CHAPTER 8

Autism Symptoms Exist but the Disorder Remains Elusive

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More than $1 billion has been spent over the past decade researching autism. In some ways, the search for its causes looks like a long-running fishing expedition, with a focus on everything from genetics to the age of the father, the weight of the mother, and how close a child lives to a freeway.  

_Stobbe (2012)_

The symptoms of autism exist. However, the billion dollars spent on autism research in the past decade has generated evidence for significant heterogeneity in autism. Chapters 1 to 6 documented heterogeneity in autism diagnostic behaviors, associated non-diagnostic behaviors, brain deficits, onset symptoms, and genetic and environmental risk factors. This evidence has found no shared pathogenesis, pathophysiology, or validated symptom set. The increasing evidence for heterogeneity makes autism a harder and harder problem to solve, while the increasing prevalence puts more and more pressure on autism researchers to solve the problem.  

Shockingly, Frances and Widiger (2012) claimed that much of autism was a fad. _Frances and Widiger (2012)_ stated, “fads meet a deeply felt need to explain, or at least to label, what would otherwise be unexplainable human suffering and deviance” (p. 115). From this definition, it would seem that psychiatry, with its deeply felt need to explain and label human suffering and deviance, must be a fad. The charge made against autism by _Frances and Widiger (2012)_ is wrong. As outlined in Chapter 7, the increase in autism has been shown to stem from diagnostic criteria changes, diagnostic substitution, special education policy changes, increased availability of services, and heightened awareness of autism, and, also perhaps a true increase in incidence. Some portrayals of autism in novels, movies, or on television may be faddish, but autism symptoms are not a fad.
The majority of autism researchers currently hold one of two competing theories. One theory is that autism is a single multi-etiology heterogeneous disorder. The other theory is that autism is a spectrum of many closely related disorders. However, these two views shade together when researchers define autism. For example, Sato et al. (2012) stated, “Autism is the prototypic form of a group of conditions, also known as ‘autism spectrum disorders’” (p. 1). Walsh et al. (2011) opened their paper by stating, “Autism spectrum disorder is the term used for a diverse group of developmental conditions that affect a person’s ability to relate to and communicate with others” (p. 603). Three pages later Walsh et al. (2012) argued that researchers needed to develop “understanding of autism as a complex condition that is probably determined by multiple, yet to be understood pathways that lead to heterogeneous outcomes” (p. 606). Even reports of a unitary feature for autism open with a tip of the hat to the theory of many autisms. For example, Wolff et al. (2012) began their paper, “Autism spectrum disorders (ASDs) are complex disorders of neurodevelopment defined by impaired social communication and restricted, repetitive behaviors” (p. 1). The researchers, however, concluded, “aberrant development of white matter pathways may … [cause] this neurodevelopmental disorder” (p. 1). Elsabbagh et al. (2012) expressed both theories in the first five words of their first sentence: “Autism spectrum disorders (henceforth autism) are diagnosed in around 1% of the population” (p. 1).

Unfortunately, a clear understanding of the nature of autism has not been generated by the billion dollars in research funding. Worse still is the cost in missing translational findings for treatment and prevention. If autism is many distinct disorders with many varied causes, there is no translational value in searching for one unifying brain dysfunction for autism. Conversely, if autism is a single complex disorder, there will be no ultimate translational results from efforts to distinguish subgroups. Walsh et al. (2011) stated, “despite huge advances in the basic scientific understanding of autism, comparatively little has been achieved to date with regard to translating the resulting evidence into clinically useful biomarkers” (pp. 609–610). Unfortunately, most of the “huge advances in the basic scientific understanding” of autism are findings for massive heterogeneity in genetic variants, chromosomal number variants, and environmental risk factors, and these “huge advances” have not solved the core question of what entity “clinically useful biomarkers” would be identifying.

This chapter has five sections. The first section argues that the higher prevalence of males than females diagnosed with autism is likely to be a composite ratio, based on the male to female ratios for many different environmental and genetic risk factors. The second section demonstrates that,
despite accumulated evidence to the contrary, most autism research has continued to search for unifying features and single predictors for autism. The third section summarizes three critical inferential problems that would be eliminated by abandoning the effort to unify autism as a disorder. The fourth section presents the argument for autism as symptoms. The fifth and concluding section proposes a way of seeing and documenting autism symptoms without defining autism as a disorder.

**THE AUTISM MALE TO FEMALE RATIO IS LIKELY TO BE A COMPOSITE**

No accepted model has explained the reason for the greater number of males than females diagnosed with autism. Recent estimates of the autism male to female ratio have remained at between 2.5 and 4 males diagnosed for every female diagnosed. However, Zwaigenbaum et al. (2012) studied 319 young siblings of children with autism and reported a significantly lower gender difference ratio of only 1.65 male siblings diagnosed with autism for every female sibling diagnosed. The researchers diagnosed autism in 57 boys among the 176 at-risk male siblings, and diagnosed autism in 28 girls of the 143 at-risk female siblings. Most surprising was that boy/girl ratios for cognition and symptoms in the autism sibling group did not differ from the boy/girl ratios for the same measures in a comparison group of typical children.

Sato et al. (2012) proposed there were three theories explaining the higher number of males than females diagnosed with autism: the extreme male brain, X chromosome gene variants, and a prenatal protective factor functioning in females.

**The Extreme Male Brain Theory of the Autism Male/Female Ratio**

Baron-Cohen et al. (2011) theorized that autism symptoms were caused by dysregulated fetal testosterone that resulted in autism symptoms being an exaggeration of typical male traits. This theory of autism argued that females are more empathetic than males, males are more analytic than females, and males have a greater drive to construct rule systems than females. Autism, in this view, is an extreme version of typical male systematizing. Challenges to this view include findings like those of Bejerot et al. (2012), who reported that women with autism displayed fewer feminine characteristics than did women without autism, and men with autism displayed fewer masculine characteristics than did men without autism. Bejerot et al. (2012) further noted that autism behaviors and traits correlated with effeminate body features in men with autism, and with less feminine facial features in
women. Conversely, James (2012) concluded that the reports of more male siblings born to mothers of boys diagnosed with autism and mothers of boys with developmental language disorders supported the extreme male brain theory because they suggested that the maternal production of high androgen levels was persistent. James (2012) noted that there were two controlling factors for typical sex ratios at birth—hormone regulation at conception, and sex-specific effects of stressors during pregnancy—and dysfunction in either factor might contribute to developmental disorders.

The X Chromosome Theory of the Autism Male/Female Ratio
Noor et al. (2010) proposed that the male to female ratio in autism was due to effects of genes of the sex chromosomes. Zwaigenbaum et al. (2012) reported that more gene variants on the X chromosome have been discovered in association with autism symptoms, each of which might confer a higher number of males with autism: neuroligins 3 and 4; PTCHD1; TMLHE; MECP2; some cases of fragile X syndrome; and, possibly, epigenetic effects from paternally imprinted X-linked genes. Baron-Cohen et al. (2011), however, argued that X-linked mutations are insufficiently prevalent in autism to account for the autism sex ratio.

The Female Protective Factor Theory of the Autism Male/Female Ratio
Szatmari et al. (2012) proposed that females possessed some trait that protected brain development, such that more genetic risk factors were needed to trigger the expression of autism symptoms in females. Sato et al. (2012) reported a rare autosomal SHANK1 deletion only in males with autism. Mutations in SHANK2 and SHANK3 have been found in association with autism symptoms; however, Sato et al. (2012) found autism symptoms only in the males in a family carrying SHANK1 deletions, and noted that their finding was the first report of an autosomal sex-limited risk factor for autism. Because the researchers also found a male with autism who carried a de novo deletion of SHANK1, they concluded that the SHANK1 deletion in the family studied was the primary cause of autism in affected male family members. Sato et al. (2012) reasoned that carrier females in this family did not express autism symptoms because they had some neural feature that protected them from the effects of the SHANK1 deletion.

Many Risk Factors are Likely to Contribute Many Different Sex Ratios to Autism
Given multiple risk factors, it is likely that the male to female sex ratio in autism is a composite of hundreds of separate male to female sex ratios, each
of which is determined by a specific causal risk etiology and the ensuing mediation of brain development.

As outlined in Chapters 4 and 5, many varied genetic, chromosomal, epigenetic, and environmental risk factors have been linked to autism symptoms. Autism symptoms may also result from prenatal interaction of maternal and child genes and the gestational environment, and may result from the effects of fetal immune system genes in the environment of the developing fetal brain. If the autism male/female ratio is a composite of many varied ratios, then gene variants on the X chromosome, epigenetic effects from paternally imprinted X-linked genes, the rare autosomal SHANK1 deletion found only in males with autism, and intrauterine testosterone might all contribute to the ratio of more males than females in autism.

Genetic and environmental risk factors have tied autism symptoms to schizophrenia, anxiety, attention deficit/hyperactivity disorder, Tourette syndrome, intellectual disability, and language development disorders. Copeland, Shanahan, Costello, and Angold (2011) conducted a prospective population study of psychiatric disorder prevalence in 1400 children aged 9–16 years. They found a 1.6 to 1 ratio of males to females for any psychiatric diagnosis. The neurocognitive disorders whose symptoms have been linked to autism through shared risk factors have demonstrated a higher prevalence of diagnosed males than females. Attention deficit/hyperactivity disorder has a 10 to 1 male to female ratio, language development disorders have a variable ratio of 2 to 4 males for 1 female, Tourette syndrome has a 6 to 1 male to female ratio, and intellectual disability has an approximately 1.8 to 1 ratio of males to females. Therefore, when autism shares risk factors with these disorders, it is likely those risk factors may contribute to the male/female diagnosis ratio found for autism.

Notably, the twin study of Hallmayer et al. (2011) suggested that environmental factors might account for more than half the variance in autism, and the researchers argued that disruptive events in the prenatal environment were likely to be an important cause for autism. Although replication of the Hallmayer et al. (2011) twin study is needed, findings for environmental risk factors outlined in Chapter 5 suggest that sex ratios for these environmental risk factors would be likely to contribute to the composite male/female ratio for autism.

**Initial Structural and Hormonal Differences Between Male and Female Brains**

Hines (2011) summarized initial differences between male and female human brains. In general, the brain is larger in males. The amygdala is also larger in
males, but the hippocampus is larger in females. Female brains have greater cortical thickness in many regions than do male brains. Human female brains show greater gyrification in parts of frontal and parietal cortex, and female brains appear to use white matter with greater efficiency than do male brains. It may be that differential features such as cortical thickness and greater white matter efficiency confer protection for the female brain.

Differences in gonadal hormones and the social neuropeptides arginine vasopressin and oxytocin between males and females may contribute to the higher male to female ratio in autism. Gonadal hormones differentiate males and females. Insel (2010) and Gordon et al. (2011) proposed models of social motivation and social behaviors that began from gonadal hormones and the social neuropeptides, arginine vasopressin and oxytocin. Insel (2010) noted that the process of mammalian pair bonding differentially involves arginine vasopressin (AVP) in males, and oxytocin (OT) in females. Ebstein, Knafo, Mankuta, Chew, and Lai (2012) argued that the OT–AVP neural pathways regulate social behavior under the influence of six crucial genes: AVP-neurophysin II, OXT neurophysin I, and their receptors, AVPR1a, AVPR1b, LNPEP, and CD38. Ebstein et al. (2012) reviewed evidence for abnormalities in AVP and OT in autism, and presented evidence for the association of autism with variants of these genes. Ebstein et al. (2012) argued, “these genes not only account for individual differences in behavior in socially intact individuals but also contribute the vulnerability to disorders of social cognition especially autism” (p. 374).

Initial sex differences in brain structure and circulating hormones, when disrupted may contribute to autism symptoms. Initial sex differences in brain structure and circulating hormones may also leave male brains more vulnerable to a range of disruptive processes, and may confer protection from disruptive processes for female brains.

**Male Brain Vulnerability During the Prenatal Period**

As noted above, Hallmayer et al. (2011) proposed that environmental factors causing autism were likely to have their effect during the prenatal period, and Chapter 5 reviewed evidence for prenatal risk factors for autism symptoms. The high male to female sex ratio found for autism may, in part, reflect that male brains, in general, are more vulnerable to insult during prenatal life (Howerton & Bale, 2012; James, 2012; Kent, Wright, Abdel-Latif, & New South Wales and Australian Capital Territory Neonatal Intensive Care Units Audit Group, 2012; Murphy et al., 2012; Peacock, Marston, Marlow, Calvert, & Greenough, 2012).
For example, Murphy et al. (2012) reported that maternal cigarette smoking significantly affected the epigenetic process of DNA methylation only in male newborns. The researchers reported that only male infants born to current smokers showed significantly elevated methylation relative to those born to mothers who quit smoking during pregnancy, and those born to mothers who never smoked. In addition, Peacock et al. (2012) reported that among 787 very preterm infants, a significantly higher percentage of the 428 male infants died, required oxygen, had a pulmonary hemorrhage, or had a major cranial ultrasound abnormality than did very preterm female infants in the their sample. These findings were significant even after adjusting for differences in male and female birth weights and gestation duration. In addition, a follow-up of these children found significantly more motor disability and cognitive delay among boys than girls.

*Initial Male–Female Brain Function Differences may be Increased During Brain Development*

Given the initial differences in male and female brain structure, gonadal hormones, and social neuropeptides, and given the risk factor disruptions mediating autism symptoms, it is possible that interaction of the initial brain differences with the disruption may confer some additional harm for male brains or stimulate protection for female brains during the processes involved in brain development. These processes include programmed brain alterations, very early learning, and even developmental brain changes occurring during sleep (Karmiloff-Smith, 2012; Reeb-Sutherland, Levitt, & Fox, 2012). Wolff et al. (2012) stated, “Both highly experience-dependent and less environmentally mediated processes contribute to the functional and structural organization of the brain, and the dynamic interplay of these processes over time yields specialized cortical circuits designed to optimally process complex information” (p. 8). Brain development produces alterations in many varied aspects of the brain. For example, the anterior insula and the anterior cingulate cortex together contribute to social responsiveness in behavior. Uddin, Supekar, Ryali, and Menon (2011) reported significant developmental changes in brain interconnectedness for right fronto–insular cortex, tissue that contributes to switching attention between outside the self and inside the self. Consequently, the anterior insula, a contributor to social responsiveness, if disrupted earlier in development may suffer additional disruption during this programmed change as the brain develops (Uddin et al., 2011). Sex differences in the disrupted brain in autism may differentially influence programmed developmental processes such as this.
Reeb-Sutherland et al. (2012) reported that individual differences in associative learning measured at 1 month of age were associated with later measures of social behavior. The researchers found a significant link between 1-month associative learning and brain activity pattern in response to familiar and unfamiliar faces. Reeb-Sutherland et al. (2012) proposed that their findings were not the result of individual differences in general cognition, and argued that infant “associative learning may serve as a major building block for the development of social behavior” (p. 2). Karmiloff-Smith (2012) noted that impaired sleep processes characterized most neurodevelopmental disorders. She pointed out that the brain changes during sleep, consolidating and reorganizing information. Because consolidation of information during sleep depends on gene expression, brain biochemistry, and psychological processes in response to environmental stimuli, abnormal sleep processes may contribute to aberration in brain function.

Sex differences in brain structure, function, gonadal hormones, and social neuropeptides, as well as other initial sex differences, may contribute to sex differences in programmed developmental changes in the brain, in associative learning, or in sleep processes subsequent to the initial effects of brain disruptions for autism.

Summary: The Male to Female Diagnosis Ratio in Autism is Likely to be a Composite Ratio

There is evidence that male brains are more vulnerable to insults and disruptions. Male and female differences in brain structure, function, gonadal hormones, and social neuropeptides, as well as other initial sex differences, may variably contribute to male prenatal brain vulnerability to insult and disruption, and may variably confer some protection against prenatal insult or disruption for female brains.

The existing evidence for multiple varied risk factors for autism makes it likely that the male to female ratio in autism is not generated by any single cause, but rather reflects the collocation of hundreds of separate male to female prevalence ratios. It is likely that different causal risk factors for autism generate distinct male to female ratios each of which is determined by a specific causal risk etiology and consequent mediation of brain development.

MUCH RESEARCH IS STILL FOCUSED ON TRYING TO UNIFY AUTISM AS A SINGLE DISORDER

Even though many researchers would define autism as a spectrum of related disorders, most researchers have continued the quest to find unifying
features for autism as if autism were a single disorder. Why this research continues is unclear. Tatsioni et al. (2007) concluded that “it can be difficult to discern whether perpetuated beliefs are based on careful consideration of all evidence and differential interpretation, inappropriate entrenchment of old information, [or] lack of dissemination of newer data” (p. 2525).

The Quest to Find a Unifying Feature for Autism Persists

There are hundreds of alternate unifying feature claims for autism. Claims for unifying features in autism have often not been replicated, or have been found to be true only of a small subset of individuals with autism. Moreover, unifying feature claims for autism have often sidestepped evidence that the unifying feature was not specific to autism.

Even in genetic research, where multiple genetic variants have been explored as causes for the autism spectrum, many researchers have worked to create unified accounts of the genetic etiology for autism. Unifying models of related gene variants and/or chromosomal number variants for autism have rarely been replicated, and there has been a rapid replacement of one genetic model with another subsequent to the discovery of new data (Abrahams & Geschwind, 2010; Bill & Geschwind, 2009; Girirajan et al., 2010; Holt & Monaco, 2011; Voineagu et al., 2011; Zhao et al., 2007).

Following are brief discussions of four selected unifying feature claims. One reports that autism includes a superior mental process of touch-to-vision memory (Nakano, Kato, & Kitazawa, 2012). A second reports that autism includes a superior visual speed discrimination skill (Chen et al., 2012). A third asserts that atypical response to eye gaze in infants predicts later autism diagnosis (Elsabbagh et al., 2012). A fourth asserts that an early atypical pattern of the brain’s white matter development predicts later autism diagnosis (Wolff et al., 2012). Following the discussions of these four unifying feature claims are brief discussions of two multi-gene models.

Two Empirical Unifying Earliest Feature Claims for Autism

Event-Related Potential Pattern to Eye Gaze Before 12 Months Predicts Autism

Elsabbagh et al. (2012) reported that 40 infants at risk for autism, when compared with 45 healthy controls, showed less P400 brain activity at 6–10 months while viewing faces with eye gaze directed toward versus away from the infant. Thus, a particular brain activity pattern known to be specifically responsive to human faces (P400) was found to be atypically relatively less active in individuals at risk for autism in infancy. The researchers proposed that their findings
were consonant with evidence that brain function measures can distinguish infants at risk for autism from typical children, and consonant with evidence for various other early predictors of risk, including a visual processing marker, an attention-switching marker, a face response marker, and a marker based on sensitivity to eye direction gaze. Elsabbagh et al. (2012) argued that atypical brain function related to eye gaze reaction precedes the onset of autism behavior.

Limitations for the Claim that Event-Related Potential Pattern to Eye Gaze Before 12 Months Predicts Autism
The researchers found that neither static gaze nor face-versus-noise contrasts reliably distinguished the ASD group from the two other groups. Thus, there was only a single significant data point (P400 on dynamic gaze shift), demonstrating lower responsivity, differentiating children at risk who later were diagnosed with autism. Moreover, Elsabbagh et al. (2012) did not discuss the implications of delayed cognitive development found for children at risk for autism.

Infant White Matter Development Pattern Predicts Autism
Wolff et al. (2012) reported that imaging of white matter tracts revealed that development of a majority of tracts differed significantly between 17 infants at risk and later diagnosed with autism, and 33 at-risk infants not diagnosed with autism. The 17 infants who later were diagnosed with autism showed evidence of larger white matter tracts at 6 months. However, these 17 infants then were found to have slower development of white matter tracts compared with infants not diagnosed with autism, and at 2 years the brains of the 17 diagnosed children showed evidence for less white matter in fiber tracts compared with children without autism. Wolff et al. (2012) concluded, “Most fiber tracts for the ASD-positive infants were characterized by higher fractional anisotropy at 6 months followed by blunted developmental trajectories such that fractional anisotropy was lower by 24 months” (p. 6).

Limitations for the Claim that Infant White Matter Development Pattern Predicts Autism
The 17 children who were later diagnosed with autism differed not only in diagnostic features. The children later diagnosed with autism had significantly lower scores on a measure of cognitive development at age 6 months, 12 months, and 24 months. Atypical white matter development is likely to be the cause of both developmental delay and abnormal social behavior. However, the Wolff et al. (2012) research report did not discuss developmental delay. Also possible is that the pattern of white matter development in the 17 was a collection of different patterns of white matter development. The
report offered no analysis or discussion of individual variation within the group of 17 children diagnosed with autism.

Wolff et al. (2012) cited the study of Barnea-Goraly, Lotspeich, and Reiss (2010) with the comment, “Studies of ASDs using diffusion tensor imaging have identified evidence of widespread abnormalities in white matter fiber tract integrity” (p. 2). However, Barnea-Goraly et al. (2010) reported that the brains of children with autism and their unaffected siblings both had reduced prefrontal white matter, and reduced white matter in the corpus callosum, cingulate gyrus, thalamus, left and right superior temporal gyrus approaching the hippocampus and the amygdala, and left and right temporoparietal junctions. Barnea-Goraly et al. (2010) found white matter structure in the children with autism and their unaffected siblings differed significantly from that of typical children, and they concluded that atypical white matter was likely to be a family trait “not directly related to the actual psychopathology” of autism (Barnea-Goraly et al., 2010, p. 1058). Wolff et al. (2012) included no discussion of these relevant Barnea-Goraly et al. (2010) data and conclusions in the interpretation of their own white matter findings.

Two Empirical Unifying Superior Skills in Autism

Superior Perceptual Integration in Autism

Nakano et al. (2012) reported that 14 adults with autism demonstrated superior performance on a test of touch-to-vision delayed matching of shape compared with 20 healthy controls. The study participants touched a shape without seeing it, and then had to identify it visually after a delay. The researchers argued that success on this task required integration of sensorimotor percepts of the felt shape into an object representation that could be mentally visualized. Nakano et al. (2012) argued that the integration of sensorimotor percepts of a shape that was later correctly identified visually contradicted the weak central coherence theory of autism. Happé and Frith (2006) had proposed the weak central coherence theory of autism, which claimed that cognitive processing in autism relied on abnormally superior processing of sensory details in the absence of ability to integrate sensory information. Nakano et al. (2012) noted that the superiority of adults with autism on the touch-to-vision task did not reflect a superiority of local or detail-focused processing because the adults with autism were no better than typical adults in their ability to discern object orientation or length. Nakano et al. (2012) proposed that future studies were necessary to explore whether superior haptic-to-visual shape perception skill was linked to savant skills found “in 10–30% of persons with ASD” (p. 7).
**Superior Discrimination of Visual Movement Speed in Autism**

Chen et al. (2012) reported that 19 adolescents with autism had better speed visual discrimination performance scores than 17 healthy controls when visual comparisons were made after a delay. In the study, all adolescents had to determine which of two displays of 200 random dots on a computer screen was moving faster. The regular interval between dot displays to be compared was a half second, and the prolonged comparison delay was six times as long, 3 seconds. The researchers argued that superior discrimination for the individuals with autism could not be the result of enhanced working memory because previous studies had reported impaired working memory in autism.

Chen et al. (2012) theorized that superior visual discrimination skill in autism was a function of an atypically longer process of visual encoding in autism. The researchers proposed that the visual system in autism had shifted visual speed processing to a slow speed range, such that brain activity in the visual system had longer latencies with smaller receptive fields. Chen et al. (2012) argued that the 3 second delay allowed for extended coding that “would afford additional processing of speed signals and allow for a perceptual advantage in this visual motion domain” (p. 737).

**Limitations for the Findings of Nakano et al. (2012) and Chen et al. (2012)**

Shared limitations of the studies of Nakano et al. (2012) and Chen et al. (2012) are small sample size and isolation of the specific finding. Sample sizes of 14 and 19 individuals cannot provide compelling evidence. Second, both findings exist in isolation from other findings in the field, and represent one data point of superiority within testing that otherwise found no differences between the sample with autism and the control sample. As noted in Chapter 2, Ioannidis (2005) stated, “There is increasing concern that in modern research, false findings may be the majority or even the vast majority of published research claims …. However, this should not be surprising. It can be proven that most claimed research findings are false” (p. 696). Ioannidis argued that small samples, selective measures, a bias for significance, and highly creative measures operating in a “hot” field all contribute to invalid significance measures. All the factors identified by Ioannidis apply to these two studies.

**Two Empirical Multiple Gene Models of Autism**

*The Multiple Hit Model of Autism*

LeBlond et al. (2012) studied 260 individuals with autism and found a deletion within the *SHANK2* gene in one individual with autism and moderate
intellectual disability. Because the affected individual’s parents did not carry this deletion, the deletion was a de novo event, new in the affected individual. LeBlond et al. (2012) reported, “In patients, the only feature associated with carriers of SHANK2 mutations compared with other patients was a trend for low IQ” (p. 11). The researchers also noted that 5% of the Finnish population was heterozygous for a SHANK2 variant without negative effects, and that “deleterious SHANK2 variants were detected in a heterozygous state in parents and in the general population without causing severe phenotypic consequences” (LeBlond et al., 2012, p. 11). The researchers concluded that the co-occurrence of de novo mutations, together with inherited variations, might be the genetic source of autism. In a larger sample, the researchers identified three patients with de novo SHANK2 deletions who also carried inherited CNVs at 15q11–q13, a region associated with neuropsychiatric disorders. The researchers concluded that these three cases supported the theory of autism as resulting from multiple genetic mutations.

Limitations for the Multiple Hit Genetic Causal Model for Autism
It is likely that cases of autism do result from “the co-occurrence of de novo mutations, together with inherited variations” (LeBlond et al., 2012, p. 12). However, the multiple hit theory cannot apply to all cases of autism. The evidence for various forms of syndromic autism, discussed in Chapter 4, has demonstrated that autism symptoms can appear as the result of single gene effects. In addition, there is evidence suggesting different forms of “myriad hits” wherein many gene variants contribute to autism symptoms.

Tumor Necrosis Factor and Beta-Estradiol Regulators as Priorities for Genetic Research in Autism
Lee, Raygada, and Rennert (2012) proposed that autism was linked to gene clusters related to PTEN/TSC1/FMR1 and mTOR/PI3K gene regulation. Lee et al. (2012) created a theoretical network of possible genes by examining 35 genes that had been linked to impaired social interaction, 8 genes linked to repetitive behavior, 74 genes linked to obsessive behavior, 146 genes linked to impaired communication, and 98 genes tied to intellectual disability. The researchers analyzed relationships between the aggregated genes and found complex regulatory networks. Two key factors in the regulatory network they constructed were tumor necrosis factor (TNF) and beta-estradiol.

The researchers proposed that TNF would be expected to operate in a systemic molecular network in autism because TNF decreases serotonin
transporter function. However, Lee et al. (2012) were surprised to find beta-estradiol-related effects in the constructed network. They noted that beta-estradiol was involved in neuroprotective and neurotropic functions mediated by estrogen receptor signaling cascades.

The researchers tried to replicate the constructed networks using evidence of actual genes found in association with autism. However, the researchers stated that, because so few genes had been identified for autism in genome-wide association studies, they could not construct a network based on genes actually found in autism. In a third analysis, the researchers reported finding a cluster for increased expression of the PTEN, TSC1, and FMR1 genes, and a cluster including genes with deletions and reduced expression linked to the mTOR/PI3K signaling pathways. The researchers concluded that a large number of non-overlapping gene networks might be the basis for autism heterogeneity.

Limitations of the Network Model
Although the researchers stated that the goal of their study was to “prioritize molecular interactions” (Lee et al., 2012, p. 9), it was not clear from the report of their study how genetic research priorities had been advanced by their efforts, nor did they propose specifically how their constructed network information might be used in future research.

Summary: All Six Studies Sought to Find a Unifying Feature or Pattern in Autism
This brief review reported four claims for behavioral unity in autism: infant diminished P400 wave to dynamic gaze shift predicting autism (Elsabbagh et al., 2012); abnormal trajectory of infant white matter development pattern predicting autism (Wolff et al., 2012); adult superior touch-to-vision delayed matching (Nakano et al., 2012); and adult superior dot movement delayed discrimination (Chen et al., 2012). Elsabbagh et al. (2012) found one pattern of brain activity, and Wolff et al. (2012) found one pattern of brain development. Each finding was proposed as a predictive early signal of autism. However, because neither research team conducted an exploratory data analysis to look for individual variation, possible evidence for variation in these proposed early predictors was not explored. Although all disorders under the autism umbrella would benefit from early intervention, autism variation might be crucially important for intervention strategies, and the patterns of individual variation cannot be adequately explored in small samples.
This section also sketched a report supporting the multiple-gene-hit model (LeBlond et al., 2012), and a gene network model (Lee et al., 2012). The translational value for these models is, as yet, unclear.

ABANDONING AUTISM AS A SINGLE DISORDER WOULD ELIMINATE THREE INFERENTIAL PROBLEMS IN AUTISM RESEARCH

Diagnostic Criteria that have Never been Validated would no Longer be Needed

As noted in Chapter 7, Hyman had worried that, as director of NIMH, he had funded hundreds of studies predicated on DSM criteria “that almost never questioned the existing diagnostic categories despite their lack of validation” (2010, p. 157).

Links Between Autism Diagnostic Symptoms have not been Validated or Explained

As noted in earlier chapters, Happé et al. (2006) provided evidence from twin studies of typical individuals that the three DSM-IV autism diagnostic symptoms of social impairment, communication difficulties, and rigid and repetitive behaviors were genetically unrelated, and resulted from three separate sets of non-overlapping genes. They concluded that the symptoms were independent of one another. Happé et al. (2006) stated, “Clearly a question remains of why these three features co-occur at above-chance rates” (p. 1219) in autism.

Similarly, Robinson et al. (2012) tested 5944 typical twin pairs and found almost no genetic causal overlap for the proposed DSM-5 two symptom groups: social impairment, and restricted and repetitive behaviors and interests or sensory abnormalities. The researchers noted that identical and fraternal twins had non-significant cross-twin correlations ranging from .02 to .19 between the two DSM-5 autism symptoms.

Boucher (2011) noted that autism symptoms were not correlated, and expressed concern that there was no explanation for how the varied etiologies, brain deficits, and diagnostic symptoms did manage to converge on a single autism brain abnormality. She hypothesized that heterogeneous brain deficits, heterogeneous etiologies and diagnostic symptom behaviors must “fan in” to converge onto a single brain abnormality. Boucher (2011) proposed that the autism diagnosis be redefined as a spectrum of many separate symptoms and physical disorders that happened to occur together in autism more than would be expected by chance. Similarly, Lord and Jones (2012) defined autism as an
“as-yet-not-understood combination of social-communication deficits and repetitive/restricted behaviors and interests that interact together to form a pattern that appears to be more than the sum of its parts” (p. 504). As Boucher (2011) noted, research has not discovered how the symptoms “interact together to form a pattern that appears to be more than the sum of its parts.”

**Autism Diagnostic Symptom Set has not been Validated**

Kanner (1943) defined infantile autism as a single disorder with two key symptoms: the profound failure to understand social interaction, with an insistence on sameness. Kanner has rightfully been honored for his identification of severe social impairment in children. However, neither neuroscience nor genetics research has validated Kanner’s autism. Researchers have not found any brain circuit or region that when disrupted will cause his two symptoms, insistence on sameness and the inability to understand social interaction, and only these two symptoms (Campbell et al., 2011; Ebisch et al., 2010; Leckam et al., 2011; Lewis & Kim, 2009; Lombardo et al., 2011; Schulte-Rüther et al., 2011). Similarly, researchers have not found a genetic or environmental cause that generates all and only all the three DSM symptoms of social interaction failure, communication impairment, and restricted and repetitive behaviors or activities (Addington & Rapoport, 2012; Geschwind, 2011; State & Levitt, 2011; Yrigollen et al., 2008).

Moreover, no animal models have been found that produce animal homologues of the three DSM symptoms. For example, Peñagarikano et al. (2011) reported that mice lacking the Cntnap2 gene associated with autism exhibited abnormal vocal communication, repetitive and restricted behaviors, and abnormal social interactions. However, Peñagarikano et al. (2011) reported that the mice were also hyperactive and suffered epileptic seizures. Malkova, Yu, Hsiao, Moore, and Patterson (2012) created a mouse model of environmental risk of autism by stimulating the immune system of female mice. Male offspring of the immune-activated mothers had truncated vocalization, decreased sociability, and high levels of repetitive behaviors. However, Malkova et al. (2012) noted that offspring of immune-activated mouse mothers “also display features of schizophrenia. These include enlarged ventricles, enhanced responses to amphetamine and hallucinogens, alterations in dopamine and serotonergic pathways, as well as … enhanced anxiety and eye blink conditioning” (p. 8).

Abandoning the quest for autism as a single disorder would eliminate the need to validate autism diagnostic criteria that have never been validated.
Viewing Behavioral Symptom Heterogeneity as Comorbidity would be Unnecessary

Coghill and Sonuga-Barke (2012) argued that heterogeneity and comorbidity made classification of diagnostic groups difficult. The researchers pointed out that comorbidity is common in childhood mental disorders. When comorbidity is reduced by eliminating some diagnostic categories, then the remaining diagnostic categories necessarily will have increased heterogeneity. In the case of autism, as argued in Chapters 4 and 7, comorbidity has often been the assignment of selected symptoms of one general brain disruption to separate disorders. Pushing out selected symptoms of complex autism phenotypes into other disorders has been an error similar to Mendel’s setting aside and discarding pea phenotypes that seemed errantly and extraneously heterogeneous thus interfering with the orderly clarity of Mendel’s inheritance model.

In fact, the extensive variation in symptoms found for individuals with autism is rarely the result of the comorbidity of a truly independent additional disorder (Addington & Rapoport, 2012; Fernandez et al., 2012; Rommelse et al., 2011; Tabet et al., 2012). Despite claims of errant clinical practice (Lord, 2011), problems in diagnosis often reflect the difficulty in assigning simplified labels to complex phenotypes. Diagnostic social impairment and diagnostic motor and sensory behaviors occur with intellectual disability or developmental delay, epilepsy, motor delay, language impairment, attention deficit/hyperactivity disorder, and other symptoms because the brain is complex, brain development is complex, and brain disruptions are so varied.

Equally important, the exclusion of non–diagnostic associated symptoms from autism phenotypes leads to problematic inferences. For example, Guinchat et al. (2012a) reported that parents’ early concerns about their children at risk for autism did not include autism symptoms:

>We found that the earliest warning signs were frequently not specific to autism ….

Motor peculiarities, sensory reactivity, atypical regulation of emotions, a lack of attention, an abnormal level of activity, or sleeping problems were some of the common features … and it is noteworthy that most of the concerns related to a diagnosis of autism were clearly not the earliest concerns evoked by parents.

Guinchat et al. (2012a, p. 598)

Although Guinchat et al. (2012a) declared that motor peculiarities, sensory reactivity, atypical regulation of emotions, a lack of attention, an abnormal level of activity, or sleeping problems were features not specific to autism or a diagnosis of autism, these features have all been found in complete autism phenotypes. If Guinchat et al. (2012a) were to view the children’s phenotypes as including all expressed symptoms, the researchers would then find
that parents had been reporting symptoms relevant to their children’s neurodevelopmental disorder.

As discussed in Chapter 7, Close et al. (2012) provided another example of an inferential problem that occurs when symptoms are assigned to a disorder thought to be comorbid with autism. The researchers compared symptoms of children who “lost” the diagnosis of autism with symptoms of children who did not lose the diagnosis of autism. The researchers looked at data from 1366 children where 453 of the children’s parents reported a past but not current diagnosis of autism spectrum disorder. The remaining parents reported a current diagnosis of ASD for their child. Close et al. (2012) found that children aged 2–5 years with a current diagnosis of autism were 9.20 times more likely to have developmental delay and 4.76 times more likely to have two current comorbid conditions than children who had a former diagnosis of ASD. Children aged 6–11 years with a current diagnosis of autism had a 3.85 times greater odds of having a past speech problem, 3.51 greater odds of having current anxiety, and were 3.19 times more likely to have two current comorbid conditions.

Do the symptoms Close et al. (2012) described as comorbid “belong to” the autism phenotype or do they belong to another comorbid disorder? A British newspaper, The Daily Mail, reported the Close et al. (2012) study findings in an article headlined “Can some children simply grow out of autism?” (Naish, 2012). England’s National Health Service (NHS) responded to the Daily Mail article by arguing that children do not grow out of autism (NHS Choice, 2012). The NHS asserted that “diagnosing ASD is challenging, especially since the condition is often accompanied by other neurodevelopmental disorders with overlapping symptoms” (NHS Choice, 2012).

The NHS claim effectively proposed that a symptom such as speech delay would be an “overlapping symptom” in a child with autism and a comorbid language disorder, because speech delay could result from the child’s autism or result from the child’s comorbid language disorder. However, the brain disruption causing the speech delay does not recognize or respect diagnostic assignment. More importantly, risk factors for autism symptoms may cause social impairment, behavioral rigidity, sensory abnormalities, and attention deficit/hyperactivity disorder, developmental delay, language development problems, and motor problems in the same individual. Therefore, when speech delay and social impairment both occur in one child, it is unlikely that the speech delay is an overlapping symptom of a separate comorbid language disorder.

Although Close et al. (2012) argued that future autism research should “focus on the factors that discriminate the co-occurring conditions whose
symptoms overlap with ASD” (p. e315), this discrimination would be likely to be scientifically counterproductive. Autism genetic and environmental risk factors produce non-diagnostic and diagnostic symptoms in an individual because risk factors cause brain-wide disruptions (Gilman et al., 2011; Wei et al., 2011). Therefore, co-occurring symptoms are most likely to be component impairments of the complete autism phenotype and are unlikely to be evidence of separate comorbid disorders.

Abandoning the diagnosis of autism as a disorder would free researchers to recognize and study the complete phenotype of children expressing neurodevelopmental social impairment.

The Problem of the Failure to Reconcile Data and Synthesize Theories in Order to Establish the Features of Autism would Disappear

Autism research has spent little effort to reconcile competing theories and conflicting findings (Waterhouse, 2008, 2009). Theories of autism as a single disorder are replaced repeatedly without efforts to reconcile findings or synthesize theories. Because no unifying brain dysfunction has been established, many of us conducting autism research have generated a series of varied theories of autism brain dysfunction.

As outlined in Chapter 1, the Duhem–Quine principle proposed that no scientific theory will fully account for all the existing variation in available evidence. Consequently, scientific understanding moves forward from one not-fully-explanatory theory to the next not-fully-explanatory theory. However, there are limits to the scientific acceptability of not-fully-explanatory theories. The extreme heterogeneity of autism has meant that far too little of the variation in autism has been explained by theories claiming autism is a single disorder.

Meehl (1990) argued that when theories explain too little variation, they are so weak that they can easily be replaced in a process that Meehl called “ad hocery.” The weak support for an existing theory allows for the creation of a new ad hoc theory whenever new empirical evidence is discovered. Viewed from a Meehl (1990) perspective, the repeated replacement of one theory of autism after another has been “ad hockery.” Rejected ad hoc theories eventually require synthesis, not replacement. Although normal science does involve a “point–counterpoint” competition between data claims, reconciliation of contradictory findings and competing theories is necessary to drive productive research.

Meehl (1990) argued that eventually, “As more and more ‘ad hockery’ piles up” (p. 112), researchers begin to doubt that they have correctly
conceptualized the problem. Researchers begin to conclude, as Szatmari (2011) did, that the research field should start over in conceptualizing autism.

**Lack of Subgroup Synthesis**

The proposed DSM-5 autism criteria have collapsed all former DSM-IV-TR diagnostic subgroups into one group, autism spectrum disorder. Unfortunately, the rationale proposed for collapsing the individual subgroups was that they shared a common pathophysiology (Kupfer & Regier, 2011), a rationale that has not been supported by empirical evidence (see Chapter 7).

Veenstra-VanderWeele and Blakely (2012) argued that because autism spectrum disorder was a heterogeneous condition, researchers should create subgroups “based on biomarkers, such as macrocephaly or indicators of mitochondrial dysfunction, or genetic findings, such as the neurexin–neuroligin system …. [or] abnormal mTOR and 5-HT signaling” (p. 206). Eapen (2011) proposed three genetic subgroups of autism. She defined syndromic ASD caused by rare, single-gene disorders as having a more complex phenotype. She defined de novo mutation ASD as a severe and specific phenotype. Eapen (2011) defined a third genetic type as broad autism caused by genetic variations in single or multiple common genes distributed across the general population.

Many indirect biomarker subgroups have also been proposed for autism. Aldridge et al. (2011) conducted a facial feature analysis of boys with autism. Aldridge et al. (2011) determined that all the boys with autism had a distinct facial phenotype characterized by an increased breadth of the mouth, orbits, and upper face, combined with a flattened nasal bridge and reduced height of the space between the nose and mouth. Aldridge et al. (2011) noted that this facial phenotype signals disruption of the embryological frontonasal process that contributes to forming the face. The researchers also found two distinctive face types within the autism group. One face pattern subgroup of 12 boys had increased autism severity scores and lower cognitive scores. A second face pattern subgroup of 5 boys had less severe autism symptoms and larger heads.

Fountain, Winter, and Bearman (2012) proposed six subgroups of autism based on the course of development: high, bloomers, medium-high, medium, low–medium, low. The low–medium and low subgroups showed little improvement in behavior from age 3 to 14. The high and medium-high groups demonstrated continuous improvement in behaviors during this same period. The one surprising group called “bloomers” showed the steepest upward development trajectory from low functioning to high functioning within the time period.
It is not clear how evidence for the six developmental trajectory subgroups proposed by Fountain et al. (2012) and the two face structure subtypes proposed by Aldridge et al. (2011) might be synthesized with the three proposed genetic subgroups—syndromic autism, de novo mutation autism, and broad autism—proposed by Eapen (2011). Similarly, it is not clear how the evidence for many hundreds of subgroups based on a wide array of different features might be reconciled.

The Hundreds of Theories Proposing a Unifying Feature for Autism would not Require Synthesis if Autism were no Longer Viewed as a Single Disorder

Data reconciliation and theory synthesis have been rare in autism research. Many researchers believe the variation in autism will be resolved by the next, better, new unifying brain dysfunction. For example, Kana, Libero, and Moore (2011) argued, “Given the complexity, heterogeneity, and the developmental nature of ASD, a global explanation or a set of explanations seems optimal … disrupted cortical connectivity may be one such explanatory model” (p. 428). Thus for Kana et al. (2011) the best response to complexity and variation was to provide a broad but unifying explanatory theory.

However, the disrupted cortical connectivity theory espoused by Kana et al. (2011) to explain all autism has been countered by other findings. Barnea-Goraly et al. (2010) reported that individuals with autism and their unaffected siblings had the same pattern of atypical white matter. Vissers et al. (2012) carefully reviewed evidence for the underconnectivity theory of autism. Vissers et al. (2012) found insufficient evidence for frontal cortex local overconnectivity. More importantly, they reported that varied patterns of abnormal functional connectivity fell outside the bounds of the theory, and thus were not explained by the theory. Wass (2011) also reviewed the underconnectivity theory of autism. Wass argued that increased short-range connectivity and decreased long-range connectivity reflected immaturity of the cortex, and are found in many other disorders, including depression, schizophrenia, Tourette’s, Williams syndrome, and developmental language disorder. Wass (2011) stated, “The overlap between how connectivity is disrupted in ASD and in other disorders remains poorly understood” (p. 25).

If autism continues to be conceptualized as a single disorder, these contradictory findings for connectivity need to be reconciled, and the theories of underconnectivity need be synthesized.

Kaiser and Pelphrey (2012) argued that although previous autism research had not found any “consistent neurochemical, neurophysiological,
or neuroanatomical abnormality” (p. 29) for autism, the researchers none-
theless argued that “disruptions in the visual perception of biological motion
were a hallmark of ASD which may serve as a channel to the pathogno-
monic deficits of the disorder” (p. 33).

However, Koldewyn, Whitney, and Rivera (2010) stated, “current results
do not support either a general dorsal stream deficit or a bias towards local
perception as explanations for visual perception differences in those with
autism” (p. 608). Koldewyn et al. (2010) and Rutherford and Troje (2012)
found that the detection of biological motion in individuals with autism
was correlated with intelligence level. More significantly, Rutherford and
Troje (2012) found no group differences in the detection of biological
motion between individuals with autism and controls, and reported that the
pattern of decline across levels of masking was similar between groups.

Can the contradictory findings for impaired detection of biological motion
be reconciled with the contradictory findings for the theory that autism is
caused by underconnectivity? Again, normal science does involve a “point–
counterpoint” theory competition, but reconciliation of contradictory find-
ings and theory synthesis are required in order to drive productive research.

Theory Predictions from Autism Data Sets Require Reconciliation
Noted and productive autism researcher Eric Courchesne has proposed more
than a dozen separate theories of autism. Only four of them are described here
(Akshoomoff, Pierce, & Courchesne, 2002; Chow et al., 2012; Kennedy &
Courchesne, 2008; Schumann, Barnes, Lord, & Courchesne, 2009). In 2002,
Akshoomoff et al. theorized that autism resulted from aberrant timing of neu-
ron growth leading to a larger than normal cerebrum and reduced cell num-
bers in the cerebellum and limbic regions. In 2008, Kennedy and Courchesne
reported evidence that the attention network regulating attention to external
events was intact in autism, but the default mode network regulating self-
internal attention was disrupted in autism. Kennedy and Courchesne (2008)
thorized that the spared dorsal external attention network supported spared
and enhanced skills in autism, while the impaired self-internal attention net-
work resulted in attention being shifted away from “social and emotional pro-
cessing, but toward a particular non-social and non-emotional cognitive
processing style” (p. 1882). In 2009, Schumann et al. reported finding larger
amygdalae in toddlers with autism and that amygdala size in males was associ-
ated with severity of autism symptoms. Schumann et al. (2009) theorized that
the larger amygdala was hyper-aroused in people with autism in response to
socially relevant stimuli, thus impairing social interaction functioning.
In 2012, Courchesne and his research team (Chow et al., 2012) compared gene expression levels in postmortem frontal lobe samples from 9 males with autism and 7 males without autism who died when they were between 2 and 14 years old. The researchers also compared gene expression levels in postmortem frontal lobe samples from 6 males with autism and 11 males without autism who died when they were between 15 and 56 years old. This total sample of 33 was selected from a larger initial sample of 57 individuals. Chow et al. (2012) found that 2017 genes had significantly different expression levels in the 15 autism brain samples compared to the 18 non-autism brain samples, and they reported that 736 genes were differentially expressed in the two age groups within the total autism sample. Chow et al. (2012) theorized that the gene expression differences they found for the younger autism sample reflected abnormal brain activity regulating cell number, proliferation, cell cycle, cortical patterning and differentiation, DNA damage response and apoptosis and survival. The researchers argued that this dysregulation was the possible cause of the 67% excess of neurons they found in the prefrontal cortex of children with autism (Courchesne et al., 2011).

All four theories proposed by Courchesne and colleagues were well developed and supported by empirical evidence. However, these four theories effectively replaced one another in the ad hoc fashion described by Meehl (1990) because Courchesne and colleagues did not attempt to reconcile conflicting claims of their own research team’s four papers, or to reconcile their findings with conflicting findings of others.

The four theories make contradictory predictions and report contradictory findings. Akshoomoff et al. (2002) theorized that abnormal growth patterns led to a smaller cerebellum and smaller limbic regions in autism. The core elements of the limbic region that would be smaller would be the hypothalamus, hippocampus, and the amygdala. Conversely, Schumann et al. (2009) found evidence for larger amygdalae in children with autism, and theorized that autism social impairment reflected hyper-activation of the amygdala. For Akshoomoff et al. (2002), the amygdala, as part of a smaller limbic system, should be smaller, not larger. Similarly, Chow et al. (2012) theorized that a set of aberrantly expressed genes explained their own team’s finding for excess neurons and aberrant organization of those neurons in autism frontal lobe tissue. If there is more tissue in the cerebrum in autism, according to Akshoomoff et al. (2002), the cerebellum and the amygdala should be smaller, but Schumann et al. (2009) found evidence for larger amygdalae in children with autism. In addition, Ecker et al. (2011) reported finding reduced amygdala size associated with autism symptoms in adults.
with autism. Ecker et al. (2011) also noted that studies have reported larger amygdalae, smaller amygdalae, and normal sized amygdalae in autism.

If the cerebrum were larger in autism as proposed by Akshoomoff et al. (2002), it would be expected that head size would be likely to reflect the larger cerebrum. However, Barnard-Brak et al. (2011) reported in the Early Childhood Longitudinal Study Birth Cohort, a nationally representative, community-based sample of approximately 9000 children, that the 100 young children with autism did not show significant head circumference difference at age 9 months, 24 months, and 36 months compared with the head circumference of the 8900 children without autism.

Kennedy and Courchesne (2008) reported evidence that the external attention network was not disrupted in autism. However, Chow et al. (2012) reported that many brain development genes have aberrant expression in the frontal lobe in autism and theorized that aberrantly expressed genes accounted for their findings of more neurons in frontal lobe tissue in autism (Courchesne et al., 2011). Given the importance of frontal lobe function to external attention (Posner, 2011), it is surprising that an aberrantly developed frontal lobe (Chow et al., 2012) in autism would cause no disruption of the external attention network (Kennedy & Courchesne, 2008). In addition, external attention deficits have been widely reported for autism (Rommelse, 2011). These discrepant findings require reconciliation.

Chow et al. (2012) did note that their gene expression results differed to those of a similar study by Voineagu et al. (2011), and suggested that genetic heterogeneity in autism and sample characteristics might explain the differences. However, Chow et al. (2011) offered no synthesis of their findings with those of Voineagu et al. (2011).

As exciting and interesting as the four theories have been (Akshoomoff et al., 2002; Chow et al., 2012; Kennedy & Courchesne, 2008; Schumann et al., 2009), this brief exercise suggests that the effort to reconcile findings and theories, if undertaken, might have been problematic.

THE EXISTING QUANDARY AND THE ARGUMENT FOR AUTISM AS SYMPTOMS

The Existing Quandary: Should the Current Paradigm of Autism be Abandoned?

Kendler and First asked the question:

*At what point does it make sense to abandon one paradigm in favour of another? Ideally, the shift should be organic, occurring at a point at which the advantages of*
the new paradigm become so overwhelming that to continue with the existing paradigm would make no sense. However, what happens if a shift is driven by a new paradigm whose advantages over the existing paradigm are tentative, more theoretical than practical, appealing but not “road tested”?

Kendler and First (2010, p. 264)

What paradigm of autism should researchers follow?

Should researchers keep searching for the unifying pathophysiology of autism in samples defined by DSM criteria and DSM diagnostic instruments? Elsabbagh et al. (2012), Chow et al. (2012), Kaiser and Pelphrey (2012), Kana et al. (2011), Wolff et al. (2012) and many other researchers have argued for this course. Lord and Jones (2012) noted that finding the neural basis for autism symptoms was “particularly important if the focus is on earlier or better diagnosis … we do want to link the neurobiology to the behaviors that we are trying to explain in ASD” (p. 492).

However, the search for the neurobiological basis for autism has a long history of failure. As noted throughout this book, no validated pathophysiology has been discovered for autism, and even the core autism symptom of social interaction impairment has not been linked to any single neurobiological cause. The existing evidence for heterogeneity of behaviors, brain deficits, and etiologies for autism argues against the possibility of finding autism-specific “valid patterns of brain function that are associated with reliably measured behavioral dimensions of ASD” (Lord & Jones, 2012, p. 492).

Should researchers attempt to exclude what they interpret as non-diagnostic symptoms from autism symptom sets in the belief that there is a unitary autism disorder or meaningful spectrum of closely related autism disorders? Close et al. (2012), Guinchat et al. (2012a), Lord and Jones (2012), and the APA DSM-5 Neurodevelopmental Disorders Work Group have argued for this view.

Lord and Jones (2012) stated that, in comparison with neurobiological research in autism, the research on social impairment was “notable in its consistency and replicability across studies” (p. 494). However, this consistency cannot include the measurement of individual variation. As noted in Chapter 1, Jones and Klin (2009) concluded, “Individuals with autism show a vast clinical variability in the expression and severity of their symptoms. This heterogeneity spans the entire range of IQ and language function and a wide array of communicative, social, and behavioral disabilities” (p. 471). Schultz noted, “If you’ve seen one child with autism, you’ve seen one child with autism. Autism’s like a snowflake” (Scott, 2011). Even Lord (2011) observed that anyone who has met more than one person with autism is struck by the variation between diagnosed individuals.
Lord and Jones (2012) proposed that “Finer-grained descriptions of behaviors associated with ASD are still needed in order to better define dimensions of social-communication deficits and restricted/repetitive behaviors on an individual level for both clinical and neurobiological purposes” (p. 504). Although finer-grain descriptions of autism symptoms would certainly yield increasing detail that would better inform differentiable clinical descriptions of individual variation within autism, finer-grain behavioral descriptions are unlikely to add information that would help to link behavior to neurobiology. To date, no validated causal specificity for autism symptoms has been determined from the wealth of heterogeneous neurobiological findings. Because finer-grain symptom descriptions will not explicate how varied neurobiological causes converge on one clinical symptom, and will not explicate how divergent clinical symptoms are generated by a single neurobiological cause, finer-grain descriptions of autism symptoms are unlikely to be useful for determining the complexities of autism neurobiology.

Should researchers view autism as a spectrum of related disorders that can be successfully divided into subgroups? Aldridge et al. (2011), Eapen (2011), Veenstra-VanderWeele and Blakely (2012), and many other researchers have held this view, but this view has yet to provide improved clarity in diagnosis and has yet to establish standard subgroups within autism. The proposed DSM-5 criteria for autism have eliminated all diagnostic subgroups for lack of distinguishing evidence to differentiate the diagnostic subgroups, and because a shared pathophysiology for autism was claimed to exist.

Kendler and First (2010) argued that psychiatric disorders could not be divided into etiological subgroups because the genetic bases for disorders have proven to be so complex that finding single etiology subgroups would be unlikely. However, genetic single etiology subgroups already exist in autism. Called syndromic autism, the diagnosis of autism has been made in individuals with fragile X syndrome, Rett syndrome, tuberous sclerosis, Joubert syndrome, Timothy syndrome, Down syndrome, Klinefelter syndrome, and Angelman syndrome, as well as in many other defined genetic syndromes.

In fact, syndromic autism demonstrates that autism symptoms may appear in association with many different forms of neurobiological brain disruption caused by many different genetic etiologies. The findings for syndromic autism also suggest that the Lord and Jones (2012) goal of linking “neurobiology to the behaviors that we are trying to explain in ASD” (p. 492) may be fraught with complex overlapping links.

Should researchers view autism as many hundreds of different autisms resulting from multiple genetic causes and multiple environmental causes?
Coleman and Gillberg (2012) have argued for this view, but the prospect is daunting. Dame Stephanie Shirley, founder of Autism Speaks in Britain, had hoped that “the causes of the various autisms should be understood by 2012” (Feinstein, 2010, p. 297). This has not happened, and for good reason: the causes are many and complex.

Most importantly, nature has blocked any easy path to inference for the discovery of multiple autisms. As noted frequently in this book, autism symptoms appear with other symptoms in association with a shared risk factor, and many different patterns of brain disruption may produce the same autism symptom. Together these two lines of evidence mean that clear causal mapping of risk factor to brain disruption to symptom will be unlikely, and suggest that etiological agents and developmental brain disruptions have not created hundreds of clearly distinguishable autism syndromes.

An additional inferential problem for forming multiple subgroups is the difficulty in identifying discrete brain deficits. The widespread brain disruptions found to date in association with autism, and the complexity of brain networks both stand against the identification of discrete brain deficits for autism subgroups. An example of the potential underlying complexity is the proposal that Schilbach et al. (2012) made for three overlapping brain networks. The researchers conducted a meta-analytic study and concluded that there was a social cognition network reflected in brain activation in the left dorsomedial prefrontal cortex, the left precuneus, the temporoparietal junction, the anterior temporal cortex, and the left superior frontal gyrus. They defined a network for emotion processing that included bilateral activation in the amygdala, the ventral and dorsal striatum, the anterior cingulate cortex and dorsomedial prefrontal cortex, the posterior cingulate cortex, precuneus, dorsal visual area V5, and insular cortex (Schilbach et al., 2012). Finally, they defined a network for introspection, the default mode network active when a person is not focused on a task, including posterior cingulate cortex, precuneus, anterior cingulate cortex, ventromedial and dorsomedial prefrontal cortex, bilateral supramarginal gyrus, bilateral temporoparietal junction, left superior and right middle temporal gyrus, left middle occipital gyrus, and left middle frontal gyrus. Schilbach et al. (2012) found two points of overlap for all three systems—the precuneus and anterior medial prefrontal cortex—which the researchers viewed as hubs that connected the three systems.

Given the existing evidence for widespread brain disruption caused by many risk factors for autism, linking disrupted components of complex systems as described by Schilbach et al. (2012) to discrete variations in autism symptoms is likely to prove impossible.
Rethinking Autism

Insel and Wang called on researchers to rethink the nature of psychiatric disorders:

> With no validated biomarkers and too little in the way of novel medical treatments since 1980, families need science to provide more than hope. Genetics and neuroscience finally have the tools to transform the diagnosis and treatment of mental illness. But first, it is time to rethink mental disorders, recognizing that these are disorders of brain circuits likely caused by developmental processes shaped by a complex interplay of genetics and experience.

_Insel and Wang (2010, p. 1971)_

This book has taken Insel and Wang’s call seriously. The research findings for autism have been reconsidered here in an effort to understand why none of us conducting research in autism has been able to find a valid shared brain deficit in autism, or a standard diagnostic symptom pattern, or replicable and meaningful clinical or neurological subgroups.

Like _Insel and Wang (2010), Kendler (2012)_ called for empirical pluralism in psychiatry. _Kendler (2012)_ argued that psychiatric disorders “are stunningly complex” (p. 385), and he, too, claimed that “having overly simplified views of them, often ideologically driven, has only hampered our field” (p. 385).

If autism is not a single disorder, if autism is not hundreds of distinct subtypes of autism, what is the entity being studied?

The Argument that Autism is Symptoms and not a Single Disorder or a Spectrum of Related Disorders

Given the totality of the existing research evidence, I believe the least speculative scientific position is that autism symptoms are just that, symptoms. The following series of claims together lead to the conclusion that autism symptoms are symptoms and not a single disorder or multiple disorders.

Claim One: Autism has not Been Validated as a Symptom Set, and Heterogeneity in Symptoms, Brain Deficits, and Etiologies Argues that Autism is not a Single Disorder

_Kanner (1943)_ defined autism with two diagnostic symptoms: the profound failure to understand social interaction, and an insistence on sameness in the environment. There has been no validation of this pairing of symptoms. DSM criteria before DSM–5 defined autism with three symptoms: social impairment, communication impairment, and restricted and repetitive behaviors. There has been no validation of this triad of symptoms. The proposed DSM–5 criteria for autism spectrum disorder have defined autism with two diagnostic symptoms: social interaction impairment; and restricted
or repetitive behaviors, interests, or activities, or sensory abnormalities. Given previous findings, this pairing is unlikely to be validated.

In addition to the lack of validation for the connection between autism diagnostic symptoms, the heterogeneity of diagnostic and associated symptoms, the wide variation in brain deficits, and the immense range of etiologies make it implausible that autism could be one disorder. No unitary pathogenesis exists for autism. No unitary pathophysiology exists for autism. No consistent unitary phenotype exists for autism.

**Claim Two: Environmental and Genetic Risk Factors for Autism Cause Brain Disruptions that are not Causally Specific to Autism Symptoms**

Genetic and environmental risk factors yield autism symptoms along with other symptoms and disorders. As Lord and Jones (2012) posited, “the most significant scientific challenge to the concept of autism as one ‘disease’ or even ‘diseases’ is the heterogeneity of the genetic findings” (p. 491). Fragile X syndrome (Bray et al., 2011), Rett syndrome (Goffin et al., 2012), and other genetic risk factors for autism symptoms have been associated with varied brain disruptions and a range of phenotypes. Variant phenotypes have included complete autism phenotypes, partial autism phenotypes, and phenotypes comprised of non-autism symptoms along with or independent of autism symptoms (Hoef et al., 2011; Wulffaert, Van Berckelaer-Onnes, & Scholte, 2009). For example, Fernandez et al. (2012) reported evidence for three large de novo (new and unique to the set of individuals studied) chromosomal copy number variants that caused both autism symptoms and tic disorders. Fernandez et al. (2012) argued that their findings supported the idea of shared genetic bases for different clinical diagnoses. As Addington and Rapoport (2012) noted, the study of mental disorders has “little reason to expect phenotypic specificity from a particular genetic variant” (p. 2).

Talkowski et al. (2012) explored balanced chromosomal abnormalities that index single gene disruptions in a large sample of individuals diagnosed with autism and individuals diagnosed with other neurodevelopmental disorders. The researchers found possible causal gene variants previously linked to neurodevelopmental disorders, single gene contributors to microdeletion syndromes, new gene variants, and genes associated with schizophrenia and bipolar disorder. Talkowski et al. (2012) proposed a polygenic basis for autism, in which differing mutations in the same sets of genes contributed in an overlapping fashion to autism, schizophrenia, psychosis, bipolar disorder, and intellectual disability.

State and Levitt (2011) made the essential point about the widespread nature of brain disruptions caused by genetic variants. They stated, “Complex
functions ... mediated by hierarchically organized circuitries that include sensory and motor, autonomic regulatory, social-emotional, and cognitive domains” (State & Levitt, 2011, p. 1) are altered in autism by varied disruptions in the “neurodevelopmental processes that are guided by thousands of genes” (State & Levitt, 2011, p. 1). In fact, alterations or combinations of alterations in organizing factors, including gene variants, chromosomal number variants, altered epigenetic processes, and untoward gene–environment interactions may impair brain circuits for many behaviors: social, perceptual, motor, cognitive, and others (Goh & Peterson, 2012; Sivakumaran et al., 2011).

Similarly, environmental risk factors for autism symptoms have yielded many varied outcomes including individuals with all diagnostic autism symptoms, with some autism symptoms, and with many other symptom patterns, along with or independent of autism symptoms. These outcomes include intellectual disability, cerebral palsy, motor disorders, and other neurocognitive impairments (Guinchat et al., 2012b). A wide range of environmental insults are possible, and evidence for environmental risk factors suggests that environmental risk factors are unlikely to disrupt only brain circuits that generate social impairment and aberrant motor and sensory behaviors. Mwaniki, Atieno, Lawn, and Newton (2012) reviewed outcomes of intrauterine and neonatal insults. They reported that epilepsy, vision problems, hearing problems, cognitive impairment, motor impairment, and social impairment were all possible outcomes of insults before or during delivery. Rees et al. (2011) stated that an adverse intrauterine environment, including fetal neuroinflammation from any cause, could confer death of gray matter in the cerebellum, hippocampus, and cortex, and cerebral white matter damage causing long-term deficits in neural connectivity. Lubsen et al. (2011) argued that glial and neuronal cell death in various brain regions occurred for children delivered prematurely. The researchers also found evidence suggesting that there was damage to neurobiological processes directing axonal growth and synaptogenesis.

An additional problem is that interconnected networks increase the vulnerability of individual circuits to developmental disruption. The many brain circuits mediating social behavior are woven through the brain's interconnections (Akil et al., 2010; Berntson et al., 2012; Koch, 2012; Molenberghs, Cunnington, & Mattingley, 2012; Solari & Stoner, 2011; Van Essen & Ugurbil, 2012). For example, consider the central autism symptom of social interaction impairment. As outlined in Chapter 3, social neuroscience research has demonstrated that social interaction depends on many different neurochemicals and many brain circuits, including those mediating social motivation, social cognition, behavioral flexibility, perceptual processing, and
many others. Evidence suggests there are multi-purpose processing centers, such as the amygdala, that mediate both social and non-social behaviors. Even presumptively dedicated social brain processing centers such as the fusiform face area may serve more general processing functions, such as discrimination and categorizing of objects. A meta-analysis of 125 studies of human mirror neuron system function conducted by Molenberghs et al. (2012) suggested that, depending on the tasks involved, the mirror system provides comprehension of action or comprehension of the emotions of others. Berntson, Norman, Hawkley, and Cacioppo (2012) argued, “complexities associated with navigating social systems in primates ... led to the evolutionary development of some of the most complex networks of the brain ... the complexity of these networks has thus far precluded a clear mapping between social and neurological processes” (p. 65).

In sum, there are many circuits mediating social behavior, many of these circuits are multi-purpose, and circuits mediating social behavior are interwoven with the totality of cortical and subcortical circuits, systems, and networks. Therefore, in order for genetic and environmental risk factors to impair social interaction, risk factors must necessarily cause brain disruptions that impair not only social-behavior-mediating brain circuits, but also brain circuits mediating other behaviors. A brain disruption yielding social impairment would therefore be likely to cause varied additional symptoms such as developmental delay, atypical motor behaviors, and language impairment or delay. As noted earlier, neuroscience findings for regional circuits, systems, and networks within the larger connectome do not suggest that there could be an easy mapping of these interwoven, overlapping, and shared circuits to specific symptoms.

For example, Wei et al. (2011) hypothesized that three major brain development processes were disrupted in autism: neuron migration; the balance of excitatory and inhibitory synapses; and synaptogenesis. All three are global brain development disruptions. Consequently, the brain disruption model outlined by Wei et al. (2011) effectively predicts that intellectual disability, motor delay, language impairment, attention deficit/hyperactivity disorder symptoms, and other non-diagnostic symptoms would be likely to co-occur with autism symptoms.

Of course, there may be rare cases, like the famous HM of memory research, wherein an individual has severe neurodevelopmental social impairment because of a specific lesion. However, there are myriad brain circuits and neurochemicals that determine the many skills needed for typical social interaction behavior. As outlined in Chapter 3, our many social
brain circuits reflect the behavioral evidence that human means for social communication are overbuilt. We have many alternate ways of communicating with one another, such as eye gaze, facial expressions, gestures, body movement, voice tone and pattern, and language. Consequently, a specific focal lesion is less likely to be able to cause severe developmental social interaction impairment.

In sum, the totality of evidence demonstrates that developmental brain disruptions caused by genetic and environmental risk factors for autism will not map one-to-one with autism symptoms. Thus, because these brain disruptions will not be causally specific for autism, efforts to validate autism as a single disorder will continue to fail. Moreover, the presence of associated symptoms with autism symptoms suggests that the autism spectrum of symptoms and the broad autism phenotype will also continue to fail to be validated.

Claim Three: Because Risk Factors Tie Autism Symptoms to Non-Autism Symptoms, Behavioral Subgroups cannot be Uniquely Autism Subgroups

Finally, because most individuals diagnosed with autism express one or more additional non-diagnostic symptoms generated by the causal risk factors for autism, associated non-autism symptoms cannot be excluded from any subgroup formation. Consequently, subgroups formed would include various combinations of symptoms, and thus would not be uniquely autism subgroups.

Taken together, these three claims and associated lines of evidence argue against the existence of autism as a single disorder, spectrum, or set of autism subgroups. If autism symptoms are not one disorder, and are not many disorders, what are they? The most parsimonious and least speculative view is that autism symptoms must be symptoms.

Summary: Autism Symptoms as Symptoms

Sanislow et al. (2010) proposed,

*a diagnosis may turn out simply to be indicative of a range of possible pathologies …. for example, depression might be viewed akin to the way that a fever is viewed today, suggesting specific tests for a panel of potentially active diagnostic markers that will steer the clinician to the appropriate treatment among any number of possible disordered processes that might underlie the depression.*

Sanislow et al. (2010, pp. 637–638)

Are autism symptoms similar to the way in which fever is a symptom? Fever is characterized by a rise in core body temperature, and the activation of
immune systems. Fever is generally temporary; autism is not. However, fever, like autism symptoms, is a sign of many different diseases, and fever, like autism symptoms, results from complex mechanisms. Gensini and Conti (2004) noted that Galen believed that fever was a disease in itself, and many theories of fever as a disease existed for several thousand years.

Fever is now understood as a physiologic response to disease mediated by immune system agents called pyrogenic cytokines (Mackowiak, 1998). Yang, Zhuang, and Servaes (2012) noted, however, that there is still much fever of unknown origin (FUO).

The discovery of pathogens was necessary in order for fever to be understood as a symptom of a pathogen’s effect on the body. The pathogen is the etiology, the pathogen’s disruption of body function is the disease, and a fever is one observable symptom of the immune system’s reaction to the pathogen, and its disruption of body functions.

Similarly, the discovery of many different brain deficits associated with autism, and the discovery of many different genetic and environmental risk factors as causes for those various brain deficits were a necessary precondition in order that autism symptoms could be seen as symptoms and not a disorder. Autism symptoms are the observable behaviors that reflect the existence of developmental brain disruptions and the causal chains leading to those brain disruptions that begin with an etiology or multiple etiologies.

CONCLUSION: AUTISM SYMPTOMS WITHOUT A DISORDER

Talkowski et al. (2012) reported that a “profound collective contribution of the disrupted genes on neurodevelopment” (p. 534) crossed many diagnostic boundaries, and Leckman and Pine (2012) asked what the best nosological approach should be given that genetic risk variants are shared by many different disorders.

Lord and Jones (2012) argued that the finding that autism shares causal risk variants with other disorders “is an important addition to, but in no way a replacement for a behavioral diagnosis” (p. 491). In fact, however, the findings for the many shared risk factors for autism and other disorders, the resultant broad and variable brain disruptions, and the mixed symptom phenotypes do argue that the behavioral diagnosis of autism as a disorder is likely to be wrong. Moreover, because the evidence, as reported in this book, has demonstrated that no form of the behavioral diagnosis of autism has been validated, and the evidence for many shared risk factors, broad brain disruptions and multi-symptom phenotypes suggests that the behavioral
diagnosis of autism is unlikely ever to be validated, scientific progress will continue to be stalled if the DSM-5 diagnosis remains in use. The most simple and minimal solution would be to replace the DSM-5 diagnosis with an open set of symptoms that makes no claims to be a disorder.

Many changes in diagnostic criteria, clinical practice, and research practice would result from the acceptance of the view that autism symptoms are symptoms. For example, while autism is understood as a disorder, the co-occurrence of the two symptoms of social impairment and intellectual disability defy a diagnostic boundary. But if social impairment and intellectual disability are seen as two observable symptoms of brain disruption, then just as a physician would never say that a person who had a rash could not be diagnosed with a fever, a clinician would no longer say that a child who had developmental delay could not be identified as having social impairment.

Box 8.1 uses the proposed DSM-5 first criterion for autism spectrum disorder as an illustration of a possible starting point for describing two neurodevelopmental social impairment symptom sets. The proposed use of DSM-5 criteria listed in Box 8.1 includes both the description of a simple neurodevelopmental social impairment symptom set and the description of a complex symptom set. The first symptom set is defined by neurodevelopmental social impairment only. The rationale for this symptom set of social impairment without other symptoms is that this phenotype has been reported in clinical populations (Mandy et al., 2011; Mattila et al., 2011). If there is a group with social impairment and no other neurodevelopmental or psychiatric disorders, this group would be of importance for research.

The second symptom set documents autism social impairment with all additional co-occurring neurodevelopmental symptoms. The rationale for this complex symptom set is that heterogeneous symptoms have been found with genetic and environmental risk factors for autism and require explanation as complex symptom sets.

The British Psychology Society recommended that any classification system should begin from symptoms. They claimed that because “two people with a diagnosis of ‘schizophrenia’ or ‘personality disorder’ may possess no two symptoms in common, it is difficult to see what communicative benefit is served by using these diagnoses” (Alan, 2011, p. 3). The British Psychological Society stated, “We believe that a description of a person’s real problems would suffice” (Alan, 2011, p. 3), and they argued that a symptom list would be preferable to DSM-5.

Adequate description of social impairment and other symptoms requires that many symptoms must be included. The range of symptoms, such as that
BOX 8.1 Two Possible Neurodevelopmental Social Impairment Phenotypes for a Transitional Symptom Nosology

Neurodevelopmental Social Impairment Only Phenotype

A. **Persistent deficits in social communication and social interaction across contexts for all three types of social impairment appearing in childhood:**

Deficits in social-emotional reciprocity; ranging from abnormal social approach and failure of normal back and forth conversation, through reduced sharing of interests, emotions, and affect and response, to total lack of initiation of social interaction.

Deficits in nonverbal communicative behaviors used for social interaction; ranging from poorly integrated verbal and nonverbal communication, through abnormalities in eye contact and body language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.

Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts, through difficulties in sharing imaginative play and in making friends, to an apparent absence of interest in people.

B. **Does not express any other neurodevelopmental symptoms including**

Atypical sensory behaviors:
- Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment (such as apparent indifference to pain/heat/cold, adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects).

Atypical motor behaviors:
- Hypotonia, motor stereotypies, self-injurious behavior …

Atypical rigidity in behaviors and interests:
- Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change (such as motoric rituals, insistence on same route or food, repetitive questioning, or extreme distress at small changes).

- Highly restricted, fixated interests that are abnormal in intensity or focus (such as strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

Atypical language development:
- Absence of language
- Delayed onset of speech
- Stereotyped or repetitive speech, echolalia, idiosyncratic phrases

Attention deficit/hyperactivity disorder symptoms

Intellectual disability or developmental delay

Seizures
Neurodevelopmental Social Impairment Multi-symptom Phenotype

A. **Persistent deficits in social communication and social interaction across contexts appearing in childhood:**

Deficits in social-emotional reciprocity; ranging from abnormal social approach and failure of normal back and forth conversation, through reduced sharing of interests, emotions, and affect and response, to total lack of initiation of social interaction.

Deficits in nonverbal communicative behaviors used for social interaction; ranging from poorly integrated verbal and nonverbal communication, through abnormalities in eye contact and body language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.

Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts, through difficulties in sharing imaginative play and in making friends, to an apparent absence of interest in people.

B. **Neurodevelopmental deficits manifested in any to all subdomains:**

Atypical sensory behaviors:
- Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment (such as apparent indifference to pain/heat/cold, adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects).

Atypical motor behaviors:
- Hypotonia, motor stereotypies, self-injurious behavior …

Atypical rigidity in behaviors and interests:
- Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change (such as motoric rituals, insistence on same route or food, repetitive questioning, or extreme distress at small changes).
- Highly restricted, fixated interests that are abnormal in intensity or focus (such as strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

Atypical language development:
- Absence of language
- Delayed onset of speech
- Stereotyped or repetitive speech, echolalia, idiosyncratic phrases

Attention deficit/hyperactivity disorder symptoms

Intellectual disability or developmental delay

Seizures
suggested in Box 8.1, could be listed and identified. The underlying brain disruptions would be known or unknown. Current unknown risk factors would continue to be identified as new findings for causal environmental insults developed over time, and as knowledge of causal gene, chromosomal, epigenetic, and gene–environment disruptions of brain development accumulated.

Rutter (2005) warned, “There is no disgrace in being wrong, but there is a disgrace in persisting with a theory when empirical findings have made it apparent that the hypothesis or claim was mistaken” (p. 255). This book has argued that empirical findings have made it apparent that the theory of autism as a single disorder or spectrum was mistaken. However, the continued quest to unify autism is not a disgrace, but a desperate search for a single clarifying solution where none is likely to exist.

Prasad, Cifu, and Ioannidis (2012) pragmatically concluded that often, “established standards must be abandoned not because a better replacement has been identified but simply because what was thought to be beneficial was not” (p. 37). This book has argued that the established theory and standard diagnosis of autism should be abandoned not because a better replacement has been identified but because the totality of empirical research has failed to validate autism as a disorder, and the evidence for heterogeneous symptoms for risk factors requires a more inclusive explanation. Translational research requires a neurobiological mechanism. Because autism symptoms are symptoms of a multitude of neurobiological mechanisms, the abandonment of belief that autism will eventually be found to have a single neurobiological mechanism should be beneficial for research.

The vision suggested here is simple. Neurodevelopmental social impairment is a symptom, sensory abnormalities are a symptom, intellectual disability is a symptom, restricted and repetitive interests and behaviors are symptoms, and other neurodevelopmental associated disorders are symptoms, all of which result from varied complex developmental brain disruptions.

Although the descriptive shift may be simple, and although shifting to a symptom view has the power to end fruitless efforts to prove that a set of symptoms is a unique disorder, the resulting research problem is immensely more difficult than searching for a singular unity. Etiologies, brain disruptions, the process of brain development, and the structure and function of the brain are each complex worlds. Finding lines of causality through and across these worlds will be a lengthy and extremely demanding challenge.
REFERENCES


Holt, R., & Monaco, A. P. (2011). Links between genetics and pathophysiology in the autism spectrum disorders. EMBO Molecular Medicine, 3, 438–450.


