Heterogeneity and Homogeneity Across the Autism Spectrum: The Role of Development

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Autism is a lifelong, highly prevalent, and strongly genetic disorder defined by impairments in social and communicative function and by pronounced behavioral rigidities.[1] Despite common areas of impairment that define autism as a condition, 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. At the level of genetics, the variability seems comparable: although more and more susceptibility loci are being identified, each is thought to account for only a small number of overall cases (e.g., see reference[2]). Likewise, de novo mutations may play a causal role in a relatively large percentage (~10%) of individuals with autism who do not have an affected first-degree family relative.[3] Pursuit of research focused on "simplex" and "multiplex" families (i.e., with only one or with more than one sibling affected) has led to insights on potential modes and risks of inheritance, necessitating a unified genetic theory for sporadic and inherited autism.[3] However, none of these advances have yet successfully addressed the phenotypic variability of autism, such as range of severity among siblings, or the skewed sex distribution (many more male subjects than female subjects are affected); in fact, there is as yet little in the new findings that inform our understanding of the behavioral and cognitive aspects of the syndrome. One possibility is that "modifier" genes may have an impact on phenotypic expression, but these have not been identified yet. However, what is certain is that genotypic heterogeneity is one of the greatest obstacles to identification of discrete causes of autism,[1] and it presents a formidable hurdle to developing effective treatments targeting the causes of the syndrome and not only its behavioral symptoms.

Given the multiplicity of possible causes, and the phenotypic expression of so many "autisms," a timely question seems to be from where does the homogeneity of autism arise? Beginning with Kanner's original description, consensus on core diagnostic features has remained relatively stable. Autism-specific diagnostic instruments have strong sensitivity and specificity, and among experienced clinicians, agreement in diagnostic assignment is typically high.[1] These factors highlight homogeneity of basic features despite the wide range of genomic causes and varying outcomes.

In an effort to understand the link between vast genotypic and phenotypic heterogeneity on the one hand and common manifestations of core disability on the other, one important factor is development. In the brief text that follows, we focus on the notion that altered development—that is, ongoing maladaptive action that fails to follow the course of normative social growth—may be an important factor that forces diverse genetic vulnerabilities into common syndromic presentation.

At present, knowledge of the early developmental course of autism is limited: because children with autism are typically identified only at later stages of childhood, there is little experimental evidence measuring syndrome manifestation in infants and toddlers (what evidence exists, although largely indirect or retrospective, suggests that abnormalities are indeed present in the first year of life). This gap in clinical and research knowledge is critical. The first 2 years of a baby's life encompass the most substantial—and rapid—period of

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neural and behavioral growth in postnatal human development.

The need to increase research on basic mechanisms of adaptive social action—mechanisms present at birth or shortly thereafter—is crucial. For human infants, one such mechanism is engagement with caregivers. Given the fragility of human infants at birth, success on this task is of immediate survival value and of fundamental evolutionary significance. It should come as little surprise that typical infants show a number of highly conserved skills that facilitate engagement with others.[4] From the first hours of life, newborns give preferential attention to people. They prefer the sound of a human voice to that of silence and prefer their own mother's voice to that of an unknown woman. Four-day-olds distinguish between a face looking toward them and a face looking away, and by 3 months, infants look more at a person's eyes than at other parts of the face (and more at a person's face than elsewhere on the body). Mutual gaze and preferential attention to the eyes, even in other species, underscore the importance of the eyes in social interaction and development.

In a recent study,[5] however, we found that, in contrast to matched controls, 2-year-olds with autism showed diminished preferential attention to the eyes of others. These results indicate a disruption to the normative process of social development. Ordinarily, this process would, in part, be predicated on spontaneous search for the eyes of others and increasing responsiveness to the gaze signals contained therein: mutual gaze, gaze following, and even language acquisition are parts of progressively more complex social interaction. Failure to look at the eyes of others during critical windows of development, and looking at other parts of the world instead, suggests an altered path for learning about the world, with cascading effects on further socialization.[4]

Of course, this altered set of experiences in and of itself is not causal of autism: we need only take the example of congenitally blind or deaf children to recognize that different paths of interaction and learning do not, by themselves, lead to the specific and lifelong impairments in social interaction and communication that are hallmarks of autism spectrum disorders. Learning about the social world is multimodal, and a variety of sensory mechanisms may, even by themselves, provide sufficient inroads into social learning. In the case of toddlers with ASD, altered patterns of looking serve as an index of both altered interaction with the normative social world and of an altered predisposition: rather than spending more time looking at the faces of people, children with autism are instead increasing their visual interaction with less socially relevant aspects of their surrounding environment. Rather than seeking social interaction via alternate channels (auditory or tactile, as a blind child might), the child with autism is using ostensibly intact sensory systems to actively seek out alternate experiences.

In another recent study,[6] we found that, relative to matched controls, 2-year-olds with autism failed to orient toward point-light shows of biological motion. In typical infants, preferential attention to biological motion emerges in the first days of life. Attention to biological motion is highly conserved across species and is believed to be critical for filial attachment and for detection of predators.[7] The neural bases of this ability overlap with brain regions involved in perception of basic social signals such as facial expression and gaze direction; preferential attention to biological motion is considered to be a precursor to the capacity for attributing intentions to others.

In both these studies, results indicate that skills present typically in young infants, as well as in chronologically, nonverbally, and verbally matched control children, were not functioning properly in children with autism at the age of 2 years. Both studies also suggested ways in which atypical developmental processes resulted from failures in social engagement. In one of the studies,[5] 2-year-olds with autism showed preferential attention to the mouths of approaching adults. In the other study,[6] 2-year-olds with autism showed preferential attention to physical contingencies (audiovisual synchronies between point lights and sounds) that were entirely disregarded by control children (The latter finding suggested an interpretation of the former: the children with autism may have preferentially attended to mouths because, in the human face, this is the greatest source of audiovisual synchrony: lip motions occur synchronously with speech sounds).

In this way, a child with autism is learning from a world dominated by physical rather than social events, and this experience is likely to bring about increasing divergence in processes having an impact on brain development.[4]

Both of these studies point to early disruptions of highly conserved mechanisms of social development. However, more importantly, they point to early departures from normative processes. Following from the experience-expectant model of child development,[8] in which the genetically determined schedule of neural

Fig 1 4/C

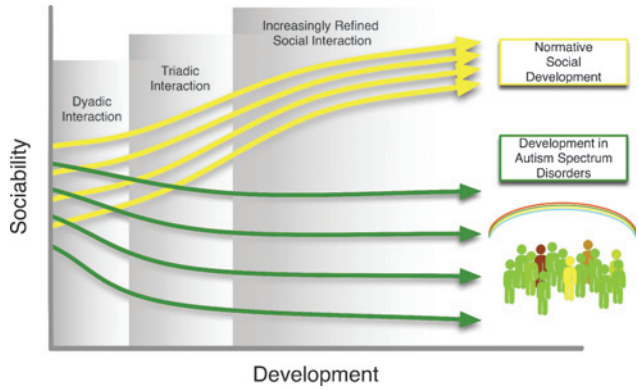

Fig. 1 Adaptive action in response to environmental demand constrains typical development toward increasingly refined forms of social interaction. In contrast, development in autism spectrum disorders, with a lack of preferential attention to socially relevant stimuli, leads to increasingly atypical behaviors. The homogeneity of autism spectrum disorders may originate from shared failings in the process of socialization as a whole, whereas the heterogeneity may stem from variable timing in the onset of individual disruptions.

maturation matches the timing of adaptive tasks, disruptions of socialization processes occurring at different times are likely to result in different outcomes. Thus, although the homogeneity of autism may originate from shared failings in the process of socialization as a whole, the heterogeneity may stem from variable timing in the onset of individual disruptions.

In typical development, success in social adaptive tasks prompts further development in an iterative process that builds on older structures to generate new ones. This process is ever ongoing, resulting in successively more complex social cognitive development. In this fashion, ontogeny typically realizes phylogenetic predispositions through the rapid movement of the child through universal social adaptive tasks, jerry-building successful social and communicative babies. However, if this process is derailed, we expect that the earlier the disruption, the greater will be the developmental consequences.

This model also predicts that blockage of the normative social adaptive trajectories will bias the child to forms of learning that are not grounded in social interaction: for example, preponderance of learning about the physical environment (e.g., physical over social contingencies), rote speech over contextualized communication, hyperlexia over conceptual reading, and memorization of facts and information over episodic and personal information—all of which are features well noted in the later-life clinical expression of autism.[4]

Intriguing as the recent experimental results[5,6] are in suggesting a developmental pathway to autism, they still refer to data on 2-year-olds with autism. By that time, typically developing children are already accomplished social interactionists, and the vast majority of children with autism is already showing symptoms of the condition and can be diagnosed.[1] Our frontier is the infancy period, the period of greatest neuroplasticity and change, and also the period of emergence of the syndrome. The exemplified mechanisms of social engagement are online from the first weeks of life. Thus, our goal is to quantify departures from normative development from as early as they are detectable and to map their timing and consequences to subsequent social cognitive growth and syndrome expression. In this way, we hope to establish early detection of autism on firm, quantifiable ground. We also hope for increased synergy between genetic and developmental social neuroscience investigations. For example, perception of biological motion is a fundamental and evolutionarily conserved social adaptive mechanism: it seems to be involved in imprinting.[7] This, in turn, should be a natural target for animal modeling in developmental neurobiology. Social behavior has long been a target in genetic investigations, albeit primarily in simpler organisms than humans.[9] If the confluence of these various disciplines were to be the process of development and its disruptions, we believe that the results of such an enterprise might likely provide sorely needed guidance to our current ventures into the sea of genomic variability in search of autism-associated genes (Fig. 1). F1

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REFERENCES

1. Volkmar F, Lord C, Bailey A, Schultz RT, Klin A. Autism and pervasive developmental disorders. *J Child Psychol Psychiatry*. 2004;45:135–170.
2. Weiss LA, Shen Y, Korn JM et al. Association between microdeletion and microduplication at 16p11.2 and autism. *N Engl J Med*. 2008;358:667–675.
3. Zhao X, Leotta A, Kustanovich V et al. A unified theory for sporadic and inherited autism. *Proc Natl Acad Sci*. 2007;104:12831–12836.
4. Klin A, Jones W, Schultz R. The enactive mind—from actions to cognition: lessons from autism. *Philos Trans R Soc Lond B Biol Sci*. 2003;358:345–360.
5. Jones W, Carr K, Klin A. Absence of preferential looking to the eyes of approaching adults predicts level of social disability in 2-year-olds with autism. *Arch Gen Psychiatry*. 2008;65:946–954.
6. Klin A, Lin DJ, Gorrindo P, Ramsay G, Jones W. Two-year-olds with autism fail to orient towards human biological motion but attend instead to non-social, physical contingencies. *Nature*. In press. AQ1
7. Johnson MH. Biological motion: a perceptual life detector? *Curr Biol*. 2006;16:R376–R377.
8. Johnson MH, Karmiloff-Smith A. Neuroscience perspectives on infant development. In: Bremner G, Slater A, eds. *Theories of Infant Development*. Malden: Blackwell; 2004:121–141.
9. Robinson GE, Fernald RD, Clayton DF. Genes and social behavior. *Science*. 2008;322:896–900.