Understanding of the etiology of autism is critical for moving research and clinical practice forward. It is now well established that both genetic and nongenetic factors contribute to an increased susceptibility to autism [1]. No single causal pathway has been identified to date. Nevertheless, evidence is stronger for the involvement of some risk factors relative to others and there is growing consensus that there are heterogeneous pathways leading to an autism outcome. Risk factors include common and rare genetic risk variants, as well as nongenetic risk factors. Common genetic variants [2] tend not to be associated with very high risk for autism relative to the general population, however, replication and confirmation of the role of these variants is still awaited. Among the clearer associations with autism are rare (defined as occurring in <1% of the general population [1,2]) copy number variants. Moreover, there is much overlap between some rare genetic syndromes and autism, including fragile X syndrome and tuberous sclerosis.

Large-scale studies are already underway aiming to ascertain the involvement of genetic risk factors in the etiology of the disorder. This implies that the utility of these discovered variants is still limited for purposes of identification of autism in the general population [3]. Nevertheless, advances in genetic testing have allowed the identification of variants that may give rise to comorbid medical problems (e.g., the medical complications associated with tuberous sclerosis and micro-deletion and -duplication syndromes, such as epilepsy, as well as renal and gastrointestinal problems). Nongenetic factors that increase the risk of autism are still poorly understood, and could include epigenetic and environmental factors [4]. Interactions between genetic and nongenetic factors can further contribute to autism risk in complex ways [5].

Motivated by this emerging understanding of the etiology of autism, the condition is no longer viewed as a narrowly defined, categorical disorder, but instead as a spectrum of conditions that affect individuals differently [6]. Individuals affected by autism may lead independent and fulfilling lives, whereas others can develop substantial medical, educational and social difficulties [7]. The heterogeneity of the condition has led some scientists to suggest that instead of one unique phenomenon, there are probably many ‘autisms’ with different underlying biological processes and developmental pathways.

The current Diagnostic and Statistical Manual of Mental Disorders [8] identifies categorical subtypes of autism including...
narrow autistic disorder and broader pervasive developmental disorders. However, research has thus far failed to map these clinical subgroups onto a specific causal or developmental pathway leading to each of these conditions. The heterogeneity in the expression of the condition is being described across numerous phenotypic dimensions, which overlap with those found in other conditions and in the general population [9,10]. As a result, the next edition of the Diagnostic and Statistical Manual of Mental Disorders will replace current categorical ‘subtypes’ with a single category labeled ‘autism spectrum disorder’.

“A better understanding of the developmental processes leading to autism could in the future benefit from mapping biological measures onto behavioral phenotypes.”

The heterogeneity in etiological pathways to autism has been further reinforced by increased understanding of the developmental processes in infancy leading to an autism diagnosis in toddlerhood [5,11]. Advances in this area have been aided by large-scale longitudinal studies of infant siblings of children with autism, who are at substantially increased risk for developing the condition. Most studies have attempted to retrospectively differentiate those at-risk infants who subsequently receive a clinical diagnosis (the ‘affected’ group) from those at-risk who do not receive a diagnosis (the ‘unaffected’ group), as well as from low-risk infants with no such familial history. Current evidence [5] indicates that those infants who later receive a diagnosis begin to be identified from around 12 months of age, on the basis of atypical social and non-social behaviors, such as unusual eye contact, lack of orientation to name and reduced flexibility in switching attention. However, there is no current evidence for any reliable behavioral marker during the first year of infancy, suggesting that the behavioral symptoms of autism emerge during development. Moreover, aside from those who go on to develop autism, some infants at-risk are likely to share characteristics related to the condition, resembling a broader set of features associated with autism known as the ‘broader phenotype’ [12,13], thereby blurring the boundary between those with and without a diagnosis. As such, it has been suggested that studying individual variability among infants at familial risk for autism may provide a powerful approach by extending the range of variability in outcomes [8].

Only a handful of studies in this area have directly examined early developing brain systems in an attempt to understand the etiology of the condition. While overt behavioral signs of autism are rarely observable in the first year, cognitive neuroscience methods have successfully differentiated groups of infants at-risk from low-risk controls. These group differences have been reported in visual processing [14] and in flexibility of switching attention [15]. Direct measurement of brain activity has also revealed early risk-group differences in response to face stimuli [16] and in sensitivity to the direction of eye gaze [5,17]. Within this early period, risk of autism appears to confer a range of differences in the developing brain.

If autism is assumed to be a narrowly defined condition, such early manifestations of risk may be expected to unfold in a predictable way into diagnostic symptoms in toddlerhood. We recently tested this possibility by recording infants’ event-related potentials around 7 months of age in response to a range of face and gaze contrasts relevant to the early development of social brain networks in autism [5]. The same children were followed up at 24 and 36 months of age, based on which a clinical diagnosis of autism was ascertained in a subgroup. Longitudinal analyses showed that characteristics of the event-related potential components evoked in response to dynamic eye gaze shifts during the first year were associated with clinical outcomes at 36 months. Typical infants show clear differentiation in their brain response when viewing faces with eye gaze directed toward versus away from the infant. This suggests that at least some manifestations of risk in the first year of life predict autism diagnosis, signaling early perturbation in the development of social brain networks that precede the overt manifestation of behavioral symptoms.

Interestingly, only one of the stimulus contrasts tested in the same study predicted the later emergence of autism, suggesting that early manifestations of risk in this group may only probabilistically predict diagnostic outcomes. Substantial variability was observed in mapping between characteristics of early brain responses...
and later diagnostic outcomes. A further intriguing pattern observed in the same study was related to brain response to a more rudimentary form of the eye gaze stimuli (static faces looking directly vs away from the infant). Response to this static stimulus contrast distinguished those infants with typical behavioral outcomes in the at-risk group. In other words, infants who were later exhibiting typical behavioral outcomes showed a distinct difference in processing of these stimuli relative to those who were later diagnosed with autism as well as the control group. As such, some early differences may in fact reflect protective factors or mechanisms of brain adaptation and resilience in those infants at-risk who go on to exhibit a typical behavioral repertoire.

Recent insights from this research area support probabilistic and indirect mapping between genetic and/or environmental factors and developmental outcomes. Dynamic gene-by-environment interactions during the period of maximal brain plasticity lead to variable developmental pathways, not readily predicted by a simple model of risk. In some cases, early manifestations of risk are compounded and amplified leading to autism in toddlerhood. In other cases, the infant brain may be resilient in the face of genetic or environmental risk, restoring the typical trajectory through processes of brain adaptation and plasticity. In both examples of risk factors potentially reflecting harmful versus protective brain responses early in life, it is likely that the use of categorical diagnostic outcomes conceals critical associations that can only be captured when the full range of individual differences is exploited. A better understanding of the developmental processes leading to autism could in the future benefit from mapping biological measures onto behavioral phenotypes, rather than diagnostic categories, in autism research as well as in the broader field of research on psychiatric conditions [18,19]. Such approaches offer promising opportunities whereby research on early brain development in autism can contribute towards our understanding of the complex etiology of the condition.

References