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Bio-social aspects of Attention Deficit Hyperactivity Disorder (ADHD): Neurophysiology, maturity, motor function and how symptoms relate to family interaction

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Associations between cerebral blood-flow measured by single photon emission computed tomography (SPECT), electro-encephalogram (EEG), behaviour symptoms, cognition and neurological soft signs in children with attention-deficit hyperactivity disorder (ADHD)

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Twenty-eight children with attention-deficit hyperactivity disorder (ADHD) were examined with SPECT (single photon emission computed tomography). Seven of the children had abnormal distribution of the regional cerebral blood-flow (rCBF) on visual evaluation and 10 had abnormal EEG findings. The only clinical finding that differentiated the group with normal from abnormal rCBF was behaviour symptom load. A factor analysis of the rCBF in different regions of interest yielded one factor with low rCBF in the temporal and cerebellar regions and high rCBF in the subcortical and thalamic regions, which was significantly associated with the degree of motor impairment and results on a cognitive test (WISC). Another factor consisting of high rCBF in frontal and parietal regions had a significant negative correlation with the degree of behaviour symptoms. There was a negative correlation between the rCBF in the right frontal regions and the degree of behaviour symptoms. The number of minor physical anomalies (MPA) was negatively correlated to the rCBF in the frontal lobes bilaterally.

These results suggest that there may be at least two functional disturbances in ADHD, one specific neurodevelopmentally determined disturbance of the frontal lobes, especially of the right hemisphere, related to behaviour deviance, and another disturbance of the integration of the temporal lobes, the cerebellum and subcortical structures, related to motor planning and aspects of cognition.

Key words: *ADHD, child behaviour problem, soft neurological signs, SPECT, WISC*

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ADHD (attention-deficit hyperactivity disorder) is a condition defined by inattention, hyperactivity and impulsivity. It is presumably a condition with multiple aetiology. Biological factors are considered most important, although social factors may affect development of the condition (1). Many biological factors have been suggested as contributing to the pathogenesis, such as non-optimal perinatal conditions (2), foods and additives (3) and maternal smoking (4). Recent studies imply that hereditary factors may be of crucial importance in a majority of cases with ADHD (5–7).

Several researchers have suggested that the frontal lobes might be involved in the aetiology and pathogenesis of ADHD (8–12). Lou and associates (13–15) reported that children with ADHD and learning disorder had a lower regional blood-flow (rCBF) in the central parts of the frontal lobes corresponding to the corpus striatum compared to a normal control group. Other SPECT studies have suggested that children with ADHD have a pattern of hypoperfusion of striatal and periventricular structures with sensorimotor cortical hyperperfusion (16). Some investigators have suggested that the right hemisphere is more involved than the left in ADHD (9). Others have demonstrated that ADHD patients had greater overall hemispheric I[123] IMP uptake asymmetry with less activity in the left frontal and parietal regions compared with a non-ADHD mixed psychiatric group (17). Quantitative EEG techniques have been suggested as differentiating specific subtypes of ADHD (18). Also, it has been proposed that ADHD children have a smaller left caudate nucleus (19). Some researchers have described reduced volume of anterior parts of corpus callosum in children with ADHD (20). Casey and associates have described different fronto-

striatal volumetric deviances measured by magnetic resonance imaging (MRI) in children with ADHD (21). It is also reported that smaller volumes in frontostriatal structures, predominantly in the right hemisphere, measured by MRI correlated with response inhibition measures in children with ADHD (22, 23).

Since there is some controversy regarding the homogeneity of the diagnosis of ADHD (24) we tested the hypothesis that children with ADHD have similar deviances in EEG and in the rCBF. We also hypothesized that the degree of the reduction of the rCBF in the frontal areas would be associated with the degree of behavioural, cognitive, neurological and physical impairment in children with ADHD.

Patients and methods

Subjects

The study included 28 children from one of four centres (Malmö–Lund) taking part in a multi-site investigation concerning the effects of long-term treatment with amphetamine of children with ADHD. This study was approved by the ethics committes of Umeå and Lund in March 1990. The children were referred to the study for symptoms suggesting a diagnosis of ADHD with marked clinical impairment. Additional requirements for participation in the study were no parental alcohol or drug abuse, that the child had an IQ of more than 50, did not meet the criteria for autistic disorder and had no severe somatic disorder. The main treatment study has been reported previously (24). The children (26 boys, 4 girls) ranged in age from 6 to 11 years (mean 9.0, SD 1.6).

Methods

Clinical interview (60–120 min) with the parents. A checklist of all the symptoms of ADHD listed in the childhood section of the DSM-III-R (25) was used for confirming the diagnosis.

Neurodevelopmental examination was performed according to Gillberg, Gillberg and Groth (26). Single items were scored with 0 = normal, 1 = small deviation from the normal, 2 = marked deviation from the normal. The total score was used as a measure of an overall degree of motor impairment.

MPA: The number of Minor Physical Anomalies which are thought to be associated with neurodevelopmental disturbances was recorded (27).

Regional cerebral blood-flow (rCBF) was measured with single photon emission computed tomography (SPECT). The rCBF measurements were done with i.v. administration of 99mTc-HMPAO. Each child was given a radioactive dose of 10 MBq per kg of body weight up to a maximum of 600 MBq (at a body weight of 60 kg). This substance in its initial lipophilic state is

delivered into the brain in proportion to the rCBF. Inside the brain cells it is converted within a few minutes to its hydrophilic form that cannot exit the brain cells through the cell membrane (28). Thus the 99mTc-HMPAO distribution in the brain remains unchanged for several hours. At the time of the 99mTc-HMPAO administration, the patients were resting in the supine position with their eyes open and instructed to remain so during the next 5 min. The room was silent except for ambient noise. About 10 min later the intracerebral distribution of 99mTc-HMPAO was recorded by a Medimatic SPECT camera.

The rCBF distribution was recorded in 10 contiguous 1-cm thick slices from 1 cm below the orbito-meatal (OM) line and upwards. The intraslice resolution was about 1 cm (FWHM). The recorded rCBF distribution was quantified by the use of a standardized three-dimensional region of interest (ROI) set based on an anatomical atlas. The ROI set was positioned and scaled to the recorded SPECT slices based on the external borders of each slice (Fig. 1). The measured value in each ROI was quantified in percent of the mean 99mTc-HMPAO concentration in the whole brain.

The SPECT rCBF results were analysed by visual interpretation by a trained clinician (E.R.) with several years of experience in using SPECT clinically as well as in research, and who knew nothing of the degree of the subjects' ADHD related handicaps. The subjects were divided into two groups: one group with normal rCBF distribution according to visual interpretation, and one group with suspected or overtly pathological rCBF distribution.

MRI (magnetic resonance imaging): Clinical routine MRI was performed on all subjects. The examinations were carried out at the Department of Radiology at the University Hospital of Malmö.

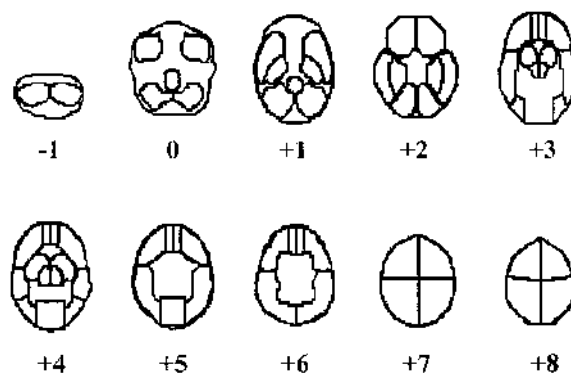*EEG* (electroencephalogram) was recorded from 20

Fig. 1. The regions of interest (ROI) set used in the quantification of the SPECT measurement results. The number under each transaxial slice denotes its position in centimeters above (+) or below (−) the orbito-meatal (OM) plane.

Table 1. Factor analysis of the rCBF in different regions of interest.

ROI	Factor 1	Factor 2	Factor 3
Cerebellum sin	**−0.767**	−0.394	−0.386
Cerebellum dx	**−0.770**		−0.444
Frontal sin			**0.818**
Frontal dx			**0.911**
Temporal sin	**−0.625**	−0.445	
Temporal dx	**−0.737**	−0.307	
Parietal sin		**0.731**	**0.668**
Parietal dx		**0.776**	**0.587**
Occipital sin		**0.809**	
Occipital dx		**0.813**	
Basal ganglia. sin	**0.713**	−0.378	
Basal ganglia. dx	**0.778**	−0.391	
Thalamus sin	**0.850**		
Thalamus dx	**0.834**		

Values >0.3 are reported.

channels according to the conventional 10–20 system (Filters: 0.5–30 Hz, sampling frequency: 128 Hz; common reference) at rest with closed eyes, and when listening with closed eyes to a story. Two to three epochs of 32 s of EEG were analysed in a Biologic Brain Atlas III[®] system. Log absolute power and relative power were calculated for each frequency band (delta: 0.5–4; theta: 4.1–8; alpha: 8.1–13; beta: 13.1–26 Hz) and averaged for each of the four quadrants of the head, left anterior (F3, F7, T3, C3), right anterior (F4, F8, T4, C4), left posterior (P3, T5, O1), right posterior (P4, T6, O2). Average relative power for delta and alpha bands collapsed over four quadrants was used for correlation between EEG and clinical and rCBF variables. The conventional EEG records were also evaluated according to general clinical practice. Twenty-six subjects were recorded before treatment, and 23 of these were also recorded during treatment with amphetamine.

Child behaviour: The Rutter questionnaire for parents was used to measure behavioural symptoms (29). The Conner's Rating Scale for Parents (30) was used to measure the degree of ADHD symptoms.

Cognitive examination: The Wechsler Intelligence Scale for Children (WISC) (31) was administered individually to each subject. In the Swedish version of the WISC test the raw scores were converted to standard scores in terms of stanine units (a scale with nine grades), with the mean of 5 and a standard deviation of 2. The total score as well as the verbal and the performance scores were used in the analysis.

Statistical methods

The Mann Whitney U-test was used for comparing the groups concerning degree of deviance in behaviour, findings of neurodevelopmental examination and cognitive function. $P < 0.05$ was regarded as significant.

The Pearson correlation coefficient was used for testing the correlation between age and relative delta power and

relative alpha power (because these variables are approximately normally distributed).

Factor analysis (Varimax, oblique rotation, factors with eigenvalues >1) was carried out on the results of the ROI analysis. The resulting factors consisted of functionally correlated anatomic regions (Table 1). The factor scores (corresponding rCBF values) were then correlated to the degree of deviance in behaviour, findings of the neurodevelopmental examination and cognitive functions by means of the Spearman rank correlation test. Additionally, the rCBFs of the frontal regions were compared to degree of deviance in behaviour, results of neurodevelopmental examination and cognitive functions by means of the Spearman rank correlation test.

Results

SPECT. Seven of the 28 children had a suspected or clear abnormality of the SPECT on visual examination. The blood-flow values for each region of interest for all 28 children were analysed by factor analysis. Every child was given a value for each of the three factors that came out of the analysis. The result of the factor analysis was interpreted as follows: *Factor 1* represented a pattern of low rCBF in the temporal regions and the cerebellum relative to the basal ganglia, which was interpreted as related to motor planning and automatization. *Factor 2*, with high biparietal and occipital loadings could be associated with variations of wakefulness and visual activity at the time of ligand fixation in the brain. *Factor 3* represented a pattern of high blood-flow in frontal and parietal regions bilaterally, which was interpreted as associated with sensorimotor integration.

EEG. By conventional interpretation, slightly abnormal EEG was found in 10 of the 26 children examined, in all cases a moderate increase of low frequency activity. Of the 10 children with slightly abnormal EEG, four had suspected or clearly abnormal SPECT. Of the 16 children with normal EEG, 4 had a suspected abnormality of SPECT. However, on quantitative analysis, relative delta and alpha power did not differ between those considered abnormal and normal. There was a significant ($r = −0.43$; $p < 0.05$) negative correlation between relative delta power and age and a tendency to positive correlation ($r = 0.37$; $p = 0.06$) between relative alpha power and age when the Pearson correlation coefficient was used. There was no correlation between relative delta or alpha power and any of the clinical variables (Conners, Rutter, WISC). There was a negative correlation between relative alpha power and SPECT factor 2 ($r = −0.42$; $p < 0.04$) and a positive correlation between relative delta power and SPECT factor 2 ($r = 0.45$; $p < 0.05$) and SPECT factor 3 ($r = 0.39$; $p < 0.05$). This result is difficult to interpret,
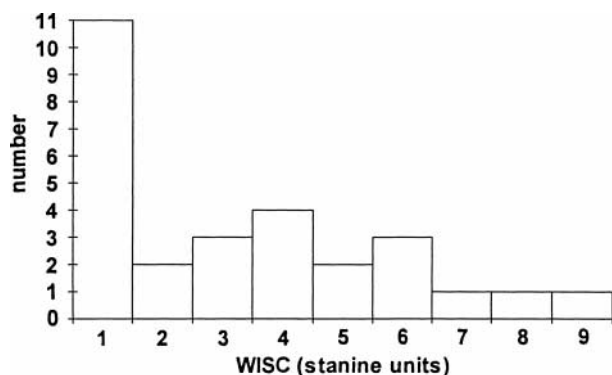
Fig. 2. Distribution of the WISC scores in stanine units among the children participating in the study.

but may reflect that different children have different degrees of alertness during the two examinations with some children more at rest with more alpha activity and lower blood-flow in the areas corresponding to factor 2. On quantitative analysis, there was no significant difference between the EEG recorded at rest compared with active listening ($n = 26$), and no significant difference between the EEG recorded during amphetamine treatment as compared with EEG recorded before treatment ($n = 23$).

MRI. The clinical routine MRI examination was normal for all 28 children in the study.

WISC. The total WISC scores were unevenly distributed among the children with two distinct peaks, one for very low scores and one for medium scores (Fig. 2). Therefore the children were divided into two groups, one with subnormal intelligence (stanine 1–3, $n = 16$) and one group with normal intelligence (stanine 4–9, $n = 12$).

Neurodevelopmental examination. The results of the neurodevelopmental examination are given in Table 2.

Table 2. Mean and standard deviation of the items of the neuropediatric examination ($n = 28$).

Item	Mean	SD	Range
Spooning	0.27	0.60	0–2
Diadochokinesis			
Left	1.29	0.76	0–2
Right	1.46	0.64	0–2
Fog's test	1.50	0.69	0–2
Walking on heels	0.96	0.64	0–2
Standing on one leg			
Left	1.25	0.801	0–2
Right	1.18	0.77	0–2
Hopping on one leg			
Left	0.59	0.75	0–2
Right	0.79	0.79	0–2
Total score	9.29	3.18	4–17
MPA ($n = 24$)	1.75	1.09	0–4

MPA = Minor Physical Anomalies.

Associations between rCBF and cognitive functions, neurodevelopmental examination and behavioural symptoms

The only significant statistical difference between the group with normal SPECT findings and the group with suspected or clearly pathological SPECT findings was in the mean scores of the Rutter Parent Scale (mean in the normal group 17.82, SD 4.40, $n = 17$, mean in the suspected or clearly abnormal group 21.43, SD 3.10 $n = 7$, $p < 0.05$).

The WISC was correlated to factors 1 and 3 within the two subgroups with subnormal and normal intelligence. In the subnormal group, the total score was significantly associated with factor 1. In the normal group, factor 1 was significantly associated with the performance score and almost significantly associated with the total score (rs = 0.45, $p = 0.073$). There was no significant correlation between the WISC and factor 3. Factor 1 was also associated with the degree of motor impairment. Factor 3 was found to be negatively associated with behaviour symptoms, measured by the Rutter Parent Scale. Significant associations are shown in Table 3.

The rCBFs in the frontal regions, which were theoretically indicated as important, were compared with total score of motor impairment, MPA, cognitive functions and behavioural symptoms. Among the items of the neurodevelopmental examination, only high scores on the MPA correlated significantly with rCBF in the frontal lobes bilaterally. Behavioural deviance measured with Conner's and Rutter's scores correlated negatively with the rCBF in the right frontal area. Significant associations are given in Table 4.

Discussion

The homogeneity of the diagnosis of ADHD has been questionned (24). We tested the assumption that children with an abnormality in one of the two neurophysiological examinations (EEG and SPECT) would also have an abnormality in the other. This hypothesis was not supported in this study. The majority of the children had no gross abnormal neurophysiological findings and the slight EEG deviances did not coincide with patients having overt SPECT abnormalities.

Since the brain is thought to function by activities in neural networks with nerve cells in different anatomical regions communicating with each other, the analysis of rCBF in single anatomical regions of interest might be of limited value. We could distinguish two different patterns of the rCBF. One pattern (factor 1) consisted of low rCBF in cerebellum and the temporal lobes relative to the basal ganglia and thalamus, which correlated with motor dysfunction in the neurological examination and cognitive-perceptual dysfunction measured with WISC. The other pattern (factor 3) consisted of low rCBF in

Table 3. Associations between the rCBF in different ROI and WISC-scores.

ROI	WISC total normal intelligence (*n* = 12)	WISC verbal normal intelligence (*n* = 12)	WISC performance normal intelligence (*n* = 12)	WISC total subnormal intelligence (*n* = 16)	WISC verbal subnormal intelligence (*n* = 16)	WISC performance subnormal intelligence (*n* = 16)
Frontal sin	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Frontal dx	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Front.lat sin	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Front.lat dx	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Front med	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Factor 1	n.s.	n.s.	0.59*	0.47*	n.s.	n.s.
Factor 2	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Factor 3	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

frontal and parietal areas (especially in the right frontal area), which correlated with high scores on the Rutter parent questionnaire reflecting behavioural deviances. The remaining factor (factor 2) had no obvious correlations.

These results indicate the existence of different types of brain dysfunction in children with ADHD. Difficulties in motor function, perception and cognition were functionally correlated with another rCBF pattern than behaviour problems. Symptoms of motor and perceptual dysfunction are required for the diagnosis of DAMP (deficits in attention motor control and perception) (32), but not for the diagnosis of ADHD. This could support the use of two separate diagnoses, those of DAMP and ADHD.

Our second assumption was that the degree of reduction of the rCBF in the frontal areas would be associated with the degree of behavioural, cognitive and physical impairment in subjects according to the hypothesis of a dysfunction in the frontal lobes in children with ADHD. This hypothesis was partly confirmed in our study, and we found that these correlations seemed to be restricted to the right frontal region, especially the fronto-lateral region. Concerning MPA, which is considered to correlate with neurodevelopment, our results of significant correlations between MPA and rCBF in the frontal lobes bilaterally were also in accordance with our hypothesis. Our results are thus in agreement with Barkley's suggestion that there is a dysfunction of the frontal lobes, especially the right, in a subgroup of children with ADHD (24).

Table 4. Associations between the rCBF in different ROI and behavioural and neurodevelopmental scores.

ROI.	Connors (*n* = 24)	Rutter (*n* = 24)	MPA (*n* = 24)	Motor impairment (*n* = 28)
Frontal sin	n.s.	n.s.	−0.36*	n.s.
Frontal dx	−0.37*	−0.48**	−0.43*	n.s.
Front.lat sin	n.s.	n.s.	−0.43*	n.s.
Front.lat dx	−0.58**	−0.49**	−0.38*	n.s.
Front.med	n.s.	n.s.	−0.47*	n.s.
Factor 1	n.s.	n.s.	n.s.	0.52**
Factor 2	n.s.	n.s.	n.s.	n.s.
Factor 3	n.s.	−0.38*	n.s.	n.s.

However, the neurological examination and the cognitive test did not show any significant correlation with rCBF in the frontal regions. Our hypothesis was thus not supported by these variables.

Lou et al. (14) found that children with ADHD (defined by hyperactivity and attention deficit) had decreased cerebral blood-flow in the striatal areas (significantly only on the right side) compared to normal. This finding was more pronounced in children with ADHD+ (additional slight mental reduction, language dysfunction and minor motor dysfunction). In addition they found slightly, not significantly, lower frontal rCBF values in the ADHD group.

We found that the degree of symptoms of ADHD correlated with lower cerebral blood-flow in the frontal regions, and that lower rCBF in the basal ganglia correlated with motor dysfunction. These findings are in some accordance with the results of Lou et al. Our method differs from that of Lou et al. in that it gives a relative measure of the blood-flow in one part of the brain as the percentage of the mean blood-flow in the whole brain, while Lou's method gives the absolute value of blood-flow in the different areas of the brain.

The investigated sample was based on clinical cases and consisted of children with severe ADHD willing to participate in a drug study. Our material is thus not a representative sample of children with ADHD in the general population. Nor did we have a normal control group of children, since it is considered unethical to perform SPECT examinations on healthy children. Since a direct quantitative comparison to the rCBF distribution of healthy children was not possible, the rCBF results were instead evaluated by correlation to quantitative evaluations of ADHD-related symptoms.

Conclusion: In a sample of children with ADHD we could distinguish two different patterns of rCBF; one associated with motor impairment and cognitive function, and one associated with behaviour symptoms.

Further studies are needed to confirm or disconfirm the results of our study. It would be of special interest to repeat our investigation in a population-based sample.

References

1. Biederman J, Milberger S, Faraone SV, Kiely K, Guite J, Mick E, et al. Impact of adversity on functioning and comorbidity in children with attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1995; 34: 1495–503

2. McIntosh DE, Mulkins RS, Dean RS. Utilization of maternal perinatal risk indicators in the differential diagnosis of ADHD and UADD children. Int J Neurosci 1995; 81: 35–46

3. Boris M, Mandel FS. Foods and adddtives are common causes of attention deficit hyperactivity disorder in children. Ann Allergy 1994; 72: 462–8

4. Milberger S, Biederman J, Faraone SV, Chen L, Jones J. Is maternal smoking during pregnancy a risk factor for attention deficit disorder in children? Am J Psychiatry 1996; 153: 1138–42

5. Biederman J, Faraone SV, Keeman K, Knee D, Tsuang Ming T. Family-genetic and psychosocial risk factors in DSM-III attention deficit disorder. J Am Acad Child Adolesc Psychiatry 1990; 29: 526–33

6. Goodman R, Stevenson J. A twin study of hyperactivity—II. The aetiological role of genes, family relationships and perinatal adversity. J Child Psychol Psychiatry 1989; 30: 691–709

7. Goodman R. Genetic factors in hyperactivity. Br Med J 1989; 298: 1407–8

8. Zametkin AJ, Nordahl TE, Gross M, King C, Semple WE, Ramsey J, et al. Cerebral blood glucose metabolism in adults with hyperactivity of childhood onset. N Engl J Med 1990; 323: 1361–6

9. Heilman KM, Voeller KKS, Nadeau SE. A possible pathophysiologic substrate of attention deficit disorder. J Child Neurol 1991; 6 Suppl: S74–9

10. Swanson JM, Posner M, Potkin S, Bonforte S, Youpa D, Fiore C, et al. Activating tasks for the study of visual–spatial attention in ADHD children: a cognitive anatomic approach. J Child Neurol 1991; 6 Suppl: 117–25

11. Benson FD. The role of frontal dysfunction in attention hyperactivity disorder. J Child Neurol 1991; 6 Suppl: 9–12

12. Chelune GJ, Ferguson W, Koon R, Dickey TO. Frontal lobe disinhibition in attention deficit disorder. Child Psychiatry Hum Dev 1986; 16: 221–34

13. Lou HC, Henriksen L, Bruhn P. Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder. Arch Neurol 1984; 41: 825–9

14. Lou HC, Henriksen L, Bruhn P, Börner H, Nielsen JB. Striatal dysfunction in attention deficit and hyperkinetic disorder. Arch Neurol 1989; 46: 48–52

15. Lou HC, Henriksen L, Bruhn P. Focal cerebral dysfunction in developmental learning disabilities. Lancet 1990; 335: 8–11

16. O'Tuama LA, Treves ST. Brain single-photon emission computed tomography for behavior disorders in children. Semin Nucl Med 1993; 23: 255–64

17. Sieg KG, Gaffney GR, Preston DF, Hellings JA. SPECT brain imaging abnormalities in attention deficit hyperactivity disorder. Clin Nucl Med 1995; 20: 55–60

18. Kuperman S, Johnson B, Arndt S, Lindgren S, Wolraich M. Quantitative EEG differences in a nonclinical sample of children with ADHD and undifferentiated ADD. J Am Acad Child Adolesc Psychiatry 1996; 35: 1009–17

19. Hynd GW, Hern KL, Novey ES, Elipoulos D, Marshall R, Gonzalez JJ, et al. Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. J Child Neurol 1993; 8: 339–47

20. Semrud-Clikeman M, Filipek PA, Biederman J, Steingard R, Kennedy D, Renshaw P, et al. Attention deficit hyperactivity disorder: magnetic resonance imaging morphometric analysis of the corpus callosum. J Am Acad Child Adolesc Psychiatry 1994; 33: 875–81

21. Casey B, Castellannos F, Giedd J, Marsh W, Hamburger SD, Schubert AB, et al. Implications of right frontostriatal circuitry in response inhibition and attention deficit/hperactivity disorder. J Am Acad Child Adolesc Psychiatry 1997; 36: 374–83

22. Filipek P, Semrud-Clikeman M, Steingard R, Renshaw P, Kennedy D, Biederman J. Volumetric MRI analysis comparing subjects having attention deficit hyperactivity disorder with normal controls. Neurology 1997; 48: 589–601

23. Castellanos F, Giedd J, Marsh W, Hamburger S. Quantitative brain magnetic resonance imaging in attention deficit hyperactivity disorder. Arch Gen Psychiatry 1996; 53: 607–16

24. Barkley R. ADHD and the nature of self-control. New York: Guilford Press, 1997

25. American Psychiatric Association. Diagnostic and Statistic Manual of Mental Disorders. (3rd rev. ed.). Washington, DC: APA; 1987

26. Gillberg IC, Gillberg C, Groth J. Children with preschool minor neurodevelopmental disorders. V: Neurodevelopmental profiles at age 13. Dev Med Child Neurol 1989; 31: 14–25

27. Waldrop M, Halverson C. Minor physical anomalies and hyperactive behavior in young children. In: Hellmuth J, editor. The exceptional infant, Vol. 2. New York: Brunner-Mazel, 1971

28. Holmes RA, Chaplin S, Royston K, et al. Cerebral uptake and retention of 99Tcm–hexamethylpropylene amine oxime (99Tcm–HM–PAO). Nucl Med Commun 1985; 6: 443–7

29. Rutter M, Graham P, Yule W. A neuropsychiatric study in childhood. In: Clinics in developmental medicine; vol 35/36. London: Heinemann; 1970

30. Conners CK. Conners Rating Scales Manual, Conners Teachers Rating Scales, Conners Parent Rating Scales. Instruments for use with Children and Adolescents. North Tonawanda, NY: Multi-health Systems; 1990

31. Wechsler D. Manual of the Wechsler Intelligence Scale for Children. San Antonio: Psychological Corporation, 1949

32. Gillberg C. Dysfunction of attention, motor control and perception. In: Clinical child neuropsychiatry. Cambridge: Cambridge University Press; 1995: 133–56