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# How We Develop

## Developmental Systems and the Emergence of Complex Behaviors

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In conjunction with the DeLTA Center at The University of Iowa

*"Research in such domains as fetal development, neuroplasticity, the functional organization of the brain, and cognition suggests that the old debates about **nature and nurture** should be thrown out in favor of something new — a unified '**developmental systems**' perspective."*

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# The development of autism spectrum disorders: variability and causal complexity

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The autism spectrum is highly variable, both behaviorally and neurodevelopmentally. Broadly speaking, four related factors contribute to this variability: (1) genetic processes, (2) environmental events, (3) gene  $\times$  environment interactions, and (4) developmental factors. Given the complexity of the relevant processes, it appears unlikely that autism spectrum atypicalities can be attributed to any one causal mechanism. Rather, the development of neural atypicality reflects an interaction of genetic and environmental risk factors. As the individual grows, changes in neural atypicality, consequent variation in behavior, and environmental response to that behavior may become linked in a positive feedback loop that amplifies deviations from the typical developmental pattern. © 2016 Wiley Periodicals, Inc.

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## INTRODUCTION

The autism spectrum consists of a wide range of mental and behavioral atypicalities<sup>a</sup> that usually appear early in childhood, change with development, and continue to manifest themselves throughout life. Individuals said to be ‘on the autism spectrum’ typically receive a diagnosis of autism spectrum disorder (ASD) based on a series of criteria developed by the American Psychiatric Association. These criteria are: (1) ‘persistent deficits in social communication and social interaction across multiple contexts...’; (2) ‘restricted, repetitive patterns of behavior, interest, or activities...’; (3) the presence of atypicalities ‘in the early developmental period...’; (4) ‘clinically significant impairment in social, occupational, or other important areas of current functioning’; and (5) ‘disturbances ... not better explained by

intellectual disability ... or global developmental delay’.<sup>1</sup> Although these criteria might appear to be narrow enough to define a relatively homogeneous entity, they are not. Because DSM criteria can be met in widely differing ways, there is considerable variation among those with the diagnosis. In this article, we will first describe this variability and then discuss some of what we know about the causal complexity that underlies it.

## WIDE VARIATIONS AMONG THOSE WITH AN ASD DIAGNOSIS

Much of the variability in ASD derives from the fact that the diagnostic criteria are complex and change with development. We consider each criterion in turn.

- Because social communication and social interaction occur in many different ways from infancy to adulthood, ‘persistent deficits’ in this area may include any or all of the following: atypical eye gaze, lack of gestural communication, overly neutral or exaggerated facial expression, impairment in use of language for

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reciprocal communication, problems initiating social interaction, sharing thoughts or feelings, or responding to social cues, or difficulties in developing, understanding, and maintaining relationships with others. Some individuals with ASD avoid eye contact, rarely smile or frown, and do not gesture or speak. Others develop some productive speech and language comprehension, but have great difficulty in using their language skills to interact socially. Still others are highly verbal but have difficulty utilizing the subtle nonverbal cues that regulate communicative exchange, facilitate fluent interaction, and promote the establishment and maintenance of relationships.

- ‘Restricted repetitive patterns of behavior, interest, and activities’ may include simple motor stereotypies such as hand and arm flapping or rocking back and forth, repetitive use of objects, involuntary repetition of another’s vocalizations, resistance to change in routines or rituals, extreme preoccupation with particular objects or events, or rigidity of thinking. This criterion can be met by hypersensitivity to sound or indifference to pain, heat, or cold. Some individuals with ASD are fascinated with objects that spin, imitate verbatim the speech of others, become agitated when a bedtime routine is altered, and find it difficult to adjust their own actions to the demands of changing situations. Others become engrossed in the movement of running water, the sound of a vacuum cleaner, or the sound and motion of a flushing toilet. Still others may be overwhelmed by the sounds and sights of a department store or insensitive to the temperature of their bath water.
- The degree to which these behaviors are observed ‘in the early developmental period’ is similarly variable. The emergence of ASD has traditionally been described as occurring in one of two ways<sup>2</sup>: (1) early onset, in which symptoms begin to appear by or before the end of the first year and become more obvious with age; and (2) regressive, in which children appear to develop well within the norm during the first year or two, then lose already-acquired skills and begin to exhibit the atypicalities characteristic of ASD. Recently, however, it has become clear that this dichotomy is too simple. Just as there are wide variations in autistic behavior, there are wide variations in the shapes of individual ASD developmental trajectories. Indeed, as Ozonoff et al. pointed out,<sup>2</sup>

there are in fact ‘many intermediate phenotypes containing mixed features and varying degrees of early deficits, subtle diminishments, failures to progress, and frank losses...’ (p. 325).

- Not surprisingly, therefore, the age at which children receive a definitive diagnosis of ASD (rarely before age two and a half and frequently later<sup>3</sup>) is also widely variable. This not only reflects the impact of variation in trajectory shape on diagnosis, it also reflects the fact that many diagnosis-relevant behaviors (e.g., difficulty using language for reciprocal communication, problems sharing thoughts or feelings, rigidity of thought) cannot be observed until children are older. This has led to work focused on identifying markers in infancy that might correctly predict a later ASD diagnosis.

While the evidence for behavioral signs of ASD in the second year is generally strong,<sup>4</sup> the search for infant markers during the first year has had very limited success. This may possibly be because researchers have been looking in the wrong place.<sup>5</sup> Given the standard characterization of ASD in terms of impairments in social communication and social interaction, attempts to identify early infant predictors of later diagnosis have tended to focus on proto-social and communicative behaviors. Unfortunately, infants later receiving an ASD diagnosis have generally been found to be indistinguishable from typically developing controls during the first year. This has been true for variables such as frequency of gaze to faces, shared smiles, socially directed vocalizations,<sup>6</sup> scanning of complex social scenes,<sup>7</sup> and affective responsivity in face-to-face interaction.<sup>8</sup> Findings such as these have led to the idea that ASD may first emerge not in the social and communicative domains but in lower level sensory and motor processes,<sup>9</sup> and/or in the general mechanisms by which infants integrate perceptual, attentional, motor, and social information.<sup>5</sup> While there is some evidence for this in reported atypicalities in visual luminance contrast sensitivity,<sup>10</sup> visual orienting latencies,<sup>11</sup> and postural symmetry,<sup>12</sup> research in these areas is just beginning; and it is probably still fair to say that infant onset of ASD (within Year 1) remains an assumption (for a review, see Ref 13).

- The fourth criterion, ‘clinically significant impairment in social, occupational, or other important areas of current functioning,’ is



extraordinarily general and subjective. By the time typically developing children are in school, for example, they are generally able to dress and undress themselves, button an overcoat, and brush hair or teeth. By contrast, even some adolescent and adult autistics<sup>b</sup> cannot carry out these everyday tasks without constant supervision and assistance. Others are able to function quite effectively in such tasks but lack the speech needed to communicate thoughts, interests, or even needs. Still others have good verbal skills but find it difficult if not impossible to make friends or to approach a stranger to ask a question. Many autistics cannot work; others function well in customized or sheltered employment; and still others are successful in holding jobs, sometimes very high-level jobs, in the community.

- The final criterion, that atypicalities are ‘not better explained by intellectual disability or global developmental delay’ is of little value as a specific diagnostic marker. Cognitive impairment is characteristic of a significant proportion (but by no means all) of the ASD population and ranges widely in severity. Developmental delay is similarly widespread among those with ASD and, in terms of the psychological processes affected, variable both among and even *within* individuals.

In short, autistics vary widely in diagnosis-relevant characteristics. They also vary in how and when in development these characteristics emerge, the degree to which they impact daily function, the areas of function that they impact, and ultimate diagnostic outcome. Furthermore, while ASD is typically thought to be a lifelong condition, a small subgroup of individuals not only eventually lose their autism specific symptoms and diagnosis, but become virtually indistinguishable from typically developing children on a variety of socialization, communication, and language measures.<sup>15</sup>

All of this variability should not be surprising. First, of course, given the numerous and complex processes (e.g., neurogenesis, migration, regionalization, synaptogenesis, synaptic pruning, and changes in short- and long-range neural connectivity) involved in neural development, it is apparent that atypicality could, in principle, arise in a wide variety of ways (see Darnell and Gilbert, *Neuroembryology*, *WIREs Dev Biol*, and Jernigan and Stiles, *Construction of the human forebrain*, *WIREs Cogn Sci*, also in the collection *How We Develop*). Second, although atypical mental and behavioral

characteristics directly reflect atypical neural development, this is by no means a unidirectional relationship. As atypical characteristics are expressed in the individual’s developing interactions with a constantly changing social and physical environment, experience is likely to be atypical; and such experience, over the course of the lifespan, provides a major source of input for continued neural development (see Bick and Nelson, *Early experience and brain development*, *WIREs Cogn Sci*, also in the collection *How We Develop*). The processes by which the nervous system and behavior develop and change throughout life, in other words, are bidirectional: the nervous system influences developing behavior and behavior influences the developing nervous system.

## NEURODEVELOPMENTAL ATYPICALITIES: EXPLANATORY ISSUES

Before discussing explanatory issues in ASD, it may be useful to distinguish between two related but separate questions of causality. The first has to do with risk factors relevant to the *occurrence* of the neurodevelopmental and cognitive atypicalities characteristic of ASD however phenotypically expressed in behavior. Roughly speaking, we can distinguish among three categories of such factors: (1) genetic risks; (2) environmental risks; and, because genetic and environmental effects cannot be understood apart from one another (3) gene–environment interactions.

The second has to do with the underlying factors that account for *autistic behavior*, i.e., for the various phenotypic expressions characteristic of ASD. Roughly speaking again, we can distinguish between two levels of explanation in this regard: (1) neurodevelopmental (theories of the developing structure and function of the brain and nervous system); and (2) cognitive (theories of the developing structure and function of the mind). Examples of the first might include early brain overgrowth,<sup>16</sup> synaptic under-pruning,<sup>17</sup> over-pruning,<sup>9</sup> imbalance between excitation and inhibition,<sup>18</sup> or impairments in long-range neural connectivity<sup>19</sup>; examples of the second might include deficits in theory of mind<sup>20</sup> or in executive functioning,<sup>21</sup> or variations in central coherence.<sup>22,23</sup>

Although the second question is a critically important one, addressing it would require an excursion well beyond the purposes of this essay. The goal here, therefore, is the more limited one of describing the broad categories of factors relevant to the

occurrence of ASD and, where evidence exists, exemplifying their likely impact on phenotypic variability.

In addition, as the effects produced by factors in each of these categories is conditioned by—and cannot be fully understood apart from—issues of development, we will conclude by discussing a set of developmental issues likely to be relevant to the explanation of ASD.

## Genetic Risk Factors

There is considerable evidence, both indirect and direct, for a significant degree of genetic risk in ASD.<sup>24,25</sup> Indirect evidence includes the observation that children who have an older sibling with ASD are more than 10 times as likely to have ASD themselves as children in the general population (e.g., see Ref 26). For twins, this rate is much higher. Depending on the study, if one member of a pair of monozygotic twins has an ASD diagnosis, the proband concordance rate (the probability that the other twin will have a diagnosis as well) ranges from .46 to .88 or higher<sup>27</sup> (for review, see Ref 28). Reported proband concordance rates for dizygotic twins, on the other hand, are much lower, ranging from 0 to .36.<sup>29</sup> The heritability of ASD is, therefore, substantial. However, it may not be as high (.90 or so) as is typically cited.<sup>30</sup> Indeed, one recent twin analysis yielded an ASD heritability estimate of .37 for autism and .38 for ASD, with 55% of the variance attributed to shared environmental factors (see Moore and Shenk, The heritability fallacy, *WIREs Cogn Sci*, also in the collection *How We Develop*).

Direct evidence comes from sources employing a variety of approaches. One such approach involves the study of syndromes of known single-gene origin with autistic behavioral characteristics (often called ‘syndromic autism’<sup>31</sup>). Two of the most widely studied forms of syndromic autism involve Fragile × Syndrome (involving the FMR1 gene and pathogenic mechanisms affecting synaptic plasticity and neuronal connectivity) and Rett Syndrome (MeCP2 gene, implicated in maintaining neuronal function). While syndromes of this sort provide clear evidence that gene-dependent neuronal pathology can be associated with autistic symptomatology, only a very small proportion of ASD cases (e.g., approximately 3–4% for Fragile × and Rett taken together) are syndromic.<sup>24</sup>

Researchers have therefore also evaluated genetic risk for nonsyndromic cases. These are cases in which ASD is the primary diagnosis rather than being secondary to a known genetic syndrome. Two of the most important approaches to assessing

genetic risk for nonsyndromic ASD involve studies evaluating *gene associations* and *whole genome linkages*. (see Charney, Genes, behavior, and behavior genetics, *WIREs Cogn Sci*, also in the collection *How We Develop*) Gene association studies focus on correlations between the occurrence of the ASD phenotype and defined genetic variants. These variants (*candidate genes*) are often chosen on the basis of a priori hypotheses concerning their probable role in aspects of neurogenesis likely to be relevant to ASD, especially impaired synaptic function or abnormal brain connectivity. In whole genome linkage studies, genetic variation throughout the genome, including rare and common inherited and *de novo* (present in the child but in neither parent) mutations, is evaluated for links with ASD.

Based on the evidence from almost 20 years of gene association studies, it is clear that ASD is genetically heterogeneous. Not only are there literally hundreds of genes that confer risk for ASD<sup>32</sup> (see also the Autism Database at <https://gene.sfari.org>), no single genetic factor is present in more than a tiny fraction (1–2%) of ASD cases. This heterogeneity is also evident in research evaluating whole genome linkages, even for siblings and identical twins. Thus, for example, when scientists sequenced the complete DNA of parents and two ASD-diagnosed siblings to examine *de novo* mutations, they found that the majority (69.4%) of the affected siblings carried *different* ASD-relevant mutations.<sup>33</sup> This is consistent with the fact that the kinds and severities of ASD-associated traits that each member of a pair of identical twins manifests may vary widely even when both have received an ASD diagnosis.<sup>34</sup>

Finally, recent analyses have provided evidence for still another mechanism underlying genetic heterogeneity in ASD. While rare inherited and *de novo* variations together only contribute about 6% of the genetic liability for ASD, a much larger contribution derives from the influence of common variants. Common variants are inherited variations that are widespread in the general population and that, taken individually, confer only slight risk for ASD. When present in significant numbers in the same individual, however, the total ASD risk that they confer may be substantial (as much as 49%<sup>30</sup>). In short, although genetic risk is a major factor in the etiology of ASD, the potential sources of that risk are many and varied.

## Environmental Risk Factors

As complex as it is, the environment may also be a major source of ASD risk. This could occur, for

example, when environmental factors increase the likelihood of *de novo* genetic mutations by contributing to oxidative DNA damage and/or by interfering with DNA repair mechanisms.<sup>35</sup> Mutagenic factors of this sort include preconceptional exposure to heavy metals (e.g., mercury, cadmium, and nickel) or chlorinated solvents (e.g., trichloroethylene and vinyl chloride) typically present in industrial pollution. They also include residence in higher latitudes, in cities, or in areas with increased precipitation, factors shown to be associated with reduction in levels of Vitamin D involved in DNA repair and protection against oxidative stress.

Another way in which environmental factors might confer ASD risk is by influencing the way in which genes are expressed during development, a process known as ‘epigenetic variation’ (see Moore, Behavioral epigenetics, *WIREs Syst Biol Med*, also in the collection *How We Develop*). Recent evidence from animal work and from research in areas such as cancer risk indicate that a variety of higher-level environmental factors such as diet, acoustic and visual stimulation, stress, exposure to toxicants, and, in humans, tobacco and alcohol use can influence factors modulating gene expression.<sup>36,37</sup> The powerful role that epigenetic variation can in turn play in the development of ASD is evident, for example, in a study of 50 identical twin pairs varying widely in ASD severity and behavioral characteristics even though they share a genome. Wong et al. examined the entire genome of each individual for a factor (DNA methylation) known to influence gene expression.<sup>38</sup> Although global levels of DNA methylation were highly correlated between members of twin pairs, large variations in methylation were found between pair members at numerous specific DNA sites. Furthermore, the particular sites at which these variations were found were not generally similar across twin pairs but rather were specific to each individual.

Although we now know that epigenetic mechanisms such as DNA methylation can influence phenotypic variation in ASD and that higher level environmental factors can, in principle, influence gene expression, direct evidence for the impact of higher-level environmental risks in ASD is still relatively limited. Only a small number of such factors have been studied; research findings have frequently been inconsistent; and the precise mechanisms by which these factors are linked to neurodevelopmental atypicalities are for the most part unknown.<sup>39</sup> In addition, most of the known environmental risk factors are associated with only small increases in ASD risk. One such factor is parental age. Mothers over

the age of 35 are approximately 1.5 times more likely than younger mothers to have a child with ASD. For older fathers, the increase in risk is slightly greater,<sup>40</sup> in part because spontaneous genetic mutations are predominantly paternal in origin.<sup>41</sup> Complications of pregnancy, including gestational diabetes and gestational bleeding have been linked to increased ASD risk, as has maternal exposure to certain chemical substances such as valproic acid (used to treat epilepsy), psychoactive medications, and pesticides.<sup>42</sup> Although prenatal viral infection has been thought to relate to a higher risk of ASD, the evidence is mixed, presumably because this association is dependent on many other factors such as the immune status of mother and fetus, amount and type of the virus, and stage of fetal development.

Finally, there are several converging sources of evidence suggesting that prenatal exposure to environmental stress may increase the risk for ASD. Mothers of children with ASD retrospectively report higher stress levels during pregnancy than comparison mothers.<sup>43</sup> Experimental manipulation of prenatal stress in animals is associated with later ASD-like behaviors (in monkeys<sup>44</sup> and rodents<sup>45,46</sup>). And studies of ASD rates in mothers exposed to naturally occurring stressful events suggest an increase in these rates. One intriguing study of this sort was carried out by Kinney et al., who began by assuming that direct exposure to a major storm during pregnancy, especially one that strikes a vulnerable population, acts as an acute source of stress.<sup>47</sup> They then employed Louisiana weather data to identify areas of the state affected by severe storms and assessed the relationship between the prevalence of ASD and three levels of storm exposure during pregnancy: *high* (direct hit and high vulnerability, which the researchers defined as birth in New Orleans), *medium* (EITHER direct hit and born outside New Orleans OR no direct hit and born in New Orleans), and *low* (no direct hit and born outside New Orleans). Results indicated a significant increase in ASD prevalence rates from about 4.49 to 6.06 to 13.32 children per 10,000 at low, intermediate, and high levels of exposure respectively.

### Gene–Environment (G × E) Interactions

One obstacle to isolating environmental factors linked to ASD is that for every child exposed to a given environmental factor who develops ASD, many others exposed to the same factor do not. This has led scientists to turn to the concept of ‘gene–environment interaction.’ In its simplest form, this is the idea that genetic risk factors (genotypes and



mechanisms of gene expression) in certain children may make them especially vulnerable to particular types of environmental risks. Atypical neural development is presumed to result when a child with a given genetic vulnerability is exposed to the relevant environmental insult (e.g., a developing child whose genetic makeup is such that the body's ability to process and excrete neurotoxic substances is impaired would be particularly vulnerable to neurotoxins). The converse of this idea is that neither a child who is genetically vulnerable but never exposed to the environmental insult nor a child who is environmentally exposed but not genetically vulnerable will develop the related atypicality. This would explain, for example, why only some children are affected by exposure to potentially harmful environmental events.

Although the existence of  $G \times E$  interactions of this type in ASD has received some support from research examining ASD-like behavioral characteristics in animal models,<sup>48–52</sup> to date there are only a few studies on humans. One such analysis, using a candidate gene approach, examined variation in ASD risk conferred by maternal and child genotypic factors when mothers failed to take prenatal vitamins.<sup>53</sup> In a second analysis using the same study population and approach, ASD risk was reduced for mothers and children with a specific genotypic variant when mothers took folate during the first month of pregnancy.<sup>54</sup> And in a third-related analysis, ASD risk was reported to reflect an interaction between a given genotype and exposure to air pollution.<sup>55</sup> Unfortunately, this research suffers from a number of methodological deficiencies and has not been replicated (for a discussion of the considerable methodological obstacles likely to be encountered in research of this type, see Ref 56).

## Developmental Factors

The fact that potentially hundreds of genetic loci, varying in expression, may confer differing degrees of susceptibility to (or protection from) scores of environmental risk factors makes it clear just how complicated the ASD causal network is likely to be. But there is yet another and perhaps even greater set of complications. The effects of  $G \times E$  interactions likely depend on *when and how* in the broader course of development the relevant mechanisms come into play.

Although a number of researchers have argued persuasively for the importance of integrating developmental accounts into the explanation of atypicality,<sup>36,57–62</sup> only a few first steps have been taken in this regard. Thus, for example, Kinney

et al. evaluated ASD prevalence in relation to storm exposure during differing gestational periods,<sup>47</sup> and Thomas et al. have implemented a neurocomputational model of ASD developmental trajectories (early onset, late onset, and regressive) as a function of variations (onset, rate, and threshold) in a connection pruning mechanism.<sup>9</sup>

Although these first steps are important, the potential of this approach with respect to ASD is still largely untapped. One undoubted reason for this is that, when taken seriously (as it should be), the developmental approach multiplies explanatory complexity by an order of magnitude. A summary of relevant developmental principles distilled from the writings of the authors identified above, taken together with ideas derived from two researchers who devoted their careers to the study of development,<sup>63–65</sup> make this evident.

### *Development Is First and Foremost Change over Time*

This may appear like a truism; but its implications for our understanding of variability in ASD are far-reaching. To date, the vast majority of ASD research consists of comparisons between those with (or at heightened risk for) ASD and CA- or MA-matched typical (or other clinical) groups on measures collected at a single time point. Even the relatively few longitudinal studies that exist have been focused less on change in phenotypic expression over time and more on the use of data from one or more time points to predict a later outcome (e.g., diagnosis). Yet the phenotypic variability in ASD is not just variation in symptom expression, it is also variability in change in symptom expression over time (both moment-to-moment and over longer durations). Although broad stroke developmental trajectories (early onset, later onset, and regressive) generally reflect the fact that symptomatic expression varies in time, they do little to capture either the time-varying nature of *specific* symptoms or the way in which moment-to-moment changes influence development over longer spans of time.

### *Developmental Change Is Change in a System of Interacting Processes That Give Rise to Progressively More Complex Structures*

Development is not just a characteristic of time-varying phenotypic behavior; it is a characteristic of the way in which the interacting processes that give rise to behavioral variation themselves change over time. One particularly clear example of this has been provided by Karmiloff-Smith in her neuroconstructivist analysis of brain development<sup>60</sup> (see D'Souza and Karmiloff-Smith, Neurodevelopmental disorders,

*WIREs Cogn Sci*, also in the collection *How We Develop*). In her view, early neural processes are low-level, relatively general and, although somewhat more relevant to processing one kind of input over others, by no means domain-specific. As these processes function over the course of development in interaction with one another and with progressively more complicated sources of environmental input, they become gradually more domain-specific. In other words, the neural processes contributing to varying typical or atypical phenotypic behavior themselves vary developmentally over the course of postnatal growth.

### ***Development Is Multileveled***

The processes that underlie variation in typical and atypical phenotypic behavior are, of course, not solely neurodevelopmental; they exist at multiple levels of analysis operating in an integrated system. In addition to those involved in the formation and operation of neural connections, they include processes of gene expression, cognitive and socioemotional growth, behavioral development, and change in the environmental contexts (e.g., family, peers, classrooms, and cultures) within which development occurs. An understanding of variability in phenotypic expression of ASD will not only require analyses at all of these levels, each complex in its own right, it will require an understanding of the way in which change emerges through cross-level relationships. How, for example, does gene expression influence neural development? How does neural development influence growth in the cognitive and socioemotional bases of behavior? How does changing behavior influence the immediate environmental contexts within which that behavior takes places? And because these influences are bidirectional at all levels of analysis, we must also ask, for example, how typical or atypical behaviors are influenced by the contexts within which they occur. How are the neural, cognitive and socioemotional bases of behavior altered as the individual's behavior changes in context? And how is gene expression altered by environmental factors themselves influenced by behavioral change in context?

### ***Development Is Systemic***

At every level of analysis, the processes operating at that level form interconnected components of higher-order systems. Obvious in gene regulation and expression and neural connectivity, systematicity is equally characteristic of the numerous cognitive and socioemotional functions that contribute to behavior. One implication of the componential relationships among processes is that components may develop at varying rates and take varying forms at different points in

development. This raises at least two issues for a developmental approach to understanding phenotypic variability. The first has to do with the relative timing of development across component processes. In typical development, this timing is presumed be relatively synchronous with all components changing appropriately in relationship to one another such that developmental outcomes appear more or less on schedule. In atypical development, however, change in one or more components may be delayed relative to change in others and variations in the form and timing of this asynchrony can have immediate and downstream effects on the pattern of emergence of phenotypic outcomes. The second involves a characteristic of development that Kagan<sup>65</sup> labeled 'heterotypic continuity.' This has to do with the fact that early processes (e.g., those involved in the emergence of fear of strangers) may be continuous with later processes (e.g., those involved in concept formation) with which they have no obvious surface similarity because they are both implementations, albeit at different points in development, of the same underlying component process (e.g., ability to distinguish small variations from prototypes). The implication of heterotypic continuity for an understanding of ASD symptom expression is that phenotypic variability may well reflect an underlying developmental continuity.

### ***Development Occurs through Reciprocal Organism × Environment Interactions***

As is evident from the previous discussion, at all levels of analysis, variation in developmental processes is best understood as a joint function of characteristics of the organism and characteristics of the environment in interaction. Here the term 'interaction' is used to emphasize the fact that in a developing system, the relationship between two variables almost always varies as a function of values taken on by other (sometimes many other) contextual variables.

Two very different examples may suffice to make this point. The first is a high-level psychological example from Bronfenbrenner's ecological theory of development.<sup>64</sup> In Bronfenbrenner's view, the effect on developmental outcomes of each of the many variables that describe the individual (e.g., IQ, temperament, physical attractiveness, sociality, curiosity, and passivity) will depend on characteristics of the environmental contexts (e.g., family, peer group, classroom, and culture) within which the individual develops; and, conversely, the effect of environmental variables (e.g., parental support, peer acceptance, and quality of teaching) on outcome will depend on characteristics of the developing individual. What is

effective teaching, for example, for a curious child may not be effective teaching for a passive child.

The second example is taken from Gottlieb's<sup>36</sup> argument for probabilistic epigenesis. There he describes research indicating that a known polymorphism in the serotonin transporter gene (5-HTT) was associated with lower levels of serotonin (and hence higher levels of impulsive aggression) in peer- but not in mother-reared monkeys. In Gottlieb's view, in other words, phenotypic outcomes depend on an interaction between genetic mechanisms and relevant life experiences.

Finally, of course, both the individual and the environment are themselves complex dynamic systems. Development, in other words, is an evolving process of organism-environment interaction where both the organism and the environment are themselves systems of interacting and evolving processes.

## CONCLUSION

ASD is characterized by phenotypic behavioral atypicalities emerging in varied forms and according to different developmental trajectories. The causal nexus underlying the emergence of these atypicalities is exceptionally complex. It may include one but probably many developmentally varying pathological mechanisms. These mechanisms may be atypical variations on normal developmental processes or normal processes unfolding with developmentally inappropriate timing. Interacting over time with individual and developmental differences in exposure to factors conferring genetic and environmental risk, these mechanisms may operate to produce variations in the timing of development and atypicality in behavior. Over the course of development, the effects of these interactions may come to extend to domains well beyond that of the original atypicality. Finally, and importantly,

delayed development and/or atypical behavior are likely in turn to lead to atypical experiences and interactions with the postnatal environment. An infant who rarely smiles or makes eye contact, a child who tantrums uncontrollably when small changes are introduced into a routine, or a child who insists on spending long hours sitting in the car because he is fascinated by cars is not likely to gain the experiences or elicit the responses from caregivers that are typical of normal development. As the child grows, neural, cognitive, and socioemotional atypicalities, consequent variation in behavior, and environmental responses to that behavior can become linked in a positive feedback loop that reinforces and amplifies deviations from the typical developmental pattern. Given the complexity of this process, it is little wonder that there is such wide behavioral variability among those who receive an ASD diagnosis.

## NOTES

<sup>a</sup> For many, ASD equates with significant, sometimes severe decrement in function. For these individuals, ASD is, as it is for the DSM-5, a 'neurodevelopmental disorder,' one that science should strive to understand, prevent, and remediate. For others, however, ASD is viewed as a form of *neurodiversity* (cf., <http://autismdigest.com/neurodiversity/>). For these individuals, ASD is neither a scientific puzzle to be solved, nor a disorder to be prevented, but a lifestyle to be celebrated. To accommodate both views, we prefer and will here use the phrase 'neurodevelopmental atypicality' rather than 'neurodevelopmental disorder.' That said, however, most of the research on ASD has been carried out within a medical/disorder model and will therefore be described in such terms.

<sup>b</sup> We follow Gernsbacher et al.<sup>14</sup> in employing the term 'autistic/s' rather than 'person/s with autism' because the former is the term by which autistic individuals prefer to be called.

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