preschool to adult life. *Arch Dis Child* 2005;90(Suppl. 1):i2–7.
4. Edbom T, Lichtenstein P, Granlund M, Larsson JO. Long-term relationships between symptoms of attention deficit hyperactivity disorder and self-esteem in a prospective longitudinal study of twins. *Acta Paediatr* 2006;95(6):650–7.
5. Elkins IJ, McGue M, Iacono WG. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder,

- and sex on adolescent substance use and abuse. *Arch Gen Psychiatry* 2007;**64**(10):1145–52.
6. Loe IM, Feldman HM. Academic and educational outcomes of children with ADHD. *J Pediatr Psychol* 2007;**32**(6):643–54.
 7. Rodriguez A, Jarvelin MR, Obel C, et al. Do inattention and hyperactivity symptoms equal scholastic impairment? Evidence from three European cohorts. *BMC Public Health* 2007;**7**(147):327.
 8. Hoza B. Peer functioning in children with ADHD. *J Pediatr Psychol* 2007;**32**(6):655–63.
 9. Sergeant JA, Geurts H, Huijbregts S, Scheres A, Oosterlaan J. The top and the bottom of ADHD: a neuropsychological perspective. *Neurosci Biobehav Rev* 2003;**27**(7):583–92.
 10. Pasini A, Paloscia C, Alessandrelli R, Porfirio MC, Curatolo P. Attention and executive functions profile in drug naive ADHD subtypes. *Brain Dev* 2007;**29**(7):400–8.
 11. Castellanos FX, Sonuga-Barke EJ, Milham MP, Tannock R. Characterizing cognition in ADHD: beyond executive dysfunction. *Trends Cogn Sci* 2006;**10**(3):117–23.
 12. Sonuga-Barke EJ. Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. *Biol Psychiatry* 2005;**57**(11):1231–8.
 13. Nigg JT, Casey BJ. An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. *Dev Psychopathol* 2005;**17**(3):785–806.
 14. Curatolo P. The neurology of attention deficit/hyperactivity disorder. *Brain Dev* 2005;**27**(8):541–3.
 15. Suskauer SJ, Simmonds DJ, Fotedar S, et al. Functional magnetic resonance imaging evidence for abnormalities in response selection in attention deficit hyperactivity disorder: differences in activation associated with response inhibition but not habitual motor response. *J Cogn Neurosci* 2008;**20**(3):478–93.
 16. Still G. The Coulstonian lectures on some abnormal physical conditions in children. Lecture 1. *Lancet* 1902;**1008–1012**(1077–1082):1163–8.
 17. Bond E, Smith L. Post-encephalitic behavior disorders: a ten-year review of the Franklin School. *Am J Psychiatry* 1935;**91**:17–31.
 18. Bradley C. The behavior of children receiving Benzedrine. *Am J Psychiatry* 1937;**94**:577–85.
 19. Denckla MB, Rudel RG. Anomalies of motor development in hyperactive boys. *Ann Neurol* 1978;**3**(3):231–3.
 20. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 3rd (DSM-III) ed. Washington: American Psychiatric Association; 1980.
 21. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th (DSM-IV) ed. Washington: American Psychiatric Association; 1994.
 22. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull* 1997;**121**(1):65–94.
 23. 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. *Biol Psychiatry* 2005;**57**(11):1336–46.
 24. Bush G, Frazier JA, Rauch SL, et al. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting Stroop. *Biol Psychiatry* 1999;**45**(12):1542–52.
 25. Rubia K, Overmeyer S, Taylor E, et al. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *Am J Psychiatry* 1999;**156**(6):891–6.
 26. Gilbert DL, Wang Z, Sallee FR, et al. Dopamine transporter genotype influences the physiological response to medication in ADHD. *Brain* 2006;**129**(Pt 8):2038–46.
 27. Moll GH, Heinrich H, Trott G, Wirth S, Rothenberger A. Deficient intracortical inhibition in drug-naive children with attention-deficit hyperactivity disorder is enhanced by methylphenidate. *Neurosci Lett* 2000;**284**(1–2):121–5.
 28. Buchmann J, Gierow W, Weber S, et al. Restoration of disturbed intracortical motor inhibition and facilitation in attention deficit hyperactivity disorder children by methylphenidate. *Biol Psychiatry* 2007;**62**(9):963–9.
 29. Faraone SV, Doyle AE. The nature and heritability of attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatr Clin N Am* 2001;**10**(2):299–316 [viii–ix].
 30. Biederman J. Attention-deficit/hyperactivity disorder: a selective overview. *Biol Psychiatry* 2005;**57**(11):1215–20.
 31. Brookes K, Xu X, Chen W, et al. The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in DRD4, DAT1 and 16 other genes. *Mol Psychiatry* 2006;**11**(10):934–53.
 32. Asherson P. Attention-deficit hyperactivity disorder in the post-genomic era. *Eur Child Adolesc Psychiatry* 2004;**13**(Suppl. 1):150–70.
 33. Ogdie MN, Fisher SE, Yang M, et al. Attention deficit hyperactivity disorder: fine mapping supports linkage to 5p13, 6q12, 16p13, and 17p11. *Am J Hum Genet* 2004;**75**(4):661–8.
 34. Gothelf D, Michaelovsky E, Frisch A, et al. Association of the low-activity COMT 158Met allele with ADHD and OCD in subjects with velocardiofacial syndrome. *Int J Neuropsychopharmacol* 2007;**10**(3):301–8.
 35. Koth CW, Cutting LE, Denckla MB. The association of neurofibromatosis type 1 and attention deficit hyperactivity disorder. *Child Neuropsychol* 2000;**6**(3):185–94.
 36. Curatolo P, Verdecchia M, Bombardieri R. Tuberous sclerosis complex: a review of neurological aspects. *Eur J Paediatr Neurol* 2002;**6**(1):15–23.
 37. Baumgardner T, Reiss A, Freund L, Abrams M. Specification of the neurobehavioral phenotype in males with fragile X syndrome. *Pediatrics* 1995;**95**(5):744–52.
 38. Mick E, Biederman J, Faraone SV, Sayer J, Kleinman S. Case-control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use, and drug use during pregnancy. *J Am Acad Child Adolesc Psychiatry* 2002;**41**(4):378–85.
 39. Hultman CM, Torrang A, Tuvblad C, et al. Birth weight and attention-deficit/hyperactivity symptoms in childhood and early adolescence: a prospective Swedish twin study. *J Am Acad Child Adolesc Psychiatry* 2007;**46**(3):370–7.
 40. McCann D, Barrett A, Cooper A, et al. Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. *Lancet* 2007;**370**(9598):1560–7.
 41. Obel C, Linnet KM, Henriksen TB, et al. Smoking during pregnancy and hyperactivity-inattention in the offspring – comparing results from three Nordic cohorts. *Int J Epidemiol*; 2008.
 42. Coffin JM, Baroody S, Schneider K, O'Neill J. Impaired cerebellar learning in children with prenatal alcohol exposure: a comparative study of eyeblink conditioning in children with ADHD and dyslexia. *Cortex* 2005;**41**(3):389–98.
 43. D'Onofrio BM, Van Hulle CA, Waldman ID, et al. Causal inferences regarding prenatal alcohol exposure and childhood externalizing problems. *Arch Gen Psychiatry* 2007;**64**(11):1296–304.
 44. Sen B, Swaminathan S. Maternal prenatal substance use and behavior problems among children in the U.S. *J Ment Health Policy Econ* 2007;**10**(4):189–206.
 45. Milberger S, Biederman J, Faraone SV, Chen L, Jones J. Is maternal smoking during pregnancy a risk factor for

- attention deficit hyperactivity disorder in children? *Am J Psychiatry* 1996;**153**(9):1138–42.
46. Kotimaa AJ, Moilanen I, Taanila A, et al. Maternal smoking and hyperactivity in 8-year-old children. *J Am Acad Child Adolesc Psychiatry* 2003;**42**(7):826–33.
 47. Potter AS, Newhouse PA, Bucci DJ. Central nicotinic cholinergic systems: a role in the cognitive dysfunction in attention-deficit/hyperactivity disorder? *Behav Brain Res* 2006;**175**(2):201–11.
 48. Weiss S, Tzavara ET, Davis RJ, et al. Functional alterations of nicotinic neurotransmission in dopamine transporter knock-out mice. *Neuropharmacology* 2007;**52**(7):1496–508.
 49. Neuman RJ, Lobos E, Reich W, et al. Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype. *Biol Psychiatry* 2007;**61**(12):1320–8.
 50. Becker K, El-Faddagh M, Schmidt MH, Esser G, Laucht M. Interaction of dopamine transporter genotype with prenatal smoke exposure on ADHD symptoms. *J Pediatr* 2008;**152**(2):263–9.
 51. Spencer TJ, Biederman J, Madras BK, et al. In vivo neuroreceptor imaging in attention-deficit/hyperactivity disorder: a focus on the dopamine transporter. *Biol Psychiatry* 2005;**57**(11):1293–300.
 52. Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2007;**61**(12):1361–9.
 53. Castellanos FX, Lee PP, Sharp W, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA* 2002;**288**(14):1740–8.
 54. Shaw P, Eckstrand K, Sharp W, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci USA* 2007;**104**(49):19649–54.
 55. Mackie S, Shaw P, Lenroot R, et al. Cerebellar development and clinical outcome in attention deficit hyperactivity disorder. *Am J Psychiatry* 2007;**164**(4):647–55.
 56. Shaw P, Lerch J, Greenstein D, et al. Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2006;**63**(5):540–9.
 57. Vaidya CJ, Austin G, Kirkorian G, et al. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. *Proc Natl Acad Sci USA* 1998;**95**(24):14494–9.
 58. Zang YF, Jin Z, Weng XC, et al. Functional MRI in attention-deficit hyperactivity disorder: evidence for hypofrontality. *Brain Dev* 2005;**27**(8):544–50.
 59. Vance A, Silk TJ, Casey M, et al. Right parietal dysfunction in children with attention deficit hyperactivity disorder, combined type: a functional MRI study. *Mol Psychiatry* 2007;**12**(9):826–32 [793].
 60. Shafritz KM, Marchione KE, Gore JC, Shaywitz SE, Shaywitz BA. The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder. *Am J Psychiatry* 2004;**161**(11):1990–7.
 61. Spencer TJ, Biederman J, Ciccone PE, et al. PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. *Am J Psychiatry* 2006;**163**(3):387–95.
 62. Volkow ND, Wang GJ, Fowler JS, Ding YS. Imaging the effects of methylphenidate on brain dopamine: new model on its therapeutic actions for attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2005;**57**(11):1410–5.
 63. Bush G, Spencer TJ, Holmes J, et al. Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Arch Gen Psychiatry* 2008;**65**(1):102–14.
 64. Pliszka SR. The neuropsychopharmacology of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2005;**57**(11):1385–90.
 65. Himmelstein J, Newcorn JH, Halperin JM. The neurobiology of attention-deficit hyperactivity disorder. *Front Biosci* 2000;**5**:D461–78.
 66. Biederman J, Spencer TJ. Psychopharmacological interventions. *Child Adolesc Psychiatr Clin N Am* 2008;**17**(2):439–58.
 67. Levy F. Pharmacological and therapeutic directions in ADHD: specificity in the PFC. *Behav Brain Funct* 2008;**4**(1):12.
 68. Swanson JM, Kraemer HC, Hinshaw SP, 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. *J Am Acad Child Adolesc Psychiatry* 2001;**40**(2):168–79.
 69. Rapoport JL, Gogtay N. Brain neuroplasticity in healthy, hyperactive and psychotic children: insights from neuroimaging. *Neuropsychopharmacology* 2008;**33**(1):181–97.
 70. Konrad K, Neufang S, Fink GR, Herpertz-Dahlmann B. Long-term effects of methylphenidate on neural networks associated with executive attention in children with ADHD: results from a longitudinal functional MRI study. *J Am Acad Child Adolesc Psychiatry* 2007;**46**(12):1633–41.
 71. Coghill DR, Rhodes SM, Matthews K. The neuropsychological effects of chronic methylphenidate on drug-naïve boys with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2007;**62**(9):954–62.
 72. Knobloch H, Pasamanick B. Syndrome of minimal cerebral damage in infancy. *J Am Med Assoc* 1959;**170**(12):1384–7.
 73. Clements S. *Minimal brain dysfunction in children: terminology and identification*. Washington, DC: US Department of Health, Education and Welfare; 1966.
 74. Durston S, Tottenham NT, Thomas KM, et al. Differential patterns of striatal activation in young children with and without ADHD. *Biol Psychiatry* 2003;**53**(10):871–8.
 75. Allen AJ, Kurlan RM, Gilbert DL, et al. Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders. *Neurology* 2005;**65**(12):1941–9.