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Review

Update on autism: A review of 1300 reports published in 2008

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ABSTRACT

This publication, by reviewing 1300 studies published on autism in 2008, represents an update on this topic. Results include possible parental influences, maternal conditions, and studies on genes and chromosomes. Possible etiological factors involve the "extreme male brain," defects in the mirror neuron system, vaccines, underconnectivity, disorders of central coherence, and many other more specific etiologies. Assessments or tests for autism are also reviewed. Characteristics of autistic individuals include repetitive behavior, language disorders, sleep disturbances, social problems, joint attention disorders, seizures, allergic reactions, and various behavioral changes. Cognitive changes involve IQ, reasoning, and verbal and language disorders. The savant syndrome is a fascinating phenomenon, at times seen in autistic individuals. Neurophysiological and neuroanatomical changes are also reviewed, as are comorbid conditions. Finally, treatment involves various medications including risperidone, ziprasidone, and antipsychotic drugs, as well as different procedures such as magnetic stimulation, acupuncture, and hyperbaric oxygen therapy. As mentioned in the 2007 survey, nearly every conceivable problem that a child can have may be found in these unfortunate children and nearly every conceivable etiology has been mentioned to account for this serious disorder.

1. Introduction

In a previous publication [1], the present author reviewed studies published on autism during the year 2007. The goal of this report is to similarly review studies on autism published during the year 2008.

2. Method

Nearly 1300 reports were listed on Medline under the title "autism." The reviewer chose to discuss in this report those studies that came to some clear conclusion or included specific data. Disregarded were studies that were published in 2008 but were not listed on Medline until 2009, and also those that were not exclusively on the topic of autism or came to no specific conclusion. Genetic studies are deemphasized here, especially because the previous report by this reviewer on 2007 studies [1] indicated that a very large number of genes and chromosomes seem to be involved, and therefore, possibly a review on this specific topic itself is required.

3. Results

3.1. Possible parental influences

3.1.1. Psychological changes

One of the major differences between the 2007 review and the present one of 2008 is the number of studies implicating the parents of children with autism. Wallace et al. [2] indicated that parents' depression is associated with the child's repetitive behavior and parents' anxiety is related to the child's social communication problems. Family history of depression and shyness were the subject of another study [3], and these family factors had the greatest influence on socialization scores of the child. The authors concluded that these results have obvious implication for genetics. Daniels et al. [4] reported that parents of children with autism are more likely to be hospitalized for some type of mental disorder than controls and that depression and personality disorders are more common among mothers than fathers. Others [5] have also emphasized parents' depression and anxiety, in addition to family conflict, as predictive of symptoms of autism in the children.

Alexithymia is the inability to cope with and to describe emotion. According to Szatmari et al. [6], parents of children with autism scored higher than controls on tests measuring this variable. Also, children of fathers who had high scores showed a greater degree of repetitive behavior, compared with children of fathers with low scores on this variable of alexithymia.

3.1.2. Age

Using data from 1251 children with autism at 8 years of age, Durkin et al. [7] showed that both maternal age and paternal age are independently associated with autism. Odds ratios (ORs) for autism increased to 1.3 for a maternal age of >35 years and to 1.4 for paternal age >40 years. Also, firstborn children of two older parents were three times more likely to develop autism than a third or later-born offspring of mothers 20–34 years of age and fathers aged <40 years.

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Another group [8] was more specific about age, concluding that increased paternal age, but not maternal age, is associated with an elevated (1.8-fold increase) risk of autism.

Weiser et al. [9] included 403,486 adolescents assessed for one characteristic of autism, poor social functioning. The investigators reported that the prevalence of the latter characteristic was increased (OR = 1.27) in fathers both <20 and >45 years of age. Also, male children of mothers >40 were 1.15 times more likely to have poor social functioning. Furthermore, other investigators [10] reported that mothers >35 were 1.7 times more likely to have a child with autism.

3.1.3. Other parental characteristics

Meltzer [11] assessed the sleep of parents who had children with autism and reported poorer sleep quality in those parents. In particular, these parents had different sleep patterns, with an earlier wake time and shorter total sleep time, compared with parents of healthy children. Also, fathers had a shorter sleep time than mothers.

In his early descriptions of autism, Kanner [12] noted that parents of children with autism often exhibited unusual social behavior themselves and so Adolphs et al. [13] assessed this particular characteristic. They reported that these parents manifested a decrease in processing the eye region of faces and an increase in viewing the mouth, just like the children with autism. These data may provide a window into a subset of genes that contribute to social cognition.

Another group [14] reported that parents of children with autism have lower Performance IQ, but not Verbal IQ. Also, these same parents had lower scores on a nonword repetition task, suggesting problems in phonological processing.

One other characteristic of parents of children with autism is that their costs for medical care for their families are substantially increased. Montes and Halterman [15] reported that the average loss of annual income for a family with a child with autism was $6200, or 14% of the reported annual income.

3.2. Maternal conditions

Wallace et al. [2] reported that maternal hypertension, albuminuria, and generalized edema were associated with higher repetitive behavior scores in the children with autism. Another group [16] reported that the following conditions in infants and mothers are associated with autism: (1) lower birth weight, (2) lower gestational age, (3) male gender, (4) chorioamnionitis, (5) acute intrapartum hemorrhage, (6) illness severity on admission and (7) abnormal MRI of the infants. The authors emphasized very low birth weight. Brown et al. [17] added further evidence that an infection during pregnancy predicts a diagnosis of autism, and concluded that other questionable factors are really not associated. These included *not* (1) vomiting in the first trimester, (2) having smell aversions, and (3) craving sweets. Another negative finding was that the risk of autism remained unassociated with maternal Rh status [18].

Rogers [19] noted the inverse association between maternal folate status and incidence of neural tube defects (NTDs). However, this author has asked the intriguing question of whether worldwide enhanced folate status during pregnancy has altered the prevalence of autism. The author has suggested that enhanced folate status has changed natural selection by decreasing miscarriage and therefore increasing survival rates during pregnancy of infants possessing the MTHFR (5-methylenetetrahydrofolate reductase) C677T polymorphism. These changes occur via a reduction in hyperhomocysteinemia associated with this genotype, thereby decreasing miscarriage rates of infants who otherwise may have not survived. This situation points to an increased rate of birth of infants with higher postnatal requirements for folic acid needed for normal methylation, leading to an increased number of cases of developmental disorders, like autism. Thus, the author points to an intriguing coincidence between a decreasing incidence of NTDs and an increasing incidence of autism.

James [20] tested the theory that various disorders, including autism, are caused by high maternal intrauterine testosterone levels by determining the number of brothers among siblings. Although the data suggest that reading disorders may be caused by high testosterone levels, the data on autism were not significant.

Other investigators [21] studied whether births at certain months of the year were associated with autism. They reported peaks of autism in April, June, and October for single births and 1 month earlier in March, May, and September for multiple births in males. In 2005, Hughes and Melyn [22] had reported peaks in May and October for all children with autism. These seasonal trends suggest a role for nonheritable factors, even in cases with a genetic susceptibility.

3.3. Genes and chromosomes

As mentioned under Methods, the discussion of genes and chromosomes is deemphasized in this report, but a few general points need to be mentioned. One of the reasons for this deemphasis can be found in a report by Wall et al. [23]. These authors identified 154 genes not previously linked to autism, of which 42% were differentially expressed in children with autism. Furthermore, the investigators uncovered 334 new genes that interact with published autism genes, of which 87% were differentially regulated in individuals with autism. Perhaps, it was the great number of implicated genes that led Freitag [24] to conclude that "the majority of autistic disorders are genetic in origin."

One new area of interest is the imprinting gene [25], expression of which is determined by the parent who contributed it. Crespi and Badcock [26] have proposed that autism is mediated in part by changes in genomic imprinting. They have suggested that imprinting genes with maternal expression engender a general pattern of neural *undergrowth*, as seen in schizophrenia. By contrast, autism appears to involve a relative bias toward effects of paternally expressed genes, which mediate *overgrowth*, as may be seen in autism.

One other interesting hypothesis [27] is that dysregulation of brain-expressed genes on the X chromosome constitutes the major predisposition to autism. This dysregulation is mediated by the hypo- or hypermethylation of cytosine guanine sites with gene promoters, leading to over- or underexpression of brain-expressed genes. This condition results in an unbalanced production of proteins responsible for brain structure and function. This same hypothesis is consistent with the predominantly sporadic occurrence of autism, male excess among children with autism, and the usual absence of malformations in this same group.

The complexity of so many genes that have thus far been named in autism is expressed by Basu et al. [28], who have established a disease-driven database in which all genes connected to autism are collected from all laboratories.

3.4. Possible etiologies

3.4.1. Extreme male brain

As females are often considered to excel over males in empathy and social relationships and deficiency of this characteristic represents the hallmark of autism, children with autism may be viewed as having "an extreme male brain." James [20] checked to see if high fetal testosterone (fT) levels could be found in mothers who had children with autism. Although fT levels in reading disabilities

and attention deficit hyperactivity disorder (ADHD) were significantly high, levels in mothers with children with autism were not. Theoretically, Barbeau et al. [29] argued that fT levels in autism fail to account for a major part of autism and the weak link between fT and autism traits hardly demonstrates the causal link between the two.

On the other hand, other investigators [30] performed amniocentesis on 193 mothers who, with their own children, completed a test measuring empathy. There was a significant negative correlation between fT levels and test scores, suggesting that deficiency in empathy may be influenced by and mediated by the effects of high androgen levels on the brain. Also, Auyeung et al. [31] reported on the relationship between levels of fT ($N = 235$) and tests measuring traits of autism. The fT levels were positively associated with higher scores on the tests measuring autism, suggesting that greater androgen exposure is related to children exhibiting more autistic traits.

Finally, another group [32] used the EEG rhythm mu waves, responsive to movements of one's self or observing those of others, as a reliable indicator of the human mirror-neuron system, viewed as deficient in autism. Females showed stronger mu suppression when viewing hand actions of others, also positively correlated with the personal distress subscale of the interpersonal reactivity test. The authors concluded that their findings lend support to the "extreme male brain" theory.

3.4.2. Deficient mirror-neuron system

Mirror neurons are those brain cells that are active not only while one is reacting but also when one is observing others in the outside world. As autism is characterized by domination of one's "inside world," these neurons are viewed as deficient in children with autism. In the aforementioned study [32], the authors concluded that the mu rhythms in the human mirror-neuron system (MNS) can be a potential biomarker of empathy. Oberman et al. [33] also used mu suppression to investigate the MNS and reported that the suppression was sensitive to the degree of familiarity of the person viewed on the screen by the subject. The authors suggested that the MNS responded to observed actions, but only when familiar individuals were seen. Another group [34] also used EEG desynchronization during observation of various scenes and reported that no desynchronization occurred in children with autism, but this phenomenon did occur in healthy children. The authors concluded there was an impairment of the MNS in autism.

Another way to judge the MNS is to compare effects on patients with autism *between* different persons versus *within* the person. Welsh et al. [35] reported that autistic individuals did not demonstrate a *between*-person effect in which they were to observe the movement of a partner, but did show a *within*-person effect, as evidence for a MNS dysfunction in autism. Another report [36] indicated that in autism there was impairment in the ability to identify envy and gloating. Also, the ability to recognize these emotions was related to scores measuring the capability to appreciate perspective. Another group [37] tested the MNS by measuring skills to convert sensory stimuli into motor representations. Individuals with autism were capable of the task only 56% of the time, in contrast to 88% for healthy individuals. This impairment of multisensory integrations was viewed as an example of an impairment of the MNS.

The MNS has as times been linked to the Theory of Mind (ToM), representing a "domain-specific mechanism for metarepresentation of mental states" [38]. The authors, Stone and Gerrans, concluded that if deficits on ToM tasks can result from deficits on low-level specific input systems (like tracking gaze) or higher-level general capacities, then postulating a separate ToM mechanism may be unnecessary. For other authors, like Colvert et al. [39], ToM is still a viable construct, measured in their study by the Strange Stories Task, with scores indicating deficiencies in a group of children with institutional deprivation who then developed autism-like symptoms.

Not all investigators have agreed with the usefulness of the concept of the MNS. Southgate and Hamilton [40] referred to the "broken mirror" theory and stated that the failure in children with autism to imitate requires much more than the MNS, which they viewed as premature. Leighton et al. [41] went one step further by stating that "impairments in imitation skills should not be cited as evidence consistent with mirror system deficient theory." They showed evidence that subjects with autism were as impaired on nonimitative tasks as on imitative tasks.

3.4.3. Vaccines (mercury-containing thimerosal)

A major controversy in autism has been whether or not thimerosal (T), a mercury-containing preservative used in some vaccines in the past, is in any way responsible for autism. In the survey of autism studies published in 2007, this reviewer presented considerable evidence against the possibility that thimerosal has played a significant role as an etiological factor of autism [1]. In 2008, Schechter and Grether [42] reported that exclusion of thimerosal from vaccines in the United States was accelerated from 1999 to 2001. As the prevalence of autism in California's developmental services system increased for each quarter from 1995 to 2007, the conclusion of the authors was that the "data do not support the hypothesis that exposure to thimerosal during childhood is a primary cause of autism." Croen et al. [18] approached the problem differently by investigating the association between prenatal exposure of maternal Rh-D status to thimerosal-containing anti-D immune globulin and the risk of autism. Their conclusion was that the risk of autism was unassociated with the latter factor, supporting the position that prenatal exposure to thimerosal-containing anti-D immune globulins does not increase the risk of autism.

A novel approach to this problem of possible mercury poisoning is found in a study by Palmer et al. [43], who determined the relationship between the proximity to sources of mercury pollution and prevalence of autism. These authors claimed that for every 1000 pounds of industrial release of mercury, there was a corresponding 2.6% increase in autism rates, but a 3.7% increase in power plant emissions. For every 10 miles from industrial sources there was an associated *decreased* autism risk of 2.0%, suggesting no clear relationship between mercury and autism.

The Food and Drug Administration [44], updated on June 3, 2008, has stated, "Thimerosal has been removed from or reduced to trace amounts of all vaccines routinely recommended for children 6 years of age and younger, with the exception of inactivated influenza vaccine. A preservative-free version of the inactivated influenza vaccine (contains trace amounts of thimerosal) is available."

Other reports, however, may be keeping this controversy alive. For example, Cave [45] provided the history on this problem, reminding us that after Leo Kanner's first description in the 1940s [12], the incidence of autism before the 1970s was said to be 1 in 10,000, but has steadily increased to 1 in 150 in 2008. Many have believed that an environmental trigger, like T, used in vaccines since 1931, may be involved. Cave also reported that the Hannah Poling vaccine decision was a landmark case. The family was awarded funds to care for their child with autism who was found to have a mitochondrial dysfunction, considered to have been exacerbated by vaccines. It is known that children with mitochondrial dysfunction at times have autism, and so the award was for the *exacerbation of that mitochondrial dysfunction* and not, as many parents of children with autism had wished, for the vaccine causing autism. A recent court decision, the "Vaccine Court Omnibus Autism Proceeding," [46] confirmed the latter point on February 16, 2009.

Another court decision on vaccines as a possible cause of autism was reviewed in the *American Medical News* on April 13, 2009: "On February 12 a panel of U.S. Court of Federal Claims judges, known as special masters, released its findings "that the vaccines were not to blame." This decision was based on 5000 pages of transcript, more than 700 pages of post-hearing briefs, 939 medical articles, 50 expert reports, and 28 expert witnesses. This decision should put an end to this controversy.

Yet still other data may continue to keep this controversy alive. Branch [47] has provided data that are based on mice, but are suggestive of the human condition. Human autism occurs nearly four to eight times more frequently in males. In this study, mice were given the maximum tolerated dose of thimerosal. Seven of seven male mice, compared with none of seven female mice, succumbed to thimerosal, indicating a gender-selective toxicity of thimerosal.

Geier et al. [48] studied biomarkers of environmental toxicity and susceptibility to autism. Participants with severe autism showed increased mercury intoxication-associated urinary porphyrins, compared with those with only mild autism. Also, they showed decreased levels of reduced glutathione, cysteine, and sulfate. The porphyrins were correlated with increasing autism scores, suggesting that mercury intoxication may be associated with autistic symptoms.

Young and the two Geiers [49] studied possible associations between neurodevelopmental disorders and exposure to thimerosal. A total of 278,624 subjects who had received vaccines from 1990 to 1996 were studied, and it was reported that increased rate ratios of mercury were observed for autism and other disorders like ADHD and tics. By contrast, none of the control outcomes had increased rate ratios with mercury exposure. Another group [50] provided evidence that acetaminophen use after MMR vaccination is associated with autism.

Smith et al. [51] were concerned about the possibility that media coverage of the measles–mumps–rubella (MMR) vaccine/autism controversy may have contributed to this question. They reported that as few as 0.77% of children in 1995 *failed* to receive MMR vaccine, increasing to 2.1% in 2000 and returning to baseline before sustained media coverage of this controversy flourished. Thus, this finding suggested a limited influence of the mainstream media on the MMR immunization/autism controversy. One other study [52] was concerned about the presence of measles virus (MV) RNA in bowel tissue of children with autism, but the authors found no difference between cases with autism and controls, as evidence against autism being related to persistent MV RNA.

3.4.4. Underconnectivity

The present reviewer [53] previously summarized the data suggesting that one firm finding in autism is underconnectivity. Further data include the report [54] that the adult brain in autism shows reduced connectivity in the right inferior frontal cortex. Molloy et al. [55] reported that the increase in seizures in children with autism and trisomy 21 may indicate a loss of connectivity, also emphasized by Rapin and Tuchman [56]. Others [57] have discussed the growing body of evidence of reduced functional and structural connectivity in autism. Wicker et al. [58] reported abnormal connectivity, especially involving the prefrontal cortex. Another investigation [59] associated the reduction in connectivity with reduced variability in motor behavior.

O'Connor and Kirk [60] associated increased activation of occipital-temporal regions and reduced connectivity with atypical social behavior in autism. Another group [61] explained the savant syndrome often associated with autism, by pointing to the long-range connectivity that is likely disrupted, but then with a compensated enhanced local connectivity to explain the superior abilities. Tommerdahl et al. [62] proposed that functional minicolumns in autism were smaller in size, leading to global dysfunctional connectivity across cortical areas. Another group [63] reported that fractional anisotropy was lower in autism for short-range fibers, but not for long-range fibers. Finally, Coben et al. [64] showed hypocoherence in EEG signals suggesting neural underconnectivity.

3.4.5. Weak central coherence: Integration of diverse detailed information

Lopez et al. [65] assumed that if there was a central integration mechanism disorder, then the performance on a memory and a face recognition task should be related. No relationship was found, suggesting that central coherence was not a unitary construct. Also, other data [66] indicated that executive impairments were neither universal nor exclusive in the group with autism, suggesting an alternative cognitive theory. However, Ring et al. [67] examined clustering of symptoms and reported results that were consistent with a unitary spectrum model, especially in those with severe autism. Another group [68] investigated whether visuospatial analysis in autism extended into the general population, concluding with support for a weak central coherence theory in autism with emphasis on details rather than the whole of any question. The same conclusion was reached by Brock et al. [69] in a study on eye movements. Finally, one group [70] studied performance on two visual tasks, concluding that children with autism showed a deficit in holistic processing as an example of the failure in autism to deal with the whole instead of the details.

3.4.6. Various specific etiologies

3.4.6.1. Mitochondrial dysfunction. As previously mentioned, Cave [45] reported that the Poling legal case was about the exacerbation of the mitochondrial dysfunction by vaccines, supporting the fact that a significant number of children with autism do have such a dysfunction.

Weissman et al. [71] explored the association between autism and mitochondrial oxidative phosphorylation. All of their patients had an initial diagnosis of idiopathic autism, but careful investigation identified clinical findings different from those of idiopathic autism. The data suggested a disturbance of mitochondrial energy production as an underlying mechanism in a subset of individuals with autism. Garcia-Penas [72] also investigated the relationship between mitochondrial disease and autism, reporting that high lactate levels in some patients suggest a disturbed bioenergetic metabolism. Like Weissman et al. [71], Garcia-Penas considered that a likely possibility may involve a dysfunction in mitochondrial oxidative phosphorylation in neurons [72]. Although this type of dysfunction may be a rare cause of autism, this etiology must be at least considered in some children with autism.

3.4.6.2. Immunological disorders. Blaylock [73] noted the relationship between food allergies, gut dysbiosis (poor vitality), and abnormal formation of the developing brain. He proposed that repeated microglial activation can result in an increase in excitotoxins, resulting in arrest of neural migration, all under the term *immunoexcitotoxicity*.

Ashwood et al. [74] provided data and also a theory involving immune dysregulation. The investigators evaluated 75 children with autism, reporting low plasma transforming growth factor (TGF) β1 levels. The levels correlated with lower adaptive behaviors and worse behavioral symptoms. These data suggested that immune responses in autism may be inappropriately regulated as a result of decreases in TGF β1 levels.

Other investigators [75] studied folate receptor (FR) autoimmunity and cerebral folate deficiency. Evaluated were children (25) with autism who showed normal serum folate levels but low cerebrospinal fluid folate levels, possibly explained by FR autoantibodies blocking the folate binding site. The conclusion was that serum

FR autoimmunity may represent an important factor in reduced folate transport in autism.

3.4.6.3. Congenital and neurological disorders. Chen et al. [76] studied 3440 children with autism and reported greatly elevated risks of congenital anomalies, like tuberous sclerosis, and neurological disorders, like epilepsy, with odds ratios of 34 and 5, respectively. The authors concluded that these disorders may provide etiological implications in autism.

As an example of a neurological disorder, Singh et al. [77] proposed that a clinically relevant measure is cortical thickness as a classifier in autism. Another example was cortical folding [78]; increased three-dimensional folding in the frontal, parietal, and temporal lobes was demonstrated in children with autism as compared with controls. These differences were greater in children than in adolescents with autism.

3.4.6.4. Deficient proteins. Hagerman [79] was concerned with the fragile X mental retardation protein (FXMRP) and reported that when some of these proteins are missing, there is a dysregulation of other proteins known to cause autism. This FXMRP protein provides for inhibition of protein production in the metabotropic glutamate receptor 5 pathway (mGluR5). The conclusion was that these mGluR5 antagonists are likely involved in a subgroup of patients with autism. Other authors [80] have agreed that protein synthesis may be an etiological factor in autism. In particular, aberrant synaptic protein synthesis was proposed by these latter investigators as leading to autism, with characteristics of cognitive impairment and savant abilities.

3.4.6.5. Metabolic disorders. Maimburg et al. [81] studied 473 children with autism and reported that infants who had hyperbilirubinemia after birth had an almost fourfold risk for autism. Also, a strong association was observed between abnormal neurological signs after birth, especially hypertonicity, and autism. One short report [82] referred to two children in Saudi Arabia with G6PD (glucose-6-phosphate dehydrogenase) deficiency, a condition that has previously been reported to be associated with autism. Austin and Shandley [83] studied atypical urinary porphyrin profiles as an indirect measure of environmental toxicity. In a sample of Australian children with autism, the authors reported a consistent trend in abnormal porphyrin levels and referred to data demonstrating porphyrinuria concomitant with autism. Geier et al. [84] evaluated transsulfuration metabolites in children with autism. They reported decreased plasma reduced glutathione, cysteine, taurine, and sulfate levels, but increased plasma oxidized glutathione levels. The authors concluded that these data are compatible with increased oxidative stress and decreased detoxification capacity in patients with autism. Vojdani et al. [85] provided additional evidence of low intracellular levels of glutathione in these children and concluded that these levels are related to low natural killer cell activity in autism. Another group [86] studied dopamine transporters and reported an increase of the latter in autism, concluding that the dopaminergic nervous system is dysfunctional in autism.

Another group of investigators [87] studied the metabolism of serotonin following the administration of L-5-hydrotryptophan (5-HTP) to persons with autism. They reported decreased dehydroepiandrosterone sulfate (DHEA-S) responses. These results suggested that autism is accompanied by a major dysequilibrium in the serotonergic system.

Rout and Dhossche [88] noted that loss of Purkinje cells and cerebellar atrophy are commonly observed in autism and proposed that this cell loss was triggered by glutamic acid decarboxylase antibody (GAD-Ab). This model accommodates to any genetic basis of autism, and the identification of GAD-Ab from pregnant mothers may allow preventive avenues.

As previously noted, Rogers [19] pointed to the increased use of folic acid in mothers, which increases the key enzyme for methylation, methylenetetrahydrofolate reductase (MTHFR), which increases plasma homocysteine. The latter hyperhomocysteinemia, in the presence of the MTHFR-C677T polymorphism, modifies miscarriage rates and may be related to the development of autism.

Another group [89] noted the involvement of digestive tract dysfunction in children with autism and found that there were lower urinary levels of essential amino acids in both treated and untreated children. The conclusion was that these results represented evidence of altered metabolic homeostasis.

Hardan et al. [90] were concerned with thalamic alterations using magnetic resonance spectroscopy (MRS) and reported lower levels of *N*-acetylaspartate, phosphocreatine, and creatine on the left side of the thalamus. Some relationships were observed between these metabolites and measures of sensory abnormalities. In another study [91] in children with autism, morning cortisol levels were reported to be decreased, whereas higher evening values were maintained, with variability in all these levels. The conclusion was that these results indicate a dysregulation of the circadian rhythms in autism.

Some studies have provided negative evidence for factors presumed in the past to be involved with autism. Russo [92] reported that a large number of autistic family members had high levels of anti-metallothionein IgG, but these antibodies did *not* correlate with autism. Also, some investigators have claimed that the urine of children with autism contains exogenously derived opioid peptides, but studies showed no differences between the urinary profiles of children with autism and those of controls [93].

3.4.6.6. Interactions. Stefanatos [94] discussed the multiple etiological factors currently hypothesized in autism, and others [95] have agreed that the etiology seems to be multifaceted, including both heritable and nonheritable factors. The present section here on possible etiological factors attests to this latter point. Another group [96] maintained that even part of the genetic load in autism may reflect gene–environment interaction. On a much more specific point of some surprise, Waldman et al. [97] showed that the prevalence of autism was positively associated with the annual precipitation of a given region. The investigators concluded that this may be an environmental trigger among genetically vulnerable children.

3.4.6.7. The intense world syndrome. Markram et al. [98], using a rat model, proposed that the autistic brain is hyperreactive with hyperplasticity of local neuronal circuits, leading to hyperperception, hyperattention, and hypermemory. This hyperfunctionality then turns debilitating, and the excessive neuronal processing renders the world painfully intense, hence the "intense world syndrome." Although a few data may be consistent with this interesting hypothesis, there are many examples of hypofunctioning neuronal circuits in autism.

3.5. Assessment

Various measures and tests have been used to assess autism. Williams et al. [99] reported assessment in school developmental disability determinations and also in a hospital setting. The rate of agreement between different evaluators was only 45%. Another group [100] compared parents' evaluation with one standard test in autism, the Modified Checklist for Autism in Toddlers (M-CHAT). The parents missed the majority (84%) of children who screened positive on the M-CHAT. Other studies [101] showed a low agreement index between mothers' and professionals' observations. Stone et al. [102] used the Screening Tool for Autism in Two-Year-Olds (STAT) and reported a positive predictive score of only

56%, with false positives highest for the age group 12–13 months. Other results [103] were consistent with the latter study, showing that the positive prediction percentage was not as good under 24 months of age than at 24 months. On the other hand, Ozonoff et al. [104] found that repetitive behaviors in children with autism as young as 12 months were related to cognitive status at 36 months. Others [105] were concerned about the usefulness of M-CHAT in Arab countries and reported a positive predictive value of 88%. Another test, the Childhood Autism Spectrum Test (CAST), was used by Williams et al. [106] on 3370 children 4–9 years of age; scores were reported to be higher in males who were predominant at a ratio of 4:1 for scores >15. These data must be considered in dealing with communication skills in boys and girls.

There are other means of testing for autism. Esposito et al. [107] used static and dynamic symmetry during walking and moving to judge autism and reported significant differences between children with autism and controls as early as 5 months of age. Early onset of autism was more likely to be found with lower levels of symmetry, which can be used as an early indicator of potential autism. Repetitive and stereotyped movements were used by others [108] to determine autism and to support the diagnostic significance of these movements under 24 months of age.

One other measure used by Schendel and Bhasin [109] comprised birth weight and gestational age. Birth weight <2500 g and preterm birth at <33 weeks gestational age were associated with a twofold increased risk for autism.

3.6. Characteristics

3.6.1. Repetitive behavior

Lam et al. [110] described three distinct factors in autism, including repetitive motor behavior (RMB), insistence on sameness, and circumscribed interests. The RMB was associated with more impairment in the social and communication domains. Other investigators [111] provided evidence that independent genes were involved in RMB, compared with the two other important impairments of social skills and communication. Another group [112] emphasized that these movements were less frequent and less severe in older individuals with autism. Phagava et al. [113] found that these children exhibited abnormal writhing and fidgety movements as early as 2–5 months. Others [114] explored whether one type of RMB, walking, could distinguish the group with autism, and after 6 months of independent walking, different patterns were seen in children with autism, similar to the aforementioned report [107]. It was during the second year that Watt et al. [115] claimed that RMB was related to social incompetence and could predict the severity of autism symptoms at 3 years.

3.6.2. Specific language impairment

Loucas et al. [116] investigated whether a specific language impairment (LI) was related to other symptoms of autism and reported that the co-occurrence of LI and other symptoms of autism was not generally associated with increased symptoms of autism, but only with greater impairment of functional communication. Williams et al. [117] would likely agree because their main emphasis was that LI in autism cannot be explained by a comorbid specific LI. Other investigators [118] were also concerned with a specific LI and investigated cerebral dominance in particular. They reported that 82% of the group with autism showed left hemisphere dominance, whereas those with a specific LI had right hemisphere (55%) or bilateral (27%) involvement. Thus, according to these authors, atypical cerebral dominance was not implicated in autism. Prosody is one characteristic of speech and another group [119] showed that adolescents with autism had difficulty using prosody to clarify syntax. With a similar age group, Baird et al. [120] reported that 38% of those with autism showed language regression, as opposed to only 3% with such regression but with developmental problems without autism. Finally, other data [121] indicated that 50% of children with autism and severe LI used challenging behavior as a form of expressive communication in a school environment.

3.6.3. Sleep disorders

Matsuura et al. [122] studied sleep patterns in children with autism and reported that young infants with autism often experience sleep difficulties. In particular, great changes in sleep onset and waking times, frequent night waking, and fragmented sleep patterns were observed in early infantile autism, in addition to an irregular sleep–wake cycle, also reported by others [123]. Krakowiak et al. [124] added further confirmation that the majority (53%) of children with autism had at least one frequent sleep problem, usually high scores on sleep onset and night waking.

3.6.4. Social problems

One group of investigators [125] attempted to identify the degree to which early symptoms of autism could be predictive of later symptoms. They reported that social interaction was closely related to one factor, namely, social communication. An additional factor was anxious and compulsive behavior that affected communication functioning. Ben-Sasson et al. [126] reported that the greatest differences between children with autism and controls with respect to symptoms of sensory modulation and affective social problems was underresponsivity, followed by overresponsivity and sensation-seeking behavior. Other investigators [127] reported that children with autism were likely less sensitive to emotional information conveyed by human movement, representing a deficit in emotional perception that would likely lead to social problems. Hartley et al. [128] provided data that would have clear impact on these social relationships. They showed high scores in the group with autism on withdrawal, attention, and aggression, as well as significant maladaptive behavior, highlighting the need to include ways to increase social engagement. One other study [129] would have possible impact on social relationships in that patients with mood disorders scored high on autism symptom scales. The authors emphasized the importance of identifying social reciprocity and communication deficits in patients with autism. Other studies include results that show withdrawn behavior and social problems [130] and, finally impairment, in identifying envy and gloating [36], in addition to bipolar mood disorders [131], low positive affect, and high negative affect [132]. These latter disorders would likely have an impact on social relationships.

3.6.5. Joint attention disorders

One group [133] studied joint attention in autism and reported that 2- to 3-year-old children with autism displayed deficits in joint attention ability, especially on high-level skills and often leading to social communicative difficulties. Roos et al. [134] pointed out that joint attention deficits may be a core feature of autism. They reported a positive correlation between initiation and response to joint attention. Also, Adamson et al. [135] emphasized the persistence of coordinated joint attention deficits. Two studies cast some doubt on how important joint attention may be in autism. For example, one investigation [136] showed that selective or sustained attention was not altered in autism, even though more problems were seen in joint attention skills. On the other hand, Rutherford et al. [137] reported that, contrary to some predictions, individuals with autism tended to show relatively smaller divided attention problems than did matched controls.

3.6.6. Seizures

Mouridsen et al. [138] reported that the mortality risk of persons with autism was nearly twice that of the general population.

Of the 26 deaths they reported, nearly one-half (46%) were associated with epilepsy. Another group [139] reviewed 2112 patients with autism and intellectual disability (ID), in addition to 1530 other patients with autism. More patients with autism and also with ID had epilepsy (21.5%) than those without ID (8%). The male:female ratio with epilepsy with 2:1, whereas the ratio without epilepsy was 3.5:1. These studies indicate that ID and female gender show a relatively high association with seizures. Other investigators [140] studied the risk problems in autism and concluded that epileptic seizures and epileptiform EEG abnormalities were the most important factors, in addition to non-right-handedness, hypotonia, and decreased IQ. Another group [141] showed that seizures were associated with behavior regression, similar to the conclusion made by other investigators [142] that epilepsy and regression were, in fact, associated. Giannotti et al. [143] also concluded that epilepsy and epileptiform patterns are more frequent in regressed children.

3.6.7. Dentition

Loo et al. [144] published results that may be surprising to some: they reported that children with autism were more likely to be caries-free and have fewer decayed, missing, or filled teeth compared with controls. However, they indicated that this group was usually uncooperative and usually required general anesthesia to carry out examinations and treatments. Also, 52% of parents were reported [145] to consider the dentition of their children with autism (52%) as excellent or very good, compared with 69% of parents of children without autism. Dentists have reminded this reviewer that stereotyped behavior likely explains why some of these children may take excellent care of their teeth. The number of children with fair or poor teeth with autism was similar to that for children without autism. Thus, the results for dentition in autism vary.

3.6.8. Allergic reactions

Some investigators [146] had noted that a subset of children with autism may have frequent infections, accompanied by a decrease in acquired skills. They measured proinflammatory and counterregulatory cytokines and concluded that the clinical features in autism were not associated with atopy, asthma, food allergy, or primary immunodeficiency. Another group [147] reported that 30% of children with autism had a family history suggestive of atopy, but none with respiratory allergy, 48% with one positive skin test, but similar to controls. The conclusion was that allergic features were not frequent in children with autism, even in those with a positive family history.

3.6.9. Various behavioral changes

Sinzig et al. [148] were concerned with executive function and reported that children with autism were impaired in planning and feasibility functions. When behavior was studied in the form of physical activity at school recess, children with autism were less active than controls [149]. Another group [60] concluded that atypical social behavior in autism was likely a consequence of a general processing difference rather than an impairment in social cognition. Minshawi [150] pointed out that self-injurious behavior was common in children with autism and recommended treatment for this type of behavior. Other investigators [151] studied symbolic play and reported that children with autism showed less playful pretend behavior. Consistent with the latter results, Preissler [152] concluded that children with autism have difficulty understanding the symbolic nature of pictures by demonstrating difficulties in learning picture–word and picture–object relationships.

One last characteristic, not directly behavioral, is the greater height and weight of children with autism, compared with controls, but the authors [153] concluded that with older age, height decreased but the risk for overweight increased.

3.7. Cognitive changes

3.7.1. IQ

Although cognitive changes could be considered one of the characteristics of autism and therefore could have been discussed in the last section, its significance and importance required it to be dealt with in a separate section. One group [154] was concerned with two different assessments: Raven's Progressive Matrices (RPM) and Wechsler Intelligence Scale for Children (WISC). Although the average RPM scores were higher than the WISC scores only for those with IQ <85, the authors recommended the WISC as the first-choice measure. Banach et al. [155] were concerned with gender and family size, reporting that in families with a single child, girls had a lower IQ than boys, but no such differences were observed in families with more than one child. Another group [156], investigating differences between children with Asperger syndrome and autism, reported that 18% of the group with autism had a Verbal IQ higher than the Performance IQ, supposedly characteristic of Asperger. The conclusion was that this IQ profile was not a valid discriminator between the two disorders.

3.7.2. Reasoning

Pijnacker et al. [157] studied defeasible reasoning (that which is capable of being undone) in high-functioning individuals with autism. Their conclusion was that this group had specific difficulty with handling exceptions during reasoning that required mental feasibility, suggesting that defeasible reasoning was also involved. The same group [158], 1 month later, reported on pragmatic reasoning, finding a deficiency in the group with autism, different from that of the individuals with Asperger syndrome. Pragmatism was also the area of interest in another study [159] dealing with illogical thinking and loose associations characteristic of autism. The authors concluded that the formal thought disorder in autism was related to pragmatic language abnormalities. De Martino et al. [160] examined emotional responses and their effect on decisions, concluding that the group with autism often failed to incorporate emotional context into the decision-making process, thus showing an "insensitivity to contextual frame." Lind and Bowler [161] investigated a slightly different aspect, in part related to reasoning: extended self-awareness. The group with autism exhibited significant impairments in the Theory of Mind tasks, manifesting as reduced use of personal pronouns to refer to themselves.

3.7.3. Verbal and general language disorders

Gabig [162] examined verbal working memory and language ability in a group with autism and concluded that the latter group showed deficits, especially in more complex verbal memory tasks. These deficits would likely affect cognition in autism. Others [163] attempted to predict various characteristics in toddlers 18–33 months old. Nonverbal cognitive ability predicted both receptive and expressive language. Furthermore, other predictors of receptive language included gestures and response to joint attention, and for expressive language, both gestures and imitation were predictors. The importance of a language disorder versus the autistic disorder and the possible confusion surrounding the differences in these two entities were well illustrated by Bishop et al. [164]. These investigators reported that 32% of patients with earlier diagnosed developmental language disorder "would nowadays be diagnosed unambiguously with autistic disorder." Another example of changing diagnoses was shown by a study [165] finding that 28% of adolescents with ID, both severe and mild ID, were later identified as being autistic. This study may also indicate why the prevalence of autism seems to be increasing. Matson and Rivet [166] explored

the differences between ID and autism in a different way. They reported that patients with autism differed from those with ID in challenging behavior, manifesting mainly as aggression, self-injurious stereotyped behavior, and disruptive behavior. The frequency of this challenging behavior increased with the severity of autistic symptoms.

3.8. Sensory changes in general

A number of studies have indicated that patients with autism have diminished sensation in general. For example, Brown et al. [167] reported that these children had significantly lower sensory processing scores in all 14 categories tested. Another group [168] reported a significant correlation between the degree of sensory abnormalities and the amount of repetitive behavior, but observed no link with cognitive function. Oberman and Ramachandran [37] asked subjects to pair nonsense shapes with nonsense words and reported that the group with autism performed poorly on this test; they concluded that there was a deficit in the multisensory integration system. Another group [169] studied sensory deficits and their anatomical basis, concluding that brainstem abnormalities, specifically in gray matter structures, were involved. One investigator [170] studied auditory perception irregularities in children with autism and concluded that they are important in understanding this condition. Roberts et al. [171], through magnetoencephalographic studies, investigated auditory processing abnormalities, offering promise for assessing developmental neuropsychiatric disorders.

On the other hand, other studies have reported effects that may be considered opposite to some of the aforementioned results. Minshew and Hobson [172] reported that 32% of participants with autism endorsed more items involving sensory hypersensitivity than controls. These results support the common occurrence of sensory symptoms reported by children with autism, likely from increased sensitivity. Markram et al. [98] would likely agree in general with the latter authors and concluded that the core pathology of the autistic brain is hyperreactivity leading to hyperperception, hyperattention, and hypermemory. The excessive neuronal processing renders the world painfully intense, leading to their "intense world syndrome." Another group that would also generally agree is Vaccarino et al. [173], who concluded that an increased number of cortical excitatory neurons may underlie the increased brain volume. This excessive network excitability would be expected to lead to sensory reactivity and seizures. Another study [174] reported an accelerated response time to a visual test, and this advantage is likely related to enhanced perceptual functioning.

The last two paragraphs have described conclusions that counter each other. Ben-Sasson et al. [175] may have a unifying study that used the Infant Toddler Sensory Profile in 170 children with autism. Three clusters were identified: (1) 44 with a low frequency of sensory symptoms, (2) 49 with a high frequency of these symptoms, and (3) 77 with mixed symptoms. Parents rated those with high or mixed frequency as higher on negative emotion and depression and also anxiety symptoms. Thus, this study indicates that either a high or a low frequency of sensory symptoms can be observed in a group with autism.

One final study dealing with sensory symptoms and perception was that by Chamak et al. [176], who summarized the highlights of the personal experiences of adults with autism. Their core symptoms in autism were unusual perceptions, in addition to impaired informational processing and disordered emotional regulation.

3.9. Visual disorders

Autism has been characterized in part as an impairment in recognizing facial expressions. Hernandez et al. [177] reported that their group with autism spent less time viewing the eye region than healthy subjects, who began their exploration of a face by looking at the eyes in the field contralateral to their dominant eye. The latter strategy was impaired in the group with autism. Webster and Potter [178] would agree that a deficit in face-to-face eye direction is usually observed in children with autism, but that this deficit typically normalizes in adolescence. Also, other data [179] showed that a deficit in rapid facial reactions disappeared with age. In addition, Sterling et al. [180] confirmed the abnormal gaze patterns in autism, but claimed normal reaction times in the group with autism. Other investigators [181] emphasized that the group with autism fixated not on the eyes, but on the mouth, even when faces were inverted. Another group [182] added that there was a decrease in face recognition accuracy, likely from autonomic reactivity to eye contact, that would interfere with facial identity processing. As Pellicano [183] summarized, children with autism gained considerably less information from the eyes and more from the mouth. On the other hand, Homer and Rutherford [184] added that children with autism do perceive at least some facial expressions correctly.

Jones et al. [185] concluded that the deficiency of looking at the eyes of others likely begins in 2-year-old children, while looking at the mouth increases at that same time. Other investigators [186] attempted to determine whether differences in visual attention could contribute to initiative difficulty, and positive evidence was found for this likelihood. Scherf et al. [187] recognized the poor face recognition skills in autism, but generalized that these deficiencies would interfere with the ability to undertake any configural processing. Other investigators [188] concluded that in these children the visual pathway was intact at lower subcortical levels, but impaired at higher cortical levels. Van Kooten et al. [189] investigated the neurons in the fusiform gyrus that supported facial processing, reporting reduction in (1) neuron densities in layer III, (2) total neuron numbers in layers III, V, and VI, and (3) mean volumes in layers V and VI. Another group [190] concluded that a dysfunction in horizontal connections within the visual areas is likely involved. Adolphs et al. [13] moved beyond the child and examined the parents, reporting that they also showed a reduction in processing the eye region and demonstrated enhanced processing of the mouth. Another group [191] expanded this type of study into siblings of children with autism, reporting that the siblings showed a prolonged latency to the occipital P400 event-related potential (ERP) in response to the direct gaze.

A number of investigators have contrasted children with autism with those with Williams' syndrome (WS), who tend to be opposite in some ways to those with autism by being outgoing toward others. Riby and Hancock [192] reported that in WS there was prolonged face gazing, and in autism, reduced face gazing. The same group of investigators [193] later added that those with WS showed greater accuracy for matching faces, using upper more than lower features. In particular, in WS, there was greater detection of the eye than the mouth, whereas children with autism showed deficits in these matches. Still later, the same group [194] summarized that the group with autism spent less time viewing people and faces, whereas those with WS fixated exaggeratingly on the eyes. Krysko and Rutherford [195] confirmed the deficiency in persons with autism who could not differentiate angry from happy faces as well as could healthy persons.

Other studies have explored beyond the deficit of facial recognition in autism. Mongillo et al. [196] reported that persons with autism scored poorly not only on visual, but also auditory tasks involving human faces and voices, but not in tasks involving emotional faces. Other data [197] indicated that those with autism performed normally with neutral faces, but were impaired with nonhuman stimuli. Anderson and Colombo [198] reported a larger pupil size at rest but a decreased pupil response to human faces.

Other investigators [199] reported a difficulty in tracking visual targets in children with autism, similar to other findings [200] that these children were poor in judging gaze direction. Franklin et al. [201] concluded that children with autism also had a deficiency in color memory.

All of the aforementioned studies have concluded that children with autism have visual deficiencies, but other studies have drawn some opposite conclusions. For example, one group [202] found that adults with autism were faster and more accurate at detecting eye gaze than controls. Rutherford and Towns [203] would have challenged some of the previously mentioned results, as they concluded that the ratio of attention to eyes/attention to mouth did not differ between the autism and control groups. Other investigators [174] determined that an accelerated response time and shorter fixations indicated an advantage in children with autism, related to enhanced perceptual functioning. Finally, one surprising finding was reported by Ashwin et al. [204], who concluded that children with autism have superior visual abilities with a significantly better visual acuity at 20:7 (!), so superior that it lies in the domain reported for birds of prey.

3.10. Diet

One group of investigators [205] explored dietetic approaches in autism. Their summary of the literature findings on diets and disorders included: (1) metabolic errors, like the phenylalanine hydroxylase deficit responsible for phenylketonuria, possibly associated with autism; (2) increased opioid activity from an excess of peptides with gluten-free or casein-free diets involved; (3) in the amino acid domain a deficiency of glutamic or aspartic acid; (4) food allergy with high Ig levels; (5) in the area of glucidic catabolism an excess of ketones; and (6) vitamin deficiencies, especially vitamin B6 and B12. The conclusion of these investigators was that despite the many studies on specialized diets, few are methodologically satisfying, side effects cannot be ignored, and vitamin supplementation seems to be the only factor that some groups could use, always with parental agreement. Herndon et al. [206] had a direct approach and contrasted the diets of children with autism with the diets of those with typical development. The group with autism consumed more vitamins B6 and E, more nondairy protein servings, less calcium, and fewer dairy servings. The lower dairy serving intake persisted in the group with autism after controlling for many other variables. One last study [207] looked at eating behavior and found only that children with autism were more likely to demonstrate "picky" eating, thus exhibiting problematic eating and feeding behavior.

3.11. Changes in adulthood

Some studies have shown negative effects with age. Melville et al. [208] reported that adults with autism had a greater prevalence of problem behaviors and were less likely to recover from these behaviors over a 2-year period than their controls. Others [209] were more specific about their findings in adults with autism who had a severe ID. Compared with controls with only ID, the adults with autism with ID showed impairments in social interaction, restricted or repetitive behaviors, and interests constituting a distinct pattern of impairment. One other negative change was mentioned by Hallahan et al. [210]: although no difference was found in head or brain volumes, adults with autism, compared with controls, had a smaller cerebellar volume but a larger volume of peripheral cerebrospinal fluid. One other study [211] reported that 92% of women with autism had a late luteal phase dysphoric disorder, compared with 11% of controls, thus indicating an increase in premenstrual syndrome in many women with autism.

Other studies have reported positive effects with age in autism. For example, Fletcher-Watson et al. [202] concluded that adults with autism were faster and more accurate at detecting eye gaze than controls. Also, age-related improvements were found in executive function from childhood to adolescence, but mature executive function was limited [212]. Another group [112] reported that restricted repetitive behavior was less frequent and less severe among older than younger individuals, corroborating that autism may somewhat abate with age. One last study [179] reported that, as children with autism age, their ability to match rapid facial reactions to appropriate emotional facial expressions increases significantly.

3.12. Savant syndrome

Savant syndrome (SS) [213] is "characterized by remarkable islands of mental ability in otherwise handicapped persons." Treffert [213] reported that 10% of persons with autism exhibit savant abilities; nearly one-half of those with SS have autism and the remaining half have other forms of developmental disability. He also pointed out that calendar calculations, various mathematical skills, and extraordinary musical abilities can be observed, adding that males show signs of SS four times more often than females. Pitch discrimination is one area that has been reviewed in a few studies. For example, Heaton et al. [214] completed studies on pitch discrimination, reporting that a subgroup of individuals with autism achieved performance scores 4–5 SD above the mean for controls. The same group [215] explored identification of fundamental pitch frequencies in complex tones, and also nine tones and words, and reported that the group with autism "was highly superior in comparison to controls." Finally, other investigators [216] described a 4-year-old boy who could identify the pitch of any isolated tone. This absolute pitch is considered to be attributable to a single gene, transmitted in an autosomal dominant fashion.

Calendar calculation is another feature of SS. One group [217] reported a shorter reaction time and fewer errors regarding past dates, but no differences were found between individuals with autism and controls in calculation of future dates. These findings imply distinct calendar calculation when processing dates of the past and present but not likely future dates.

Studies on superior visual abilities have also been reported. Grinter et al. [68] claimed that individuals with autism were faster and more accurate on visuospatial analysis tests. As previously mentioned, another group [174] reported that the individuals with autism had an accelerated response time and shorter fixation compared with controls, indicating that these results of the eye movements indicate an advantage in autism. Also, as previously mentioned, Ashwin et al. [204] reported extraordinary visual acuity at 20:7 in the group with autism, as an example of sensory supersensitivity.

Takahata and Kato [61] addressed the issue of neural mechanisms involved with SS. They classified the cognitive models of SS into three categories: (1) savant skills develop from existing or dormant cognitive functions, such as memory; (2) "paradoxical functional facilitation" explains how pathological states may lead to great skills, especially through reciprocal inhibitory interactions between different brain areas; (3) the "autistic model" involves underconnectivity for long-range connectivity, but a more enhanced *local* connectivity. The enhanced connectivity in the local brain regions likely results in specialization and facilitation of cognitive processing.

3.13. Prevalence

A wider range of values for prevalence can be found within the United States and around the world, likely for many reasons,

especially that different definitions exist and also testing for autism varies significantly. If there are no clear criteria or tests for autism in a given region, the stated prevalence for that region will likely be low.

Rapin and Tuchman [56] provided the number that most individuals have recognized and is usually reported in the media as the prevalence in the United States, namely, *1 in 150* children; they also claimed that there is no epidemic. In December 2008 Kogan et al. [218], using the 2005–2006 survey of national data, indicated the prevalence as 86 per 10,000 children aged 3–17, which is equal to *1 per 116* children. Also, among children with special health care needs, 5.6% (1 of 18 children) had autism. Other authors [95] have also indicated that autism was more common than previously believed at 1 in 166 or 1 in 150.

Some investigators have determined the prevalence in a given state. Nicholas et al. [219] sampled the prevalence and determined the value in South Carolina to be 6.2/1000 or 1 in 161. In Olmsted County in Minnesota [220], a *clinical diagnosis* of autism was given to 1.5 per 100,000 (1/60,000) in 1980–1983 but to 33.1 per 100,000 (1/3000) in 1995–1997. In contrast, the prevalence of *research*-identified autism increased from 5.5 (1/18,000) in 1980–1983 to 44.9 (1/2200) in 1995–1997. These very different values demonstrate the variation between a "clinical diagnosis" of autism and "research-identified" autism, but the values from 1997 differ because the definitions and tests for autism were not the same then as they are now.

An important study from Denmark [221] helps to clarify why the prevalence of autism seems to have increased over time. All children born in Demark (407,458) from January 1, 1994 to December 31, 1999 were the subjects. The numbers of children with autism were counted separately for the periods 1994–1995, 1996–1997, and 1998–1999 and were diagnosed on average at ages 5.9, 5.8, and 5.3 years, respectively. The conclusion was that shifts in age at diagnosis inflated the observed prevalence and the apparent increase in autism in recent years was, in part, attributable to a decrease in the age at diagnosis over time. Thus, for a given survey at a given time, more children would already have the diagnosis of autism.

Other countries have provided prevalence values. From China, Wong and Hui [222] included in their study 4,247,206 person–years from 1986 to 2005 for those <15 years of age, and from Hong Kong, 1,174,322 person–years for those <5 years old. The prevalence for both populations was estimated at 16.1 per 10,000 (1/625) for children <15 years old. The authors claimed that these values were similar to those for Australia and North America and lower than those for Europe. From the United Kingdom, Williams et al. [223] reported a prevalence of 51.1 per 10,000 (1/200) for those with a multiprofessional diagnosis and 61.9 per 10,000 (1/162) from the Schools Census. The median age at diagnosis was 45 months. From Australia, another group [224] provided data for 6- to 12-year-old children from 2003 to 2004: 9.6–40.8 per 10,000 for state and territory data and 35.7–121 for national data. These values (at the highest level) represent 1 in 277 and 1 in 244, respectively. From Sweden, another group [225] attempted to determine if children with a Somali background were overrepresented among those with autism. The prevalence was found to be three to four times higher in the Somali group than in the non-Somali group. The values were 0.7 and 0.19%, equal to 1 in 143 and 1 in 526 children, respectively. Finally, for Latinos [226] the prevalence was 26 per 10,000 (1/385) compared to non-Latinos at 51 per 10,000 (1/196).

3.14. Neurophysiology

3.14.1. Electroencephalography

Mu activity at 7–12 Hz can be recorded from the central scalp areas and is suppressed by movements or thoughts of movement and also when the subject is observing others' movements. The latter refers to the mirror neuron system (MNS) and is normally active when observing others, proposed as deficient in autism. Thus, suppression of mu activity, as a manifestation of the MNS, was studied by Oberman et al. [33] who reported that the group with autism showed mu suppression according to the degree of familiarity of the individuals who were viewed. Thus, the MNS responded in individuals with autism, but only when observing a familiar face. Cheng et al. [32] also used mu waves as an indicator of the MNS and reported that females showed stronger mu suppression than males, supporting the theory that autism represents an "extreme male brain."

Milne et al. [227] studied stimulus-induced changes in the alpha and gamma frequencies near the striate and extrastriate areas. The group with autism showed a smaller effect and also a reduced time to peak alpha power. The investigators concluded that these results represent atypical processes during perception of visual stimuli.

Hrdlicka [142] studied the relationship between the EEG and autistic regression and reported that the data do not support such a relationship, although acknowledging an association between epilepsy and regression. However, other data [143] showed an association between regression and a circadian rhythm disorder. Another group [228] also reported on epilepsy and epileptiform activity on the EEG, stating that 67% of children with autism had EEG discharges, similar (59%) to what the present reviewer reported 4 years ago [22]. Also, the former group [228] found a lower synchronization in NREM sleep stages, confirming the validity of the underconnectivity model in autism. Also confirming underconnectivity was a study by Coben et al. [64] reporting low coherence for most frequency bands. The study reporting on epileptiform activity in autism [228] would likely require an EEG sleep study, which could be best achieved in patients with autism by using dexmedetomidine, according to one report [229].

3.14.2. Magnetoencephalography (MEG)

One group [230] claimed that most autism patients (22) had no EEG abnormalities (!), but all children (!) with autism showed MEG abnormalities as spikes, "as well as acute waves," mainly in the perisylvian areas. This report of normal EEGs in most children with autism and MEG patterns as "acute waves" is very surprising and could be challenged.

3.14.3. Evoked potentials and event-related potentials

Some investigators [231] have studied sensory gating by recording auditory evoked responses. The P450 component was suppressed to a second click, and especially reduced in those with both autism and mental retardation, and also was associated with increased EEG gamma power. The conclusion was that these results provided evidence for an ineffective inhibitory control of sensory processing for the retarded group in autism. Another group [232] studied evoked brainstem responses to speech syllables, reporting evidence for a deficient pitch tracking, suggesting subcortical involvement for the prosody-encoding deficits in autism. Other investigators [233] recorded via the event-related potentials (ERPs) (and MEG) at 400 and 750 ms to sentences with congruous and incongruous words, with results suggesting that the group with autism used unusual strategies for resolving semantic ambiguity. Rojas et al. [234] also used MEG to record evoked gamma band power, which was found to be reduced in children with autism, as was the phase-locking factor, showing a deficient phase consistency of neuronal responses to external stimuli. Other authors [235] used ERPs and reported decreased components in response to repetitive *speech*, but not to repetitive *nonspeech*. Also, decreased orienting to novel tones was found in a sequence of *speech* sounds, but not in a sequence of *tones*. The conclusion

was that in the group with autism, inhibition was used to decrease responses to repeated streams of speech. Another group [236] used ERPs for both error-related negativity (*n*) and positivity (*p*) to an auditory task. Both the *n* and *p* components were reduced in the group with autism, indicating an insensitivity to detect the possibility of errors and suggesting perseverative behavior, as is often noted in children with autism.

A few studies have used specific visual stimuli in studying autism. Lazarev et al. [237] studied photic driving on the EEG, showing, in the group with autism, reduced driving on the right hemisphere, providing evidence for a neurophysiological disturbance within that hemisphere. With 128-channel ERPs, responses to face detection were weaker in the group with autism, suggesting aberrant neurophysiological processing of facial emotion [238]. Trachtman [239] summarized all visual abnormalities in autism, including abnormal electroretinograms (ERGs), deficient evoked potentials (EPs), atypical opticokinetic nystagmus, and finally increased incidence of strabismus and oculomotor deficiencies in children with autism.

3.15. Neuroanatomical relationships

3.15.1. Prefrontal = frontopolar area

Montag et al. [240] investigated concentrations of glutamate by magnetic resonance spectroscopy (MRS) and reported an association between the concentration in the prefrontal (pF) area and an interpersonal reactivity index, concluding that control of behavior was mediated by pF glutamatergic projections. Also, brain scans showed reduced activity in the ventral medial pF cortex (also in the anterior cingulate cortex) across all judgment conditions and also during a restful condition [241]. The results were considered to provide a more detailed view of the default network functionality and, thus, an abnormality in autism. Wicker et al. [58] used network models and reported that the pF cortex was the key site for the dysfunction of explicit emotion, also providing evidence of abnormal long-range connectivity between the pF area and other structures. On the other hand, microcircuit changes in the pF cortex in a rat model showed hyperconnectivity and hyperplasticity in the pF cortex, suggesting that deficits in autism should be interpreted in the light of a hyperfunctional pF cortex [242].

Uddin et al. [243] used event-related fMRI data to investigate the brain's responsiveness to images of the subject's own face and the faces of others. The group with autism recruited the pF system only while viewing images of their own faces, suggesting that this group lacked the shared neural representation for self and also for others. Bookheimer et al. [244] reported that fMRI showed a different activation in the pF and amygdala areas in social cognition. Another group [245] reviewed neurocognitive functioning as a predictor of developmental variability, concluding that the ventromedial pF (and also the medial temporal lobe) system was useful in this prediction. Takahata and Kato [61] studied savant syndrome and provided evidence that disruption of connectivity between the pF cortex and other regions was an important factor, also concluding that the pF region showed the most influential inhibitory control over other cortical areas. Buckner et al. [246] has helped to define the brain's default network, a brain system that is active when individuals are not focused on their external environment. One of the two systems was the medial pF subsystem that facilitates the flexible use of information from prior experiences, likely deficient in autism. Finally, late ERPs and long-latency gamma oscillations were stronger over pF (and central) areas to certain words, indicating to the investigators an abnormal semantic organization [233]. ERP responses related to mental state decoding were weaker in the medial pF areas, representing aberrant cortical specialization within brain networks [238].

3.15.2. Frontal cortex

A number of investigators have emphasized the *right* frontal area. Lee et al. [54] studied functional connectivity MRI (fcMRI), especially of the inferior frontal cortex, reporting, in adults with autism, a reduced connectivity of this frontal area but only on the *right*. The authors concluded that an atypical developmental trajectory exists for the right inferior frontal connectivity with other neural regions. Kleinhans et al. [247] reported that greater social impairment was associated with an increased face area and right frontal connectivity. The same authors [247] also concluded that it was the right frontal (and right temporal) lobe that showed greater activation in fMRI to letter fluency in the group with autism. Also, by checking functional asymmetry in the frontal cortex, reduced lateralization of activation patterns was observed. The authors suggested that this functional organization may contribute to the language impairment in autism. One other study [248] showed differential modulation of right lateral midfrontal activation by high arousal stimuli in autism. Finally, Ke et al. [249] reported that an enlargement was seen in the right medial frontal gyrus along with other areas in autism.

One study [250] emphasized the *left* frontal area in an MRI study on a language task. Males with autism had stronger activation than controls in Broca's area, less lateralized on the left, suggesting differences in semantic organization in autism.

Other studies of the frontal lobe in autism have emphasized *both* frontal areas. One group [251] studied SPECT scans in autism, reporting hypoperfusion in various areas, including the bilateral cortex in some scans, in the right inferior frontal and left superior frontal areas in other scans. The same type of hypoperfusion was found in the parents and also the siblings. Keehn et al. [252] used event-related fMRI to visual stimuli to show greater activation in frontal (also parieto-occipital) regions in individuals with autism than in controls. The conclusion was that a search efficiency in autism may be related to *increased* modulation of visual attention.

On the other hand, similar to the studies of the aforementioned group [251], most investigations have emphasized *deficiencies* in the frontal lobe, exemplified by one study [154] reporting an alteration of receptor GABRA1 in the superior frontal cortex. Makkonen et al. [253] concluded that only in the medial frontal cortex was there reduced serotonin transporter binding capacity, possibly related to a smaller number of serotonergic nerve terminals in autism. Bonilha et al. [254] summarized MRI findings in autism, reporting an increase in gray matter in medial and dorsolateral frontal areas, but a decrease in white matter, also seen in other regions. The investigators considered that this enlarged cortex, but with reduced white matter, may be the structural basis for some symptoms in autism.

3.15.3. Cingulate cortex

One group of investigators [255] studied metabolites in autism through proton MRS, reporting an increase in myo-inositol and choline peak areas and also in the myo-inositol/creatine ratio in the anterior cingulate (and also left striatum). Using MRI, Chiu et al. [256] reported a severely diminished cingulate response when males with autism were playing a game with a human partner. In another kind of game, a trust game with a partner, an unusual lack of brain activity was reported in the midcingulate cortex when the group with autism made their ''investments'' [257]. The speculation was that the results may arise because the group with autism may have been unaware that in this game the partner's trust would likely have changed. In an aforementioned study using scanning studies [241], the ventral anterior cingulate cortex (with the pF cortex) showed a reduction across all judgment conditions and also during a resting condition, suggesting a dysfunction independent of tasks. Another study on functional neuroimaging [258] showed hypoactivation in the perigenual anterior cingulate cortex

in social tasks and also in the dorsal portion in nonsocial tasks, possibly part of a default mode network regulation in autism. In EEG studies, Milne et al. [227] interpreted the increase in the induced alpha power in the cingulate gyrus as possibly related to atypical perception in autism. Another group [236] used ERPs to conclude that error-related negativity was smaller in the group with autism localized in the anterior cingulate cortex, possibly related to perseverative behavior, often noted in autism. Buckner et al. [246] also were concerned with the brain's default network, concluding that the subsystems' coverage for integration include the posterior cingulate cortex. Finally, event-related MRI was used to examine neural substrates of monetary rewards in autism, with the conclusion that such rewards were associated with greater activation in the left anterior cingulate gyrus [259]. Also, activation of this region was negatively correlated with social interactions and this same region is also known to be responsible for attention and arousal. The emphasis placed on the anterior cingulate by Thakkar et al. [260] was related to rigid and repetitive behavior, presumably associated with disconnections in this structure.

3.15.4. Cerebellum

Knickmeyer et al. [261] performed a structural MRI study of brain development from birth to 2 years of age, reporting that cerebellum (CBL) volume increased by 240% in the first year of life, with gray matter increasing substantially and white matter growth much slower. The study suggests a structural underpinning of development in early childhood and also a potential pathogenesis of developmental disorders like autism. Hrdlicka [262] confirmed a larger CBL volume in autism, as did others [258]. Another group [263] reported that GABBR1 and GABBR2 receptors were significantly reduced in the CBL, possibly helping to explain, according to the authors, the occurrence of seizures in autism. The same group [264], at another time, had confirmed that GABRA1 and GABRB2 receptors were altered in autism. Wills et al. [265] studied autoantibodies to neural cells of the CBL in the plasma of a group with autism. They found that 21% of the children with autism had antibodies with a specific reactivity to a CBL protein. Also, an intense immunoreactivity to Golgi cells of the CBL was noted in 21% of the group with autism, not seen in controls. Rout and Dhossche [88] postulated that anti-glutamic acid decarboxylase antibodies were the basis of many autistic symptoms, associated with Purkinje cell loss and CBL atrophy. Finally, another group [266] used quantitative MRI analysis and concluded that macrocephalic individuals with autism tended to have smaller CBL volumes and surface areas. As the CBL is under discussion here, the posterior fossa is relevant. Williams [267] has stated that a large head size predisposes to autism, and the larger posterior fossa in the male fetus allows higher peaks of pressure in the lateral ventricles, resulting in a larger head size, often seen in autism.

3.15.5. Amygdala

Kleinhans et al. [247] dealt with abnormal functional connectivity in autism and reported that greater social impairment was associated with reduced connections between the fusiform face area and the amygdala, representing an abnormal neural connection within the limbic system. Another group [268] confirmed the impaired connectivity between the amygdala and other critical regions in the "social brain." Conturo et al. [269] used MRI diffusion-tensor tracking and reported abnormal microstructure in the amygdala–fusiform pathways, also showing increased across-fiber and along-fiber diffusivity. With fMRI during a face processing task, abnormalities appeared in the amygdala (and pF cortex), implicated in social cognition, specifically during face processing [244]. Ashwin et al. [270] presented the "amygdala theory" in autism, characterized by deficits in understanding others, possibly related to atypical function of the amygdala, especially because patients with acquired amygdala damage show similar symptoms. Evidence included less accuracy in the group with autism on the emotion recognition task, involving negative basic emotions. Another group [271] reported that amygdala function was associated with a genetic variation in the gene AVPRIA, a vasopressin regulator gene. These results indicated a neural mechanism mediating a genetic risk for autism through an impact on amygdala signaling. Finally, Gabis et al. [272] used MRS markers of cognitive and language ability in autism, showing lower NAA/CR ratios in the hippocampus–amygdala region and also an elevated choline/CR ratio on the left side of that same region.

3.15.6. Temporal and associated areas

In a SPECT study, one group [251] observed hypoperfusion in the temporal lobe and also in other areas. Also, in other areas in an fMRI study, children with autism failed to show a correlation between temporal and frontal language area activation in the left hemisphere while controls showed such a correlation [250]. These results suggest differences in semantic organization in autism. Munson et al. [245] concluded that the important predictors of developmental variability are found in the medial temporal lobe (and also pF areas). In addition, data [273] indicated that difficulties in emotional awareness were related to hypoactivity in the anterior insula. Kleinhans et al. [274] studied language in autism and found greater activation in the superior temporal lobes (and also right frontal lobe) in letter fluency, suggesting a reduced hemispheric differentiation for verbal fluency tasks in autism.

The anatomy was the interest in two studies. One group [254] concluded that an increase in gray matter was found throughout the temporal lobe, but also a decrease in white matter appeared along with other areas. Also, Awate et al. [78], in a group with autism, showed increased cortical folding in the temporal lobe (also in the frontal and parietal lobes) possibly related to increasing neural complexity.

Neurophysiological studies have also been performed. Some investigators [230] used MEG and reported spike discharges, especially in the perisylvian regions. Also, ERPs recorded with MEG by another group [233] showed weak responses to incongruous words over the left temporal cortices. The authors concluded that children with autism use unusual strategies for resolving semantic ambiguity. Finally, Pierce and Redcay [275] reported that a selective deficit appeared in the nearby fusiform gyrus only when the group with autism viewed faces of strangers.

3.15.7. Visual cortex

Bolte et al. [276] performed an MRI study of perception in autism, reporting that the processing of a design test was associated with altered responses of selective neurons in the right ventral quadrant of part of the visual cortex. A visual search test revealed greater activation in the visual cortex (also frontoparietal), likely related to enhanced discrimination and increased modulation of visual attention [252]. Finally, Bonilha et al. [254] reported that patients with autism showed a decrease in white matter in the visual cortex (as well as the frontal, temporal, and parietal cortex) in association with a generally enlarged cortex.

3.15.8. Subcortical structures

Jou et al. [169] studied brainstem volumetric changes in autism, reporting a decrease in brainstem gray matter volume, but without changes in white matter volume, possibly related to sensory deficits. Mehler and Purpura [277] were specific about the subcortical structure involved, namely, the locus coeruleus. They noted that some children with autism improve their behavior during febrile episodes, hypothesizing the normalization of an impaired locus coeruleus–noradrenergic (LC–NA) system. They suggested that autistic behavior resulted from developmental dysregulation of

the LC–NA system. This hypothesis has implications for designing biological detection systems and also therapeutic agents that target this system. Kulesza and Mangunay [278] were concerned with auditory deficits and examined the superior olive, which functions in sound source localization. They reported a disruption in the morphology in the medial superior olive in the group with autism to explain hearing difficulties in this group. Other investigators [90] have studied MRS metabolites and reported lower levels of NAA, phosphocreatine, creatine, and choline-containing metabolites on the left side of the thalamus without finding differences in thalamic volume. Kilian et al. [279] studied the corpus callosum, which is often observed to be decreased in size in autism. They reported that the normocephalic group with autism had a smaller corpus callosum genu and midbody, but in the macrocephalic group with autism, the entire corpus callosum was larger.

3.15.9. Brain in general

Vaccarino et al. [173] acknowledged that an increase in brain size is common in children with autism, proposing also an increased number of excitatory neurons, minicolumn pathology, and excessive network excitability, leading to sensory hyperreactivity and seizures. They suggested that fibroblast growth factors, regulating cortical size and connectivity, may be responsible for the developmental alterations. Brain size was also the concern of another report [210], concluding no difference in head or brain volume in the group with autism. However, these authors also reported a reduction in the bulk of the cerebellum and an increase in peripheral cerebrospinal fluid. Another group [280] dealt with somatic cortical maps with MEG and reported a larger distance between the cortical representations of the thumb and lip, which is the first demonstration of abnormality in the sensory organization in the brains of children with autism. Amaral et al. [281] were also concerned with the brain in general, concluding that the heterogeneity of both the core and comorbid features predicts a heterogenous pattern of neuropathology in autism. Another group [282] studied cerebral blood flow, reporting right-to-left asymmetry of hemispheric perfusion with right prevalence and a left hemispheric dysfunction in the group with autism.

3.16. Comorbid conditions

3.16.1. Down syndrome

Bolte et al. [55] stated that autism occurs 10 times more often in children with Down syndrome (DS) than in the general population. Patients with both autism and DS performed more poorly on all assessments than those with DS without autism, especially on language, cognitive, and adaptive skills, seizures, social interaction, and repetitive and stereotyped behavior. The same group [283] earlier had compared the children with both autism and DS with those with only autism. They reported that those with both autism and DS acquired use of single words at 41 months, in contrast to 15 months for the group with only autism. The mean age for loss of language during regression was, however, 62 months for the group with autism and DS, compared with 20 months for the group with only autism.

3.16.2. Cornelia de Lange and Cri du Chat syndromes

Moss et al. [284] evaluated children with both syndromes and reported that 62% of those with Cornelia de Lange and 39% of those with Cri du Chat scored above the cut off on the Autism Diagnostic Observation Schedule. Others [285] have also studied patients with Cornelia de Lange, reporting that severe autism was found in 32% of the latter group, who also showed compulsive behavior.

3.16.3. Tuberous sclerosis

Kothur et al. [286] reported that patients with tuberous sclerosis constitute 1–4% of those with autism, and individuals with autism and tubers were more likely to have them in the temporal areas than patients with tubers without autism. De Vries [287] added that a similar 1–5% of individuals with autism have tuberous sclerosis and that up to 50% of patients with tuberous sclerosis met criteria for autism. The author suggested that dysregulation of intracellular signaling through the TSC½–mTOR (tuberous sclerosis complex ½–mammalian target of rapamycin) pathway may be sufficient to lead to autism and drugs that are TOR inhibitors may reverse some aspects of the deficits in tuberous sclerosis.

3.16.4. Psychiatric disorders

Mouridsen et al. [288] conducted a Danish study with the mean observation time of 33 years and mean age at follow-up of 41 years. Among those with infantile autism, 48% had been in contact with psychiatric hospitals, 17% had a comorbid psychiatric diagnosis, but only 3% were diagnosed with schizophrenia and 3% with affective disorders. Simonoff et al. [289] added more impressive values, stating that 70% had at least one comorbid psychiatric disorder and 41% had two or more. Also, the most common diagnoses were social anxiety disorder (29%), attention deficit hyperactivity disorder (29%), and oppositional and defiant disorder (28%). Finally, other investigators [290] added that 16% developed a definite new psychiatric disorder, but none had schizophrenia.

3.16.5. Attention deficit hyperactivity disorder

One of the aforementioned groups [289] pointed out that 29% of the group with autism had ADHD. Ronald et al. [291] studied 6771 twin families and reported significant correlations (0.54) between autistic and ADHD traits. Also, 41% of children with ADHD met criteria for autism. These data are relevant to the question of molecular genetic influences. Reiersen et al. [292] also studied twins (851) who had ADHD and reported that children with the combination of motor coordination deficits and ADHD were more likely to have high levels of autistic symptoms.

3.16.6. Fragile X syndrome

One group [293] studied fragile X syndrome (FXS) with and without autism, reporting that a difference in the incidence of medical problems was found between those with both FXS and autism (37%) and those with FXS alone (18%). The conclusion was that this additional brain disorder is likely associated with medical problems that enhance the risk of autism. Zingerevich et al. [294] were more specific about the relationship, reporting that 60% of the children with FXS met criteria for autism (or a pervasive developmental disorder). The latter group with autism had lower fine motor scores, and the authors concluded that children with FXS and autism are therefore at risk for impaired motor abilities.

3.16.7. Various other disorders

One group [295] investigated 95 patients with infantile spasm and reported that the odds ratio (OR) for autism associated with infantile spasms was 5.53, and that when adjusted for symptomatic seizures it was 1.55. The OR for autism associated with symptomatic seizures adjusted for infantile spasms was 8.73. The conclusion was that infantile spasms predicted the risk for autism, but this was explained in part by the association of autism with the symptomatic origin of seizures. Ozgen et al. [296] studied minor physical anomalies and reported that pooled results of seven studies indicate a correlation of minor physical anomalies in autism at the level of 0.84. Van Rijn et al. [297] studied patients with Klinefelter syndrome and reported increased distress during social

interactions for those patients, indicating a vulnerability to autism in this syndrome.

3.17. Treatment

3.17.1. Risperidone

Risperidone is usually the drug most often mentioned for the treatment of autism. Canitano and Scandurra [298] have concluded that risperidone "seems to be moderately efficacious and safe for treating." Others [299] have reminded us that risperidone acts via dopamine D(2) and serotonin 5HT(2A) receptor antagonism. Those authors concluded that the drug reduces irritability and other behavioral symptoms associated with autism. Adverse events were mild-moderate in intensity, involving weight gain, somnolence, and hyperglycemia. Aman et al. [300] added that doses up to 3.5 mg for up to 8 weeks produced no decline in any performance, and specifically better performance on cognitive and learning tasks.

3.17.2. Ziprasidone

Ziprasidone was studied by Malone et al. [301], who concluded that it was weight neutral and that 75% of the group with autism responded to treatment.

3.17.3. Atypical antipsychotic medications

Posey et al. [302] concluded that atypical antipsychotic drugs have become indispensable, and are used in autism to treat irritability, aggression, self-injury, hyperactivity, and stereotyped behavior. They also reviewed the possible problems of weight gain and tardive dyskinesia. "Second-generation antipsychotic medications" were studied by others [303] who reported that these medications seem to reduce psychomotor agitation and aggressive behavior. Fido and Al-Saad [304] reported on olanzapine in particular, concluding that this treatment can alleviate irritability, hyperactivity, and lethargy. Side effects, like weight gain and tardive dyskinesia, could not be studied because of the short period of the study.

3.17.4. Psychostimulants

Nichols et al. [305] used psychostimulants and reported favorable responses in 69%, but at least one side effect was seen in 66%. The conclusion was that these medications may improve hyperactivity, impulsivity, disinhibition, and inattention. Another study [306] reviewed data from 21 trials on tianeptine, methylphenidate, risperidone, clonidine, and maltrexone, but methylphenidate and risperidone were the only drugs for which results were replicated in at least two studies. Clonidine was investigated by Ming et al. [307], who reported decreased sleep latency and night awakening and improved attention deficits, mood instability, and aggressiveness.

3.17.5. Various other medications

James et al. [308] were concerned with metabolic abnormalities, like transmethylation metabolites and glutathione redux status, and therefore they examined the effects of treatment with methylcobalamin and folinic acid for 3 months. Pretreatment concentrations were different from those of controls, and after-treatment increases in cysteine, cysteinglycine, and glutathione were observed. The investigators concluded that this nutritional intervention could be beneficial in autism. Other authors [309] used melatonin for insomnia in autism and reported that 60% had improved sleep with this safe and well-tolerated treatment. Meguid et al. [310] reported that Efalex (fish oil), a free polyunsaturated fatty acid (PUFA), produced clinical and biochemical improvement, associated with high levels of linolenic and docosahexaenoic acid, in 66% of children with autism. Finally, one group [311] used propranolol to decrease noradrenergic activity, for verbal problems in autism; children with autism benefited on a test of simple anagrams, whereas controls were impaired on the propranolol.

3.17.6. Therapeutic procedures

Investigators [312] used low-frequency repetitive transcranial magnetic stimulation, possibly to increase the surround inhibition of minicolumns. Improvement was based on ERPs and induced gamma activity, and it was specifically behavioral improvement that was reported. Whittingham et al. [313] used the positive parenting program (Triple P) and reported improvements in parental statements about their own child's behavior. Scalp acupuncture has also been used, with improvement in cognitive and expressive language skills [314]. Burrows et al. [315] used service dogs as a sentinel of safety, facilitating public outings and improving social recognition, but with continuing data collection on this method. Earlier, the same group [316] had been more specific about service dogs, claiming that the dogs formed social relationships with both the parents and children and therefore were helpful to the children with autism. "Transcranial micropolarization," small direct currents of 300–500 μA for 30–40 min, was used in Russia [317], where it increased mental functions and development of communicative skills. Montes and Halterman [318] reported that greater use of child care services was related to a higher probability of better employment decisions. Teaching patients with autism to initiate and respond to bids for joint attention has also been urged [319]. In Thailand, one group [320] using hyperbaric oxygen therapy reported a 75% improvement rate with 1.3 atm for 10 sessions. Helt et al. [321] addressed the question of whether children with autism could ever recover and, if so, how? They reviewed evidence that 3–25% lose their diagnosis and become normal in time. Predictors of recovery were relatively high intelligence, receptive language ability, verbal and motor imitation, and also motor development, but not symptom severity. Seizures, mental retardation, and genetic syndromes were unfavorable signs. Tics, depression, and phobias were frequent residual comorbidities after some recovery. Mechanisms of recovery include normalizing input by trying to encourage attention outward, enriching the environment, promoting the reinforcement value of social stimuli, preventing interfering behaviors, practicing weak skills, reducing stress, stabilizing arousal, and improving nutrition and sleep quality. Finally, Spreckley and Boyd [322] reported that "applied behavioral intervention" had not proven effective and "standard of care" is advised.

4. Summary

The goal of this report was to survey 1300 publications on autism published in 2008 and to summarize the findings of those studies that came to specific conclusions or included relevant data.

One of the major differences between the present review of 2008 publications and the previous review of the 2007 studies [1] is the present emphasis on the observation of similar characteristics in children with autism and their parents. The psychological changes include parents' depression, shyness, personality disorders, anxiety, family conflict, and alexithymia, which are related to many of the symptoms of autism. Age of the parents, especially >35 years for mothers and >40 years for fathers of firstborn children, was at times associated with autism. Other parental characteristics included poor sleep quality, decrease in processing the eye region in faces of others, and lower Performance IQ.

Maternal conditions relevant to autism included hypertension, albuminuria, generalized edema, chorioamnionitis, and intrapartum hemorrhage. One intriguing question is whether the worldwide increased folate status of mothers during pregnancy has altered the prevalence of autism by decreasing the number of mis-

carriages through reduction of hyperhomocysteinemia with the genotype MTHFR C677T polymorphism. To test the theory that autism represents an "extreme male brain," data on the number of brothers among siblings did not prove to be significant. Births of children with autism peaked in April, June, and October for single births and one month earlier for multiple births.

The topic of genes and chromosomes was deemphasized in this review mainly because at least 334 new genes are now known to interact with many published genes, and so a separate review is required. One new area is that of imprinting genes, expression of which is determined by the parent who contributed them. Autism appears to involve a bias of paternally expressed genes which may mediate neuronal overgrowth. One other hypothesis is that autism may be involved with the dysregulation of brain-expressed genes on the X chromosome, resulting in an unbalanced production of proteins responsible for brain structure and function.

Possible etiological factors are numerous. First is the aforementioned "extreme male brain," suggested because females tend to excel in social relationships and empathy, which are usually deficient in autism. One study reported that fetal testosterone levels were not high in mothers with children with autism. However, high fetal testosterone levels did correlate with deficiencies in empathy and symptoms suggestive of autism. Finally, females showed stronger suppression of mu EEG waves, supporting the "extreme male brain."

Another theory involves the mirror-neuron system, cells that are active when viewing the movements of others, which is considered deficient in autism. One marker was mu suppression seen in one study only when familiar individuals were viewed by children with autism; this suppression is also reported as diminished in autism. Children with autism did not show a "between-person" effect, but did show a "within-person" effect consistent with a core feature of autism. The mirror-neuron system is linked to the Theory of Mind, a metarepresentation of mental states, likely a viable construct.

A major controversy has been whether thimerosal, a mercury-containing preservative in some vaccines, is in any way responsible for autism. There is considerable evidence against this possibility, including statements from the FDA, updated on June 3, 2008, that for years this preservative has been removed from nearly all vaccines. However, a few studies have kept this controversy alive. In the Hannah Poling legal case, the patient and the family were awarded funds because a vaccine exacerbated a mitochondrial disorder in the child who also had autism. Thus, the funds were awarded not because the vaccine caused autism, but because the vaccine worsened the mitochondrial disorder that was possibly related to the autism. Male mice more often succumb to thimerosal than female mice, possibly related to the greater prevalence of males with autism. Children with severe autism showed increased urinary porphyrins possibly associated with mercury intoxication, and increased rate ratios of mercury over time have been reported in autism as well as other disorders. On February 12, 2009, the U.S. Court of Federal Claims announced its decision that "vaccines were not to blame." This decision was based on an enormous amount of data.

There exists considerable evidence of one firm finding in autism: cortical underconnectivity. Additional data include reduced connectivity in the right inferior frontal cortex and decreased connections between the fusiform face area and the amygdala also involving the prefrontal cortex. Savant syndrome can be viewed as increased local hyperconnectivity in compensation for general underconnectivity. Hypocoherence in EEG activity also has been observed and is consistent with deficient cortical connections.

Another hypothesis in autism deals with a mechanism of deficient central coherence, the integration of diverse information on details and a deficiency in dealing with the general. As evidence against the relevance of this concept, performances on memory and face recognition tasks were not related and executive impairments were not universal. However, clustering of symptoms does at times occur, and visual tasks may show a deficit in holistic processing.

Specific etiologies include mitochondrial dysfunction with evidence of a disturbance in mitochondrial energy production and also high lactate levels. Immunological disorders include evidence of immunoexcitotoxicity with repeated microglial activation, decrease in transforming growth factor β1 levels, and folate receptor autoimmunity. Congenital disorders, especially tuberous sclerosis, greatly overlap with autism. Also, cortical thickness and folding are likely relevant. Deficient proteins include fragile X mental retardation protein, in addition to mGluR5 antagonists and aberrant synaptic protein synthesis. Metabolic disorders include hyperbilirubinemia, glucose-6-phosphate dehydrogenase deficiency, atypical porphyrin levels, abnormal transsulfuration metabolites, dysfunctional dopamine transporters, abnormal serotonin metabolism, glutamic acid decarboxylase antibody, and increased folic acid levels in mothers. Low levels of essential amino acids, of *N*-acetylaspartate and creatine, and also of cortisol have been reported. Interactions involve both heritable and nonheritable factors; even an increase in local precipitation has been mentioned as a possible factor. The intense world syndrome, resulting from hyperfunctionality in autism, can also be considered. Assessments of autism include the popular Modified Checklist for Autism in Toddlers and the Childhood Autism Spectrum Test, for children 2–9 years of age, movement symmetry, repetitive movements, and also birth weight and gestational age.

Characteristics of children with autism include repetitive behavior, language impairment, sleep disorders, social problems, deficient joint attention, seizures, allergic reactions, and abnormal behavior. Cognitive changes involve abnormal reasoning and verbal and language disorders. Children with autism have sensory changes in general, either hyporeactivity or hyperreactivity. Adults with autism most often complain of unusual perceptions, impaired informational processing, and a disordered emotional regulation. Visual disorders include the decrease in exploration of the eyes of others in favor of concentrating on the mouth, resulting in poor face recognition, although other data would challenge this generality. Diet data have shown an increase in vitamins B6 and E taken by those with autism. Changes in adulthood were often positive with faster and more accurate detection of eye gaze, improvement in executive function, and less frequent repetitive behavior. Savant syndrome, a fascinating phenomenon, is observed in 10% of those with autism, mainly in males, and is possibly a compensation in minicolumn structure for overall general underconnectivity.

The prevalence of autism in the United States has usually been stated as 1 in 150 children, but a more recent (December 2008) national study put it at 1 in 116. Reported rates of prevalence vary significantly throughout the world, likely because of differences in the tests and criteria used for autism. There is evidence that autism is being discovered and often diagnosed at an earlier age over time, resulting in the appearance of an increasing prevalence.

EEGs reveal neurophysiological changes, especially the suppression of mu waves as an indication of the mirror-neuron system or attention to the outside world, usually deficient in autism. Also, reduced alpha power, a large number of epileptiform discharges, and low levels of coherence and syndronization have been reported. MEG data include spikes. Inhibition of auditory evoked potentials and (MEG) event-related potentials have shown evidence of unusual strategies for resolving semantic ambiguity. Also reported were reduced gamma power and responses to repetitive speech, in addition to decreased responses suggestive of perseverative behavior. Finally, reduced photic driving on the right, weak event-related potentials to face detection, and abnormal electroretinograms have been reported.

Neuroanatomical relationships involve the prefrontal area with its significant glutamate concentration, decreased electrical activity in the ventral medial portion, evidence of hyperplasticity in this cortex, deficient responses to faces of others, and use of the ventral medial portion to predict developmental variability. The prefrontal area is viewed by some investigators as the most influential in inhibitory control over other cortical areas, and the medial portion is seen as a center for information from prior experience, with weaker event-related potentials representing mental state decoding. The frontal cortex is perhaps mentioned more than any other area. There is evidence of reduced connectivity from the right frontal areas, where responses to high arousal stimuli are associated with social impairment and letter fluency; enlargement has been reported in the right medial frontal gyrus. The left frontal area was implicated on a language task. Both frontal areas were involved with language impairment, showing hypoperfusion, as well as greater activation in responses to visual stimuli there; changes in receptor GABRA1 in the superior portion were reported. Reduced serotonin transporter binding capacity and increased gray but decreased white matter have been reported in the frontal areas. Cingulate cortex has often been mentioned in studies of autism, especially in relation to an increase in myo-inositol and choline levels, decreased responses during certain activities, reduction of rhythms in the ventral-anterior portions, and hypoactivation in the perigenual part associated with social tasks and in the dorsal part linked to nonsocial tasks. Also, increased alpha EEG power has been reported in cingulate cortex, as has convergence for integration in the posterior portion. The left anterior cingulate is viewed as the area for reward appreciation, likely responsible for attention and arousal, in addition to rigid and repetitive behavior.

The cerebellum has also played a prominent role, increasing gray matter by 240% in the first year but less for white matter. Also reported were altered receptors GABBR1 and GABBR2, intense immune reactivity to Golgi cells, and the presence of anti-glutamic acid decarboxylase antibodies, associated with Purkinje cell loss and cerebellar atrophy. The amygdala has shown abnormal functional connectivity, reduced connections with the fusiform face area and with other cortical regions of the "social brain." According to the amygdala theory, deficits in understanding others are related to this structure, which is also involved with less accurate recognition of emotion. Finally, lower *N*-acetylaspartate/creatine ratios in the amygdala, as well as the hippocampus, are related to cognitive and language deficits.

The temporal lobe has also been the subject of a number of investigations in autism. SPECT studies have reported hypoperfusion, MEGs have recorded spikes, and anatomical studies have reported increased cortical folding. No correlation has been found between temporal areas and language area activation, but the medial portion is an important predictor of developmental variability. The superior temporal lobe is related to letter fluency, and in general an increase in gray matter and a decease in white has usually been reported.

The ventral quadrant of the visual cortex of children with autism is associated with processing of a design. Greater activation of this cortex has been observed on a visual search test, but a decrease in white matter has also been found.

Subcortical structures are also involved. A decrease in brainstem gray matter without changes in white matter was reported, and the locus coeruleus is considered a site for developmental regulation. A disrupted superior olive nucleus has been considered to explain disorders of sound localization. Metabolites on the left side of the thalamus were reported as diminished without changes in the volume of this structure.

The autistic brain, in general, is increased in size, possibly through the activity of fibroblast growth factors. Changes in somatic cortical maps are reported, as is right-to-left asymmetry in hemispheric perfusion.

Comorbid conditions include Down, Cornelia de Lange, and Cri du Chat syndromes, tuberous sclerosis, various psychiatric disorders, attention deficit hyperactivity disorder, fragile X syndrome, infantile spasms, minor physical anomalies, and also Klinefelter syndrome.

Treatment includes the frequently mentioned risperidone; ziprasidone; various atypical antipsychotic medications, especially olanzapine; and psychostimulants, especially methylphenidate and clonidine. Other medications were melatonin for sleep, Efalex for biochemical improvement, and propranolol for verbal problems. Repetitive transcranial magnetic stimulation, positive parenting programs, scalp acupuncture, service dogs, transcranial micropolarization, child care services, and hyperbaric oxygen are therapeutic procedures that have been helpful. Other therapeutic measures include encouraging outward attention, enriching the environment, promoting reinforcement value of social stimuli, preventing interfering behavior, practicing weak skills, reducing stress, stabilizing arousal, and improving nutrition and sleep quality.

As was mentioned in this author's review of 2007 [1], nearly every disorder a child can have may be observed in children with autism. Optimistically, there are data suggesting that some symptoms may ameliorate over time.

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