Structural neuroimaging in autism

Michal Hrdlicka[1,2]

1. Department of Child Psychiatry, Charles University, 2nd Faculty of Medicine, V Uvalu 84, 15006 Prague, Czech Republic.
2. Charles University, 1st Medical Faculty, Kateřinska 32, 12108 Prague, Czech Republic.

Correspondence to: Michal Hrdlicka, M.D., Ph.D., Professor
Department of Child Psychiatry, Charles University,
2nd Faculty of Medicine, V Uvalu 84, 15006 Prague, Czech Republic
TEL.: +420 224 433 400; FAX: +420 224 433 420
EMAIL: michal.hrdlicka@lfmotol.cuni.cz

Submitted: 2008-05-11 Accepted: 2008-05-30 Published online: 2008-06-24

Key words: **autism; MRI; brain volume; cerebellum; caudate nucleus; thalamus; corpus callosum; amygdala; hippocampus**

Neuroendocrinol Lett 2008; **29**(3):281–286 **PMID:** 18580841 NEL290308R01

Abstract

Structural neuroimaging studies done by means of magnetic resonance imaging (MRI) have provided important insights into the neurobiological basis for autism. The aim of this article is to review the current state of knowledge regarding structural brain abnormalities in autism. Results of MRI studies dealing with total brain volume, the volume of the cerebellum, caudate nucleus, thalamus, amygdala, hippocampus and the area of the corpus callosum are summarized. Existing research suggests that autistic individuals have larger total brain, cerebellar and caudate nucleus volumes; however, the area of the corpus callosum is reduced. Results of studies involving the amygdala and hippocampus volume in autistic subjects remain inconsistent and no changes have been detected in thalamic volume.

REVIEW

Abbreviations & units:

ASDs	– autism spectrum disorders
CC	– corpus callosum
ES	– effect size
ICD-10	– International Classification of Diseases, 10th Revision
IQ	– intelligence quotient
MRI	– magnetic resonance imaging
PDDs	– pervasive developmental disorders
TBV	– total brain volume

INTRODUCTION

Autism is a complex developmental disability characterized by impairments in social interaction, communication, and behavior. Autism, or Childhood autism, as described by the International Classification of Diseases, 10th Revision (ICD-10; World Health Organization, 1992), seems to be the most important member of the group of Pervasive Developmental Disorders (PDDs), also called Autism Spectrum Disorders (ASDs).

A large number of studies, many published in the past decade, link autism with specific neural and neurochemical abnormalities (Volkmar *et al.* 2005; Penn, 2006; Oslejskova *et al.* 2007). Research results indicate that autism is largely caused by genetic factors that lead to abnormal brain development (Nicolson & Szatmari, 2003). Quantitative analyses have indicated heritability in excess of 90% (Volkmar *et al.* 2005). Alternative etiological theories do exist and included, for example, negative effects of vaccines and/or vaccine preservatives, e.g. thimerosal (Geier & Geier, 2006a), altered metabolic pathways (Shattock *et al.* 1990, Sliwinski *et al.* 2006), immunological dysregulation (Jyonouchi *et al.* 2005; Molloy *et al.* 2006), and hormonal imbalances (Geier & Geier, 2006b; Geier & Geier, 2007). However, the majority of al-

ternative etiological explanations have not been accepted by academic psychiatry (Rutter, 2005; Volkmar *et al.* 2005).

Structural neuroimaging studies, done by means of magnetic resonance imaging (MRI), have provided important insights into the neurobiological basis for autism (Nicolson & Szatmari, 2003) and a large number of structural MRI studies have been published. A recent systematic review found 46 structural controlled neuroimaging studies involving over 800 individuals with autism and similar numbers of controls (Stanfield *et al.* 2007). The aim of present review is to describe and discuss structural abnormalities detected by neuroimaging studies in autism.

TOTAL BRAIN VOLUME

There have been numerous studies on the topic of total brain volume (e.g. Filipek *et al.* 1992; Piven *et al.* 1995; Townsend *et al.* 1999; Haznedar *et al.* 2000; Aylward *et al.* 2002; Sparks *et al.* 2002; Hardan *et al.* 2003; Herbert *et al.* 2003; Tsatsanis *et al.* 2003; Kates *et al.* 2004; McAlonan *et al.* 2005; Vidal *et al.* 2006; Girgis *et al.* 2007) and there is consistent evidence for increased total brain volume (TBV) in autism (Brambilla *et al.* 2003; Palmen & van Engeland, 2004; Sokol & Edwards-Brown, 2004; Penn, 2006; Stanfield *et al.* 2007).

An earlier review, which focused on brain volume, as well as on area measurements, identified 12 studies: 7 of these studies reported brain enlargement, while 5 studies failed to find any change; none of the studies reported a decrease in total brain size (Brambilla *et al.* 2003). The most recent meta-analysis identified 16 volumetric studies, and found significantly increased TBV in autistic subjects compared to controls, with a standardized effect size (ES) = 0.32 (Stanfield *et al.* 2007).

Several studies have suggested that brain enlargement was restricted to early childhood (Aylward *et al.* 2002; Courchesne *et al.* 2001), while other studies reported brain enlargement which persisted into adulthood (Hardan *et al.*, 2001a; Piven *et al.* 1995; Piven *et al.* 1996). Some authors also stressed that level of intelligence (IQ), sex, handedness, height and weight, socioeconomic status and the use of neuroleptic medication could also be associated with the size of brain structures (Brambilla *et al.* 2003; Palmen & van Engeland, 2004). However, a recent meta-analysis failed to reveal any significant influence of age or IQ on TBV (Stanfield *et al.* 2007).

CEREBELLUM

Generally, the cerebellum is associated with motor integration and may seem an unlikely candidate to account for the profound effects of autism (Sokol & Edwards-Brown, 2004). Studies of cerebellar structure have been more inconsistent than studies of TBV. The first cerebellum studies reported a range of results including: (i) smaller cerebellar hemispheric areas (Gaffney *et al.* 1987a; Murakami *et al.* 1989), (ii) hypoplasia of lobules VI and VII (Courchesne *et al.* 1988; Cieselski *et al.* 1997), (iii) hypoplasia of the entire cerebellar vermis (Hashimoto *et al.* 1995), (iv) hyperplasia of lobules VI and VII (Courchesne *et al.* 1994a, 1994b, 1994c), and (v) no change in vermis lobules VI and VII (Filipek *et al.* 1992; Piven *et al.*, 1992). However, more recent studies have found increased cerebellar volume in both autistic children (Sparks *et al.* 2002; Herbert *et al.* 2003), and autistic adults (Piven *et al.* 1997a; Hardan *et al.* 2001b).

In his review, Brambilla *et al.* (2003), reported 3 studies which found an increase in the size of cerebellar hemispheres, 2 studies which found a decrease in the size of cerebellar hemispheres, and 3 studies that failed to demonstrate any changes in size. His review also reported 2 studies which found an increase in the size of cerebellar lobules VI and VII, 5 studies which reported a decrease in size, and 11 studies which failed to demonstrate any changes. A meta-analysis by Stanfield *et al.* (2007) found significantly enlarged cerebellar hemispheres in autistic subjects compared to controls, with a standardized effect size = 0.72. In contrast, vermis lobules VI and VII (ES = −0.27) as well as vermis lobules VIII–X (ES = −0.43) were significantly smaller in autistic subjects compared to controls. Significant relationships were also found between the effect size for the cerebellar vermis lobules VI and VII and the mean age and IQ of autistic subjects.

BASAL GANGLIA

The basal ganglia, consisting of the caudate nucleus, putamen, and globus pallidus, are believed to be involved with stereotyped and repetitive behaviors seen in autism (Palmen & van Engeland, 2004). Several studies have found the caudate nucleus volume to be increased either bilaterally (Sears *et al.* 1999; Voelbel *et al.* 2006; Langen *et al.*2007) or on the right side only (Hollander *et al.* 2005; Haznedar *et al.* 2006). Some of the studies performed a correction of results, based on total brain volume; even after correction, the results remained significant (Sears *et al.* 1999; Hollander *et al.* 2005; Langen *et al.* 2007). One reviewed study failed to demonstrate any differences in caudate nucleus and putamen between autistic subjects and controls (Hardan *et al.* 2003) and one study found an increase in the volume of the globus pallidus – putamen, which was proportional to the increase in brain volume, but found no differences in the caudate nucleus (Herbert *et al.* 2003).

Only three of the studies mentioned above (Sears *et al.* 1999; Hardan *et al.* 2003; Herbert *et al.* 2003) were included in the Stanfield *et al.* (2007) meta-analysis; which found significantly increased caudate volume in autistic subjects compared to controls, with a standardized effect size = 0.41.

There have been attempts to connect basal ganglia size with underlying psychopathology. In the Sears *et al*. (1999) study, caudate volume was associated with compulsions and rituals, difficulties with minor change, and complex motor mannerisms in autism. Similarly, in a study by Hollander *et al*. (2005), the right caudate and total putamen volumes correlated positively with repetitive behavior. Voelbel *et al*. (2006) found that larger caudate volumes were related to impaired problem solving. On the other hand, Hardan *et al*. (2003) failed to demonstrate such a relationship. They suggested that the motor deficits observed in autism might not be related to structural abnormalities of the basal ganglia, but instead, other brain regions, such as the cerebellum and the frontal lobe, might be involved in the pathophysiology of motor disturbances in autism.

THALAMUS

The thalamus has been implicated in the attention, memory, language, and emotional processing deficits seen in autism (Palmen & van Engeland, 2004). However, results of neuroimaging studies have been disappointing. Herbert *et al*. (2003) reported increased thalamic volume before, but not after correction for brain volume. However, the majority of studies did not observe any differences between autistic and control groups relative to unadjusted thalamic volumes (Tsatsanis *et al*. 2003; Hardan *et al*. 2006; Haznedar *et al*. 2006).

The meta-analysis by Stanfield *et al*. (2007) found only a negligible effect size in autistic subjects compared to controls with regard to thalamus volume (ES −0.05 for the left thalamus and ES −0.04 for the right thalamus).

CORPUS CALLOSUM

The corpus callosum (CC) is a brain structure involved in interhemispheric transfer of information and has become important in the study of cortical connectivity in the brain. Cortical connectivity and therefore the CC are thought to be abnormal in autism. The first study investigating the CC did not find a significant difference compared to healthy controls (Gaffney *et al*. 1987b). Later studies reported a significant reduction in the anterior part (involving the genu and rostrum) of the CC (Hardan *et al*. 2000), in the body of the CC (Manes *et al*. 1999), in the body and posterior subregions of the CC (Piven *et al*. 1997b), and in the genu and splenium (Just *et al*. 2007). Vidal *et al* (2006) noted that traditional morphometric methods used in their study detected a significant reduction in the total callosal area in the anterior third of the CC in autistic patients; however, 3D maps revealed significant reductions in both the genu and splenium of the CC in autistic patients.

The meta-analysis carried out by Stanfield *et al*. (2007) found a significantly smaller corpus callosum in autistic subjects compared to controls (ES = −0.28).

AMYGDALA

The amygdala is a brain structure of key importance relative to social behavior and cognition, and compelling evidence for amygdala dysfunction in people with autism has been collected (Baron-Cohen *et al*. 2000; Pierce *et al*. 2001; Pierce *et al*. 2004). Despite this, results of studies that have investigated amygdala volume in autism have been contradictory. Various studies have reported (i) increased amygdala volume (Abell *et al*. 1999; Howard *et al*. 2000; Sparks *et al*. 2002), (ii) decreased amygdala volume (Aylward *et al*. 1999; Pierce *et al*. 2001; Herbert *et al*. 2003; Nacewicz *et al*. 2006), and (iii) no change in amygdala volume (Haznedar *et al*. 2000). Schumann *et al*. (2004) found that the amygdala was enlarged in children with autism but not adolescents with autism. The meta-analysis by Stanfield *et al*. (2007) supported this finding, and demonstrated that as age increased, amygdala volume in autistic subjects decreased relative to controls. Significant relationships were found between age and effect size for the left and right amygdala. Additionally, effect size was different for the left amygdala (ES = 0.15) and right amygdala (ES = 0.28).

Several studies have attempted to link amygdala volume or size with autistic psychopathology. Hrdlicka *et al*. (2005) performed a cluster analysis based on structural MRI measurements and found that the least impaired autistic individuals were in the cluster with the largest amygdala size. Munson *et al*. (2006) reported that, in children, ages 3 and 4 years, increased right amygdalar volume was associated with more severe social and communication impairments. On the other hand, Nacewicz *et al*. (2006) found that individuals with autism who had small amygdalae were the slowest to distinguish emotional from neutral expressions and showed the least fixation of eye regions. Juranek *et al*. (2006) reported that symptoms of anxiety/depression in autistic children were significantly correlated with increased total amygdala volume and right amygdala volume.

HIPPOCAMPUS

Abnormalities of the hippocampus and related limbic structures have been considered relevant to the pathophysiology of autism because of their role in learning, social functioning, and emotion functions; these same functions are typically affected in autism (Nicolson *et al*. 2006). As in the amygdala studies, no consistent findings have been published. Although there have been studies which reported (i) increased hippocampal volume (Sparks *et al*. 2002; Schumann *et al*. 2004), (ii) de-

creased hippocampal volume (Aylward *et al*. 1999; Herbert *et al*. 2003; Saitoh *et al*. 2001), and (iii) no change in hippocampal volume (Saitoh *et al*. 1995; Piven *et al*. 1998; Haznedar *et al*. 2000; Howard *et al*. 2000; Nicolson *et al*. 2006; Dager *et al*. 2007). The meta-analysis by Stanfield *et al*. (2007) revealed no statistically significant changes between autistic subjects and controls.

Dager *et al*. (2007) reported that it wasn't volumetric measurements but instead hippocampal shape measures that distinguished children with ASDs from those with typical development. Hippocampal-shape alterations in children with ASDs correlated with the degree of mental retardation and performance deficits seen on tests of medial temporal lobe function.

DISCUSSION

Early structural studies were often plagued by methodological deficits such as: small sample sizes; the use of patients with associated medical and neurological conditions; the use of medically ill controls instead of healthy controls, no matching of confounding factors (e.g. age, sex, IQ, and medication status), low power of the magnetic field strength (0.5 Tesla), and thick (more than 1.5 mm) slices (Mink & McKinstry, 2002; Palmen & van Engeland, 2004). These issues create difficulties when evaluating study results.

There have been various attempts to define a reliable quality rating protocol for neuroimaging studies in general. For example, Brambilla *et al*. (2003) introduced a checklist of 12 points, divided into three categories. The criteria are still useful when evaluating the results of a study:

Category 1: Subjects

1. Patients evaluated prospectively, specific diagnostic criteria applied, and demographical data reported;
2. Healthy comparison subjects evaluated prospectively, psychiatric and medical illnesses excluded, and demographical data reported;
3. Important confounds (e.g. age, gender, IQ, handedness, socioeconomic status, height or total brain measures) controlled either by stratification or statistically;
4. Sample size: at least 20 per group.

Category 2: Methods for image acquisition and analysis

5. All anatomic measurements made blind to group assignment and to the subject's identity;
6. Measures for brain structures reported.
7. MRI slice-thickness of 3 mm or less and more than one slice identified and traced;
8. Imaging techniques clearly described so as to be reproducible;
9. Measurements clearly described so as to be reproducible;
10. Regions-of-interest defined so as to be reproducible;

Category 3: Results and conclusions

11. Statistical parameters for significant and important non-significant differences provided;
12. Conclusions consistent with results with a discussion of study limitations.

The quality of MRI studies has continuously improved over the last decade. As Palmen & van Engeland (2004) wrote, "most studies investigated more homogeneous groups of patients and more extensively matched control groups and used more sophisticated MRI techniques" at that time.

CONCLUSIONS

There is good agreement among existing studies that autistic individuals have larger total brain, cerebellar and caudate nucleus volumes; while the area of corpus callosum is reduced. Studies of amygdala and hippocampus volumes in autistic subjects have produced inconsistent results; and no studies have reported changes in thalamic volume associated autism.

Acknowledgements.
Supported by grants MSM 0021620849 and FNM MZ000064203.

REFERENCES

1 Abell F, Krams M, Ashburner J, Passingham R, Friston K, Frackowiak R, *et al*. (1999). The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans. NeuroReport. **10**: 1647–1651.
2 Aylward EH, Minshew NJ, Goldstein G, Honeycutt NA, Augustine AM, Yates KO, *et al*. (1999). MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. Neurology. **53**: 2145–2150.
3 Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N (2002) Effects of age on brain volume and head circumference in autism. Neurology. **59**: 175–183.
4 Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, Williams SCR (2000). The amygdala theory of autism. Neurosci Biobehav Reviews. **24**: 355–364.
5 Brambilla P, Hardan A, Ucelli di Nemi S, Perez J, Soares JC, Barale F (2003). Brain anatomy and development in autism: review of structural MRI studies. Brain Res Bull. **61**: 557–569.
6 Cieselski KT, Harris RJ, Hart BL, Pabst HF (1997). Cerebellar hypoplasia and frontal lobe cognitive deficits in disorders of early childhood. Neuropsychologia. **35**: 643–655.
7 Courchesne E, Yeung- Courchesne R, Press G, Hesselink J, Jernigan T (1988). Hypoplasia of cerebellar vermal lobules VI and VII in autism. N Engl J Med. **318**: 1349–1354.
8 Courchesne E, Saitoh O, Townsend JP, Yeung- Courchesne R, Press GA, Lincoln AJ, *et al*. (1994a). Cerebellar hypoplasia and hyperplasia in infantile autism. Lancet. **343**: 63–64.

9 Courchesne E, Townsend JP, Saitoh O (1994b). The brain in infantile autism: posterior fossa structures are abnormal. Neurology. **44**: 214–223.
10 Courchesne E, Saitoh O, Yeung- Courchesne R, Press GA, Lincoln AJ,Haas RH *et al*. (1994c). Abnormality of cerebellar vermian lobules VI and VII in patients with infantile autism: identification of hypoplastic and hyperplastic subgroups with MR imaging. Am J Roentgenol. **162**: 123–130.
11 Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, *et al*. (2001) Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. Neurology. **57**: 245–254.
12 Dager SR, Wang L, Friedman SD, Shaw DW, Constantino JN, Artru AA, *et al*. (2007). Shape mapping of the hippocampus in young children with autism spectrum disorder. Am J Neuroradiol. **28**: 672–677.
13 Filipek PA, Richelme C, Kennedy DN, Rademacher J, Pitcher DA, Zidel S, *et al*. (1992). Morphometric analysis of the brain in developmental language disorders and autism. Ann Neurol. **32**: 475–475.
14 Gaffney GR, Tsai LY, Kuperman S, Minchin S (1987a). Cerebellar structure in autism. Am J Dis Child. **141**: 1330–1332.
15 Gaffney GR, Kuperman, S, Tsai LY, Minchin S, Hassanein KM (1987). Midsagittal magnetic resonance imaging of autism. Br J Psychiatry. **151**: 831–833.
16 Geier DA, Geier MR (2006a). A meta – analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States. Neuroendocrinol Lett. **27**: 401–413.
17 Geier DA, Geier MR (2006b). A clinical trial of combined antiandrogen and anti-heavy metal therapy in autistic disorders. Neuroendocrinol Lett. **27**: 833–838.
18 Geier DA, Geier MR (2007). A prospective assessment of androgen levels in patients with autistic spectrum disorders: biochemical underpinnings and suggested therapies. Neuroendocrinol Lett. **28**: 565–573.
19 Girgis RR, Minshew NJ, Melhem NM, Nutche JJ, Keshavan MS, Hardan AY (2007). Volumetric alterations of the orbitofrontal cortex in autism. Prog Neuropsychopharmacol Biol Psychiatry. **31**: 41–45.
20 Hardan AY, Minshew NJ, Keshavan MS (2000). Corpus callosum size in autism. Neurology. **55**: 1033–1036.
21 Hardan AY, Minshew NJ, Millikarjuhn M, Keshavan MS (2001a). Brain volume in autism. J Child Neurol. **16**: 421–424.
22 Hardan AY, Minshew NJ, Harenski K, Keshavan MS (2001b). Posterior fossa magnetic resonance imaging in autism. J Am Acad Child Adolesc Psychiatry. **40**: 666–672.
23 Hardan AY, Kilpatrick M, Keshavan MS, Minshew NJ (2003). Motor performance and anatomic magnetic resonance imaging (MRI) of the basal ganglia in autism. J Child Neurol. **18**: 317–324.
24 Hardan AY, Girgis RR, Adams J, Gilbert AR, Keshavan MS, Minshew NJ (2006) Abnormal brain size effect on the thalamus in autism. Psychiatry Res. **147**: 145–151.
25 Haznedar MM, Buchsbaum MS, Wei TC, Hof PR, Cartwright C, Bienstock CA, *et al*. (2000). Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging. Am J Psychiatry. **157**: 1994–2001.
26 Haznedar MM, Buchsbaum MS, Hazlett EA, Licalzi EM, Cartwright C, Hollander E (2006). Volumetric analysis and three-dimensional glucose metabolic mapping of the striatum and thalamus in patients with autism spectrum disorders. Am J Psychiatry. **163**: 1252–1263.
27 Herbert MR, Ziegler DA, Deutsch CK, O´Brien LM, Lange N, Bakardjiev A, *et al*. (2003). Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain. **126**: 1182–1192.
28 Hollander E, Anagnostou E, Chaplin W, Esposito K, Haznedar MM, Licalzi E, *et al*. (2005). Striatal volume on magnetic resonance imaging and repetitive behaviors in autism. Biol Psychiatry. **58**: 226–232.
29 Howard MA, Cowell PE, Boucher J,, Broks P, Mayes A, Farrant A, *et al*. (2000). Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. NeuroReport. **11**: 2931–2935.
30 Hrdlicka M, Dudova I, Beranova I, Lisy J, Belsan T, Neuwirth J, *et al*. (2005). Subtypes of autism by cluster analysis based on structural MRI data. Eur Child Adolesc Psychiatry. **14**: 138–144.
31 Juranek J, Filipek PA, Berenji GR, Modahl C, Osann K, Spence A (2006). Association between amygdala volume and anxiety level: magnetic resonance imaging (MRI) study in autistic children. J Child Neurol. **21**: 1051–1058.
32 Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ (2007). Functional and anatomical cortical underconnectivity in autism: evidence from an fMRI study of an executive function task and corpus callosum morphometry. Cerebral Cortex. **17**: 951–961.
33 Jyonouchi H, Geng L, Ruby A, Zimmerman-Bier B (2005). Dysregulated innate immune responses in young children with autism spectrum disorders: their relationship to gastrointestinal symptoms and dietary intervention. Neuropsychobiology. **51**: 77–85.
34 Kates WR, Burnette CP, Eliez S, Strunge LA, Kaplan D, Landa R, *et al*. (2004). Neuroanatomic variation in monozygotic twin pairs discordant for the narrow phenotype of autism. Am J Psychiatry. **161**: 539–546.
35 Langen M, Durston S, Staal WG, Palmen SJMC, van Engeland H (2007). Caudate nucleus is enlarged in high-functioning medication-naive subjects with autism. Biol Psychiatry. **62**: 262–266.
36 Manes F, Piven J, Vrancic D, Nanclares V, Plebst C, Starkstein SE (1999). An MRI study of the corpus callosum and cerebellum in mentally retarded autistic individuals. J Neuropsychiatry Clin Neurosci. **11**: 470–474.
37 McAlonan GM, Cheung V, Cheung C, Suckling J, Lam GY, Tai KS, *et al*. (2005). Mapping the brain in autism. A voxel-based MRI study of volumetric differences and intercorrelations in autism. Brain. **128** (Pt 2): 268–276.
38 Mink JW, McKinstry RC (2002). Volumetric MRI in autism: Can high-tech craniometry provide neurobiological insights ? Neurology. **59**: 158–159.
39 Molloy CA, Morrow AL, Meinzen-Derr J, Dawson G, Bernier R, Dunn M, *et al*. (2006). Familial autoimmune thyroid disease as a risk factor for regression in children with autism spectrum disorder: a CPEA study. J Autism Dev Disord. **36**: 317–324.
40 Munson J, Dawson G, Abbott R, Faja S, Webb SJ, Friedman SD, *et al*. (2006). Amygdalar volume and behavioral development in autism. Arch Gen Psychiatry. **63**: 686–693.
41 Murakami JW, Courchesne E, Press GA, Yeung- Courchesne R, Hesselink JR (1989). Reduced cerebellar hemisphere size and its relationship to vermal hypoplasia in autism. Arch Neurol. **46**: 689–694.
42 Oslejskova H, Kontrova I, Foralova R, Dusek L, Nemethova D (2007). The course of diagnosis in autistic patients: the delay between recognition of the first symptoms by parents and correct diagnosis. Neuroendocrinol Lett. **28**: 895–900.
43 Nacewicz BM, Dalton KM, Johnstone T, Long MT, McAuliff EM, Oakes TR, *et al*. (2006). Amygdala volume and nonverbal social impairment in adolescent and adult males with autism. Arch Gen Psychiatry. **63**: 1417–1428.
44 Nicolson R, Szatmari P (2003). Genetic and neurodevelopmental influences in autistic disorder. Can J Psychiatry. **48**: 526–537.
45 Nicolson R, DeVito TJ,, Vidal CN, Sui Y, Hayashi KM, Drost DJ, *et al*. (2006). Detection and mapping of hippocampal abnormalities in autism. Psychiatry Res Neuroimaging. **148**: 11–21.
46 Palmen SJMC, van Engeland H (2004). Review of structural neuroimaging findings in autism. J Neural Transm. **111**: 903–929.
47 Penn H (2006). Neurobiological correlates of autism: a review of recent research. Child Neuropsychol. **12**: 57–79.
48 Pierce K, Muller RA, Ambrose J, Allen G, Courchesne E (2001). Face processing occurs outside the fusiform "face area" in autism: evidence from functional MRI. Brain. **124**: 2059–2073.
49 Pierce K, Haist F, Sedaghat F, Courchesne E (2004). The brain response to personally familiar faces in autism: findings of fusiform activity and beyond. Brain. **127**: 2703–2716.

50 Piven J, Nehme E, Simon J, Barta P, Pearlson G, Folstein SE (1992). Magnetic resonance imaging in autism: measurements of the cerebellum, pons, and fourth ventricle. Biol Psychiatry. **31**: 491–504.
51 Piven J, Arndt S, Bailey J, Haverkamo, S, Andreasen NC, Palmer P (1995) An MRI study of brain size in autism. Am J Psychiatry. **152**: 1145–1149.
52 Piven J, Arndt S, Bailey J, Andreasen NC (1996). Regional brain enlargement in autism: a magnetic resonance imaging study. J Am Acad Child Adolesc Psychiatry. **35**: 530–536.
53 Piven J. Saliba K, Bailey J, Arndt S (1997a). An MRI study of autism: the cerebellum revisited. Neurology. **49**: 546–551.
54 Piven J, Bailey J, Ranson BJ, Arndt S (1997b). An MRI study of the corpus callosum in autism. Am J Psychiatry. **154**: 1051–1056.
55 Piven J, Bailey J, Ranson BJ, Arndt S (1998). No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals. J Autism Dev Disord. **28**: 105–110.
56 Rutter M (2005). Incidence of autism spectrum disorders: changes over time and their meaning. Acta Pediatr. **94**: 2–15.
57 Saitoh O, Courchesne E, Egaas B, Lincoln AJ, Screibman L (1995). Cross-sectional area of the posterior hippocampus in autistic patients with cerebellar and corpus callosum abnormalities. Neurology. **45**: 317–324.
58 Saitoh O, Karns CM, Courchesne E (2001). Development of the hippocampal formation from 2 to 42 years: MRI evidence of smaller area dentata in autism. Brain. **124**: 1317–1324.
59 Schumann CM, Hamstra J, Goodlin-Jones BL, Lotspeich LJ, Kwon H, Buonocore MH (2004). The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J Neurosci. **24**: 6392–6401.
60 Sears LL, Vest C, Mohamed S, Bailey J, Ranson B, Piven J (1999). An MRI study of the basal ganglia in autism. Prog Neuro – Psychopharmacol Biol Psychiat. **23**: 613–624.
61 Shattock P, Kennedy A, Rowell F, Berney T (1990). Role of neuropeptides in autism and their relationships with classical neurotransmitters. Brain Dysfunct. **3**: 328–345.
62 Sliwinski S, Croonenberghs J, Christophe A, Deboutte D, Maes M. (2006) Polyunsaturated fatty acids: do they have a role in the pathophysiology of autism ? Neuroendocrinol Lett. **27**: 465–471.
63 Sokol DK, Edwards-Brown ME (2004). Neuroimaging in autistic spectrum disorders. J Neuroimaging. **14**: 8–15.
64 Sparks BF, Friedman SD, Shaw DW, Aylward EH, Echelard D, Artru AA, *et al*. (2002). Brain structural abnormalities in young children with autism spectrum disorders. Neurology. **59**: 184–192.
65 Stanfield AC, McIntosh AM, Spencer MD, Philip R, Gaur S, Lawrie SM (2007). Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. Eur Psychiatry. 2007 Aug 30 (Epub ahead of print).
66 Townsend J, Courchesne E, Covington J, Westerfield M, Harris NS, Lyden P, *et al*. (1999). Spatial attention deficits in patients with acquired or developmental cerebellar abnormality. J Neurosci. **19**: 5632–5643.
67 Tsatsanis KD, Rourke BP, Klin A, Volkmar FR, Cicchetti D, Schultz RT (2003). Reduced thalamic volume in high-functioning individuals with autism. Biol Psychiatry. **53**: 121–129.
68 Vidal CN, Nicolson R, FeVito TJ, Hayashi KM, Geaga JA, Drost DJ, *et al*. (2006). Mapping corpus callosum deficits in autism: an index of aberrant cortical connectivity. Biol Psychiatry. **60**: 218–225.
69 Voelbel GT, Bates ME, Buckman JF, Pandina G, Hendren RL (2006). Caudate nucleus volume and cognitive performance: are they related in childhood psychopathology ? Biol Psychiatry. **60**: 942–950.
70 Volkmar FR, Paul R, Klin A, Cohen D, editors (2005). Handbook of autism and pervasive developmental disorders. 3rd ed. Hoboken (NJ): John Wiley & Sons.
71 World Health Organization (1992). International Classification of Diseases, 10th ed. Geneva: WHO.