Review Article

Current understanding of Neurobiology of Autism Spectrum Disorders and its Nosological Implications

M.S. Bhatia*, G. Rajender*, S. Malhotra, K. Kanwal***, D. Chaudhary*****
** Department of Psychiatry, UCMS & GTB Hospital, Delhi, University of Delhi*
*** Department of Clinical Psychology, IHBAS, Delhi*
****SMS Medical College, Jaipur*

Introduction

The term autism spectrum disorders (ASD) also known as pervasive developmental disorders [PDDs] refers to early onset, developmental disorders of varying clinical presentation characterized by pervasive qualitative impairment , delay and deviance in the development of reciprocal social, communicative and other skills. In contrast to the lack of interest in social environment, unusual sensitivity to inanimate environment is typical characteristic of ASDs. According to DSM-IV-TR[1] these ASDs include Autistic disorder, Rett's Syndrome, Childhood Disintegrative Disorder, Asperger's Syndrome and PDD Not otherwise specified. In the past decade, researchers and clinicians have broadened the diagnostic concept to include milder and atypical forms of autism and autism-related disorders that are represented as a spectrum. These disorders are estimated to occur at a much higher rate than previously thought, making it likely for the average physician to encounter patients with ASDs in his or her practice. A complete understanding of what comprises ASDs and the underlying etiological mechanisms will require a dramatic change in how these disorders are conceptualized. Here the authors review the recent literature on neurobiology of ASDs along with its nosological implications.

Approaches to Understanding PDD

- *Multi Dimensional Approach*

Most behavioural, neurobiological and genetic research has approached autism categorically. However, over the years, a number of researches have suggested that autism may be better understood by examining the component behavioural and cognitive abnormalities. McBride et al.[2] propounded a dimensional approach to understanding autism proposing that the various impaired components must be considered individually and that there should be equal consideration given to the interaction between these domains.

- *Autism Continuum*

Studies suggest that autistic like symptoms fit to a multivariately distributed dimensional trait than to a categorical entity. Many researchers have argued for an autistic continuum without sharp boundaries between an autistic core group and other PDD remainder groups rather than for a sharp cut off between these groups[3-6]. In this continuum, multiple and interacting biological and group influences are believed to determine the severity of impairment. According to Wing[7], autistic continuum is characterized by a set of three features with a strong tendency to cluster together, known as triad of impairments :

1. Impairments of reciprocal social interaction
2. Verbal and non verbal communication
3. Imagination (identified as being closely related to the narrow, rigid, repetitive pattern of behaviour). Within this concept of an autistic continuum there is little evidence to suggest where the cut off from normality actually falls. There is evidence from family studies of an elevated risk for social, communication, and repetitive impairments among relatives of probands with autism. The social difficulties are

qualitatively similar to, although, milder, than those who typify autism and are sometimes apparent in childhood[8]. This poses a risk of the diagnosis of autism being extended to include any individual with minimal behavioural anomalies pertaining to the impairment triad creating diagnostic over inclusion[6] .

- *Autism Spectrum*

The severity of autism's deficits is extremely variable. In view of the above stated limitations of autism continuum, many researchers have argued for the existence of autism spectrum rather than an autism continuum. The term "Autism continuum" suggests a simple straight line from mild to severe. With respect to autistic disorders, the situation seems to be more complex as the manifestations of the impairment triad vary widely in type and severity; with varied combinations. Some of these combinations have been identified to be specific syndromes. Many other combinations have not yet been assigned a separate syndrome status. The term "Spectrum" is used to indicate the fact that although there is a common denominator, different types of children with a PDD present with their own pattern of symptoms. That is, patients differ by nature of symptoms and not just by degree[9]. Therefore, the term autism spectrum disorders (ASDs) is appropriate because it denotes a bell shaped curve of impairment. The DSM-IV TR[1] and ICD-10 refer to the autism spectrum as pervasive developmental disorders (PDD) and refer to autistic disorder (AD; widely shortened to autism in the literature) as the classic, more severe end of the distribution.

Autism Spectrum Disorder: Nosological status

There is evidence that only certain disorders can be included in ASD. Three PDDs are typically considered ASDs: Autism, Asperger's disorder, and PDD not otherwise specified (PDD NOS) [11]. The ICD-10, in addition to these three also includes Rett's Syndrome and Childhood Disintegrative disorders.

The scientific committee for DSM-V has proposed new category, Autism Spectrum Disorder, which is proposed to include Autistic disorder (autism), Asperger's disorder, Childhood disintegrative disorder, and Pervasive Developmental Disorder Not Otherwise Specified (PDD NOS). For the diagnosis of ASD it is proposed that the child must meet criteria 1, 2, and 3:

1. Clinically significant, persistent deficits in social communication and interactions, as manifest by all of the following:
   a. Marked deficits in nonverbal and verbal communication used for social interaction:
   b. Lack of social reciprocity;
   c. Failure to develop and maintain peer relationships appropriate to developmental level
2. Restricted, repetitive patterns of behavior, interests, and activities, as manifested by at least TWO of the following:
   a. Stereotyped motor or verbal behaviors, or unusual sensory behaviors
   b. Excessive adherence to routines and ritualized patterns of behavior
   c. Restricted, fixated interests
3. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities)

It was stressed that a single spectrum disorder is a better reflection of the current state of knowledge about neurobiology, pathology and clinical presentation. Differentiation of ASD from typical development and other "non-spectrum" disorders is done reliably and with validity; while distinctions among disorders have been found to be inconsistent over time, variable across sites and often associated with severity, language level or intelligence rather than features of the disorder. Because autism is defined by a common set of behaviors, it is best represented as a single diagnostic category that is adapted to the individual's clinical presentation by inclusion of clinical specifiers (e.g., severity, verbal abilities and others) and associated features (e.g., known genetic disorders, epilepsy, intellectual disability and others.)

The symptomatology can be grouped into two domains, as deficits in communication and social behaviors are inseparable and more accurately considered as a single set of symptoms with contextual and environmental specificities. Also delays in language are neither unique nor universal in ASD and are more accurately considered as a factor that influences the clinical symptoms of ASD,

rather than defining the ASD diagnosis.

Requiring two symptom manifestations for repetitive behavior and fixated interests was considered to improve the specificity of the criterion of DSM-IV without significant decrements in sensitivity. The presence, via clinical observation and caregiver report, of a history of fixated interests, routines or rituals and repetitive behaviors can considerably increase the stability of ASD over time and the differentiation between ASD and other disorders.

Rett's Disorder patients often have autistic symptoms for only a brief period during early childhood, so inclusion in the autism spectrum is not currently being considered appropriate for most individuals. ASD is proposed to be defined by specific sets of behaviors and not by etiology hence Rett's Disorder is being proposed to be excluded from ASD.

CDD was included in DSM-IV in order to encourage research. However, previous data had indicated that CDD is a rare condition, (prevalence of 2/100,000)[12] and that regression is not a dichotomous phenomenon[13] and that many children with autism undergo a loss of skills at one time or another, but that this can occur in the setting of previously typical development or superimposed on an already aberrant developmental trajectory[14]. Careful review of the current criteria demonstrates that there is ambiguity which can make it difficult for practitioners to separate these two entities, particularly with respect to regressions between the second and third year of life.

Review of cases in the published literature did not support the idea that CDD was a distinct disorder from regressive autism. Specifically, in several cases it was difficult to make the distinction between autism and CDD due to age overlap of regression occurring between ages two and three [15-16]. In addition, in some cases a diagnosis was difficult to make because of lack of proof for typical development before regression[17]. Several cases were reported to include onset of psychotic symptoms[17] or symptoms that abated (and/or developmental skills regained) within a short time frame with appropriate treatment[18]. In addition, studies that have compared individuals diagnosed with CDD to those diagnosed with autism (and regression) have not found No substantial differences in a variety of outcome measures between them have been reported[19]. These data suggest that CDD is not separate enough from autism to sustain its own diagnosis.

Although all ASDs involve impairments in reciprocal social interaction skills, the degree of impairment in communication skills and cognitive abilities and the form disorder is associated with a slightly different set of diagnostic criteria as described in this article.

Autism

Autistic Disorder is also known as infantile autism, childhood autism and early infantile autism. Current diagnostic criteria for autism specify multiple impairments in social functioning and communication as well as restricted and repetitive behavior present before the age of 3 years [20-21].

The manifestations of this disorder vary greatly in terms of the degree of impairment, ranging from early estimates of 75% of individuals having comorbid mental retardation [to recent reviews suggesting as few as 30% to 60% of individuals with this specific comorbidity[22]. People with autism experience substantial social impairments that have an impact on almost every aspect of their interactions with others. Peer interactions are often avoided, and play behaviors often remain stereotypic and lacking in pretense. Even within the first 12 to 18 months of life, difficulties in joint attention, social responsiveness, and eye contact are noted and have been confirmed by retrospective videotaped studies[23]. These social impairments contribute greatly to subsequent language delays by dramatically limiting the number of meaningful learning opportunities during a critical developmental period. Moderate to profound language impairments typically are the first symptoms to draw the pediatrician's notice. Many children with autism fail to develop language at all unless dramatic intervention procedures are pursued[24]. Restricted and repetitive behaviors occur more commonly in older preschool- and school-aged children than in young children or adolescents and adults] and commonly include hand flapping, toe walking, and rocking [25].

Asperger's disorder

The criteria for Asperger's disorder share some

similarities with autism. To qualify for a diagnosis of Asperger's disorder, an individual must demonstrate at least two characteristic criteria in the area of impaired social interaction and one characteristic criterion in the area of restricted, repetitive, and stereotyped patterns[20]. Individuals with Asperger's disorder do not have clinically significant delays in language skills, cognitive development, or age-appropriate self-help skills or adaptive behavior.[20] In fact, individuals with Asperger's disorder are often verbally fluent and have above-average intelligence in many areas, whereas clear deficits and learning disabilities may be evident in other areas[26]. Finally, developmental milestones are often within normal to advanced limits; thus, identification of these children typically occurs at a later age as difficulties develop on entry into preschool or daycare or into general education environments[26]. The work group of DSM-V has recommended to subsume Asperger's disorder into ASD.A number of published papers have argued that the DSM-IV Asperger's disorder criteria did not work in the clinic[27]. 'Asperger's syndrome'(as defined in DSM-IV) was used loosely with little agreement: For example, a survey of 466 professionals reporting on 348 relevant cases, showed 44% of children given Asperger's, PDD-NOS, atypical autism, or 'other ASD' label actually fulfilled criteria for Autistic Disorder (overall agreement between clinician's label and DSM-IV criteria; Kappa 0.31).[28] Research suggests early language criteria do *not* demarcate a distinct subgroup with different course/outcome, cause/aetiology, neuro-cognitive profile and treatment needs/response. Current research suggests that Asperger disorder is part of the autism spectrum, although with possible over-use of the term it is quite likely that other (non-ASD) types of individuals have received this label. Asperger disorder may

1. Not be substantially different from other forms of 'high functioning' autism (HFA)
2. May be distinct from other subgroups within the autism spectrum[29].

There is no strong, replicated support for new or modified criteria likely to distinguish a meaningfully different group with Asperger disorder versus autism with good (current) language and IQ perhaps more comprehensive review concludes Reviews suggest that there is little evidence that Asperger's is distinct, and that *current IQ* is the main differentiating factor[30]. Bennett et al's[31] follow-up study suggests that *language impairment* at 6-8years might have greater prognostic value than early language milestones, and Szatmari et al[32] argue (on the basis of later developmental trajectory) for a distinction between ASD with (autism) versus without (Asperger's) structural language impairment at 6-8 years.

Rett's Syndrome

This is a progressive condition that develops after some months of apparently normal development including normal perinatal head circumference. However, between five months to forty eight months (usually between six months to one year), head growth begins to decelerate followed by a loss of hand skills and appearance of midline stereotypic hand wringing movements or hand washing stereotypies.

Once established, the disorder contains autistic features, such as impairments in social interactions, communication; and stereotyped behaviours. However, Rett's disorder has enough distinguishing features to be considered an independent diagnostic entity. For instance, the course of the disorder is different from autism; with Rett's disorder progressing to various forms of neurological impairments that are not seen in autism.

Childhood Disintegrative Disorder (CDD)

CDD is a rare condition characterized by: 1) onset of condition after a fairly prolonged period of normal development; and 2) marked deterioration in multiple developmental areas accompanied by development of various "autistic like features". Children with CDD clearly resemble autistic children of the same intellectual leveling terms of their behaviour, limited communication skills, pattern of long term outcome, and the need for various special services. Although available data are limited, the disorder has been reported to be quite rare[33]. A prevalence estimate of 1 in 1,00,000 children has been suggested. More recent data suggest a preponderance of the condition in boys.

Pervasive developmental disorder not otherwise specified

A diagnosis of PDD-NOS is used for milder problems on the spectrum when an individual

displays a severe impairment in the development of reciprocal social interaction associated with verbal or nonverbal communication skills or with the presence of stereotyped behavior, interests, and activities but without meeting criteria for another PDD[20].

Differential Diagnosis

The rigorous phenotyping of autism or phenotyping subgroups of children who have autism is essential. At a clinical level, there are many signs and symptoms of autism that also occur in other developmental disorders. Table 1 outlines some of the most salient diagnostic features that differentiate the diagnosis of ASDs from other developmental disorders. One feature that differentiates autism from other developmental disorders is the social deficit. Although autism remains a clinical diagnosis, studies that use standardized criteria can home in on the neurobiology with much greater precision. In addition, outcome can be more clearly studied and interventions compared.

Table 1. Summary of Useful differential diagnostic features of ASDs with other developmental disorders

ASDs	Other Developmental Disorders
Language impairment	**Developmental language disorders**
• Pragmatics (language use, conversational skill) and prosody universally impaired. • Semantics (word choices) often unusual. • Grammar and speech articulation impaired in a minority of children; others may speak fluently and grammatically but with abnormal features. • Abnormal features salient (e.g., echolalia, scripts, perseveration, incessant questioning, answering besides the point frequent) • Comprehension may be worse than expression; often specific difficulty answering questions to which they know the answer	• Pragmatics spared, try to communicate any available way • Vocabulary impoverished • Mostly, grammar and speech articulation impaired. In severe cases, speech is sparse, effortful, poorly intelligible. • Abnormal features unusual; perseveration in some cases of OCD • Comprehension usually equal to orsuperior to expression, may be normalfor age in expressive language subtypes
Attention and sleep	**ADHD/ADD and sleep**
• Most troublesome is impaired joint attention • Attention may be long for self-selected activities • Impulsivity reflects poor judgment • Multiple sleep awakenings, poor consolidation of circadian sleep cycle	• Inattention is ubiquitous but variable • Restlessness, fidgetiness in ADHD • Impulsivity, especially in ADHD • Decreased need for sleep, difficulty falling sleep, early awakenings
Sensorimotor issues	**Tics/Tourette's syndrome, OCD**
Stereotypies (repetitive purposeless rhythmic movements) frequent, especially in low-functioning children Decrease in number and amplitude with age in high, not low-functioning children Increased and decreased responses tosensory stimuli in any or all modalities Self-injury frequent, especially in low functioning Children	Tics: more rapid and irregular; may be simple or complex. Preceded by an urge, followed by relief; compulsive touching in Tourette's and OCD varies over time Not a feature except in severe mental retardation (in which low-functioning autism might be the correct diagnosis)

ADD : attention-deficit disorder; ADHD : attention-deficit/hyperactivity disorder; OCD : obsessive-compulsive disorder.

Neurobiology

Among the many areas of progress in unraveling the neurobiology of autism spectrum disorders, the research in genetics, immunology, imaging, and electrophysiology are discussed.

Genetics

Autism is highly heritable, yet most (perhaps 80%–90%) of affected individuals are the only affected members of their families, usually with no explanation for their condition Some of the remaining 10% to 20% have a plausible non genetic cause such as intrauterine rubella[34] or cytomegalovirus[35]. A few have a chromosomal abnormality; for example, an alteration in chromosome number or a balanced or unbalanced duplication, deletion, or translocation microscopically visible on banded preparations[36].

In some families, autism is but one symptom of a defined mitochondrial[37] or mendelian disorder expressed in the brain, such as fragile X[38] or tuberous sclerosis[39]. Thus, although a large variety of diagnosable disorders have been associated with autism (some in very few individuals or families), each disorder is rare, and by no means do all individuals who have that condition have autism.

Whole-genome searches using newly developed comparative microarray techniques applied to large samples of rigorously diagnosed unaffected control subjects and probands in families that have several affected members (multiplex families), in families that have only one affected member, and in monozygotic and dizygotic twins have identified several recurrent single-stranded DNA micro deletions, micro duplications, or other gene rearrangements[40]. Deletions or duplications at 16p11.2 fragile site have been found in approximately 1% of three different populations of individuals who have autism[41-43]. These gene copy number variations (CNVs) are dominantly heritable, most arise from new (de novo) mutations and may be more numerous in autism than in the general population. Most CNVs are found only de novo in the probands, not in the patient's parents. Therefore, one is justified in assuming that the mutation occurred in the gonad of one or the other CNV-negative parent who passed it on to the affected offspring but who is at vanishingly low risk of having another affected child. Which parent is more likely to have undergone the mutation is disputed, some studies implicating older fathers on the basis of the life-long turnover of sperm[44].

For reasons yet to be determined, CNVs are transmitted to 50% of male offspring, as expected from a highly penetrant dominant mutation, but to only 20% to 30% of female offspring, which explains well-documented male-to-male transmission in some families[44]. This sex-skewed transmission contributes to, but does not fully account for, the preponderance of male patients and probably multiple genes interact in its causation. CNV deletions and duplications suggest that the breakage site inactivates one or more non-coding regulatory genes, resulting in the silencing of one or more other genes.

Evidence implicates potent posttranslational environmental or epigenetic editing of the genome to be an important contributing factor. Epigenetics refers to stable heritable or potentially heritable post mitotic alterations in gene expression that do not entail a change in nucleotide sequences[45]. Among non coding RNAs, micro RNAs (miRNAs), only approximately 22 nucleotides long, make a major contribution to RNA editing in post mitotic neurons, their exquisite sensitivity to environmental stimuli regulates neural transmission[46] and alter individual genetically determined risk factors for diseases In autism the multiple gene interactions and environmental epigenetic influences on the expression of each individual's genome plays a crucial role. Consequently, unless a known gene defect with a defined inheritance pattern and predictable phenotype is detected, only general risk factors can be provided to families and, even then, prediction of the severity of the expected phenotype is often uncertain.

Immunology

33 % parents report the occurrence of language regression or a developmental plateau associated with loss of sociability in their child between approximately 12 to 30 months of age, usually with no known trigger. The retrospective finding of elevated levels of certain cytokines in the cord bloods of infants who were later diagnosed as autistic with or without cognitive impairment or as mentally retarded without autism (but not in the bloods of normal children or of those who have

cerebral palsy) supported covert intrauterine inflammation as a potential causative factor[47]. The widespread activation of microglia and astrocytes (part of the innate immune system) found in 11 brains of individuals aged 4 to 44 years who had autism (but not found in control subjects) implicated inflammation as a contributory factor[48]. No evidence of T- or B-lymphocytic infiltration was noticed in these brains which suggest activation of the adaptive immune system.

The potential role in autism of genetic risk factors for covert infection or autoimmune inflammatory factors has been investigated for over a decade. There are reports of linkage of autism to several classes of HLA genes.[49-51] A survey in the families of affected children indicated a higher prevalence of autoimmune disorders like rheumatoid arthritis, lupus, and thyroiditis compared with control families[52], a finding not corroborated in another study[53]. Raised levels of brain-specific auto-antibodies were reported in the sera of children who had autism[54-55]. The contribution of elevated cytokines, antigens, antibodies, and other evidence for dysregulation of the immune system in particular subtypes of autism are subjects of active investigation in humans and animal models; but no coherent evidence has emerged emerge.

Brain Imaging

The pathology and the imaging of autism over the years have implicated numerous brain structures, including the frontal lobes, amygdala, and cerebellum[56], cortical white matter[57], and a tendency toward unusually large brains in young autistic children, with later growth deceleration[58]. An area of interest in imaging is mapping regions of the brain relevant to social competence.

Functional MRI (fMRI) studies done with paradigms to investigate the ''social brain'' suggest the involvement of networks that include, in particular, the orbitofrontal cortex, superior temporal gyrus, and amygdala. fMRI studies suggest that individuals who have autism activate frontotemporal regions, but not the amygdala, when making mentalistic inferences from the eyes, as opposed to typical individuals who activate the superior temporal gyrus, amygdala, and parts of the prefrontal cortex[59]. Presented with stimuli of varying fearfulness, typical individuals activate the left and right amygdala differentially, but those who have high-functioning autism or Asperger's syndrome do not[60].

Perception of facial expression and facial recognition is linked to the fusiform area of the ventral temporal lobe[61]. This linkage and that of the amygdala in emotional processing suggest that deficits in the amygdala–fusiform network may underlie the social cognitive impairments characteristic of individuals who have ASDs. Four lines of evidence strongly implicate dysfunction in multiple networks as a basis for autism's social cognitive impairments. This includes: alterations in neocortical mini columns in the frontal and temporal lobes[63], abnormal trajectory of head growth, atypical fMRI activation, and diffusion tensor imaging of white matter tracts during early development[64]. The current working model, supported by imaging studies, is the brain under connectivity model[65].

Electrophysiology

Children who have isolated language regression are more likely to have epileptiform activity on their EEGs than children who undergo language regression within the context of a broader autistic regression. 52 The current clinical recommendation is to obtain an EEG in children who have epilepsy or when epilepsy is suspected clinically but not in every child who has autism with or without language regression. In children who have autism, automatic discrimination of infrequent changes in tonal stimuli matures later than in control subjects; detection required active attention until age 9 years compared with its automaticity from age 4 years in control subjects[66]. Such low-level auditory processing deficits have a likely impact in the development of language skills.

There is preliminary electrophysiologic data linking the EEG—specifically, frequency (8–13Hz) wave suppression—to specific imitation skills in children who have autism[67-68]. Magnetoencephalography (MEG) has shown auditory processing deficits in children who have autism and deficient language[69]. High-frequency EEG rhythms in the gamma range (30–100 Hz) are thought to be of importance in perceptual and cognitive processes and in intersensory synchronization and binding[70].

Using MEG and a steady-state auditory stimulus, children and adolescents who have autism, found that the production or maintenance of left-hemispheric gamma oscillations as abnormal [71]. It has been hypothesized that the high-frequency EEG rhythms found in some children who have autism may reflect an imbalance in the excitation–inhibition homeostasis of their brains[72]. The developmental dysfunction of GABA transmitting interneurons, minicolumn abnormalities mentioned earlier, and gamma rhythm abnormalities suggest that the socio-cognitive deficits found in ASDs may be reflections of abnormal development of neuronal network connectivity[73]. Investigators using quantitative EEG in children who have ASDs have demonstrated impaired integration of frontal and posterior brain regions suggestive of a pattern of neural underconnectivity[74]. Electrophysiologic and imaging technologies are defining the neural networks and interconnectivities that underlie the complex deficits that characterize ASDs.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition [text revision]. Washington, DC: American Psychiatric Association; 2000.
2. McBride PA, Anderson GM, Shapiro T. Autism research: bringing together the researches to pull apart the disorder. Arch Gen Psychiatry, 1996; 53 : 980-983.
3. Waterhouse L, Wing L, Fein D. Re-evaluating the syndrome of autism in the light of empirical research. In: Dawson G, editor. Autism: nature, diagnosis and treatment. New York: Guilford Press; 1989, pp 263-81.
4. Myhr G. Autism and other pervasive developmental disorders: exploring the dimensional view. Can J Psychiatry 1998, 43: 589-595.
5. Wing L. The continuum of autistic characteristics. In Schopler E, Mesibov G, editors. Diagnosis and assessment in autism. New York: Plenum Press; 1988. pp91-110.
6. Berney TP. Autism : an evolving concept. Br J Psychiatry 2000, 176 : 20-25.
7. Wing L, Gould J. Severe impairments of social interaction and associated abnormalities in children: epidemiology and classification. J Autism Dev Disord 1979, 9: 11-29.
8. Bailey A, Palferman S, Heavey L. Autism : the phenotype in relatives. J Autism Dev Disord 1998; 28 : 369-391.
9. Van der Gaag RJ, Buitelaar J, Van dr Ban E. A controlled multivariate chart review of multiple complex developmental disorders. J Am Acad Child Adolesc Psychiatry 1995, 34 : 1096-106.
10. Ghosh S. Diagnosis of Autism Spectrum Disorders : A Combined fMRI-DTI Perspective. Delhi Psychiatry J 2009; 2 : 291-296.
11. Volkmar FR, Lord C, Bailey A, et al. Autism and pervasive developmental disorders. J Child Psychol Psychiatry 2004; 45 : 135–70.
12. Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res 2009, 65: 591-8.
13. Ozonoff S, Heung K, Byrd R, Hansen R, Hertz-Picciotto I. The onset of autism: patterns of symptom emergence in the first years of life. Autism Res 2008; 1 : 320-8.
14. Ozonoff S, Williams B, Landa R. Parental report of the early development of children with regressive autism: the delays-plus-regression phenotype. Autism 2005, 9 : 461.
15. Malhotra S, Gupta N. Childhood disintegrative disorder. Re-examination of the current concept. Eur Child Adolesc Psychiatry 2002, 11 : 108-14.
16. Volkmar FR, Rutter M. Childhood disintegrative disorder: results of the DSM-IV autism field trial. J Am Acad Child Adolesc Psychiatry 1995, 34 : 1092-5.
17. Agarwal V, Sitholey P, Mohan I. Childhood Disintegrative Disorder, an atypical presentation: a case report. J Autism Dev Disord 2005, 35 : 873-4.
18. Mordekar SR, Prendergast M, Chattopadhyay AK, Baxter PS. Corticosteroid treatment of behaviour, language and motor regression in childhood disintegrative disorder. Eur J Paediatr Neurol 2009, 13 : 367-9.
19. Kurita H, Koyama T, Osada H. Comparison of childhood disintegrative disorder and disintegrative psychosis not diagnosed as childhood disintegrative disorder. Psychiatry Clin Neurosci 2005, 59 : 200-5.
20. Bartak L, Rutter M. Differences between mentally retarded and normally intelligent

autistic children. J Autism Childhood Schiz 1976, 6 : 109-120.
21. Tidmarsh L, Volkmar FR. Diagnosis and epidemiology of autism spectrum disorders. Can J Psychiatry 2003; 48 : 517–25.
22. Fombonne E. Epidemiological surveys of autism and other pervasive developmental disorders: an update. J Autism Dev Disord 2003; 33 : 365–82.
23. Osterling JA, Dawson G, Munson JA. Early recognition of 1-year-old infants with autism spectrum disorder versus mental retardation. Dev Psychopathol 2002; 12 : 239–51.2.
24. Lovaas OI. Behavioral treatment and normal educational and intellectual functioning in young autistic children. J Consult Clin Psychol 1987; 55 : 3–9.
25. Lord C, Pickles A, McLennan J, et al. Diagnosing autism: analyses of data from the autism diagnostic interview. J Autism Dev Disord 1997; 30 : 205–23.
26. Klin A, McPartland J, Volkmar FR, et al. Asperger syndrome. In: Volkmar FR, Paul R, Klin A, editors. Handbook of autism and pervasive developmental disorders, vol. 1. 3rd edition. Hoboken (NJ): Wiley; 2005. p. 88–125.
27. Mayes SD, Calhoun SL, Crites DL. Does DSM-IV Asperger's disorder exist? J Abnorm Child Psychol 2001; 29 : 263–271.
28. Williams K, Tuck M, Helmer M, Bartak L, Mellis C, Peat JK. Diagnostic labelling of autism spectrum disorders in NSW. J Paed Child Health 2008; 4 : 108-113.
29. Matson JL, Wilkins J. Nosology and diagnosis of Asperger's syndrome. Res Autism Spectrum Disord 2008; 2 : 288-300.
30. Witwer AN, Lecavalier L. Validity of autism spectrum disorder subtypes. J Autism Develop Disord 2008; 38 : 1611–1624.
31. Bennett TA, Szatmari P, Bryson SE, Volden J, Zwaigenbaum L, Vaccarella L, Duku E, Boyle MH. Differentiating autism and Asperger syndrome on the basis of language delay or impairment. J Autism Develop Disord 2008; 38 : 616–625.
32. Szatmari P, Bryson S, Duku E, Boyle MH. Similar developmental trajectories in autism and Asperger's syndrome: from early childhood to adolescence. J Child Psychol Psychiatry 2009; 50 (12) : 1459-67.
33. Volkmar FR. Childhood Disintegrative Disorder: issues for DSM –IV. J Autism Dev Disord 1992; 22 : 625-42.
34. Chess S. Autism in children with congenital rubella. J Autism Child Schizophr 1971; 1(1) : 33–47.
35. Sweeten TL, Posey DJ, McDougle CJ. Brief report: autistic disorder in three children with cytomegalovirus infection. J Autism Dev Disord 2004; 34(5) : 583–6.
36. Bugge M, Bruun–Petersen G, Brondum–Nielsen K, et al. Disease associated balanced chromosome rearrangements: a resource for large scale genotype-phenotype delineation in man. J Med Genet 2000; 37(11) : 858–65.
37. Lepagnol–Bestel AM, Maussion G, Boda B, et al. SLC25A12 expression is associated with neurite outgrowth and is upregulated in the prefrontal cortex of autistic subjects. Mol Psychiatry 2008; 15 : 2541–51.
38. Hagerman RJ, Ono MY, Hagerman PJ. Recent advances in fragile X: a model for autism and neurodegeneration. Curr Opin Psychiatry 2005; 18(5) : 490–6.
39. Asano E, Chugani DC, Muzik O, et al. Autism in tuberous sclerosis complex is related to both cortical and subcortical dysfunction. Neurology 2001; 57(7) : 1269–77.
40. Zhao X, Leotta A, Kustanovich V, et al. A unified genetic theory for sporadic and inherited autism. Proc Natl Acad Sci U S A 2007; 104(31) : 12831–6.
41. Weiss LA, Shen Y, Korn JM, et al. Association between microdeletion and microduplication at 16p11.2 and autism. N Engl J Med 2008; 358(7) : 667–75.
42. Kumar RA, Kara Mohamed S, Sudi J, et al. Recurrent 16p11.2 microdeletions in autism. Hum Mol Genet 2008; 17(4) : 628–38.
43. Sebat J, Lakshmi B, Malhotra D, et al. Strong association of de novo copy number mutations with autism. Science 2007; 316(5823) : 445–9.
44. Reichenberg A, Gross R, Weiser M, et al. Advancing paternal age and autism. Arch Gen Psychiatry 2006; 63(9) : 1026–32.
45. Jiang YH, Bressler J, Beaudet AL. Epigenetics and human disease. Annu Rev Genomics Hum Genet 2004; 5 : 479–510.

46. Mattick JS, Mehler MF. RNA editing, DNA recoding and the evolution of human cognition. Trends Neurosci 2008; 31(5) : 227–33.
47. Nelson PG, Kuddo T, Song EY, et al. Selected neurotrophins, neuropeptides, and cytokines: developmental trajectory and concentrations in neonatal blood of children with autism or Down syndrome. Int J Dev Neurosci 2006; 24(1) : 73–80.
48. Pardo CA, Vargas DL, Zimmerman AW. Immunity, neuroglia and neuroinflammation in autism. Int Rev Psychiatry 2005; 17(6) : 485–95.
49. Lee LC, Zachary AA, Leffell MS, et al. HLA-DR4 in families with autism. Pediatr Neurol 2006; 35(5) : 303–7.
50. Torres AR, Sweeten TL, Cutler A, et al. The association and linkage of the HLA-A2 class I allele with autism. Hum Immunol 2006; 67(4–5) : 346–51.
51. Warren RP, Odell JD, Warren WL, et al. Strong association of the third hypervariable region of HLA-DR beta 1 with autism. J Neuroimmunol 1996; 67(2) : 97–102.
52. Comi AM, Zimmerman AW, Frye VH, et al. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. J Child Neurol 1999; 14(6) : 388–94.
53. Mouridsen SE, Rich B, Isager T, et al. Autoimmune diseases in parents of children with infantile autism: a case-control study. Dev Med Child Neurol 2007; 49(6) : 429–32.
54. Wills S, Cabanlit M, Bennett J, et al. Autoantibodies in autism spectrum disorders (ASD). Ann N Y Acad Sci 2007; 1107 : 79–91.
55. Connolly AM, Chez M, Streif EM, et al. Brain-derived neurotrophic factor and autoantibodies to neural antigens in sera of children with autistic spectrum disorders, Landau–Kleffner syndrome, and epilepsy. Biol Psychiatry 2006; 59(4) : 354–63.
56. Amaral DG, Schumann CM, Nordahl CW. Neuroanatomy of autism. Trends Neurosci 2008; 31(3) : 137–45.
57. Herbert MR, Ziegler DA, Deutsch CK, et al. Brain asymmetries in autism and developmental language disorder: a nested whole-brain analysis. Brain 2005; 128 (Pt 1) : 213–26.
58. Courchesne E, Redcay E, Kennedy DP. The autistic brain: birth through adulthood. Curr Opin Neurol 2004; 17(4) : 489–96.
59. Baron–Cohen S, Ring HA, Wheelwright S, et al. Social intelligence in the normal and autistic brain: an fMRI study. Eur J Neurosci 1999; 11(6) : 1891–8.
60. Ashwin C, Baron–Cohen S, Wheelwright S, et al. Differential activation of the amygdala and the 'social brain' during fearful face-processing in Asperger syndrome. Neuro-psychologia 2007; 45(1) : 2–14.
61. Schultz RT, Grelotti DJ, Klin A, et al. The role of the fusiform face area in social cognition: implications for the pathobiology of autism. Philos Trans R Soc Lond B Biol Sci 2003; 358(1430) : 415–27.
62. Schultz RT. Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. Int J Dev Neurosci 2005; 23(2–3) : 125–41.
63. Casanova MF, Buxhoeveden DP, Switala AE, et al. Minicolumnar pathology in autism. Neurology 2002; 58(3) : 428–32.
64. Courchesne E, Pierce K, Schumann CM, et al. Mapping early brain development in autism. Neuron 2007; 56(2) : 399–413.
65. Minshew NJ, Williams DL. The new neurobiology of autism: cortex, connectivity, and neuronal organization. Arch Neurol 2007; 64(7) : 945–50.
66. Dunn MA, Gomes H, Gravel J. Mismatch negativity in children with autism and typical development. J Autism Dev Disord 2008; 38(1) : 52–71.
67. Oberman LM, Ramachandran VS, Pineda JA. Modulation of mu suppression in children with autism spectrum disorders in response to familiar or unfamiliar stimuli: the mirror neuron hypothesis. Neuropsychologia 2008; 46(5) : 558–65.
68. Oberman LM, Hubbard EM, McCleery JP, et al. EEG evidence for mirror neuron dysfunction in autism spectrum disorders. Brain Res Cogn Brain Res 2005; 24(2) : 190–8.
69. Roberts TP, Schmidt GL, Egeth M, et al. Electrophysiological signatures: magneto-encephalographic studies of the neural correlates of language impairment in autism spectrum disorders. Int J Psychophysiol 2008.

70. Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 2006; 52(1) : 155–68.
71. Wilson TW, Rojas DC, Reite ML, et al. Children and adolescents with autism exhibit reduced MEG steady-state gamma responses. Biol Psychiatry 2007; 62(3) : 192–7.
72. Orekhova EV, Stroganova TA, Nygren G, et al. Excess of high frequency electroencephalogram oscillations in boys with autism. Biol Psychiatry 2007; 62(9) : 1022–9.
73. Levitt P. Disruption of interneuron development. Epilepsia 2005; 46(Suppl 7) : 22–8.
74. Coben R, Clarke AR, Hudspeth W, et al. EEG power and coherence in autistic spectrum disorder. Clin Neurophysiol 2008; 119(5) : 1002–9.