# The etiology of attention-deficit hyperactivity disorder: imaging evidence for neonatal hypoxic-ischemia

*Scott L. Hess (BSc. Hons) Neuroscience, University of Lethbridge, Lethbridge, Alberta, Canada*
*Current MSc student, Psychiatry, University of Alberta, Alberta Canada*

**Correspondence to: slhess@ualberta.ca**
**#211 8515 112 St NW,**
**Edmonton AB T6G 1K7**
**780-637-1085**
Current Interests: Treatments for neonatal hypoxic-ischemia

## INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most prevalent psychiatric disorders in children as diagnosed by the DSM-IV-TR and it greatly impairs social and cognitive functions in affected individuals (1). The two most likely causes of ADHD are inheritance of the disorder and early lesions to the brain (2). Hypoxic-ischemia (HI) is a common cause of brain lesions in neonates and it has been reported to be responsible for up to 25% of all brain damage in neonates (3). HI-induced lesions in infants have also been correlated with the development of ADHD later on in life (4). Magnetic Resonance Imaging (MRI) is a structural imaging technique that has been used to identify brain abnormalities and lesions in ADHD children. In addition to structural findings, changes in the levels of various neurotransmitters and proteins in the brain have been observed using Magnetic Resonance Spectroscopy (MRS). These changes can result from HI damage and have been correlated to symptoms of ADHD in addition to lesions.

## DSM-IV-TR CRITERIA FOR ADHD

The DSM-IV-TR criteria for ADHD include 6 or more symptoms of either inattention (type A) or hyperactivity-impulsivity (type B) persisting for 6 months and leading to abnormal behaviour for the individual's developmental age (5). Although ADHD can occur in both children and adults, it is seen primarily in children and the current paper will focus on childhood ADHD. Symptoms of inattention (Type A symptoms) include an inability to remain focused on any type of task, difficulty organizing behaviour and planning action, as well as ease of distraction. Hyperactivity-impulsivity symptoms or Type B symptoms include an inability to control voluntary motor activity and spontaneous generation of socially-inappropriate behaviours. These behaviours must also be developmentally inappropriate relative to the age of the individual child (6). Three types of ADHD have been identified and these are "Predominantly Inattentive ADHD" which includes only Type A symptoms, "Predominantly Hyperactive-Impulsive ADHD" involving only Type B symptoms, and "Combined Type ADHD" which includes both type A and type B symptoms.

## PREVALENCE OF ADHD

ADHD occurs in 8-12% of children worldwide and is more prevalent in males than females (7). The higher reported prevalence of ADHD in males may be due to social factors related to the identification and diagnosis of ADHD. Such factors include teacher bias towards males, as symptoms observed in the classroom setting are weighed heavily in the diagnosis of childhood ADHD (8). Sex differences in the prevalence of ADHD may also be accounted for the decreased lateralization of cognitive functions in females, which is thought to provide an advantage against some developmental disorders including ADHD (9).

ADHD's onset occurs around 3 years of age in both sexes (10). ADHD occurs chronically rather than episodically and symptoms present in childhood may continue to manifest into adulthood in many cases (1). However, ADHD symptoms usually lessen with age such that the rate of persistence is only 15% by age 25 (11). Persistence of ADHD symptoms is correlated with social adversity during childhood, exposure to severe stress while growing up, and severity of ADHD symptoms at onset (12).

## HYPOXIC-ISCHEMIA AND BRAIN LESIONS

Although genetic factors are implicated as a cause of ADHD (13), there is evidence for perinatal brain lesions as well (14). HI is an example of an insult to the brain that can cause perinatal lesions. Hypoxia refers to a lack of oxygen in the blood while ischemia refers to a reduction in blood supply to a particular tissue. HI can occur by means of a reduction in uterine and umbilical circulation due to contraction of the uterus, compression of the umbilical cord or premature separation of the placenta from the uterus, which is referred to as abruptio placentae (15).

The prolonged absence of blood and oxygen caused by HI results in brain cells exhausting their available energy stores. The result is cellular energy failure, which leads to a variety of pathological conditions that cause cell death (Figure 1.).

HI can vary in severity depending on the particular conditions of the event. Damage tends to be amplified in areas that have lower circulation, higher metabolic demands, and high densities of excitatory neurons (15). In newborns with weaker physiological functions such as low-weight preterm babies, HI damage is more common and low birth weight is correlated with a higher incidence of ADHD (16). Minor HI at birth has been correlated with ADHD along with mild brain abnormalities and reductions in brain volume as seen by MRI (4). For instance, many studies have shown that ischemic insults can easily damage the mesotelencephalic dopamine pathways, which are implicated in ADHD (17).

## BRAIN DAMAGE IN ADHD

Smaller overall brain volume and reduced cortical volume has been observed in ADHD children in MRI studies. Castellanos et al. (18) have found total brain volume reductions of 5% in ADHD children. Examples of specific volume reductions include smaller prefrontal cortex (PFC) and anterior temporal cortices bilaterally (19). MRI work by Carmona et al. (20) has shown more specific reductions in grey matter of the left fronto-parietal cortex, left cingulate cortex, bilateral parietal and temporal cortex and cerebellum in ADHD children (Figure 2.). Focal lesions to the medial and orbital PFC have been associated strongly with ADHD symptoms as well (21).

The striatum has been shown to be vulnerable to damage caused by neonatal HI and its role in context recognition and behaviour implicates it in the symptoms of ADHD (14). A variety of striatal lesions have been identified in ADHD. For instance, a MRI study by Max et al. (22) found damage in the posterior ventral putamen in ADHD children. Longitudinal MRI studies have also shown decreased volume of the caudate nucleus in ADHD children throughout development (23). Studies examining the globus pallidus have shown volume reductions both bilaterally in the left hemisphere as well as unilaterally in both hemispheres (24). Asymmetry in the caudate nucleus has also been correlated with ADHD symptoms, with the right caudate typically being larger than the left (25). Other asymmetry findings derived from MRI work have found unilateral caudate nucleus infarcts (26). These results may indicate that minor lesions of the striatum are independent causes of ADHD apart from PFC lesions.

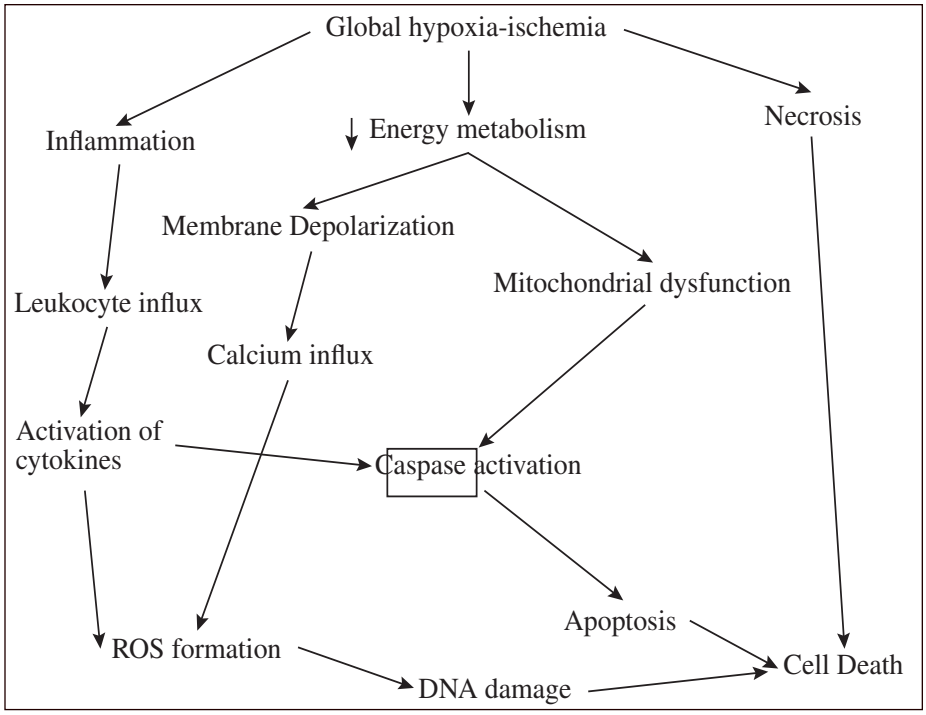


***Figure 1.*** *Energy loss due to hypoxic-ischemia can damage neurons of the brain by means of several pathways and mechanisms. Extreme energy loss leads to necrosis, while inflammation and lowered energy metabolism can lead to apoptotic cell death or DNA damage from Reactive Oxygen Species (ROS) (15). (Reproduced with Permission)*

Loss of connectivity between different brain regions such as the striatum and the PFC due to white matter damage can also explain ADHD symptoms (19). Damage to right frontostriatal brain circuitry has been correlated with symptoms of ADHD (27). Similar to focal damage to the striatum, loss of connectivity may impair executive function and motor control by reducing input from the striatum to the PFC. Evidence for such damage includes reductions in white matter in right anterior areas of the brain (28). On the left side of the brain, reductions in white matter in the PFC have also been noted (19).

Interhemispheric connectivity may also be abnormal in ADHD, as smaller relative corpus callosum volume has been observed in ADHD children (29, 19). These reductions in volume are localized to posterior regions of the corpus callosum linked to temporal and parietal cortices, indicating a reduction in interhemispheric function in these regions (27). The resulting reduction in interhemispheric connectivity has been linked to poorer attention (30).

Alterations in the dopamine (DA) system have been identified in ADHD, and HI has been implicated as a cause of many of these alterations (31, 32, 17). Changes to DA systems implicated in ADHD include a decrease in DA activity and D1 receptor density in the striatum (31). An upregulation of D1 receptors in the striatum of animals that are exposed to HI as neonates has also been noted (31). The result of an increase in D1 receptor density in the striatum is decreased extracellular dopamine, which has been related to ADHD-like symptoms in animal models (33). Genes that upregulate D1 receptors have also been implicated in ADHD (34), and the effects of hypoxia may produce a similar result by upregulating D1 receptors in the striatum.

## NEUROCHEMICAL ABNORMALITIES IN ADHD: MRS FINDINGS

MRS is an imaging method that utilizes

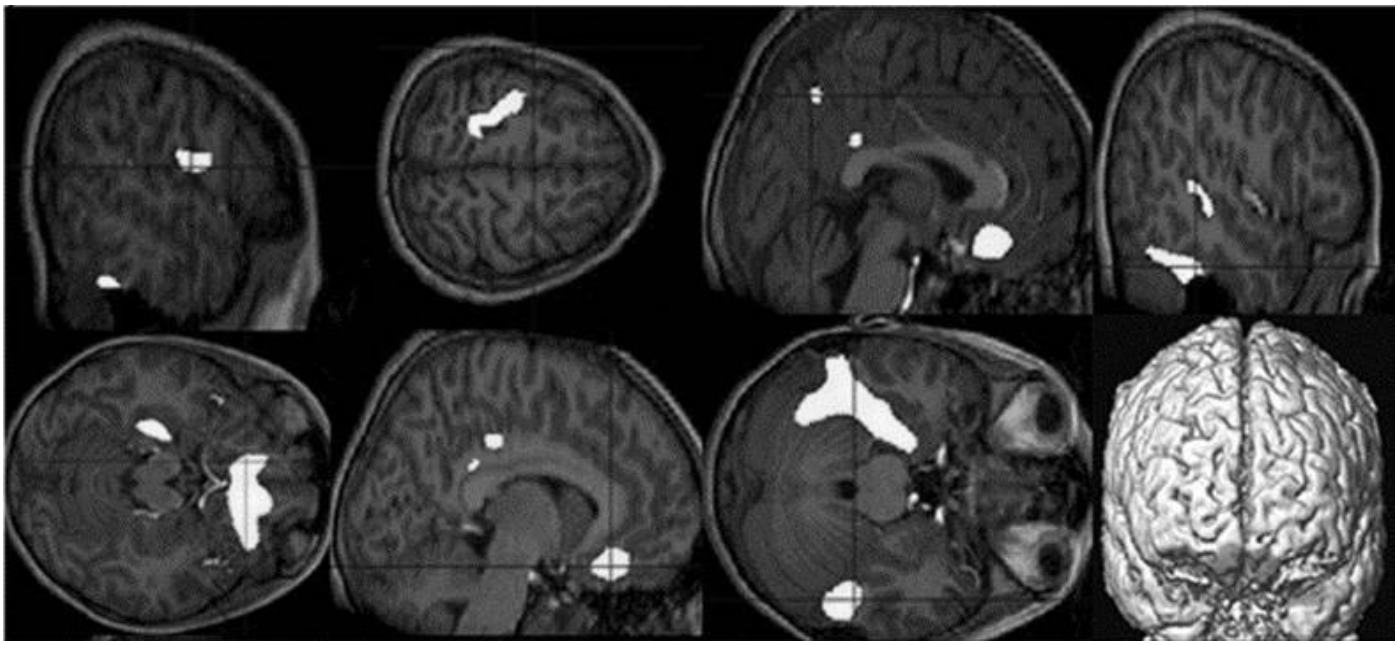

***Figure 2.*** *A MRI study by Carmona et al. (20) found region reductions in gray matter throughout the cortex and cerebellum. Highlighted areas are those that show smaller gray matter volume in ADHD children. These areas include the left precentral, paracentral, and postcentral gyri, as well as the right rectal, frontal inferior orbital, and frontal superior orbital gyri. Bilateral decreases in the cerebellum are also seen. (Reproduced with Permission)*

a radiofrequency pulse to identify the quantities of particular compounds in a in in vivo tissue. As a result, the amount of a particular molecule in a certain brain region can be estimated. Abnormalities in different neurochemicals in the brains of ADHD children are indicators of different neurological dysfunctions that can be related to lesions and damage from neonatal HI insults. N-Acetylaspartate (NAA) is indicative of neuronal and axonal density and viability (6). NAA is synthesized primarily in neurons, allowing inferences about neurons and their axons to be made, although its exact function in the cell is not known (35). NAA reductions can be interpreted as evidence for neuronal/axonal loss and dysfunction in a particular area (36). In contrast, increases in the levels of NAA are indicative of hypermetabolism and increased neuronal/axonal activity (37).

MRS studies investigating the levels of NAA in the brains of ADHD children have shown increases in the right PFC when compared to controls (38). Increased NAA has also been found in white matter areas that are part of frontostriatal pathways in ADHD children (Figure 3.) (37). Hyperactivity in white matter tracts may contribute to frontostriatal dysregulation by altering striatal inputs to the PFC.

There have also been findings of decreased NAA in ADHD children. For example, Jin et al. (39) found NAA reductions as great as 20-25% in striatal areas such as the globus pallidus and lenticular nucleus of ADHD children. These results may show that neurons of the striatum function poorly in the brains of ADHD children, contributing to frontostriatal dysfunction. HI during the neonatal period has been associated with decreases in NAA in sensitive brain areas such as the striatum (40) as well as white matter regions (41). The finding of decreased striatal NAA and increased white matter NAA may reflect the fact that ADHD can be caused by focal damage localized to the striatum rather than directly to the white matter tracts. The activity of white matter tracts may also be increased in response to striatal damage.

Levels of glutamate and glutamine (α-glx) are indicative of major excitatory and inhibitory neuronal function in particular regions of the brain (39). For instance, increased α-glx levels have been found in anterior cingulate cortex in ADHD children (42). An increase in α-glx in the right PFC and frontostriatal pathways has also been observed (43). The increase in neurotransmission in these areas may be indicative of neuronal hyperactivity similar to findings of increased NAA.

Increased levels of α-glx may also be related to changes in dopamine levels associated with ADHD. A decrease in extracellular dopamine (DA) levels in the striatum has been found to cause an increase in glutamate release in the PFC in rodent models of ADHD (44). Evidence for the relationship between DA and glutamate comes from the finding that levels of these neurotransmitters return to normal after administration of drugs that increase DA transmission such as amphetamine (42). Reductions in striatal DA levels resulting from neonatal hypoxia have been implicated in ADHD (31) and they may explain the increased PFC α-glx levels seen in ADHD children.

## CONCLUSIONS

ADHD is a developmental psychiatric disorder that may result from insults to the brain during the neonatal period. HI can damage the neonatal brain, particularly in the PFC, striatum, and frontostriatal white matter tracts to produce symptoms of ADHD. Evidence for HI lesions in ADHD children comes from MRI work showing smaller overall

brain volume and signs of cell loss in the striatum, PFC, and cerebellum (20). Damage to frontostriatal pathways has been implicated in ADHD (27), and damage to the brain at either end of this pathway (PFC or striatum) or in its white matter connections may be responsible for producing ADHD symptoms. Neurochemical changes in ADHD children include increases in NAA in the PFC and white matter tracts (38) and decreases in the striatum (39). Changes in glutamate levels have also been seen using MRS. These changes indicate altered neurotransmission related to early brain damage affecting levels of DA in the striatum (42).

Future imaging studies on brain dysfunction in ADHD may focus on the use of new techniques such as magnetoencephalography (MEG) to more accurately discriminate the neural pathways and dysfunctional brain regions in ADHD children. MEG studies could greatly enhance what is known about brain dysfunction in ADHD, since this imaging method can more accurately record neuronal events temporally and spatially in the brain than functional MRI (fMRI) (45). Prevention of HI injury in neonates to prevent brain injury is another important avenue of research not only for ADHD, but also for other developmental neuropsychiatric disorders resulting from early lesions to the brain. Hypothermia has shown great promise in preventing damage to the brain after neonatal HI and it may have the capacity to prevent brain damage precipitating ADHD (46).

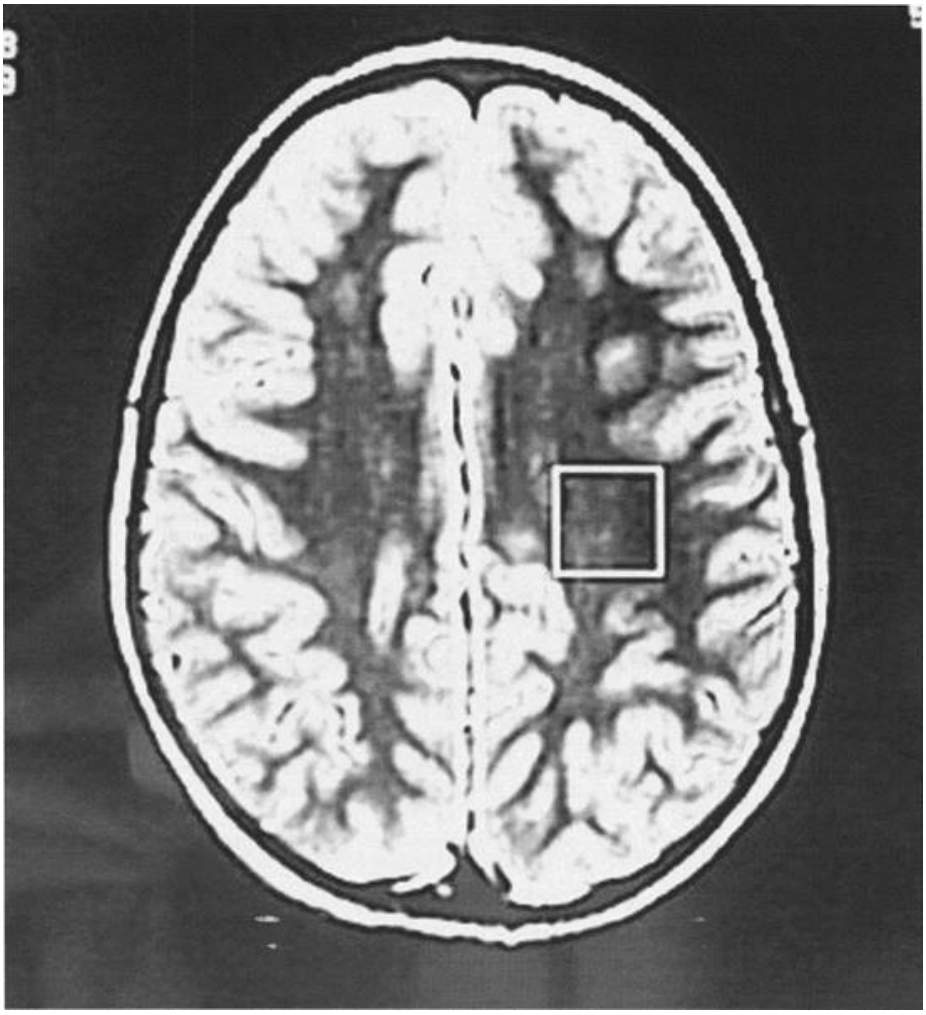

***Figure 3.*** *The white matter voxel selected by Fayed and Modrego (37). An increase in NAA in this white matter region may be related to dysfunction in frontostriatal pathways leading to ADHD. (Reproduced with Permission)*

## ACKNOWLEDGEMENTS

The author would like to acknowledge the assistance of Dr. Kathryn Todd and Dr. Glen Baker of the Neurochemical Research Unit in writing this review paper.

## REFERENCES

5. American Psychiatric Association. Childhood Disorders. American Psychiatric Association editor. Diagnostic and Statistical Manual of Mental Disorders (4th ed) Revised. Washington, DC: American Psychiatry Association, 2000.

24. Aylward EH, Reiss AL, Reader MJ, Singer HS, Brown JE, Denckla MB. Basal ganglia volumes in children with attention-deficit hyperactivity disorder. J Child Neurol, 11: 112-115; 1996

35. Baslow MH. Evidence supporting a role for N-acetyl-L-aspartate as a molecular water pump in myelinated neurons in the central nervous system. An analytical review. Neurochem Int, 40: 295-300; 2002

7. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet, 366: 237-248; 2005

32. Boksa P, El-Khodor BF. Birth insult interacts with stress at adulthood to alter dopaminergic function in animal models: possible implications for schizophrenia and other disorders. Neurosci Biobehav Rev, 27: 91-101; 2003

3. Cadman D, Rosenbaum P, Boyle M, Offord DR. Children with chronic illness: family and parent demographic characteristics and psychosocial adjustment. Pediatrics, 87: 884-889; 1991

15. Calvert JW, Zhang JH. Pathophysiology of an hypoxic-ischemic insult during the perinatal period. Neurol Res, 27: 246-260; 2005

40. Cappellini M, Rapisardi G, Cioni ML, Fonda C. Acute hypoxic encephalopathy in the full-term newborn: correlation between Magnetic Resonance Spectroscopy and neurological evaluation at short and long term. Radiol Med (Torino), 104: 332-340; 2002

20. Carmona S, Vilarroya O, Bielsa A, Tremols V, Soliva JC, Rovira M, Tomas J, Raheb C, Gispert JD, Batlle S, Bulbena A. Global and regional gray matter reductions in ADHD: a voxel-based morphometric study. Neurosci Lett, 389: 88-93; 2005

18. Castellanos FX, Giedd JN, Eckburg P, Marsh WL, Vaituzis AC, Kaysen D, Hamburger SD, Rapoport JL. Quantitative morphology of the caudate nucleus in attention deficit hyperactivity disorder. Am J Psychiatry, 151: 1791-1796; 1994

26. Castellanos FX, Sharp WS, Gottesman RF, Greenstein DK, Giedd JN, Rapoport JL. Anatomic brain abnormalities in

monozygotic twins discordant for attention deficit hyperactivity disorder. Am J Psychiatry, 160: 1693-1696; 2003

38. Courvoisie H, Hooper SR, Fine C, Kwock L, Castillo M. Neurometabolic functioning and neuropsychological correlates in children with ADHD-H: preliminary findings. J Neuropsychiatry Clin Neurosci, 16: 63-69; 2004

31. Decker MJ, Jones KA, Solomon IG, Keating GL, Rye DB. Reduced extracellular dopamine and increased responsiveness to novelty: neurochemical and behavioral sequelae of intermittent hypoxia. Sleep, 28: 169-176; 2005

17. Decker MJ, Rye DB. Neonatal intermittent hypoxia impairs dopamine signaling and executive functioning. Sleep Breath, 6: 205-210; 2002

36. Deicken RF, Johnson C, Pegues M. Proton magnetic resonance spectroscopy of the human brain in schizophrenia. Rev Neurosci, 11: 147-158; 2000

46. Eicher DJ, Wagner CL, Katikaneni LP, Hulsey TC, Bass WT, Kaufman DA, Horgan MJ, Languani S, Bhatia JJ, Givelichian LM, Sankaran K, Yager JY. Moderate hypothermia in neonatal encephalopathy: efficacy outcomes. Pediatr Neurol, 32: 11-17; 2005

11. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol Med, 36: 159-165; 2006

37. Fayed N, Modrego PJ. Comparative study of cerebral white matter in autism and attention-deficit/hyperactivity disorder by means of magnetic resonance spectroscopy. Acad Radiol, 12: 566-569; 2005

41. Groenendaal F, van der Grond J, van Haastert IC, Eken P, Mali WP, de Vries LS. Findings in cerebral proton spin resonance spectroscopy in newborn infants with asphyxia, and psychomotor development. Ned Tijdschr Geneeskd, 140: 255-259; 1996

8. Havey JM, Olson JM, McCormick C, Cates GL. Teachers' perceptions of the incidence and management of attention-deficit hyperactivity disorder. Appl Neuropsychology, 12: 120-127; 2005

29. Hill DE, Yeo RA, Campbell RA, Hart B, Vigil J, Brooks W. Magnetic resonance imaging correlates of attention-deficit/hyperactivity disorder in children. Neuropsychology, 17: 496-506; 2003

9. Holden C. Sex and the suffering brain. Science, 308: 1574; 2005

39. Jin Z, Zang Y, Zeng Y, Zhang L, Wang Y. Striatal neuronal loss or dysfunction and choline rise in children with attention-deficit hyperactivity disorder: a 1H-magnetic resonance spectroscopy study. Neurosci Lett, 315: 45-48; 2001

12. Kessler RC, Adler LA, Barkley R, Biederman J, Conners CK, Faraone SV, Greenhill LL, Jaeger S, Secnik K, Spencer T, Ustun TB, Zaslavsky AM. Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: results from the national comorbidity survey replication. Biol Psychiatry. 57: 1442-1451; 2005

4. Krageloh-Mann I, Toft P, Lunding J, Andresen J, Pryds O, Lou HC. Brain lesions in preterms: origin, consequences and compensation. Acta Pediatr. 88: 897-908; 1999

19. Krain AL, Castellanos FX. Brain development and ADHD. Clin Psychol Rev. In Press

2. Lou HC. Etiology and pathogenesis of attention-deficit hyperactivity disorder (ADHD): significance of prematurity and perinatal hypoxic-haemodynamic encephalopathy. Acta Pediatr, 85: 1266-1271; 1996

43. MacMaster FP, Carrey N, Sparkes S, Kusumakar V. Proton spectroscopy in medication-free pediatric attention-deficit/hyperactivity disorder. Biol Psychiatry, 53: 184-187; 2003

34. Madras BK, Miller GM, Fischman AJ. The dopamine transporter and attention-deficit/hyperactivity disorder. Biol Psychiatry, 57: 1397-1409; 2005

22. Max JE, Fox PT, Lancaster JL, Kochunov P, Mathews K, Manes FF, Robertson BA, Arndt S, Robin DA, Lansing AE. Putamen lesions and the development of attention-deficit/hyperactivity symptomatology. J Am Acad Child Adolesc Psychiatry, 41: 563-571; 2002

21. Max JE, Manes FF, Robertson BA, Mathews K, Fox PT, Lancaster J. Prefrontal and executive attention network lesions and the development of attention-deficit/hyperactivity symptomatology. J Am Acad Child Adolesc Psychiatry, 44: 443-450; 2005

1. McCracken JM, Attention-Deficit Disorders. In: Sadock B, Sadock V, editors. Comprehensive Textbook of Psychiatry Vol 1. (7th ed). Philadelphia, PN: Lippincott, Williams, & Wilkins, 2000

42. Moore CM, Biederman J, Wozniak J, Mick E, Aleardi M, Wardrop M, Dougherty M, Harpold T, Hammerness P, Randall E, Renshaw PF. Differences in brain chemistry in children and adolescents with attention deficit hyperactivity disorder with and without comorbid bipolar disorder: a proton magnetic resonance spectroscopy study. Am J Psychiatry, 163: 316-318; 2006

10. Neuman RJ, Sitdhiraksa N, Reich W, Ji TH, Joyner CA, Sun LW, Todd RD. Estimation of prevalence of DSM-IV and latent class-defined ADHD subtypes in a population-based sample of child and adolescent twins. Twin Res Human Genet, 8: 392-401; 2005

28. Paule MG, Rowland AS, Ferguson SA, Chelonis JJ, Tannock R, Swanson JM, Castellanos FX. Neurotoxicol Tetratol, 22: 631-651; 2000

16. Peterson BS, Thomas P, Kane MJ, Scahill L, Zhang H, Bronen R, King RA, Leckman JF, Staib L. Basal Ganglia volumes in patients with Gilles de la Tourette syndrome. Arch Gen Psychiatry, 60: 415-424; 2003

44. Russell, VA. The nucleus accumbens motor-limbic interface of the spontaneously hypertensive rat as studied in vitro by the superfusion slice technique. Neurosci Biobehav Rev, 24: 133-136; 2000

33. Russell VA, Sagvolden T, Johansen EB. Animal models of attention-deficit hyperactivity disorder. Behav Brain Funct, 15: 9; 2005

25. Schrimsher GW, Billingsley RL, Slopis JM, Moore BD 3rd. Caudate nucleus volume asymmetry predicts attention-deficit hyperactivity disorder (ADHD) symptomatology in children. J Child Neurol, 17: 877-884; 2002

27. Seidman LJ, Valera EM, Makris N. Structural brain imaging of attention-deficit/hyperactivity disorder. Biol Psychiatry, 57: 1263-1272; 2005

30. Semrud-Clikeman M, Filipek PA, Biederman J, Steingard R, Kennedy D, Renshaw P, Bekken K. Attention-deficit hyperactivity disorder: magnetic resonance imaging morphometric analysis of the corpus callosum. J Am Acad Child Adolesc Psychiatry, 33: 875-881; 1994

6. Sun L, Jin Z, Zang YF, Zeng YW, Liu G, Li Y, Seidman LJ, Faraone SV, Wang YF. Differences between attention-deficit disorder with and without hyperactivity: a H1 magnetic resonance spectroscopy study. Brain Dev, 27: 340-344; 2005

14. Toft PB. Prenatal and perinatal striatal injury: a hypothetical cause of attention-deficit-hyperactivity disorder? Pediatr Neurol, 21: 602-610; 1999

23. Toga AW, Thompson PM, Sowell ER. Mapping brain maturation. Trends Neurosci, 29: 148-159; 2006

45. Toplak ME, Dockstader C, Tannock R. Temporal information processing in ADHD: Findings to date and new methods. J Neurosci Methods, 151: 15-29; 2006

13. Waldman ID, Gizer IR. The genetics of attention deficit hyperactivity disorder. Clin Psychol Rev. In Press