Autism
Autism
Oxidative Stress, Inflammation, and Immune Abnormalities

Edited by
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This book is dedicated to the children and adults who have Autism spectrum disorders, to the family members and health care professionals who provide care for them, and to the scientists and sponsoring agencies devoted to research on autism and related disorders.
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Preface

Autism spectrum disorders (ASD) are a group of behaviorally defined neurodevelopmental disorders characterized by deficits in social interaction; impairments in verbal and nonverbal communication; and restricted, stereotyped patterns of behaviors and interests. In 2007, the Centers for Disease Control and Prevention issued an “autism alarm,” with 1 in 150 children estimated to be affected by ASD. Epidemiological studies suggest that more than 1.5 million people in the United States are affected with this disorder. Autism is the most severe disorder in the broad spectrum of pervasive developmental disorders (PDDs), which also include Asperger’s syndrome, Rett’s disorder, childhood disintegrative disorder, and PDD-not otherwise specified. Within this spectrum, there are variations in the severity, level of cognitive functioning, the presence or absence of associated medical conditions such as seizures or other neurological disorders, and whether or not there is a history of regression from apparent normal development. Currently, there is no biochemical or genetic marker to support the behavioral diagnosis of autism.

Autism is a heterogeneous disorder, both etiologically and phenotypically. While the cause of autism remains elusive, autism is considered a multifactorial disorder that is influenced by genetic, epigenetic, and environmental factors. Accumulating evidence from our studies and that of other groups suggests that oxidative stress may be a common feature in autism linking the mechanism through which the environmental factors exert their deleterious effects with the purported genetic alterations in autism. The oxidative stress and intracellular redox imbalance can be induced or triggered in autism by prenatal or postnatal exposure to certain environmental factors such as heavy metals, viruses, bacterial infections, air pollutants, toxins, valproic acid, thalidomide, terbutaline, retinoic acid, and ethanol. Genetic factors can also modulate the threshold for vulnerability to oxidative stress in autism. In addition to behavior impairments, some individuals with autism may have a higher prevalence of gastrointestinal (GI) disturbances. Several studies suggest that inflammatory phenomena, immune dysregulation, and certain autoimmune risk factors may also contribute to the development and pathogenesis of autism. The chapters in this book provide a comprehensive overview of neuropathological abnormalities, genetics, oxidative stress, inflammation, immune dysfunction, aberrant cellular signaling, gene–environment interactions, diagnostic tools, and treatment in autism.

In Chapter 1, Jerzy Wegiel and colleagues review neuropathological changes in autism contributing to the clinical phenotype. These changes include (a) pathological acceleration of brain growth in early childhood, (b) developmental heterochronicity with different rates of growth for different brain regions/structures, (c) brain structure–specific delay of neuronal growth in early childhood and partial correction of cell size in late childhood/adulthood, and (d) regional cytoarchitectonic abnormalities with consistent changes of structure of minicolumns, and variable topography and severity of dysplastic changes and ectopias. These developmental abnormalities are paralleled by signs of metabolic changes with modified expression and processing.
of β-amyloid precursor protein, enhanced turnover of cell organelle and pigment accumulation, as well as oxidative stress.

Under normal conditions, a dynamic equilibrium exists between the production of reactive oxygen species (ROS) and the antioxidant capacity of the cell. Oxidative stress occurs when ROS levels exceed the antioxidant capacity of a cell. These ROS are highly toxic and oxidize vital cellular components such as lipids, proteins, and DNA, thus causing cellular damage and subsequent cell death via apoptosis or necrosis. Oxidative stress is known to be associated with premature aging of cells and can lead to inflammation, damaged cell membranes, autoimmunity, and cell death. In this book, several chapters present evidence that support the concept of oxidative stress in autism.

The brain is highly vulnerable to oxidative stress because of its limited antioxidant capacity, higher energy requirement, and high amounts of unsaturated lipids and iron. Based on immunocytochemical and biochemical studies, in Chapter 2, Xiongwei Zhu and colleagues demonstrate lipid-derived oxidative protein modifications in postmortem brain samples from autistic subjects and suggest carboxyethyl pyrrole (CEP) and iso[e]levuglandin E2 protein adducts as possible oxidative stress markers for the autistic brain. From a structural perspective, their findings suggest that axons of cholinergic neurons in the white matter are the primary site of oxidative damage. At the molecular level, they have identified neurofilament heavy chain to be the major target for CEP-modification. In Chapter 3, Elizabeth Sajdel-Sulkowska reviews the evidence of oxidative stress–related protein and DNA modifications in autism, and discusses data supporting altered neurotrophin signaling in autism and the possible association between oxidative stress and altered neurotrophin expression. These findings not only support the notion that brain oxidative stress plays an important role in autism but also warrant future in-depth mechanistic studies to provide new targets for therapeutic intervention.

The genetics underlying autism is highly complex, with estimates of heritability at greater than 90%. While no single gene has been found to be associated with autism, multiple genes and interactions between genetic and environmental factors have been postulated in autism. In Chapter 4, Ted Brown reviews this subject. The association of single-gene disorders, such as fragile X syndrome with autism, and the role of copy number variations, noncoding RNAs, parental age, and prenatal environmental stressors, such as exposure to hurricanes in autism, are discussed in this chapter.

Reactive oxygen and nitrogen species are generated endogenously during oxidative metabolism and energy production by mitochondria in the cell. While oxidative phosphorylation in the mitochondria generates superoxide anions, the enzymatic oxidation of biogenic amines by monoamine oxidase (MAO) in mitochondrial outer membrane produces H₂O₂. A functional polymorphism in the monoamine oxidase A (MAOA) promoter region has been reported to be associated with the severity of autism. MAOA catalyzes the oxidation of amine-containing neurotransmitters, such as serotonin and norepinephrine. Several studies suggest that serotonin function is abnormal in autism. In Chapter 5, Ira Cohen reviews evidence on maternal depression and a polymorphism in the MAOA gene affecting the severity of autism using a PDD behavior inventory (PDDBI). He also discusses the advantages of using the PDDBI.
In Chapter 6, Maria Dronca and Sergiu Pașca present evidence for the involvement of paraoxonase 1 (PON1) in the pathogenesis of ASD. PON1, an esterase/lactonase enzyme, plays an important role in hydrolyzing pesticides, protecting against oxidative stress, and modulating the immune/inflammatory response. First, the authors review the general biochemical properties of PON1, with the recent biochemical and genetic studies indicating impaired PON1 status in ASD and the literature suggesting a correlation between pesticide (mainly organophosphates) exposure and neurodevelopmental delays or neuropsychiatric conditions. Second, the authors describe several gene × environment models for autism, which include PON1: organophosphates exposure × reelin × PON1 and organophosphates exposure × acetylcholine receptor (AchR) × PON1. Finally, they illustrate how PON1 could contribute to the aberrant immune response and abnormal redox status in autism. They also discuss how these disturbances could affect the PON1 status and further increase the susceptibility to various environmental neurotoxic agents during neurodevelopment.

Sulfur metabolism serves a number of critical roles, including the maintenance of cellular redox status and support for several methylation reactions. Methylation capacity is reduced during oxidative stress, affecting many processes such as epigenetic regulation of gene expression, which is critical for development, as well as dopamine-stimulated phospholipid methylation, which is involved in the synchronization of neuronal firing. The unique features of sulfur metabolism in the brain make it highly vulnerable to heavy metals, which bind with high affinity to thiol and selenocysteine oxidoreductases and interfere with redox regulation. Methionine synthase (folate and vitamin B12–dependent enzyme) plays a key role as a monitor of cellular redox status and as a regulator of the flux of homocysteine through transsulfuration to glutathione synthesis. Levels of methionione synthase mRNA are significantly lower in brain samples from autistic subjects, reflecting an adaptive response to neuroinflammation and oxidative stress. These factors allow the formulation of a “redox/methylation hypothesis of autism,” described by Richard Deth in Chapter 7, which outlines a molecular mechanism whereby heavy metals promote oxidative stress and impaired methylation, leading to disrupted development and autism.

In Chapter 8, George Wagner and colleagues describe novel models of autism in which mice are exposed either pre- or post-natally to toxicants such as valproic acid and methylmercury. The early toxicant exposure results in neurodevelopmental deficits in mice that are analogous to deficits observed in humans affected by autism. Evidence that oxidative stress is involved in autism is provided by the ability of pretreatment with antioxidants (trolox, a water-soluble vitamin E derivative) to fully protect the developing mice against the neurobehavioral deficits induced by these toxicants. These observations are discussed in the context of autism prevention.

In Chapter 9, Woody McGinnis and colleagues discuss an interesting hypothesis for the unexplained phenomenon of regression in autism. In their model, visceral dysfunction in autism occurs in conjunction with lost phonation and social function because of selective toxicant effects on a relatively minute region of the brainstem, which is known to remain permeable to a broad class of neurotoxins after the closure of the blood–brain barrier elsewhere. By converging on the same site and sharing oxidative modes of injury, these toxins may act independently, additively, or sequentially to result in autistic regression.
In Chapter 10, Ved Chauhan and I review evidence that ASD are associated with abnormalities in lipid metabolism, membrane-associated proteins, and signal transduction. Phospholipids and their lipid raft domain play important roles in cellular signaling, and phosphoinositides are major signaling molecules in G protein–coupled receptor signaling. We discuss our findings on altered levels of amino-glycerophospholipids in the membrane, increased peroxidation of lipids, decreased membrane fluidity, increased activity of phospholipase A2 (lipid-metabolizing enzyme), and altered activities of protein kinase C and protein kinase A in autism, suggesting that membrane signaling may be affected in autism. We also review the evidence of an association of the phosphatidylinositol 3-kinase gene in autism, altered brain levels of Bcl2 and p53 (involved in apoptosis), altered levels of cytokines and inflammation and mutational changes in the proteins involved in cell signaling such as neurelins, Pten, SHANK3, Wnt, reelin, and voltage-dependent calcium channels, all suggesting impairment in signal transduction in autism. These abnormalities in the signal system may account for some of the structural changes and cognitive deficits in the brains of individuals with autism.

Mitochondria play a major role in ROS generation and cytosolic calcium sequestration, and a primary defect in mitochondrial electron transport and oxidative phosphorylation impairs both processes. Conversely, abnormal calcium signaling will secondarily perturb these mitochondrial functions, as the mitochondria have recently been shown to participate with the endoplasmic reticulum in this important process that governs a wide array of cellular functions. In Chapter 11, Jay Gargus presents a genetic scheme as the basis for the elevated levels of ROS observed in autism, which integrates earlier observations of genetic and functional mitochondrial dysfunction in autism with newer observations of defects in calcium signaling in the disease. Recently, Timothy syndrome, a rare monogenic form of autism, was shown to be a channelopathy caused by a mutation in a calcium channel. In addition, diseases comorbid with autism, such as migraine and seizures, share a channelopathy pathogenesis, strengthening the notion that defects in calcium signaling may be a cardinal aspect of the disorder that may represent a target for novel therapeutics.

Some parents of autistic children report frequent infection, prolonged illness, or chronic sinopulmonary symptoms, which are suggestive of immune abnormalities in autism. Emerging evidence from several independent research groups indicates the role of the immune system and inflammation in the pathogenesis and pathophysiology of ASD. Increased oxidative damage and/or mitochondrial dysfunction can also lead to inflammation because oxidative stress serves as a major upstream component in the signaling cascade involved in the activation of redox-sensitive transcription factors and pro-inflammatory gene expression resulting in an inflammatory response.

Recently, it has become evident that the neuroimmune network is crucial for immune homeostasis and the function of the central nervous system (CNS). In Chapter 12, Carlos Pardo-Villamizar and Andrew Zimmerman review the findings on the activation of neuroglia and the neuroimmune system, as evidenced by neuroinflammation in brains, reactive astrogliosis, activated microglia, and cytokine abnormalities. They also discuss the role of the maternal immune environment and immunogenetic factors in autism.
Innate immunity plays a key role in the neuroimmune network. However, the role of innate immunity in the onset and progression of ASD is not well understood. In Chapter 13, Harumi Jyonouchi reviews immune abnormalities reported in children with ASD, following an overview of innate immunity in the GI tract and the CNS. Finally, the possible impact of innate immunity on neuroimmune interactions in autistic children is discussed. In Chapter 14, Paul Ashwood and colleagues review cell-mediated immune response, autoimmunity, cytokine abnormalities, gut inflammation, and GI dysfunction and suggest a relationship between GI-related immune dysfunction and autistic behaviors. Abnormal immune responses may predispose individuals to frequent infections, adverse reactions to benign environmental factors, and possibly autoimmune conditions, leading to increased oxidative stress.

Oxytocin (OT) is known to be dysregulated in some autistic children. In Chapter 15, Martha Welch and Benjamin Klein offer the hypothesis that autism arises from the dysregulation of a unified gut/brain system rather than originating in the brain alone. They postulate that autism stems from physiological stress, including oxidative stress, which, if unmodulated, triggers a cascade of adverse interrelated autonomic, endocrinological, neurological, and immunological reactions. They review evidence that dysregulated OT levels and signaling pathways downstream of the oxytocin receptor combined with oxidative stress in the gut may dysregulate a unified gut/brain network and be involved in the pathogenesis of a subset of autism. They also discuss a chain of possible cellular events in gut Paneth cells, involving ROS, β-catenin, matrix metalloproteinase-7, prodefensin, and defensin, which could impact various ion channels in enteric neurons and ultimately influence behavior. A possible mechanism for dysregulation of gut/brain signaling under conditions of abnormal OT levels during a time window critical for newborn development is discussed and compared with the same mechanism when modulated by adequate OT levels in normal newborns. Finally, they discuss possible early therapeutic interventions aimed at the OT-related mechanism postulated in this chapter.

Cytokines play an important role in the regulation of inflammatory responses and are involved in the regulation of both innate and acquired immunities. They are often encoded by highly polymorphic genes. Some of these polymorphisms are responsible for quantitative interindividual differences in cytokine production, thereby influencing the relative strength of immune responses. In the last 10 years, evidence has accumulated that increased levels of some pro-inflammatory cytokines are present in the peripheral blood mononuclear cells of children with ASD. In Chapter 16, Fabián Crespo and colleagues suggest that there are phenotypes of the immune system that are predisposed to stronger or weaker inflammatory immune responses, and these phenotypes can manifest from several different combinations of genotypes of different cytokine genes with variable expressions. They propose that certain expression polymorphisms in key cytokine genes may contribute to the etiology or the emergence of autism by predisposing individuals carrying those genotypes (or their mothers) to altered immune activation to certain antigens. The authors also suggest that the maternal immunogenetic makeup may be associated with the fetal pathogenesis of ASD since cytokines are able to cross the placenta.

In Chapter 17, William Johnson and colleagues discuss alleles of maternal genes that act in the mother to contribute to the phenotype of their affected offspring. These
alleles most likely act in the mother during pregnancy to modify the development of the embryo or fetus, for example, brain development in the affected children. Of the 34 reports so far of these maternal alleles, nearly all were in neurodevelopmental disorders, including autism. *HLA-DR4* was originally suspected of being a maternally acting gene allele for autism because its allele frequency was increased in individuals with autism and their mothers, but not their fathers. This has now been confirmed by a case–parent study design. *HLA-DR4* may act in autism by affecting synapse development, by a mechanism including oxidative stress, by a combination of these, or by an as-yet-unknown mechanism.

Chapter 18 is a commentary by Martha Herbert. On the basis of active pathophysiological processes, such as oxidative stress and inflammation in autism, she discusses that the classical autism model, which frames ASD as a genetically determined developmental disorder of the brain whose main manifestation is behavioral alterations, does not predict persistent pathophysiological disturbances in autism. Herbert describes a pathophysiology-centered model of autism, in which it is argued that ASD is not only developmental but also a chronic condition based on active pathophysiology; is not only behavioral but also has somatic and systemic features; is not only genetic but also environmental; and is not a static encephalopathy but is a dynamic, recalcitrant encephalopathy.

The history of the treatment of autism has been dominated by a technical approach mostly highlighted by applied behavior analysis and, to a lesser extent, by psychopharmacology. In Chapter 19, Eric London proposes the utility of using the biopsychosocial method elaborated by George Engel as a conceptual way to treat autism. The implications of these concepts for both research and clinical works are discussed.

I would like to express my gratitude to my coeditors, Drs. Ved Chauhan and Ted Brown, for their help in the review process, and to all the contributors for their chapters. My sincere thanks to CRC Press/Taylor & Francis Group, especially Barbara Norwitz, Patricia Roberson and Jennifer Smith, for their support in compiling and publishing this book. I hope that it will stimulate hypothesis-driven research and be a valuable reference source not only to scientists in the laboratory but also to clinicians and caregivers in the field of autism and related disorders.

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As a National Science Talent Scholar, Dr. Chauhan received her BS (chemistry honors) in 1976 from the University of Delhi, her MS (biochemistry) in 1978 and her PhD in 1982 from the Department of Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh, India. From 1983 to 1984, she worked as a research associate in the Department of Biochemistry at the Mount Sinai School of Medicine, New York. Dr. Chauhan then joined the Department of Neurochemistry at IBR, where she has over 60 publications in the fields of membrane biochemistry, signal transduction, Alzheimer’s disease, and autism.

Currently, Dr. Chauhan’s major interest is to investigate the biochemical and immunological changes associated with autism in blood samples, lymphoblast cell cultures, and postmortem brain samples, particularly as they relate to markers of oxidative stress, inflammatory response, and the function of the immune system. She is also studying the relationship, if any, between these abnormalities and low- or high-functioning autism groups, as well as the severity of behavior deficits and neuropathological abnormalities in autism. She has been awarded research grants as a principal investigator from the Department of Defense, Autism Speaks, and the Autism Research Institute for her work on autism.

In 2008, Dr. Chauhan served as the guest editor of the “Special Issue on Autism Spectrum Disorders” of the American Journal of Biochemistry and Biotechnology (April 2008). She also organized and chaired a colloquium on “Oxidative Stress and Inflammation in Autism Spectrum Disorders” at the American Society for Neurochemistry Meeting in 2009.

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Dr. Chauhan has published more than 70 research articles in peer-reviewed journals. His work includes but is not limited to phospholipid methylation, calcium traversal across bilayers, the role of phosphoinositides in the activation of protein kinase C, lipid and amyloid β-protein interactions, hydrophobic domain formation by fibrillar amyloid β-protein and its regulation by gelsolin, and membrane abnormalities and cellular signaling in autism.
Dr. Chauhan is a member of the editorial board of the *International Archives of Medicine*, an associate editor of the *Journal of Alzheimer’s Disease*, and an associate editor of the “Special Issue on Autism Spectrum Disorders” of the *American Journal of Biochemistry and Biotechnology* (April 2008). He has organized and chaired several national and international symposia on autism.

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Dr. Brown received his BA in 1967, his MA in 1969 and his PhD in biophysics in 1973 from The Johns Hopkins University, Baltimore, Maryland. He received his MD from Harvard Medical School (cum laude) in 1974. He trained in internal medicine in New York City, undertook a fellowship in clinical genetics, and was appointed as an assistant professor of medicine at the New York Hospital-Cornell University Medical Center in 1978. He began research into premature aging syndromes and Down syndrome while on the Cornell Medical School Faculty, and was an attending physician at New York Hospital and a faculty member of Rockefeller University. In 1981, he became the chairperson of the Department of Human Genetics at IBR. In 1991, he was appointed the director of IBR’s Jervis Clinic, and in 2005, he became the director of IBR.

Dr. Brown is the author of more than 300 publications. At IBR, his initial research was on Down syndrome genes. He then focused his research on the fragile X syndrome, which was then newly recognized and is now considered the most common inherited cause of mental retardation. At IBR, he established a DNA diagnostic and molecular laboratory and developed a screening and prenatal testing program for fragile X. He was the first to discover a relationship between autism and the fragile X syndrome. His work on fragile X has ranged from clinical studies relating to phenotype, to family inheritance studies, to mouse model development, and to basic molecular research. His current research focuses on autism genetics and the fragile X syndrome. Dr. Brown is also a recognized world authority on progeria, a rare and tragic disease that affects young children with premature aging. He was instrumental in the discovery of the genetic mutation that causes this disease.

Dr. Brown serves on the editorial board of the *American Journal of Intellectual and Developmental Disability*. He has served on the scientific advisory board for Cure Autism Now, the Progeria Research Foundation, and the National Fragile X Foundation.
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1 Type, Topography, and Sequelae of Neuropathological Changes Shaping Clinical Phenotype of Autism

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1.1 INTRODUCTION

The aim of this chapter is to identify the type, topography, and sequelae of neuropathological changes that contribute to the clinical phenotype of autism. Results of recent magnetic resonance imaging (MRI) and postmortem neuropathological and stereological studies of autism brain suggest a dynamic model of sequential subdivision of age- and brain-specific structural and functional changes. Acceleration of brain growth in the first year of life and deceleration in the second and third years appear to play a pivotal role in the onset of clinical signs of autism (Courchesne and Pierce, 2005b; Courchesne et al., 2001, 2003; Dawson et al., 2007; Dementieva et al., 2005; Gillberg and de Souza, 2002; Redcay and Courchesne, 2005). The range of deviation from the normal trajectory of brain growth may be a factor determining the severity of the disease (Courchesne et al., 2003). Developmental heterochronicity (differential rates of growth of various brain regions compared to controls), resulting in selective overgrowth of some brain
regions, appears to be a key factor determining topography and brain region-specific type of cytoarchitectonic changes (Carper and Courchesne, 2005; Carper et al., 2002; Courchesne et al., 2001; Hazlett et al., 2005; Sparks et al., 2002). Topographic developmental heterochronicity may result in impairment of both local and global connectivity, leading to local overconnectivity and impairment of long-distance connectivity (Baron-Cohen, 2004; Casanova et al., 2006; Courchesne and Pierce, 2005a). Stereological studies have revealed neuronal developmental heterochronicity in early childhood, resulting in selective developmental delay of the growth of neurons in some subcortical structures and the cerebellum during the most critical stage of development of social behaviors and communication skills (Wegiel et al., 2008). Distortions of brain and neuronal development are reflected in abnormal cortical minicolumn organization (Casanova et al., 2002, 2006), local dysgenesis, and ectopias (Bauman and Kemper, 1985; Bauman et al., 1997; Kemper and Bauman, 1993, 1998). These complex developmental abnormalities appear to lay the foundation for secondary and tertiary metabolic, structural, and functional changes, including seizures and risk of sudden unexpected death; signs of oxidative stress, early and enhanced accumulation of products of cell organelle degradation with lipofuscin deposition; modified processing of β-amyloid precursor protein with accumulation of truncated amyloid beta; and other as of yet unidentified changes. Secondary pathologic changes appear to be indicators of the susceptibility of abnormally developing neurons to further modifications during cell maturation and aging. The pattern of morphological changes emerging from these multidisciplinary studies appears to represent a major trend. However, modifications of the course of disease and sub-patterns of developmental changes result in a broad spectrum of morphological and clinical interindividual differences.

1.2 CLINICAL, ETIOLOGICAL, AND NEUROPATHOLOGICAL DIVERSITY IN AUTISM

Autism is the prototype of a pervasive developmental disorder (PDD) and is characterized by (a) qualitative impairments in reciprocal social interactions, (b) qualitative impairments in verbal and nonverbal communication, (c) restricted repetitive and stereotyped patterns of behavior, interests, and activities, and (d) onset prior to the age of 3 years. PDD also includes childhood disintegrative disorder, Asperger’s disorder, Rett syndrome, and pervasive developmental disorder—not otherwise specified (PDD-NOS). The common features of all these disorders are qualitative deficits in social behavior and communication (American Psychiatric Association, 2000).

1.2.1 CLINIC

In most cases (90%–95%), it is not presently possible to detect a known or specific etiology. These cases are referred to as idiopathic or nonsyndromic autism (Boddaert et al., 2009; Gillberg and Coleman, 1996). In 6% (Fombonne, 2003), 5% (Tuchman et al., 1991), or 10% (Rutter et al., 1994) of cases, autism was diagnosed in association with other disorders. About 30% of children with idiopathic autism have complex autism, defined by the presence of dysmorphic features, microcephaly and/or a structural brain
malformation (Miles et al., 2005). About 70% of children with autism have essential autism, defined by the absence of physical abnormalities. For most children, the onset of autism is gradual. However, a multisite study revealed significant regression at ages of 18 to 33 months (regressive autism) in about 13.8% (Colorado) to 31.6% (Utah) of autistic subjects (Department of Health and Human Services, 2007). Moreover, the manifestations of autism vary greatly, depending on developmental level and chronological age of the affected individual. The majority of patients exhibit serious social and communicative impairments throughout life but some improve enough to be able to live relatively independently as adults. In 44.6% of children, autism is associated with cognitive impairment (defined as having intelligence quotient scores of <70; Department of Health and Human Services, 2007). Expressive language function in individuals with autism may vary from mutism to verbal fluency (Rapin, 1996; Stone et al., 1997; Wetherby et al., 1998). Sensorimotor deficits also show significant interindividual differences, with more frequent and severe impairments of gross and fine motor function (motor stereotypes, hypotonia, limbic apraxia) in subjects with lower IQ (Rogers et al., 1996). Hand mannerisms and body rocking are reported in 37% to 95% of individuals with autism (Lord and Rutter, 1995; Rapin, 1996; Rogers et al., 1996), whereas preoccupation with sensory features of objects, abnormal responsiveness to environmental stimuli, or paradoxical responses to sensory stimuli are seen in 42% to 88% of people with autism (Kientz and Dunn, 1997). Epilepsy is a comorbid complication, occurring in up to 33% of individuals with autism (Tuchman and Rapin, 2002).

1.2.2 Etiology

The clinical diversity of autism reflects the etiologic heterogeneity of this disorder. Genetic factors; pre-, peri-, and postnatal pathological factors; and concurrent diseases may contribute to autism (Muhle et al., 2004; Newschaffer et al., 2002; Rutter et al., 1994). About 5% to 10% of cases are associated with several distinct genetic conditions including fragile X syndrome, tuberous sclerosis, phenylketonuria, Rett syndrome, and chromosomal anomalies such as Down syndrome (DS) (Folstein and Rosen-Sheidley, 2001; Fombonne, 2003; Smalley et al., 1988; Yonan et al., 2003). Autism spectrum disorders (ASDs) in people with DS have been described in several reports (Ghaziuddin et al., 1992; Howlin et al., 1995; Prasher and Clarke, 1996; Wakabayashi, 1979), and the prevalence of autism in boys with DS was estimated as at least 7% (Kent et al., 1999). The prevalence of autism in the fragile X syndrome is estimated as 15%–28% (Hagerman, 2002). Cytogenetic abnormalities (partial duplications, deletions, inversions) in the 15q11-q13 region account for 1% to 4% of autism cases (Cook, 1998; Gillberg, 1998). Several potential candidate genes have been identified in both autosomes and X chromosomes, including the tuberous sclerosis gene on chromosomes 9 and 16; serotonin transporter on chromosome 17; gamma-aminobutyric acid receptor-beta 3 on chromosome 15; neuroligins on the X chromosome (see Vorstman et al., 2006); and possibly PTEN on chromosome 10 (Butler et al., 2005). Modifications in the tryptophan hydroxylase gene may play a modest role in autism susceptibility (Coon et al., 2005).
1.2.3 Neuropathology

While knowledge of the clinical and genetic factors in autism is based on examination of thousands of patients, postmortem neuropathological studies are based on reports of a very small number of brains. A review by Palmen et al. (2004) revealed that between 1980 and 2003, only 58 brains of individuals with autism have been examined, and results of only a few neuropathological and stereological studies were published. Usually, neuropathological reports and morphometric reports were based on evaluation of one or several brains. Due to the broad age spectrum and the etiological and clinical diversity in autism, the pattern of neuropathological changes reported is incomplete and often inconsistent. As a result, the morphological markers and neuropathological diagnostic criteria of autism have not yet been established (Lord et al., 2000; Pickett and London, 2005). In the past, the contribution of postmortem studies to the detection and characterization of neuropathological changes and mechanisms leading to structural and functional manifestations of autism was limited because of (a) the deficit of autism brains, resulting in a lack of statistical power, (b) the lack of efficient mechanisms for sharing the limited tissue resources, (c) the lack of complex studies of the dynamic of changes during the life span, (d) the infrequent application of unbiased morphometric methods to detect quantitative differences, and (e) the averaging of results from subjects with different clinical and morphological manifestations of autism. Heterogeneity within the autism spectrum is the major obstacle to autism research at all levels (Newschaffer et al., 2002), including neuropathological studies and attempts at detection of clinicopathological correlations. Recent evidence of genetic fractionation of social impairment, communication difficulties, and rigid and repetitive behaviors indicates that heterogeneity in ASD could be an unavoidable consequence of the contribution of nonoverlapping genes. If different features of autism are caused by different genes associated with different brain regions and related to different core cognitive impairments (Happe et al., 2006), it seems likely that many brain networks are involved in the pathology of autism. The diversity of neuropathological findings and the commonly reported inconsistencies in regional findings correspond to developmental impairments in many interacting brain networks and to expansion from “local” abnormalities to “nonlocal” effects of the emerging cognitive system. In spite of these limitations, “localizing” models are still the main approach to the identification of pathological changes as a component of the structural and functional abnormalities of the networks (Müller, 2007).

The possibility that autism is associated with neuropathological changes was explored in the first studies reported between 1980 and 1989 (Bauman and Kemper, 1985; Courchesne et al., 1987, 1988; Damasio et al., 1980; Gaffney et al., 1987; Hashimoto et al., 1989, 1993; Murakami et al., 1989; Ritvo et al., 1986). Expansion of these studies through examination of larger cohorts and application of stereology, functional and structural MRI, and biochemistry resulted in the identification of several major forms of pathology contributing to the clinical phenotype including abnormal acceleration of brain growth in early childhood (Redcay and Courchesne, 2005), delay of neuronal growth (Wegiel et al., 2008), changes in brain cytoarchitecture (Bailey et al., 1998; Bauman and Kemper, 1985; Casanova et al., 2002, 2006),...
metabolic modifications with abnormal amyloid precursor protein (APP) processing (Bailey et al., 2008; Brown et al., 2008; Sokol et al., 2006), enhanced oxidative stress (reviewed in Chauhan and Chauhan, 2006), and turnover of cell organelle with pigment accumulation and glial activation (Lopez-Hurtado and Prieto, 2008).

1.3 DEREGULATION OF BRAIN GROWTH IN EARLY CHILDHOOD

The major measures of age-related changes are head circumference, MRI-based volumetry of the brain and brain structures, and postmortem brain weight and volume of brain subdivisions. Between 1990 and 2000, several groups reported increased head circumference (Bailey et al., 1995; Bolton et al., 1995; Davidovitch et al., 1996; Fidler et al., 2000; Fombonne et al., 1999; Lainhart et al., 1997; Miles et al., 2000; Steg and Rapoport, 1975; Stevenson et al., 1997), whereas MRI-based studies revealed increased brain volume (Piven et al., 1995, 1996). According to Fombonne et al. (1999), the prevalence of macrocephaly in autism is about 20%. In a report by Bailey et al. (1998), four of six subjects with autism 4 to 24 years of age had macrocephaly. Increased brain weight was reported in postmortem studies by Bailey et al. (1993) and Kemper and Bauman (1998). Increase in the volume was regional and not generalized, with the greatest enlargement in the occipital and parietal lobes (Filipek, 1996; Filipek et al., 1999; Piven et al., 1995, 1996). However, in several studies, an increase in brain size was not detected (Garber and Ritvo, 1992; Haznedar et al., 2000). Inconsistency in detection of abnormal head and brain size can be associated with interindividual differences, the age of examined individuals, and the methods applied. Courchesne et al. (2003) integrated their work and that of other researchers into the concept of four phases of modified brain growth, described below.

At birth, the head circumference of neonates later diagnosed with autism is normal or slightly less than that observed in normally developing children (Courchesne et al., 2003; Dawson et al., 2007; Dementieva et al., 2005; Dissanayake et al., 2006; Gillberg and de Souza, 2002; Hazlett et al., 2005; Lainhart et al., 1997; Mason-Brothers et al., 1990; Stevenson et al., 1997). Slight undergrowth is independent of body growth and may be a reflection of prenatal neural developmental defects corresponding to pathology detected in postmortem studies of the brains of autistic adults (Bailey et al., 1998; Casanova et al., 2002; Courchesne et al., 2003; Kemper and Bauman, 1998). In only 5% of neonates diagnosed later as autistic was the head circumference more than that in normally developing infants (Courchesne et al., 2003; Dementieva et al., 2005).

In the second phase, by 1 or 2 years of age, a rapid and large increase in head circumference distinguished children diagnosed later with autism from normally developing children (Courchesne et al., 2003; Dawson et al., 2007; Dementieva et al., 2005; Dissanayake et al., 2006; Hazlett et al., 2005). Ninety percent of 2- and 3-year-old children with autism had brain volumes larger than those of control children (Courchesne et al., 2001). According to Dawson et al. (2007), a period of exceptionally rapid head growth is limited to the first year of life, and head growth decelerates after 12 months of age. Acceleration of growth in head circumference appears to begin at about 4 months (Courchesne and Pierce, 2005a; Gillberg and
de Souza, 2002; Redcay and Courchesne, 2005). Using meta-analysis based on evaluation of head circumference converted to brain volume, brain volume measured from MRI, and brain weight from postmortem studies, Redcay and Courchesne (2005) revealed that brain size increases from 13% smaller than in control subjects at birth to 10% larger than in control infants at 1 year, but only 2% greater by adolescence. The greater growth rate of head circumference in the first year, and its return to normal rates thereafter, is not accounted for by an overall growth in stature. Studies of behavioral development in infants later diagnosed with autism suggest that the period of acceleration of head growth precedes and overlaps with the onset of behavioral changes, and that the period of deceleration coincides with a period of behavioral decline or worsening of symptoms in the second year of life (Dawson et al., 2007). Coincidence of acceleration of brain growth rate with onset and worsening of clinical symptoms may indicate that structural developmental changes critical for a lifelong phenotype occur in early infancy. Acceleration of brain growth in the first year and deceleration in the second year of life suggest that failure of the mechanism controlling brain growth in the first year of life plays an essential role in the onset of clinical features of autism. Identification of these mechanisms may lead to conceptualization of early preventive treatments.

In the third phase, of 2 to 4 years, the overall rate of brain growth slows but is still 10% more than in normally developing children (Carper et al., 2002; Courchesne et al., 2001; Hazlett et al., 2005; Sparks et al., 2002). In 4- to 5-year-old autistic children, MRI-based estimated brain volume is 1350 mL, whereas in normally developing children, a comparable volume (1360 mL) is reached about 8 years later. In postmortem studies, the brain weight of 3- to 5-year-old autistic males was 15% higher (1451 g) than in control males of this age (1259 g) (Redcay and Courchesne, 2005).

In the fourth phase, the volume of the brain decreases, and this trend extends from middle/late childhood through adulthood. Head (Aylward et al., 2002) or brain enlargement (Bailey et al., 1998; Hardan et al., 2001; Lainhart et al., 1997; Piven et al., 1995, 1996) has also been observed in studies of older populations of autistic individuals. However, by adolescence and adulthood, the average size of the brain is only 1% to 3% greater in autistic than in control cohorts (Redcay and Courchesne, 2005).

Moreover, the pattern of brain growth reflects the severity of clinical manifestation of autism (Courchesne et al., 2003). Among infants who have the more severe form of autism, 71% showed increases during their first year of more than 1.5 S.D., with 59% showing increases between 2.0 and 4.3 S.D. In children with a less severe form of autism, PDD-NOS, acceleration of brain growth is observed later, and the increase is less pronounced. Later onset and slower rate of progression of autism appear to be associated with a better outcome.

1.3.1 DEVELOPMENTAL HETEROCHRONICITY

Developmental heterochronicity studies indicate that autism is a disorder involving a transient period of pathological acceleration of brain growth. Developmental heterochronicity, with different rates of growth for different brain regions/structures, appears to be the second major factor contributing to the clinical phenotype. MRI studies showed that overgrowth of the frontal and temporal lobes and amygdala, brain
regions that are involved in cognitive, social, and emotional functions as well as language development, is synchronized with brain overgrowth in 2- to 4-year-old autistic children in contrast to a different rate of growth of the occipital cortex (Carper and Courchesne, 2005; Carper et al., 2002; Courchesne et al., 2001; Hazlett et al., 2005; Sparks et al., 2002). The reduced size of the body and posterior subregions of the corpus callosum noted in subjects with autism may indicate disproportions in brain subregions development (Piven et al., 1997b). The cellular and molecular basis for transient acceleration of brain growth and enhanced growth of some brain regions is not known, but Courchesne et al. (2003) proposed that the observed pattern is associated with an excessive number of neurons, enhanced rate of growth of size of neurons, and increased number of minicolumns as well as excessive and premature expansion of the dendritic tree.

1.3.2 Functional Consequences of Abnormal Brain Development

Using a computational model analogue of autism, Cohen (2007) has argued that an interaction between stochastic and above-average or “excessive” numbers of neural connection factors has implications for understanding the disorder. In particular, a relative excess of connections could lead to enhanced recognition of complex patterns in the environment. In Cohen’s chapter, it was noted that if large and complex brains are in part familial (Courchesne et al., 2003; Fidler et al., 2000), and brain size is heritable (Pfefferbaum et al., 2000), then behavioral outcomes both within and across generations of family members could result in (a) individuals who may be unusually gifted in their ability to handle complex nonlinear problems such as mathematics or computer science, (b) individuals with autism, or (c) individuals with a combination of autism or autistic-like behavior and giftedness (many typical Asperger’s cases). These trends are detected among relatives of subjects with autism (Folstein and Rutter, 1988).

The effect of an abnormal trajectory of brain development observed in autism are well-validated characteristics of the learning style of children with autism, including (a) greater attention to idiosyncratic than socially relevant stimuli, (b) stimulus overselectivity or a lack of drive for central coherence, (c) problems with acquiring fuzzy concepts, (d) development of savant skills, (e) problems with generalization of previously acquired skills, (f) rigidity and resistance to change, (g) social and communication deficits, and (h) difficulty in learning complex higher-order concepts (Cohen, 2007).

1.4 Cortical and Subcortical Neuropathology

1.4.1 Cortical Dysgenesis, Lamination Defects, Migration Disturbances

The fundamental characteristics of the neuropathological changes described by Kemper and Bauman (1993, 1998), Bauman and Kemper (1985, 1996), and Bauman et al. (1997) suggest three major neuropathologies in the brain of people with autism: (a) curtailed development of neurons in the structures that are substrates for memory and emotions—the entorhinal cortex, hippocampus, subiculum, anterior cingulate
gyrus and mamillary body; (b) a congenital decrease in the number of Purkinje cells in the cerebellum; and (c) age-related differences in cell size and number of neurons in the cerebellar nuclei and in the inferior olivary nucleus. Microdysgenesis is represented by increased neuronal density in the cortical layer, clustering of cortical neurons, disorganization of cortical layers, neuron cytomegaly, ectopic neurons, and nodular heterotopias. A detailed study of serial sections from the brain of a 29-year-old man with autism revealed reduced neuronal size and increased cell-packing density (Bauman and Kemper, 1985), both features of an immature brain (Friede, 1975). Cell-packing density was increased by 66% in the hypothalamus and mamillary body, and by 54% in the medial septal nucleus, with smaller nerve cells. The reduced size of neurons and the selective increase in cell-packing density were seen in central (40%), medial (28%), and cortical nuclei (35%). Atrophy of the neocerebellar cortex, with marked loss of Purkinje cells and, to a lesser extent, of granule cells, was present in gracile, tonsil, and inferior semilunar lobules. Changes were not detected in the anterior lobe or the vermis. Reduced numbers of cells were noticed in fastigial, globose, and emboliform nuclei, and cells were small and pale. The dentate nucleus was distorted. Retrograde neuronal loss in the inferior olive related to neuronal loss in cerebellar cortex was not found, but olivary neurons were small and pale. Brain cytoarchitecture abnormalities were not associated with gliosis. In a 21-year-old female with autism, Rodier et al. (1996) found that the brain was smaller than a control brain, and the length of facial nerve nucleus was less than 500 μm as compared to 2610 μm in the control subject.

1.4.2 Brain Structure–Specific Delay of Neuronal Growth

The reduced size of neurons and their nuclei in the cortex of autistic subjects reported by Casanova et al. (2006) could be an indicator of reduced or impaired functional connectivity between distant cortical regions (Casanova et al., 2006; Just et al., 2004; Koshino et al., 2005). Our ongoing studies of series of brains from age-matched autistic and control subjects (Wegiel et al., 2008) indicate that reduced size of neurons is a brain structure–specific marker. In 4- to 7-year-old autistic children, Purkinje cells were smaller by 38%. Neurons in the dentate nucleus were reduced by 26%; in the amygdala, by 24%; in the nucleus accumbens, by 41%; in caudate, by 20%; and in the putamen, by 27%. Neurons in the nucleus of the facial nerve and the nucleus olivaris did not show a significant difference from controls. The second significant feature of the pattern of neuronal size abnormalities is the partial or complete correction of the size of neurons (for example, in the nucleus accumbens) observed in late childhood or adulthood. This study indicates that the delay of growth of neurons is the most consistent pathology detected in the brains of examined people with autism. Pathology is brain structure–specific. Changes may range from no delay to severe developmental delay. The youngest examined children (4 to 7 years old) show the most severe deficit in the volume of the neuronal body and nucleus. Partial correction of cell volume is observed in late childhood and adulthood, which indicates that brain structure and function undergo modifications during the life span. The study of basal ganglia and cerebellum supports the hypothesis that clinical manifestations of autism are the result of regional neuronal maldevelopment.
One may assume that mechanisms regulating growth of the neuron in early childhood are the target of factors that are the cause of autism. The result of deregulation of these mechanisms could be (a) significantly delayed growth of neuronal body, nucleus, dendritic tree, spines, and reduced number of synapses and (b) functional deficits corresponding to these structural developmental delays. These abnormalities of very early childhood might be the major contributor to clinical deficits that are the basis for the clinical diagnosis of autism at the age of 3 years.

1.4.3 MINICOLUMNAR ABNORMALITIES IN AUTISM

The next significant contribution to detection of neocortical developmental pathology is the result of studies of minicolumns by Casanova’s group (Buxhoeveden and Casanova, 2002; Casanova et al., 2002, 2006). Malformations of cortical development are observed in heterogeneous disorders caused by abnormalities of cell proliferation, apoptosis, cell migration, cortical organization, and axon pathfinding (Hevner, 2007). Clinically malformations of cortical development are significant causes of mental retardation, seizures, cerebral palsy, and neuropsychiatric disorders (Barkovich et al., 2005; Guerrini and Marini, 2006; Sarnat and Flores-Sarnat, 2004). Minicolumns are considered a basic architectonic and functional unit of the human neocortex (Buxhoeveden and Casanova, 2002; Casanova et al., 2002). Increased neuron density by 23%, reduced size of neurons in minicolumns, and a concomitant increase in the total number of minicolumns appears to illustrate the bias of local rather than global information processing (Casanova et al., 2002, 2006), resulting in a “hyper-specific brain” (McClelland, 2000). Synchronization of interactions requiring the involvement of distant brain regions is impaired in autism as a result of developmental connectivity deficits (underconnectivity) of smaller neurons (Just et al., 2004; Koshino et al., 2005; Zilbovicius et al., 1995). Structural imaging studies also suggest the overrepresentation of short association fibers in autism, with a regional increase in the volume of white matter (Herbert et al., 2004) favoring the local information processing observed in autistic subjects (Happe, 1999).

1.5 NEURONAL OXIDATIVE STRESS AND METABOLIC CHANGES

An increasing body of evidence suggests that the abnormal rate of development of neurons and neuronal networks in early infancy is followed by metabolic changes, with signs of oxidative stress, enhanced autophagocytosis, and lipofuscin accumulation, leading to early selective neuronal structural and functional changes.

1.5.1 OXIDATIVE STRESS IN AUTISM

Oxidative stress is known to be associated with premature aging of cells and can lead to inflammation, damaged cell membranes, autoimmunity, and cell death. The brain is highly vulnerable to oxidative stress due to its limited antioxidant capacity, higher energy requirement, and high amounts of unsaturated lipids and iron (Juurlink and Peterson, 1998). The brain makes up about 2% of body mass but consumes 20% of metabolic oxygen. The vast majority of energy is used by the neurons (Shulman et al., 2004). Glutathione (GSH) is the most important antioxidant for detoxification
and elimination of environmental toxins. Due to the lack of glutathione-producing capacity by neurons, the brain has a limited capacity to detoxify reactive oxygen species (ROS). Therefore, neurons are the first cells to be affected by the increase in ROS and shortage of antioxidants and, as a result, they are most susceptible to oxidative stress. Antioxidants are required for neuronal survival during the early critical period (Perry et al., 2004). Children are more vulnerable than adults to oxidative stress because of their naturally low glutathione levels from conception through infancy (Erden-Inal et al., 2002; Ono et al., 2001). The risk created by this natural deficit in detoxification capacity in infants is increased by the fact that some environmental factors that induce oxidative stress are found at higher concentrations in developing infants than in their mothers, and accumulate in the placenta.

Accumulating evidence from our and other groups suggests increased oxidative stress in autism (reviewed in Chauhan and Chauhan, 2006). Lipid peroxidation is a chain reaction between polyunsaturated fatty acids and ROS, producing lipid peroxides and hydrocarbon polymers that are both highly toxic to the cell. We have reported that levels of malondialdehyde (MDA), a marker of lipid peroxidation, are increased in the plasma from children with autism (Chauhan et al., 2004). Other studies on erythrocytes (Zoroglu et al., 2004) and urine samples (Ming et al., 2005) have also indicated increased levels of lipid peroxidation markers in autism, thus confirming an increased oxidative stress in autism. Recent studies with the postmortem brain samples from autism and control subjects have provided further evidence on increased oxidative stress in autism. Increased levels of lipid-derived oxidative protein modifications, i.e., carboxyethylpyrrole and iso[4]levuglandin E2–protein adducts, and heme-oxygenase-1 (an inducible antioxidant enzyme) have been reported in the autistic brain, primarily in the white matter (Evans et al., 2008). Sajdel-Sulkowska et al. (2008) have reported elevated levels of 3-nitrotyrosine (a specific marker for oxidative damage to proteins) in the cerebella of subjects with autism. In addition, we have observed increased lipid peroxidation in cerebellum and temporal cortex of brain in autism (Chauhan et al., 2009). MDA levels were significantly increased by 124% in the cerebellum, and by 256% in the temporal cortex in autism as compared to control subjects.

1.5.2 Lipofuscin in Autism

Lopez-Hurtado and Prieto (2008) revealed a significant increase in the number of lipofuscin-containing cells in the brain of 7- to 14-year-old autistic subjects (by 69% in area 22, 149% in area 39, and 45% in area 44). The increase in the number of lipofuscin-containing cells was paralleled by neuronal loss and glial proliferation. Lipofuscin accumulation is a component of aging (Brunk and Terman 2002a,b; Brunk et al., 1992; Szweda et al., 2003), the neurodegeneration observed in Alzheimer’s (Stojanovic et al., 1994) and Parkinson’s diseases (Tórsdóttir et al., 1999), developmental syndromes such as Rett syndrome (Jellinger et al., 1988), and autism (Lopez-Hurtado and Prieto, 2008), and such psychiatric disorders as bipolar affective disorder (Yanik et al., 2004) and schizophrenia (Akyol et al., 2002; Herken et al., 2001).

Lipofuscin is an intralysosomal deposit of products of autophagocytosis and degradation of cytoplasmic components, including mitochondria, which cannot be degraded further or exocytosed. Oxidative stress is considered the factor contributing to lipid and protein damage and degradation, resulting in lipofuscin production
and accumulation (Brunk et al., 1992; Sohal and Brunk, 1989). The presence of oxidatively modified proteins and lipids in lipofuscin supports the causative link between enhanced oxidative stress, autophagocytosis, and deposition of products of degradation in the lysosomal pathway and lipofuscin (Brunk and Terman, 2002a,b; Szweda et al., 2003; Terman and Brunk, 2004) and suggests that in autism, abnormal development is associated with early signs of oxidative stress and enhanced degradation and, possibly, turnover of cytoplasmic components.

1.5.3 β-AMYLOID PRECURSOR PROTEIN AND INTRANEURONAL AMYLOID β IN AUTISM

Sokol et al. (2006) detected signs of overexpression of APP in about 40% of autistic subjects. The levels of secreted APP in plasma in children with severe autistic behavior and aggression were two or more times the levels in children without autism, and up to fourfold more than in children with mild autism. The trend observed in autistic children, with higher levels of secreted β-APP and nonamyloidogenic secreted β-APP, and lower levels of Aβ 1–40 compared to controls, suggests an increased α-secretase pathway in autism (anabolic nonamyloidogenic APP processing). Enzyme-linked immunosorbent assay (ELISA) study of blood plasma from 25 autistic children 2–4 years of age and 25 age-matched control children revealed significantly increased level of secreted amyloid precursor protein alpha (sAPP-α) in 60% of autistic children (Bailey et al., 2008). Western blotting analysis confirmed higher levels of sAPP-α in autistic children.

Amino-terminally truncated intraneuronal amyloid (Aβ) is present in the neurons of control subjects, and the amount of intraneuronal Aβ increases with age (Wegiel et al., 2007). This study of 10 brains of autistic people revealed enhanced intraneuronal accumulation of amino-terminally truncated Aβ in 50% of autistic subjects, including in one 5-year-old child and four adults 20, 23, 52, and 62 years of age. A similar pattern was also found in four examined brains of people with autism and isodicentric chromosome 15 (idic15) (Brown et al., 2008). In idic15, excessive accumulation of intraneuronal Aβ might be related to an extra copy of one of the amyloid precursor protein-binding protein (APBA-2) genes localized on chromosome 15. In many brain regions, Aβ is accumulated in large cytoplasmic granules corresponding to deposits of lipofuscin. Numerous large lipofuscin deposits with very strong Aβ immunoreactivity in the neurons of several children and adults with autism appear to reflect severe metabolic stress affecting all of the neurons in the amygdala, all large neurons in the caudate/putamen, a majority of Purkinje cells, and the neurons in the dentate nucleus and nucleus olivaris, but only about 30%–40% of cortical pyramidal neurons. Accumulation of truncated Aβ appears to be a by-product of enhanced degradation of transmembrane APP. The aggregated intracellular Aβ induces the production of ROS and lipid peroxidation products and ultimately results in leakage of the lysosomal membrane (Glabe, 2001). This process appears to affect many neuronal populations, not only in young and old adults, but also in children diagnosed with autism. A metabolic shift with Aβ accumulation in neurons in these brain areas that are involved in the expression of emotions, stereotypic behaviors, and social deficits, such as the amygdala, hippocampus, some
striatal subdivisions, and cerebellum, may contribute to cellular dysfunction and the clinical expression of autism.

1.6 CLINICOPATHOLOGICAL CORRELATIONS

Studies of clinicopathological correlations cover several domains of functional deficits in people with autism, including (a) speech, language, and verbal and nonverbal communication, (b) social deficits and face perception, (c) sensorimotor deficits, and (d) cognitive deficits.

1.6.1 SPEECH, LANGUAGE, AND VERBAL AND NONVERBAL COMMUNICATION

Expressive language function of individuals with autism ranges from complete mutism to verbal fluency. Verbal abilities are often accompanied by errors in word meaning (semantics) or language and communicative deficits in social context (social pragmatics) (Rapin, 1996; Stone et al., 1997; Wetherby et al., 1998). Studies of the language-related neocortex, including Wernicke’s area (BA 22, speech recognition), Broca’s area (BA 44, speech production) and the gyrus angularis (BA 39, reading) of 7- to 44-year-old autistic and 8- to 56-year-old control individuals, revealed reduced numerical density of neurons by 38% in area 22, and by 24% in area 39 in autistic subjects, as well as an increased numerical density of lipofuscin-containing neurons by 50% in BA 22, and 44% in BA 44. These neuronal changes were paralleled by an increase of numerical density of glial cells in all three examined regions. Lopez-Hurtado and Prieto (2008) hypothesized that structural alteration in one or more of these cortical areas may contribute to the communication impairment observed in autism.

1.6.2 FACE PERCEPTION

All subjects with ASDs have disturbance of social behavior, including abnormalities in social reciprocity and difficulties in use of eye contact, facial expression, and social motivation. Social functioning includes eye contact, processing of faces, identification of individuals, and monitoring of face expression (Baron-Cohen et al., 1994). Patients with autism reveal deficits in face-processing (Grelotti et al., 2001), perception (Schultz, 2005), and recognition (Joseph and Tanaka, 2003).

The face-processing network includes the visual cortex (BA17), which projects via the inferior occipital gyrus to the fusiform gyrus. Fibers from the fusiform gyrus project to the amygdala, and inferior frontal gyrus and orbital cortex (Fairhall and Ishai, 2007; van Kooten et al., 2008). Functional magnetic resonance imaging (fMRI) identified the fusiform gyrus and other cortical regions as supporting face-processing in control subjects, and hypoactivity of the fusiform gyrus in autistic patients (Bolte et al., 2006; Kanwisher et al., 1999; Pierce et al., 2004). Hypoactivation of the fusiform gyrus is believed to be associated with the failure to make direct eye contact in autism (Dalton et al., 2005). Results of imaging-based fusiform volume estimation are inconsistent. Increased (Waiter et al., 2004) and unchanged (Pierce et al., 2001) volume in both hemispheres and increased fusiform gyrus in the left hemisphere (Herbert et al., 2002) were reported. Morphometric studies of the brain of 7 autistic
and 10 control subjects revealed a reduced number of neurons in layers III, V, and VI, and reduced volume of neuronal soma in layers V and VI in the fusiform gyrus. No alterations in Brodman area 17 in these autistic individuals suggest that the input from the visual cortex to the fusiform gyrus is intact. These results indicate the underdevelopment of connections in the fusiform gyrus that may contribute to abnormal face perception in autism (van Kooten et al., 2008).

Bailey et al. (1998) noted abnormalities in cytoarchitectonic organization and neuronal density in the superior frontal cortex and superior temporal gyrus in autism. Neurons in the superior temporal sulcus are sensitive to the angle of gaze (Perrett et al., 1985). Neurons that are attuned to particular facial expressions were found in the inferior and superior temporal lobes (Hasselmo et al., 1989). Cortical areas responsive to faces, facial expressions, and angle of gaze send direct projections to the amygdala (Stefanacci and Amaral, 2000). Pathological changes in the amygdala may play a central role in the dysfunction seen in autism, including disturbed components of social cognition such as attention to and interpretation of facial expressions. fMRI studies show that judging from the expression of another person’s eyes what the other person might be thinking or feeling is associated with activation in the superior temporal gyrus, frontal cortex, and amygdala, whereas in subjects with autism, activation appears in the temporal and frontal cortex but not in the amygdala (Baron-Cohen et al., 1999).

1.6.3 Social Attachment—The Role of the Hypothalamus in Behavioral Deficits

Experimental studies revealed that the hypothalamic nucleus paraventricularis (NPV) and the nucleus supraopticus (NSO), producing oxytocin (OT) and vasopressin (VAS), regulate emotional responses, social attachment, cognitive functions, sleep, and appetite (Barden, 2004; Ehlert et al., 2001; Manaye et al., 2005). OT and VAS are relayed from the human brain into the bloodstream via the posterior pituitary. The presence of receptors for both peptides throughout the forebrain, limbic system, thalamus, brain stem, and spinal cord (Raggenbass, 2001) indicates that hypothalamic neuropeptides modulate the function of many brain regions. Developmental changes in the distribution and expression of receptors suggest that the hypothalamic peptides play a significant role both in brain development and function (Shapiro and Insel, 1989). OT is required for the development of social memory. In OT knockout mice, the loss of social memory could be rescued by OT treatment (Ferguson et al., 2000). VAS is necessary for the formation of social memory and OT for retention of newly formed social memories (Popik and Van Ree, 1992; Popik et al., 1992). OT facilitates the learning of social interactions and the formation of associations that are specifically related to the mother (Nelson and Panksepp, 1996).

The initial product of oxytocin mRNA is a polypeptide containing both nanopeptide OT and neurophysin I, separated by tripeptide glycine-lysine-arginine. The result of enzymatic cleavage are intermediate forms containing 10, 11, or 12 amino acids, collectively referred to as carboxy-extended forms of OT (OT-X), and oxytocin (Gabreels et al., 1998; Gainer et al., 1995; Mitchell et al., 1998; Rao et al., 1992). In 5.8- to 11.5-year-old autistic individuals, reduced plasma OT level, deficits in OT prohormone
processing (increase in OT-X), and an increase in the ratio of C-terminal extended forms to OT were found. In control children, nearly all OT-X is metabolized to OT, whereas in autistic children, the immature OT forms serve as the primary circulating molecule in the absence of or in compensation for OT (Green et al., 2001). However, experimental studies show that OT-X is not an effective agonist at OT-sensitive sites (Mitchell et al., 1998). Deficient conversion of OT-X to OT in autism could be the result of alterations in the level of prohormone convertases associated with genetic defects (Cook, 1998; Szatmari et al., 1998). The identification of four single nucleotide polymorphisms located within the OT receptor gene of 195 Chinese autistic subjects indicates that abnormal modulation of the OT receptor results in autism (Wu et al., 2005). OT and VAS are known to play a role in repetitive behaviors. Patients with ASDs show a significant reduction in repetitive behaviors following OT infusion (Hollander et al., 2003). In about 60% of subjects with autism, abnormal sleep patterns are observed. VAS is involved in the control of circadian rhythmicity (Swaab, 1997). VAS enhances aggressiveness, anxiety, stress levels, and the consolidation of fear memory (Bielsky et al., 2004; Griebel et al., 2002; Landgraf and Neumann, 2004). OT decreases anxiety and stress; facilitates social encounters, maternal care, and the extinction of conditioned avoidance behavior (Bale et al., 2001; Champagne et al., 2001; Windle et al., 1997); reduces activation of the amygdala and modulates fear processing (Kirsch et al., 2005). The presence of abnormal levels of hypothalamic neuropeptides in patients with autism provides strong evidence that an abnormality in OT, VAS and other hypothalamic neuropeptides may have a significant contribution to the behavioral features of autism. However, the morphology and biochemistry of the hypothalamus of autistic subjects remains unknown. The only study of the hypothalamic mammillary body of a 26-year-old autistic man revealed that the cell-packing density was increased by 66% (Bauman and Kemper, 1985).

1.6.4 SENSORIMOTOR DEFICITS, AND REPETITIVE AND STEREOTYPED BEHAVIORS

In individuals with autism, impairments of gross and fine motor function recognized as hypotonia, limbic apraxia, and motor stereotypes are common findings and are more severe in subjects with lower IQ (Rogers et al., 1996). Hand mannerisms, body rocking, or unusual posturing are reported in 37% to 95% of individuals (Lord, 1995; Rapin, 1996; Rogers et al., 1996). In 42% to 88% of subjects with autism, aberrant sensory processing results in a preoccupation with sensory features of objects, over- or underresponsive-ness to environmental stimuli or paradoxical responses to sensory stimuli (Kientz and Dunn, 1997). Sensorimotor deficits may by associated with pathological changes in both the nigrostriatal system (basal ganglia) and the cerebellum (Bailey et al., 1998; Kemper and Bauman, 1998; Ritvo et al., 1986; Saitoh and Courchesne, 1998; Sears et al., 1999). Cerebellar abnormality with a deficit/loss of Purkinje cells (Bailey et al., 1998; Kemper and Bauman, 1993, 1998; Ritvo et al., 1986) has been a common finding. Individuals with autism have been classified as affected by cerebellar hyper- or hypoplasia (Saitoh and Courchesne, 1998). A reduced number of Purkinje cells without significant glial activation and a reduced size of Purkinje cells were noticed in the majority of cerebellar reports (Bailey et al., 1998; Fehlow et al., 1993; Kemper and Bauman, 1993; Lee et al., 2002; Ritvo et al., 1986) in 21 of 29 examined cases (Palmen et al., 2004).
Results of evaluation of the size of the cerebellum using MRI are inconsistent. In several MRI studies, smaller cerebellar hemispheres (Gaffney et al., 1987; Murakami et al., 1989) and vermis (Ciesielski et al., 1997; Courchesne et al., 1988; Hashimoto et al., 1995) were reported. In a study by Piven et al. (1997a), the total cerebellar volume was found to be greater in subjects with autism than in the control group, and the increase was proportional to the increased total brain volume. In the cerebellum, boys with autism had less gray matter, a smaller ratio of gray to white matter, and smaller lobules VI and VII than did controls. Despite the inconsistency of reports characterizing topographic autism-associated vermian hypoplasia (Hashimoto et al., 1993; Kaufmann et al., 2003; Levitt et al., 1999; Piven et al., 1997a; Schaefer et al., 1996), several reports show associations between the size of the vermis and deficits in attention-orienting (Harris et al., 1999; Townsend et al., 1999), stereotypic behavior, and reduced exploration in autism (Pierce and Courchesne, 2001).

The reduced size of the pons, midbrain, and medulla in autism reported by Hashimoto et al. (1992, 1993, 1995) was not confirmed in other studies (Hsu et al., 1991; Piven et al., 1992).

Changes in neurons in the deep cerebellar nuclei were noticed by some authors (Kemper and Bauman, 1998) but not by others (Bailey et al., 1998). Structural MRI shows variable patterns of changes. Volumetry of the cerebellum may show no change, hypoplasia, or hyperplasia. Courchesne et al. (1988) reported selective hypertrophy of lobules VI and VII, but these results were not confirmed in other subjects. In part, the pattern may correspond to the functional status of subjects. In highly functioning subjects with autism, hypoplasia of the cerebellum has not been detected (Holttum et al., 1992).

A decrease in the number of GABAergic Purkinje cells is considered the most consistent neuropathological finding in autism, as it was detected in at least 50% of examined cases (Arin et al., 1991; Bailey et al., 1998). Recent studies indicate that preserved Purkinje cells reveal a 40% decrease in the expression of glutamic acid decarboxylase 67 (GAD67) mRNA in autistic subjects relative to control patients (Yip et al., 2007). Moreover, in autism, the basket cells likely provide increased GABAergic feed-forward inhibition to Purkinje cells. The result may include disruption in the timing of Purkinje cell firing and altered inhibition of the cerebellar nuclei, which could directly affect cerebellocortical output, leading to changes in motor behavior and cognition (Yip et al., 2008).

Repetitive and stereotyped behaviors defined as recurring, nonfunctional activities, or interests that occur regularly and interfere with daily functioning are a defining signs of autism. These behaviors include lower-order repetitive motor behavior, intense circumscribed patterns of interests, and higher-order rituals and compulsions (Gabriels et al., 2005). Several studies implicated the role of basal ganglia and frontostriatal circuitry in the pathophysiology of autism, especially in repetitive and stereotyped behaviors. Increased volume of the basal ganglia was reported in several MRI studies (Herbert et al., 2003; Hollander et al., 2005; Langen et al., 2007; Sears et al., 1999). Sears et al. (1999) and Hollander et al. (2005) observed a positive correlation between caudate volumes and repetitive behavior scores. A significant increase in caudate nucleus volume, disproportional to brain volume, was detected in MRI studies in two independent samples of medication-naive subjects with autism.
(21 high-functioning children and adolescents, and 21 typically developing subjects; 21 high-functioning adolescents and young adults, and 21 healthy subjects) (Langen et al., 2007). Our studies showing a significantly smaller size of neurons in the caudate, putamen, and nucleus accumbens, especially in the brains of children 4–7 years of age suggest a developmental delay in the growth of neurons in the basal ganglia of autistic subjects, which may contribute to basal ganglia dysfunction (Wegiel et al., 2008). MRI and postmortem morphometric studies support the hypothesis that developmental abnormalities in frontostriatal circuitry contribute to repetitive and stereotyped behaviors, which are one of three defining symptoms of autism.

1.6.5 COGNITIVE DEFICITS

Many individuals with autism demonstrate a particular pattern on intellectual tests that is characteristic of autism. Performance IQ is usually higher than verbal IQ, and block design is the highest subtest, whereas comprehension is usually the lowest (Siegel et al., 1996). Individuals with autism have poorer adaptive function than would be predicted by IQ alone (Volkmar et al., 1993).

Cognitive deficits might be related in part to the memory system and limbic region abnormalities. Reduced volume of both the hippocampal formation and amygdala were noticed in subjects examined by Aylward et al. (1999), but not in populations examined by other researchers (Piven et al., 1998). Neurons in the hippocampus have reduced complexity of dendritic arbors. They are smaller and more densely packed in various portions of the hippocampal formation, entorhinal cortex, medial nuclei of the amygdala, medial septal nucleus, mammillary nuclei, and anterior cingulate gyrus (Bauman and Kemper, 1985; Kemper and Bauman, 1993). Haznedar et al. (1997) observed reduced volume of the anterior cingulate gyrus and decreased positron emission tomography (PET) activity in subjects with autism. Because the cerebellum is involved in a variety of cognitive and affective processes, abnormalities of both the limbic system and the cerebellum may be linked to the core social and communicative deficits in autism.

The caudate nucleus is an integral component of the frontostriatal network involved in cognitive functions (Chow and Cummings, 1999; Voelbel et al., 2006), including learning (Poldrack et al., 1999), short- and long-term memory (Fuh and Wang, 1995), and planning and problem-solving (Mendez et al., 1989; Schmidtke et al., 2002). The increased volume of the caudate observed in autistic children may be indicative of impaired neuronal pruning, contributing to a decrease in executive function (Voelbel et al., 2006).

1.6.6 EPILEPSY-ASSOCIATED PATHOLOGY

The 1% prevalence of epilepsy in the general population increases to 8% in DS, 10% in AD (Menendez, 2005; Risse et al., 1990; Velez and Selwa, 2003), and 33% in autism (Tuchman and Rapin, 2002). The interpretation of developmental changes in autism has been challenged by the need to differentiate among lesions that are not associated with epilepsy, that cause epilepsy, and that are produced by epilepsy (Sutula and Pitkanen, 2001). Recent studies support the hypothesis that epilepsy
induces brain alterations that contribute to changes in circuitry, which potentiates the seizure-genic focus (Armstrong, 2005).

Studies of nonautistic subjects indicate that epilepsy-associated pathology includes patchy or laminar neuronal loss and gliosis in the cerebral cortex in one or both hemispheres. In temporal epilepsy, abnormalities were reported in 75% of the specimens examined, and hippocampal sclerosis was found in 50% (Bruton, 1988). Loss of hippocampal neurons correlates with the frequency of tonic-cloning seizures and the total duration of epilepsy (Dam, 1980; Tasch et al., 1999). Loss is accentuated in the CA4 sector and is observed in the granule cell layer in the dentate gyrus. Dispersion of dentate gyrus granular neurons might be a result of seizure-related, disturbed migration of neurons (Bengzon et al., 1997), or epilepsy-enhanced neurogenesis (Ericksson et al., 1998). Ammon horn sclerosis is a progressive lesion that can be induced and propagated by seizures (Armstrong, 2005).

In nearly all cases with hippocampal pathology, changes are also observed in other brain regions. In about 25%, the amygdala, thalamus and mammillary body are affected with neuronal loss. More severe neuronal loss and gliosis in the hippocampus is paralleled by severe neuronal loss and gliosis in the lateral nucleus in the amygdala (Bruton, 1988; Hudson et al., 1993; Thom et al., 1999). Ectopias with more than 8 neurons per 2 sq. mm of white matter occurred in 43% of epileptic patients but in none of the controls (Hardiman et al., 1988). In 45% of severely affected epileptics, significant neuronal loss and astrocytosis spreading out into the overlying molecular layer is observed in the cerebellar cortex. The severity of the cerebellar damage may range from gross atrophy of most or many folia to the restricted neuronal loss in some folia, especially at their basal portion (Gessaga and Urich, 1985).

Central apnea, asphyxia, and pulmonary edema occurring during a seizure (Nashef et al., 1996) as well as life-threatening cardiac arrhythmias during seizures (Earnest et al., 1992; Jallon, 1997; Nashef et al., 1996; Reeves et al., 1996; Saussu et al., 1998) have been suggested as possible causes of sudden unexpected death in epilepsy (Thom et al., 1999).

Enhanced electric activity of neurons and/or increased cell synaptic transmission with enhanced vesicle exocytosis, both in normal and in disease-affected brains are a common cause of modifications of APP processing and Aβ levels. Epilepsy is associated with an elevation of APP expression (Sheng et al., 1994) and occurs in 10 of 11 examined subjects with diffuse nonfibrillar Aβ plaque formation (mean age 47.9 ± 8.8 years of age) (Mackenzie and Miller, 1994; Mackenzie et al., 1996).

### 1.7 MECHANISMS AFFECTING BRAIN DEVELOPMENT

#### 1.7.1 BDNF AND NEUROTROPHINS IN AUTISM

The neurotrophins, a related family of growth factors, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophins (NT) NT-3 and NT-4/5, have a major role in the survival, growth, and differentiation of neurons (Conner et al., 1997). During typical brain development, only neurons making
the appropriate connections survive and form synapses, whereas neurons that fail to obtain adequate neurotrophins die (Oppenheim, 1991). BDNF is broadly distributed throughout the human central nervous system (CNS) and provides neurotrophic support for many neuronal populations in the cortex, amygdala, hippocampus, and striatum (Murer et al., 2001; Schmidt-Kastner et al., 1996; Tapia-Arancibia et al., 2004). The hypothalamus is the brain structure that contains the highest BDNF protein levels (Katoh-Semba et al., 1997; Nawa et al., 1995; Yan et al., 1997) and BDNF mRNA (Castren et al., 1995; Kawamoto et al., 1996; Yan et al., 1997). In the cerebellum, immunoreactivity was observed in Purkinje cells and the olivary complex of the nuclei (Kawamoto et al., 1996; Murer et al., 2001).

In the basal forebrain of autistic individuals, the level of BDNF was three times higher than in controls (Perry et al., 2001). Miyazaki et al. (2004) observed a higher level of BDNF in the blood samples of young children with autism than in adult control subjects. The mean BDNF levels in sera of children diagnosed with autism and childhood disintegrative disorder were about four times higher than in control children (Connolly et al., 2006). Children with autism and childhood disintegrative disorder have both elevated BDNF levels and levels of autoantibodies against BDNF. Serum BDNF has been shown to be increased after seizures (Binder et al., 2001; Chavko et al., 2002).

1.7.2 Brain Stem and the Role of Serotonin in Brain Development and Clinical Features of Autism

Because 5-hydroxytryptamine (5-HT; serotonin) serves as both a neurotransmitter and an important developmental signal in the brain, dysregulation of the 5-HT system during development may be responsible for many of the abnormalities seen in autism (Whitaker-Azmitia, 2005). In fact, all known chemical inducers of autism including cocaine, thalidomide, valproate, and alcohol modulate 5-HT levels in the brain (Harris et al., 1995; Kramer et al., 1994; Narita et al., 2002; Rathbun and Druse, 1985; Stromland et al., 1994; Williams et al., 2001). A high proportion of children with autism exhibit elevated blood 5-HT levels (hyperserotonemia) and specific alterations in 5-HT biosynthesis. The severity of hyperserotonemia is correlated with the severity of autistic behaviors (Chandana et al., 2005; Chugani et al., 1999; Kuperman et al., 1987). A causal role for serotonergic abnormalities in the etiology of autism is also suggested by studies indicating autism-specific genetic polymorphisms in 5-HT metabolizing enzyme, transporter, or receptor genes (Cohen et al., 2003; Sutcliffe et al., 2005). Also, gender-specific differences in serotonergic regulation during development (Chandana et al., 2005; Chugani et al., 1999), combined with a 52% higher rate of 5-HT biosynthesis in the male than female brain (Nishizawa et al., 1997), and the increased susceptibility of males to early insults imposed by elevated levels of 5-HT (Johns et al., 2002), may contribute to the fourfold higher propensity of males to develop autism compared to females.

As a result of the regulatory role of serotonin affecting the size of neurons, the size of dendritic tree and the number of synapses in innervated cortical and subcortical structures and cerebellum, developmental abnormalities in the serotonergic
The caudal raphe system innervates the lower brain stem and the spinal cord (Aitken and Törk, 1988; Lidov and Molliver, 1982). The functions of serotonin are mediated by 14 subtypes of 5-HT receptors in the nervous system (Hoyer et al., 1994; Martin and Humphrey, 1994; Saudou and Hen, 1994a,b). The serotonin2A (5-HT2A) receptor is known to be one of the major subtypes and is associated with psychological and mental events (Roth, 1994). The 5-HT2A receptor plays a role in facilitating the formation and maintenance of synapses (Niitsu et al., 1995). Staining for 5-HT2A shows the entire somata and dendritic tree of Purkinje cells in a rat cerebellum (Maeshima et al., 1998). In vitro studies have shown that that 5-HT inhibits the growth and arborization of Purkinje cell dendrites through 5-HT2A receptors and stimulates them through the 5-HT1A receptor (Kondoh et al., 2004). 5-HT promotes the formation of synapses in developing and mature brain and spinal cord (Chen et al., 1997; Niitsu et al., 1995; Okado et al., 1993), and this process is mediated by the 5-HT2A receptor in the spinal cord (Niitsu et al., 1995). Biochemical studies support the hypothesis that developmental defects of the raphe nuclei may make a major contribution to the structural and functional defects of cortical and subcortical structures. However, raphe nuclei have not yet been examined in autistic subjects.

1.8 CLOSING REMARKS

The detected brain structure–specific patterns of structural aberrations in a majority of examined anatomic subdivisions in autism brain may contribute to deficits in expression of emotions, processing of social stimuli, learning of social behaviors, verbal and nonverbal communication, and stereotypic behaviors. Pathological acceleration of brain growth and immaturity of neurons and neuronal networks in early childhood indicate that (a) a significant portion of structural/functional defects starts in early infancy and (b) causative factors dysregulate the mechanisms controlling brain/neuron development. The deceleration of brain growth in the second year of life and the increase of neuronal size in late childhood/adulthood suggests delayed activation of correcting mechanisms. However, the delayed correction of brain and neuronal size does not result in functional recovery. Analysis of the detected pattern of abnormal brain development in autism indicates that early diagnosis and early treatment may prevent or reduce developmental delay, reduce/eliminate secondary structural and functional changes, and improve clinical status throughout the life span.

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FIGURE 14.1 (See color insert following page 200.) Possible mechanism by which GI dysfunction may trigger autistic behaviors in children with autism and GI disturbance. Cross BBB Peripheral cytokines activate CNS immune response Neuronal damage mediated by cross-reactive Ab’s and/or T cells Direct cytokine action in brain Molecular mimicry leading to cross-reactive Ab’s and/or T cells Egress of microbial/dietary antigens Proinflammatory cytokines (e.g., TNF-α and IFN-γ) Regulatory cytokines (e.g., IL-10) Altered GI permeability Innate/adaptive immune dysfunction GI inflammation


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